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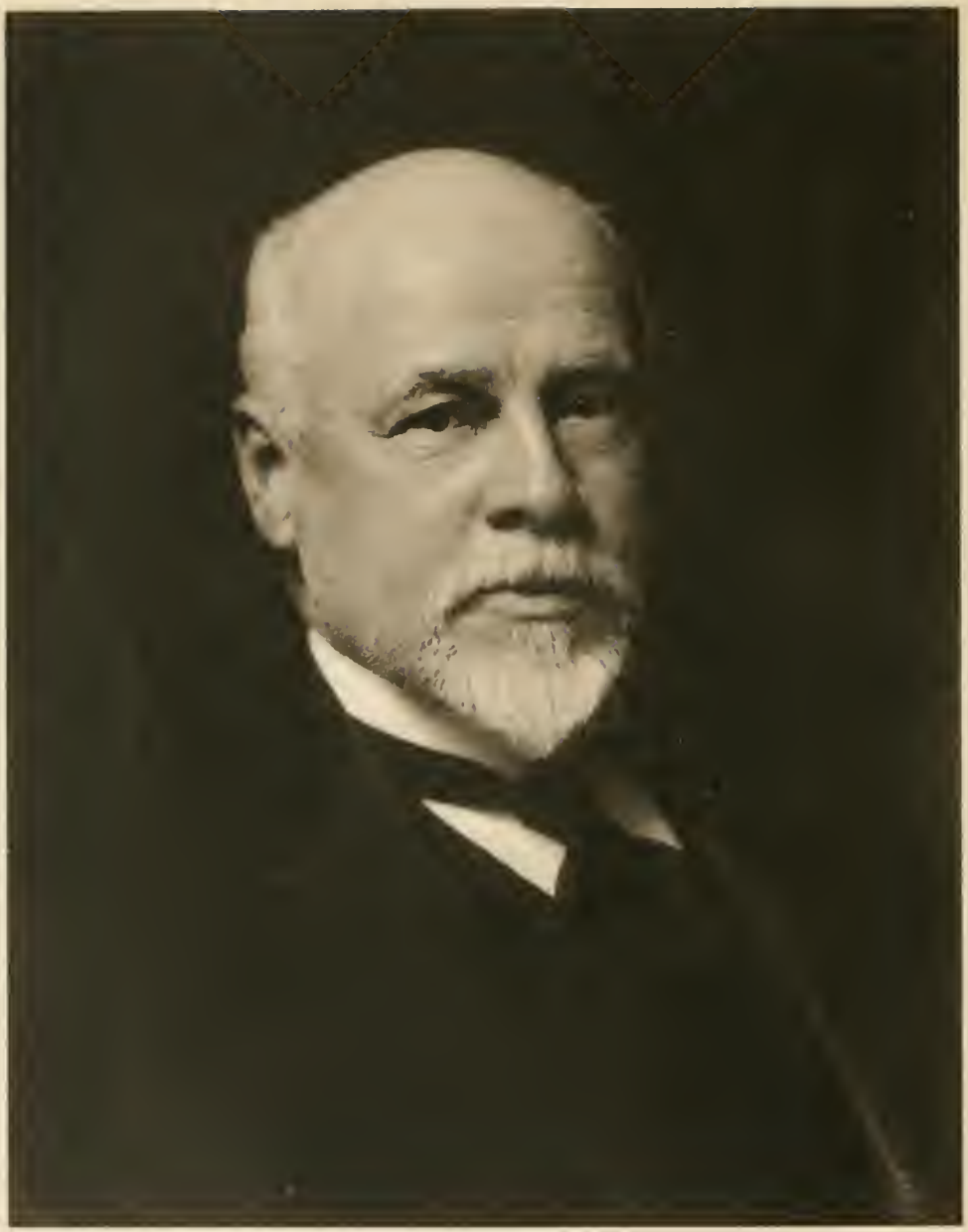
PAPERS AND ADDRESSES

BY

WILLIAM HENRY WELCH



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William H. Welch

PAPERS AND ADDRESSES

BY

WILLIAM HENRY WELCH

IN THREE VOLUMES

VOL. I

PATHOLOGY

PREVENTIVE MEDICINE

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IN HONOR OF

WILLIAM HENRY WELCH

UPON

THE SEVENTIETH ANNIVERSARY OF HIS BIRTH

THIS COLLECTED EDITION

OF HIS PAPERS AND ADDRESSES IS PUBLISHED

AS A TOKEN OF AFFECTION, GRATITUDE AND ESTEEM

BY HIS ASSOCIATES AND PUPILS

EDITORIAL NOTE

On the eighth of last April Dr. Welch attained his seventieth birthday. To many of his friends it seemed that such an occasion ought not to pass without some manifestation of affection and admiration on the part of the medical profession of America to one who has long stood as its leader, and that a worthy expression would be the preservation in suitable form of the chief contributions from his pen.

Dr. Welch's writings are scattered through a great variety of publications, many of which are more or less inaccessible. It was accordingly decided to bring together and to publish the more important of his numerous papers and addresses of the past forty-two years, publications which reveal the great part he has played in the development of medical science and medical education.

With the permission of Dr. Welch, the editor, in his student days, had collected these papers and addresses with a view to republication. When it became evident that the work would be interrupted by the war the appended Bibliography was published. On his return from France after the Armistice the editor was invited by the Publication Committee to undertake, under its supervision, the editing of these volumes.

The collected material covers a period during which there have been great advances in medicine, especially through the impetus following the development of cellular pathology, the discovery and study of pathogenic microorganisms, and the more widespread adoption of experimental methods. It will be noted that a number of the papers, and especially addresses and discussions, are from stenographic reports. Some of these have been revised and given appropriate titles, but no attempt has been made in these or other articles to alter the subject matter so as to bring it up to the later state of knowledge. In view of the fact that these publications have appeared

in England, Germany, and America during a period covering nearly a half century, the orthography is not consistent throughout the volumes.

The volumes include studies in pathology, preventive medicine, bacteriology, medical education, the relation of medicine to other sciences, and the history of medicine in the United States and elsewhere. Papers on similar subjects, although scattered over a number of years, have been placed together chronologically in groups.

In behalf of the Publication Committee the editor desires to thank the editors and publishers of books and periodicals for their hearty cooperation in consenting to the use of articles appearing in these volumes. Especial thanks are due to Sir Clifford Allbutt of Cambridge, England; Dr. Frederic S. Dennis, New York; the Macmillan Company, London; Lea and Febiger, Philadelphia; to the editors of the Bulletin of The Johns Hopkins Hospital, the Transactions of the Association of American Physicians, the Journal of the American Medical Association, the Bulletin of the Medical and Chirurgical Faculty of Maryland, the Maryland Medical Journal, the Journal of Experimental Medicine, Science, and numerous other publications; and to Mr. Max Broedel, who has redrawn some of the illustrations.

It is largely through the active interest and advice of Dr. William Stewart Halsted and Dr. Henry M. Hurd in every phase of the publication that this tribute to Dr. Welch has come to pass. A great debt of appreciation is due to Dr. Simon Flexner for his preparation of the Introduction. To Lieut. Col. Fielding H. Garrison, M. C., U. S. Army, Dr. William Sydney Thayer, Dr. William G. MacCallum, Dr. John Howland, Dr. Lewellys F. Barker, Dr. J. Whitridge Williams, Dr. Ralph B. Seem, Miss Minnie Blogg, The Johns Hopkins Press, Mr. Nathan Billstein of the Lord Baltimore Press, and many other friends of the author who have given valuable assistance the editor expresses his indebtedness.

WALTER C. BURKET.

DECEMBER 1920.

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PREVENTIVE MEDICINE

WILLIAM HENRY WELCH

A BIOGRAPHICAL SKETCH

My Dear Associates:

On this memorable and beautiful occasion I have the cherished honor of having been chosen to perform, as it were, the duties of chronicler, in order that we may all be led to review in our minds the successive steps by which our great leader and master rose to such high distinction and wrought the miracle of giving to medicine a new birth in this country; and in order, also, that our successors, lighting their lamps at the shrine of Pathology and studying the treasures which these precious volumes enclose, may catch a gleam of what manner of man he was who produced them, and who by the vigor of his living example and the charm of a rare personality, as well as by the power of his spoken and written word, in the short span of a lifetime raised medicine in the United States from a beneficent art to an expanding science.

William Henry Welch was born in Norfolk, Connecticut, April 8, 1850. He was the son of William and Emeline (Collin) Welch. His father was a practising physician, as were four of his father's brothers. Moreover, a great grandfather and grandfather were also physicians. When about one year of age, William Henry's mother died; thereafter he was taken care of and brought up by his paternal grandmother, who resided with the father. A contemporary describes the youth as a great favorite in the village, interested in all kinds of sports and athletic exercises. During the Civil War, the youthful William became captain of a company of zouaves, who, dressed in regulation costume and provided with guns, drilled regularly on the village green. When about twelve years old, William was sent to a nearby boarding school at Winchester Centre, conducted by the Reverend Ira W. Pettibone, an uncle by marriage. Here he prepared for Yale College which he entered in 1866, in his sixteenth year, and from which he was graduated in 1870, with the A. B. degree, standing third in his class. During his college period he impressed his teachers and classmates with the possession of the gifts which afterwards distinguished him in so large a measure. After graduation and before entering upon his medical studies, Welch taught school for one year at Norwich, New York.

Thus it was in his twenty-first year that Welch matriculated at the College of Physicians and Surgeons, in New York City. But this first venture into

medicine was very brief. An almost prophetic vision into the future gave him pause and led to his return to New Haven for a year of study in chemistry, which field even at that early date he perceived to hold great future possibilities for the study of medicine. This intermediate year was spent jointly at the Sheffield Scientific School and at the Yale Medical School. In the former, Welch came under the influence of Professor Oscar H. Allen who strongly stimulated his interest in science in general and in chemistry in particular. This rather unconventional and solitary personality, who was not only chemist, but geologist, mineralogist and botanist as well, proved to be an inspiring teacher. At the Yale Medical School the professor of chemistry was George Frederic Barker, afterwards professor of physics at the University of Pennsylvania and a member of the National Academy of Sciences, who was deeply interested at the time in organic chemistry and thus turned his pupil's attention to the writings of Kekulé which were just then exerting a dominant influence on chemical thought. Within the year the student was mastering the concepts of Kekulé in the original German. The breadth of interest of the two able teachers under whom Welch had the good fortune to come during this preparatory year, may well have exercised a directive if latent influence on the gifted and impressionable pupil which at a somewhat distant day was to assert itself in the determination to break with the traditional and alluring career of private and consultative practice, and to embark upon the hazardous one of pathology. This decision was not, however, arrived at immediately or even at the outset of his medical work, but came later as part of a widening knowledge and an enlarging experience.

It was fated also that the two men who, each in his own although different way, were to influence the rise of pathology in the United States, should first come together in the chemical laboratory of the Sheffield Scientific School. T. Mitchell Prudden had gone through the School at about the time when William H. Welch passed through the College; but as in that day the two sets of students—academic and scientific—rarely met and never mingled, the two men were not brought into contact. When Welch entered the laboratory, Prudden was already there, filling a kind of voluntary instructorship; and thus the two men whose paths were to cross and recross in the many subsequent years of sympathy, perfect understanding and common endeavor, first discovered in each other, albeit still in embryo as it were, that devotion to science and its ideals which as the years lengthened was to prove secure against the many and insistent allurements and pecuniary rewards of medical practice.

The year of chemical study over, Welch returned definitely to his medical studies. It will aid us a little later in the understanding of the change about to be wrought in the pursuit of pathology—in the making of advances in

which the then unsuspecting medical student was to play so large a part—if we pause to sketch in broad outline the kind of educational discipline offered the medical student at the College of Physicians and Surgeons, a leading institution, in the period embraced by the years 1872 to 1875.

In 1872, when Welch entered, the College of Physicians and Surgeons had been in operation for sixty-five years and led all its competitors in the number of its students and in teaching facilities. The College occupied a building of its own on Twenty-third Street, regarded as commodious, and was a part of Columbia University. The term of instruction had been extended from four to five months, and three instead of two sessions of attendance upon lectures were required for graduation. The precarious supply of material for dissection and for instruction in operative surgery and the method of obtaining it had been superseded and made fairly adequate by legal enactment. The courses in anatomy and to a less degree those in medical chemistry comprised the entire provision for objective or practical teaching, aside from the out-patient clinic at the College and the clinical lectures given at the New York and Bellevue Hospitals and the Almshouse. A voluntary course of lectures on pathological anatomy with demonstration of organs removed at autopsy was offered during the summer session by Francis Delafield.

While the preceptorial system was still in vogue and the medical student was still expected to obtain the main part of his clinical training during the long interval between sessions, in the office and on the rounds of his preceptor, the few outstanding students could hope to enter Bellevue Hospital for an interneship, which might begin even six months before graduation. But the didactic lecture, of which the instruction still chiefly consisted, was expected to fill the mind of the student with the medical lore of the day, while it served also to impress his imagination with the vigorous personality and high authority of the eminent teachers under whom he sat, in a manner now wholly foreign to the spirit of medical teaching.

But to the able, energetic and ambitious student the plan, imperfect as it was as an educational discipline, admitted of a choice of subject and disposition of effort not contemplated in the system. And thus we find Welch in the early period of his medical studies enticed away from the lecture halls into the more alluring atmosphere of the dissecting room and very soon serving as prosector to the professors of anatomy.

With the curriculum as indicated, it is obvious that no opportunity existed to acquire thorough training in any subject, aside possibly from the grosser aspects of human anatomy. The provision for pathology was extremely meagre. Although a chair of physiology and pathology, filled by Alonzo Clark, had been created in 1847, in the early seventies of the last century,

pathology had not become an independent subject of teaching, but was attached to the chair of medicine, still, as it happened, under Doctor Clark, who had been transferred to the professorship of pathology and clinical medicine.

There is no reason to suppose that Clark treated pathology otherwise than by lectures, with perhaps at most the occasional use of specimens from the deadhouse. On the other hand, Francis Delafield, who had become adjunct professor of pathology and clinical medicine, was already studying assiduously with the microscope the pathological changes in the kidneys in Bright's disease and still other morbid processes, as viewed indeed from the standpoint of the new cellular pathology just struggling into the light. But of opportunity for the student himself to acquire even the rudiments of the technique of the microscopic study of the organs and tissues in health and disease, there was none. It was not, therefore, just at this juncture in Welch's history that his interest in pathology asserted itself.

A compelling circumstance was, however, imminent. Among the prizes offered to students was one provided by Doctor Seguin, then the professor of diseases of the nervous system, for the best report of his clinical and didactic lectures. It consisted of a Varick microscope fitted with superior French triplex lenses. This prize was won by Welch, and it proved indeed to be the spark which ignited the tinder of his latent interest in pathology and caused it to burst into flame. Fortunately Welch now entered in October, 1874, upon his interneship at Bellevue Hospital, where this strongly aroused impulse was to find an abundant field for expression. He now also came more directly under Delafield's influence, and was thrown with the elder Janeway. Much of his time was spent in the deadhouse performing autopsies, first on his own and then on many other cases; and it is a remarkable tribute to his technical skill and acumen of observation, as well as felicity of description, that Delafield invited him to use his special book for recording the protocols of the postmortem examinations, and that he was made a curator of the Wood Museum attached to the Hospital.

Although it was perhaps not clearly perceptible at the time, it now appears that the circumstances surrounding and thus acting upon the sensitive imagination of Welch, the student, were favorable to his development; for notwithstanding the poverty of material resources and of laboratory facilities of the era, he had the good fortune to come under the influence in the medical college of not a few men of remarkable mental vigor and attainments. Besides those already mentioned, there were on the faculty of the College in his day Dalton and Curtis in physiology, St. John and Chandler in chemistry, Edward Curtis in materia medica, Markoe in surgery, Sands and Sabine in anatomy and McLane in obstetrics; weekly clinical lectures

were given by Willard Parker and T. Gaillard Thomas, the prestige of whose strong personalities and eminent careers in surgery and in obstetrics and gynecology respectively must have been potent forces. He was thrown as prosector into close association with Sabine and with the demonstrators of anatomy, John Curtis and McBurney. It was especially at the suggestion of Sabine that Welch wrote his graduating thesis upon goitre, which received the first prize, and in the preparation of which he familiarized himself with medical literature and bibliography at the New York Hospital Library. At Bellevue Hospital his contacts with Delafield and with Janeway became numerous and close, the forerunner, as it chanced, of a relationship destined to become even more intimate and significant at a somewhat later period.

Moreover, the era in which the young student found himself was one of fundamental flux of belief brought about by the new cellular pathology and the discoveries of Pasteur just impending. Into this whirlpool of shifting ideas, which were to move in the next succeeding years with ever-increasing speed, Welch with his eager, open and responsive mind was thrown. That his imagination was powerfully stirred by the intellectual ferment of the time may be assumed. One circumstance is, however, quite clear: at this stage pathology as an independent career had not been seriously before his mind, nor was it so to present itself until a whole new set of experiences had been passed through.

The year and a half's interneship over, Welch is about to take ship for what proved to be for him and us a great adventure. In April, 1876, in company with his friend and fellow townsman, Dr. Frederic S. Dennis, he sailed on the Cunarder "Bothnia" for Liverpool. From Liverpool he went to London where he spent a few days, crossed the channel from Harwich to Rotterdam and made his way leisurely along the flowering Dutch and Belgian fields as the spring was passing into the mild early summer months, toward Strassburg, the first stopping place on the long but important road which was about to fascinate his view.

Welch's European experience begins with Waldeyer, the Director of the Anatomical Institute in Strassburg, with whom he studied normal histology. This subject was of course taken up on account of its fundamental importance as a basis for pathological histology. But it is significant that the interest in chemistry, also as a foundation subject, which carried Welch to New Haven on the very threshold of entrance to his medical studies, had remained alive; hence part of his time was spent in Hoppe-Seyler's laboratory, under the master himself and his assistant Baumann, in working through the former's well-known textbook in physiological chemistry. In addition, time was found to attend von Recklinghausen's autopsies and demonstration course, although at this period no further courses were taken with this master of

pathology and for the reason that Welch concluded that until a grounding in normal histology was secured, it would not be profitable to pursue pathological histology.

The summer semester at an end, Welch left Strassburg for Leipzig, the summer vacation being spent with a friend in a pedestrian tour in Switzerland and northern Italy. It is of interest to inquire just what was the lure of Leipzig. Obviously Waldeyer was the attraction in Strassburg; now it was Heubner and Wagner who drew the student to Leipzig. At that time Heubner had not entered the field of pediatrics in which he afterwards became celebrated, but he was working rather in the field of neurology; and, indeed, it was his important book on the diseases of the blood vessels of the brain,[1] which Welch had read, that determined the choice. If we undertake to penetrate further into the source of Heubner's attraction for Welch, we are led back to the days at the College of Physicians and Surgeons in New York and the lectures of Seguin which had exerted a strong influence on Welch, so that if we had then inquired whither he was tending in medical specialization we should have discovered that he was looking to diseases of the nervous system as the field for practice, while pathology remained his main interest and subject of training in Germany, although he could not then anticipate its pursuit as a means of livelihood on his return to America.

Circumstances were, however, to defeat this consciously worked out program. In due course Welch subscribed for Heubner's course, only to find very quickly that the latter was not then interested in teaching; soon the course began to languish and the students to absent themselves, and it was not long until Welch was looking elsewhere to fill his time. Wagner, who later succeeded Wunderlich in the chair of internal medicine, was at the time professor of pathological anatomy. Welch found Wagner's courses and the opportunities afforded for independent work by his institute admirably adapted for his own purpose. Here he attended autopsies and obtained specimens of tissue for microscopic examination. At first the blocks were given as a favor; but later Wagner's interest having become aroused he would personally select the specimens for examination and for report. In this manner Welch occupied his mornings; the afternoons were, however, still free. He attended Wagner's polyclinic, which kept him in touch with practical medicine.

At this period Ludwig's laboratory was the centre of attraction for the talented men in Germany and also for many foreigners especially interested in physiology. Welch decided to offer himself and was accepted by Ludwig. That the choice was a propitious one is shown by the group of men at that time working with Ludwig and with whom Welch was now associated. The

[1] Heubner. Die luetische Erkrankungen der Hirnarterien, Leipzig, 1874.

first assistant was the gifted and inspiring Kronecker with whom Welch formed an enduring friendship. Among foreign students was Pawlow, and Drechsel and Flechsig were in charge of the chemical and the histological divisions of Ludwig's laboratory. Welch was set by Ludwig to study the ganglia and nerves of the auricular septum of the frog's heart with the gold chloride impregnation method, in the course of which he actually brought into view the ganglionic cells with T-shaped fibres which Ranvier described in detail somewhat later. The semester closed and the usual *"Abschied"* supper was given by Kronecker. Of course Welch was invited and there was characteristically exhibited a model of the ganglion cell with fibres both entering and leaving it—a novel and as we now know a histologically highly important event.

The first year of Welch's European study was now over. It had been spent in preparing himself in normal histology, physiological chemistry, pathological anatomy and physiology; and it may be asked to what purpose and for what ultimate end? The answer is, in order to be ready to study with Virchow, whose institute he had visited during a short stay in Berlin. This expectation was indeed the force back of the concentration on normal histology, the reason for embracing eagerly a histological problem from Ludwig, the motive in following Wagner's autopsy and microscopic courses; and, after all, the wish was to be frustrated and Welch's activities were to be directed along a wholly new direction and into fresh channels.

The new impulse came from Ludwig who did not share the enthusiasm, at least in the overwhelming degree then current, for the cellular pathology of the period. Perhaps this response was the less hearty because he did not have the strong sense, as so many seemed to have, of a great innovation, but rather viewed Virchow's doctrines as the extension, perhaps even the consummation, of the earlier conceptions and discoveries of Schwann, Schleiden, Remak and Reichert; or possibly it was his physiological bias or even a subtler appreciation of the impending influence of the study of function on the growth of pathology, which led him to induce Welch to alter his plans and to offer himself to the brilliant young pathologist Cohnheim to whom he undertook to write urging him to receive Welch and to furnish him with a rewarding (*lohnendes*) theme.

This choice proved highly fortunate. As one reviews Welch's own published work, his immediate influence on his students, or the more general effect which his career has had on medical education, it is now quite obvious that his intellectual temper was of the order called dynamic, and his vigorous responses were to concepts built on facts of function far more than of form and structure. The summer semester of 1877 with Cohnheim in Breslau was perhaps the most delightful and satisfying of all the time Welch spent

abroad; and fortunately we possess a pen picture of him at that particular time, drawn in clear and sympathetic lines.

Salomonsen, afterwards professor of pathology at Copenhagen and the present Nestor of medicine in Denmark, had also come to Breslau for the summer semester. The two foreign students, the first foreigners who studied with Cohnheim, were at once thrown together; there existed, indeed, that subtle quality in the temperaments of the two men that quickly made for close association and then intimate friendship—a rare relation which neither distance nor fleeting years have severed. Salomonsen states that the two men who most influenced his own life were Carl Weigert and William H. Welch. He goes on to enlarge and say that he and Welch had many points of contact: both were sons of physicians, both on return to their own countries hoped to become pathologists to municipal hospitals, and both regarded it as a matter of course that anyone wishing to enter on the career of pathologist should aspire to work under Cohnheim.

The two foreigners were proud of the distinction—what two eager young men would not be?—of being the only foreigners in the laboratory among such present or prospective stars as Weigert, Ehrlich, Lassar, Lichtheim, Albert Neisser, Senftleben and O. Rosenbach. They were always together—from early morning to late afternoon—and they were taken up cordially by their German colleagues of whose intimate circle they made a part. I venture to quote a particularly appropriate paragraph from Salomonsen:

"That by accident I should have found so gifted a man and investigator as Welch in Breslau, I at that time as well as later, regarded as the greatest good luck. Cohnheim knew well how to appreciate Welch, and he recommended him for the professorship of pathology at the Johns Hopkins University where Welch exerted a profound influence on the development of medical education in the United States, and where the present generation of American pathologists calls him master."

It was in this remarkable atmosphere that Welch spent a precious semester. The work of the laboratory was pretty sharply divided between the autopsies conducted mostly by Weigert, and the experimental investigations in which Cohnheim shone ever brighter and brighter. The particular problem which Cohnheim assigned to Welch was the ascertaining of the origin of acute general oedema of the lungs. This is perhaps not the place to go into minutiae of that splendidly conceived and executed piece of experimental work. It was in many ways fortunate that Cohnheim was too preoccupied at the time reflecting on his theory of tumors and in the preparation of his textbook on general pathology to do more than propose the problem which Welch developed largely according to his own notions of logical sequence. Cohnheim, indeed, was greatly surprised when contrary to his preconception

of the process, Welch found the factors involved in it to be mechanical. The masterly paper describing this piece of work as it appears in *Virchows Archiv* was written out by Welch in German and printed quite as he prepared it. Cohnheim seems not to have altered essentially the composition, the mode of presentation or the conclusions arrived at. Unfortunately for future controversy Cohnheim misconstrued the implications of Welch's experiments and in his epochal Lectures on General Pathology he substituted for the term disproportion (*Missverhältniss*) employed by Welch to express the disharmony (often caused by spasm) in action of the two cardiac ventricles, the term paralysis (*Lähmung*), which implies only one form of disharmony.

The by-products of this semester on Welch's development were as important as the direct influences. Salomonsen's studies on tuberculosis of the eye initiated him into the experimental side of the tuberculosis problem. Salomonsen relates an incident showing the great impression made upon the two foreign students by the first example of generalized tuberculosis in the guinea pig which they observed. Their enthusiasm evoked hearty laughter from Cohnheim. It was, moreover, the period of Heidenhain's early brilliant work, of the rich harvest of Cohn, the botanist; and to cap the climax, the occasion of Koch's visit to Breslau to lay before Cohnheim and Cohn the facts of his studies on anthrax, in the demonstration of which all the workers in Cohnheim's laboratory were permitted to share. Finally, Weigert with Ehrlich was just applying the aniline dyes to the staining of tissue elements and bacteria and had recently completed his study of smallpox, in the course of which he demonstrated by staining methods the masses of micrococci within the pustules. Ehrlich also, although not yet graduated, was literally dabbling in the aniline stains and it was a common event to see him with hands covered up to the wrists with dyes of many colors. The close friendship of Welch with Weigert and Ehrlich dates from this period.

It is significant that the spirit of the Institute was favorable to the new bacteriology and that Cohnheim and his associates were all looking to the new science to unlock doors still concealing the origin of the diseases called infectious—an attitude striking in its difference from the skeptical and rather disdainful one of the Virchow school of pathology. Thus on leaving Breslau, Cohnheim sent Welch to Vienna by way of Prague, in order that he might visit Klebs who was engaged in the study of acute endocarditis from the microbiological side. There he spent several stimulating days, during which Klebs showed him through his excellent museum and demonstrated his preparations showing microorganisms (micrococci) in the ulcerative lesions of acute endocarditis. The impression which Klebs made upon Welch was very strong; and in the light of present knowledge, the accuracy and presci-

ence of Klebs' work, well in advance of his period, not only on endocarditis but on diphtheria and experimental syphilis as well, have become clearly apparent.

The next stop in the educational journey was made at Vienna which was still a kind of Mecca for foreign medical students of all nationalities. The immediate objective was a place in Stricker's laboratory, in order to continue his studies in experimental pathology. As an index of the high feelings prevailing at the time it may be mentioned that once Stricker learned that Welch had been with the heterodox Cohnheim who taught that the pus cell was merely an emigrated leukocyte, he was not inclined to receive him as a worker in his laboratory. One purpose of the visit to Vienna was to study embryology under Schenck, but the choice was not fortunate and Schenck was soon forsaken. It is interesting to note that Welch and Prudden found themselves together in Vienna in their search for an opportunity to study embryology.

On the whole, the chief lure of Vienna for the pathologist was its almost inexhaustible store of pathological anatomical material. The reign of Rokitansky was over, and his successor was Heschl, the discoverer of the methyl-violet reaction for amyloid, but a far less significant personality. The greater attraction was the young Chiari who was teaching and working with the vigor which afterwards became so notable and carried him by way of Prague to Strassburg to succeed the eminent von Recklinghausen. To him Welch went, but not to spend his entire time. There survived in his mind, it appears, a residue of distrust that pathology would after all afford him a career in America, or was it the love still for the more immediately practical aspects of medicine which led him to enter upon courses on the skin under Hebra, on neurology and psychiatry under Meynert, on the eye, and other special subjects? But Vienna meant for Welch much more than gross pathology and the medical specialties. The great city with its splendid museums of art, its grand opera and its vivid life introduced features of another order into his experience, feeding that general culture in literature, history, and the fine arts which came to distinguish him quite as much as his many-sided medical attainments. Welch remained in Vienna until the Christmas holidays, when he turned his steps for a second time toward Strassburg, spending a few days *en route* in Würzburg with Rindfleisch and his assistant Ziegler.

The second pilgrimage to Strassburg was the carrying out of a plan formed by Welch at the outset of his European study. He recognized in von Recklinghausen the outstanding representative of the Virchow school of pathologists, and his attendance upon the autopsies at the Pathological Institute, while he was a pupil of Waldeyer, had stimulated his zeal to work directly

under the master. This desire could not be at once appeased, for as we have seen, Welch lacked the preparation in normal histology which he regarded as essential. But now that this requisite was supplied and the work with Ludwig and with Cohnheim had provided a fair foundation for further building, Welch offered himself to von Recklinghausen and was accepted.

As another indication of the commotion which Cohnheim's investigations were making in the placid waters of Virchowian pathology, it may be cited that once von Recklinghausen learned Welch was fresh from the laboratory of that heretical pathologist, he chose as a theme for his special study the inflammation of the cornea of the frog induced by various caustic chemicals. The essential point of difference involved in the contentions of the Virchow and the Cohnheim schools related to the origin of the pus cell. Was it derived by multiplication from the fixed tissue cells, or was it a leukocyte emigrated from the blood? The controversy has long been settled in favor of the latter, or Cohnheim view; but in January, 1878, and for many years thereafter it raged with vigor and even bitterness. The cornea was selected because of its condition of non-vascularity. The novel experimental procedure employed at von Recklinghausen's suggestion by Welch was the excision of the cornea after the injury and immersion in the aqueous humor of the frog or bullock, and observation continued over long hours under the microscope. That cells moved toward the injured spot in the non-vascular specimen was shown beyond peradventure and even that they divided; what was simpler, therefore, than to conclude that migration is not dependent on the presence of the blood, and hence pus cells are not translated leukocytes? This inference, however, was not drawn by Welch, who recognized that the reasoning is fallacious. The full explanation of the observed phenomena waited on later studies and even on recent discoveries. We now know that connective tissue cells, among which the corneal corpuscles and the cells of Descemet's membrane are classed, are motile; and as cells endowed with movement they are attracted by certain stimuli called "chemical," such for example as arise in tissue constituents acted on by chemicals and in other ways. Moreover, as we now know, these fixed tissue cells readily multiply *in vitro,* and thus we arrive at the conclusion that the chemically altered spot in the cornea attracts towards itself neighboring uninjured, motile corneal and other cells, that these cells aggregate about the site of the injury and even multiply there, and thus give what may be called a spurious appearance of a collection of pus cells. For it should be remembered that we are dealing with a period in which tissues were not yet being stained with certain nuclear and other dyes that bring into view brilliant and subtle distinctions of cellular structure; but that the "inflamed" cornea was merely silvered in order that the cell

outlines might become perceptible, and, if desired, was subsequently stained with haematoxylin to show the nuclei.

This practice of putting to the test new discoveries and contentions even under somewhat hostile circumstances was not a poor discipline for the future teacher of pathology in the United States. The experience may indeed be regarded as having brought into play under favoring circumstances a critical faculty inclined perhaps to leniency, while it held up as it were to the mirror of his perceptions in a somewhat summary fashion the facts of the ultimate and ineradicable residue of personal bias in all men, no matter how great. In the long future years during which Welch dispensed knowledge and, what is rarer, wisdom at The Johns Hopkins University and elsewhere, he came as near as it is perhaps possible for a mere mortal to come, in escaping the blemish of preconception and prejudice and in preserving and presenting the ideal of the open though balanced mind.

But it would be wrong to infer that there was not also a constructive side to this period with von Recklinghausen. The pathologist was great in attainments, and stimulating as a teacher. He engaged Welch in discussion of many topics in pathology which were current at the time. One of these related to the origin of tumors, regarding which von Recklinghausen was endeavoring to formulate his views along lines which have since become more familiar. He inclined to the conception that a kind of fertilization, whether by conjugation or otherwise, took place among the cells, leading to the unconstrained multiplication characteristic of cancer and other tumors, in consequence of which irregularities of division arose that were the striking obvious signs of the cellular abnormality. Welch always retained an admiration for von Recklinghausen as a great pathological anatomist.

The first European adventure was now approaching its conclusion and was to receive a suitable ending by a first visit to Paris and a second to London. It is far simpler and more satisfying perhaps to leave to the imagination the picture of Welch in the great and beautiful French city with its wealth of present interests and of historic backgrounds everywhere insistent. The fact may, however, be mentioned that time was found during the two or three weeks of his stay to hear Ranvier, whom he admired greatly and whose book on histology had been his guide, and to visit the main hospitals. In London he heard Lister lecture at Kings College Hospital, and shared in the prevailing excitement which arose from Lister's daring surgical exploit of opening the knee joint. The next was the final act, namely taking ship at Liverpool for the United States.

The arrival in New York in the spring of 1878 brought forward a question which could be permitted to remain in the background in Europe, but now

must be answered. Undoubtedly Welch possessed wares garnered at home and abroad—but to what market were they to be taken? That the practice of medicine would be a necessary corollary to any other ambition he might indulge, seemed never to have been doubted by him. Where else were the necessary pecuniary rewards to come from? There seemed no alternative but to decide immediately whether he should choose New York or Norfolk as a field of operations. In Norfolk his father was still busily, if not very remuneratively, engaged in country practice, in the course of which he dispensed much kindness and, according to tradition, worldly wisdom with his medicines. It strikes one now as very odd that Welch should have hesitated at this juncture in his choice of New York or of Norfolk. The anomaly can best perhaps be explained by taking into account his remarkable modesty. It seems almost impossible of belief that one so gifted and innately so forceful should not be aware in some degree of the part which nature had cast for him. But whatever pangs of indecision he may have suffered were about to be allayed by destiny in the form of Doctor Goldthwaite.

Success in attaining interneships in hospital or appointments to the medical services of the Army and Navy was still determined by the results of competitive examination. To meet this situation the private "quiz" had arisen and operated about the medical schools and upon the aspiring medical students. The practice has now been generally discredited and discontinued; but in 1878 and for many years afterwards the "quiz" if successful was a reputable and a relatively highly remunerative affair. The "quiz" masters adapted the cramming process to the peculiarities and foibles of the individual examiners, which they sedulously set themselves to learn. It is now obvious that on joining Goldthwaite's "quiz" Welch never regarded the undertaking as more than a stop-gap. It should not now surprise us to learn that the combination of Goldthwaite and Welch proved irresistible and soon outdistanced all competitors; it could choose the most promising students and its product gained the prize interneships. Welch endured the "quiz" three years, after which and while it was at the height of its popularity he withdrew. The reason is sufficiently apparent now, but then with the system intrenched as it were, it required insight and force to convict it of its salient defect, namely that of being a bad method, viewed from the standpoint of educational discipline.

The "quiz" was, after all, merely an incident, the main import of which was that it ensured the necessary income, while leaving much of Welch's time for more engrossing pursuits. As a matter of fact, Welch had offered himself for practice and occupied at this period rooms with his friend Dennis at 21 East Twenty-first Street, adjacent to the office of his old teacher, Alonzo

Clark, who would refer occasional patients to the young men. The volume of Welch's practice never became embarrassing, so that he was still free to follow his major bent, which was to teach pathology.

The outlook for pathology in New York in 1878 was not bright. The extent and the nature of the teaching had not changed materially since Welch was a student in the medical college. New York was as much cut off from the strong currents moving in Germany and France along the three main lines of pathology—pathological anatomy, experimental pathology and bacteriology—as if Europe and America were not connected by a common intellectual bond. Welch was, indeed, destined to play the principal part in breaking the barrier of American isolation, but at this time when he was offered by Dr. Francis Delafield the lectures on pathology during the summer semester at the College of Physicians and Surgeons, he declined the opportunity, because it carried with it no chance to set up a laboratory, which was the one essential of Welch's aspiration. But what was denied him at the College of Physicians and Surgeons, was about to be put before him at Bellevue Hospital Medical College. This rival institution proposed to build two small rooms over a hallway, which, added to another room, Welch could turn into a laboratory.

The invitation was accepted at once, and Welch made his first break with the established traditions in New York. For this was the heyday of schism in medical schools and feelings ran high among the several faculties, and the position of his alma mater, the "P. and S.," in the medical hierarchy of the time was regarded as supreme. Certain of Welch's friends were not happy over his choice and even considered that he had made "the mistake of his life." Perhaps there were disadvantages of a kind in a Bellevue connection as contrasted with the far greater prominence of the "P. and S." establishment, but whatever they may have been in general, they were more than compensated for by the laboratory and its proximity to the deadhouse at Bellevue. The new pathological laboratory became at once an influential factor in the medical educational system of New York, and students came there to Welch from all three medical schools.

The leaven worked rapidly, for very soon the College of Physicians and Surgeons awoke to the growing demands of pathology. A part of the faculty had not ceased to view Welch's defection regretfully, and now that the Alumni Association proposed to set up, under Delafield's general direction, a pathological laboratory, its direct conduct was offered to Welch. The invitation was not accepted, but in declining it Welch characteristically, as we should now say, put in another strong stroke for pathology, as the

following letter, which also explains his sense of obligation to the Bellevue College, illustrates:

"New York, October 9, 1878.

"My dear Doctor Prudden:

"A few days ago Professor Delafield told me of the following scheme which the Twenty-third Street Medical College has on foot. A laboratory for histology and pathology is to be established in connection with the college, by means of a fund given for the purpose by the alumni. It is to be taken hold of in an earnest way, for the laboratory is to hold the same relation to the college as the dissecting room does; that is, each student will be obliged during some part of his course to work there before he can take his degree. Doctor Delafield proposed that I should go in as his first assistant and have charge of the histological department, and assist him as much as necessary in the pathological part. The salary was to be five hundred dollars for the first year, and I believe more subsequently. I was naturally delighted with the offer and thought it to be just what I wanted, an opportunity to work in the direction where I had studied most. Upon speaking of the matter, before coming to a decision, with some of the professors at Bellevue, I find that they are reluctant to have me leave there, and even represent it as not the square thing for me to go at present. The latter motive especially has influenced me to stay, as I do not believe it pays to do anything unfair. I feel as if I were relinquishing a great opportunity and do not see any equivalent for it at present at Bellevue, but as there is a feeling there that it would not be right for me to leave, I am going to stay and have so told Doctor Delafield. He asked me if I knew anyone who would be competent for the position, saying there are a great many in New York who think they are, but few who really are.

"I immediately suggested your name and he at once seemed pleased, and deputed me to hunt you up by a letter and communicate the proposal to you. I really think the offer an advantageous one, in fact presenting an opportunity better than any other I know for one with the tastes and resolution which you have formed. I do not know anyone who could do greater justice to the work there than yourself, and it seems to me to present great possibilities for the future. Personally I should like to have you here in New York, for I fear I am going to rust out unless I have someone to talk with and help me on concerning the subject in which we are both interested.

"I do not know whether this letter will even reach you. Will you at least drop me a postal card when you receive it, for if I do not hear from you in a day or two, I am going to resort to further means of hunting you up. I should also like to know how you decide."

With Prudden's installation at the College of Physicians and Surgeons, pathology had come to be recognized as a subject of independent merit and proportions, to be taught practically, by two of the leading medical schools of the country. Prudden was a pupil of Arnold of Heidelberg, under whom he had mastered a precise and delicate pathological histological technique; and later at Vienna, in part alongside Welch, he had imbibed the essence of

the teaching of morbid anatomy. Thus and at last in the persons of Welch and Prudden, American pathology had come to be united with the best sources of its inspiration abroad; and from now on the main task was to widen and diversify this stream in the accomplishment of which purpose Welch's career stands forth preeminent.

Welch was now fairly launched on a career in pathology, but his struggles were not all over. The serious question all along was the economic one. Pathology was not a remunerative profession at the time. The fees from students taking the course were small, the occasional windfall from a private autopsy was precarious. There were, of course, the fees for the examination of specimens for physicians and surgeons, and the possibility existed then as now of turning this practice into considerable income. But Welch shrank from an enterprise which would consume his time and yield no corresponding scientific return. After the abandonment of the "quiz" a way out was found in that he became first, assistant demonstrator and later demonstrator of anatomy at Bellevue, both paid positions; and then he offered himself for practice. That his neighbor and teacher, Alonzo Clark, sent him patients, we have seen; it remains, however, to add that the now elderly gentleman formed the habit of referring his surgical cases to Welch.

This was also the period of Welch's association with the elder Flint, then at the zenith of his prominent career as teacher and consultant. He was professor of medicine and the leading spirit at the Bellevue College, and a great social and professional figure in New York. Flint was engaged at the time in bringing out a new edition of his Practice of Medicine and asked Welch to revise the sections on pathology. Welch "jumped at the chance" and was given a free hand, except for two or three topics which were reserved for his son, Austin Flint, Jr. Anyone today reading Flint's Practice of Medicine will recognize the superior merit of the introductory chapters on general pathology and the sections on the pathology of the special diseases there given, the whole amounting to a textbook on pathology.

It was Flint's habit to precede his lectures on "practice" with a sketch of the pathology of the subject to be presented. Pretty soon these preliminary lectures were turned over to Welch, who lost apparently no opportunity to increase the prestige of pathology in the curriculum. Thus he introduced the class autopsy, which he held once a week in a room filled with students. Notwithstanding these clear indications of Welch's unmistakable bent and trend, Flint assumed all along that Welch would become a consultant and succeed him in the professorship of medicine. Indeed, he took steps by having the faculty elect Welch to the clinical professorship of medicine to make his succession certain. Welch on learning of this action brought about its revocation, first because of the injustice which he considered done

to the then incumbent of the clinical professorship, and next because of his great interest in pathology.

Looking backward it can be perceived that these many shifts and activities were incidental to the laboratory of pathology. First the "quiz," second the demonstratorship in anatomy, third practice—each in turn supplied the necessary income in money to cover living expenses. Each in turn was followed with energy and success, and abandoned as soon as the needed income was available from a source less exacting of the precious time to devote to autopsies and laboratory, or freer from considerations violating fundamental beliefs in sound educational method. Pretty soon his skill in performing autopsies and his eagerness for pathological material brought to Welch privileges from the Babies' Hospital and also from the coroner, with whom Welch stipulated that he was not to testify in court. It is of passing interest to note that none of these were paid positions, but that at this time a small stipend came to Welch from the registrarship of the Woman's Hospital, which position he then held, and where he made the autopsies and studied the specimens, mainly ovarian tumors, removed at operations.

Half a dozen years had passed since his return from the European studies, and Welch had intrenched himself deeply in the medical life of New York. He was the outstanding pathologist and representative of the new pathology, and there came to him to study or to work, the alert and ambitious among the medical students and young practitioners of the day. These years had contained not a little that was pleasant, but much also that was discouraging to one who possessed a deeper feeling for and a wider outlook on medical education. It is true that improvements were creeping into the medical curriculum; the annual sessions at this time were indeed extended from five to seven months and more emphasis was being placed on the laboratory and less on the purely didactic form of instruction; but progress was painfully slow and medical teaching lagged sadly behind that of continental schools. However, a turn in medical affairs was impending which was to transform within a few years the entire educational structure.

The Johns Hopkins Hospital was approaching completion and the thoughts of President Gilman and the boards of trustees of The Johns Hopkins University and Hospital were turning toward the establishment of the medical school provided for in the splendid gift of Johns Hopkins. A leader to guide the new enterprise was sought, and it is quite clear from Salomonsen's statement that President Gilman asked Cohnheim's advice, and doubtless the advice of others at home and abroad. Welch seems to have been the unanimous first choice. Dr. John S. Billings, so intimately associated with the planning of the Hospital, visited Welch at Bellevue, doubtless in this connection, and Welch was invited to become professor of pathology in the

University and pathologist to the Hospital. The great opportunity for which he had waited and labored and toward which his dearest aspirations turned had now come to Welch.

There was no doubt in Welch's mind that the Baltimore venture was full of promise and should be embraced. In the meantime, however, his position in New York had become so important, it is not surprising that a strong effort should be made to retain him. At first Welch's friends failed to see how anyone could exchange the professional opportunities of New York for those of provincial Baltimore. The incidents of the transition from the "P. and S." to Bellevue College were recalled in this almost grotesque adventure. But there was no doubting Welch's seriousness, and hence steps were taken at once to thwart his plans. The fear of losing Welch was the immediate incentive which brought the Carnegie Laboratory into being. Doctor Dennis, an intimate friend and admirer of Welch, obtained a sum of $50,000 from Mr. Carnegie for the erection of the laboratory. But there is reason to believe that Doctor Dennis had in mind, besides the purpose of anchoring Welch to New York, the setting up of the laboratory as an integral part of the medical educational system of the United States.

But the Carnegie Laboratory was, after all, a building only, with such simple and necessary equipment as was demanded by the work of the period in pathological anatomy and in bacteriology, just at its beginnings in the United States. There was no provision made for a paid staff, and there were no funds for daily running expenses. Just what might have happened had these essentials been provided, it is impossible to say, for undoubtedly with the erection of the Carnegie Laboratory the outlook for pathology in New York had suddenly brightened. But the vista opened before Welch's eyes at Baltimore was extremely fascinating, and strong as now may have been the motive to remain in New York, the unprecedented position which The Johns Hopkins University, at the zenith of its great reputation, had attained in fostering science, was a lure not to be resisted. Everything about the opportunity at Baltimore attracted Welch, who wished above all to be free to develop pathology in a manner approaching that which he had come to know in Germany; and fortunately for the history of medical progress in the United States, he yielded to manifest destiny, although in doing so he was breaking with old and devoted friendships and turning his back on a position in New York never yet attained by a devotee of a laboratory branch of medical science.

In the six years which had elapsed since Welch had returned from his first period of foreign study, the center of interest had begun to shift from the purely cellular pathology of Virchow to that of the microbiology of Pasteur and Koch, in which the bacteria appear as the direct incitants of

disease. Here at last, it seemed, were to be discovered the agencies whose actions are the immediate excitants of those organic and cellular changes or lesions constituting the visible reactions of the tissues to the injurious influences taking place in the course of the phenomenal process designated disease. This new direction of development was highly sympathetic to Welch who had been a spectator at Breslau, at the prologue to this swiftly moving drama, when Koch visited Cohn and Cohnheim in order to exhibit his anthrax cultures. Welch desired first-hand knowledge of and experience in the new field, and as The Johns Hopkins Hospital was still in process of construction, we find him setting out again, in the summer of 1884, for Germany.

The new goal was Koch in Berlin. But an interview with him at the *Reichsgesundheitsamt* led Welch on Koch's advice to go to Munich for the autumn to study under Frobenius in Bollinger's laboratory, preparatory to work under the master at a later date. It appears that Koch was soon to leave the *Gesundheitsamt* to be established in the Hygienic Institute under university auspices, near the Alexanderplatz. Frobenius proved a slavish teacher of Koch's technique, which he communicated to his pupils along with such comments as he had gleaned from conversations with Koch. Still, it was a beginning in the new field, and the relatively unfavorable conditions led again, as once before at Leipzig, to connections of great future importance. Here Welch made the acquaintance of Hans Buchner and also of Escherich, Lehmann, Neumann, Celli and others who had come to follow the first course in bacteriology given in a university. Especially with Celli, who had already begun his studies of the malarial parasite, he formed an intimate and enduring friendship. Welch followed at this time Kitt's demonstrations in animal pathology in the veterinary school and worked in von Pettenkofer's institute of hygiene with the master himself and his assistant, Renk. All was grist that came to Welch's mill for in after years the former experience was to bear fruit in his important studies on the swine diseases and the close interest in Theobald Smith's work, and the latter to contribute to that comprehensive grasp of the subject of hygiene now being embodied in the new school of public health at Baltimore, his latest and highly remarkable creation.

Welch did not go at once from Munich to Berlin but acting still under Koch's direction went in January to Göttingen to work under Flügge, who was professor of hygiene and much closer to Koch and being advised by him. This period was in every way advantageous, as Flügge was a far more inspiring and systematic teacher than Frobenius, and his influence proved lasting and valuable. Here again he became acquainted with fellow students gathered in Göttingen for the same purpose, who afterward became distinguished bacteriologists, such as MacFadyen, Nicolaier and Wyssokowitch.

The final touch in Welch's preparation in the new bacteriology was administered by Koch himself—a vivid teacher—who himself conducted the courses, which he had previously organized for military doctors and which had such far-reaching consequences. Fortune again threw Welch and Prudden together, for the latter who had taken over the laboratory at the College of Physicians and Surgeons established by the Alumni Association, was now in Berlin also seeking training in the new science of bacteriology. The course, which was of a few weeks' duration, consisted essentially in the practice of isolating bacterial species by means of Koch's solid culture technique or by passage of them through the animal body, in order to effect separation of virulent from other varieties, and in the consideration of form, staining reactions and physiological and pathogenic propensities. The climax of the course was the study of the bacillus inducing Asiatic cholera. At this period not a little apprehension existed that Europe might again be visited by that scourge. The disease had raged in India and Egypt and the year before had gained a foothold in Europe in certain Mediterranean ports—hence the desirability of mobilizing a small army of trained bacteriologists to combat that plague should it threaten in earnest. Koch himself was deeply impressed with the danger; indeed so appalling did he consider the calamity of an epidemic outbreak of cholera in Europe that he did not trust himself to bring with him to Berlin cultures of the bacillus isolated in India or Egypt, but preferred to destroy them lest by inadvertence they should gain access to food or water. Now, however, that cholera actually existed on European soil and danger of its spread was imminent, the circumstances not only justified but compelled instruction in its bacteriological detection, and for this purpose he went to Toulon to secure anew fresh cultures.

But Koch admonished his pupils not to carry away from the laboratory living cultures of the cholera bacillus. This piece of sound advice, following the end of the course at a *Kneipe* held in honor of the *Geheimrath* led to an amusing incident. The next morning Welch and Prudden met accidentally at an early hour on one of the bridges spanning the Spree, each, as it seems, seeking secrecy. It developed that each had gone to an apothecary's shop and purchased concentrated sulphuric acid (or was it a saturated solution of corrosive sublimate?), which they had poured over the surface of tube cultures of the cholera bacillus originally intended to be taken with them to America and that they now proceeded to drop into the Spree. They expected, of course, to see the tubes sink immediately out of sight, instead of which they had the momentary disquieting experience of observing them bobbing up and down as they slowly floated down stream. The guilty pair hurried away, just, it is said, as a large *Schutzmann* appeared on the scene.

An impression of Koch and the influence of his instruction at the time is given by Prudden:

"Thus the course in the study of bacteria, of one month's duration, in Koch's laboratory was brought to an end, and the writer cannot refrain from remarking that the calm, judicial mind of Doctor Koch—the master worker in his field—his marvelous skill and patience as an experimenter, his wide range of knowledge and his modest, unassuming presentation of his views are all calculated to inspire confidence in the results of his own work, to stimulate his students to personal exertion in this field, and to lend certainty to the already wide-spread hope that ere long through the resources of science we shall be able to cope successfully with those most terrible and fatal enemies of the human race—the acute infectious diseases." [2]

Welch arrived in Baltimore in September, 1885, and there found Councilman at work in pathology. He immediately joined Welch and together they set up a laboratory in a couple of rooms on the top floor of the biological laboratory, offered them by Newell Martin. The two-storied building at the Hospital, designed as a deadhouse, was hurriedly completed and converted into a pathological laboratory. This arrangement was intended merely as a stop-gap in the emergency and until the buildings for the medical school, then expected soon to be organized and constructed, could be provided. As it happened, the consummation of the medical school project was long delayed and the small quarters intended merely for a deadhouse and its essential adjuncts, became the permanent home of the pathological department, as well as indeed the actual physical foundation on which were later erected two additional stories to house temporarily the departments of anatomy and pharmacology of the medical school. When in a few years those two departments secured elsewhere other and more adequate quarters, the pathological department spread through all the vacated space, which, in view of its expanding activities, was sorely needed.

The history of the pathological department of The Johns Hopkins University and Hospital, that was to play so profound a part in the educational progress of the United States, dates from 1886 at which time Welch began to exert the influence which peculiarly distinguishes his career from that of his predecessors in this country and elsewhere. Hitherto there had been abroad departments or institutes of pathology by which was usually meant pathological anatomy and histology, and sometimes experimental pathology or bacteriology. Welch's receptive and constructive mind responded powerfully to the training he received in these several branches of science, so that he became master not of one branch only, but of all. Thus it came about

[2] Prudden, T. M., on Koch's method of studying bacteria. Report to the Connecticut State Board of Health for 1885, pages 225-226.

that in setting up the pathological department in Baltimore he inevitably, and doubtless unconsciously, employed all these resources of knowledge and progress, and in so doing inaugurated a new era. Hereafter pathology, at least in the United States, could hope to develop symmetrically, utilizing for its advancement the materials and methods not of one branch of the science merely but of all branches, main and collateral, which being directed toward it might suffice to render a pathological phenomenon more comprehensible or afford the solution of a problem in medicine otherwise elusive.

The purpose when Welch was called to Baltimore was to proceed immediately with the selection not only of the staff for The Johns Hopkins Hospital but of the faculty of the medical school as well. Unforeseen economic conditions postponed the realization of the latter design; but as the hospital's resources had not been reduced by the unhappy accident which crippled the finances of the University, a clinical faculty was brought together. Welch's part in the choosing in 1888 and 1889 of Doctors Osler, Halsted, and Kelly was conspicuous and decisive, just as later with the opening of the medical school in 1893 it was his acquaintance with their work and his unerring judgment of them as men which added to the distinguished trio Doctors Mall, Howell, and Abel in the completion of the first major faculty of The Johns Hopkins Medical School. But Welch did not await the opening of the hospital or the consummation of the plan for a medical school to start active teaching and to get under way problems of research. Work was begun in an informal manner with medical graduates and advanced students in biology, and the quality of the material and the effects of Welch's influence can be gathered from the list of names of the first group to assemble under him. In it were Councilman, Mall, Nuttall, Abbott, and Bolton. Before long this informal plan was superseded by systematic courses in pathology, including pathological histology and bacteriology, and university lectures. These were not permitted, however, to degenerate merely into short, superficial series of demonstrations, lectures and exercises; but they always carried with them the freshness of the unexpected from the wide variety of activities going on in the laboratory and also the incentive to individual endeavor when any new point arose exciting to someone's curiosity.

With the founding of the medical school along the lines now familiar but none the less at that time novel to the point of revolution, the break with the past was complete and the aspiration which for so long kept Welch a student and a teacher was to be realized, and in full measure. Henceforth medical education in the United States was to be on a basis equalling at least the best continental model. The faculty of the medical school was to lose its local and provincial character and to be representative of the most potent forces in the country, while the young men and women seeking to enter

medicine were to possess a foundation training in physical, chemical and biological science and to be equipped so as to follow in the original tongues the greater scientific medical literatures of the French and the Germans. This was revolution indeed; but like all of Welch's reforming acts it was a programme of construction not of destruction. Welch's career stands forth supreme as a force for advancement, whether in research, education, hospital organization or public health; but one searches in vain his writings or the records of his public utterances for evidence of vehemence or denunciation. His was too understanding and sympathetic a spirit to judge men and things harshly for faults and shortcomings, the origins of which were sunk deeply into a past whose circumstances were so unlike those of the present. He made use rather of the gentler art of persuasion by exposition and example, leavening now here and now there, until the cumulative power of the intellectual and social ferment induced became so great as to be irresistible, and the whole mass was moved forward.

From the outset Welch was the central figure and guiding genius of the medical group. The pathological laboratory became an active centre of research and teaching. Welch's life quickly became filled to overflowing. He conducted investigations of his own, launched others on productive themes, and saw to it that the invaluable pathological specimens from the surgeons and gynecologists were made use of to advance knowledge and train a generation of special pathologists in those important fields. He lectured on special and general subjects in pathology and bacteriology in a manner so learned and fascinating as to produce impressions not only immediately stimulating to his auditors in high degree but of enduring permanence. The suggestiveness of these lectures led frequently to new undertakings in research. Moreover, the autopsies he performed, his demonstrations of gross pathological specimens and his teachings at the microscope stand out as unsurpassable models. He entered also into the medical activities of Baltimore and of the State of Maryland, and became a great influence for betterment in private and public medicine. He was, of course, the first dean of the medical school and guided the policy of the new institution into the productive channels that have so eminently distinguished it. His many talents were therefore called into constant play, and heavily overtaxed as they must often have been there was never indication of exhaustion. When occasion arose he was always ready, eager and able for a new advance, as witness his leading part in the recent development of the full-time system, so-called, in the clinical branches of medical teaching, in establishing a model school of public health and hygiene, and in serving on scientific and philanthropic boards possessing great wealth, for promoting scientific

discovery and for carrying the benefits of medical knowledge to the furthest parts of the world.

The achievements of Welch as an investigator, teacher and reformer in medicine are so many and varied that it is not possible to do justice to them in detail in a mere sketch. This is particularly true of that part of his career covered by the Baltimore and Johns Hopkins period. These three noble volumes of his collected papers and addresses are the best expression of his many-sided activities. And yet precious as they are, they afford no real insight into Welch's almost flawless personality, the depth of his friendship and wealth of his kindness, his faculty of intense application and devotion to the work in hand whether in laboratory or in public interest, his commanding influence and guiding spirit over the work of his associates and many pupils, the stimulating wholesomeness of his public activities, and his rarely unselfish and tolerant nature which led him to shower his great gifts prodigally and far and wide. The recipient of almost every honor in the gift of his colleagues, he fortunately, in time, saw the return of his labors, increased many-fold, enriching science through progress made in education, in deeds performed and discoveries by the men and institutions over whose destinies he had presided. And lastly these volumes fail to show us still another side of Welch's accomplishments as remarkable almost as those of the science we so love to laud in him. I refer to his culture outside the realm of medicine in the field of literature, in which he possesses an almost unerring taste for the best in poetry and prose, and in the domain of the fine arts. His mind is indeed stored with the beautiful creations of other men's minds from ancient times to our own day. It is to all these remarkable qualities, innate and acquired, united in one man, that we owe that thrice rare personality William Henry Welch, master in medicine and beloved of men.

SIMON FLEXNER.

PATHOLOGY

ZUR PATHOLOGIE DES LUNGENÖDEMS[1]

(Aus dem pathologischen Institut in Breslau)

Obwohl das Lungenödem der häufigste pathologische Befund am Sectionstische ist, so ist es doch niemals der Gegenstand einer experimentellen Untersuchungsreihe gewesen, und seit Laennec's Beschreibungen[2] ist unseren Kenntnissen über diesen häufigen und wichtigen pathologischen Zustand überhaupt Weniges hinzugefügt worden. Seit der Zeit, in welcher ein Verhältniss zwischen erhöhtem Blutdruck in den Capillaren und vermehrter Ausscheidung aus denselben vermuthet worden ist, hat man angenommen, dass das Hauptmoment beim Zustandekommen von Lungenödem in einer gesteigerten Spannung der Lungencapillaren zu suchen sei. Da aber die Betrachtungen, welche dieses Moment zu würdigen versucht haben, zum grössten Theile ohne Berücksichtigung der Eigenthümlichkeiten des Lungenkreislaufs oder unter irrthümlichen Voraussetzungen über denselben gemacht worden sind, so habe ich nach dem Vorschlag des Herrn Prof. Cohnheim eine Reihe von Versuchen an Kaninchen und Hunden im Breslauer pathologischen Institute angestellt, welche den Zweck hatten mit Rücksicht auf die neueren Forschungen über den Pulmonalkreislauf unsere Kenntnisse von den Ursachen des Lungenödems zu erweitern. Meinem hochverehrten Lehrer spreche ich hiermit für seine freundliche und thätige Hülfe meinen herzlichsten Dank aus.

Nach der gangbaren Anschauung ist das Lungenödem die Folge entweder einer Hydrämie oder einer Hyperämie, arterieller oder venöser.

Was das hydrämische Oedem betrifft, so haben die Versuche von Cohnheim und Lichtheim[3] ergeben, dass das Lungenödem nach Infundirung grosser Mengen von Kochsalzlösung zwar bei Kaninchen kein seltenes Ereigniss ist, doch nicht constant eintritt, und bei Hunden selten beobachtet wird. Daraus dürfen wir schliessen, die hydrämische Plethora allein, obwohl ein begünstigendes Moment, ist nicht im Stande Lungenödem zu erzeugen. sondern das Zustandekommen desselben erfordert noch einen zweiten Factor. Ueber diesen letzteren werden wir später zu handeln haben.

In den systematischen Lehrbüchern der Medicin werden Lungenhyperämie und Lungenödem gewöhnlich in demselben Capitel und ungetrennt

[1] Arch. f. path. Anat. u. Physiol. u. f. klin. Med., Berl., 1878, LXXII, 375-412.

[2] Laennec, De l'auscultation médiate. T. II. Paris, 1819.

[3] Virchows Archiv Bd. 69. S. 106.

behandelt. Darnach kann jede Hyperämie, seien ihre Natur und ihre Ursachen welche sie wollen, wenn sie hochgradig genug ist, Lungenödem zur Folge haben. Des Näheren glaube ich die gegenwärtigen Anschauungen am richtigsten darzulegen, wenn ich die Ansichten über Hyperämie und Oedem der Lunge wiedergebe, welche in dem Lehrbuch von Niemeyer[4] und dem Handbuch der Medicin von v. Ziemssen[5] enthalten sind.

Die Hyperämie der Lunge wird in Fluxion und in Blutstockung oder passive Hyperämie getheilt.

Als Ursachen einer Fluxion werden von Niemeyer angeführt:

1. Gesteigerte Herzaction,

2. Directe Reize, wie Einathmen heisser oder mit reizenden Substanzen vermischter Luft,

3. Collaterale Hyperämie,

4. Verdünnung der Luft in den Alveolen (verengerte Glottis). Diesen Ursachen fügt Hertz hinzu:

5. Wirkung des kalten Trunks bei erhitztem Körper und Abkühlung der Körperperipherie,

6. Entzündliche Zustände.

Als Ursachen einer Blutstockung werden erwähnt:

1. Störung des Abflusses des Blutes aus den Pulmonalvenen, namentlich Stenose und Insufficienz der Mitralis (seltener Klappenaffectionen der Aorta),

2. Jede geschwächte Herzaction.

Bevor wir erwägen, inwieweit diese verschiedenen Momente fähig sind, Lungenödem zu verursachen, werde ich zuerst an die folgenden wohlbekannten Charaktere, welche dasselbe darbietet, erinnern. Gewöhnlich tritt das Lungenödem plötzlich auf und kann fast ebenso rasch verschwinden, wie es entstanden ist; es ergreift beide Lungen; es erscheint bei den verschiedenartigsten Krankheiten und ist ein constanter Begleiter von keiner; es tritt oftmals bei der Agonie auf, eine Begleiterscheinung eher als eine Ursache des Todes; die mikroskopische Untersuchung einer ödematösen Lunge zeigt die hochgradigste Füllung der Capillaren und zahlreiche ausgetretene rothe Blutkörperchen. Von dem acut auftretenden allgemeinen Lungenödem, wovon hier ausschliesslich die Rede ist, muss dagegen das seröse Transsudat unterschieden werden, welches sich häufig in der Nähe entzündeter Lungentheile befindet und gewöhnlich als ein collaterales Oedem bezeichnet wird.

Wenden wir uns also zunächst zu einer Kritik der verschiedenen, oben angegebenen Ursachen des Lungenödems!

[4] Niemeyer, Lehrb. d. spec. Path. u. Therap. Bd. 1. Berlin, 1874.

[5] Hertz, Anämie Hyperämie und Oedem der Lungen. v. Ziemssen's Handb. der spec. Path. u. Therap. Bd. 5. Leipzig, 1874.

1. Gesteigerte Herzaction. Wenn wir aus den Verhältnissen im grossen Kreislauf einen Schluss auf den Lungenkreislauf ziehen dürfen, dann ist es von vornherein sehr unwahrscheinlich, dass vermehrte Blutzufuhr (Fluxion) zu einer Lunge, welche sich nicht in entzündlichem Zustande befindet, und aus deren Venen der Abfluss nicht gehindert ist, zu Oedem führen sollte. Zu anderen Körpertheilen kann der arterielle Zufluss beträchtlich vermehrt werden, zum Beispiel durch Erweiterung der zuführenden Arterien oder durch Verengerung oder Verlegung anderer Gefässgebiete, ohne dass eine vermehrte Abscheidung aus den Capillaren folgt.[6] Es soll aber nach Henle,[7] Niemeyer, Hertz u. A. ein besonderer Grund existiren, aus welchem bei gesteigerter Herzaction das Blut sich in den Lungen häufen soll. Dieser von vielen Seiten behauptete Grund ist der, dass die Lungencapillaren weniger resistent gegen vermehrten Bludruck seien, als die Capillaren anderer Organe. Dass in dieser Beziehung ein absoluter Unterschied existirt, ist kaum zu leugnen, aber Druck und Widerstände im Pulmonalkreislauf sind um Vieles geringer als im Aortensystem, und es ist kein Grund anzunehmen, dass im Verhältnisse zu diesem Drucke und zu diesen Widerständen die Lungencapillaren weniger resistent sind, als andere Capillaren. In diesem Gebiete aber, auf welchem uns die meisten Factoren unbekannt sind, ist es gefährlich zu speculiren und glücklicherweise können wir auch ohne alle Speculationen auskommen. Bei jeder compensirten hochgradigen Mitralstenose muss der Druck in der Pulmonalarterie höher sein, als ihn ein nicht hypertrophisches Herz in einer Lunge, in der keine Hindernisse für den Abfluss des Blutes existiren, zu Stande bringen kann, und doch giebt es in diesem Stadium keine Anzeichen, dass die „Resistenz der Capillaren" überwunden ist. Dass hier keine allmählich sich entwickelnde Vermehrung der Widerstandsfähigkeit der Capillaren in Betracht zu ziehen ist, beweist der Umstand, dass nach einem künstlich angelegten Aorten- oder Mitralisfehler der Blutdruck in der Arteria carotis sich nicht ändert.[8] Die Versuche von Lichtheim[9] über Unterbindung einer Lungenarterie sowohl, wie die Versuche über Unterbindung der Lungenvenen, welche unten berichtet werden sollen, deuten eher auf eine relativ grössere als auf eine relativ kleinere Resistenz der Lungencapillaren im Vergleich mit denen anderer Organe hin. Weder physiologische noch pathologische Beobachtungen sprechen dafür, dass erhöhte Herzkraft allein, ohne Hinzutreten anderer Momente, in den Lungen leichter als in den übrigen Körpertheilen Oedem erzeugen könne.

[6] Emminghaus, Arbeiten aus. d. phys. Anstalt zu Leipzig. 1873. S. 68.
[7] Handbuch d. rationellen Pathologie. Bd. II. S. 421. Braunschweig, 1847.
[8] Cohnheim, Vorlesungen über allgemeine Pathologie. S. 38. Berlin, 1877.
[9] Lichtheim, Die Störungen des Lungenkreislaufs und ihr Einfluss auf den Blutdruck. Breslau, 1876.

2. Directe Reize. Diese können, insofern sie nicht durch Störung der Athmungsvorgänge oder durch ihre Wirkung auf andere Organe tödten, als Entzündungserreger für die Luftwege und die Lungen betrachtet werden.[10] Lassar[11] beobachtete Lungenödem als eine inconstante Begleiterscheinung des Todes in Erstickungsfällen, welche ausnahmsweise der Einathmung von Säuredämpfen folgen. Die Seltenheit, mit welcher Lungenödem nach der Einwirkung von directen Reizen auf die Lunge erscheint, macht es wahrscheinlich, dass es nicht der unmittelbare Effect des Reizes sei, sondern denselben Ursprung hat, wie dasjenige Oedem, welches bei den verschiedensten Todesarten entsteht, und für welches ich unten versuchen werde, eine Erklärung zu geben.

3. Collaterale Hyperämie. Gerade bei der Lunge hat das sogenannte collaterale Oedem eine grosse Rolle gespielt. Wenn die Circulation in einem Lungenlappen oder einer ganzen Lunge gehemmt wird, dann entwickelt sich in den freien Theilen eine compensatorische Hyperämie, welche der gangbaren Anschauung zufolge zum Oedem führen kann. Als die Folge solcher collateralen Fluxion fasst Virchow[12] das Lungenödem auf, welches er durch Injection von Oel in die Venen erzeugte. Die Versuche von Lichtheim[13] haben uns schon gelehrt, dass, wenn Aeste der Lungenarterie bis zu drei Viertel der Arterienbahn verlegt werden, der Druck in der Arteria carotis keine wesentliche Veränderung erleidet, und der Druck in den offen gebliebenen Arterien der Lunge eine gewisse Steigerung zeigt, welche im Verhältnisse zu dem normalen niedrigen Werthe desselben steht. Als Folge aber dieser selten in so hohem Grade beim Menschen zu beobachtenden collateralen Hyperämie hat er niemals Lungenödem gesehen, und auch ich war nicht im Stande ein collaterales Oedem zu erzeugen. Dass in den Fällen, in welchen ein allgemeines acutes Oedem nach embolischer Verstopfung einer Lungenarterie entsteht, dieses auf anderen Momenten als der collateralen Hyperämie beruht, beweisen die eben erwähnten Versuche und auch die Inconstanz seines Auftretens unter diesen Umständen. Der häufige Befund von Lungenembolien, welche ohne jegliche symptomatische oder anatomische Folgeerscheinung entstanden sind, ist jedem erfahrenen Pathologen bekannt.

Wenn aber das sogenannte collaterale Oedem sich nicht auf die compensatorische Hyperämie zurückführen lässt, woher kommt es sonst? Mit jenem Namen werden zwei verschiedene Zustände bezeichnet, einmal das allgemeine acut auftretende Oedem, welches bei Krankheiten entsteht, die

[10] R. Heidenhain, Dieses Archiv. Bd. 70. S. 441.
[11] Zeitschrift für phys. Chemie. Bd. I. Hft. 3.
[12] Spec. Path. u. Therap. Bd. I. S. 191. Erlangen, 1854.
[13] Op. cit.

eine Hemmung der Circulation in einem Theile der Lunge verursachen, für's zweite die locale seröse Durchfeuchtung des Lungengewebes in der Nähe von entzündlichen Heerden, Neubildungen u. s. w. Der erstere Zustand, glaube ich, ist denselben noch zu besprechenden Ursachen zuzuschreiben, wie das allgemeine Lungenödem überhaupt, der letztere dagegen als ein entzündliches Oedem aufzufassen. Schwer in Einklang zu bringen mit der Hypothese, dass das locale collaterale Oedem die Folge blos einer compensatorischen Blutdrucksteigerung sei, ist der Umstand, dass die Verbreitung desselben oftmals in keinem Verhältnisse zu der Grösse der Gefässverengerung steht. Einerseits sieht man häufig um kleine lobuläre Pneumonien, kleine embolische Infarcte u. s. w. eine verhältnissmässig grosse ödematöse Zone, andererseits kann man dieselbe gänzlich vermissen bei Krankheiten, welche grosse Abschnitte des Lungenparenchyms für die Circulation unwegsam machen. Wenn einmal eine entzündliche Gefässveränderung existirt, dann kann bekanntlich vermehrte Blutzufuhr zu gesteigerter Transsudation in dem betreffenden Theile führen,[14] und deshalb dürfen wir nicht einer collateralen Hyperämie jeden Einfluss absprechen, das Hauptmoment aber ist die vorhergehende Gefässwandveränderung.[15]

4. Verdünnung der Luft in den Alveolen. Vor 30 Jahren stellte Mendelssohn[16] eine merkwürdige Theorie auf, nach welcher das Wesen der Lungenhyperämie überhaupt in einer Luftverdünnung in gewissen Lungenpartien zu suchen sei. Er ging von der falschen Hypothese aus, dass die Veränderungen der Lunge nach Vagusdurchschneidung auf einer Verdünnung der Luft in den Alveolen beruhen. „Diese Luft verhält sich zur Schleimhaut der Lunge wie die unter einem trockenen Schröpfkopf.“[17] Die Versuche von O. Frey[18] in Betreff der Verengerung der Trachea sprechen nicht dafür, dass eine bedeutende Lungenhyperämie durch Hindernisse, welche den Eintritt der Luft in die Luftwege beeinträchtigen, entstehe. Eine Verengerung der Glottis als eine Ursache des Lungenödems zu betrachten, entbehrt jedenfalls der experimentellen und der klinischen Grundlage.

5. Wirkung des kalten Trunks und Erkältung des Körpers, oder allgemeiner ausgedrückt, Widerstände im grossen

[14] Gianuzzi, Berichte d. königl. sächsischen Gesellschaft der Wissenschaften, 1866. Cohnheim u. Lichtheim, l. c. S. 139.

[15] Cohnheim, Vorles. über allg. Pathologie. S. 261, 416, 419.

[16] Mendelssohn, Der Mechanismus der Respiration und Circulation, oder das explicirte Wesen der Lungenhyperämie. Berlin, 1845.

[17] Arch. f. phys. Heilk. 1845. S. 277.

[18] Die pathologischen Lungenveränderungen nach Lähmung der Nervi vagi. Leipzig, 1877.

Kreislaufe im Allgemeinen. Eine Erklärung für die Entstehung der Lungenhyperämie in Folge der Wirkung der Kälte auf den Magen oder auf die Hautoberfläche hat man in der Thatsache zu finden geglaubt, dass nach Verengerung ausgedehnter Gefässgebiete (Baucheingeweide, Haut) der Blutdruck in anderen Theilen des Aortensystems steigt.[19] Die Versuche von Lichtheim aber haben nachgewiesen, dass die Spannung im kleinen Kreislauf in hohem Grade von Druckveränderungen des grossen Kreislaufs unabhängig ist. In Uebereinstimmung damit finde ich, dass beim Hunde der Pulmonaldruck ohne wesentliche Veränderung bleibt, wenn den einzigen offenen Weg für das Blut aus dem linken Ventrikel in den Körperkreislauf die eine Arteria carotis oder die eine Subclavia bildet. Der Druck in der Carotis kann in Folge von Hindernissen in der Circulation zu mehr als dem Doppelten seiner normalen Höhe gebracht werden, ohne dass der Pulmonaldruck steigt. In Hinblick auf diese Thatsache dürfen wir nicht eine Lungenhyperämie in Folge von Erkältung unmittelbar von einer collateralen Blutdrucksteigerung herleiten. Die Erkältung für eine Ursache von Hydrops pulmonum zu halten, entbehrt übrigens der klinischen Berechtigung, und in den seltenen Fällen, in welchen ein Zusammenhang vorhanden zu sein scheint, sind sicher andere Momente im Spiele.

6. Entzündliche Zustände. Das locale collaterale Lungenödem hat Cohnheim schon mit Recht als ein entzündliches angesprochen. Wirft man nun die Frage auf, ob es ein primäres, idiopathisches, entzündliches Lungenödem giebt, so liegt kein Grund vor, ein allgemeines Lungenödem entzündlicher Natur anzunehmen. Das erste Stadium freilich der Vaguspneumonie und das der croupösen Pneumonie haben eine grosse Verwandtschaft mit localem Lungenödem.[20] Wenn wir aber in diesen Fällen von einem entzündlichen Lungenödem sprechen dürfen, so ist damit nur gemeint, dass in Folge einer entzündlichen Veränderung der Gefässwände ein Zustand entsteht, welcher die grösste Aehnlichkeit mit dem Zustande der Lungen bei gewöhnlichem Lungenödem besitzt. Dass aber das Stauungs- und das entzündliche Oedem nicht zu identificiren sind, beweisen, von allem Andern abgesehen, die Untersuchungen von Lassar[21] über die Beschaffenheit der Lymphe bei der Entzündung.

Blutstockung. Je skeptischer uns unsere Erfahrungen über das Zustandekommen von Wassersucht im grossen Kreislaufe hinsichtlich der

[19] Hermann und Ganz, Pflüger's Archiv für Phys. 1870. S. 8.

[20] Friedländer, Untersuchungen über die Lungenentzündungen. Berlin, 1873.

Unverricht, Studien über die Lungenentzündung. Inaug.-Diss. Breslau, 1877.

[21] Virchows Archiv Bd. 69. S. 516.

Möglichkeit der Entstehung des Lungenödems durch fluxionäre Hyperämie machen, mit desto grösserer Sicherheit werden wir von der Blutstauung oder venösen Hyperämie einen derartigen Effect erwarten. Weder die anatomische Structur noch die physiologischen Eigenschaften der Lungencapillaren, so weit sie uns bekannt, geben uns Grund anzunehmen, dass sie nicht, wie andere Capillaren, eine beträchtliche Behinderung des Venenabflusses mit seröser Ausschwitzung beantworten.

Als Ursachen der Blutstockung in der Lunge werden angeführt: Störung des Abflusses des Blutes aus den Pulmonalvenen und geschwächte Herzaction.

1. Störung des Abflusses aus den Lungenvenen. Als ein typisches Paradigma von behindertem Abflusse aus den Lungenvenen können wir beispielsweise eine Mitralstenose betrachten. Wie allgemein bekannt, kann eine beträchtliche Verengerung des Mitralorificium eine Zeit lang existiren ohne nennenswerthe Störungen von Seiten des Gefässsystems. Dieser Zustand wird das Stadium der Compensation genannt. Während desselben strömt durch jeden Querschnitt der gesammten Gefässbahn dieselbe Menge Blut in der Zeiteinheit wie unter normalen Verhältnissen. Es fliesst deshalb in der Zeiteinheit von den Lungenvenen durch das verengerte Orificium dieselbe Menge Blut in das linke Herz wie vorher durch das normal weite Ostium. Wegen der vermehrten Widerstände muss der rechte Ventrikel mit grösserer Kraft arbeiten. In Folge des erschwerten Abflusses und der vermehrten Geschwindigkeit, welche das rechte Herz der ausgetriebenen Blutmasse ertheilt, muss der Seitendruck in allen Theilen des Pulmonalgefässsystems steigen. Dass unter diesen Umständen Lungenödem niemals eintritt, führt v. Dusch zu der Bemerkung[23]: „Dass das Lungenödem nicht oder doch nicht vorzugsweise durch die Drucksteigerung in den Lungenvenen hervorgebracht wird, geht daraus hervor, dass in den Fällen höchster Drucksteigerung bei genügender Compensation ein relativ günstiger Zustand für den Kranken hergestellt wird.“ Ist v. Dusch berechtigt anzunehmen, dass der Druck in den Lungenvenen am grössten in dem Stadium der Compensation ist? Die Beantwortung dieser Frage ist mit grossen Schwierigkeiten verbunden. v. Dusch geht von der Voraussetzung aus, dass die Menge Blut, welche ein Ventrikel in der Zeiteinheit empfängt, allein von dem Drucke in den unmittelbar vor demselben gelegenen Venen abhängt, und, da diese Blutmenge am grössten während der Compensation ist, so schliesst er, dass der Venendruck dann am höchsten sein muss. Die Geschwindigkeit aber, mit welcher das Blut aus den Venen in den entsprechenden Vorhof einfliesst, hängt nicht allein von dem Drucke ab, sondern von einer Kraft, welche der Summe der Widerstandshöhe

[23] Lehrbuch der Herzkrankheiten. S. 96. Leipzig, 1868.

(Seitendruck) und der Geschwindigkeitshöhe in den betreffenden Venen gleicht. In den Körperarterien ist der Werth der Geschwindigkeitshöhe im Vergleich mit der Widerstandshöhe so klein, dass er bei Druckmessungen vernachlässigt wird, aber in den Venen, wo die Widerstände so gering sind, ist derselbe für die Fortbewegung des Blutes nicht ausser Acht zu lassen. Im Stadium der gestörten Compensation ist die bewegende Kraft des rechten Ventrikels vermindert; dem entsprechend ist die Spannung in der Lungenarterie geringer geworden, aber die Gesammtmenge Blut, welche die Lungen enthalten, kann unverändert bleiben oder sogar vermehrt werden. Entsprechend der verminderten Spannung in den Arterien der Lunge vertheilt sich das Blut anders; die Lungenvenen enthalten mehr, die Arterien weniger als vorher. Jetzt gilt es die schwierige Frage zu erörtern, ob diese Vermehrung des Inhalts der Lungenvenen eine Drucksteigerung in denselben zu Stande bringt. Setzen wir die Geschwindigkeitshöhe in den Lungenvenen = G, die Widerstandshöhe = W, so haben wir die bewegende Kraft in denselben K = W + G. Sollte die Summe W + G den Werth erreichen, welchen sie während des Compensationsstadiums hat, so würde bei gleichbleibenden Widerständen der linke Ventrikel die normale Menge Blut erhalten, und, vorausgesetzt dass seine Kraft unbeeinträchtigt ist, fortbewegen. Deshalb kann der Seitendruck W im höchsten Falle um eine Grösse steigen, welche G während der Compensationsperiode gleichkommt. Der Werth von G ist uns unbekannt. Volkmann[23] berechnet den Werth der Geschwindigkeitshöhe im Anfange der Aorta zu 8,2 Mm. auf die Höhe einer Blutsäule bezogen. Selbst wenn wir annehmen, dass der Gesammtquerschnitt der Lungenvenen nur die Hälfte dessen der Aorta ist, so wird doch die Grösse von G weniger als $1\frac{1}{2}$ Mm. Quecksilber betragen. Setzen wir ferner voraus, dass die Geschwindigkeitshöhe während des Compensationsstadiums um das Mehrfache gesteigert sei, so wird doch immer der Werth von G so klein bleiben, dass die Maximalgrenze einer vermuthlichen Druckerhöhung bei gestörter Compensation zu niedrig ausfallen muss, um—im Hinblick auf die unten zu berichtenden Versuche über Pulmonaldruck beim Zustandekommen von Lungenödem—die Entstehung desselben bei ungenügender Compensation den mechanischen Hindernissen und der wegen verminderter Kraft des rechten Ventrikels geänderten Vertheilung des Blutes allein zuschreiben zu dürfen.

Jedenfalls steht so viel fest, dass ein beträchtliches Hinderniss für den Abfluss des Blutes aus den Lungenvenen existiren kann, ohne dass dadurch, so lange dieses Hinderniss durch vermehrte Arbeit des rechten Ventrikels ausgeglichen wird, die Entstehung von Lungenödem herbeigeführt wird.

[23] Die Hämodynamik. S. 214. Leipzig, 1850.

Wir kommen zu der letzten der oben angeführten Ursachen des Lungenödems.

2. Geschwächte Herzaction.[24] Dieses Moment scheint der Schwerpunkt der Sache zu sein. Die anderen angeblichen Ursachen haben sich nicht als causae efficientes erwiesen und könnten im besten Falle nur von beschränkter Bedeutung sein im Vergleiche mit diesem anscheinend allgemein wirksamen Factor. Selbst in den Fällen, wo andere Veränderungen im Spiele sind, hat man sich doch auf Herzschwäche als einen mitwirkenden Factor berufen, weil in der That in der Mehrzahl der Fälle von allgemeinem Lungenödem die Thätigkeit des Herzens herabgesetzt ist. Wenn wir aber annehmen, dass eine allgemeine Herzschwäche wirklich Lungenödem herbeizuführen vermag, so ist das entstehende Oedem nicht die Folge einer Drucksteigerung in den Capillaren und Venen, mit anderen Worten kein Stauungsödem. Es ist unmöglich, dass durch Herzschwäche der Druck in den Lungenvenen die Höhe erreichen soll, welche bei unverminderter Herzkraft in den Lungenarterien herrscht. Da aber nach Unterbindung der Venen der einen Lunge, diese Venen wie blinde Anhängsel der entsprechenden Arterie zu betrachten sind, so muss der Druck in diesen derselbe sein, wie in der Arterie (oder annähernd derselbe, indem keine wesentliche Erleichterung seitens der Bronchialvenen stattfindet, wie, von anatomischen Gründen abgesehen, das Auftreten von vollständiger, hämorrhagischer Infarcirung der betreffenden Lunge beweist) und doch entsteht unter diesen Umständen niemals Oedem.[25] Da in dem analogen Falle im Körperkreislauf, wo sämmtliche von einer Extremität abführenden Venen zugebunden werden, Oedem entsteht, so müssen wir den Lungencapillaren im Verhältnisse zum Drucke im Pulmonalkreislauf eine grössere relative Impermeabilität zurechnen, als den Capillaren anderer Organe.

Ist aber die Folge der Herzschwäche Lungenödem? Die nothwendige Folge ist es unbedingt nicht. Eine Syncope kann noch so lange dauern und führt niemals zum Hydrops pulmonum. Durch Vagusreizung können wir die bewegende Kraft des Herzens vernichten, so dass die Spannung in den Gefässen der des ruhenden Blutes gleich wird und es entstehen nicht die geringsten Zeichen eines Lungenödems. In den allerseltensten Fällen überhaupt ist der Tod die Folge eines plötzlichen Erlöschens der Herzkraft; diese sinkt vielmehr allmählich von ihrer normalen Grösse bis auf Null, und doch sterben nicht alle Menschen an Lungenödem. Aber, erwidert

[24] Was ich hier über Herzschwäche zu sagen habe, bezieht sich ausschliesslich auf die gewöhnliche Auffassung dieses Zustandes, scil. eine gleichzeitige und gleichmässige Schwächung beider Herzhälften. Eine Schwächung, bei welcher die Kraft des einen Ventrikels verhältnissmässig weniger herabgesetzt wird, als die des anderen, lasse ich vorläufig ausser Betracht.

[25] Cohnheim, Op. cit. S. 419.

man, wenn Lungenödem eintreten soll, muss die Herzschwäche lange dauern! Als eine derartige in der That nicht seltene Folge der Herzschwäche, welche Tage und Wochen lang, besonders bei cachechtischen und fieberhaften Krankheiten, gedauert hat, wird das sogenannte hypostatische Oedem vielseitig aufgefasst. Ein Hauptmerkmal aber des allgemeinen Lungenödems ist eben sein acutes Auftreten, welches für eine plötzlich eintretende Ursache spricht, und in vielen Fällen ist dem Lungenödem keine langdauernde Herzschwäche vorhergegangen. Die Beobachtung am Menschen berechtigt uns deshalb zu dem Schlusse, dass eine Erniedrigung der Herzkraft an und für sich kein Oedem erzeugt, das Experiment wird uns lehren, dass eine Schwächung des rechten Ventrikels in gewissem Sinne sogar ein ungünstiges Moment für das Zustandekommen von Lungenödem ist.

Ich habe im Vorhergehenden die gangbaren Anschauungen über die Ursachen von Lungenödem einer Kritik unterzogen, und wir kommen nunmehr zu dem Schlusse, dass keine uns eine genügende Erklärung darbietet. Obwohl die meisten der oben erwähnten Bedingungen auf falschen theoretischen Voraussetzungen begründet worden sind, bin ich denselben doch so wenig wie möglich von theoretischen Gesichtspunkten und so viel wie möglich von Seiten der Beobachtung und des Versuches entgegengetreten. Sollen wir nun aber von allen mechanischen Momenten absehen und die Ursachen des allgemeinen Lungenödems in anderen Bedingungen suchen? Es scheint allerdings, als ob nach unseren bisherigen Betrachtungen dem Lungenödem eine ganz aparte Stellung im Vergleich mit den Wassersuchten anderer Körpertheile einzuräumen sei. Bei dieser Lage der Sache können wir nur durch das Experiment einer Lösung des complicirten Problems etwas näher zu treten hoffen.

Die erste zu beantwortende Frage ist: Giebt es überhaupt ein Stauungsödem in der Lunge? Denn eigentlich haben wir bis jetzt keinen Grund gefunden, die Existenz desselben beim Menschen anzunehmen.

Eine Stauung in der Lunge können wir zu Stande bringen durch Hindernisse in den Lungenvenen, in dem linken Vorhofe, in dem linken Ventrikel und in der Aorta.

Die Versuche wurden an Kaninchen und an Hunden gemacht. Hunde bieten den Vortheil, dass an ihnen der Druck in der Pulmonalarterie leicht zu messen ist. Bei Kaninchen entsteht andererseits Lungenödem leichter als bei Hunden. Bei beiden Thieren giebt die Aorta zuerst den Truncus anonymus ab, von welchem die linke Carotis, die rechte Subclavia und die rechte Carotis ihren Ursprung zu nehmen pflegen. Der zweite Hauptast der Aorta ist die linke Subclavia.

Wenn man einem Kaninchen den Aortenbogen zwischen dem Truncus anonymus und der linken Subclavia unterbindet, so wird das Thier an den

hinteren und der linken vorderen Extremität gelähmt und leidet wegen Lähmung des Zwerchfells und der Musculi intercostales an starker Dyspnoe. Nach ½—1 Stunde stirbt es, ohne dass besondere Veränderungen an den Lungen zu bemerken sind. Mit Hülfe der künstlichen Athmung, welche in fast allen diesen Versuchen benutzt wurde, lebt das Thier länger, jedoch gleichfalls ohne dass die Lungen nach dem Tode etwas Bemerkenswerthes darbieten. Wenn gleichzeitig die eine Carotis communis durch eine endständige Manometercanüle verlegt wird, so steigt der Druck in derselben um 50 bis 100 pCt. über seine normale Höhe. In diesem Falle, wo blos die andere Carotis und die rechte Subclavia offen sind, habe ich gewöhnlich kein Lungenödem nach dem Tode gefunden; gelegentlich jedoch, besonders bei jungen Kaninchen, erfolgt ein mässiges Oedem. Erst wenn der Aortenbogen zwischen Truncus anonymus und linke Subclavia und zwei Aeste des Truncus anonymus geschlossen werden, d. h. wenn die einzige Abflussröhre aus der Aorta (die Kranzarterien ausgenommen) die eine Carotis oder die rechte Subclavia bildet, entsteht ganz regelmässig Lungenödem. Das Thier wird gleich nach der Unterbindung unruhig, in 1 — 2 Minuten bekommt es Krämpfe und stirbt unter den bekannten Erstickungserscheinungen. Wenn man, wie C. Friedländer[26] schon gethan hat, die Aorta zwischen dem Herzen und dem Truncus anonymus zuklemmt oder unterbindet, so stirbt das Thier nach einigen Secunden mit heftigen Krämpfen, und die Untersuchung der Lungen gleich nach dem Tode zeigt starkes Oedem. Die Lungen werden grösser und blutreicher als normal gefunden, und aus der Trachea und den Bronchien fliesst eine schaumige, wässrige Flüssigkeit von gelblichem oder gelblich-röthlichem Farbenton aus. Wenn man die Trachea zuerst öffnet, ohne die Lungen zu berühren, findet man nicht selten gar keine seröse Flüssigkeit in derselben; doch genügt, wenn Oedem vorhanden ist, ein leichter Druck auf die Lungen, um das seröse Transsudat herauszupressen.

Die Unterbindung der oben genannten Arterien bietet keine Schwierigkeiten. Der Hautschnitt, welcher vorher gemacht worden ist, um die Trachealcanüle einzusetzen, wird in der Mittellinie bis zu 3—4 Cm. unterhalb des oberen Sternalrandes verlängert. Obwohl es möglich ist, die Aorta und die Aeste des Truncus anonymus mit gekrümmten Haken von oberhalb des Sternums her zu erreichen, wird doch die Operation um Vieles erlichtert, wenn man die Crista an dem oberen Theile des Sternums abschneidet und das Sternum in der Ausdehnung von 1—2 Cm. mit starker Scheere spaltet. Dies geht ohne Blutung vor sich, wenn der Schnitt in der Mittellinie geführt

[26] Op. cit.

wird. Will man die Aorta dicht am Herzen unterbinden, so muss man das Sternum weiter spalten und den oberen Theil des Herzbeutels eröffnen. Mit einiger Sorgfalt kann man sehr gut das Brustbein bis zum Ansatz des Zwerchfells in der Mittellinie spalten, ohne dass eine von beiden Pleurahöhlen geöffnet wird. Nachdem die im vorderen Mediastinum gelegene Drüsen- und Fettmasse, welche den Aortenbogen und seine Aeste bedeckt, mittelst Pincetten zerrissen worden ist, liegen diese frei zu Tage.

Versuch, welche den Zweck hatten zu untersuchen, um wie viel es nöthig sei die aufsteigende Aorta zu verengern, um Oedem zu erzeugen, ergaben, dass das Lumen der Aorta fast zu Verschluss verengert werden muss, ehe Lungenödem eintritt.

Bei diesen Versuchen machte ich die interessante Beobachtung, dass bei Kaninchen Verengerung des aufsteigenden Aortenbogens bis zu einem gewissen Grade eine Drucksteigerung jenseits (peripher) der verengten Stelle bewirkt. Um die Arterie, ohne Zerrung der anliegenden Gebilde, zu verengen, wurde ein Graefe'sches Ligaturstäbchen benutzt, welches Verkleinerung des Gefässlumens in jedem beliebigen Grade bis zur vollständigen Verschliessung erlaubt. Als ein Beispiel für das interessante Verhalten des Carotisdruckes nach Verengerung der aufsteigenden Aorta, führe ich das Folgende aus einem Versuchsprotokoll an.

Versuch 1. Grosses Kaninchen. Tracheotomie. Künstliche Athmung. Quecksilbermanometer in Verbindung mit rechter Carotis. Druck schwankt zwischen 100 und 115 Mm. Brustbein in der Mittellinie gespalten, Aortenbogen freigelegt, Herzbeutel geöffnet. Starker Faden um die Aorta zwischen Herz und Truncus anonymus gelegt und an dem Graefe'schen Ligaturstäbchen befestigt. Durch Zuschraubung wird die Aorta allmählich verengert, wodurch der Druck in der Carotis von 100 bis zu 140 Mm. steigt. Bei weiterer Verengerung bleibt der Druck einige Zeit auf dieser Höhe und dann, nachdem die Verkleinerung des Gefässquerschnitts einen gewissen Grad überschritten hat, fängt er an allmählich zu sinken. Eine Wiederholung des Versuches giebt dasselbe Resultat. Gewöhnlich aber nach Wiedereröffnung des Gefässlumens steigt der Druck etwas über seinen früheren Werth (auf 130—140) und sinkt dann wieder bis zu einem Punkte zwischen 100—115. Als der Faden noch fester zugeschnürt wird, so dass das Gefässlumen fast ganz verschlossen ist, bekommt das Thier Krämpfe; der Knoten um die Aorta wird gleich losgemacht, so dass die Arterie ihre normale Weite wieder erhält. Während der Erstickungskrämpfe steigt der Druck bis zu 180 und zeigt die bekannten rhythmischen Schwankungen. Nach den Krämpfen ist das Thier bewegungslos und unerregbar, athmet nicht selbständig, Druck 120. Jetzt bei jeder Verengerung der Aorta sinkt der Druck pari passu in der Carotis, und obwohl das Thier sich etwas erholt, so dass es selbständig athmet und die Hornhaut etwas erregbar wird, bringt doch eine Aortenverengerung nicht mehr eine Drucksteigerung in der Carotis zu Stande. Das Thier wird

getödtet durch Einspritzung von Curare in die Vena jugularis ext., um eine plötzliche Herzlähmung während mässiger Verengerung der Aorta zu erzeugen. Die Obduction ergiebt kein Lungenödem.

Diese Drucksteigerung nach Verengerung der Strombahn aus dem linken Ventrikel ist wahrscheinlich derselben Natur wie diejenige, welche S. Mayer[27] nach Unterbindung der Hirnarterien beobachtet hat, und einer Reizung der vasomotorischen Centren durch Hirnanämie zuzuschreiben. Man könnte auch an eine Reizung des linken Ventrikels denken, durch welche derselbe zu grösserer Arbeit erregt wird, als um die vermehrten Widerstände zu überwinden nöthig sei. Dafür spricht vielleicht der Umstand, dass nach Herstellung der normalen Gefässweite der Druck über seine normale Höhe steigt (in einem Falle von 100 bis zu 160). Es ist von Interesse zu bemerken, dass in dem obigen Versuche, nachdem die allgemeine Erregbarkeit vernichtet worden, die Drucksteigerung ausblieb welches Verhalten vielleicht einer gleichzeitigen Unerregbarkeit der vasomotorischen Centren zugeschrieben werden kann. Bei verschiedenen Kaninchen fällt die Druckerhöhung sehr ungleichmässig aus; bei Hunden habe ich sie überhaupt nicht beobachtet.

Was lehren diese Versuche über die Entstehung von Lungenödem? Sollen wir annehmen, dass ein Widerstand für den Abfluss des Blutes aus der Aorta, welcher den Carotisdruck um das Zweifache erhöht, keine Stauung in der Lunge verursacht, oder dass die Stauung nicht ausreicht, um Oedem zu Stande zu bringen? Diese Fragen sind zu beantworten nur durch Messung des Pulmonaldruckes während Verschliessung der Aorta oder ihrer Aeste. Zu diesem Zwecke wurden Versuche an Hunden angestellt.

Lichtheim hat gefunden, dass nach Unterbindung der Brustaorta dicht über dem Zwerchfell bei undurchschnittenem Halsmarke der Druck in der Lungenarterie unverändert bleibt, während der Carotisdruck bekanntlich bedeutend steigt. Meine Versuche haben seine Resultate nicht nur bestätigt, sondern sogar ergeben, dass der Druck in beiden Arteriensystemen in noch höherem Grade von einander unabhängig ist, als aus jenen Versuchen hervorgeht.

Das Verfahren bei Messung des Lungenarteriendruckes war im Wesentlichen dasselbe, welches Lichtheim benutzte, auf dessen Beschreibung ich verweise.[28] Ich legte aber das Fenster in der linken Thoraxhälfte höher als er, nehmlich zwischen erster und vierter oder zweiter und fünfter Rippe, weil von einem solchen Fenster sowohl die Aorta in ihrer ganzen Länge bis zum Zwerchfell wie deren Aeste ohne grosse Schwierigkeit zugänglich sind. Man kann von derselben Thoraxöffnung, welche für Druckmessung

[27] Wiener Sitzungsberichte. LXXIII. Abth. III. S. 85.
[28] Op. cit. S. 26.

in dem zum unteren Lappen gehenden Aste der linken Lungenarterie dient, den Truncus anonymus oder seine drei Aeste, die linke Subclavia und den Aortenbogen an irgend einer beliebigen Stelle zuklemmen oder unterbinden. Wenn man diese Gefässe ohne Oeffnung einer Pleurahöhle erreichen will, dann ist dasselbe Verfahren wie bei Kaninchen anwendbar, i. e. Spaltung des Brustbeins in der Mittellinie. Wegen der grösseren Tiefe des vorderen Mediastinums bei Hunden ist es empfehlenswerth, nach Eröffnung des Thorax in der Mittellinie die Arteriae mammariae gleich zu unterbinden, weil sie bei Blosslegung der grossen Arterienstämme leicht verletzt werden können. Mit Ausnahme einiger Controlversuche waren sämmtliche Versuche an curarisirten Hunden angestellt, die durch künstliche Athmung am Leben erhalten wurden. Bei allen Versuchen wurden die Arterien nach dem Tode von dem linken Ventrikel oder Anfangstheile der Aorta aus mit einer Aufschwemmung von chromsaurem Blei ausgespritzt. Dieses Verfahren ist unbedingt nöthig, erstens um zu beweisen, dass die Arterien an den Unterbindungsstellen festverschlossen sind und zweitens um festzustellen, ob andere Wege, als man glaubt, offen geblieben sind. Die Aorta besonders muss sehr fest zugebunden werden. In seltenen Fällen nimmt die rechte Subclavia von dem Aortenbogen selbst, hinter der linken Subclavia, ihren Ursprung.

Obwohl Lichtheim nachgewiesen hatte, dass Oeffnung einer Pleurahöhle keinen Einfluss auf den Pulmonal- oder Carotisdruck ausübt, machte ich doch zuerst die Versuche ohne Pneumothorax, aber die Ergebnisse waren dieselben wie bei offenem Thorax.

Um die Grenze zu finden, bei welcher die Hindernisse für den Ausfluss des Blutes aus dem linken Ventrikel hinreichend gross sind, um Lungenödem zu Folge zu haben, wurden zuerst die Aorta peripher von der linken Subclavia, dann gleichzeitig die linke Subclavia selbst und endlich die Aeste des Truncus anonymus unterbunden. In einer nicht unbedeutenden Anzahl von Versuchen ist es mir nicht gelungen Lungenödem bei Hunden zu erzielen, ehe jeder Ausfluss aus dem Aortenbogen abgeschlossen worden war. Entweder muss der Aortenbogen zwischen dem Herzen und der Ursprungsstelle des Truncus anonymus, oder gleichzeitig alle vorher abgegebenen Aeste verschlossen werden.

Versuch 2. Mittelgrosser, curarisirter Hund. Arterien, ohne, Verletzung der Pleura, in der folgenden Reihe verlegt. Endständige Hg.-Manometercanüle in linker Carotis communis, Unterbindung der linken Subclavia nahe an ihrem Ursprung, der Aorta dicht jenseits der letzteren, der rechten Carotis communis und der rechten Subclavia dicht peripher von der Art. vertebralis. Der Carotisdruck steigt von 80 bis zu 220 Mm. Die Pulse sind von Zeit zu Zeit durch Traube'sche Wellen unterbrochen. Erst nach einer Stunde ist der Carotisdruck bis ungefähr Null gesunken. Die

Section ergiebt kein Lungenödem. Einspritzung mit chromsaurem Blei zeigt, dass die Art. vertebralis dextra der einzige offene Weg für das Blut aus der Aorta gewesen ist.

Versuch 3. Mittelgrosser, curarisirter Hund mit Hg.-Manometer in Verbindung mit linker Carotis und mit dem unteren Aste der linken Lungenarterie. Carotisdruck 80—90. Lungenarteriendruck 18 Mm. Unterbindung der linken Subclavia nahe an ihrer Ursprungsstelle. Druck in beiden Arterien unverändert. Unterbindung der Aorta dicht jenseits der linken Subclavia. Carotisdruck steigt von 80 bis zu 160 Mm. Lungenarteriendruck bleibt unverändert. (Vago-sympathici durchschnitten um die grossen Druckschwankungen zu beseitigen.) Unterbindung des Truncus anonymus dicht an seiner Ursprungsstelle. Der Druck in der Lungenarterie steigt von 18 Mm. bis zu 60 Mm. Hg. Nach 5 Minuten sinkt er allmählich zu 16 Mm. Section ergiebt starke Stauung und Oedem beider Lungen.

In diesem Falle erreichte der Pulmonalisdruck nach Unterbindung der Aorta und seiner Aeste eine Höhe, welche ungefähr das $3\frac{1}{2}$ fache seines ursprünglichen Werthes betragt. Nach Unterbindung der Aorta allein dicht peripher von der Art. subclavia sinistra entsteht entweder keine Veränderung in dem Drucke der Lungenarterie oder er steigt im höchsten Falle 4—5 Mm. Quecksilber. Diese kleinen Druckveränderungen werden natürlich am besten an einem Sodamanometer studirt. In einem Versuche, in welchem die einzig offen gebliebene Arterie rechte Subclavia war, stieg der Pulmonalisdruck von 180 (seiner ursprünglichen Höhe) bis zu 230 Mm. Soda (blos 4 Mm. Hg.). In einem anderen Versuche, in welchem mit Ausnahme der linken Subclavia jeder Abfluss aus dem Aortenbogen verschlossen worden war, stieg der Pulmonaldruck von 170 Mm. Soda bis zu 230 Mm. ($35\frac{1}{3}$ pCt.), während der mit einem endständigen Manometer gemessene Druck in der Carotis von 60 bis zu 230 Mm. Quecksilber (300 pCt.) gestiegen war.

Diese erstaunliche Immunität des Pulmonalkreislaufs gegen Druckveränderungen im Körperkreislauf giebt uns die Antwort auf die oben aufgeworfene Frage. Das Ausbleiben von Lungenödem bei solchen Hindernissen, welche den Carotidendruck zwei- bis vierfach erhöhen können, ist kein Beweis, dass eine Stauung in der Lunge kein Oedem zu Folge hat, da solche colossale Widerstände existiren können, ohne dass eine irgend beträchtliche Steigerung des Druckes im kleinen Kreislauf statthat; es beweist im besten Falle blos, was wir schon von der Beobachtung am Menschen wussten, dass ein gewisser Grad von Lungenstauung vorhanden sein kann, ohne Oedem herbeizuführen. Lungenödem entsteht bei Kaninchen, wenn die eine Carotis oder die eine Subclavia die einzige Ausflussröhre bildet, und bei Hunden, wenn der Abfluss noch mehr erschwert wird. und erst bei solcher Einengung der Gefässbahnen erleidet der Pulmonaldruck eine bedeutende Steigerung!

Das Ergebniss der Versuche betreffs Unterbindung der grossen Arterienstämme ist also, dass durch dieselbe Lungenödem und zwar ein Stauungsödem erzeugt werden kann, dass aber eine bedeutende Stauung in der Lunge in Folge von Wilderständen im grossen Kreislaufe erste dann entsteht, wenn diese eine Höhe erreicht haben, von welcher beim Menschen kaum die Rede sein kann.

Diese Stauung ist, wie jede Stauung, dadurch bedingt, dass mehr Flüssigkeit zufliesst als abfliessen kann. Die Kräfte, welche das Blut noch in's rechte Herz treiben, nachdem die bewegende Kraft des linken Ventrikels zum grössten Theile oder gänzlich aufgehoben worden ist, sind die höhere arterielle Spannung, der Gefässtonus und möglicherweise eine saugende Wirkung des rechten Ventrikels. Dass der Gefässtonus von Einfluss bei diesem Vorgange ist, beweisen die Versuche von Goltz,[29] und die Beobachtung von Bezold und Gscheidlen,[30] welche fanden, dass nach Absperrung des Blutabflusses aus dem linken Ventrikel der venöse und der arterielle Druck sich langsamer ausgleichen, wenn der Gefässtonus durch Durchschneidung des Halsmarkes herabgesetzt wird. Als ich bei einem Hunde die Aorta dicht hinter der linken Subclavia zuklemmte, sank der Druck gleichzeitig in der Arteria femoralis (von 100 bis zu 20 Hg.) und in der Vena femoralis (von 30 bis zu 15 Soda), während er sowohl in der Vena jugularis externa (von 5 bis zu 25 Soda), wie in der Carotis communis (von 100 bis zu 150) stieg. Dagegen nach Zuklemmung der Aorta zwischen linkem Ventrikel und Truncus anonymus stieg der Druck in der Vena jugularis und der Vena femoralis (in der ersteren von 0—5 bis zu 50 Soda, in der letzteren nicht genau messbar wegen ungenügender Länge der Manometerröhre). Ob bei Zuklemmung hinter der linken Subclavia die Vermehrung des Zuflusses zum Herzen durch die obere Hohlvene die Verminderung desselben durch die untere Hohlvene deckt, muss ich dahingestellt lassen, dafür aber spricht die Unveränderlichkeit des Pulmonaldruckes. Bei Verschluss der Aorta ascendens andererseits ist die Drucksteigerung in den Körpervenen am wahrscheinlichsten der Stauung im kleinen Kreislauf zuzuschreiben.

Von besonderem Interesse wäre es zu constatiren, in welcher Weise das Zustandekommen von Lungenödem bei Unterbindung der Arterien durch die Herzkraft beeinflusst sei. In Anblick der geläufigen Anschauungen über die Bedeutung von Herzschwäche als eine Ursache von Lungenödem, könnte

[29] Virchow's Archiv Bd. 28, S. 428. 1864.

[30] Untersuchungen aus dem physiol. Laboratorium in Würzburg. 1867. Hft. 2.

man vielleicht geneigt sein zu glauben, dass eine Verminderung der Herzkraft die Entstehung von Lungenödem bei diesen Experimenten begünstigt hätte.[31] Andererseits wäre aber zu erwägen, ob nicht vielmehr eine grosse Schwäche des rechten Ventrikels ein Hinderniss für das Zustandekommen derjenigen Drucksteigerung in der Lunge sein muss, welche für die Entstehung von Oedem nöthig ist. Oefter als erwünscht war die Gelegenheit vorhanden, die Probe auf diese Ueberlegung zu machen. Bei Hunden, denen entweder zu viel Curare eingespritzt war, oder bei welchen die Operation mit offener Pleurahöhle lange gedauert hatte, wurde oftmals die Herzkraft so niedig (oder, wie von einigen Beobachtungen wahrscheinlicher ist, der rechte Ventrikel so unerregbar), dass Unterbindung des Aortenbogens und aller seiner Aeste kein Oedem mehr erzeugte. Dem entsprechend stieg der Druck in der Pulmonalarterie weniger als in den Fällen, wo Oedem eintritt.

Versuch 4. Bei einem tief curarisirten kleinen Hunde war 2 Stunden nach Anfang der Operation der Carotisdruck bis zu 30 Mm. Hg. gesunken, als die Arterien in der folgenden Reihe unterbunden wurden: Truncus anonymus zwischen linker Carotis und rechter Subclavia, linke Subclavia vor Abgabe eines Astes, und die Aorta dicht hinter der linken Subclavia. Da eine Manometercanüle in der linken Carotis steckt, so ist der grosse Kreislauf jetzt vollkommen unterbrochen. Die linke Carotis zeigt zuerst hohen Druck mit colossalen Schwankungen. Durch die Systole wird der Druck bis zu 340 Mm. Hg. getrieben, während der langdauernden Diastole sinkt er auf 40 Mm. Dabei ist ein ausgesprochener Pulsus bigeminus vorhanden. Nach diesen grossen Schwankungen tritt eine Periode eine von hohem Drucke, schnellem Pulse und kleinen Schwankungen (Mitteldruck 250—260 Mm.). Diese zwei Arten von Perioden alterniren in je 10 Minuten. Nach einer halben Stunde, während welcher die künstliche Athmung erhalten worden ist, ist der Druck bis auf 50 Mm. gesunken.

Nach Unterbindung der Arterien bleibt der Pulmonaldruck anderthalb Minuten unverändert, dann fängt er an zu steigen und im Laufe von 3—4 Minuten erreicht er eine Höhe von 35 Mm. Hg., von welcher er bald wieder auf 18 Mm. sinkt. Es entstand kein Oedem.

Obwohl ein Druck von 35 Mm. Hg. in der Pulmonalarterie nach den Messungen von Lichtheim und von mir immerhin ein hoher genannt werden muss, ist er doch nicht zu vergleichen mit dem Drucke, welcher in den Versuchen zu Stande kam, wo das Herz bei der Gefässunterbindung kräftig war und Lungenödem entstand (cfr. Vers. 3). Das Ausbleiben von Lungenödem in diesen Fällen, wo die sonstigen Bedingungen vorhanden

[31] Wie es kaum nöthig zu betonen ist, wird hier nur von einer allgemeinen Herzschwäche geredet; eine auf den linken Ventrikel beschränkte Schwächung würde selbstverständlich die Entstehung von Lungenödem im gegebenen Falle erleichtern.

sind, ist kaum anders zu erklären als dadurch, dass die Kraft des rechten Ventrikels zu gering ist, um die nöthige Blutmasse in die Lungen hineinzuschaffen. Es kann auch sein, dass die Stromkraft und der Gefässtonus gleichzeitig so herabgesetzt sind, dass keine genügende Blutmasse in die Venen und in's rechte Herz hineinfliesst. Ich möchte aber bezweifeln, dass eine für die Entstehung von Lungenödem hinreichende Blutmasse nicht zur Verfügung des rechten Ventrikels stehe, da in einem ähnlichen Versuche, in welchem der Druck in der Arteria pulmonalis durch die Unterbindung wenig beeinflusst war, der Druck in der Vena jugularis von 0—10 bis zu 60 Mm. Soda stieg.

In gleichem Sinne spricht ein versuch an einem Kaninchen bei welchem gleich nach Unterbindung der Aorta zwischen Truncus anonymus und linker Subclavia und des Truncus anonymus zwischen linker und rechter Carotis der Carotisdruck von 100 Mm. bis zu 40 Mm. Hg. sank, anstatt, wie gewöhnlich, um das Zweibis Dreifache zu steigen. Dieser ist der einzige Falls aus zahlreichen Versuchen, bei welchem die Unterbindung der Aorta und ihrer Aeste an einem Kaninchen nicht starkes Lungenödem hervorrief, und wir haben den besten Beweis durch das Verhalten das Carotisdrucks, dass die plötzliche Unterbrechung des Blutstroms eine Herzlähmung bewirkte. Hier war ein hoher Druck vorhanden, als die Arterien unterbunden wurden, so dass wir das Ausbleiben von Lungenödem in diesem Falle ausschliesslich der geschwächten Kraft des rechten Ventrikels zuschreiben müssen, während die Stromkraft und der Gefässtonus zur Zeit der Unterbindung normal waren. Uebrigens sei hier erwähnt, dass dies der einzige Fall war, wo eine plötzliche Herzlähmung die Folge der Unterbindung der Aorta war.

Das Verhalten des Herzens nach Unterbrechung des Kreislaufs durch Verschliessung der grossen Arterien ist nicht ohne Interesse. Es fährt nehmlich bei erhaltener künstlicher Athmung oftmals eine Zeit lang fort mit hohem Drucke zu pulsiren. Nachdem der grosse Kreislauf Stillstand gebracht worden ist, kann man mit einer endständigen Manometercanüle in der linken Carotis und einem Sodamanometer in einem Aste der Arteria pulmonalis den Druck in diesen Gefässen messen, während das Herz die vor ihm stehende Blutsäule noch kräftig hin und her treibt. Die Arterien werden wie in Versuch 4 zugebunden. Wie aus diesem Versuch ersichtlich ist, bleibt der Druck eine Zeit lang hoch; bei Hunden kann er sogar noch eine halbe bis eine Stunde eine beträchtliche Höhe behaupten. Um sicher zu sein, dass aller Blutzufluss ausgeschlossen sei, habe ich nach einiger Zeit die beiden Hohlvenen unterbunden, ohne das Versuchsresultat dadurch zu verändern. Der Puls zeigt die oft erwähnten, grossen, rhythmischen,

periodischen Schwankungen, der Druck sinkt sehr allmählich und nicht ganz regelmässig, sondern erhebt sich von Zeit zu Zeit.

Eine interessante Frage ist, ob unter diesen Verhältnissen der Coronarkreislauf noch existirt. Als Beweise für seine Existenz erwähne ich das Folgende. Ich habe mehrmals beobachtet, dass, wenn die künstliche Athmung unterbrochen wird, nach 3—4 Minuten der Druck anfängt zu sinken und zwar rascher sinkt als bei Fortsetzung derselben. Nach Herstellung der künstlichen Athmung steigt er wieder, aber diese Steigerung fängt nicht gleich nach Beginn der Athmung an. In einem Versuche an einem Hunde, nachdem der Carotisdruck von 170 bis zu 80 bei sistenter künstlicher Respiration gesunken war, hat er seine frühere Höhe nach Herstellung der künstlichen Athmung wieder erreicht. Bei einem Kaninchen, an dem der grosse Kreislauf unterbrochen war, habe ich beobachtet, dass nach Einstellung der künstlichen Athmung das Blut im Vorhofe und der Coronararterien allmählich dunkel wurde, und dass die Athmung die rothe Farbe wieder hervorrief. Man könnte vielleicht glauben, dass das Missverhältniss zwischen der Blutmenge und dem Gefässrauminhalt unter diesen Umständen so gross sei, dass der Blutdruck überhaupt nicht auf Null sinken würde, das ist aber nicht der Fall.

Ein Säugethierherz, welches so machtig unter dem Reize des hohen Blutdrucks für eine halbe bis eine Stunde pulsirt, bei welchem die Kraft der Systole durch Druckmesser ermittelt werden kann, bei welchem centrales Nervensystem und Gefässtonus ausser Wirkung gesetzt sind, und bei dem der Coronarkreislauf noch existirt, wäre kein unwürdiger Gegenstand für weitere Untersuchungen. Die Dauer und die einzelnen Phasen des Phänomens sind variabel, aber die Bedingungen derselben habe ich nicht weiter verfolgt. Hunde sind am besten für die Beobachtung derselben geeignet. Bei Kaninchen scheint es am vortheilhaftesten, die Gefässe in der folgenden Reihe zu unterbinden, die Aorta zwischen Truncus anonymus und linker Subclavia, die untere Hohlvene im Thorax, der Truncus anonymus dicht peripher von linker Subclavia (Hg.-Manometer in linker Subclavia). Wenn man bei einem Kaninchen die aufsteigende Aorta zubindet, pulsirt der linke Ventrikel gewöhnlich nicht lange fort und das Herz steht weit mit Blut ausgedehnt still. Nicht selten habe ich kleine Blutungen unter dem Visceralblatt des Pericards nach Unterbindung der Aorta beobachtet.

Da wir bisher nur die Erzeugung von Lungenödem durch Stromhindernisse im grossen Kreislauf besprochen haben, so bleibt noch übrig, die Entstehung desselben in Folge von vermehrten Widerständen im kleinen Kreislauf selbst und im linken Abschnitte des Herzens zu betrachten.

Um die Lungenvenen zu unterbinden macht man ein Fenster im Thorax, wie für Druckmessung an der Lungenarterie. Beim Kaninchen sind gewöhnlich zwei Venenäste, beim Hunde drei der linken Lunge, deren Unterbindung keine sonderliche Schwierigkeit bietet. Beim Kaninchen ist es rathsam, ohne künstliche Athmung zu operiren, da die Lunge dann zusammengefallen ist, aber man muss sich in Acht nehmen, bei der Umlegung eines Fadens um den unteren Venenast, nicht die Pleura der rechten Seite zu verletzen, weil dies die Anwendung der künstlichen Athmung sogleich unabweislich macht. Die Venenäste zu dem oberen und dem mittleren Lappen der rechten Lunge sind leicht zu erreichen, aber der Ast zu dem unteren Lappen und besonders der zu dem zungenförmigen hinter der unteren Hohlvene liegenden Lappen sind nur mit grosser Schwierigkeit zu fassen, so dass ich, wenn es darauf ankam sämmtliche Lungenvenen zu unterbinden, es vorgezogen habe, die Wurzel der rechten Lunge entweder im Ganzen oder in ihrem unteren Theile en masse zuzubinden, wodurch natürlich in dem betreffenden Theile der arterielle Zufluss abgeschlossen wird, was nach den Untersuchungen von Lichtheim die Blutmasse in den freien Theilen vermehren muss. Sowohl wenn man seine Wurzel en masse unterbinden will, als wenn man seine Vene sucht, ist es nöthig diesen zungenförmigen Lappen hinter der Vena cava herauszuziehen und eine Art von Ligamentum, welches sein Pleurafortsatz bildet, mit den Fingern sorgfältig zu zerreissen, was sich ohne Blutung ausführen lässt.

Wie schon erwähnt, bedingt die Verschliessung sämmtlicher Venen der einen Lunge kein Oedem. Das Thier lebt mehrere Stunden nach der Operation und nach dem Tode findet man die betreffende Lunge vollständig hämorrhagisch infarcirt. Im Gegensatz zu dem Auftreten von Lungenödem braucht es eine verhältnissmässig geraume Zeit, ehe diese Infarcirung zu Stande kommt, während das Oedem gleich erscheint, wenn der Blutabfluss hinreichend gehemmt wird. Wenn ausser den Venen der linken Lunge, die Venen, welche von dem oberen und dem mittleren rechten Lappen kommen, zugebunden werden, bleibt auch das Lungenödem aus. In der That muss man den Abflussweg aus den Lungenvenen fast vollständig verlegen, ehe es zur serösen Ausschwitzung kommt. So lange ein Ast zweiter Ordnung offen bleibt, ist das Hinderniss noch nicht gross genug. Kaninchen und Hunde verhalten sich in dieser Beziehung ungefähr gleich.

Versuch 5. Mittelgrosser curarisiter Hund. Hg.-Manometer in Verbindung mit linker Carotis. Druck 60—70. Soda-Manometer im unteren Aste der linken Lungenarterie. Druck 120. Nach Unterbindung des Hilus der rechten Lunge bleibt der Carotisdruck unverändert, während der Pulmonaldruck bis zu 300 steigt. Gleich danach werden die Venen der

linken Lunge, mit Ausnahme eines kleinen Astes der unteren Vene, unterbunden. Der Carotisdruck sinkt auf 40 Mm., wo er 5—6 Minuten unverändert bleibt, und sinkt dann weiter. Ein Hg.-Manometer, welcher anstatt des zu niedrigen Soda-Manometers in Verbindung mit demselben Aste der Lungenarterie gesetzt worden ist, zeigt eine Druckhöhe von 55 Mm. Hg. in Folge der Venenunterbindung. Die Obduction ergiebt sehr starke Stauung und Oedem der linken Lunge; rechte Herzhälfte ausgedehnt, linke fast leer. Einspritzung von chromsaurem Blei in den linken Vorhof zeigt, dass alle die Gefässe, wie oben angegeben, fest verschlossen sind und dass nur ein kleiner Ast des linken unteren Venenstammes offen bleibt.

Unterbindung sämmtlicher Lungenvenen, so dass aller Abfluss aus denselben so plötzlich wie möglich aufhört, ist weniger günstig für das Zustandekommen von Lungenödem, als wenn, wie in dem eben beschriebenen Versuche, ein sehr geringes Ausfliessen in den linken Ventrikel ermöglicht wird. Nach Verschliessung sämmtlicher Lungenvenen stirbt das Thier äusserst rasch und das Herz pulsirt nachher nur kurze Zeit. Bei vier Versuchen an Kaninchen verursachte die Unterbindung der Lungenvenen (i. e. der Wurzel der rechten Lunge und sämmtlicher Venen der linken) zweimal Lungenödem.

Versuch 6. Starkes Kaninchen. Tracheotomie. Druck in rechter Carotis 100—115 Mm. Hg. Fäden um die beiden Venen der linken Lunge gelegt. Künstliche Athmung. Unterbindung der ganzen Wurzel der rechten Lunge. Carotisdruck bleibt unverändert. Gleich nachher die beiden linken Lungenvenen zugebunden. Carotisdruck sinkt gleich auf Null. In 10 Secunden nach vollendeter Unterbindung wird das Thier unruhig, in 20 Secunden bekommt es heftige Krämpfe und in 45 Secunden ist es todt. Die sofortige Obduction ergiebt deutliches, aber nicht starkes Oedem der linken Lunge. Beide Lungen hyperämisch, die rechte dunkelroth, die linke hellroth. Rechte Herzhälfte stark ausgedehnt, linker Ventrikel leer, zusammengezogen. Körpervenen gestaut.

Verengerung der Venenbahn der Lunge scheint den Carotisdruck ebensowenig herabzusetzen wie die Verschliessung entsprechender Abschnitte der Lungenarterien. Man kann die Lungenvenen wenigstens bis zu drei Viertel ihrer Capacität verschliessen, ohne dass der Carotisdruck wesentlich beeinflusst wird, aber nach Ueberschreitung einer gewissen Grenze fängt der Druck im Aortensystem an zu sinken.

Der Druck in der Pulmonalarterie steigt weniger nach Unterbindung von Aesten der Lungenvenen als nach Verschliessung entsprechender Arterien.

Versuch 7. Grosser, curarisirter Hund. Druck in linker Carotis 100—120 Mm., im unteren Aste der Art. pulmonalis sinistra 20 Mm. Hg. Zubindung der drei linken Lungenvenen bewirkt Veränderung weder im Carotis- noch im Pulmonalisdruck. Unterbindung der Venen, welche von dem oberen und dem mittleren rechten Lappen herkommen, hat keinen

Einfluss auf den Carotisdruck, aber der Druck in der Art. pulmonalis steigt 4 Mm. Es bleibt jetzt blos die Vene offen, allerdings eine grosse, welche von dem rechten unteren Lappen herkommt. Die Wurzel der rechten Lunge wird en masse fest zugebunden. Der Druck in der Carotis sinkt gleich fast auf Null; der Pulmonalisdruck steigt für einen Augenblick rasch, sinkt dann plötzlich und das Herz steht still und löst keine Contraction mehr aus. Die Obduction zeigt beide Lungen blutreich, aber kein Oedem. Einspritzung mit chromsaurem Blei ergiebt, dass bei der Unterbindung der Lungenwurzel nur der Venenstamm des rechten unteren Lappens offen geblieben war.

Der plötzliche Herzstillstand, welcher der Zubindung der rechten Lungenwurzel in diesem Falle folgte, erklärt zur Genüge das Ausbleiben von Lungenödem. Wie schon oben erwähnt, tritt oft unmittelbar nach Unterbindung der Venen der einen Lunge und der Wurzel der anderen, wenn nicht eine vollständige Paralyse, so doch eine deutliche Schwächung des Herzens ein. Eine Parese des rechten Ventrikels aber, wie wir sie bei Unterbindung der Aorta schon gefunden haben, ist ein ungünstiger Zustand im Betreff des Zustandekommens von Lungenödem, obwohl sie einen beträchtlichen Grad erreichen muss, ehe die Entstehung des Lungenödems verhindert wird.

Ist die Herzlähmung, welche in einigen Fällen beobachtet wurde, die Folge des plötzlichen Verschlusses des Ausfliessens aus den Lungenvenen, wobei der Coronarkreislauf zum Stillstand gebracht wird (im Gegensatz zur Unterbindung der Aorta, S. 23), oder die Folge der langdauernden und tiefeingreifenden Operation? Die Eröffnung beider Pleurahöhlen, die unvermeidliche Störung und Zerrung der dem Herzen anliegenden Gebilde, die Berührung und Verschiebung des Herzens selbst bei Zubindung der tiefliegenden unteren und hinteren Venen der rechten Lunge oder der Lungenwurzel, und die lange Dauer der Operation beim Lufteintritt in die Pleurahöhlen sind alles Momente, welche wohl die Herzkraft bedeutend herabsetzen können. Beutner[32] hat darauf aufmerksam gemacht, dass bei offener Pleurahöhle die rechte Herzkraft sich bedeutender abschwächt als die linke, dass die erstere im Sinken begriffen sein kann, während die letztere noch steigt. Eine mögliche Erklärung findet er darin, „dass das linke Herz sich weniger leicht abkühlt wegen seiner dickeren Muskelmasse". Für uns liegen die Verhältnisse, wie wir sehen werden, gerade umgekehrt: Schwächung des linken Ventrikels bei so wenig wie möglich beeinträchtigter Kraft des rechten Ventrikels ist es, welche die Entstehung von Lungenödem begünstigt. Desshalb sind die bei Unterbindung der Lungenvenen nothwendigen Eingriffe für unseren Zweck direct entgegenwirkender Natur. Die Versuche von Bezold[33] über Zuklemmung der Kranzarterien erlauben uns

[32] Ueber die Strom- und Druckkräfte des Blutes in der Arteria und Vena pulmonalis. Zeitschrift für rat. Med. N. F. Bd. 2, S. 119. 1852.

[33] Untersuch. aus d. physiol. Laborat. in Würzburg. 1867. Hft. 2.

auch nicht dem Aufhören des Coronarkreislaufs allen Einfluss abzusprechen, um so mehr da beim Einfliessen einer sehr kleinen Blutmenge Lungenödem leichter zu Stande kommt, als bei vollständiger Absperrung der Blutzufuhr vom linken Ventrikel.

Das für unseren Zweck wichtigste Ergebniss der Versuche über Einsetzung von Hindernissen in den Abfluss des Blutes aus den Lungenvenen in den linken Ventrikel ist, dass dadurch zwar Lungenödem erzeugt werden kann, dass aber diese Hindernisse enorm, ja dass fast sämmtliche Lungenvenenäste verlegt werden müssen, ehe Oedem entsteht, und dass erst bei diesen colossalen Widerständen der Druck in der Pulmonalarterie eine bedeutende Steigerung erleidet.

Demjenigen, der mit Untersuchungen über den Lungenkreislauf nicht näher vertraut ist, kann es vielleicht auffallen, dass ich mir Schlüsse über den Druck in den Lungenvenen aus Messungen in der Lungenarterie erlaubt habe. Alle Forscher[34] aber, welche Druckmessungen in den Lungengefässen angestellt haben, stimmen darin überein, dass die Widerstände in den Lungencapillaren so klein sind, dass Druckerhöhung in den Lungenvenen von einer gleichsinnigen Veränderung in der Lungenarterie begleitet ist. Die Untersuchungen von Lichtheim haben es wahrscheinlich gemacht, dass der Tonus der Lungengefässe äusserst gering ist. Beutner fand bei einer Katze 9 Mm. Hg. als Maximalwerth der Differenz der Druckkräfte in der Arterie und in der Vene am Vorhofe. Wir aber sind bei unseren Untersuchungen um so mehr berechtigt, von dem Druckwerthe in der Lungenarterie einen Schluss auf die relative Spannung in der Vene zu ziehen, als es sich um ganz grobe Abweichungen von der Norm handelt.

Weniger weil es von principieller Bedeutung ist, als um alle Wege zu untersuchen, auf welchen mechanische Hindernisse den Abfluss des Blutes aus der Lunge hemmen können, habe ich bei Kaninchen durch Abbindung des grössten Theiles des linken Vorhofes und durch Zuklemmung des linken Ventrikels Lungenödem zu Stande gebracht. Es ist erstaunlich, ein wie grosser Abschnitt des Vorhofes oder des Ventrikels verlegt werden muss, nicht, nur ehe Lungenödem eintritt, sondern auch ehe der Carotisdruck zu sinken anfängt. Ich möchte sagen, dass wenigstens drei Viertel der Capacität des linken Ventrikels ausgeschaltet werden müssen, um Lungenödem zu verursachen. Die Zuklemmung geschah mit stark federnden, breiten Charrière'schen Klemmpincetten. In einem Versuche lebte das Thier eine

[34] Beutner, G. Colin, Badoud, Hofmokl, Lichtheim.

halbe Stunde, nachdem wenigstens die Hälfte des linken Ventrikels zugeklemmt war und starb mit Erstickungserscheinungen ohne Lungenödem. Die erste Wirkung einer partiellen Zuklemmung besteht darin, durch Herzreizung (oder durch Hirnanämie?) den Druck in der Art. carotis zu erhöhen, welcher auch nach Abnahme der Klemmpincetten hoch bleibt. In einem Versuche habe ich beobachtet, dass, gleich nachdem der grösste Theil des linken Ventrikels zugeklemmt wurde, das Thier in einen tetanischen Zustand gerieth. Dasselbe wurde bewusstlos und blieb unerregbar bis zum Tode, welcher (durch Drucksinkung erkennbar) nach ungefähr 15 Minuten ohne Krämpfe oder Dyspnoe, aber mit starkem Lungenödem, eintrat.

Nachdem wir die Bedingungen ermittelt haben, unter welchen ein mechanisches Oedem der Lunge an Kaninchen und Hunden experimentell herbeizuführen ist, so entsteht die Frage: welches Licht werfen die vorliegenden Beobachtungen auf die Ursachen des Lungenödems beim Menschen? Es liegen gewiss die Bedingungen des Lungenödems, welches ich durch mechanische Momente zu Stande gebracht habe, sehr weit entfernt von denjenigen, welche in der grössten Mehrzahl der Fälle von acutem, allgemeinem Hydrops pulmonum beim Menschen herrschen, und über die Entstehung des letzteren können die Ergebnisse der oben erwähnten Versuche anscheinend wenig Positives aussagen. Und doch liegt, meiner Meinung nach, in ihnen der Schlüssel zur Lösung des Problems, das uns beschäftigt.

Das Oedem, welches ich künstlich erzielt habe, ist ein Stauungsödem und tritt erst dann ein, wenn der Druck im Lungenkreislauf bedeutend erhöht ist. Das mikroskopische Bild dieses Oedems stimmt in allen seinen wesentlichen Charakteren mit dem des allgemeinen Lungenödems beim Menschen überein. Bei beiden sieht man hochgradige Füllung der Lungencapillaren und zahlreiche ausgetretene rothe Blutkörperchen. Diese Uebereinstimmung bestärkt an sich die ohne genügende Gründe gewöhnlich angenommene Ansicht, dass das Lungenödem ein Stauungsödem sei. Indess haben die obigen Versuche die geläufigen Erklärungen dieses Oedems entkräftigt. Von denselben giebt es eigentlich nur zwei, welche Anspruch auf Wahrscheinlichkeit machen können und in Einklang mit klinischen Erfahrungen zu stehen scheinen. Dies sind die beiden oben angegebenen Ursachen der venösen Stauung, Störung des Abflusses des Blutes aus den Pulmonalvenen durch Klappenfehler des linken Ventrikels und geschwächte Herzaction. Es fehlt, meiner Ansicht nach, ohnehin nicht an Gründen, um die Unzulänglichkeit beider Momente für die Erklärung des Zustandekommens des Oedema pulmonum nachzuweisen; jedenfalls lassen die Ergebnisse des Experiments ihre Unhaltbarkeit klar zu Tage treten. Eine „Störung des Abflusses des Blutes aus den Pulmonalvenen“ durch mechanische Hinder-

nisse verursacht erst dann Oedem der Lunge, wenn dadurch fast sämmtliche Venenäste verlegt worden sind. Von solchen Hindernissen im grossen oder im kleinen Kreislauf kann beim Menschen kaum die Rede sein; wenigstens müssen wir diesem Momente eine allgemeine Bedeutung bei der Lösung unseres Problems absprechen. Geschwächte Action des ganzen Herzens erzeugt nicht nur an und für sich kein Oedem, sondern, wenn selbst die sonstigen Bedingungen vorhanden sind, kann sie das Auftreten desselben hintanhalten.

Giebt es denn keine andere Ursache für Lungenstauung, welche wir als die Bedingung von Lungenödem betrachten können, ohne mit den bekannten Eigenschaften der Pulmonalcirculation und den klinischen Beobachtungen in Widerspruch zu treten? Oder sollen wir etwa auf die Wirkung mechanischer Momente verzichten und unsere Zuflucht zu der Annahme einer unbekannten Gefässwandveränderung nehmen? Zu solch einem Schritt wird sich, denke ich, schwerlich jemand entschliessen, so lange nicht alle mechanischen Erklärungsmöglichkeiten erschöpft sind. Eine solche aber scheint mir jedes Missverhältniss zwischen der Kraft des linken und der des rechten Ventrikels zu sein, wobei der erstere nur einen Bruchtheil der Blutmenge in der Zeiteinheit heraustreiben kann, welche der letztere in die Lungenarterie hineinschafft, d. h. eine linksseitige Lähmung des Herzens.

Wenn ich das Wort Missverhältniss gebrauche, so denke ich selbstverständlich nicht an den absoluten Unterschied zwischen der Kraft des rechten und der des linken Ventrikels. Diese Kraft steht bekanntlich in directem Verhältnisse mit der Widerstandshöhe am Anfang des grossen resp. des kleinen Kreislaufs. Die Triebkraft des linken Ventrikels kann bedeutend vermindert werden, während die des rechten unverändert bleibt oder sogar erhöht wird, ohne dass ein Missverhältniss zwischen denselben sich ausbildet, vorausgesetzt, dass die Widerstände im gleichen Sinne und in demselben Verhältnisse sich ändern. Ein solch relatives Missverhältniss zwischen der arbeitskraft des linken Ventrikels und der des rechten bedeutet dagegen, dass bei gleichbleibenden Widerständen das linke Herz nicht dieselbe Blutmenge in der Zeiteinheit hinauszutreiben vermag, wie das rechte.

Gesetzt den Fall, der linke Ventrikel wird gelähmt, der rechte arbeitet mit unverminderter Kraft fort und empfängt nicht weniger Blut als vorher, was muss geschehen? Das Blut muss sich in den Lungengefässen häufen, bis der beharrliche Zustand, der bei jedem Kreislaufe eine Nothwendigkeit ist, eintritt. Dieser kommt erst dann zu Stande, wenn die Widerstandshöhe in der Lungenarterie so gross geworden ist, dass der rechte Ventrikel nur dieselbe Menge Blut in der Zeiteinheit hineintreiben kann, wie aus den

Lungenvenen herausfliesst. Es ist klar, dass je schwächer der linke Ventrikel einerseits und je stärker der rechte andererseits, desto grösser die Druckhöhe in dem Lungenkreislauf ausfallen wird, bei welcher der beharrliche Zustand entsteht.

Ob diese Druckerhöhung in einem gegebenen Falle Lungenödem verursachen wird, ja ob sie überhaupt dazu hinreicht, ist von vornherein nicht mit Bestimmtheit zu sagen. Es bedarf keiner Erörterung, dass die dynamischen Momente andere sind als bei mechanischen Hindernissen für den Abfluss des Blutes aus den Lungenvenen, wo eine geringe Drucksteigerung genügt, um erhebliche Widerstände zu überwinden. Selbst wenn ich keine experimentellen Beweise dafür beibringen könnte, dass eine linksseitige Herzschwächung ausreicht um Lungenödem zu erzeugen, so glaube ich doch in Ansicht der Mangelhaftigkeit anderer Theorien, dass es nicht unnütz wäre auf diese Hypothese aufmerksam zu machen, welche uns wenigstens eine sehr plausible Erklärung der Entstehung von Lungenödem, im Widerspruch weder mit den bekannten Eigenschaften der Pulmonalcirculation noch mit der klinischen Beobachtung, darbietet. Selbstverständlich aber muss die Hypothese eine ganz andere Stellung gewinnen, wenn es sich beweisen liesse, dass eine linksseitige Herzschwächung an und für sich genügt um Lungenödem zu Stande zu bringen, und deshalb schien es geboten, dieselbe einer experimentellen Prüfung zu unterwerfen.

Durch welche Mittel aber ist es möglich eine einseitige Herzlähmung zu erzeugen? Unter den verschiedenen Herzgiften hat keines, so viel mir bekannt, die Eigenschaft allein oder hauptsächlich auf den einen Ventrikel zu wirken. Die Kalisalze, Jodsalze, Kohlenoxyd, Strychnin können alle als eine inconstante Folge ihrer giftigen Wirkung Lungenödem herbeiführen. Aber wegen der Inconstanz dieser Erscheinung und wegen der Schwierigkeit einen Beweis zu liefern, dass in einem gegebenen Falle der eine Ventrikel stärker afficirt sei als der andere, musste ich bald vom Experimentiren mit den Herzgiften absehen. Wenn nach dem Tode der rechte Ventrikel sich zusammenzieht, während der linke stillsteht, os ist dieses kein Beweis, dass der letztere gelähmt gewesen ist, da bekanntlich bei allen absterbenden Herzen das rechte Herz seine Contractionsfähigkeit länger bewahrt als das linke, und Du Bois Reymond gezeigt hat, dass der kräftigere Muskel seine Reizbarkeit rascher einbüsst als der weniger reizbare.

Auch die locale Einwirkung schädlicher Stoffe auf die Aussenfläche des linken Ventrikels erwies sich als für unseren Zweck völlig ungenügend. Ich versuchte durch Aufstreuen von Kalisalzen, durch Aufgiessen von Chloroform, durch Eis, durch Hitze die Kraft des linken Ventrikels zu beeinträchtigen. Er zeigte aber eine erstaunliche Widerstandsfähigkeit. Es gelang mir in den meisten Fällen nur eine stärkere Action des Herzens und

erhöhten Carotisdruck zu erzielen, und wenn einmal der linke Ventrikel stillstand, so wurde der rechte auch ruhig.

Endlich erreichte ich das erwünschte Ziel durch Quetschung der Wand des linken Ventrikels. Für diesen Zweck sind die Finger das beste Instrument, Pincetten u. s. w. zerreissen die Muskelwand zu leicht. Ich habe den Eingriff blos am Kaninchenherzen gemacht, da das Herz des Hunds zu starkwandig und kräftig ist. Der linke Ventrikel wird zwischen den Daumen und einen oder zwei Finger genommen, so dass so viel wie möglich seiner Muskelwand inclusive des Septum ventriculorum gefasst wird, ohne den rechten Ventrikel zu beeinträchtigen, und dann stark zusammengedrückt. Es erfordert eine nicht geringe Kraft um den Ventrikel wirklich zu lähmen. Ein Hg.-Manometer muss in Verbindung mit einer Carotis stehen, damit man die Kraft des linken Ventrikels beurtheilen kann. Durch diese Methode habe ich in vielen Fällen den linken Ventrikel entweder zum Stillstand gebracht, oder mehr oder weniger vollständig gelähmt, während der rechte noch einige Zeit stark pulsirt. In vielen Fällen aber hatte der Eingriff andere Wirkungen. Nicht selten stand das ganze Herz plötzlich still, selbst nachdem ein verhältnissmässig geringer Druck auf dasselbe ausgeübt worden war; oft wurden beide Ventrikel gleichmässig und gleichzeitig geschwächt. War endlich die Quetschung nicht stark oder nicht ausgedehnt genug ausfallen, so wirkte häufig der Eingriff als ein Reiz für den Herzmuskel.

Obwohl ein einziger Fall von unzweideutiger Lähmung des linken Ventrikels bei Fortarbeiten des rechten genügt hätte, um die Möglichkeit dieses Zustandes zu beweisen und die Folgen desselben zu beobachten, suchte ich doch durch ein grösseres Beobachtungsmaterial die daraus gezogenen Schlüsse ausser allem Zweifel zu setzen. Dabei wurden viele Thiere nutzlos geopfert; doch ist es mir gelungen in einer grossen Anzahl von Versuchen eine deutliche allein oder hauptsächlich auf den linken Ventrikel beschränkte Lähmung zu erzielen, und ich kann mit Bestimmtheit behaupten, dass bei einer gewissen Kraft des rechten Ventrikels eine hinreichend hochgradige Schwächung des linken Lungenödem herbeiführt.

Versuch 8. Mittelgrosses Kaninchen. Künstliche Athmung. Quecksilberdruck in rechter Carotis 100—120 Mm. Thorax in der Mittellinie geöffnet und das Herz durch Eröffnung des Pericards blossgelegt. Der linke Ventrikel wird zwischen den Fingern stark zusammengedrückt. Derselbe steht in Contraction absolut still und löst keine erkennbare Pulsation mehr aus. Der Carotisdruck sinkt auf 20 Mm. Der rechte Ventrikel, der zuerst stillstand, fängt nach einigen Secunden an wieder zu pulsiren und zieht sich 3 Minuten lang anscheinend kräftig und in regelmässigem Rhythmus zusammen. Die beiden Vorhöfe pulsiren ungefähr dreimal so schnell als der Ventrikel. Die Arteria pulmonalis und die beiden Vorhöfe werden

stark, der rechte Ventrikel mässig ausgedehnt. Nach 2—3 Minuten bekommt das Thier Krämpfe und stirbt. Die Obduction ergiebt sehr starkes Oedem beider Lungen.

Versuch 9. Grosses Kaninchen. Künstliche Athmung. Druck in linker Carotis 90 Mm. Hg. Eröffnung des Thorax in der Mittellinie und des Herzbeutels. Der linke Ventrikel inclusive des Septums wird mit den Fingern stark comprimirt. Carotisdruck sinkt auf 30. Der linke Ventrikel pulsirt einige Secunden mit diesem geringen Drucke und dann erholt er sich allmählich. Nach wiederholter Quetschung sinkt der Druck wieder auf 30 und allmählich noch tiefer. Im Gegensatz zu dem linken Ventrikel arbeitet der rechte 3—4 Minuten anscheinend ungeschwächt fort, während welcher Zeit sich das Blut in der Lungenarterie, den beiden Vorhöfen, dem rechten Ventrikel und den Körpervenen deutlich staut. Der Carotisdruck sinkt bis Null und nach 5 Minuten wird die künstliche Athmung sistirt. Das Thier stirbt ohne Krämpfe. Die Section ergiebt starkes Lungenödem. Es finden sich kleine Blutungen in der gequetschten Muskelwand des linken Ventrikels und kleine Fibrinauflagerungen auf seiner Innenfläche.

Versuch 10. Kleines Kaninchen. Künstliche Athmung. Druck in linker Carotis 90—100 Mm. Hg. Der ganze linke Ventrikel wird zwischen zwei auf den Branchen einer Pincette befestigten Korkplatte comprimirt. Der Carotisdruck sinkt ziemlich rasch bis Null. Der rechte Ventrikel pulsirt 1½—2 Minuten fort und dann stirbt das Thier unter Erstickungserscheinungen. Nachdem der rechte Ventrikel zu pulsiren aufgehört hat, schlagen wie gewöhnlich die Vorhöfe noch weiter, am längsten der rechte. Die Section ergiebt Oedem beider Lungen. Die Pulmonalarterie und rechte Herzhälfte sind stark ausgedehnt, die Körpervenen gestaut.

In einigen Fällen wurde der linke Ventrikel durch die Quetschung vollkommen zum Stillstande gebracht, in anderen pulsirte er noch mit schwachem Drucke fort, in allen aber, bei welchen Lungenödem entstand, schlug der rechte Ventrikel noch einige Zeit rhythmisch und anscheinend mit ungeschwächter Kraft fort. Natürlich aber genügt der Augenschein nicht und es war zur Controlle unbedingt nöthig, den rechten Ventrikel gleichfalls zu lähmen und zwar sowohl ohne Beeinträchtigung des linken wie auch mit gleichzeitiger Lähmung desselben.

Man kann den rechten Ventrikel in derselben Weise wie den linken zur Lähmung bringen, nur wird dies durch die Dünnwandigkeit desselben erleichtert. Ich habe eine deutliche Lähmung des rechten Ventrikels sowohl ohne gleichzeitige Beeinträchtigung des linken, wie auch mit Quetschung des letzteren, mehrmals erzeugt, und nie Lungenödem in Folge davon beobachtet. Einen Versuch will ich als Beispiel anführen.

Versuch 11. Mittelgrosses Kaninchen. Künstliche Athmung. Quecksilberdruck in rechter Carotis 100 Mm. Eröffnung des Thorax in der Mittellinie und des Pericards. Rechter Ventrikel zwischen den Fingern zusammengepresst. Der Carotisdruck sinkt bis 30, aber nach einer Minute ist er wieder auf 100—110 Mm. gestiegen. Der rechte Ventrikel wird wieder gequetscht, Carotisdruck 20. Der rechte Ventrikel ist deutlich gelähmt und

wird mit Blut ausgedehnt, in viel stärkerem Grade staut sich das Blut in dem rechten Vorhofe. Der linke Ventrikel pulsirt fort und bietet einen auffallenden Contrast zum rechten, welcher nach kurzer Zeit blos wurmförmige und dann vibrirende Bewegungen macht. Nach ungefähr 2½ Minuten stirbt das Thier mit Krämpfen. Bei der Section zeigen sich der linke Ventrikel und die Arterien blutleer, dagegen die Venen strotzend gefüllt. Es ist kein Lungenödem vorhanden.

In Berücksichtigung der Ergebnisse dieser Versuche dürfen wir ohne Bedenken linksseitige Herzparalyse als eine Causa efficiens von Lungenödem betrachten. Theoretische Ueberlegungen lassen es kaum anders erwarten. Wenn der rechte Ventrikel fortfährt Blut in die Lungengefässe hineinzupumpen, während der linke nur einen Bruchtheil davon forttreiben kann, wenn der Unterschied zwischen den Kräften der beiden Ventrikel einen gewissen Grenzwerth überschritten hat, dann muss, scheint mir, der Druck in den Lungencapillaren so hoch steigen, dass Lungenödem die Folge wird. Der Einwand, dass die verminderte Kraft des linken Ventrikels die Stromkraft im grossen Kreislauf so herabsetzt, dass keine für diese Drucksteigerung hinreichende Blutmenge in den rechten Ventrikel einfliesst, ist am besten durch das Ergebniss des Versuches beantwortet. Darüber wie die Stromgeschwindigkeit sich dabei verhält, auch über die absolute Höhe des für das Zustandekommen von Lungenödem nöthigen Kraftunterschiedes der beiden Ventrikel habe ich keine experimentellen Data, und theoretische Betrachtungen über diese Punkte hätten keinen Werth.

Diese durch das Experiment gestützte Hypothese bietet meiner Meinung nach die beste Erklärung der Eigenthümlichkeiten des Auftretens von Lungenödem beim Menschen.

Die grössere Schnelligkeit, mit welcher Oedem sich in der Lunge entwickelt als in anderen Körpertheilen, findet seine Erklärung in der absolut grösseren Durchlässigkeit der Lungencapillaren, oder, besser ausgedrückt, in der grösseren Differenz zwischen dem Seitendruck in den Gefässen und den Widerständen, welche der durchdringenden Flüssigkeit entgegenstehen. Einerseits bedingen die Ursachen von Lungenödem einen für den Pulmonalkreislauf verhältnissmässig hohen Seitendruck, andererseits finden die Lungencapillaren nur eine schwache Stütze an dem Lungengewebe. Wenn man bedenkt, dass unter normalen Verhältnissen die Spannung in den Lungengefässen sehr gering ist, dass sie zu einem erstaunlichen Grade gegen Druckveränderungen im grossen Kreislauf geschützt sind, dass selbst bedeutende Störungen im Lungenkreislauf mit geringen Druckänderungen ausgeglichen werden können, so begreift man, dass sie gegenüber den physiologischen und vielen pathologischen Verhältnissen einer grösseren Stärke nicht bedürfen. Wegen der günstigen Abdunstungsbedingungen in der Lunge

und wegen des durch histologische Untersuchungen wahrscheinlich gemachten reichlichen Lymphabflusses aus derselben, wäre es überdies leicht erklärlich, dass eine bei leichten Drucksteigerungen möglicherweise eintretende vermehrte Ausscheidung aus den Lungencapillaren ohne störende Erscheinungen ablaufen könnte. Wenn aber eine plötzliche und hochgradige Drucksteigerung in den Lungencapillaren eintritt, für welche die obigen Versuche Beispiele darbieten, dann verrathen die Capillaren ihre absolut geringere Widerstandsfähigkeit dadurch, dass Lungenödem in der Zeit von einer oder zwei Minuten und noch schneller entstehen kann. Es ist eben dieses stürmische Auftreten, welches eine grosse Anzahl der Fälle von Oedema pulmonum beim Menschen charakterisirt. Seine Erklärung liegt auf der Hand, wenn wir die Ursache desselben in einer plötzlichen Schwächung des linken Ventrikels suchen. Mit anderen Erklärungsweisen scheint es mir dagegen nicht leicht diesen Charakter des Lungenödems in Einklang zu bringen.

Ein weiteres Merkmal des Lungenödems ist die Inconstanz seiner Entstehung bei anscheinend gleichen Bedingungen. Wenn Lungenödem bei der Todesagonie wegen der allgemeinen Herzschwäche entstünde, wenn die collaterale Hyperämie Oedem der einen Lunge bei Hepatisation der anderen herbeiführte, wenn bei einer Mitralstenose das mechanische Hinderniss des Blutabflusses oder bei Morbus Brightii die Hydrämie die Ursache des Oedems bildete, warum erscheint es dann in dem einen Falle und bleibt in dem anderen aus, obwohl in beiden diese Bedingungen anscheinend in gleichem Grade vorhanden sind? Diese unter den obigen Voraussetzungen so räthselhafte Inconstanz ist wohl erklärlich, wenn wir jene Zustände als begünstigende Momente (Dispositio ad morbum) betrachten, aber eine vorwiegende Schwäche des linken Ventrikels als die nächste Ursache annehmen. Wenn bei der Agonie zum Beispiel die beiden Herzhälften beim Absterben gleichen Schritt halten, so entsteht kein Lungenödem, wenn aber der linke Ventrikel vorauseilt und rascher gelähmt wird, als der rechte, dann kann es zu Stande kommen. Dabei wird natürlich nicht gesagt, dass der rechte Ventrikel nicht gleichzeitig auch schwächer werde; er ist sogar wahrscheinlich in den meisten Fällen von Lungenödem geschwächt. Diese Schwäche aber begünstigt an und für sich nicht das Auftreten von Lungenödem. Gewiss freilich verliert der linke Ventrikel sein wunderbares Anpassungsvermögen an wechselnde Widerstände, veränderlichen Füllungsdruck und was auch sonst für regulatorische Einrichtigungen der Herzkraft im Spiel sein mögen, nicht eher vollständig, als bis die Leistungsfähigkeit des ganzen Herzens angegriffen worden ist. So entsteht das Lungenödem, welches in Verlauf von Herz-, Lungen-, Nierenkrankheiten u. s. w. auftritt erst dann, wenn die Gesammtthätigkeit des Herzens herabge-

setzt ist, und deshalb ist man zu der irrthümlichen Meinung gekommen, dass allgemeine Herzschwäche allein eine Causa efficiens des Hydrops pulmonum sei.

Hier möchte ich einem Einwand begegnen, welcher sich folgendermaassen ausdrücken liesse. Wenn zum Beispiel bei einer uncompensirten Mitralstenose der rechte Ventrikel den vorhandenen Widerständen nicht gewachsen ist, wie kann man annehmen, dass bei noch grösseren Hindernissen seine Kraft ausreichen werde, um die für die Entstehung von Lungenödem nöthige Druckhöhe zu Stande zu bringen? Aber eben diese vermehrten Widerstände sind ein Reiz für das rechte Herz; wahrscheinlich ist der Hauptregulator der Herzkraft in den vor ihm liegenden Widerständen gelegen, und obwohl der rechte Ventrikel, wahrscheinlich selbst in normalem Zustande, nicht auf die Dauer die Druckhöhe behaupten könnte, welche für die Entstehung von Lungenödem nöthig ist, reagirt er doch, selbst in geschwächtem Zustande, für eine kurze Zeit auf die plötzlich vermehrten Widerstände mit dem nöthigen Kraftaufwand. Das rasche Zurücktreten von Lungenödem in vielen Fällen ist vielleicht ebenso sehr auf die ungenügende Kraft des rechten Ventrikels die Stauung länger zu behaupten, wie auf Herstellung der Kraft des linken Herzens zu beziehen. Dass es eine minimale Grenze giebt, unter welcher die Kraft des rechten Ventrikels nicht mehr fähig ist, ein Stauungsödem zu erzeugen, betrachte ich als sehr wahrscheinlich, aber es sind keine Anhaltspunkte vorhanden, um zu bestimmen, wo diese Grenze liegt. Und vielleicht ist es mehr verminderte Erregbarkeit. als verminderte Kraft des rechten Ventrikels, welche der Entstehung von Lungenödem hinderlich wird. Da aber das Oedem, welches ohne vorhergehende bedeutende allgemeine Herzschwäche — wie gelegentlich bei Krankheiten der Kreislaufsorgane, sowie bei Gehirnkrankheiten, besonders traumatischer Natur — plötzlich auftritt, das stärkste und von den bedrohlichsten suffocatorischen Erscheinungen begleitet ist, während dasjenige der Todesagonie oftmals so gering ausfällt, dass man zweifelt, ob es überhaupt den Namen verdient, so können wir schliessen, dass es für den Grad des Lungenödems nicht gleichgültig ist, ob eine beträchtliche allgemeine Herzschwäche vorhergegangen ist oder nicht.

Wenn ich eine linksseitige Herzparalyse als die Causa proxima des acuten allgemeinen Lungenödems in Anspruch nehme, so meine ich nicht, dass anderen Momenten, als Herzfehlern, Hydrämie etc., aller Einfluss abzusprechen ist, sondern nur, dass diese a l l e i n uns keine befriedigende Erklärung der Entstehung des Oedema pulmonum geben.

In der Entstehungsweise und in den Erscheinungen von Lungenödem beim Menschen ist nichts, was, so viel ich sehe, gegen die auseinandergesetzte Hypothese spricht, während vieles seine vollkommene Erklärung

dadurch findet. Ob das Vorhandensein des vorausgesetzten Zustandes des Herzens am Menschen zu beweisen sei, scheint mir zweifelhaft. Das von klinischer Seite [35] hervorgehobene Symptom des acuten allgemeinen Lungenödems, starker Herzschlag bei schwachem Pulse, scheint eine Stütze für unsere Auffassung darzubieten, doch möchte ich nicht zu vieles Gewicht darauf legen, da auch eine Lungenstauung aus irgend welcher anderen Ursache den rechten Ventrikel secundär zu stärkerer Arbeit veranlassen könnte. Da es nur in untergeordnetem Grade auf die absolute Kraftleistung des linken oder des rechten Ventrikels, vielmehr vorzugsweise auf das Verhältniss zwischen beiden ankommt, so mag es schwierig sein, diese relative Verschiedenheit klinisch zu constatiren, indess trotzdem wird sich vielleicht die Aufmerksamkeit der Kliniker in Zukunft auf diesen Punkt richten.

Das mikroskopische Bild des allgemeinen Lungenödems lässt sich mit wenigen Worten zusammenfassen. Erzeugt man künstlich Lungenödem, zum Beispiel durch Unterbindung der aufsteigenden Aorta, und nimmt, ohne die Lungen berührt zu haben, etwas von der Oedemflüssigkeit sorgfältig mit einer Pipette aus der Trachea heraus, so finden sich darin folgende körperliche Elemente: zahlreiche rothe Blutkörperchen, Bronchialepithelien, sparsame Lungenepithelien und freie Körnchen von demselben Aussehen, wie diejenigen in den Lungenepithelzellen, selten weisse Blutkörperchen. Die als Lungenepithelien angesprochenen Zellen sind platt, zwei- bis viermal so gross als weisse Blutkörperchen, grob granulirt, rund oder oval, enthalten jede einen bläschenförmigen, ovalen Kern, selten deren zwei, und kommen meistens vereinzelt vor. Im Verhältnisse zu der Menge der rothen Blutkörperchen ist jedenfalls die Anzahl aller übrigen Elemente verschwindend klein.

Schnitte aus der menschlichen ödematösen Lunge zeigen die prachtvollste natürliche Injection der Capillaren. In diesen liegen oft die Blutkörperchen zu zweien oder dreien in einem Querschnitt, während gewöhnlich, selbst in hyperämischen Lungen, blos ein einziges Blutkörperchen in einem Querschnitt Platz findet. Die Capillaren sind mit anderen Worten zwei- bis dreifach über ihre normale Weite ausgedehnt. Ausserhalb der Gefässe finden sich viele rothe Blutkörperchen in den Alveolen und den Interstitien.

Die oben als Lungenepithel erwähnten Zellen findet man in grosser Menge an Schnitten aus der frischen Lunge. Aber, wie schon Friedländer hervorgehoben hat, sind sie eben so zahlreich und mit demselben Aussehen an Schnitten jeder frischen Lunge zu sehen und bieten deshalb nichts für

[35] Lebert, Handbuch d. pract. Medicin.

Lungenödem Charakteristisches. Der Befund derselben in der Trachealflüssigkeit macht es wahrscheinlich, dass die seröse Ausschwitzung die Epithelien in derselben Weise ablöst, wie dies eine indifferente Zusatzflüssigkeit bei der mikroskopischen Untersuchung thut. Im frischen Zustand ist für diese Zellen das am meisten Charakteristische ihr körniger Inhalt. Derselbe besteht aus Körnchen von ziemlich starkem Glanz, welche oftmals dicht um den Kern gehäuft liegen. Zwischen dem körnigen Inhalt und der einfachen Zellcontour befindet sich ein blasser Hof, welcher sich nach Wasserzusatz aufbläht. Die Körnchen sind theils eiweissartiger, theils fettiger Natur. Nach Zusatz von Essigsäure werden die Zellen blasser, aber ein bedeutender Theil der Körnchen bleiben noch. An Schnitten von in Alkohol gehärteten Präparaten sind die Epithelzellen schwer als solche zu erkennen, weil ihr körniger Inhalt meistens verschwunden ist, und die Kerne nicht leicht von den Capillarkernen zu unterscheiden sind.

THEORY OF PULMONARY OEDEMA[1]

I am glad to comply with your kind invitation to say something concerning the theory of the causation of certain forms of pulmonary oedema which I advanced 25 years ago on the basis of an experimental research undertaken at the suggestion and under the supervision of my honored teacher, Professor Cohnheim, in his laboratory in Breslau. This research was the first experimental study of the subject, and Professor Sahli, one of the leading critics of the theory, has been good enough to say that "even the opponents of the theory need not hesitate to give it praise of having for the first time directed, upon the firm foundation of pathological experiment, the pathology of pulmonary oedema into straight and serviceable paths."

Permit me to recall some of the leading results and conclusions of my investigation, published in "Virchow's Archiv," in March, 1878. These related to acute general oedema of the lungs, from which the inflammatory forms of oedema were separated. The various hypotheses current at that time, concerning the causation of pulmonary oedema, were subjected to a critical analysis, based in part upon experimental work, and all were rejected

[1] The following is an introductory note by S. J. Meltzer which states the reason for including a letter from Dr. Welch in Meltzer's publication on Oedema in 1904: "Welch's Theory of Pulmonary Edema.—In discussing the various forms of edema in the first edition of his brilliant lectures on general pathology, Cohnheim remarked that there is one form of edema, a most important one, for which he could as yet offer no adequate explanation; this is pulmonary edema. But soon after, pulmonary edema was elucidated by a theory which still occupies a commanding position in general pathology. The theory was based upon an extensive series of experiments carried out in the laboratory of Cohnheim by an investigator who is now our foremost pathologist in this country—I refer to Dr. William H. Welch, of Johns Hopkins University. It is just twenty-five years since the theory was advanced. In the course of this quarter of a century the theory was tested experimentally, discussed and criticized by Sahli, Grossmann, and Löwit. It seemed to me that it would be highly instructive to hear the originator of this theory present and discuss it again in his concise way. Professor Welch complied with my request, for which I wish here to express my gratitude. Permit me to read to you the remarks written down by Prof. Welch on his theory of pulmonary edema."

In: Edema, a Consideration of the Physiologic and Pathologic Factors Concerned in its Formation, by S. J. Meltzer. New York.

Am. Med., Phila., 1904, VIII, 195-196.

as unsupported or directly opposed by established facts. Although some of these hypothetic causes of pulmonary oedema, such as active hyperaemia, enfeebled action of the entire heart, and passive hyperaemia due to mitral and aortic valvular disease, continue to be prominently mentioned in some textbooks, I consider that the criticism passed upon them is still valid, and that no satisfactory additional evidence in their support has been furnished.

My investigations were directed mainly toward a solution of the question whether acute general pulmonary oedema belongs to the group of the so-called mechanical oedemas, referable to passive hyperaemia, or to that other group, of more obscure causation, which includes the hydraemic or cachectic oedemas, and which was at that time, and is still, often attributed to changes in the vascular walls. Even 25 years ago it was recognized by Cohnheim that other than mechanical factors are concerned in the oedemas due to venous congestion, and especially that these are not the direct result of rise of of intracapillary pressure, but for the purposes of my research it was not deemed necessary to consider how passive hyperaemia induced oedema. The essential thing was to determine whether or not acute general oedema of the lungs belongs to this latter category.

Acute general oedema of the lungs is characterized by several features, which seem to give it a position quite apart from oedemas of other parts of the body. Among these distinctive features may be mentioned the often rapid or sudden onset of the affection, sometimes its quick disappearance, its occurrence as an occasional complication of a great variety of acute and of chronic diseases, although a constant accompaniment of none, and its frequency as a terminal or even agonal event. Whatever be the explanation adopted, it must take cognizance of these and other peculiar characters of pulmonary oedema. In view of these characters, and of previous work by himself and Lichtheim, relating to the pulmonary circulation, Professor Cohnheim, when I began my experiments, considered it improbable that oedema of the lungs would be shown to be a "Stauungsœdem" or congestive oedema.

I endeavored in the first place to determine whether it is possible to produce, experimentally, oedema of the lungs by obstruction to the outflow of blood from the pulmonary veins. The previous experiments of Cohnheim and Lichtheim had already demonstrated that very great increase of the blood-pressure in the aorta may occur with relatively little effect upon the pressure in the pulmonary vessels, and also that the right ventricle is capable of overcoming enormous obstacles in the pulmonary circulation without material lowering of the aortic pressure. My experiments confirmed and extended these results. I succeeded, however, in producing oedema of the lungs, both by ligation of the aorta and its branches, and by ligation of pul-

monary veins; but the degree of obstruction to the circulation in the aorta or in the pulmonary veins necessary to bring about this result, was found to be so enormous that it is scarcely conceivable that it could, under any circumstances, occur in human beings.

The experiments thus far, while proving the possibility of the occurrence of pulmonary oedema in consequence of passive hyperaemia, not only shed no light upon the conditions actually concerned in the production of this affection in human beings, but, on the other hand, tended to discredit the causative factors which had previously been based upon this assumption.

The possible ways in which venous hyperaemia of the lungs might be induced were not, however, exhausted by experiments mentioned. There occurred to me as a possible mechanical explanation of pulmonary oedema, a condition which I described in the following words: "*A disproportion between the working power of the left ventricle and of the right ventricle of such character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart.*" I lay some stress upon this mode of statement of my theory, and emphasized it by the type in my article. It is true that I mentioned and examined experimentally only paralysis of the left ventricle as a cause of this incongruity between the two sides of the heart, but it is evident, as was mentioned by Cohnheim soon afterward, that spasm of the left ventricle might bring about the same result.

The experimental test of this hypothesis is a matter of great difficulty. I sought in vain for some poison which would act in the desired way upon the left ventricle. Although several poisons occasionally produced oedema of the lungs, none did so constantly, and I was unable to demonstrate in this way an isolated, paralyzing effect on the left ventricle. I succeeded, however, in paralyzing the left ventricle of rabbits by the coarse procedure of squeezing it between the fingers, and I observed in many instances after this manipulation, continued, apparently forcible action of the right ventricle with diminished force of the left ventricle, as indicated by the pressure in the carotid artery. Under these circumstances well-marked pulmonary oedema resulted. It is this experiment upon the rabbit which constituted the experimental basis of the theory of pulmonary oedema advanced in my article on the subject.

I considered briefly the nature of the forces which might be operative in supplying the right ventricle with the requisite amount of blood for the production of pulmonary oedema after lessened output from the left ventricle, and to this aspect of the subject Sigmund Mayer, shortly after my publication, devoted especial attention.

I was not unmindful of the fact that this theory, if applicable to human beings, must conform to clinical and anatomical observations, and I endeavored to point out that it not only was not contradicted by such observations, but that it furnished a better explanation than any other hypothesis, known at that time, of many cases of acute general pulmonary oedema in man.

Of the fate of this theory during the quarter of a century since its publication it is impossible for me to speak in detail in this necessarily brief communication, but there are a few points upon which I should like to touch. The theory has obtained wide, although by no means universal acceptance, in German and Russian publications, being unreservedly adopted, for example, by such eminent clinicians as Strümpell and Eichhorst. It seems to be little known and has been but little discussed by American, English and French writers. The experimental results have been abundantly confirmed and extended, although not all are agreed in their interpretation.

Grossmann, in an interesting experimental study of pulmonary oedema due to poisoning by muscarin, believes that he has demonstrated that this form of oedema is due to spasm of the left ventricle with resulting venous hyperaemia of the lungs, and that the same condition of the left ventricle is present in many cases of human pulmonary oedema. This opinion is not, as Grossmann seems to suppose, opposed to the fundamental conception underlying my theory—namely, a disproportion between the action of the two ventricles in the sense that the left ventricle propels in a unit of time only a fraction of the quantity of blood expelled by the right ventricle into the pulmonary artery. It seems to me, however, more probable that an enfeebled action of the left ventricle, rather than a spasmodic action, is likely to be the cause of this disproportion under the conditions in which pulmonary oedema ordinarily occurs.

The most important criticism to which my theory of pulmonary oedema has been subjected, is by Sahli, in a valuable paper published in 1885. The strongest points in his argument against the theory are that the radial pulse in cases of pulmonary oedema to which my explanation might be applied, does not indicate paralysis of the left ventricle, and that the anatomical condition is not one of hyperaemia. Both of these possible objections had occurred to me, and Sahli is in error in stating that my theory was promulgated without consideration on my part whether the pathological-anatomical condition of human oedematous lungs is one of hyperaemia.

I stated in my article that it seemed to me doubtful whether clinical methods could determine whether the assumed relative disproportion between the work of the two ventricles existed or not. In my judgment, Sahli is mistaken in supposing that the paralysis of the left ventricle must be almost complete in order that the degree of passive hyperaemia requisite for the

production of pulmonary oedema should ensue. As is well known, it is absolutely essential for the integrity of the circulation and the continuance of life, that each ventricle should pump into its artery the same quantity of blood in a given time. This is the central fact of the circulation, and is secured under normal conditions by regulatory mechanisms of the most perfect order. The disturbance implied by interference with this mechanism is profound, and hence, in accordance with my theory, pulmonary oedema is practically unknown in previously healthy persons. Let, however, this mechanism be so disturbed that at each systole, the right ventricle throws even a little more blood into the pulmonary artery than does the left ventricle into the aorta; then it will not be long before there is a large excess of blood in the pulmonary vessels. What is in the first instance essential is not the absolute force of either the right or of the left ventricle, but rather the relation between these. Hence I do not consider that the condition of the peripheral pulse affords satisfactory indication whether the heart is disturbed in the sense required by my theory.

The difficulty or impracticability of upsetting, in the case of healthy animals, the remarkable mechanism which coordinates the relative force of the two ventricles by an experimental procedure which stops short of a high degree of paralysis of the left ventricle, is doubtless what might be expected under these conditions, but it is reasonable to suppose that in those severe affections of human beings which are associated with general pulmonary oedema, this coordinating mechanism may be disturbed far more readily and without extreme grade of paralysis of the left ventricle. The experiment upon the rabbit, already cited in support of the theory, must be considered as only a crude and imperfect reproduction of the condition assumed to underlie the onset of pulmonary oedema in man.

Sahli contends that the pallor of many oedematous lungs proves that the oedema is not of a congestive type. He seems to have made no microscopical examination of such lungs. I describe in my article the microscopical characters of general pulmonary oedema in human beings, and there, it seems to me, show conclusively that the oedema is one usually associated with venous hyperaemia. Certainly the enormous distention of the capillaries, the large number of corpuscles in the serous transudate and the richness in albumin of this transudate, are features of congestive rather than of hydraemic or cachectic oedema. The color of dropsical tissues is an unsafe guide for judging their blood-contents, and, while in my experience, lungs which are the seat of general oedema, often enough show to the naked eye the evidences of hyperaemia, I have often been surprised to find, even in the paler lungs, by microscopical examination, marked hyperaemia and diapedesis of red corpuscles. Renant and others have made similar observations.

Löwit, in an experimental research published in 1893, reached the conclusion that congestive oedema of the lungs is the result of obstructed outflow of blood from the pulmonary veins associated with increased inflow of blood into the pulmonary artery. It is only through a misconception of my theory of disproportionate action of the two ventricles, that Löwit should find any conflict between his conclusion and the essence of this theory. Löwit's main contention, however, that rise of pressure in the pulmonary artery attends obstructed outflow from the pulmonary veins only when the supply of blood to the pulmonary artery is increased, is opposed by the results not only of his predecessors, but also of Grossmann and other experimenters. I agree also with Grossmann, in opposition to Löwit, that increased supply of blood to the pulmonary artery is not essential for the production of congestive oedema of the lungs, although it is a self-evident corollary of my theory, as was pointed out in my article, that given the requisite disproportion between the action of the two ventricles, the higher the pressure in the pulmonary artery, the more favorable are the conditions for the production of pulmonary oedema.

Incomprehensible to me, as indeed it has been to others, and entirely without experimental support, is the opinion expressed in a criticism of my theory by Jürgensen, that paralysis of the right ventricle leads to pulmonary hyperaemia and oedema of the lungs.

It is hardly necessary to state that such factors as changes in osmotic pressure, alterations in the capillary endothelium, interference with the absorption of lymph, which have become prominent in the later discussions of the causation of oedema may be utilized in the explanations of pulmonary oedema, as of congestive oedema elsewhere, but I find great difficulty in conceiving any of these factors alone to be the primary cause of acute general oedema of the lungs.

In one respect I am in agreement with Sahli; namely, that a larger number of cases of pulmonary oedema are referable to inflammatory changes in the vascular walls than is generally supposed. My opinion is based upon the results of the systematic bacteriological examinations which are made at all autopsies at the Johns Hopkins Hospital. Not only in irregular and localized oedemas, but also in not a few extensive and even general pulmonary oedemas, plate cultures from the lungs show numerous colonies of bacteria, most frequently streptococci and lanceolate micrococci, so numerous that they must have been in active growth in the lungs.

THE BEHAVIOUR OF THE RED BLOOD-CORPUSCLES WHEN SHAKEN WITH INDIFFERENT SUBSTANCES[1]

While the action of chemical reagents upon the red blood-corpuscles has been often studied, comparatively little attention has been given to the changes produced in the corpuscles by agents which act mechanically. As regards the effect of forcible compression of the red blood-corpuscles, Vintschgau observed that by pressing the cover-glass upon a drop of blood, sharp-bordered fragments of the red blood-corpuscles are produced. Another possible mode of acting mechanically upon the red blood-corpuscles and the one which we have adopted is to shake the blood with finely and coarsely granular insoluble substances. Although we at first undertook these experiments with reference to their bearing upon another theme, it was found that the results of these provisional experiments were not so simple or so easily obtained as had been anticipated, so that they seem to merit a separate communication.

Rollett[2] has already adopted the procedure of shaking the blood with insoluble substances, but from a chemical not from a mechanical point of view. He observed that by shaking the blood with certain insoluble substances oxyhaemoglobin is reduced to haemoglobin. Rollett supposed that after long-continued shaking some blood-corpuscles must be destroyed inasmuch as the red colour of the blood cannot be restored by shaking with air.

We at first adopted the simple method of shaking the blood in a test tube with iron-filings for ten to fifteen minutes. Although this seemed to cause a diminution in the number of red blood-corpuscles the results were not sufficiently clear and unmistakable, especially when undiluted blood was used. It is not necessary to mention here all of the other methods which were attempted, for all difficulties were overcome as soon as it became possible to shake the blood as long as it was wished. Through the kindness of Mr. Carl H. Schultz there was placed at our disposal in his manufactory of mineral waters a machine for shaking bottles. This machine, which could be kept in motion the whole day, possessed an apparatus on which several bottles could be fastened parallel to each other and shaken to and fro longitudinally. There were 180 excursions a minute, the length of each excursion was 39 cm., the velocity was therefore 1.17 M. per second. We

[1] S. J. Meltzer and W. H. Welch.
J. Physiol., Lond., 1884-85, V, 255-260.

[2] Rollett: Sitzgber. d. Wiener Akad. Math.-naturwis. Cl. LII, Abth. 2.

were thus enabled to shake the blood not only hours but days and weeks at a time. By shaking different bottles at the same time and under the same conditions it was possible to study the action of different substances as well as the action of the same substance according to the coarseness of its particles.

When it was not our object to observe the effect of varying the ratio between the quantity of the substance and that of the blood, we took 15 c.c. each of the substance and of the blood, either undiluted or diluted with physiological salt solution (0.6%). Bottles holding 100 c.c. were always employed, so that there was a column of air over the fluid to be shaken (in contrast with Rollett's experiments with exclusion of air). The fresh defibrinated blood of the ox was used. This is especially mentioned because according to Rollett the blood of different species of animals is reduced with varying degrees of rapidity.

In general it may be said that after shaking the blood for a considerable time with granular insoluble substances a period is reached when the blood attains the maximum degree of darkness in colour and all the red blood-corpuscles have disappeared.

Furthermore, the blood-corpuscles disappear the sooner; (*a*) the greater the specific gravity of the substance used, (*b*) the finer the particles of the substance, (*c*) the larger the quantity of the substance in proportion to that of the blood, and (*d*) the smaller the number of blood-corpuscles contained in the fluid, that is more rapidly in diluted blood than in undiluted blood.

The blood was shaken with fragments of pumice-stone, sand, iron, lead, copper, brass and quicksilver. Iron and brass were employed in varying degrees of fineness of the particles.[3] We also used with success lead-shot about 2 mm. in diameter. The longest time necessary for the disappearance of the red blood-corpuscles—nearly three days—was required by lead-shot on account of the coarseness of the particles, and by pumice-stone on account of the low specific gravity. The shortest time—7 to 8 hours—was required by quicksilver on account of its weight and the fineness of the particles into which it can be divided. Rollett[4] asserts that the reduction of oxyhaemoglobin takes place with silver much more slowly than with iron, and that quicksilver and platinum are without reducing power. For our

[3] Rollett in Hermann's Handb. d. Phys. Bd. IV, 1, p. 55, says: "Oxyhaemoglobin yields its loosely combined oxygen to reducing substances.....iron filings (Rollett), still better Ferrum hydrarg. reduct. (Ludwig and A. Schmidt) and is changed to reduced haemoglobin." The original article of Ludwig and Schmidt was not accessible to us. It is possible that the greater efficacy of ferrum reductum is due to the greater fineness of its particles. We found also in our experiments that reduced iron is more effective than iron filings. This was not, however, the case when the finest powder obtained by straining the substance was used.

[4] Rollett, *loc. cit.*

purpose, however, we have found quicksilver the most effective of all agents, so that in our further experiments we have used it exclusively.

In order to study the transitional stages before the complete disappearance of the red blood-corpuscles we have shaken for different periods of time—one hour, two hours, three hours, etc.—several bottles each containing 15 c.c. of blood and 15 c.c. of mercury. With the naked eye one can clearly follow the gradual change in colour. At the end of an hour the blood appears much darker in colour than the unshaken specimen. From hour to hour the shaken blood becomes darker and darker in colour, until at the end of about 7 hours it becomes absolutely black, and from that time on no further change can be observed. Microscopically no distinct change can be seen until the third hour. From that time on the red blood-corpuscles disappear more and more, those which remain seem to become somewhat paler while the intervening fluid becomes less clear and transparent. The diminution in number of the red blood-corpuscles continues for several hours, not, however with uniformity. The largest number of corpuscles disappear somewhat suddenly between the 5th and 6th hour. Up to this time the diminution is relatively small. The few corpuscles which remain after the main loss often resist destruction for a long time.

There can be no doubt that the cause of the disappearance of the red blood-corpuscles is a mechanical one. The reduction of haemoglobin which follows shaking the blood for a short time was interpreted by Rollett as a mechanical effect, although this view rested on a less firm basis than in our experiments, for he failed to obtain this reduction by the heaviest metals. In our experiments we have found that the result depended not upon the chemical constitution of the substances employed but upon their quantity, their specific gravity, and the fineness of their particles, all purely mechanical conditions.

In what way, however, the blood-corpuscles disappear and just what becomes of them we could not positively determine. It was to be expected that the blood-corpuscles by being shaken with finely divided indifferent substances either would be broken into fragments, as by pressure upon the cover-glass, or would lose their haemoglobin and be converted into stromata or shadows. We have diligently sought both for fragments and for shadows of the blood-corpuscles, but we have not been able to discover either, although in the course of our experiments, reagents were found capable of demonstrating the most invisible shadows. The destruction of the red blood-corpuscles under these circumstances appears therefore to be molecular and tolerably sudden. A certain commotion of the haemoglobin in the blood-corpuscles appears to precede their complete destruction. It has already been mentioned that before their disappearance the red blood-corpuscles lose some of their colouring matter. To this fact is to be added the following noteworthy

observation. If the blood be shaken with any of the substances mentioned for a period so short that no visible change in the blood has occurred, and then the blood be allowed to stand at rest, it will be found that at the end of 15 to 18 hours nearly all the red blood-corpuscles have completely lost their colouring matter, while the corpuscles in the control-specimen are still wholly intact. A shaking therefore of only short duration suffices to render less firm the combination between stroma and haemoglobin. It is perhaps only this loosening of the combination between haemoglobin and stroma and not the expulsion of the haemoglobin which is accomplished by the shaking. The complete separation of the haemoglobin from the corpuscle and its solution in the surrounding fluid occurs afterward. Continued shaking hastens but little, it may be, the separation of the haemoglobin from the blood-corpuscles; it causes apparently a molecular destruction of the blood-corpuscles before the haemoglobin has left them.

It may also be noted that all blood-corpuscles do not possess equal power of resistance (cohesion?). Mention has already been made of Rollett's observation that the reduction of haemoglobin takes place with varying rapidity in the blood of different species of animals. In our experiments it was found that the greater number of red blood-corpuscles disappeared at about the same time, while a small fraction disappeared either earlier or later. May not this be interpreted as in favour of a greater or less cohesive power in certain corpuscles in contrast with the average cohesive power of the majority of corpuscles? A similar supposition is made with reference to those corpuscles which resist for a long time the action of water.

We have also studied the effect produced by shaking with quick-silver blood to which various reagents have been added. The addition of concentrated solutions of common salt, sulphate of magnesium, sulphate of sodium, sulphate of zinc, acetate of lead and sugar has no appreciable influence upon the result as above described. On the other hand after the addition to the blood of solutions of pyrogallic acid, tannin, alcohol, chlorate of potash, nitrate of silver, and sulphate of copper, the red blood-corpuscles are unaffected by shaking, no matter how long this be continued. It is not necessary to describe here the action upon the red blood-corpuscles of the various reagents in the latter group. This has already been described by various investigators. We used strong alcohol, pyrogallic acid in 20% solution, tannin and sulphate of copper in 10%, chlorate of potash in 6.25% (1:16 the maximum of its solubility at the ordinary temperature) and nitrate of silver in 3% solution. Two parts of the solution were added to one part of the blood. As regards the formation of shadows, the blood-corpuscles are affected but little by the first three reagents and not at all by the last three. No matter how long the shaking be continued, the blood-corpuscles remain unaffected by it. The experiments were frequently repeated, always

with a control-specimen, and always with the same result. With some of these reagents (chlorate of potash, pyrogallic acid and nitrate of silver) we have shaken the blood over two weeks. The blood-corpuscles appeared as intact at the end as at the beginning of the experiment. It is hardly necessary to add that under these circumstances solution of the haemoglobin does not occur upon allowing the blood to stand after it has been shaken.

As no change was produced by shaking the blood for two weeks it did not seem necessary to continue the procedure any longer. The effect of these reagents does not seem to be merely an increase in the cohesion of the red blood-corpuscles. In fact sugar and sulphate of sodium are credited with the power of hardening the red blood-corpuscles,[5] and in our experiments these substances were without influence. The reagents of the active group must produce some change in the constitution of the red blood-corpuscles which renders them wholly insusceptible to such mechanical influences as we employed. The different substances of this group have as approximately common properties, (*a*) the power of coagulating albumen, and (*b*) the power of changing haemoglobin into meta-haemoglobin. We content ourselves merely with reference to these points, as the subject is not sufficiently matured to warrant fuller consideration.

In the endeavor to discover shadows of the red blood-corpuscles in the shaken blood we found the reagents customarily recommended little adapted for this purpose. These reagents themselves transform blood-corpuscles into shadows, and moreover they are of little service when the shadows are very pale and the fluid turbid. While the idea previously seems to have been to demonstrate the shadows by means of colouring agents (eosin, vesuvin, etc.), we have found that other reagents are more suitable. It would seem that all reagents which cause a coagulation of albumen are adapted to render visible the palest stromata. We have used successfully for this purpose picric acid (saturated solution), pyrogallic acid (20%), bichromate of potash (2%) tannin (10%), sulphate of copper (10%), nitrate of silver (3%), chlorate of potash (1 : 16) and diluted mineral acids. The stromata appear after the addition of these reagents in a few seconds as pale rings, except in the case of chlorate of potash, which makes them appear as bluish-white round discs. The clearest outlines are produced by picric acid, pyrogallic acid, chlorate of potash and nitrate of silver. The first two reagents are, however, not adapted for the study of normal blood, as they, like most of the other reagents, cause more or less separation of haemoglobin. On the other hand, nitrate of silver and chlorate of potash are admirable reagents for the purpose in view. If two parts of the reagent (of the before mentioned concentration) be mixed with one part of blood, then the shadows come plainly to view while the intact corpuscles remain unchanged.

[5] Joh. Müller: Hand. d. Physiol. Figuera, Ann. d. Chim. u. Phys. XL.

THE STRUCTURE OF WHITE THROMBI[1]

A year ago, upon an occasion similar to this, you had the pleasure of listening to Dr. J. Collins Warren's address upon the healing of arteries after ligature. As his researches were directed especially toward the later stages of the changes which follow injury of the bloodvessels, it will, perhaps, not be acceptable if I call your attention to the histological structure of those plugs which often constitute the earliest alteration following such injury.

While all that pertains to the subject of thrombosis is of importance, recent investigations have lent special interest to the study of the minute structure and the mode of formation of white thrombi.

Since Virchow's memorable publications[2] upon the subject of thrombosis, it has been generally believed that a thrombus is essentially a blood coagulum, and differs from an ordinary post-mortem clot only in the arrangement and the relative proportion of the constituent histological elements. The most important of the differences noted by Virchow are the characteristic lamination of thrombi, and their greater richness in white blood-corpuscles, and in granular material. These differences were believed to be sufficiently explained by the slow formation of thrombi from the circulating blood, in contrast with the rapid coagulation of blood at rest, and by secondary changes in the thrombus.

During the two decades following the publication of Virchow's researches on this subject, more attention was paid to the causes, to the effects, and to the metamorphoses of thrombi, more particularly to their so-called organization, than to the intimate structure of recently formed thrombi. Zahn's investigations of thrombosis, published in 1875, marked an epoch in the history of our subject.[3] Zahn had been preceded by Mantegazza,[4] who, in 1869, called attention to the rôle played by white blood-corpuscles in the formation of white thrombi, but the observations of the latter author had remained comparatively unknown.

Zahn emphasized the most important differences existing between thrombi formed from the blood in repose, the so-called red thrombi, and those

[1] Delivered before the Pathological Society of Philadelphia, April 28, 1887. Tr. Path. Soc., Phila., 1885-7, XIII, 281-300.

[2] Virchow: Gesammelte Abhandlungen. Frankfurt a. M., 1856.

[3] Zahn: Virchow's Archiv, 1875, Bd. 62, p. 81.

[4] Mantegazza: Gaz. med. Lombarda, 1869.

developed from circulating blood, viz., the white and the mixed thrombi. Whereas the former do not differ from an ordinary coagulum of blood, the latter, according to Zahn, originate from clumps of white corpuscles. Zahn observed microscopically in the mesenteric vessels of the living frog, the first formation of white thrombi out of white blood-corpuscles which accumulated in vessels at places which had been subjected to various injuries. The white corpuscles thus accumulated, if they were not detached by the circulation, rapidly disintegrated into a mass of granular material which Zahn considered to be granular fibrin. According to the widely accepted views of Zahn, therefore, a white thrombus at its inception consists essentially of white blood-corpuscles, which, after a short time, break up into a mass of granules identical with fibrin in their reactions.

The observations of Mantegazza and of Zahn were confirmed, in 1876, by Pitres,[5] who made corresponding observations of the living circulation in warm-blooded animals, whereas Zahn studied the circulation only in frogs. Pitres, however, did not, like Zahn, identify the granular material resulting from the disintegration of white blood-corpuscles with fibrin.

The rôle thus assigned to the white corpuscles in the formation of white thrombi certainly seemed to be at variance with Virchow's view that all thrombi are coagula. A reconciliation, however, was effected between the new observations and the old doctrine, chiefly through the investigations of Weigert.[6] This pathologist, adopting the views of A. Schmidt as to the part taken by the white corpuscles in the spontaneous coagulation of the blood, assigned to these corpuscles essentially the same rôle in white thrombi. The coagulation necrosis of leucocytes in thrombi is a process differing, according to Weigert, morphologically, but not in essence, from the dissolution of white corpuscles and the formation of fibrillated fibrin in the ordinary coagulation of the blood. White thrombi, therefore, continued to be regarded as in the main genuine coagula.

The first opposition to the views of Zahn came from Hayem,[7] who, in 1878, attempted to prove that the coagulation of fibrin is a function of the small bodies, called by him hæmatoblasts, and subsequently, by Bizzozero, blood plates, the name now generally adopted. Osler, who was among the first to observe the existence of human thrombi composed almost exclusively of blood plates (or plâques, as he, accepting the suggestion of Kemp, prefers

[5] Pitres: Arch. de Phys. norm. et path., 1876, p. 230.

[6] Weigert: Virchow's Archiv, Bd. 70, 1877, and Bd. 79, 1880. Fortschritte d. Medicin, 1883.

[7] Hayem: Recherches sur l'Anatomie norm. et path. du Sang. Paris, 1878. Comptes Rendus de l'Acad. d. Sc., 1882, 18 Juli.

to call them), has presented fully in the last series of Cartwright Lectures, the existing state of our knowledge concerning these bodies.[8] In 1882, Hayem published his observations on the structure of thrombi. He found that the thrombi which are formed in wounds of arteries are made up of blood plates.

A few months later Bizzozero[9] described, with much detail, both the fibrin-forming properties of the blood plates, and their presence as the essential and primary constituent of white thrombi, in these respects confirming the opinions of Hayem. Bizzozero was the first to study the formation of thrombi from blood plates in the living circulation, usuing for this purpose the mesentery of warm-blooded animals.

In the following year, Hlava.[10] working under Weigert's direction, was unable to confirm the views of Hayem, and of Bizzozero, and upheld the doctrine of Zahn and of Weigert, that white thrombi, in their earliest formation, consist mainly of leucocytes, which subsequently undergo coagulation necrosis.

Lubnitzky,[11] working under the direction of Langhans, published, in 1885, an interesting article, in which she claimed that the thrombi which are formed in arterial wounds, and which are the chief agent of nature in checking hemorrhage from this source, are composed primarily of blood plates. The blood plates, when thus accumulated, are, according to Lubnitzky, either identical with fibrin, or are quickly transformed into this substance.

The most thorough study hitherto made of the share taken by the blood plates in the formation of thrombi we owe to Eberth and Schimmelbusch.[12] These authors consider that sufficient proof of the existence of blood plates in the normal circulation is afforded by the observation of the plates in the circulating blood of the mesenteric vessels of dogs and rabbits examined under physiological salt solution, with high magnifying powers. In opposition to Hayem and to Bizzozero, they deny that the plates have any share in the coagulation of fibrin, which they regard rather as a kind of crystallization in the plasma. The plates, when removed from the natural conditions of their existence, rapidly undergo a metamorphosis, called by Eberth and Schimmelbusch viscous metamorphosis, and characterized especially by the

[8] Osler: On Certain Problems in the Physiology of the Blood Corpuscles. The Medical News, April 3, 10, 17, 1886.

[9] Bizzozero: Virchow's Archiv, 1882, Bd. 90, p. 261.

[10] Hlava: Arch. f. exp. Path. u. Pharm., 1883, Bd. 17, p. 392.

[11] Lubnitzky: Arch. f. exp. Path. u. Pharm., 1885, Bd. 19, p. 185.

[12] Eberth u. Schimmelbusch: Virchow's Archiv, 1885, Bd. 101; 1886, Bd. 103, Bd. 105.

sticking of the plates to each other and to foreign substances. Under normal conditions the plates circulate with the red corpuscles in the axial blood current, but they make their appearance in the plasmatic zone when the rapidity of the circulation is diminished. A moderate slowing of the blood current is attended by the formation of the so-called border zones, or accumulation of white corpuscles in the plasmatic current, whereas a greater diminution of the velocity of the stream is characterized by fewer leucocytes, and more plates in the peripheral current. Other irregularities of the circulation, such as the little eddies produced by obstacles or projections in the stream, or by dilatations of its bed, may likewise throw the plates from the axis into the periphery of the stream. Mere slowing of the circulation is not attended by the formation of thrombi. In order to observe this formation, Eberth and Schimmelbusch subjected the living mesenteric vessels, chiefly of dogs, to various mechanical and chemical injuries. They then observed under the microscope, in many, but not in all instances, the accumulation of blood plates at the seat of injury. Here the plates became adherent to each other and to the wall of the vessel, in consequence of their viscous metamorphosis, and thus formed plugs which were often subsequently washed away, but which sometimes increased in size so as to obstruct completely the lumen of the vessel. Red and white corpuscles may be included in the mass of plates, but their presence is purely accidental, and they are not to be regarded as an essential constituent of the primary thrombus.

As the result of their microscopical observations of the formation of thrombi in living bloodvessels of warm-blooded animals, Eberth and Schimmelbusch, therefore, conclude that white thrombi are at first composed essentially of blood plates, and that the chief factors in the causation of such thrombi are slowing of the circulation or other irregularities in the current, and the viscous metamorphosis of the blood plates. This metamorphosis may be the result of various influences, such as contact with injured or diseased vascular walls and with foreign substances.

These conclusions as to the structure of white thrombi at their earliest formation Eberth and Schimmelbusch confirmed by the microscopical examination of sections of thrombi produced artificially by various injuries to the vessels. In experimental thrombi produced by mechanical injury of the vessels, as by wounds or by temporary ligation, they failed to find any fibrillated fibrin, whereas, in thrombi formed around foreign bodies introduced into the lumen of a bloodvessel, they observed some fibrin, situated usually between masses of plates, although even here they think it probable that fibrin is absent in the very earliest stages. They also detected fibrin, but in less amount, in thrombi produced by cauterization of the vessel walls.

While the investigations of Eberth and Schimmelbusch confirm the view of Hayem, Bizzozero, and Lubnitzky that white thrombi are made up primarily of an accumulation of blood plates and not of leucocytes as Zahn had led us to believe,[13] they are opposed in one important particular to the conclusions of the latter group of authors. They deny that the blood plates are in any way concerned in the generation of fibrin or are transformed into a substance resembling fibrin. They, therefore, deny that a white thrombus is primarily a coagulum, as has hitherto been unquestionably believed. They regard the process of thrombosis, here under consideration, as a *conglutination* of bodies preexistent in the blood and not as a coagulation.

The arguments brought forward by the preceding investigators in favor of the existence of blood plates in large number in the normal circulation, convincing as they may seem, are nevertheless opposed by several observers. In view of the researches of Löwit,[14] this must for the present be considered as an open question.

Notwithstanding the brief period which has elapsed since the publication of Eberth and Schimmelbusch's researches upon thrombosis, their conclusions have already met with considerable opposition. It was hardly to be expected that such a radical overturning of accepted beliefs as these recent investigations involve should pass unchallenged.

While there is general agreement of opinion as to the important participation of blood plates in the composition of white thrombi, Eberth and Schimmelbusch's conception of the process of thrombosis as a conglutination of blood plates which have undergone a viscous metamorphosis is opposed by Hanau[15] on the ground that thrombi never have a viscid consistence. In support of the coagulative nature of the accumulation and metamorphoses of blood plates in white thrombi Hanau finds that plates as well as fibrin are transformed into hyaline, that a rim of hyaline forms around masses

[13] Since the delivery of this address Eberth and Schimmelbusch have published the results of their repetition of Zahn's experiments on the mesenteric vessels of frogs, and they find that fusiform corpuscles, which they consider to correspond to the mammalian blood plates, are the main constituents of white thrombi artificially produced in these animals. Vide Virchow's Archiv, Bd. 108, 1887. Löwit, on the other hand, regards these fusiform corpuscles as a variety of the white corpuscles and not as the analogues of blood plates, and he confirms the original statements of Zahn regarding the formation of white thrombi in frogs. Archiv f. exp. Path. u. Pharm., Bd. 23, 1887.

[14] Löwit: Beiträge z. Lehre von d. Blutgerinnung, Sitzb. d. k. Akad. d. Wiss. Wien, Bd. 89, Abth. III, u. Bd. 90, Abth. III, and Tageblatt d. 59ter Versaml Deutscher Naturforscher u. Aertze in Berlin, p. 306, 1886.

[15] Hanau: Fortschritte der Medicin, No. 3, 1887.

of plates, and that fibrin and plates often take the place one of the other in thrombi.

Weigert[16] protests even more vigorously against the effort of Eberth and Schimmelbusch to remove a large class of thrombi from the category of coagula. He has made a careful examination of human white thrombi, and points out especially their richness in fibrillated fibrin, which he demonstrates by a new staining process, and the abundance of leucocytes. He is unable to identify these anatomical thrombi with the experimental thrombi of Eberth and Schimmelbusch, and argues that until some reconciliation is effected between the two we should continue to base our conception of the nature of thrombi upon the study of the anatomical thrombi. Eberth and Schimmelbusch reply that their studies have been directed to the very earliest stages of the process of thrombosis, whereas the thrombi examined by Weigert belonged to subsequent metamorphoses.[17]

It is apparent from the foregoing review of recent investigations concerning the nature and structure of thrombi that unanimity of opinion on this subject has not been reached. There is general agreement that the blood plates play an important rôle in the early formation of many thrombi. Further investigations are needed to determine whether or not the plates are present in the perfectly normal circulation. For a proper understanding of the process of thrombosis it is important to determine whether or not the blood plates when accumulated to form a thrombus, are products of coagulation or subsequently undergo any metamorphosis which can be called coagulation. To determine this the gross characters of the plate thrombi, such as their color and consistence, will serve as important criteria, as has been pointed out by Weigert. It is, of course, of capital importance to learn whether the experimental white thrombi differ in their nature from human thrombi as seems to be intimated by Weigert. Before far-reaching conclusions can be drawn it is necessary to demonstrate the identity of the experimental and of the anatomical process of thrombosis. The microscopical study of human thrombi certainly seems opposed to the opinion that fibrin and leucocytes are unessential constituents of white thrombi. So constant and so abundant are these elements in post-mortem white thrombi that pathological anatomists will not readily admit that their presence is

[16] Weigert: Tageblatt der 59ter Versamml. Deutscher Naturforscher u. Aerzte in Berlin, p. 306, 1886.

[17] Schimmelbusch: Tageblatt d. 59ter Versamml. Deutscher Naturforscher in Berlin, p. 306, 1886. Eberth u. Schimmelbusch, Fortschritte der Medicin, No. 6, 1887. The paper of Löwit, on thrombosis, who is opposed in many important particulars to Eberth and Schimmelbusch, appeared after the delivery of this address. Arch. f. exp. Path. u. Pharmak. Bd. 22, 1887.

accidental or unessential to our conception of the nature of the thrombotic process.

In view of the fundamental importance of the question last touched upon, I have undertaken some investigations, first, as to the structure of human white thrombi; and second, as to the structure of thrombi produced experimentally in animals by mechanical injury of the bloodvessels. In the study of experimental thrombi I have directed my attention, in the first place, to their constitution at their earliest formation, and especially to the presence or absence of fibrin and of leucocytes at this period. It has seemed to me that a control with reference to the latter point of observations of Hayem, Bizzozero, Lubnitzky, and especially of Eberth and Schimmelbusch, notwithstanding the carefulness of these observations, might not be unwelcome. I have also studied the structure of experimental thrombi in their later stages. It is undoubtedly upon this point that our knowledge is the least complete, and it is to be expected that when this gap is filled up there will be less divergence of opinion as to the relation between the experimental and the human thrombi.

There will be found on exhibition under the microscopes sections of human marantic thrombi formed in various infectious and wasting diseases. Among others specimens are present from a case of widespread thrombosis following parturition. In this case there were fresh thrombi in the femoral and iliac veins, the inferior vena cava, the branches of the pulmonary artery, and the cerebral sinuses. The constituent elements of these thrombi are fibrillated fibrin, hyaline substance, red blood-corpuscles, leucocytes, fragmented nuclei, and granular material, of which a considerable part can be recognized as blood plates. The proportion of each of these elements in the composition of thrombi varies much in different cases, and it will be well to consider the share taken by each in the formation of thrombi.

There have been various opinions as to the nature of the granular material found in thrombi. Thus it has been regarded as produced by the breaking up of fibrillated fibrin (Virchow), as molecular or granular fibrin deposited as such from the blood—a view advocated by the majority of the older (Mandl, Addison) and by many recent authors—as granular fibrin formed by the necrosis of white corpuscles (Zahn), as the result of simple disintegration of white corpuscles (Pitres). At present, however, there can be no doubt that most of what has been called in thrombi granular fibrin, or the products of disintegration of leucocytes, consists of more or less altered blood plates. The acquisition of this knowledge is an important advance in pathology, whatever may be thought of the nature of the plates.

Blood plates seem to be a constant constituent of fresh marantic thrombi. The plates are often present in such thrombi in as recognizable form and

arrangement as in recent experimental thrombi. I have found thrombi, particularly some endocardial vegetations and parietal arterial thrombi, which at first glance appear to be composed of nothing but plates; but careful examination in such cases has always revealed the presence also of fibrillated fibrin and leucocytes. In the majority of cases, however, the part of the thrombus composed of plates is less extensive then that made up of fibrin and leucocytes. Frequently the plates are arranged in massed between which lie the fibrin and leucocytes. Such masses of plates, which are more frequently situated in the interior of the thrombus than adjacent to the vessel-wall, are often enveloped in a rim of dense material resembling fibrin. In sections stained with hæmatoxylin and eosin the areas occupied by the plates can often be recognized with a low power by the various manner in which the different constituents of the thrombus stain.

All of the granular material in thrombi cannot be demonstrated to be composed of plates, but it is probable that most of this formless granular matter is the result of the disintegration and metamorphosis of the plates. That some of the granules are produced by the disintegration of leucocytes is probable, for it is not difficult to demonstrate the destruction of leucocytes in many thrombi. I believe also that a granular precipitate in thrombi is sometimes caused by the hardening agents.

As regards fibrin, I can confirm the recent statements of Weigert as to the abundance and the constant presence of this substance in all marantic thrombi, except in softened foci where it is absent. Some thrombi are composed almost wholly of fibrin. The fibrin may assume various forms, such as the form of a delicate network, or of coarse interlacing or parallel bands, or of irregular masses, or of the so-called canalized fibrin. In sufficiently thin sections, such as can be made from specimens imbedded in paraffine, there is generally no difficulty in demonstrating in thrombi a rich network of fibrin even without the aid of Weigert's special stain for this purpose. Leaving out of question, therefore, the nature of the blood plates, there can be no doubt that human thrombi, as we meet them at autopsies, are genuine coagula, save in the foci of so-called puriform softening.

Hyaline material appears to be formed both out of fibrin and out of blood plates. Thrombi composed wholly of hyaline I have found in the liver of a cat in which a few drops of croton-oil had been injected, in hemorrhagic infarctions of the lungs, and in corroding ulcers of the duodenum and of the stomach. Hyaline is an inconstant constituent of thrombi, but its presence is not rare.

The accumulation of leucocytes in human white thrombi is so well known that there would be no necessity of emphasizing it here, were it not that the recent study of experimental thrombi has led to a revision of the doctrine

that white thrombi are composed primarily of masses of white blood-corpuscles. While it is true, as has already been mentioned, that there are thrombi which are composed almost entirely of plates, or of fibrin, or of hyaline, or of these substances in combination, this is the exception, and in the vast majority of fresh thrombi leucocytes are present in large number. In inflammatory thrombi leucocytes may be so abundant as to obscure all other constituents. Usually the leucocytes in marantic thrombi are not scattered uniformly throughout the thrombus, but are massed together in clumps; these clumps of leucocytes, unlike the clumps of plates, are generally pervaded by a network of fibrin.

It is not at all infrequent to find in old thrombi leucocytes and even masses of them which are devoid of nuclei. In undergoing this necrosis the nuclei of the white blood-corpuscles may be broken up into fragments which can be recognized as small irregular particles which assume a nuclear staining, but this nuclear fragmentation does not seem to be the rule. Generally the necrotic leucocytes can be recognized simply by their form, without any trace of nuclei.

Red corpuscles are present in variable numbers in marantic thrombi. They cannot be regarded as an essential constituent of the thrombus. I find in many marantic thrombi the so-called shadows of the red blood-corpuscles, which can be easily overlooked unless especial attention be given to searching for them.

In properly prepared sections it is not rare to find colonies of micrococci even in thrombi not connected with pyæmic processes, especially in marantic thrombi from cases of typhoid fever or other infectious diseases.

From the foregoing summary of the histological characters of human white thrombi, it is apparent that any satisfactory explanation of the process of thrombosis must account for the presence of blood plates, of fibrin, and of leucocytes, for these are essential constituents of thrombi. The valuable investigations by Eberth and Schimmelbusch of experimental thrombi have led them to regard the blood plates as the sole primary elements in these plugs. Further investigations are needed to determine the rôle played by fibrin and white blood-corpuscles in the formation of experimental thrombi.

My experiments upon the production of thrombi have been made mostly on dogs. The vessels selected have been the femoral artery, the femoral vein, and the jugular vein, in the majority of cases the femoral vessels. Various methods were employed to produce thrombi, such as the application of caustics, the introduction of foreign bodies, and various mechanical injuries. I have given the most attention to the thrombi resulting from mechanical injuries, for it is admitted by Eberth and Schimmelbusch that the thrombi following the application of caustics, and those formed around foreign sub-

stances, contain, in an early stage, if not at their beginning, fibrin as well as blood plates. These authors assert that "coagulation is a process which plays only a modest rôle in the circulating blood, whereas here the most prominent and frequent phenomenon is conglutination, which, indeed, is solely concerned in the practically most important form of thrombosis, viz., that following simple mechanical injury of the vessel-wall, in whatever way this may have been produced." [13]

The following two modes of producing mechanically thrombi have given good results. One method is to tie a stout ligature tightly and suddenly around the vessel and at once cut the ligature loose. In this way the intima and a part of the media are usually torn. It is only when great force is used that the vessel is ruptured. The ligature leaves a whitish ring around the vessel at the seat of its application. If, as often happens, the walls of the vessel remain stuck together after removal of the ligature, then moulding the vessel slightly between the fingers will restore the lumen, which now presents a fusiform dilatation at the seat of injury. The adventitia in this situation often becomes infiltrated with blood.

Another method which I have employed, is to push into a branch of the femoral artery or femoral vein one of the hooked instruments or gouges employed by dentists and called excavators, and then, after pressing the hooked extremity forward into the main trunk to scrape the inner wall of the vessel to any extent desired. The stem of the instrument, if necessary, can be filed down so as to render its introduction easier. After the withdrawal of the instrument the opened branch of the vessel is secured by two ligatures. Of the various shapes which the working extremities of these instruments possess, those with a small cup-shaped gouge bent at right angles to the handle (spoon excavator) I have found particularly suitable.

The animals experimented upon have been tied down and anæsthetized, usually with morphine and chloral, or morphine and ether, or morphine alone.

It is important, when the vessel is removed from the body, that four ligatures should be applied, two above and two below the seat of injury, and that any collateral branches included between the pairs of ligatures should also be tied. These ligatures should be applied with as little disturbance of the vessel as possible. If the vessel be cut out without the preliminary application of ligatures, the contents of the vessel are partly discharged, and in this way the thrombus may be lost or its position changed.

Various hardening fluids were employed, such as corrosive sublimate, alcohol, Müller's fluid, picric acid, osmic acid, and Flemming's solution.

[13] Eberth and Schimmelbusch. Virchow's Archiv, Bd. 105, p. 459.

Of these, warm saturated solutions of corrosive sublimate are decidedly the best. This fluid preserves the blood plates and other elements almost perfectly and admits satisfactory subsequent staining of the specimens.

The procedure adopted in hardening in corrosive sublimate is the following: A clear, saturated aqueous solution containing some undissolved sublimate at the bottom is heated to 40° C., and in this is suspended the specimen to be hardened. After a few minutes I have usually cut away the ligatures at the ends of the vessel, as there is now no danger of the escape of the contents. The vessel containing the sublimate solution and specimen is kept in a thermostat at a temperature of 40° for one to two hours. The specimen is then washed in water having a temperature of 40° and afterward placed in a mixture of half alcohol and half water, and kept in this mixture at a temperature of 40° for a number of hours, often over night. This prolonged washing is to remove crystals which otherwise are present in large number. Even after this treatment sometimes peculiar crystals are present, which, however, do not materially interfere with the study of the sections. The addition of a little iodine to the washing fluid, as suggested to me by Prof. Gaule, assists in removing the crystals. From the fifty per cent alcohol the specimen is transferred to strong, and finally to absolute alcohol. I have made use almost exclusively of paraffine as an imbedding medium, as much thinner sections can be obtained in this way than by imbedding in celloidine. Satisfactory results can be obtained by staining the specimens *en masse* in hæmatoxylin and in eosin, but, as a rule, the sections have been stained after causing them to adhere to the slide. When serial sections were desired, they were cut in the form of ribbons. Gaule's method of making the sections adhere to the slide by placing upon each section laid dry upon the slide a drop or two of forty or fifty per cent alcohol, and after ten minutes putting the slides in a thermostat at a temperature of 40° and keeping them there for two hours, is the simplest and best with which I am acquainted. After this treatment the sections are so firmly adherent that all the manipulations of staining and preparing the sections for mounting can be carried on without fear of their detachment. In sections stained with hæmatoxylin and eosin the plates have a violet tint, and when in masses can be readily recognized with a low power.

I wish first to direct your attention to the macroscopic and the microscopic appearances of fresh experimental plate thrombi. Such a thrombus may be conveniently produced by tying forcibly a coarse string around the femoral artery of a dog and then at once cutting the string loose in the manner already described. After the time desired for the production of the thrombus has elapsed, the injured part of the artery inclosed between

two pairs of ligatures is to be removed and the artery is to be carefully slit up with a pair of delicate scissors.

Let us examine an artery treated in this way which contains a thrombus formed within five minutes. There will be found, closely adherent to the torn inner wall of the vessel, a parietal thrombus which at this period does not usually extend in a longitudinal direction much beyond the ring of lacerated tissue. The thrombus can be readily distinguished by its color from the blood which envelops it and which can be washed away with salt solution. The thrombus projects irregularly into the lumen of the vessel, the projecting part being made up usually of round or irregular masses which are connected together.

The thrombus has a homogeneous, grayish, translucent appearance, comparable to particles of boiled sago, and resembling, therefore, the color of the Malpighian bodies in a waxy spleen. When bits of the thrombus are pressed into thin layers between the slide and the cover-glass they present a bluish transparency almost glass-like. The epithet hyaline can be appropriately applied to the naked-eye appearance of the thrombus.

The consistence of the thrombus is soft, the weight of the cover-glass sufficing to make bits of the thrombus spread out into thin layers. In attempting to tease apart portions of the thrombus, it is found that this does not break up into little granules, as would be the case if the blood plates which compose it had undergone no changes and were simply in apposition to each other; but, on the other hand, the thrombus possesses considerable cohesion, and in breaking it into fragments with teasing needles fine sticky threads can be drawn out a short distance which break apart, or, if the tension be removed, retract. Portions of the thrombus pressed between the fingers present a sticky, gelatinous consistence. In view of Hanau's objection, already mentioned, to Eberth and Schimmelbusch's designation of the change by which the plates adhere to each other as a viscous metamorphosis, it is to be emphasized that fresh plate thrombi have a somewhat viscid consistence, which becomes more marked in the course of an hour after the removal of the thrombus. I cannot, therefore, accept Hanau's objection, so far as this point is concerned, as valid.

If parts of the fresh thrombus be teased in physiological salt solution or in Bizzozero's methyl-violet salt solution, or in Hayem's solution, there will be seen masses of blood plates and a large number of free plates floating in the liquid. The plates appear as pale, well differentiated, round or somewhat irregular bodies varying in size, the average being about one-quarter the diameter of a red blood-corpuscle. Masses of plates resemble colonies of large micrococci. They can be made to assume feeble tints with a variety of coloring agents, but I have not been able to give them, in their fresh

state, a sharp, elective staining. In water the plates become paler and somewhat swollen; in very dilute acetic acid they become darker in color and more distinct, in strong acetic acid they disappear from view.

By tapping with a needle upon the cover-glass it can be seen that the individuals composing the masses of plates adhere to each other. Such masses may be readily flattened out and compressed. The plates, especially when in masses, may be drawn out lengthwise by currents of fluid or by pressure. The remarkable viscidity of the plates can be demonstrated by placing a bit of filter paper at the edge of the cover-glass and thus causing currents in the fluid which fail to draw along even the isolated plates.

In order to see the regular and characteristic appearance of the fresh plates when arranged in masses, it is necessary that they should not be subjected to any pressure. When masses of plates are compressed even by the weight of the cover-glass they often appear to be made up wholly or in part of pale lines instead of coarse granules. This appearance of lines or threads seems to be due to an elongation and coalescence of the plates. These lines are often arranged with considerable regularity. They might be mistaken for threads of fibrin. A similar appearance of threads produced by coalescence of the plates is sometimes seen in hardened specimens where the threads are often varicose. Whether this appearance is due to the action of the hardening agent or to some other influence, such as the force of the circulating blood, must be left unsettled.

Although the plates make up the great mass of the thrombus leucocytes are present even at this early stage (during the first five minutes), and rapidly increase in number, so that at the end of half an hour the thrombus usually contains them in abundance. My investigations have not led me to assign so insignificant a rôle to the leucocytes in experimental thrombi as is done by Eberth and Schimmelbusch. I agree with these authors in finding that thrombi produced mechanically in the manner mentioned consist in their inception essentially of blood plates. At the end of five minutes the leucocytes may be so scanty as not to attract attention. Usually, however, by this time clumps of leucocytes as well as scattered leucocytes are present here and there in the thrombus, and, as already mentioned, their number continues to increase. I have found them at the end of six hours, in mechanical thrombi, as numerous as in many human marantic thrombi. It is true that much diversity exists as regards the number of leucocytes even in thrombi of the same age, still it is the rule that white corpuscles, while they do not collect so rapidly or in such number as the blood plates, do accumulate and form a constituent part of experimental mechanical thrombi. In order to study the situation of the leucocytes sections of hardened specimens are necessary, but portions of

fresh thrombi teased apart and treated with dilute acetic acid are favorable for ascertaining their number.

In searching for fibrin in fresh thrombi, it is important not to mistake for fibrin the threads produced by compression of the clumps of plates in the manner already mentioned. If these flattened-out masses of plates be washed with water, or, better still, with dilute Lugol's solution, there may be produced an appearance of interlacing and of parallel threads, which bear considerable resemblance to fibrin, but which are paler and which do not project beyond the margins of the clumps. Unmistakable fibrin in the form of fibrils, however, is to be found in experimental mechanical thrombi, but, so far as my observations go, not in the earliest stage of their formation. I have found fibrin in thrombi at the end of five minutes; frequently at the end of fifteen minutes, and usually at the end of half an hour. Fibrin is often found in so much larger amount in the fresh thrombi than in sections of the hardened thrombi that it is probable that it is formed in part after the removal of the vessel. As will be mentioned subsequently, fibrin can be demonstrated, also, in the hardened specimens, although not in the youngest thrombi. I am not able, therefore, to agree with Eberth and Schimmelbusch in denying altogether the presence of fibrillated fibrin in experimental thrombi produced by mechanical injury of the vessel, although our observations are in accord regarding the youngest thrombi.

I have dwelt thus at length upon the appearances of the fresh experimental thrombi because I have been unable to find any description of these appearances. With the exception of a brief allusion by Lubnitzky to sections of frozen thrombi, all the previous observations seem to have been made either upon the mode of formation of these thrombi in the living circulation or upon sections of hardened specimens. As has been suggested by Weigert, and as is apparent from the foregoing description, a knowledge of the gross appearances of the plate thrombi is important in forming a judgment as to their nature. Sections are, of course, necessary to enable us to study more carefully the constituents of the thrombi and particularly their arrangement.

As already mentioned, I have made use chiefly of corrosive sublimate as a hardening agent, of paraffine as an imbedding medium, and of hæmatoxylin and eosin as staining agents.[19] In sections prepared in this way the plates can be seen with a distinctness and uniformity in shape that leave nothing to be desired. I am led to believe that most of the appearances

[19] Since the delivery of this address I have also made use of Weigert's new method of staining fibrin on specimens hardened in alcohol.

which have been described as changes in the plates occurring during the first half hour (Lubnitzky and others), are due to imperfect methods of hardening. Eberth and Schimmelbusch recognize this fact in their preparations.

Plate thrombi can be recognized in sections as well as in the fresh state by their peculiar translucence. I can only confirm the statments of Eberth and Schimmelbusch as to the composition of the experimental thrombi in their earliest formation. They are made up of blood plates. To the torn and partly detached internal elastic lamella as well as to the lacerated media masses of plates are attached, which extend into the lumen of the vessel. Upon sections clumps of plates often appear to lie free in the lumen surrounded by blood, but subsequent sections show the connection of these clumps with others or with parts of the vascular wall. The thrombus often forms a complete ring around the torn inner wall of the vessel. Not every injured part of the internal wall of the vessel is covered with a thrombus. One is often surprised to find such parts, even when severely lacerated, entirely free from thrombi or with only a thin layer of plates, recognized with a high magnifying power. The mass of plates composing the thrombus does not always appear uniform, but often, especially in older thrombi, there are lighted and darker portions, due apparently to greater density in the number of plates in some places than in others.

An appearance mentioned by Hanau is of interest, namely, the presence of a dark band around the margin of masses or islands of plates. Similar dense lines can often be seen running irregularly through sections of the thrombus. These denser bands have been interpreted as hyaline or as fibrin. It is not easy to determine their exact nature. They look like fibrin in many cases, but it is possible that they are produced by coalescence of the plates as the result of pressure or traction from the circulating blood in a manner similar to the lines which can be artificially produced in masses of fresh plates by pressure in the manner already described. Plates are not confined to the interior of the vessel, but when the internal elastic lamella and the media have been ruptured they often find their way in masses into the layers of the torn media or even into the adventitia. It is interesting to note the absence of any transition, as a rule, between the thrombus and the blood. The plates are just as dense usually at the margin of the thrombus as in the interior, and immediately adjacent to the peripheral plates come the red blood-corpuscles where the blood was still circulating before the vessel was removed.

Leucocytes are not generally present in large number in thrombi during the first five minutes of their formation. If serial sections be examined, here and there clumps of white corpuscles can be found even at this early stage. There are often more white corpuscles mingled with the plate masses

in the coats of the vessel than in the thrombus proper. Leucocytes, scanty at first, continue to accumulate in larger and larger number, until they form a prominent part of the thrombus. I have found them in great abundance at the end of half an hour, although sometimes at this period their number is small. The leucocytes are generally arranged in clumps between masses of plates, although some are usually scattered in among the plates. It is probable that the clumps of leucocytes are deposited in that form directly from the circulating blood. There is reason to believe that the leucocytes may also wander into the thrombus, for in sublimate specimens elongated nuclei, such as are seen in undoubtedly wandering white corpuscles in the wall of the vessel, can also be occasionally detected in the masses of plates. Moreover, the number of leucocytes within these masses increases with time. In successfully prepared sections the protoplasm can be seen around the nuclei of the white corpuscles, so that I do not agree with Lubnitzky that this has become merged with the plates. Sometimes the leucocytes are surrounded with a clear zone as if they lay in little spaces within the mass of plates, but this appearance is probably due to the action of the hardening fluid. Both uninuclear and multinuclear white corpuscles are present, but the latter predominate, and in the later stages many of the nuclei often appear much broken up.

Although I have not seen any appearances which indicate that the white corpuscles disintegrate into granules, still non-nucleated white corpuscles can sometimes be detected, so that a necrosis or death of these corpuscles may take place within the thrombus. This does not seem, however, to be a common or extensive process.

As has already been stated, fibrillated fibrin is present in experimental thrombi produced by mechanical injury of the vessel. It is not, however, found in the youngest thrombi, and the date of its appearance varies in different cases. I have found it in hardened specimens at the end of five minutes, but this is exceptional. It is not uncommon to find it at the end of fifteen minutes. I exhibit under the microscope sections of a thrombus of one-half hour's duration, in which there is a considerable amount of distinct fibrillated fibrin. The amount of fibrin increases with the age of the thrombus, and in thrombi of twenty-four hours' duration fibrin makes up usually a large part of the thrombus.

The fibrin appears in islands and bands between the masses of plates, and often extends in coarse fibres into the surrounding blood. The net-work is usually coarse, but fine threads are also present. After a time the clumps of white and of red corpuscles included in the thrombus are pervaded by a net-work of fibrin, whereas, this is absent in the dense clumps of plates. I have the impression that there is, in general, a relation between the number of

leucocytes and the amount of fibrin, although the former appear in considerable quantity before the latter.

Inasmuch as in older thrombi (twenty-four to forty-eight hours) fibrin and leucocytes compose a large part of the thrombus, whereas, at its inception the thrombus is made up almost entirely of blood plates, one is tempted to believe that the plates may be transformed into fibrin, but of this transformation I can bring no positive proof. The plate-masses, after a time, lose their regular granular appearance and appear darker in color and more homogeneous, but typical plates may be found in large number in thrombi forty-eight hours old.

It is apparent from the foregoing description, that experimental thrombi acquire with time all of the characteristics of human thrombi. The suspicion which has been raised that they represent a distinct class of thrombi, from the study of which we can draw no conclusion as to the formation of human thrombi, is unjustifiable. It is another question whether we are to suppose that all human white thrombi are formed in the manner described. Although I have not succeeded in producing permanent leucocytic thrombi experimentally, still there is every reason to believe that some human thrombi are composed from the beginning essentially of leucocytes. In observations which I have made recently for another purpose, of the living circulation in the mesentery of dogs, I have observed the formation of small parietal thrombi composed of white corpuscles, but these have invariably been washed away after a short time.

We may, it seems to me, think of the mode of formation of the experimental thrombi, which we have studied, and doubtless also of many human thrombi as follows: Given suitable conditions, such as alteration of the vessel wall, slowing and irregularity of the circulation, the first constituents of the thrombus to accumulate are the blood plates. But although the plates collect at first in larger number and more rapidly, the leucocytes do not long remain absent, and in the course of time they are present in such quantity that they must be considered an essental constituent of the completed thrombus. At first the conditions for the coagulation of fibrin are not present, but with the increasing accumulation of leucocytes these conditions appear and fibrillated fibrin is deposited. It is in harmony with the current ideas concerning the cause of the coagulation of fibrin, to suppose that at first the fibrin ferment is absent, and that this is subsequently furnished by the leucocytes. The absence of fibrin in the early thrombi composed wholly of plates, is an argument additional to the evidence brought forward by Löwit and others, that the plates do not furnish the fibrin ferment. It is apparently only after the leucocytes have been included for a time in the thrombus that they die or undergo some alteration in their constitution

which leads to the formation of the fibrin ferment. The final result is a plug composed of plates, leucocytes, and fibrin, and included red blood-corpuscles.

It seems to me an error to base our conception of the nature of a thrombus exclusively upon the constitution of the thrombus in its inception. While admitting that the thrombus is at first composed wholly of blood plates, we do not, as a matter of fact, meet with human thrombi in this early stage, or at least, only under exceptional circumstances. Our ideas as to the constitution of thrombi are based upon the examinations of the completed plugs which contain fibrin and leucocytes as well as plates. The study of the experimental thrombi enables us to form a clearer conception of the mode of formation of the thrombus, but does not necessitate any radical change in our ideas as to what constitutes a thrombus.

The question as to whether a thrombus is a coagulum or not, is, of course, open to discussion only regarding the plate thrombi in their earliest formation. Whether or not we are to regard the plate thrombi before fibrin has made its appearance as coagula, is a question which is not likely to be settled until we acquire more definite information as to the origin and nature of the blood plates. There is nothing in the gross appearances of these plate thrombi which would prevent us from considering them as soft, gelatinous coagula. Wooldridge, Löwit, and others believe that the plates are allied to fibrin but are not identical with it. I purposely avoid entering into any discussion here as to their existence in the normal circulation, for this is a point which must still be regarded as *sub judice,* and which is not likely to be settled by the experimental study of thrombi.

The attempt of Eberth and Schimmelbusch to draw a sharp distinction between thrombi formed by conglutination and thrombi formed by coagulation, seems to me unwarranted. In the first place the process which they designate as conglutination may be, so far as we at present know, a form of coagulation. In the second place, whatever we may think as to the nature of the process of conglutination, the preceding investigations have demonstrated the transformation of conglutionation thrombi into undoubted coagulation thrombi.

As regards the relation between changes in the walls of the vessels and thrombosis, I have reached the same conclusion as that expressed by von Recklinghausen, Eberth and Schimmelbusch, and others, that Cohnheim's views on this point were too exclusive. It is possible to produce experimentally severe injury of the internal coats of bloodvessels without any resulting thrombus. Among many positive results I have also in my notes the records of not a few negative results which have followed injury of the walls of the vessels by caustics, by forcible application of rough clamps, by scraping the interior of the vessel, etc. As is urged by these writers as well

as by Weigert and others, slowing of the circulation and irregularities of the circulation produced by abnormalities in the lumen of the bloodvessels, are factors no less important in the production of thrombi than alterations in the vessel walls.

There is much which speaks for the correctness of the view advocated by Köhler, Hanau, and others, that some thrombi are caused by fermentative changes in the blood. Cases such as the one already mentioned, of extensive thrombosis of a large number of the bloodvessels throughout the body, are most naturally interpreted as examples of fermentation thrombosis.

HEMORRHAGIC INFARCTION[1]

Of the various aspects of the subject of hemorrhagic infarction, I have selected for my contribution to this discussion that which relates to the mechanism by which the hemorrhage is produced in the infarction.

Together with Dr. F. P. Mall, Fellow in Pathology of the Johns Hopkins University, I have undertaken some experiments in order, if possible, to be able to form an independent and positive judgment as to some of the unsettled questions which pertain to hemorrhagic infarction. It seemed to me hardly worth while to present to an audience of this character, merely a critical review of the many opinions which have been and are held as to the mode of production of hemorrhagic infarction.

Before communicating the results of our experiments, I will call your attention to the history of opinion concerning the nature of hemorrhagic infarction, in order that we may understand the present aspect of the subject.

The first clear anatomical description of hemorrhagic infarction was given by Laennec,[2] in 1819, under the name of pulmonary apoplexy. He seems to have regarded the condition as analogous to cerebral hemorrhage, but he expressed no positive opinion as to the causation.

After Laennec, Bouillaud,[3] Cruveilhier,[4] and several other noted the presence of coagula in the arteries and veins adjacent to hemorrhagic infarctions, but, in accordance with the pathological views of that time, they interpreted these coagula as evidence of phlebitis. This gave origin to the doctrine, advocated especially by Bochdalek,[5] that hemorrhagic infarctions are inflammatory in their nature and due to a primary capillary phlebitis.

Rokitansky, in the first edition of his "Pathological Anatomy," also attributed the origin of hemorrhagic infarction to capillary thrombosis, but, in conformity with the humoral pathology of the Vienna school, he regarded this thrombosis of the capillaries as referable not to inflammation but to a change in the constitution of the blood.[6]

[1] Delivered before the Association of American Physicians, Army Medical Museum, Washington, D. C., June 2, 1887.

Tr. Ass. Am. Physicians, Phila., 1887, II, 121-132.

[2] Laennec: De l'Auscultation Médiate, t. II, p. 41. Paris, 1819.

[3] Bouillaud: Arch. gén., 1826, t. XII, p. 392.

[4] Cruveilhier: Anat. Path., livr. III.

[5] Bochdalek: Prager Vierteljahrsschrift, 1846, Bd. IX.

[6] Rokitansky: Handb. d. Path. Anat., Bd. II, p. 680 et seq., Wien, 1844. Bd. I, p. 243, Wien, 1846.

Virchow,[7] by his memorable articles on thrombosis and embolism, published between 1846 and 1856, overthrew phlebitis from the dominant rôle in pathology which it had assumed through the teachings of Cruveilhier, and he introduced and established upon a firm basis the doctrine of embolism. He did not, however, reach any positive conclusion as to the nature and mode of production of hemorrhagic infarction. In his earlier writings he was inclined to regard the ante-mortem coagula occluding arteries leading to pulmonary hemorrhagic infarctions as secondary to the infarction and not concerned in its causation. This view was based chiefly upon his failure to produce hemorrhagic infarction experimentally by injecting into the blood emboli which lodged in branches of the pulmonary artery.

Virchow subsequently became doubtful as to the secondary nature of the plugs occluding the arteries leading to infarctions by the observation of cases of hemorrhagic infarction of the intestine in connection with embolism of the superior mesenteric artery. In an article published in 1852, reporting a case of embolism of the superior mesenteric artery, he suggested as possibilities most of the explanations which have since been advanced to account for the apparently paradoxical phenomenon that the occlusion of an artery is followed by hyperæmia and hemorrhage in the region supplied by this artery. He laid especial emphasis upon changes in the vascular wall as the result of prolonged ischæmia and upon increased pressure in the collateral vessels. He also dwelt upon irregularities in the circulation leading to stasis in some of the open vessels of the district whose artery is occluded. In another connection, when treating of ischæmia, Virchow calls attention to the possibility of a regurgitant flow of blood from the veins when the corresponding arteries are obstructed.[8] Virchow's chief motive in adducing changes in the walls of the bloodvessels as an essential factor in the causation of hemorrhagic infarction is the apparent impossibility of explaining the occurrence of the hemorrhage on purely mechanical grounds.

Notwithstanding the cautious manner in which Virchow expressed himself upon the relation between embolism and hemorrhagic infarction, it has been accepted by nearly all subsequent writers that obstruction of an artery may lead to hemorrhagic infarction in the region supplied by that artery, provided suitable conditions in the collateral circulation exist

[7] Virchow: Gesammelte Abhandlungen, 1856.

[8] Virchow: Handb. d. spec. Path. u. Ther., Bd. I, p. 127. Erlangen, 1857. It is true, as pointed out by Mögling (Ziegler u. Nauwerck's Beiträge z. Path. Anat., Bd. 1, p. 145. Jena, 1886), that Virchow does not apply this factor to the explanation of the production of hemorrhagic infarction, but it is apparent that the reasoning which he employs to explain venous regurgitation in partial anæmia applies to the condition present when hemorrhagic infarction follows arterial obstruction.

The first to apply directly to the explanation of hemorrhagic infarction a regurgitant flow of blood through the veins of the district the artery of which is obstructed, was B. Cohn.[9] in 1856. This view, however, he subsequently abandoned [10] on the ground of experiments, which, nearly twenty years afterward, were repeated by Litten. Cohn found that not only do hyperæmia and hemorrhagic infarction occur when both artery and vein of a part are tied, but the hyperæmia is more intense than when the artery alone is ligated. Moreover, when all connection of a part with the circulation, except through the vein, is cut off, no hemorrhage follows. Cohn, in his later work, regarded most hemorrahgic infarctions as referable essentially to capillary obstruction, and, as a rule, not capable of production merely by occlusion of a main artery. He did not separate infarction, particularly renal and pulmonary infarctions, clearly from inflammation, an error into which Panum also fell.[11]

Regurgitation of venous blood was accepted by Beckmann [12] as the explanation of hemorrhagic infarction of the intestine following embolism of the superior mesenteric artery. He refers to the statments upon this point of Virchow and of Cohn, and says that it is difficult to conceive that the blood which produces the uniform hemorrhagic extravasation over nearly the whole extent of the small intestine can come from the distant arterial anastomoses. To Beckmann belongs the credit of pointing out that most of the infarctions of the kidney are from the beginning pale and unattended with much hemorrhage.[13]

Blessig,[14] in an experimental work on changes in the kidney following ligation of the renal artery, performed under Virchow's direction, came to the conclusion that obstruction of an artery is followed by hemorrhagic infarction only when the corresponding vein is likewise occluded. It is noteworthy that he observed hemorrhagic extravasation in the kidney after ligation of both renal artery and vein.

An epoch in the history of our subjects is marked by the publication, in 1872, of Cohnheim's "Investigations Concerning the Embolic Processes."[15] Cohnheim studied microscopically, in the tongue of curarized frogs, the process of formation of hemorrhagic infarctions produced by artificial emboli which, after introduction into the aorta, lodged in branches

[9] B. Cohn: De Embolia ejusque sequelis. Diss., 1856.
[10] B. Cohn: Klinik d. embolischen gefässkrankh. Berlin, 1860.
[11] Panum: Virchow's Archiv, 1862, Bd. 25, p. 433.
[12] Beckmann: Virchow's Archiv, 1858, Bd. 13, p. 504.
[13] Ibid., op. cit., 1861, Bd. 20, p. 219.
[14] Blessig: Virchow's Archiv, 1859, Bd. 16, p. 120.
[15] Cohnheim: Untersuchungen über die embolischen Processe. Berlin, 1872.

of the lingual arteries. He reached the conclusions that the blood which produces the infarction is derived by regurgitant flow from the veins, that the hemorrhage occurs by diapedesis, and that the diapedesis is the result of some molecular alteration in the vascular walls deprived of their normal circulation. The hemorrhage occurs some time after the embolic occlusion of the artery. In this article Cohnheim also considers the peculiarities of the circulation in the organs which are most frequently the seat of infarction, and thereby laid down his doctrine of terminal arteries (endarterien)—that is, arteries the branches of which do not anastomose with each other.

Although Cohnheim made no attempt to reconcile his views with the opposing conclusions reached experimentally by Cohn and Blessig, nevertheless the authority of his name, the clear and admirable presentation of his experiments, the inherent reasonableness of his views, and the fact that they were deduced from actual observation under the microscope, combined to win general acceptance for Cohnheim's explanation of hemorrhagic infarction.

This explanation, however, did not long remain unchallenged, for in the year following Cohnheim's publication, Zielonko,[16] who worked under von Recklinghausen's direction, reached a different conclusion as to the causation of hemorrhages following arterial obstruction. Zielonko's observations were upon the web of the frog's foot. The main points in Zielonko's conclusions which interest us, are that the blood which produces the hemorrhages after obstruction of an artery, comes from the collateral vessels and not by a reflux from the veins, and that the hemorrhage is at least quite as much the result of stasis in the capillaries, and consequently increased pressure, as of changes in the vascular walls. A regurgitant flow of blood in the veins may occur, but this does not extend so far back as the capillaries, and has no share in the formation of the stases.

Similar results were obtained by Kossuchin,[17] who worked under Afanassiew's direction, and published his article in 1876. He repeated Cohnheim's experiments upon the frog's tongue. He was unable to observe reflux of blood from the veins into the capillaries belonging to the obstructed arteries, and he attributes the hyperæmia of the district whose artery is occluded chiefly to collateral fluxion. Hemorrhages occur by diapedesis only in the periphery of the embolized area and in the surrounding zone of collateral hyperæmia; at a later period, when necrosis sets in, hemorrhages occur throughout the embolized area, and are due probably to necrosis

[16] Zielonko: Virchow's Archiv, 1873, Bd. 57, p. 436.

[17] Kossuchin: Virchow's Archiv, 1876, Bd. 67, p. 449.

of the vessel walls. The early hemorrhages occur especially from capillaries in the condition of stasis, or adjacent to such stases, and are probably referable to increased blood pressure.

The careful observations of Zielonko and Kossuchin seem to have had little or no influence in preventing the general acceptance of Cohnheim's teachings. On the other hand, the more pointed attack of Litten[18] upon Cohnheim's doctrine has had greater influence upon the current views concerning the production of hemorrhagic infarction. Litten concludes that the hyperæmia and hemorrhage which follow ligation of the renal artery cannot be due to a regurgitant flow of blood in the renal vein, because the same or an even greater hyperæmia follows when both artery and vein are ligated, and no such result occurs if all connection of the kidney with the circulation, save through the renal vein, be cut off. The only possible source for the increased supply of blood is the collateral circulation. Similar experiments were made upon the lung and the spleen. Litten's experiments upon this point are essentially a repetition of those performed twenty years previously, with the same results, by Cohn. Of Cohn's manifold experiments upon the kidney, spleen, and intestine, to disprove the agency of regurgitation of venous blood in the causation of hemorrhagic infarction, Litten seems to have been ignorant, for they are not mentioned in his article. Litten also denies the efficacy of a second factor, which Virchow and Cohnheim had adduced to explain the occurrence of hemorrhagic infarction, namely, changes in the walls of the vessels produced by prolonged ischæmia. This denial is based first upon the fact that hyperæmia and diapedesis begin in a very short time after ligation of the renal artery, and, secondly, upon the absence of any hemorrhage which can possibly be attributed to changes in the vascular walls, in cases when the circulation has been reestablished in the kidney of the rabbit after its cessation for three or four hours. The same conclusions had been previously drawn by Kossuchin from experiments of the same nature made upon frogs.

Von Recklinghausen,[19] in an admirable chapter upon thrombosis and embolism, has called attention to a new factor in the causation of hemorrhagic infarction, namely, hyaline thrombosis of the capillaries. He has observed hyaline thrombi in the capillaries in all hemorrhagic infarctions of the lung examined in recent years, as well as in hemorrhagic infarctions of the spleen. The obstruction to the circulation produced by these thrombi

[18] Litten: Zeitschrift f. klin. Med., Bd. 1, p. 131.

[19] Von Recklinghausen: Handb. d. Allg. Path. d. Kreislaufs u. d. Ernährung, p. 160. Stuttgart, 1883.

causes, he believes, a rise in pressure and hemorrhage. The blood enters from the collateral channels.

This review of the history of opinion concerning hemorrhagic infarction makes it evident that there is still much to explain in the causation of this condition, and that there is abundant opportunity for further experimental work.

The experiments of Dr. Mall and myself relate to hemorrhagic infarction of the intestine, and were performed almost wholly upon dogs. The intestine offers many advantages for the experimental study of hemorrhagic infarction. It is easy to produce infarction in this situation, whereas it is difficult to produce hemorrhagic infarction of the lung artificially. The circulation of blood in the spleen is of so peculiar a nature that this organ is less adapted to our purpose than the intestine. Infarction of the kidney in man is usually a white infarction, with only a margin of extravasated blood. As is well known, occlusion of the superior mesenteric artery in man is followed by hemorrhagic infarction extending throughout nearly the whole length of the small intestine, and even into the upper part of the large intestine.

In the mesentery the condition of the circulation can be modified in many ways. The branches of the superior mesenteric artery anastomose freely, forming in the dog only one row of arches, from the summits of which branches are given off which enter the walls of the intestine. It is possible to convert any one of these main arteries into a terminal artery. The collateral circulation can be limited to any extent desired. The intestine offers the advantage that it is easy to look over its whole extent and determine the exact situation and character of an infarction.

Of importance is the high pressure in the veins leading from the intestine. The blood pressure in the mesenteric and portal veins is higher than in any portion of the venous system. We have found the pressure in the superior mesenteric vein equal to from 30 to 50 mm. of mercury. If regurgitation of blood from the veins is a factor in the production of hemorrhagic infarction, it should be apparent here.

If the superior mesenteric artery be ligated near its origin, there follows an intense hemorrhagic infarction which begins about five or six hours after the ligation, and increases in intensity until it reaches its maximum about seven or eight hours after the obstruction was produced. If the animal be now killed, it is found that the hemorrhagic infarction begins abruptly with a sharp line of demarcation in the lower part of the duodenum. It reaches its greatest intensity within an inch or two of its beginning, and extends throughout the whole length of the small intestine into the colon, where it gradually diminishes in intensity, but still ends somewhat abruptly.

The hyperæmia and hemorrhage begin in the mucous membrane, and are more intense there than in any of the other coats. The mucous membrane is of a dark red, almost black color. The submucous coat also becomes infiltrated with blood, but the muscular coat is much prone to hemorrhage. The lumen of the intestine contains much dark blood mixed with mucus. Upon microscopical examination the capillaries and veins, particularly of the mucosa, are engorged with blood, and there is extravasation of blood into the tissues.

The first point which we wished to settle is the source of the blood which causes the hyperæmia and hemorrhage after ligation of the superior mesenteric artery. This blood must come either from the collateral arterial and capillary anastomoses or by a regurgitant flow from the veins. The collateral anastomosis above is with the pancreatico-duodenal artery, that below with the inferior mesenteric artery.

In order to determine whether a regurgitant flow of blood from the veins is the source, we ligated the superior mesenteric vein coincidently with ligation of the artery, and found that the infarction, instead of diminishing in intensity, became more marked, and was established at an earlier period. The same results were obtained by ligation of the superior and inferior mesenteric veins, and by ligation of the portal vein at the same time, with that of the superior mesenteric artery. It seemed, therefore, certain that a regurgitant flow of blood from the veins is not the cause of the infarction. In order to remove all doubt, we isolated the intestine from all its connections with the circulation, except through the superior mesenteric vein. And, although we convinced ourselves that no thrombosis had occurred in this vein, there resulted no hyperæmia or hemorrhage in the intestine. We have repeated this experiment with a loop of intestine, and always with the same result, death of the part, but no hemorrhagic infarction. It will be remembered that the pressure in the veins is high, so that if a regurgitant flow of blood in the veins is a factor, it should certainly be manifest here.

In order to determine to what extent the collateral circulation may be cut off, and still hemorrhagic infarction follow, we ligated the superior mesenteric artery, cœliac axis, and portal vein, and in another series of experiments, in addition to the ligation of these vessels, we ligated the duodenum and the ileum, not far from the ileocœcal valve. Under these circumstances the collateral anastomosis must be slight, and yet hemorrhagic infarction occurred. The collateral anastomoses, however, without being completely cut off, may be so reduced that they do not suffice for the production of hemorrhagic infarction. Thus, if the vessels (including the subintestinal plexus) and the intestine be so tied that the blood can enter only through the vessels in the intestinal wall at the lower end of the loop,

it is found, if the loop be a long one, that hemorrhage makes its appearance only in the lower end, and, after extending a short distance, ceases, to be replaced first by patches of hemorrhages, and then by simple anæmic necrosis.

We wished to determine another point, of some theoretical interest at least, namely, whether the blood which produces hemorrhagic infarction must enter from the collateral channels. For this purpose we ligated all of the vascular communications of the intestine, with the exception of the main artery and the main vein, and then tied the intestine above and below, so that the included intestine was supplied only by the main artery, and the blood returned by the main vein. Under these circumstances no infarction results. We then placed a rubber clamp around the artery, and gradually tightened it, so that the blood circulated with less and less force. We carried the compression so far that the pulsations disappeared in the branches of the artery, although the blood still continued to flow, as was demonstrated by cutting one of the branches. By thus obstructing the circulation in the main artery, while all collateral anastomoses were cut off, we succeeded in producing hemorrhagic infarction of the included part of the intestine. This experiment sheds some light upon the condition of the circulation during the production of hemorrhagic infarction.

We wished to measure the blood pressure in a part in which hemorrhagic infarction is taking place. To accomplish this we inserted a canula, connected with a mercury manometer, into a branch of the superior mesenteric artery. Immediately after ligation of the superior mesenteric artery, the pressure fell from 130 mm. to about 30 mm., and remained at about this point during the whole time the infarction was taking place. We may, therefore, conclude that the arterial tension in a part where hemorrhagic infarction is occurring, is very low. As is apparent from the historical review which has been given, it was important for us to determine whether changes in the walls of the blood vessels are a factor in the production of hemorrhagic infarction. The only change of which one can think in this connection is that caused by insufficient nutrition, in consequence of deficient supply of arterial blood. We shut out for variable periods of time parts of the intestine from the circulation, either by tying tightly rubber tubing around an intestinal loop with the corresponding mesentery, or, after ligating the intestine and all its vessels, except the main artery, by compressing this artery by means of a flat rubber clamp. After about three hours peristalsis ceases, and cannot be reproduced by stimulation of the intestine. If then, or even at a later period, the ligature or clamp be removed, the blood at once shoots in with great rapidity, and the arteries, veins, and capillaries, which were previously shut out from the circulation, become distended with blood. As a rule, during the period of ligation, no thrombosis has occurred

in the vessels. In no instance in which the veins were free from thrombi, were we able to produce a hemorrhagic infarction in this way. Even if, after the circulation has been reestablished, the superior mesenteric artery be ligated, we could not observe that the hemorrhagic infarction appeared earlier, or was more intense in a part of the intestine which had been previously deprived of its circulation for three or four hours, than in the remainder of the small intestine. Our experiments upon this point were manifold, and afforded no evidence in favor of the view that hemorrhagic infarction is in any way dependent upon alterations in the vascular walls.

In view of the observations made by Cohnheim upon the frog's tongue, we regarded it as of great importance to devise some means of studying the circulation in the mesentery under the conditions in which hemorrhagic infarction occurs. Our observations upon this point are not yet completed. One of the methods which we adopted was a modification of that of Eberth and Schimmelbusch.[20] We employed an electric light submerged in the salt solution, and placed beneath the stage of the microscope in order to illumine the object. We also obtained fairly satisfactory results by simply drawing the mesentery out over a glass plate, and keeping it irrigated with warm physiological salt solution.

Immediately after occlusion of the superior mesenteric artery the circulation ceases in the veins, arteries, and capillaries of the mesentery. In a very short time the circulation returns and has the following characters. The arteries contain a much smaller quantity of blood than normal, and they appear contracted. The blood flows in the arteries with considerable, although much diminished, rapidity and without distinct pulsation. The movement of blood in the veins and capillaries is sluggish and irregular. In some of the veins the direction of the current is normal; in others it is backward, but we were not able to trace the regurgitant flow into the capillaries. In many of the veins and capillaries there is entire cessation of the current. Frequently the circulation becomes reestablished in vessels where it had previously ceased, and in other vessels stasis occurs. The distinction between axial and plasmatic current is obliterated. Gradually the veins become more and more distended with blood, and these as well as many of the capillaries become filled with homogeneous red cylinders of blood. Sometimes the red corpuscles become clumped together, and such clumps can be seen moving in the veins. We also noticed frequently clumps of white corpuscles in the circulation. The extravasations of blood took place chiefly from the small and medium sized veins, but also from the capillaries, and at least, in part, by the process of diapedesis. The microscopical appearances

[20] Eberth u. Schimmelbusch. Virchow's Archiv, Bd. 103, p. 57.

in the veins and capillaries resembled those seen in passive congestion resulting from venous obstruction, and yet we were unable to discover coagula in the larger veins.

I have now presented to you the most important results of the experiments which we have thus far performed. I have not regarded this as an appropriate occasion to describe in detail the methods employed, or to weary you with the minutiæ of individual experiments. These, together with the results of other experiments bearing upon this question, we hope to publish in more complete form elsewhere.

Our experiments justify the following conclusions:

1. The blood which produces hemorrhagic infarction comes from the collateral circulation and not by reflux from the veins.

2. The blood pressure is very low in the region where hemorrhagic infarction is taking place in consequence of the occlusion of the main artery.

3. If the force of the arterial and capillary circulation sinks below a certain point, no hemorrhagic infarction occurs.

4. There is no evidence that changes in the vascular walls are concerned in the production of hemorrhagic infarction.

5. Where hemorrhagic infarction, resulting from arterial obstruction, is taking place, the large and small veins are distended with blood, and the arteries contain less blood than normal. The circulation is sluggish and irregular in the veins and capillaries, in many of which stasis and probably physical alterations in the red corpuscles occur.

6. The hemorrhage occurs by diapedesis.

It would appear that hemorrhagic infarction, occurring under the conditions described, is the result simply of mechanical alterations of the circulation, although it is not easy to give an entirely satisfactory mechanical explanation of all of the phenomena. We should remember that our knowledge of the dynamics of the circulation of the blood is still imperfect. We have to do with a circulation influenced by complicated physiological conditions, and with a fluid containing solid particles of complicated physical properties.

The distention of the veins may be explained by the insufficient force with which the blood is propelled through them. This force is so feeble that the blood corpuscles cannot be pushed through them as rapidly as they are sent in from the arteries and capillaries. The red corpuscles thus accumulating in the veins generally block them up, and there are appearances which speak for some physical alteration in the red corpuscles when thus massed together. When many of the veins and capillaries are thus plugged with stationary or feebly propelled columns of red corpuscles, it is con-

ceivable that a pressure far below the normal may suffice to push the red corpuscles through the vascular walls, inasmuch as their progress in the normal direction is impeded. That the character of the tissue surrounding the vessels is an important factor is evident from the more rapid occurrence and greater degree of the hemorrhage in the lax mucous than in the dense muscular coat of the intestine.

The conclusions which we have drawn from our experiments apply strictly only to infarction of the intestine. There is, apparently, no reason why the same inferences do not apply to hemorrhagic infarctions in other situations. Still the conditions should be investigated separately for each organ of the body subject to hemorrhagic infarction.

EXPERIMENTAL STUDY OF HAEMORRHAGIC INFARCTION OF THE SMALL INTESTINE IN THE DOG[1]

The experiments described in this paper were undertaken to determine the circulatory conditions and the source of the blood in the production of haemorrhagic infarction, the time of onset of the infarction, as well as other pertinent factors. In order to subject this question to experimentation it is necessary to make tests upon an organ in which haemorrhagic infarction invariably follows occlusion of its main artery. Furthermore it is necessary that the vascular system of the organ be accessible throughout its whole extent. Both these requirements are present in the small intestine of the dog.

Anatomy and Physiology.

The arteries of the small intestine are arranged in such a manner that the pressure in the arterioles of the different parts of the intestine is practically the same. This condition of things exists in the whole small intestine, as it is supplied with a single arterial trunk. Soon after the superior mesenteric artery leaves the aorta it passes over the duodenum and forms a semicircular curve between the two layers of the mesentery. From this curved vessel the branches to the intestine arise—first a branch to the duodenum and then branches of different sizes to the rest of the small intestine. The smallest of these branches pass directly to the mesenteric border of the intestine, while the larger divide several times and the ultimate twigs of all anastomose to form a single series of mesenteric arches. From these arches branches arise about every half centimeter, pass alternately to opposite sides of the intestine and penetrate the muscle-wall near the mesenteric attachment, to be distributed as a rich plexus (Heller's) in the submucosa. Before these branches (long arteries) pass through the submucosa they give rise to two or three twigs which anastomose with like branches from their neighbors, and thus form an arterial plexus just outside of the intestine. From this arterial plexus many small branches arise and penetrate the muscular coats at right angles to be distributed to the submucosa of the mesenteric side of the intestine. The arrangement is such that before the arteries reach the villi there are three distinct sets of arterial anastomoses: the arches, the extraintestinal plexus and Heller's plexus of the submucosa.

[1] William H. Welch and Franklin P. Mall. This paper, written in 1887, has not previously been published.

A study of the vessels of the intestine suggests the following:

1. Since but one artery supplies the intestine, the circulation through the intestine depends entirely upon the pressure at the beginning of the superior mesenteric artery.

2. Since all the terminal branches of the superior mesenteric artery are about equally distant from their origin, it is probable that with a given pressure and rapidity, equal parts of the intestine are supplied with equal quantities of blood.[2]

3. The fact that the artery divides into some fifteen branches, and these in turn into several smaller branches, each of which has an independent muscular coat, makes it possible that a simple contraction of the circular muscle coat at any point can mitigate the flow of the blood to the intestine supplied by the arterial branch. This statement applies to the smallest arterioles.

4. The rich anastomosis in the submucosa aids materially to equalize the flow through the mucosa when the capillary resistance in the mucosa is increased or diminished, due to contraction or relaxation of the muscularis mucosae or Bruecke's muscle.[3]

Our experiments were performed in a systematic manner to determine the following question: (1) Through what channels, under what pressure and other circulatory conditions, and at what time does the blood enter the vessels to produce haemorrhagic infarction? (2) These factors having been determined can we produce haemorrhagic infarction of the intestine by other methods than ligation or complete occlusion of the main arterial branches? (3) In case this is possible in the living animal can it be accomplished also in the isolated intestine when nourished by artificial circulation?

[2] A more careful statement would probably be about this: If we consider the intestine to be divided into equal parts, a to z, a will receive m amount of blood; b, $m - n$; c, $m - 2n$; and j, $m - 25n$, being much less than half of m. This statement is more nearly correct for I, as one passes from the duodenum down to the caecum the vessels gradually become larger and longer. 2. Injections of the intestine first fill the vessels of the duodenum and then those lower down the gut until the caecum is reached. 3. During digestion fat absorption seems to take place more in the upper part of the intestine and diminishes as the caecum is approached. 4. Haemorrhagic infarction after ligation of the superior mesenteric artery is as a rule more intense in the duodenum than elsewhere. But since the diameter of the intestine becomes less and less as the caecum is approched, it is reasonable to suppose that a given length of intestine in the duodenum must obtain more blood than the same length nearer the caecum, so ultimately it may be provided that a villus from the ileum obtains as much blood as one from the duodenum.

[3] For a more detailed account of the blood-vessels of the dog's intestine see Mall: Blut. u. Lymphwege im Dünndarm d. Hundes. Abhandl. d. K. K. Ges. d. Wiss., Bd XIV, 1887, Leipzig.

Ligature of the Superior Mesenteric Artery.[4]

Immediately after ligating the superior mesenteric artery the muscular walls of the intestine contract and become anaemic. This condition continues for some three to four hours, when the intestinal walls gradually relax and the mucous membrance becomes first hyperaemic and then infarcted, the process extending from the middle of the duodenum downward. The infarction is complete at the end of six to eight hours; after this time its intensity is not generally increased as the excess of blood now leaves the tissues and enters the lumen of the intestine. The various experiments upon which the above statements are made are given in Table I.

TABLE I

Condition of the Intestine after the Superior Mesenteric Artery had been Ligated for 3 to 21 Hours

Experiment	Duration of the experiment	Condition of the intestine	Remarks
1	3 hrs.	Muscle walls pale, mucosa hyperaemic.	
2	4 "	Somewhat more hyperaemic than No. 1.	
3	5 "	Hyperaemia of mucosa, more intense than No. 2.	
4	5 "	Mucosa of parts supplied by the artery hyperaemic.	The artery ligated was one of the large branches of the superior mesenteric.
5	5 "	Infarction of the entire mucosa.	
6	6 "	" " " " "	
7	7 "	" " " " "	
8	7 "	Infarction more intense than No. 7.	
9	12 "	Complete infarction of the intestine.	There was much blood within the lumen of the intestine.
10	21 "	Cat. The infarction is mottled and not complete.	Considerable blood within the lymphatic channels.
11	18 "	Intestine dilated and flabby; mucosa very haemorrhagic.	Intestine filled with gas and blood.

In all the experiments either the hyperaemia or the infarction begins abruptly in the middle of the duodenum, marked by the junction of the superior mesenteric artery and the pancreaticoduodenal artery, gradually becomes somewhat less intense as the caecum is approached and ends very

[4] In all the experiments the animals were anaesthetized with ether or ether and morphia combined.

abruptly in the middle of the large intestine opposite the junction of the superior and inferior mesenteric arteries. Not only is the infarction somewhat more marked in the upper part of the intestine than in the lower, but it also begins earlier and becomes more intense in the villi than in the intestinal glands (crypts), the rapidity and intensity of the infarction thus corresponding in both instances with the physiological activity of these parts when viewed from the standpoint of absorption.

After the infarction is complete the muscular walls of the intestine gradually become flabby the process beginning in the duodenum, then gradually extending to the caecum. The intestine dilates, putrefaction takes place within the lumen and gas is formed which gradually distends the walls and discolors the haemorrhagic mucous membrane. Even in extreme states of relaxation the muscular walls are not necessarily dead, for they often respond to strong irritants.

What has been determined from the foregoing experiments regarding the time required in the production of an infarction can also be determined from a single experiment. After ligature of the superior mesenteric artery the intestine is to be examined from hour to hour, at each time removing a piece of it in order to examine the mucosa as well as for comparison. Immediately after ligating the superior mesenteric artery the intestinal contractions become very active and continue for several hours. During the third hour the contractions diminish greatly, the veins begin to dilate and the intestine takes on a bluish tinge. During the fourth hour the intestine is motionless and the blueness increases. This stage is followed by hyperaemia and then still greater hyperaemia and infarction. The same result is obtained if the intestine is observed by the method of Sanders Ezn and van Braam Houckgeest, as well as by the method of artificial circulation through the isolated, but living, intestine.

It was noted in the foregoing experiments that the boundaries of the infarcted region are sharply defined by the distribution of the branches of the artery ligated. To test this question in detail a special set of experiments was made.

Ligature of Branches of the Superior Mesenteric Artery.

The experiments given in Table I show that the anastomoses with the inferior mesenteric and the pancreatico-duodenal arteries are not sufficiently large to reestablish the circulation through the intestine after the main trunk of the artery has been ligated. It now remains to determine to what extent the anastomoses between the mesenteric arches can reestablish the circulation when a main branch of the superior mesenteric artery has been tied. Furthermore it is desirable to determine to what extent the arterial

plexus in the submucosa can re-establish the circulation through the mucosa after all the extra-intestinal arteries have been cut off. To answer this second question the experiments given in Table II were made (Fig. 1).

TABLE II

LIGATURE OF THE MAIN BRANCHES OF THE SUPERIOR MESENTERIC ARTERIES AS WELL AS OF THE TERMINAL TWIGS TO THE INTESTINE

Experiment	Vessels ligated	Length of the loop of intestine cut off	Duration of the experiment	Results
12	Mesenteric branch and arches as shown in Fig. 1, a, a', a''.	13 cm.	5 hrs.	Mucosa opposite branch ligated, haemorrhagic.
13	Same as No. 12 with an additional ligature of the intestine at a'.	13 "	5 "	Mucosa opposite branch ligated extremely hyperaemic.
14	As No. 12	5 "	5 "	Mucosa not changed.
15	5 long intestinal arteries on either side.	2.5 "	4 "	Mucosa hyperaemic.
16	4 long intestinal arteries on either side.	2 "	7 "	" "
17	4 long intestinal arteries on either side.	2 "	4 "	Mucosa not changed.
18	3 long intestinal arteries on either side.	1.5 "	7 "	Mucosa hyperaemic.
19	3 long intestinal arteries on either side.	1.5 "	4 "	Mucosa not changed.
20	2 long intestinal arteries an either side.	1 "	7 "	Mucosa hyperaemic.
21	2 long intestinal arteries on either side.	1 "	7 "	" "
22	2 long intestinal arteries on either side.	1 "	7 "	Mucosa not changed.
23	2 long intestinal arteries on either side.	1 "	4 "	" " "
24	1 long intestinal artery on either side.	.5 "	4 "	" " "
25	6 long intestinal arteries on one side.	3 "	4 "	" " "
26	5 long intestinal arteries on one side.	2.5 "	4 "	" " "
27	4 long intestinal arteries on one side.	2 "	4 "	" " "
28	3 long intestinal arteries on one side.	1.5 "	4 "	" " "
29	2 long intestinal arteries on one side.	1 "	4 "	" " "
30	1 long intestinal artery on one side.	.5 "	4 "	" " "

Where the ligated extra-intestinal arteries belonged to the arches it was found that the plexus of the submucosa is sufficiently large to reestablish the circulation through the mucosa in a loop of intestine 5 cm. long but not

large enough for a loop 13 cm. long. If only the long intestinal arteries are ligated it is found that in case they are ligated on both sides of the intestine this submucous plexus can barely reestablish the circulation in a section of intestine 1 cm. long, while if the same vessels are ligated only on one side of the intestine the lateral anastomoses as well as those of the submucosa from the opposite side can easily reestablish the circulation through a loop 3 cm. long, and probably much longer. These two groups of experiments indicate the presence of the additional set of anastomoses (subintestinal plexus) between the mesenteric arches and the submucous plexus.

In order to determine more exactly the length of the intestine which can be nourished through the submucous plexus and mesenteric arches respectively the experiments, given in Table III, were made. The idea underlying

TABLE III

LIGATURE OF THE BRANCHES OF THE SUPERIOR MESENTERIC ARTERY INCLUDING THE DUODENUM, WITH OR WITHOUT LIGATURE OF ALL OF THE MESENTERIC ARCHES

Experiment	Vessels ligated	Length of the intestine experimented upon	Duration of the experiment	Results
31	All the mesenteric branches and arches ligated as shown in Fig. 1, with ligature of the duodenum.	128 cm.	5 hrs.	The mucosa supplied by the artery x^1 is infarcted, that by the next artery x^2 less infarcted and that by the third artery x^3 is hyperaemic. The remainder of the mucosa is anaemic.
32	Mesenteric branches and the duodenum including its arch ligated as shown in Fig. 2.	145 "	6 "	The mucosa supplied by the first branch is unchanged, that supplied by the second branch is infarcted, and the rest of the mucosa is anaemic.
33	Same as No. 32.....	120 "	18 "	The mucosa of the part supplied by the first branch is hyperaemic, that of the second and third branches (12 cm. long) haemorrhagic, the remainder (90 cm.) is necrotic.

experiment 31 is to determine the change in the mucosa after ligature of all the arteries entering the intestine with the exception of the submucous plexus near the caecum, as shown by the diagrammatic Fig. 1. The result in this experiment is so definite that it at once gives us a key to the origin of the infarcted blood, at the same time refuting completely the Cohnheim doctrine of venous regurgitation.

Had a venous regurgitation taken place in this experiment, then the whole mucosa of the intestine would have been equally infarcted. The sharp zone marked by the degree of hyperaemia in the mucous membrane shows that the origin of the blood is not from the veins, as the veins have not been interfered with in any portion of the intestines. The zone of infarction begins sharply opposite the ligature of the last mesenteric arch, and extends equally throughout the mucosa supplied by this branch, X_1. The mucosa supplied by the next branch, X_2, is very hyperaemic, while that of the third branch, X_3 is slightly hyperaemic. The rest of the intestine is anaemic.

The only suitable explanation of this experiment is that a sufficient quantity of blood entered the artery X_1 through the submucous plexus to produce the infarction of the mucosa, the blood being equally distributed because the pressure as well as the quantity of blood was equalized by the arterial branch X_1 communicating freely with all parts of the infarcted region. The second zone received its flow from the first zone, and the third from the second. From the fourth zone onward there is anaemia as the heart-beat was not strong enough to overcome the increased resistance of more than three dilatations in the arterial bed, produced by the operation. Therefore, a certain quantity of blood is required for normal circulation, less quantity produces haemorrhagic infarction, still less hyperaemia, while finally when the quantity is very small anaemia and necrosis follow.

While experiment 31 determines the relative extent of the circulation through the mucosa with the blood entering the submucous plexus, experiments 32 and 33 (Fig. 2) determine it with the blood entering through the mesenteric arches. In these two experiments the vascular system of the intestine is reduced to series of mesenteric arches communicating on one end only with the main trunk of the artery. The experiment shows that the first arch carried a sufficient quantity of blood to the mucosa (20 cm. long) of the first system to re-establish the circulation through it. The second system, however, is haemorrhagic; the remaining systems anaemic and necrotic. In experiment 33 the first communicating arch is a very tiny vessel, and the first zone of mucosa is not haemorrhagic but hyperaemic, the second and third zones are haemorrhagic and the remainder of the intestine is anaemic and necrotic. So, therefore, these experiments show that a slight diminution of blood supply produces hyperaemia, less blood supply haemorrhagic infarction, still less hyperaemia, and finally if the quantity is greatly diminished anaemia and necrosis of the intestine.

Combination Experiments Made to Show the Source of the Blood in Haemorrhagic Infarction.

If it is true that the blood required to produce an haemorrhagic infarction of the intestine after ligature of the artery enters through the collateral

arterial branches and is not obtained through venous regurgitation, then ligature of the vein with the artery must increase the intensity of the infarction rather than diminish it. In the infarction which follows ligature of the artery the blood has still a free outlet into the vein, while if this channel is also obstructed the infarction must be intensified. The experiments of Cohn, of Litten, as well as our own, support this view. As the smaller branches of the mesenteric vessels are approached the veins become relatively larger and larger and therefore the ligature of a peripheral vein with its artery does not intensify the infarction so much as the ligature of a larger vein with its artery. These statements which are drawn in a general way from the experiments to follow point towards the mechanical explanation of haemorrhagic infarction. Experiment 34 is a repetition of 33 with the exception that the accompanying veins are ligated with the arteries. In this experiment the infarction and hyperaemia of the mucosa are but slightly intensified by the ligature of the veins in addition to the arteries. In case the anastomoses are smaller, as they are in 36 and 37, including the veins in the ligature intensifies the infarction.

The same is true in experiments 41 and 42, as well as all the experiments given (Table VII) in which the main large veins were ligated with the artery. This result is to be explained by the ratio between the sectional area of the arteries and veins not occluded in the experiment. Fig. 4 is the scheme of Experiment 34 (Fig. 3). The average sectional area of artery a is 0.28 square millimeters; of a' 0.032. The area of the vein v' 0.152. In general the area of the vein is five times that of the accompanying artery. In case the veins are ligated as indicated in Fig. 4, it is found that the capillaries of the mucosa of c^1 and c^2 remain normal; those of c^3 become hyperaemic, and those of c^4 and c^5 become haemorrhagic. If the anastomosing arteries are considered to have rigid walls the relative quantity of blood entering these capillaries of these different systems would be for c, $1/1$; c^1, $1/9$; c^2, $1/9^2$; . . . . . c^5, $1/9^5$. In reality, however the dilatation of the anastomosing arteries increases this quantity considerably. On the other hand the sectional area of the veins being at least five times that of the accompanying arteries they can with ease carry off the diminished quantity of blood from the region becoming infarcted and in no way favor stagnation. The result is different when the area of the veins more nearly reaches that of the arteries, as in the case of the submucous plexus and in the very large veins. Here, occlusion of the veins with the arteries intensifies the degree of the infarction.

All the necessary experiments to produce the different degrees of an infarction can be performed to advantage on small loops of intestine as given in Fig. 6 and Table V. The sectional area of the veins of the sub-

mucosa approaches nearly that of the arteries, so this factor can also be included to advantage in making the different experiments. The experiments together point toward the cause of the infarction in the showing of the normal circulation.

Given the proper degree of stagnation, the greater the capillary blood pressure the more rapidly is the infarction produced and the greater is its intensity. In case the artery only is obstructed, the stagnation of circulation and the blood pressure must be pretty definite in relation to production of haemorrhagic infarction, for a slight increase or diminution of these two factors is followed by only hyperaemia (and occasionally oedema) on the one hand, or anaemic necrosis on the other, as the experiments of Tables III and IV illustrate.

TABLE IV

COMBINATION EXPERIMENTS SIMILAR TO THOSE GIVEN IN TABLE III WITH THE VEINS INCLUDED WITH THE ARTERIES

Experiment	Vessels ligated	Length of loops operated upon	Duration of the experiment	Result
34	Both mesenteric arteries and veins ligated as shown in Fig. 3.	120 cm.	7 hrs.	Mucosa of first and second systems apparently normal; third system hyperaemic; fourth, fifth and sixth, haemorrhagic; seventh hyperaemic, and so on, see Fig. 3.
35	All of the arteries and veins including the duodenum and ileum ligated with the exception of one large arterial branch and its vein to the middle of the intestine ligated. Only through this artery could blood reach the intestine.	.....	5 "	The part of the intestine supplied by the patent artery and vein were apparently normal; the mucosa on either side of this was hyperaemic; the remaining intestine both above and below haemorrhagic, the upper part being more intense than the lower.
36	Arteries and veins with the exception of a small central twig, as indicated in Fig. 5, No. 36, ligated.	16 cm.	7 "	Mucosa supplied by the open artery and vein normal, with hyperaemia on one side and infarction and hyperaemia on the other.
37	Single arterial branch and mesenteric arches with veins ligated. Fig. 5, No. 37.	7 "	7 "	Infarction, although not intense throughout the entire mucosa of the experimental region.
38	Experiment like No. 36 excepting that the length of the loop of intestine is shorter. Fig. 5, No. 38.	6 "	7 "	Mucosa unchanged.

TABLE V

EXPERIMENTS UPON LOOPS OF INTESTINE FROM 5 TO 6 CM. LONG TO TEST THE EFFECT OF LIGATING DIFFERENT VESSELS UPON THE MUCOUS MEMBRANE OF THE INTESTINE. THE DURATION OF THE EXPERIMENTS IS IN ALL INSTANCES SIX HOURS

Experiment	Vessels ligated	Results
39	Both venous and arterial arches and intestine on both ends ligated. Fig. 6, *a*.	Mucosa unchanged.
40	Artery and both arterial and venous arches. Fig. 6, *b*.	" "
41	The same with the intestine on one end ligated. Fig. 6, *c*.	Mucosa hyperaemic.
42	Artery and veins and arches with intestine on one end ligated. Fig. 6, *d*.	Complete infarction more intense near intestinal ligature.
43	The same as above with the main artery open. Fig. 6, *e*.	Same as above.
44	Artery and vein and arches ligated. Fig. 6, *f*.	Complete infarction of the mucosa, being sharply marked above and below.
45	The same with the artery open. Fig. 6, *g*.	The infarction is not as intense as the above (No. 44).
46	All the veins and arteries with the exception of the main artery ligated. Fig. 6, *h*.	Extreme infarction of the intestine.
47	All the arteries and veins with the exception of the main vein ligated. Fig. 6, *i*.	The intestine is necrotic, anaemic and flabby.

Another instructive combination in tying the arteries is given in the experiments of Table VI. They may be considered as experiments within

TABLE VI

EXPERIMENTS WITHIN EXPERIMENTS

Experiment	Vessels ligated	Duration of the experiment	Results
48	Two main branches and peripheral arches of both arteries and veins ligated. The same experiment was then performed on smaller vessels in the middle of the first, as shown in Fig. 7.	.....	Infarction of the entire mucosa being more intense opposite the second experiment than elsewhere (see Fig. 7).
49	Ligature of the superior mesenteric artery with additional ligature of four of its main branches side by side. Fig. 8.	4½ hrs.	Infarction of the mucosa of the whole small intestine with the exception of 50 cm. near the caecum. The infarcted zone extends into the part supplied by the secondary vessels which have been ligated.
50	Ligature of the superior mesenteric artery as well as all of its main branches.	5 "	Infarction of the intestine at its upper as well as its lower end. The middle anaemic zone is considerably longer than in Experiment 49.

experiments. In case the inclosed experiment does not cover a great area, as shown in Fig. 7, *b*, the infarction in it is intensified. In case the inclosed experiment is of such an extent that by itself it will cause intense infarction, placing it within another experiment, *x*, results in diminution of the infarction. In Experiment 49, the second group of arteries ligated, Fig. 8, x^1 supplied nearly 100 cm. of intestine, about enough to produce an infarction in its middle 50 cm., judging by Experiment 32, Fig. 2. Tying the main artery in addition reverses the result upon the loop supplied by the arteries marked x^1. What should be normal upon the periphery, beyond *a*, is now haemorrhagic and what should have been haemorrhagic, between *a* and *a*, is anaemic.

After making these experiments upon the loops of the intestine to determine the origin of the blood in haemorrhagic infarction it is easier now to consider in an intelligible way the results after ligature of the coarser vessels of the intestine. These experiments are given in Table VII; they can be compared to advantage with those given in Table I. In Experiments 51 to 56 the inferior mesenteric artery as well as other anastomoses in some cases, were left open, and these vessels account sufficiently for the blood required to produce the infarction. In 57, however, all possible circulation through the arteries was eliminated, only the portal vein having been left open; no infarction followed. In case the veins alone are ligated there is no infarction of the intestine, provided the anastomoses are sufficiently large to carry off the blood. As the veins through which the venous blood may escape are ligated the intestine gradually becomes more and more infarcted, as shown in Experiments 62, 63 and 64.

Under certain conditions which can happen only in an experiment, infarction of the intestine may be caused by venous regurgitation. In Experiment 65 the entire root of the mesentery with the exception of the inferior mesenteric vein was ligated, the ligature, of course, including the duodenum and colon. The experiment is similar to No. 56. The extreme infarction which followed must have been caused by the blood which entered the portal system through the inferior mesenteric artery and vein. In this experiment the portal pressure was soon raised to the arterial and an infarction followed, for we have here the favorable condition; that is, stagnation and pressure. No. 66 is a similar experiment on a smaller scale (Fig. 9). The arteries and veins of two neighboring loops were ligated in such a manner that in one loop, Fig. 9, *A*, there was high arterial pressure with the veins ligated, while in the other loop, *B*, high venous pressure with the artery ligated. In both loops an intense infarction followed. When the artery of the loop *B* is cut open at *E*, Fig. 9, the condition in this loop is very similar to that in the intestine after simple ligature of the superior mesenteric

TABLE VII

LIGATURE OF DIFFERENT LARGE ARTERIES AND VEINS OF THE ABDOMINAL VISCERA

Experiment	Vessels ligated	Duration of the experiment	Results
51	Superior mesenteric artery and vein and inferior mesenteric vein.	10 hrs.	Infarction throughout entire small intestine.
52	Superior mesenteric artery and portal vein.	5 "	Extreme infarction throughout the small intestine; duodenum and stomach hyperaemic.
53	Coeliac axis, superior mesenteric artery and portal vein.	6 "	Extreme infarction of the small intestine.
54	The same as above.....	6 "	The same as above.
55	Coeliac axis, superior mesenteric artery, portal vein and duodenum including mesenteric arch.	6 "	Infarction of the entire intestine.
56	Coeliac axis, superior mesenteric artery, portal vein and duodenum and ileum.	3 "	Infarction of intestine, stomach and spleen. Fatty metamorphosis of liver.
57	Whole root of mesentery with the exception of portal vein.	10 "	No haemorrhagic infarction.
58	Superior mesenteric vein.	48 "	No infarction.
59	Superior mesenteric and pancreatico-duodenal veins.	21 "	" "
60	All the veins of a loop 15 cm. long with the exception of one arch.	12 days.	The anastomosing vein dilated and varicose.
61	The same as Experiment 60	4 "	Coagulative necrosis and haemorrhagic infarction of loop.
62	Superior and inferior mesenteric veins.	2½ hrs.	Mucosa hyperaemic and infarcted.
63	Superior mesenteric, inferior mesenteric and pancreatico-duodenal veins.	1 hr.	Extreme infarction of whole small intestine.
64	Portal vein.....	½ "	Intestine hyperaemic.
65	Root of mesentery with the exception of the inferior mesenteric.	3 hrs.	Extreme degree of infarction.
66	The vessels and intestine of two intestinal loops ligated as indicated in Fig. 9. The circulation was forced to take the direction of the arrows.	4 "	The loop *B* became blue first, and then loop *A*. The intestine of both loops was internally haemorrhagic.
67	The same as above.....	4 "	The same as above.
68	The same as above only that the artery was cut open at *E* (Fig. 9).	4 "	First the loop *A* became hyperaemic, then the loop *B*. At the end of four hours the loop *A* was very haemorrhagic; the loop *B* was less so.
69	The same as above.....	4 "	The same as above.

artery, with the difference that the direction of the circulation is reversed. Under these conditions, haemorrhagic infarction follows (68 and 69).

We have here again absence of the pulse wave, retarded circulation and capillary pressure, factors which are essential in the production of an infarction, provided there is no obstruction in the outflow of blood.

Ligature of Either Arteries, Veins or Both, at the Same Time Reducing the Blood Pressure in One of Them to Zero.

The results obtained by ligating the different vessels in the study of haemorrhagic infarction are in general confirmatory of those obtained by Cohn some forty years ago. In order to gain a deeper insight of this question it is necessary not only to study the vessels from without but also from within.

The first experiments we performed to study the blood pressure in the intestine during the production of an infarction are given in Table VIII.

TABLE VIII

Experiments Made to Produce Haemorrhagic Infarction of a Loop of Intestine at the Same Time Opening Either the Artery, the Vein or Both

Experiment	Vessels ligated	Vessels opened	Length of the loop of intestine	Duration of the experiment	Results
70	Artery and mesenteric arches.	Artery.	8 cm.	4 hrs.	Mucosa not changed.
71	Artery, vein and mesenteric arches.	None.	8 "	4 "	Mucosa hyperaemic.
72	The same	Artery and vein.	8 "	4 "	Mucosa slightly hyperaemic.
73	Artery and arches	None.	12 "	10 "(?)	Mucosa haemorrhagic.
74	Artery, vein and arches.	"	12 "	10 "(?)	The same.
75	" " " "	Vein.	12 "	10 "(?)	" "
76	" " " "	Artery.	12 "	10 "(?)	Mucosa very haemorrhagic.
77	Artery, vein, mesenteric arches and intestine on one side.	None.	10 "	5 "	Mucosa oedematous and somewhat haemorrhagic.
78	The same	Artery.	10 "	5 "	Mucosa haemorrhagic.
79	" "	Vein.	10 "	5 "	The same.

In these experiments the pressure in either the artery or the vein was reduced to zero by simply opening a branch of either of them after ligature of the main trunk.

It is fair to assume that when an arterial or venous branch is cut open and constantly observed, to see that it is bleeding freely and does not become plugged with clots, the pressure within it will fall nearly to zero. As the average pressure in the vena porta is usually 6 mm. Hg., reducing the pressure to zero after the artery has been ligated should have little effect upon the production of the infarction as is proved to be the case. On the other hand, reducing the arterial pressure to zero, as in Experiments 70, 76 and 78, no infarction should follow, but in some of these experiments the intestine became more haemorrhagic than it would have been had the artery not been opened. The result in these three experiments is not uniform; in 70, in which the vein was not operated upon, the intestine did not even become hyperaemic, while in 76 and 78 in which the veins were also ligated the intestine became haemorrhagic. In Experiments 75 and 76, which were done under like conditions upon the same animal, the veins were not opened until the loops had become very hyperaemic, due to the ligatures which had been applied. Opening the vein (75) relieved this hyperaemia at once, while opening the artery (76) made no perceptible effect upon it. In this point of difference may be the key to the cause of the intensified infarction after ligature of both artery and vein with the arterial pressure reduced to zero. To test this question a step further, Experiments 77, 78 and 79 were made under like conditions upon the same animal. In Experiment 78 the blood flowed from the cut end of the artery at the rate of 3.5 c. c. per hour, and out of the cut vein at the rate of 43 c. c. per hour, confirming what was observed regarding the hyperaemia in Experiments 75 and 76. The blood which produces the infarction in the above experiments can enter the loops only through the submucous arterial plexus. And it is very remarkable that under these conditions it appears easier for blood to pass over from the submucous arterial plexus through the capillaries than simply backwards and out of the opened artery. Other factors, as constriction of the artery due to contraction of its muscular coats when the blood pressure is low, or as muscular contractions of the walls of the intestine, may play a rôle in this remarkable experiment. Under certain conditions the contractions of the muscular coats of the intestine accelerates the circulation through its wall to such a marked degree that the venous pressure may exceed the arterial.[5] This condition is also observed in Experiment 82. Until the normal circulation through the intestine is more thoroughly understood it will remain difficult to explain Experiments 76 and 78.

[5] Mall: Johns Hopkins Hospital Reports, I, p. 54.

Blood Pressure in the Arteries and Veins of the Intestine During the Production of an Haemorrhagic Infarction After Ligature of the Superior Mesenteric Artery.

The experiments given in Table VIII indicate that it is essential to record the pressure in the distal end of the superior mesenteric artery after the main branch has been ligated, during the production of an infarction. In the experiments recorded in Table IX cannulae were introduced into a

TABLE IX

Blood Pressure in the Distal Ends of the Superior Mesenteric Artery and Vein after Ligation of One or Both of these Vessels

Experiment	Vessel ligated	Blood pressure in mm. Hg.				Duration of experiment	Result
		Before ligature		After ligature			
		Artery	Vein	Artery	Vein		
80	Superior mesenteric artery.	128	..	29	..	5 hrs.	Infarction of the entire mucosa.
81	Artery and vein.	131	7	30	8	4 "	The same.
82	Artery, vein and pancreatico-duodenal.	...	..	60	25	?	Extreme infarction. In the first part of the experiment the pressure in the artery and vein is given for every 10 minutes. After the first hour it was more irregular.

branch of the superior mesenteric artery and vein, pointing centrally. Then the main trunks were ligated. The pressures were recorded upon the moving drum and the cannulae and intestines observed during the entire experiment.

After ligature of the artery the intestine became very irritable and pale and remained so into the third hour. Then it gradually became quiet and hyperaemic the infarction taking place during the fourth and fifth hours. Immediately after ligature of the artery the pressure in both the artery and vein fell to its lowest point. In the course of five minutes, however, the pressure gradually rose and remained stationary during the whole experiment. In Experiments 80 and 81 the arterial pressure fell to about one-fourth the normal after ligature of the artery. In 82 the venous outflow was completely obstructed so the pressure in the artery gradually rose, but the venous pressure rose more rapidly and at one time exceeded the arterial. The infarction followed very rapidly. These few experiments, together with

many others, show that a considerable blood pressure is present in the peripheral end of the artery after its ligation, while haemorrhagic infarction is taking place, and Experiments 80 and 81 fix this pressure at one-fourth the normal.

Production of Haemorrhagic Infarction of the Intestine by Partly Occluding the Superior Mesenteric Artery After all the Anastomoses Have Been Ligated.

In case the initial cause of the infarction which follows ligature of the superior mesenteric artery is simply reduction of the arterial pressure, then infarction should always result when the arterial pressure is reduced by other means than by tying the main artery. This view is substantiated by the experiments recorded in Table X.

TABLE X

Experiments in which the Arterial Pressure was Reduced by Clamping the Main Trunk of the Superior Mesenteric Artery after Ligature of all of its Arterial Anastomoses Including the Intestine Above and Below

Experiment	Vessel clamped	Degree of clamping	Duration of clamping	Result
83	Superior mesenteric artery.	Arterial pressure reduced to ¼ 30 mm.	3 hrs.	Mucosa very hyperaemic.
84	Artery to loop of intestine.	Until pulse nearly disappeared.	6 "	Mucosa hyperaemic.
85	The same.....	Until pulse disappeared.	6 "	Mucosa hyperaemic and infarcted.
86	" "	The same.....	6 "	Mucosa hyperaemic.
87	" "	" "	6 "	Infarction.
88	All arterial anastomoses tied and clamp on superior mesenteric artery.	" "	8 "	Extreme haemorrhagic infarction.
89	The same.....	" "	8 "	The same.

In making the experiments the main artery and vein were isolated and all of the remaining tissues at the root of the mesentery, including the duodenum and colon, were ligated. By this method the blood entered the intestine through the main stem of the artery only. The same precautions were employed when experimenting upon a loop of intestine. In this experiment it is necessary to clamp the main trunk of the artery in such a manner that no kinking is possible to obstruct the circulation entirely. This was

accomplished by a double-screw clamp encircling the artery with a thick-walled rubber tube 4 mm. in diameter and 10 cm. long on either side of it. In screwing down the clamp most of the force was spent in compressing the rubber tube, thus making the clamp firm. The length of the rubber tube kept the clamp in place. By this method of constricting, the artery lies in a firm slot which cannot kink it.

The degree of constriction of the artery was regulated in Experiment 83 by measuring the pressure in the distal end of the artery. The clots which formed in the cannula were, however, very troublesome, so another method of determining the proper reduction of arterial pressure was employed. In all of the experiments in which the superior mesenteric artery was ligated it was observed that there was no detectable pulse wave in the arteries of the mesentery. The same was true in Experiment 83. So in most of the experiments given in the table, the main artery was compressed until the pulse wave in the distal branches had just disappeared. A small branch was then cut open and it was found that the blood oozed out of it drop by drop, as it did from the one cut in Experiment 83. By this method not only was the pressure of the artery quickly reduced, but the pulse wave was also arrested.

The result of Experiments 84, 85 and 86 was not as satisfactory as was expected beforehand, but in 87, 88 and 89 the infarction was in every respect as intense as could be obtained by ligature of the main trunk with the anastomoses open. Furthermore there was a great quantity of blood within the lumen of the intestine of Experiments 88 and 89.

These experiments, as all others, indicate that in the production of an haemorrhagic infarction the rapidity of the circulation through the capillaries is greatly diminished. In infarctions following partial occlusion of the artery, the circulation is sufficiently slow to produce infarction when the arterial pressure is reduced to one-fourth the normal, which is also just the point at which the perceptible pulse wave is lost.

Experiments Made to Test the Effect of Ischaemia Upon Haemorrhagic Infarcation.

It is observed in the foregoing experiments that a very definite period of time elapses after ligature of the superior mesenteric artery, or its branches, before the beginning of haemorrhagic infarction. After diapedesis is well started the further progress of the infarction is fairly rapid. These facts induced Virchow to suspect that capillary necrosis is caused by the ischaemia, thus favoring the escape of blood into the tissues. This idea in turn served as a basis for Cohnheim's theory, who in addition accounted for the necessary blood through venous regurgitation. The experiments which

follow contradict the idea that capillary necrosis plays any rôle whatever in the production of haemorrhagic infarction.

Table XI gives a group of experiments in which either the whole intestine or one of its loops was deprived entirely of arterial blood for from 30 minutes to 3 hours, after which the circulation was reestablished.

TABLE XI

EXPERIMENTS IN WHICH THE ISCHAEMIC INTESTINE WAS FOLLOWED BY RE-ESTABLISHMENT OF THE CIRCULATION

Experiment	First operation	Duration.	Second operation	Duration	Result
90	Ischaemia of a loop of intestine.	½ hr.	Circulation reestablished.	20 hrs.	Intestine apparently normal.
91	The same.....	½ "	The same.	20 "	The same.
92	Ischaemia of entire intestine.	2½ hrs.	" "	8 "	" "
93	Ischaemia of a loop of intestine.	2½ "	" "	3 "	Mucosa slightly hyperaemic.
94	The same.....	3 "	" "	3 "	Mucosa apparently normal.
95	The same. The vein was not closed.	3 "	" "	3 "	The same.
96	Ischaemia of entire intestine. The superior mesenteric vein left open.	3 "	" "	3 "	" "
97	Loop of intestine ischaemic. Main vein was left open.	3 "	" "	2 "	" "

In making these experiments all possible anastomoses, including those through the intestinal walls were first ligated, after which the main artery and vein was compressed by tying it between two blocks of rubber. In every experiment a small arterial twig of the mesentery was opened immediately after clamping the main artery, and before as well as after the renewal of the clamp, in order to determine the condition of the circulation in the experimental loop. In all cases it was found that the method is satisfactory, for in no instance were we troubled with clot-formation either in the artery or the vein. It was also found that after several hours of ischaemia the intestine was quiet and would barely respond to irritants. Under this condition reestablishing the circulation was followed by a gush of blood through the arteries over into the veins, the intestine at the same time becoming very hyperaemic.

In no instance, however, did haemorrhagic infarction follow. In Experiments 95, 96 and 97 the vein was not included in the clamp in order to give the "venous reflux" every possible chance in the production of the infarction. Yet the result here was also negative.

In the second group of experiments, Table XII, a loop of intestine was

TABLE XII

ISCHAEMIA OF THE INTESTINE FOLLOWED BY REESTABLISHMENT OF THE CIRCULATION AND LIGATURE OF THE SUPERIOR MESENTERIC ARTERY

Experiment	First operation	Duration	Second operation	Duration	Result
98	Ischaemia of loop of intestine.	2½ hrs.	Superior mesenteric ligated.	12 hrs.	Loop no more infarcted than the rest of the mucosa.
99	The same.....	3 "	The same..	5 "	The same.
100	" "	3 "	" "	5 "	" "
101	Ischaemia of loop and vein cut open.	3 "	" "	15 "	Mucosa of loop less infarcted than rest of intestine.
102	Ischaemia of loop of intestine.	3 "	The same and portal vein ligated.	4 "	Loop more infarcted than mucosa of immediate neighborhood, but not as much as that of duodenum.
103	Ischaemia of loop of intestine with an additional ligature around the superior mesenteric artery.	2½ "	Ligature removed from loop.	8½ "	Mucosa with the exception of loop extremely haemorrhagic.

first made ischaemic for a number of hours, after which the circulation was reestablished in order to exclude the possibility of clot-formation within the vessels of the experimental loop. As soon as this possibility was excluded the superior mesenteric artery was ligated. In this group of experiments a loop of the intestine was ischaemic some hours longer than the rest of the intestine, and therefore if ischaemia is favorable to the production of an infarction that in the loop should be increased. With the exception of 102, this was not the case.

In fact, there seemed to be a tendency for the experimental loop to be less infarcted than the remaining intestine. It may be of some value to add a note regarding Experiment 102. After the clamp was removed from the vessels of the experimental loop the intestine became very hyperaemic. Ligature of the superior mesenteric artery was followed by anemia and

violent contraction of the whole intestine with the exception of the loop. Next, the portal vein was ligated and then the intestine became much bluer than the loop.

In the third group of experiments the proper vessels were clamped for a sufficient length of time to produce an infarction after which the circulation was reestablished. The test in these experiments is to determine whether an "ischaemia," under which an infarction does follow, favors increased infarction in case the blood pressure is increased. The result was again decidedly negative. When the clamp was removed from the main artery its branches began to pulsate, and the blue intestine became pink as the blood shot through its veins. It appears as if the infarction is at once washed out instead of becoming increased, and in the course of from 10 to 20 hours the condition of the intestine is nearly normal in appearance.

TABLE XIII

VESSELS CLAMPED A SUFFICIENTLY LONG TIME TO PRODUCE AN INFARCTION AFTER WHICH REESTABLISHING THE CIRCULATION WASHED IT OUT

Experiment	Vessels clamped	Duration	Condition of loop	Time between removing the clamp and ending the experiment	Result
104	Artery of large loop clamped.	4 hrs.	Loop very hyperaemic.	20 hrs.	Hyperaemic spots in mucosa of loop.
105	Superior mesenteric artery.	6½ "	The same ...	.....	Infarction.
106	Superior mesenteric and pancreatico-duodenal arteries.	4 "	.....	20 hrs.	Slight infarction.
107	Artery and arches of loop 35 cm. long.	5½ "	.....	10 "	Mucosa slightly hyperaemic.
108	Arteries and veins of large loop.	4 "	.....	17 "	The same.
109	Artery and vein to loop 20 cm. long.	5½ "	.....	10 "	Mucosa normal.
110	Artery, vein and mesenteric arches to large loop.	4 "	.....	20 "	Mucosa necrotic and of brownish-red color.
111	Artery and vein of loop 20 cm. long.	5½ "	.....	10 "	Mucosa but slightly tinged.
112	Vein and mesenteric arches of loop 20 cm. long.	5½ "	.....	10 "	Mucosa somewhat more colored than that in immediate neighborhood.

The Production of Haemorrhagic Infarction in the Isolated Intestine with Artificial Circulation.

The experiments made upon the intestine within the living animal indicate that the cause of haemorrhagic infarction after ligature of the superior mesenteric artery is not to be found in the necrosis of the capillaries nor in venous regurgitation, but in physical conditions within the blood stream itself, due to a slowing of the circulation with absence of an arterial pulse wave.

In case this is true, artificial circulation through the isolated intestine with whipped blood under a low but constant pressure will result in haemorrhagic infarction, provided that an important factor does not lie in the difference between whipped and normal blood. The experiments given in Table XIV show that with the circulation in the isolated intestine similar to

TABLE XIV

Experiments in which Artificial Circulation was Carried on Through the Isolated Intestine with Whipped Blood Diluted with Normal Saline Solution at 37° C.

Experiment	Arterial pressure	Venous pressure	Duration of experiment	Note	Result
113	0–120	0–30	1 hr.	.....	Hyperaemia.
114	66	0–40	35 min.	Rythmic contractions of a large loop while venous pressure was high.	Loop with rythmic contractions hyperaemic; rest of intestine haemorrhagic.
115	0–93	0–50	1 hr.	Vermicular contractions active.	Haemorrhagic infarction.
116	100	?	20 min.	No blood came from the vein.	The same.
117	15	8	4½ hrs.	Intestine handled a great deal.	Spotted infarction.
118	10–80	10	5½ "	The same.....	Hyperaemia.
119	65	4	4½ "	Vermicular contractions active.	No infarction.
120	27	7	4½ "	.....	Infarction.
121	40–65	4	5 "	Parallel experiments. Neither specimen disturbed.	Hyperaemia. Intestine contracted.
122	20–35	1	5 "	The same.....	Infarction.
123	65	1	4½ "	Parallel experiments on two specimens which had been preserved upon ice for 48 hours.	Hyperaemia.
124	20	1	4½ "	The same.....	Infarction.

that in the intestine after ligature of the superior mesenteric artery, haemorrhagic infarction takes place very rapidly.

It has been found that the muscular walls of the intestine show great activity in the isolated intestine for a number of hours after its removal from the body, provided it is nourished with blood through its arteries and is kept at normal body temperature. The short time which elapses (this need not exceed five minutes) while the intestine is being removed from the animal to the warm chamber does not seem to affect this, for in experiments made in this way the activity of the contraction of the muscular walls is as vigorous as when the artificial circulation is established before the normal is broken.

In performing the operation the only precaution necessary is to ligate the duodenum and colon with their mesenteric arches and then cut out the whole intestine with an abundance of the root of the mesentery. The cannulae and the rest are easily applied. In all of the experiments the whipped blood from the same animal diluted a number of times with normal saline solution was used. The pure blood appears to be much too thick for this experiment, as it is difficult to inject it through the capillaries (Exp. 116). In case a large quantity of blood was needed, that which flowed from the vein was whipped and again injected into the artery.

Microscopic Examination of the Mesenteric Circulation. Rate of Venous Outflow.

In Experiments 113-118 the vessels of the mesentery were constantly examined with the low power of the microscope, and similar microscopical examinations were made of the mesenteric circulation after ligature of the superior mesenteric artery in the living animal. Examinations of this sort proved to be difficult for obvious reasons, yet the impressions obtained from continuous study of the same specimen during consecutive hours are fairly definite.

Our apparatus consisted of a microscope illuminated by electric light and completely immersed in the saline solution of the warm bath in which the intestine and mesentery were floated. It was necessary to be careful in handling the mesentery for any stretching of it interfered materially with the circulation. Either hyperaemia or infarction followed in every case.

In these experiments the arteries are at first contracted, but they soon dilate as the blood shoots through them. At first the red corpuscles barely touch one another as they flow through the capillaries, but as they reach the smaller veins there is a tendency for them to accumulate in clumps which are then broken up and carried on into the larger veins. This clumping is observed only here and there, being rapidly broken up by the advancing

column of blood, but it gradually appears in more and more of the veins, and in some it becomes permanent, producing an evident obstacle to the forward movement of the blood. These clumps and columns of red blood corpuscles in the veins may be pushed along by the current or they may move to and fro or eventually become stationary. Similar phenomena of distention with red blood corpuscles, to and fro movement of the same and eventual stasis can also be observed somewhat later in the capillaries. An interesting appearance, often observed in the veins and capillaries, is that of interrupted columns of compacted red blood corpuscles with intervening clear spaces which are sometimes clumps of white corpuscles, sometimes of platelets, sometimes only clear plasma.

Coincident with this partial blocking of the veins and capillaries, red blood corpuscles begin to pass through the walls of these vessels by diapedesis; and after a time the haemorrhage becomes so great that it is difficult to observe the conditions within the vessels. The venous outflow is diminished immediately or shortly after the beginning of the experiment, it then rises, but later on it continuously falls to a minimum.

Fig. 10 gives the pressure curve and the venous outflow of Experiment 118. After the experiment was well under way the blood elements were easily seen in the arterioles, capillaries and small veins. The branching of the artery appeared to be the cause of an equal distribution of the corpuscles within the capillaries. Frequently the red discs stuck together, but these clumps were shattered as the stream of blood broke to enter the branches of the artery. Throughout the capillaries the red corpuscles were well separated, but as they entered the small veins the corpuscles again began to form into clumps. These clumps of corpuscles were nearly always headed by hyaline masses apparently composed of blood platelets. So long as a clump of blood corpuscles met no obstacles on its way to a larger vein nothing happened, but as soon as a clump met another clump as the venous bed became smaller, a complete obliteration of a main branch followed. Frequently pictures, as shown in Fig. 11, were seen—columns of blood headed by hyaline masses would come against, but not enter, a venous stream, *b*, which remained unbroken. It seemed as if the force back of the column, *a*, was not strong enough to drive it into the main current, *b*, which was very rapid. Increasing the arterial pressure forced column, *c*, to enter the main stream but it was extremely difficult to dislodge the column, *a*. After raising the arterial pressure several times to 70 mm. Hg. the column, *a*, began to vibrate, then to advance slowly and finally it shot into the main stream. After the experiment had continued for two hours nearly all the veins were blocked, but raising the arterial pressure removed the obstruction. During the fourth and fifth hours (Fig. 10) obstruction due to the forma-

tion of clumps in the veins, took place a second time. Each time this condition accompanied low arterial pressure, and it was followed by a diminished venous outflow and an intense hyperaemia of the intestine.

In Experiment 119 the arterial and venous pressure were kept constant during its entire duration, but the venous outflow varied greatly, as shown in Fig. 12. The intestine was handled very little in observing the capillary circulation with the microscope.

Throughout the experiment there was but slight tendency for the corpuscles to form in clumps and no infarction followed. During the third hour there was a marked dilatation of the veins and an increased outflow of blood. At this time the lymphatic channels of the mesentery carried off a great deal of lymph in which there was a considerable number of red blood corpuscles.

The record of Experiment 120 is given in Fig. 13. The high arterial pressure at the beginning and again at the end of the experiment need not be taken into consideration for the intervening four hours can be considered alone. Again we had the curve of the venous outflow, which towards the end of the experiment gradually fell nearly to zero. At this time the infarction of the mucosa was complete and the second rise of arterial pressure caused it to intensify greatly.

Experiments 121 and 122 were made upon the intestine of dogs of the same size and under like conditions at the same time, differing only in that the arterial pressure in one was high and in the other low. Fig. 14 gives the curves of Experiment 121. The outflow curve is the usual one. There was no infarction of the mucosa, it was only hyperaemic.

The arterial pressure of Experiment 122 was changed several times in order to reduce the venous outflow to the lowest possible amount. During the whole experiment 500 c. c. of blood entered the artery and but 116 c. c. came from the vein. The rest was used in the production of the infarction which followed.

The whipped blood and the intestines used in making Experiments 123 and 124 were first placed in the ice box for 48 hours, then placed in the warm chamber and artificial circulation carried on through one of them at 65 mm. and the other at 20 mm. Hg. The outflow curve of 123 is given in Fig. 15; no blood came from the vein in 124. In these two experiments the conditions were entirely mechanical as the intestine as well as the blood was dead. With the low pressure infarction followed, while with the high pressure the mucosa was only hyperaemic at the end of the experiment.

Conditions for Production of Haemorrhagic Infarction

The experiments given in Table XIV prove that haemorrhagic infarction is produced in the isolated intestine under conditions similar to those under

which it occurs within the living body. Moreover whipped blood appears to hasten the infarction. The amount of blood which flows from the veins when the pressure is constant, sometimes after a transitory diminution, increases during the first hour of the experiment then gradually diminishes. The first or the first and second variations of the venous outflow seems to run parallel with the activity of the contractions of the muscular walls of the intestine. Similar curves have been demonstrated by Mosso in other organs either alive or dead through which circulation is carried on with whipped blood or with blood serum.

The cause of the final diminution of the venous outflow, while the intestinal mucosa is becoming hyperaemic and infarcted, is to be sought within the blood current due to the absence of a pulse wave as already demonstrated by von Frey. Von Frey made the discovery that if artificial circulation is carried on through an organ with an intermittent pressure imitating the normal pulse, the venous outflow equals the arterial inflow. When, however, the arterial pressure is constant the venous outflow diminishes, due partly to contraction of the capillary walls and partly to a remarkable clogging of the capillaries with red blood corpuscles, as we have found in our experiments. According to von Frey a red corpuscle is first caught at the junction of two capillaries, partly obstructs their lumina, thus acting as a filter which catches up more red corpuscles which finally cause complete obstruction. A pulsating arterial pressure will easily dislodge the first corpuscle and thus keep the capillary stream open.

In our experiments we found that the first obstruction began by clumps of corpuscles lodging in small veins, but we were unable to determine whether these are first formed in the capillaries, as described by von Frey, then become dislodged, to be carried on into the smaller veins and in turn obstruct them. In the intestine the sectional area of the capillaries is 300 times that of the main artery; in the smallest veins it falls to 170, and in the main vein to 4. The moving column of blood must divide at least 50 million times during a small fraction of a second in passing from the main arteries to the capillaries. This rapid divison and subdivision of the column appears to be sufficient to keep the corpuscles within the arterial stream from sticking together. But when the capillaries are reached we have a stream which is composed of a single row of corpuscles which can no longer be divided, and also a relatively slow circulation. Everything is favorable for them to cling to the capillary walls at their points of division as described by von Frey. If the clumps here formed are dislodged they must at once enter a venous bed, which is but half as large as the capillary bed and which further on diminishes in section area very rapidly, the speed of the circulation at the same time increasing in the inverse ratio of the area of the venous bed. The clumps already started in the capillaries are carried to the small veins and

soon obstruct them, and this in turn favors further obstruction of the capillaries, as well as of the neighboring veins for a greater quantity of blood must now pass through them. Finally the rapidity of the capillary circulation is greatly diminished and the arterial blood pressure is now extended in greater part than before to the capillaries.

It is evident from the preceding description that the phenomena observed under these peculiar circulatory conditions are in large part dependent upon the physical properties of the blood especially upon its viscosity and the presence and physical characters of suspended particles which readily stick together; and differ in important respects from those which would occur under similar conditions with a thin homogeneous fluid. The pressure gradient from the arteries to the veins in the ischaemic area is so low that the red blood corpuscles cannot fully overcome the resistance in the veins and capillaries. They accumulate in these situations and probably undergo some physical change by which they become adherent to one another and to the vascular wall. The absence of the normal pulse-waves prevents the breaking up of these masses of corpuscles, the long pulse-waves sometimes observed, having little or no effect in distintegrating the masses. In this way numerous small veins and capillaries become blocked, with the resulting rise of intracapillary pressure and diminution of outflow of blood through the veins.

The diapedesis is due to stagnation of the blood, and to blood pressure. Without a certain height of pressure there is no diapedesis; and with a given retardation and stasis of blood-current, the higher the intracapillary and intravenous pressure the greater the amount of the diapedesis. The matter which needs explanation is that the diapedesis may occur with lower than normal arterial pressure, and through vessels walls apparently unaltered. This we attribute to the fact that the red corpuscles, in consequence of the slow circulation and absence of pulse-wave, have opportunity to become engaged in the narrow paths followed by the lymph as it passes between the endothelial cells. Diapedesis is a slow process, and the channels for it are much smaller than the diameter of red corpuscles. Unless the red corpuscles can get started on the path between the endothelial cells, they cannot traverse it; and unless the circulation is very much slowed and the outer plasmatic current obliterated there is no opportunity for the corpuscles to become engaged between the endothelial cells, provided, that is, the vascular wall is normal. With greatly retarded circulation there is this opportunity and when the way in front is blocked by compact masses of red corpuscles, and sometimes by actual agglutinative thrombi, the only path open for the corpuscles is that followed by the lymph between the endothelial cells. This, then, becomes the direction of the least resistance for their movement.

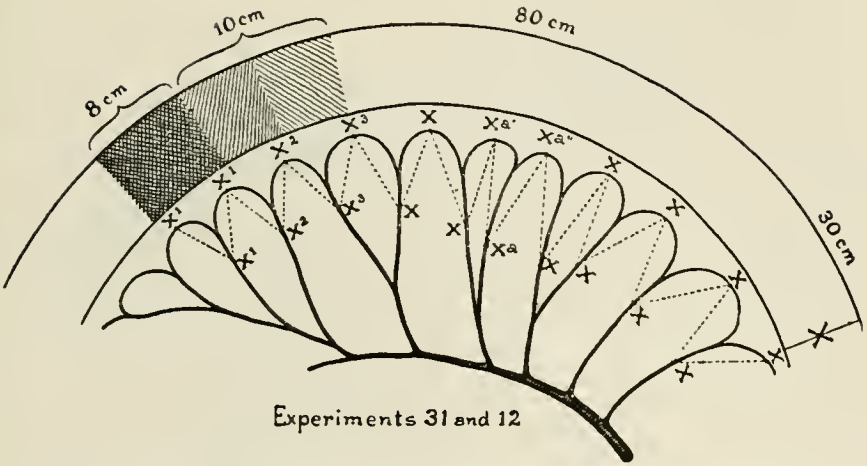


FIG. 1.—Diagram of the Superior Mesenteric Artery and Small Intestine to illustrate Experiment 31. Ligatures were applied at the points marked *X*. The degree of shading of the intestine indicates the intensity of the infarction of the mucosa. The numbers opposite the convex border give the length in centimeters of the infarcted zones. The letters *a*, *a'* and *a''* refer to Experiment 12.

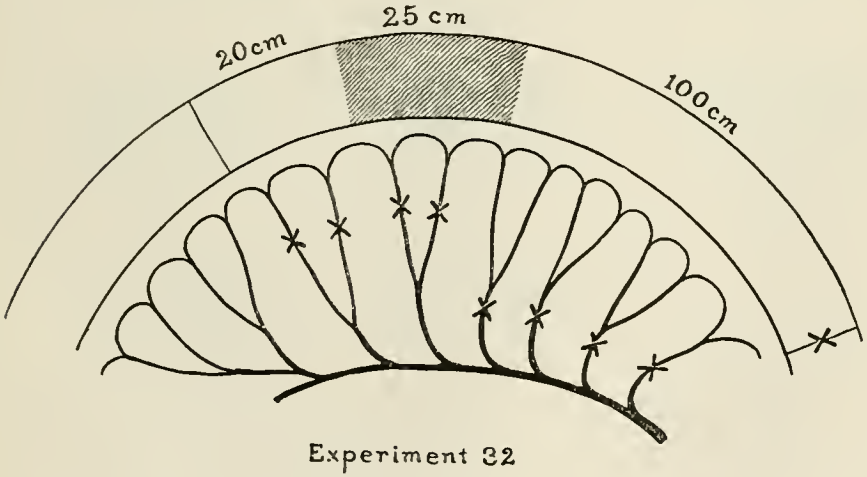


FIG. 2.—Diagram to illustrate Experiment 32. *X*, point of ligatures of the arteries and intestine. The infarction is marked by the shaded area.

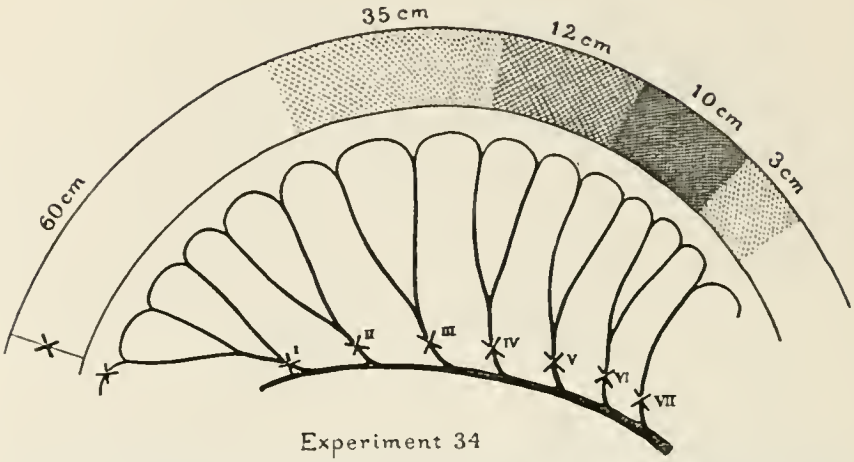


Fig. 3.—Diagram to illustrate Experiment 34. *X*, point of ligatures of the arteries and intestine. The zone of mucosa 3 cm. long is oedematous, the zone 10 cm. long is infarcted and so on.

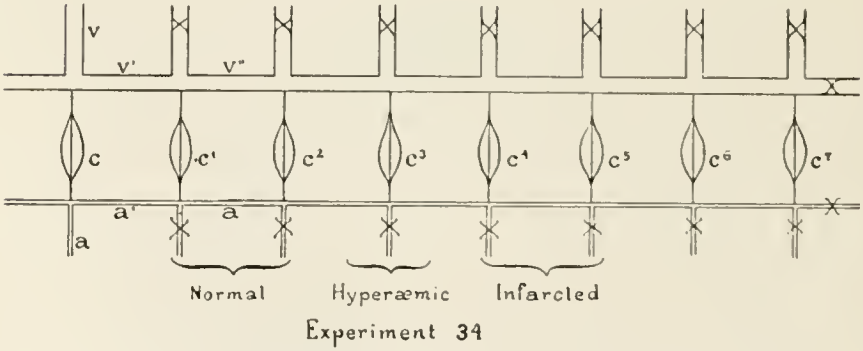


Fig. 4.—Scheme of vessels of Experiment 34. *A*, artery; *v*, vein; *c*, capillary.

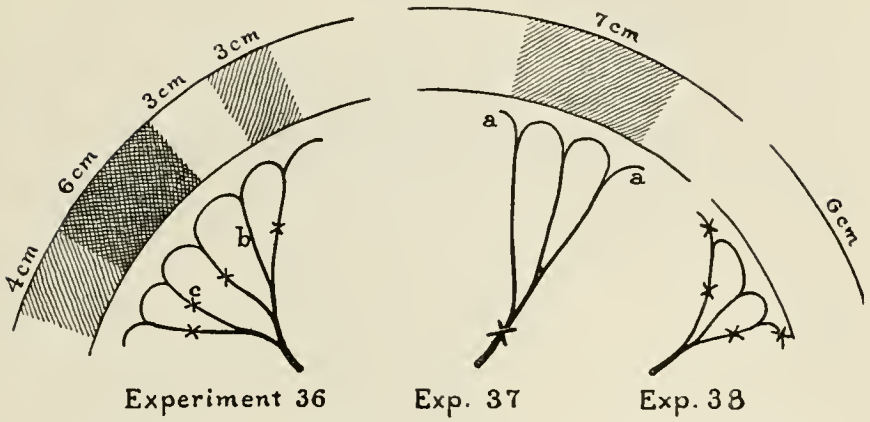


FIG. 5.—Diagram of Experiments 36, 37, and 38. *X*, point of ligature.

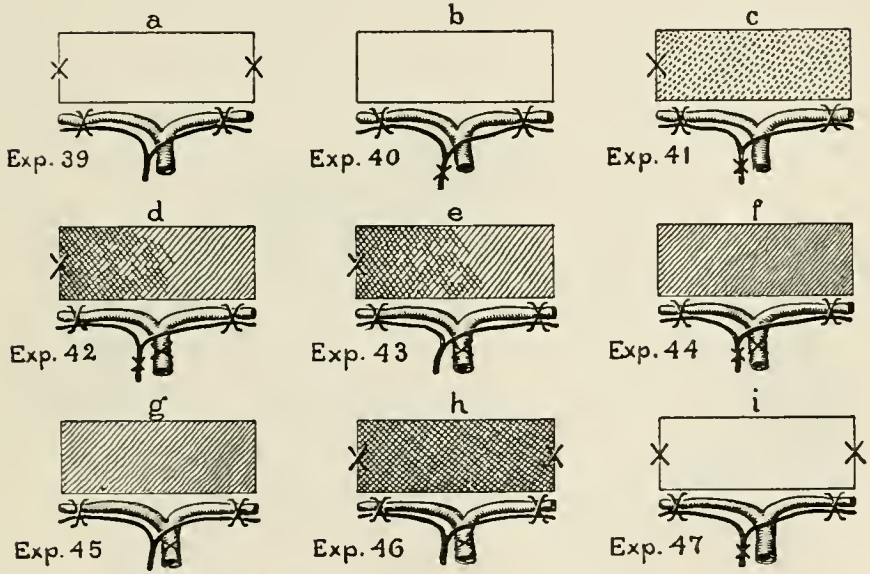
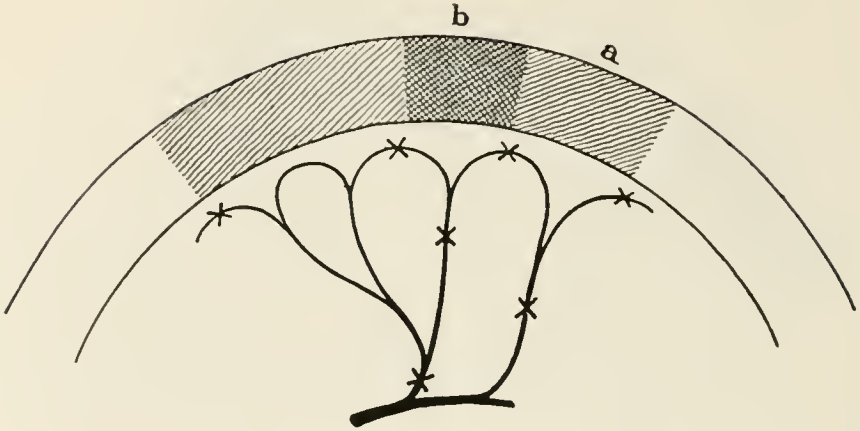
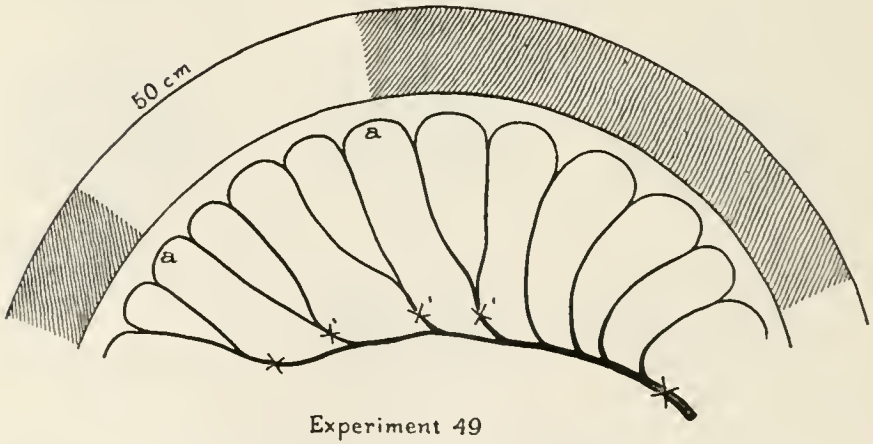


FIG. 6.—Diagram of Experiments 39 to 47. The artery is solid and the vein outlined; *X*, point of ligature; the shading indicates the intensity of the hyperaemia or the infarction of the mucosa.



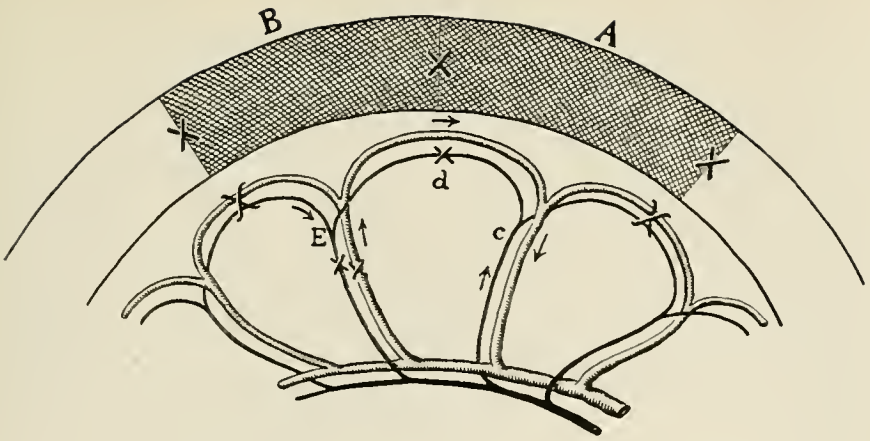
Experiment 48

FIG. 7.—Diagram of Experiment 48.



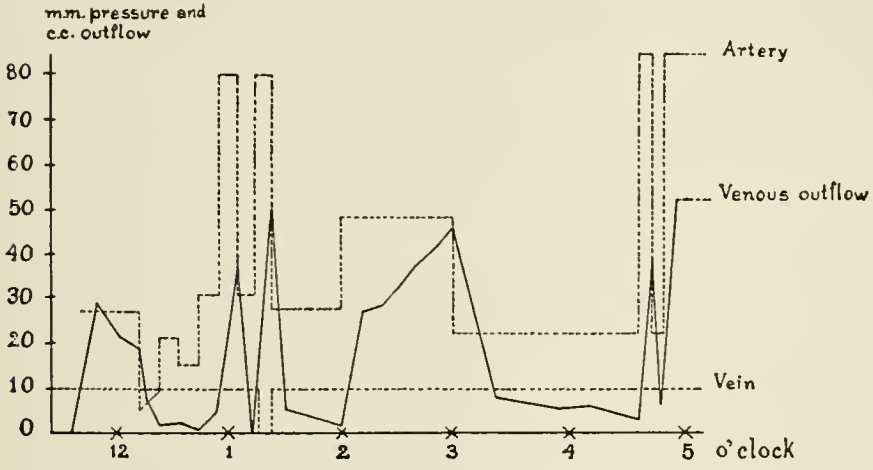
Experiment 49

FIG. 8.—Diagram of Experiment 49.



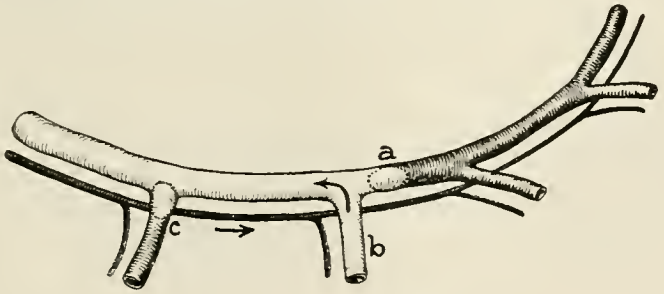
Experiments 66, 68 and 69.

FIG. 9.—Diagram of Experiment 66. *X*, points of ligatnre; arrow shows direction of the circulation. The solid vessel represents the artery and the outlined vessel the vein. *E*, point artery was opened in Experiments 68 and 69.



Experiment 118

FIG. 10.—Curve of Experiment 118. The broken line represents the arterial pressure; the dotted line the venous pressure; the unbroken line the average outflow in c. c. for 5 minutes reduced 5 times.



Experiment 118

FIG. 11.—Tracing of a small vein partly blocked with clumped red corpuscles or agglutinative thrombi from Experiment 118.

FIG. 12.—Curve of Experiment 119. The outflow curve is reduced 12 times.

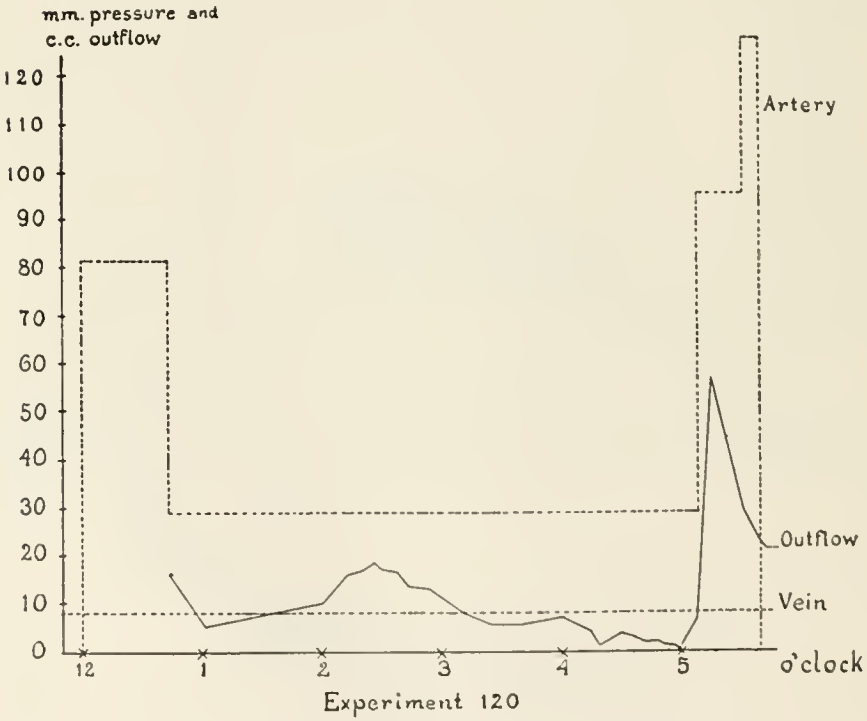


FIG. 13.—Curve of Experiment 120. The outflow curve is reduced 10 times.

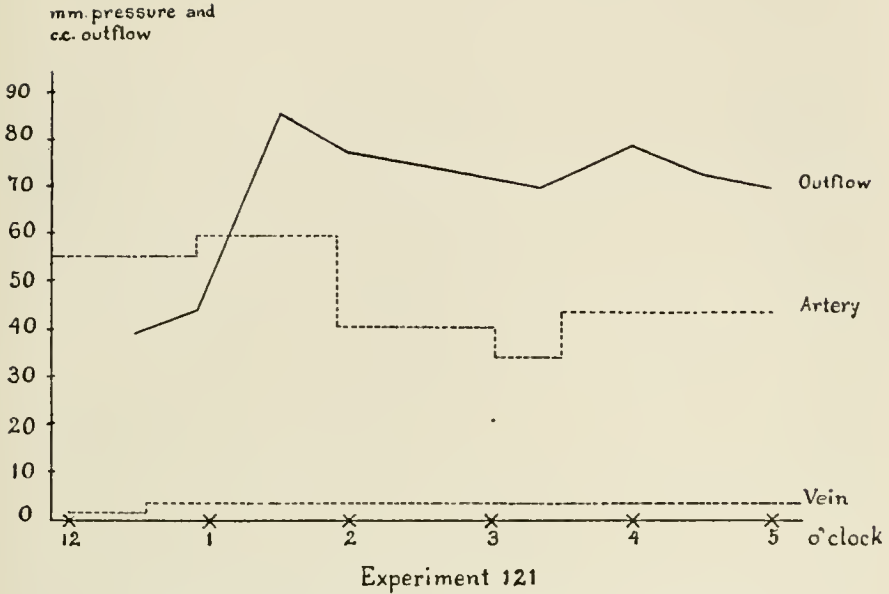


FIG. 14.—Curve of Experiment 121. The outflow curve is reduced 6 times.

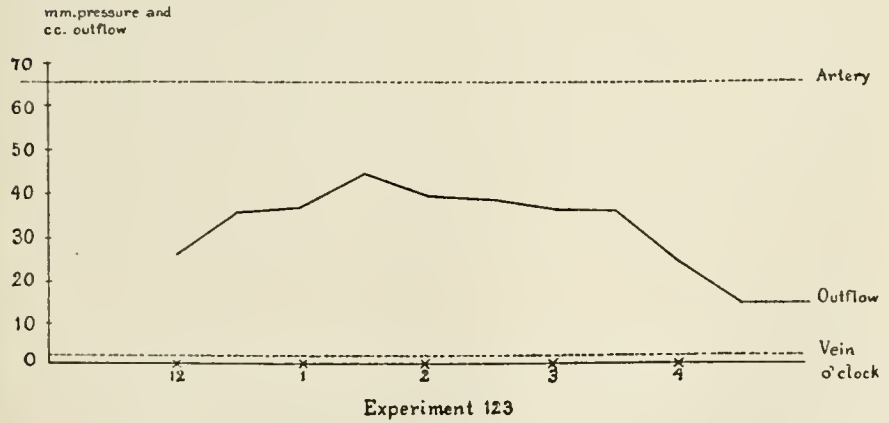


FIG. 15.—Curve of Experiment 123. The outflow curve is reduced 6 times.

THROMBOSIS[1]

Definition.—A thrombus is usually defined as a blood-coagulum, formed in the heart or vessels during life. This definition applies to most cases; but, in order to meet the objections of those who do not concede that all thrombi are genuine coagula, and to give due prominence to the participation of blood-platelets and corpuscles, a thrombus may be more broadly defined as a solid mass or plug formed in the living heart or vessels from constituents of blood. Thrombosis is the act or process of formation of a thrombus, or the condition characterised by its presence.

Structure of Thrombi.—The formed elements which may enter into the composition of fresh thrombi are blood-platelets, fibrin, leucocytes, and red corpuscles. These elements may be present in varying number, proportion, and arrangement, whence there results great diversity in the appearance and structure of different thrombi.

The two main anatomical groups of thrombi are the red and the white thrombi. Many of the mixed thrombi may be regarded as a variety of the white thrombus. In addition there are thrombi of relatively minor importance composed wholly or chiefly of leucocytes, of fibrillated fibrin or of hyaline material.

Red Thrombi.—These are formed from stagnating blood, and in the recent state do not differ in appearance and structure from clots formed in shed blood. They are made up of fibrillated fibrin and of red and white corpuscles in the same proportions as in the circulating blood, or the white corpuscles may be somewhat in excess. If any part of such a red thrombus be exposed to circulating blood, white material, consisting of platelets with fibrin and leucocytes, is deposited upon it. This deposit may aid in distinguishing the thrombus from a post-mortem clot.

White and Mixed Thrombi.—Most thrombi are formed from the circulating blood, and are white, or of a mixed red and white colour. The white or gray colour is due to the presence of platelets, fibrin, and leucocytes, occurring singly, or, more frequently, in combination. The admixture with red corpuscles is not an essential character of the thrombus, although it may be sufficient to give it a predominantly red colour.

Fresh white human thrombi, when examined microscopically, are seen to be composed of a granular material, usually in islands or strands of vary-

[1] In: Syst. Med. (Allbutt), Macmillan Co., Lond., 1899, VII, 155-285.

ing shape and size, around and between which are fibrin and leucocytes with a larger or smaller number of entangled red corpuscles. The granular matter, to which the older observers attached comparatively little importance, and which they interpreted as granular or molecular fibrin or the detritus of white corpuscles, is now known to be an essential constituent of the white thrombus, and is composed chiefly of altered blood-platelets. Intact polynuclear leucocytes are usually numerous in the margins of and between the masses of platelets, and may be scattered among the individual platelets. Not less important is the fibrillated fibrin, which is generally present in large amount. It is particularly dense in the borders of the platelet-masses, and stretches between them in anastomosing strands, or as a finer network containing red and white corpuscles. Within the accumulations of platelets in fresh thrombi fibrin is often absent, or is in small amount. These various constituents of the thrombus often present a definite architectural arrangement, and soon undergo metamorphoses which will be described subsequently.

Thrombi of the kind just described, and as we find them at autopsies on human beings, are completed products, and it is difficult, indeed generally impossible, from their examination to come to any conclusion as to the exact manner of their formation; particularly as regards the sequence and relative importance of their different constituents. So long as the knowledge of the structure of thrombi was limited to that derived from the study of these completed plugs, the coagulation of fibrin was generally believed to be the primary and essential step in their formation; although Virchow pointed out the greater richness in white corpuscles as a feature distinguishing them from postmortem clots.

Zahn, in 1872, was the first to make a systematic experimental study, mainly in frogs, of the mode of formation of thrombi. He came to the conclusion that the process is initiated by the accumulation of white corpuscles which, by their disintegration, give rise to granular detritus. This is quickly followed by the appearance of fibrin, which was readily accounted for by Weigert on the basis of Alexander Schmidt's well-known suggestion of the origin of fibrin ferment from disintegrated leucocytes. Zahn's views, anticipated in part by Mantegazza in 1869, and confirmed by Pitres in 1876, gained prompt and wide acceptance.

Continued experimental study of the subject, however, especially upon mammals, led to opposition to Zahn's conclusions, and favoured the opinion, now generally accepted, that the ordinary white thrombus starts as an accumulation not of leucocytes but of blood-platelets. The investigators chiefly concerned in the establishment of this doctrine are Osler (1881-82), Hayem (1882), Bizzozero (1882), Lubnitzky (1885), and Eberth and Schimmelbusch (1885-86).

There is no difficulty in producing thrombi experimentally by injury, either mechanical or chemical, to the vessel-wall; or by the introduction of foreign bodies into the circulation. If the early formation of such a thrombus be observed under the microscope in the living mesenteric vessels of a dog, as was done by Eberth and Schimmelbusch, it is seen that the first step consists in the accumulation of blood-platelets at the seat of injury. These plates, in consequence of their viscous metamorphosis, at once become adherent to each other and to the wall of the vessel, and thus form plugs which may be subsequently washed away into the circulation, but which sometimes so increase in size as to obstruct the lumen of the vessel completely. Red and white corpuscles may be included in the mass of platelets; but their presence at this stage is purely accidental; they are not to be regarded as essential constituents of the thrombus in its inception.

The microscopial examination of young experimental thrombi confirms the results of these direct observations, and affords information as to their further development. To obtain a clear idea of this development, thrombi should be examined at intervals of minutes from their beginning to those half an hour old or older. I reported the results of such an experimental study in 1887. The material composing the youngest thrombi formed from the circulating blood appears macroscopically as a soft, homogeneous, gray, translucent substance of viscid consistence. Microscopically it is made up chiefly of platelets, which are seen as pale, round, or somewhat irregular bodies, varying in size but averaging about one-quarter the diameter of a red corpuscle.

Leucocytes, which may be present in small number at the beginning, rapidly increase in number, and within the first fifteen minutes to half an hour they are usually in such abundance that at this stage of its formation they must be considered an essential constituent of the thrombus. They tend to collect at the margins of the platelet-masses and between them. These leucocytes are nearly all polynuclear, and usually present no evidence of necrosis or disintegration.

With the accumulation of leucocytes, fibrillated fibrin, which at first was absent, makes its appearance; being, as pointed out by Hanau, especially well marked and dense in the margins of the masses of platelets. Within these masses it is usually absent. The rapidity with which leucocytes and fibrin are added to the masses of platelets varies much in different cases. At the end of half an hour the thrombus may be composed of platelets, leucocytes, and fibrin with entangled red corpuscles, in essentially the same proportions and with the same arrangement as in the human thrombi already described; or even after several hours it may still consist almost wholly of platelets.

The prevailing view is that platelets exist in normal blood, where they circulate with the red corpuscles in the axial current. In accordance with this view, many observers, following Eberth and Schimmelbusch, explain the beginning of a white thrombus by the accumulation of pre-existing platelets upon a foreign body, or, in consequence of slowing or other irregularities of the blood-flow, on the damaged inner wall of the heart or vessels. Contact with the abnormal surface sets up an immediate viscous metamorphosis of the platelets, whereby they adhere to each other and to the foreign body or vascular wall. Eberth and Schimmelbusch designate this process as conglutination, and distinguish it sharply from coagulation, which they regard as a later event in the development of the thrombus.

Those who hold with Löwit, that platelets do not exist in normal blood, believe that they are produced at the moment of formation of the thrombus, as the result of injury to the blood; and many who believe that they are in normal blood not as independent elements, but as derivatives from leucocytes or red corpuscles, consider it probable that those in the thrombus are formed, at least in part, in consequence of such injury. Although there are observations which suggest that platelets may be derived from leucocytes, there is no evidence that the masses of platelets found in incipient thrombi come from leucocytes previously attracted to the spot.

Strong evidence has been recently presented, by Arnold, F. Müller, and Determann, in favour of the origin of platelets from red corpuscles. Wlassow, working in Ziegler's laboratory, finds that the white thrombus is formed primarily by the destruction of red corpuscles, and is composed at the very beginning of shadows of red corpuscles, corpuscular fragments both with and without hæmoglobin, granular material and platelets of nucleo-proteid substance; all derived from disintegrating red corpuscles. A similar view is entertained by Mosso, Klebs, Arnold, Ziegler, and F. Müller.

The accumulation of leucocytes in the young thrombus may be explained partly by mechanical causes,—the most evident being the projecting, irregular, sticky substance of the platelet masses associated with slowing and eddies of the blood-stream,—and partly by chemiotactic influences.

Whatever difficulties there may be, in accounting for the fibrin, relate to the general subject of coagulation of the blood (see Professor Foster's article in Allbutt's "System of Medicine," VI, p. 403) rather than to the special conditions of the thrombus. As to the participation of platelets in the production of fibrin, opinion is divided; and upon this point the study of thrombi has not afforded conclusive evidence one way or the other. The usual absence of fibrin within the platelet masses for a considerable time after their formation may be thought to speak against the generation of fibrin-ferment by the platelets. But if, as is probable, the platelets contain

nucleo-proteid, it would be reasonable to suppose, in accordance with current physiological ideas, that they can yield one of the fibrin factors; and it may be that in these compact masses there is not enough fibrinogen furnished by the plasma to generate an appreciable amount of fibrin. The characteristic dense ring of fibrin immediately around the platelet masses, where there is abundant fibrinogen, could be interpreted in favour of the liberation of fibrin-ferment by the collected platelets. By the time, however, that the fibrin appears, leucocytes have also accumulated in the same situation; and they, either alone or together with the platelets, may be the source of the ferment; although, as already stated, the leucocytes in young thrombi generally show apparently intact nuclei and cytoplasm.

Does the recognition of the described mode of development of a white thrombus necessitate a radical break, such as that made by Eberth and Schimmelbusch, with the old and still common conception that a thrombus is essentially a blood coagulum? This question applies only to the first stage of formation of a white thrombus, for the completed thrombus is undoubtely a coagulum. It is, however, of both scientific and practical interest to inquire whether coagulative phenomena usher in the process of thrombosis or are merely secondary. A decisive answer to this question cannot be given until we are better informed than at present concerning the chemistry and morphology of coagulative processes, and the source and properties of the granular material constituting the youngest thrombi. The possibility that this material is already coagulated; and falls into the category of the coagulative necroses, has been suggested by Weigert; but without any proof of this view. There is greater probability that the accumulation and metamorphoses of the so-called platelets in beginning thrombi represent a preparation for coagulation or a first step in the process. As Hammersten has pointed out, two chemical phases are to be distinguished in the process of coagulation; namely, the formation of fibrin ferment from its zymogen, and the transformation of fibrinogen into fibrin under the influence of this ferment. Morphological phases may also be distinguished, and the platelet stage of thrombus formation may be interpreted as the first morphological phase of coagulation in circulating blood. According to Wlassow a similar morphological phase may be recognised in the clotting produced by whipping shed blood. It would lead too far afield to enter here into a discussion of the arguments in favor of this view; but much in its support is found in recent chemical and morphological studies of extravascular and intravascular coagulation, and of the anatomical and chemical characters of blood platelets.[1] It does not appear,

[1] This recent work has been critically reviewed by Löwit in Lubarsch-Ostertag's Ergebnisse, 1897.

therefore, that we are called upon at present to make any such radical revision of the traditional conception of white thrombi as coagula, as has been advocated of late years by some writers.

Leucocytic Thrombi.—As has already been explained, leucocytes, although they do not usher in the process of ordinary thrombosis, make their appearance at an early stage, and other accumulate in such numbers as to constitute a large part of the thrombus. My studies of experimental and human thrombi have led me to assign to them a more important part in the construction of white thrombi than that indicated by Eberth and Schimmelbusch. Whether the regular mural white thrombi ever arise as a collection of leucocytes, in the manner described by Zahn, is uncertain. Such a mode of development, if it occurs, is, I think, exceptional. Intravascular plugs, however, occur, which are made up wholly or predominantly of polynuclear leucocytes. These are found mainly in small vessels in acutely inflamed regions, where they are to be regarded as inflammatory and probably chemiotactic in origin. Leucocytic masses may also be found after death in small vessels in leucocythæmia, and in diseases with marked leucocytosis; but it is probable that these are not genuine obstructing plugs.

Purely Fibrinous Thrombi.—As will be described subsequently, fibrin usually increases in amount with the age of the thrombus. The masses of platelets may be replaced by fibrin, and leucocytes may degenerate; so that many old, unorganised thrombi consist of practically nothing but dense fibrin, in places hyaline. I do not, however, desire now to call especial attention to these old, metamorphosed thrombi.

One sometimes finds in inflamed areas, less frequently under other circumstances, the vessels, particularly those of small size, partly or completely filled with fibrillated fibrin, presenting such an arrangement and configuration as to indicate coagulation during life. Neither leucocytes nor platelets need take part in the formation of these plugs of pure fibrin, although sometimes they are present. K. Zenker has well described the microscopical appearances in these cases. Whorls or brush-like clumps of fibrin may spring at intervals from the wall of the vessel, where they are attached especially to necrotic endothelium or to points devoid of endothelium. The fibrin may be disposed regularly, often in stellate figures, around definite centres in which, perhaps, a necrotic cell or fragment, endothelial or leucocytic, or a clump of platelets can be demonstrated. The fibrin is often notably coarse. The affected vessels are not usually filled completely with fibrin, and they can be artificially injected. In croupous pneumonia such fibrinous masses are regularly present, both in capillaries and larger vessels of the hepatised area. These purely fibrinous coagula are of anatomical rather than clinical interest.

Hyaline Thrombi.—These are of more interest and importance than the purely fibrinous and leucocytic thrombi just described. The presence of hyaline material in old white thrombi will be spoken of subsequently. To von Recklinghausen we especially owe the recognition of hyaline thrombi as a distinct class. They are found especially in the capillaries, but may occur also in the smaller arteries and veins. The capillaries are filled with a refractive, homogeneous, translucent, colourless or faintly yellow material, which stains well with Weigert's fibrin dye. The same material may partly or completely fill the smaller arteries and veins. Balls, as well as cylindrical masses, of this hyaline substance may be found, especially in the cerebral vessels.

This hyaline thrombosis has been observed in a variety of conditions, partly general, partly local. It occurs especially in infective and toxic diseases. Kriege found extensive hyaline thrombosis in the small vessels after freezing the rabbit's ear. Von Recklinghausen had previously attributed to this cause spontaneous gangrene of both feet occurring in an old woman who had suffered repeatedly from slight frost-bites; and he likewise found the same hyaline vascular plugs in cases of mortification following experimental ergotism. Capillary hyaline thromboses are common in the lungs in pneumonia, and in hæmorrhage infarcts. In general infective and toxic states they may be present in the liver, the lungs, and, above all, in the kidneys.

The most striking examples of this form of thrombosis, with which I am acquainted, are encountered in the renal capillaries, chiefly of the glomeruli, of swine dead of hog-cholera; or of animals infected with the hog-cholera bacillus. In extreme cases there is complete anuria; and it may be impossible to force more than a minimal amount of injecting fluid into the renal vessels. Sections stained with Weigert's fibrin-stain look as if the capillaries had been injected with Berlin blue. Ribbert found similar hyaline thrombi in the kidneys of rabbits inoculated with *S. pyogenes aureus*. I have repeatedly found them in various experimental infections, and in human infections. They occur in eclampsia. Bacteria are not necessarily present, so that toxins are probably the underlying causative factor, and for this there is experimental evidence.

Klebs and others have thought that the hyaline material is derived from coalesced and altered red corpuscles. Red corpuscles may in fact be so crowded together, and apparently coalesced, as to appear as nearly homogeneous yellowish cylinders (globular stasis). The genuine hyaline thrombi have the staining reactions of fibrin, and are often continuous with ordinary fibrillated fibrin in larger vessels. Transitions between fibrillated fibrin and the hyaline material can sometimes be seen; but it is often impossible

by any staining to resolve the latter into a fibrinous network. If the recent views previously mentioned concerning the origin of platelets from red corpuscles and the participation of these corpuscles in the process of coagulation be accepted, there would be no difficulty in adopting Klebs's hypothesis as to the origin of hyaline thrombi from red corpuscles. Von Recklinghausen and Kriege find evidence that the hyaline substance is derived from leucocytes.

Growth, Metamorphoses, and Organisation of Thrombi.—Thrombi in their growth assume various characters to which special epithets are applied. A thrombus formed from the circulating blood is at first parietal or mural, but by continued growth it may fill the vessel and become an occluding or obstructing thrombus. A primitive or autochthonous thrombus, caused by local conditions, may be the starting-point of a continued or propagated thrombus, extending in the course of the thrombosed vessel and perhaps into communicating vessels. A secondary or encapsulating thrombus is one which starts from an embolus of thrombotic material. A continued thrombus is also often spoken of as secondary. Thrombi are, with rare exceptions, adherent, at least in places, to the wall of the vessel or the heart. Mural thrombi appear more or less flattened against the vessel wall, or they may project in a globular or polypoid form into the lumen. Their free surface is generally rough. Loose thrombi in the heart are called ball-thrombi.

The thrombus grows in length chiefly in the direction of the current of blood; but it may grow in the opposite direction. The intact and growing end of the thrombus is a flattened blunt cone usually not adherent to the wall of the vessel; it is sometimes compared in shape to a serpent's head. A venous thrombus extends in the direction of the circulating blood, not only as far as the next branch, but frequently a greater or less distance beyond it, in the form of a mural thrombus. A thrombus is at first soft in consistence and moist; but by contraction and extrusion of fluid it becomes more compact, firmer, drier, and more granular in texture.

Mural thrombi, especially small ones, such as fresh vegetations on the cardiac valves, may occur without any definite arrangement of the constituent elements. Such thrombi may consist almost wholly of platelets; but it is most exceptional not to find at least some admixture with leucocytes and fibrin coagulated *intra vitam*.

The larger white and mixed thrombi often present a typical architecture. The stratified structure has long been known and emphasised. More recently Zahn has directed especial attention to the rib-like markings on the free

surfaces,[3] and Aschoff to the internal architecture of white and mixed thrombi. Microscopical sections of these thrombi often show an exquisitely trabecular structure due to irregularly contoured, anastomosing columns and lamellæ, of varying size and shape, which spring at intervals from the wall of the vessel and extend, usually in an oblique or twisting direction, toward the free surface of the thrombus, upon which their extremities from the network of whitish lines or the transverse ribs noted by Zahn. If the thrombus be detached from the inner wall of the vessel, similar projecting lines and dots can be seen on its attached surface and often on the inner lining of the vessel. This trabecular framework of the thrombus is composed of masses of platelets with cortical layers of fibrin and leucocytes, as already described. The whole arrangement is aptly compared by Aschoff to branching coral stems. The spaces between the trabeculæ contain blood which during life may be fluid or may have coagulated; or they may contain only fibrin and leucocytes, or an indefinite mixture of platelets, fibrin and red and white corpuscles. Between the lamellæ and columns bands of fibrin with or without platelets, often stretch loosely and in a curved manner, the concavity of the curve looking toward the axis of the vessel. Aschoff explains the coral-like architecture and the ribbed surface of the thrombus partly by the oscillatory or wave-like motion of the flowing blood, which, as previously suggested by Zahn, may account for the ribs, and partly by slight irregularities of surface level normally present in the inner lining of vessels. Zahn finds an analogy between the ribs of a thrombus and the ripple-marks in sand at the edge of the sea, or at the bottom of flowing streams. Before Zahn, Wickham Legg, in 1878, described the surface of a cardiac thrombus as "marked by lines resembling the impressions made by the waves on a sandy shore."

The usual explanation of the red and white stratification of mixed thrombi is that the thrombus is deposited in successive layers, of which the red are formed rapidly and the white more slowly. There are manifest difficulties in such an explanation. It is more probable that the red layers are error clots formed from blood brought to a standstill. Blood entering crevices, spaces, and clefts resulting from the irregular mode of growth of the thrombus, or from its contraction, or from the blood-stream, often with increase of pressure in consequence of the thrombotic barrier, undermining and splitting the white substance, at first soft and later brittle, of the thrombus, may readily stagnate and clot. Indications of such a splitting of the thrombus

[3] A number of writers before Zahn observed the markings on the surfaces of thrombi. Bristowe in 1855 spoke of the "peculiar ribbed appearance" of the surface of cardiac thrombi (Trans. Path. Soc. London, VII, p. 141).

by the circulating blood are often seen in horizontal white lamellæ covering red layers and present within them: these lamellæ are apparently split off from the general framework and bent in the direction of the blood-current. The typical architecture of the thrombus may not appear, or may be obscured or destroyed by displacement of its parts through the blood-stream, especially when this is forcible: hence it is often missed in arterial thrombi. White thrombi are, as a rule, microscopically mixed thrombi; and in colour there is every transition from these to thrombi so red that careful examination is required for the detection of the white substance.

In long propagated venous thrombi smaller white thrombus-masses often alternate in a longitudinal direction with longer red ones. The explanation of this is that a primary white thrombus is formed, often starting from a valvular pocket. This becomes an occluding thrombus, and the column of blood reaching to the nearest branch, or to the confluence of two important veins, is brought to a standstill, and forms a red, obstructing thrombus. At the extremity of this, where the blood enters from the branch, another white occluding thrombus may be formed, to be followed again by a red thrombus, and so on. Thrombi are sometimes described as red in consequence of failure to detect the small white autochthonous part of the thrombus. In fact the term mixed thrombus is applied to three different appearances of thrombi: (*a*) an intimate mixture of gray and red substances; (*b*) stratification in successive gray and red layers, and (*c*) red propagated clots consecutive to autochthonous white or mixed thrombi.

In old thrombi various metamorphoses have occurred which obscure or obliterate the typical structure and architecture of the younger ones. The masses of platelets, although they may persist a long time, become finely granular, sometimes almost or quite homogeneous in texture. They are invaded by fibrin, especially along the edges of spaces and clefts which appear. Notwithstanding these profound changes a certain configuration and a differentiation in staining properties often enable us to recognise the sites of the original columns and lamellæ of platelets. The leucocytes, often at an early date, undergo fatty degeneration and necrosis, their nuclei disappearing both by karyolysis and karyorrhexis. The leucocytic detritus adds to the granular material of the thrombus. The red corpuscles are decolourised and fragmented. The hæmoglobin is in part dissolved and, after organisation begins, is partly transformed into amorphous and crystalline hæmatoidin. These pigmentary transformations impart a brownish red colour to red and mixed thrombi. Fibrin increases in amount and becomes coarse and dense. The part of the thrombus adjacent to the vessel-wall is often converted into compact concentric layers of fibrin at a period when masses of platelets are well preserved nearer the lumen. The hyaline material, which

is very frequently found in layers and clumps in old thrombi, may be derived both from fibrin and from platelets; perhaps also from red corpuscles and leucocytes. It may stain well by Weigert's fibrin-stain, or only faintly, or not at all. Small spaces and canals, often containing nucleated cells, may be present in the homogenous fibrin or hyaline substance (canalised fibrin of Langhans).

Of special importance are the liquefactive softenings which may occur in old thrombi. These are distinguished as simple or bland, septic or purulent, and putrid softenings.

The simple softenings occur in bland thrombi, being especially common in globular cardiac thrombi which, when old, regularly contain in their interior an opaque whitish or reddish thick fluid. This in old days was mistaken for pus, and hence the name puriform softening (purulent cysts). The liquid or pulpy material is the result of granular disintegration and liquefaction of the solid constituents of the thrombus, and consists of necrotic fatty leucocytes, albuminous and fatty granules, blood pigment and altered red corpuscles; the varying red tint of the fluid depending upon the number of red corpuscles originally present in the thrombus. Occasionally acicular crystals of fatty acid are present. This form of softening is probably due to the action of some ferment; it occurs in ordinary bland thrombi, and is distinguished from the infective forms. It is not generally supposed that micro-organisms are in any way concerned in the process: bacteria, however, have been found of late years repeatedly in these thrombi; and it may be that they are not so absolutely unconcerned in simple thrombotic softening as is generally thought to be the case.

There is no question as to the participation of bacteria in the other forms of softening. Septic or purulent softening, met with most frequently in infective thrombo-phlebitis, is a true suppuration; being the result of the accumulation of polynuclear leucocytes with fermentative liquefaction of the thrombus. The leucocytes are attracted in part from the blood of the thrombosed vessel and in part from the vasa vasorum and surrounding capillaries and veins. Pyogenetic bacteria, most frequently streptococci, are present in the thrombus and the walls of the vessel. Putrid softening is due to the invasion of putrefactive bacteria. Here the thrombus is of a dirty brown or green colour, and of foul odour.

These various softenings often lead to the separation of thrombotic fragments to be transported by the circulation as emboli,—bland, septic, or putrid according to the nature of the process.

White thrombi in veins, far less frequently in arteries, may undergo calcification, forming phleboliths or arterioliths. They are generally approximately spherical, and lie loosely or slightly adherent in the lumen. They

are found most frequently in the veins around the prostate and bladder of men, in the plexus pampiniformes of women, and in the spleen.

One of the most interesting adaptive pathological processes is the so-called organisation of thrombi, which is the substitution for the thrombus of vascularised connective tissue. The thrombus itself takes no active part in the process, but behaves as a foreign body. It is gradually disintegrated and absorbed, largely through the activities of phagocytes. The new tissue springs from the wall of the vessel or the heart; the tissue-forming cells being derived both from the endothelium and from other fixed cells in the wall. New vessels spring from the vasa vasorum. Lacunar spaces in the thrombus, or between the thrombus and the vascular wall, may become lined with endothelium, and also serve as channels for the circulating blood. These new vessels may establish communication with the lumen of the thrombosed vessel above or below the thrombus, or on both sides. The new tissue, which at first is rich in cells, becomes fibrous, and contracts. The result may be a solid fibrous plug, or a cavernous structure with large blood-spaces; or, by disappearance of the septa, a restoration of the lumen, with perhaps a few fibrous threads or bands stretching across it, as in the normal cerebral venous sinuses.

There are great diversities in individual cases as to the rapidity of onset and the course of the organising process; these differences depending upon various circumstances, the most important of which are the location of the thrombus, the condition of the wall of the vessel or heart, the general state of the patient, and the presence or absence of infection. In favourable cases the process may be well under way within a week. The wall of the vessel, or of the heart, may be so diseased as to be incapable of furnishing any new tissue; as is usually the case in aneurysmal sacs, and often in varices and in cardiac disease. The presence of pyogenetic bacteria prevents or delays the process of organisation. The process is a proliferative angeiitis. It is this angeiitis which leads to the closure of a vessel after ligation. If the ligature be applied aseptically, and without injury to the internal coats, usually no thrombus is formed, or only a very small one. The formation of a thrombus is of no assistance in securing obliteration of a ligated vessel, in fact it impedes the development of the obliterating endarteritis.

The causes of organisation of thrombi are probably to be sought partly in the influence exerted by the thrombus as a foreign body, and partly in slowing or cessation of the blood-current and lowering of the tension of the vessel-wall (Thoma, Beneke). Whether, in addition, growth of cells may be determined by chemical substances derived from the thrombus is uncertain.

Etiology.—The recognition of the three classes of causes assigned for thrombosis, namely, alterations in the blood, mechanical disturbances of the

circulation and lesions of the vascular or cardiac wall, is not of recent date. The dyscrastic theory is the oldest. John Hunter introduced and Cruveilhier elaborated the conception of primary phlebitis with consecutive plugging of the vein; and Baillie, Laennec, Davy and others emphasised stasis as a cause of intravascular clotting. Virchow's name, however, is the one especially associated with mechanical explanations of thrombosis. The experiments of Brücke, showing the importance of integrity of the vascular wall in keeping the blood fluid, led to general recognition of the part taken by alterations of this wall in the etiology of thrombosis.

While it is generally agreed that slowing and other irregularities of the circulation, contact of the blood with abnormal surfaces, and changes in the composition of the blood are concerned, singly or in combination, in the causation of thrombosis, there is much difference of opinion as to the relative importance of each of these factors, and as to the part of each as a proximate, as a remote, or as an accessory cause.

Slowing and Other Irregularities of the Circulation.—Diminished velocity of the blood-current is not by itself an efficient cause of thrombosis. The circulation may be at a low ebb for a long time without the occurrence of thrombi. A stationary column of blood included in an artery or vein between two carefully applied aseptic ligatures within the living body may remain fluid for weeks (Glénard, Baumgarten). Slow circulation, however, in combination with lesions of the cardiac or vascular wall, or with the presence of micro-organisms or other changes in the blood, is an important predisposing cause of thrombosis, and frequently determines the localisation of the thrombus. This is evident from the relative infrequency of thrombi upon diseased patches of the inner coat of large arteries in contrast with their frequency upon similar patches in the small arteries and in the veins; and in general from the predilection of thrombi for those parts of the circulatory channels in which the blood-flow is normally, or as the result of disease, slow. Extensive injury to the walls of arteries may be experimentally produced without resulting thrombosis.

Eberth and Schimmelbusch find that under normal conditions the platelets circulate with the red corpuscles in the axial blood-current, but make their appearance in the outer still zone when the rapidity of the circulation is sufficiently diminished. Moderate slowing is attended by the accumulation of white corpuscles in this zone, while a further slackening of the stream is characterised by fewer leucocytes and more platelets in the peripheral layer. Mere slowing of the circulation, however, does not suffice to form thrombi; there must be some abnormality of the inner lining of the vessel-wall, with which the platelets are brought into contact, in order to induce the viscous metamorphosis of these bodies essential in the formation of plugs. Hence

Eberth and Schimmelbusch conclude that it is only by the combination of slowing of the circulation with changes in the inner lining that the formation of white thrombi can be explained.

Von Recklinghausen attaches more importance to a whirling or eddying motion (Wirbelbewegung) than to mere slowness of the circulation. He has pointed out that eddies are produced when the blood enters normally or pathologically dilated channels from smaller ones, or passes into a cul-de-sac, or over obstructions; and he has considered in an interesting way the special conditions causing this motion and its influence upon the production of thrombi. This irregularity of the blood-current will be referred to again in considering the localisation of venous thrombi (p. 138). Von Recklinghausen's observations make a valuable contribution to our knowledge of the mechanical disturbances of the circulation which favour the development of thrombi.

Thrombi attributed to slowing of the blood-current, often combined with eddying motion of the blood, are called stagnation-thrombi. Of these two groups are distinguished: (*a*) those due to local circulatory disturbances, as from interruption or narrowing of the lumen of vessels by ligation or compression, or from circumscribed dilatations, as aneurysms or varices; and (*b*) marantic thrombi resulting from weakened heart's action, with consequent feebleness of the general circulation. Virchow gave the name "marantic thrombi" to all or nearly all thrombi complicating or following anæmic and cachectic states, general infective diseases—as enteric fever, typhus fever, and the like, and certain constitutional diseases. He considered a condition of marasmus, or great prostration, to be the common underlying factor. As we shall see subsequently, there are serious objections to this explanation of these thromboses, which indeed constitute the class of chief medical interest. The designation "marantic thromboses" for this group is still, however, in common use. Although it is proper in these groups of thrombi to emphasise the mechanical disturbances of the circulation as an important accessory factor, it is evident, from what has been said, that the class of stagnation-thrombi cannot be maintained in the strict sense originally advocated by Virchow. Other factors, especially lesions of the walls of the heart or vessels, enter decisively into their causation.

Contact of the Blood with Abnormal Surfaces. Lesions of the Cardiac and Vascular Walls.—It is universally recognised that the influence of the endothelial lining of the vascular channels in maintaining the fluid state of the blood is of the first importance. This influence appears to be partly physical and partly chemical. The smooth, non-adhesive character of the inner surface of the heart and vessels is the physical property which comes primarily into consideration. Whereas the introduction of such foreign bodies as

threads, or bristles with rough surface, into the circulation is an efficient cause of thrombosis, perfectly smooth, indifferent bodies, as small glass balls, may be introduced without causing any coagulation (Zahn). Freund has shown that blood collected with proper precautions in vessels lined with oil or vaseline remains fluid for a long time. Mere contact with a foreign surface, therefore, does not suffice to induce clotting; the result depends upon the character of this surface. Freund concludes that the essential thing is that the surface shall be such as to permit adhesion to occur between it and the corpuscles, particularly the red corpuscles; the normal lining of the blood-vessels being characterised by the absence of this adhesive property. Without adopting Freund's theory of coagulation, which does not here concern us, we can apply, with much satisfaction in the explanation of many thrombi, his observations concerning the importance of adhesive surfaces in causing coagulation. There should also be taken into consideration the damage known to be inflicted by adhesive contact with abnormal surfaces upon platelets or red corpuscles; if these be regarded as the source of the granular material and platelets in thrombi.

Changes, therefore, which impair or destroy the smooth, non-adhesive surface of the normal inner lining of the vessels play an important part in the etiology of thrombosis; and thrombi thus caused may be called adhesion-thrombi. The efficiency of these lesions in causing thrombi is increased if, by projection into the lumen, they obstruct the blood-flow; or by their rough, irregular surface set up an eddying motion of the blood.

Although we have very little definite information about any chemical activities of the normal vascular endothelium concerned in the preservation of the fluidity of the circulating blood, there is evidence that lesions of the intima, through chemical as well as physical influences, may incite thrombosis. That necrotic endothelial and intimal cells may liberate fibrin-ferment is in accordance with both physiological and pathological observations relating to the origin of this ferment from dead or disintegrated protoplasm in general. Reference has already been made to observations of Zenker indicating the coagulative influence of necrotic endothelium, and of the intima deprived of endothelium.

Strong support for a belief in the participation of chemical substances in the causation of certain thrombi due to intimal lesions is to be found in contrasting the effects of mere traumatism with those of traumatism combined with infection of the intima. This has been especially brought out in the experimental studies of valvular lesions of the heart. Aseptic laceration of the cardiac valves generally leads to but slight production of thrombi upon the injured surfaces; whereas the same traumatic lesions, combined with the lodgment and growth of pyogenetic bacteria, are usually attended

by the formation of considerable thrombotic vegetations. The differences in the result can hardly be explained by differences in the physical characters of the lesions in the two cases; but we have no definite knowledge concerning the nature and mode of action of the chemical bacterial products concerned in causing the thrombi. We may draw the conclusion that lesions of the intima, apart from their more manifest characters, may possess certain specific properties especially favourable to the production of thrombi.

The most important of the structural changes of the vascular and cardiac walls which cause thrombosis are those due to inflammation, atheroma, calcification, necrosis, other degenerations, tumours, compression, and injury. Here again may be emphasised the importance of retardation and other irregularities of the circulation in rendering these various lesions effective causes of thrombosis. The aorta, for example, may be the seat of most extensive deforming endarteritis, with irregular projecting calcific plates and ragged atheromatous ulcers, without a trace of thrombotic deposit. The forcible pulsating current prevents the adhesion and accumulation of the formed elements consituting the beginning thrombus, or quickly washes them away. The presence in some instances of white mural thrombi in the aorta upon an intima apparently but slightly damaged indicates the importance of certain specific, although little understood, characters of intimal lesions in association with changes in the blood.

Foreign bodies, which have penetrated the blood-channels and set up thrombosis, have been observed repeatedly in human beings, especially in the heart and abdominal veins. Such accidents have followed swallowing fish-bones, needles, nails, bits of wire and the like. A blood-clot or thrombus in a vessel, or projecting into the lumen from a wound of the vessel, may itself be looked upon as a foreign body, and lead to further extension of the thrombus. There seems to be a certain self-propagating power in a thrombus. Similar effects are produced by the entrance of large parasites, such as distomata, by the invasion of tumour-masses, and by the penetration of parenchymatous cells into the circulatory channels (p. 228).

Infective Thrombi. Thrombo-Phlebitis.—Phlebitis, as a cause of thrombosis, has reacquired within the last few years so much importance that it is here singled out from other lesions of the vascular wall for special consideration.

In the first half of the present century, mainly through the influence of John Hunter and of Cruveilhier, thrombosis was by many regarded only as an expression of inflammation of the inner lining of the vessels. The material composing the thrombus was considered to be, at least in part, an exudate of coagulable lymph from the inflamed vascular wall. Virchow, by his monumental work on thrombosis and embolism, dating from 1846,

reversed this order of things, and made, for the great majority of cases, the thrombus the primary and essential phenomenon, and the inflammation of the wall, if present, a merely secondary effect. Phlebitis disappeared, as a chapter, from works on internal medicine, and thrombosis took its place. Within recent years, and again chiefly through the work of French investigators, the pendulum has swung back, and phlebitis has once more come to the front as a common and important cause of thrombosis, and resumed an important place in many systematic treatises on medicine. This rehabilitation of phlebitis is due mainly to bacteriological investigations of thrombosed vessels, especially of the so-called marantic thrombi of infective and cachectic diseases.

The distinction between bland thrombi and infective thrombi is an old and important one. The thrombi in septic and suppurative phlebitis, concerned especially in pyæmic processes and surgical affections were for a long time the chief, indeed almost the only recognised representatives of the class of infective thrombi. There has been a gradual extension of the domain of infective thrombosis, until now many thrombi, previously classified as bland, are considered to be of infective origin. This is notably true of a large number of thrombi, formerly and still often called marantic, complicating many infective diseases, wasting and cachectic conditions, and anæmia. In 1887 Weigert stated that by means of his fibrin-stain he had found unsuspected micro-organisms in marantic thrombi with surprising frequency: and since then there have been numerous similar observations, as well as not a few negative ones. In France the studies of Cornil and his pupils, especially Widal, and of Vaquez have had the greatest influence in developing the doctrine of the mycotic origin of this class of thrombi, and particularly that of primary phlebitis as the cause of these thromboses. It should not be forgotten that Paget, in 1866, contended for the primarily phlebitic nature of thrombosis in gout.

Phlegmasia alba dolens of the puerperium is the prototype of this class of thromboses. In the articles on various infective diseases, particularly enteric fever (see Allbutt's "System of Medicine," I, p. 817) and influenza (Allbutt's "System of Medicine," I, p. 683), attention has been called to the occurrence of thrombosis as a complication or sequel. Similar thromboses occur in pneumonia, typhus, acute rheumatism, erysipelas, cholera, scarlatina, variola, tuberculosis, syphilis—in fact with greater or less frequency in nearly all acute and chronic infections. Likewise in chlorosis, gout, leukæmia, senile debility, and chronic wasting and cachectic diseases, particularly cancer, thrombosis is a recognised complication. The more important associations of thrombosis with these various diseases will be considered more in detail subsequently (p. 149).

These various thromboses, occurring very rarely as primary affections, usually secondary to infective or constitutional diseases, compose the great majority of those of medical, as distinguished from surgical interest. Clinically and anatomically they undoubtedly have much in common. Is there any common etiological point of view from which they may be regarded? Virchow thought so in calling them marantic thrombi, and attributing their causation to enfeebled circulation. The same causative factor still remains the underlying one with those who, like Cohnheim, interpolate nutritive changes in the endothelium between the slow circulation and the beginning of the thrombus.

Impaired circulation cannot serve as a common etiological shelter for this whole class of thromboses. There is no definite and constant relationship between the condition of the circulation and the occurrence of these thrombi. While many appear during great debility, others of the same nature, and often in the same disease, occur when the heart's action is not notably weak. Thrombosis may ensue early in influenza. It is oftener a sequel than an accompaniment of enteric fever. On the other hand, the circulation may be extremely feeble for days without the appearance of thrombosis.

Many of these so-called marantic thrombi are unquestionably of infective origin. Vaquez, in his monograph on phlebitis of the extremities, published in 1894, has brought together the results of the observations of others, and especially those of his own and Widal's investigations, which demonstrate that bacteria are often present in these thrombi and in the adjacent vascular wall. Since the appearance of Vaquez' monograph there have been a number of confirmatory observations. Widal emphasises the importance of searching for bacteria in fresh thrombi, and in the autochthonous part of the thrombus and the adjacent wall of the vessel. The largest contingent of positive results has been furnished by the examination of puerperal thrombi—many of which indeed are examples of septic thrombo-phlebitis, and of the marantic thrombi of chronic pulmonary tuberculosis; but bacteria have also been found in thrombi complicating or following typhoid fever, influenza, pneumonia, cancer, and other infective and cachectic conditions.

In relatively few instances has the specific micro-organism of the primary disease, as the typhoid or the tubercle bacillus, for example, been present in the thrombus; more frequently secondary invaders, especially streptococci and other pyogenetic bacteria, have been detected: so that the thrombosis is considered to be oftener the result of some secondary infection than of the primary one. Colon bacilli have been found in typhoidal and other thrombi; but as these bacteria are found so commonly in the blood and organs after death from all sorts of causes, no great importance can be attached to their mere demonstration without some further evidence of their pathogenetic

activity. As might be expected, streptococci are the bacteria found most frequently in puerperal thromboses. Singer believes that gonorrhœal infection is also a possible factor.

Not only in thrombi of infective diseases but also in cachectic thromboses have bacteria, and here again most frequently pyogenetic forms, been demonstrated. Nor is this surprising when we consider the frequency of secondary infections in chronic diseases, especially as a terminal event; as has been clearly brought out in the analyses, by Flexner, of the autopsies at the Johns Hopkins Hospital, where bacteriological examination is a routine procedure at the post-mortem table. Many of these infections are unsuspected during life.

The supposition that in all of these cases the bacteria are accidentally or secondarily present, and in no way concerned in the causation of the thrombi, is extremely improbable. They are often in such number, in such arrangement and associated with such lesions, that they must have multiplied in the thrombus and in the vessel wall.

The problem whether the bacteria have led to thrombosis by first invading the vascular wall and setting up inflammation is not solved by the mere demonstration of their presence. Certainly, in some instances, this sequence of events is plainly indicated by the microscopical appearances; but in many it is impossible to decide to what extent inflammatory changes in the wall antedated the thrombus, for the latter, especially when infected by bacteria, induces a secondary angeiitis. Opportunities to study very recent infective marantic thrombi with reference to this point are not common.

In a case, which I examined, of multiple venous thrombosis complicating leucocythæmia, there was a primary mycotic endophlebitis with secondary thrombosis. There was a secondary streptococcus infection. In the intima of the thrombosed vessels were numerous scattered foci in which large numbers of streptococci were present. In these areas there was necrosis of endothelial and other intimal cells, with proliferation of surrounding cells and many polynuclear leucocytes. These foci formed little whitish elevations capped with platelets, fibrin, and leucocytes; the whole presenting an appearance similar to that of endocardial vegetations. There was marked nuclear fragmentation both in the infected intima and in the thrombus. Fresh mixed thrombi, containing fewer streptococci, were connected with these phlebitic vegetations. Although the vasa vasorum were hyperæmic, and were the seat of a moderate migration of leucocytes, streptococci were absent from the adventitia; and the appearances spoke decidly for the direct penetration of the streptococci from the circulating blood into the intima. I have examined three other similar cases. A similar form of mycotic endophlebitis has been described by Vaquez (endophlébite végétante). In other

cases the intima is more diffusely inflamed. After a short time there is no distinct line of demarcation between the thrombus and the intima, and all of the coats of the vessel are more or less inflamed.

Although the bacteria found in the intima may gain access from without through the vasa vasorum, or the lymphatics, it is probable that in the class of cases here under consideration they more frequently enter directly from the blood circulating in the main channel. There may be very extensive bacterial inflammation of the venous wall, even with bulging of the intima into the lumen, without any thrombosis.

We do not possess sufficiently numerous and careful bacteriological examinations of the thrombi of infective and wasting diseases to enable us to say in what proportion of cases they contain micro-organisms. It is certain that in many instances such examinations have yielded negative results. It is quite possible that in some of these negative cases bacteria, originally present, have died out; but although by some authors much use is made of this explanation, it is not in general a satisfactory one. Many of the examinations were of thrombi sufficiently recent to exclude this possibility.

To explain these non-bacterial cases, the French writers assume the existence of a primary toxic endophlebitis, the toxins being either of bacterial origin or derived from other sources. Ponfick, many years ago, called attention to the occurrence of degenerations of the vascular endothelium in infective diseases; and there can be no doubt of the frequency of both degenerative and inflammatory changes of the intima in toxic and infective conditions.

A lesion which I have seen in the intima of veins (less frequently of arteries) in typhoid fever, diphtheria, variola, and other infective diseases, is a nodular, sometimes a more diffuse, accumulation of lymphoid and endothelioid cells beneath the endothelium. These cells, as well as the covering endothelium, may undergo necrosis; indeed the appearances sometimes suggest primary necrosis with secondary accumulation of wandering cells and proliferation of fixed cells. These foci are not unlike the so-called lymphomatous nodules found in the liver in typhoid and other infections. They may unquestionably be the starting-point of thrombi, as has been shown by Mallory in his study of the vascular lesions in typhoid fever. Although this form of endophlebitis or endarteritis resembles that demonstrably caused by the actual presence of bacteria in the intima, bacteria are often absent, even in the fresh lesions; so that it is reasonable to suppose that the affection may be caused by toxins. I think that this toxic endangeiitis is of importance in the causation of thrombosis complicating infective and cachectic states.

There are, however, instances of so-called marantic thrombosis where no visible alteration of the intima can be made out at the site of the thrombus, or only the slight fatty degeneration of the endothelium which is such an extremely common condition that it does not afford a satisfactory explanation.

It is obvious that bacteria are likely to find especially favourable opportunities to gain lodgment, and toxic substances to do injury, in situations where the blood-current is slow and thrown into eddies; but the localisation in these situations of thromboses complicating infective and chronic diseases has perhaps been unduly emphasised. These thromboses may occur elsewhere, even in the aorta and larger arteries. Pre-existing diseases of the veins, especially chronic endophlebitis and varicosities, are conditions predisposing to infective and cachectic thromboses.

While we are justified in assigning a far more prominent place to the agency of micro-organisms and to primary phlebitis in the etiology of thrombosis than, until recent years, has been customary since Virchow's fundamental investigations, recent attempts to refer all thromboses, formerly called marantic, to the direct invasions of microorganisms and to phlebitis go beyond demonstrated facts. We have not at present any satisfactory bacteriological and anatomical substratum for so wide a generalisation. The whole field, although difficult, is an inviting and fruitful one for further investigation. The clinical arguments in favour of the phlebitic origin of thrombosis will be considered below (p. 172).

What has been said regarding the relation of phlebitis to thrombosis complicating infective and constitutional diseases applies also to that of arteritis to the similar arterial thromboses which, although less common than the venous, are more frequent than was formerly supposed; this will appear when we take up the association of thrombosis with particular diseases (p. 149).

It is of course understood that the preceding remarks on the relation of phlebitis and arteritis to thrombosis relate only to the medical thromboses, and not to the septic and suppurative thrombophlebitides of the surgeon, of the bacterial origin of which there is no question; although these latter may be concerned in diseases, such as suppurative pylephlebitis, which are in the province of the physician.

Chemical Changes in the Blood. Ferment-Thrombi.—The old ideas of chemical changes in the blood as causes of intravascular clotting, embodied in such terms as acre coagulatorium, hyperinosis, inopexia, are now of historical interest only. There appears to be no definite and constant relation between the amount of fibrin obtainable from the blood, or the rapidity of its coagulation in the test tube, and the occurrence of thrombosis in human beings. Peripheral thrombosis is a less common complication of pneu-

monia and acute articular rheumatism, which are characterised by high fibrin-content of the blood, than of enteric fever and certain cachectic states in which the fibrin-content is approximately normal or reduced.

In dogs whose blood was rendered incoagulable by injection of "peptone" (albumose) Schimmelbusch produced platelet-thrombi experimentally. On the other hand, Sahli with Eguet observed no collection of platelets or formation of thrombi around hog's bristles or silk threads inserted into the jugular veins of rabbits having incoagulable blood from injection of leech extract; although control experiments regularly gave positive results. These latter experiments show that chemical changes in the blood may influence the process of thrombosis.

The main support of the belief entertained by some that the liberation of fibrin-ferment in the general blood-stream is an important cause of human thrombosis, is based on the results of experiments which demonstrate that the injection of various substances into the circulation may cause intravascular clottings. The most important of the substances which have been observed to produce this effect are laky blood (Naunyn), biliary salts (Ranke), ether (Naunyn, Hanau), fresh defibrinated blood (Köhler), emulsions or extracts from cells, especially lymphoid cells (Groth, Wooldridge), transfusion of blood (Landois, Ponfick), and snake-venom (C. J. Martin, art. "Snake-poison and Snake-bite," vol. iii. p. 819). The coagulating effect of laky blood is attributable to the stromata of red corpuscles rather than to dissolved hæmoglobin (Wooldridge). The coagulating principle here, as well as of the various tissue-extracts, is believed to be a nucleo-proteid which, by combination with calcium, forms the fibrin-ferment. It is to the presence of this ferment or the subsequent liberation of the ferment that the dangerous intravascular clots following the injection of defibrinated blood or the transfusion of foreign blood are due. The coagulative effect of snake-venom under certain conditions is referred by Halliburton to proteoses free from phosphorus, and therefore not nucleo-proteids. The action of snake-venom upon coagulation is probably analogous to that of various toxic albumoses, bacterial and vegetable. They are in general to be ranked among anti-coagulating substances; but the result varies with the dose, the manner of injection, and other circumstances. Wooldridge has shown that thromboses are particularly prone to occur in the territory of the portal system after the injection of various substances favouring coagulation. Fibrin-ferment may be used up in the process of intravascular clotting, so that after this has taken place the remaining blood may be incoagulable.

Interesting as these experimental results are to the physiologist, and with reference to the theories of the coagulation of blood, it is difficult to utilise them in any satisfactory way in the explanation of ordinary human

thrombosis. Most of the experimenters make no statement as to the microscopical structure of the intravascular clots, which are described generally as soft, dark red masses; and they seem to identify them with ordinary human thrombi, being apparently not familiar with the researches on the peculiar constitution of the latter. Some of the substances used for the experiments cause precipitates in the blood, and many are very destructive to the red corpuscles. Hanau, however, has shown that masses of platelets may be present in these clots.

Conditions analogous to those set up in these experiments may occur in human beings; but they are, so far as we know, most exceptional. Especially do we lack satisfactory observations, in cases of thrombosis in human beings, of increase of fibrin-ferment in the blood. Considerable quantities of fibrin-ferment, more than are likely to be liberated under any probable circumstances in man, can be injected into the circulation without causing coagulation. Still it is possible that the mechanism by which this excess of fibrin-ferment is neutralised and coagulation prevented may be paralysed under certain conditions. There are certain instances of rapidly-formed red thrombi in vessels with apparently normal walls which, in the absence of other explanation, it would be very convenient to refer to ferment-intoxication. Köhler and Hanau consider that many thrombi, especially those complicating infective and cachectic states, are best explained by supposing a liberation of fibrin-ferment in the blood, and they call them, therefore, ferment-thrombi.

Hayem designates as thrombi from precipitation (thromboses par précipitation) many which others call ferment-thrombi; especially those following injection of various destructive substances into the circulation, and those caused by burns and freezing.

Silbermann and others assert that thrombosis, particularly multiple capillary thrombosis, plays an important part in extensive superficial burns, and in poisoning with various substances destructive to the blood corpuscles, such as anilin, potassium chlorate, arsenic, phosphorus, sublimate, carbonous oxide, illuminating gas. These views need further confirmation before they can be accepted, as several observers have obtained only negative results in searching for thrombi in the same class of cases.

Notwithstanding the lack of a substantial basis of demonstrated facts for the opinion that human thrombosis is often caused by liberation of fibrin-ferment in the general blood-stream, it would be quite unreasonable to suppose that chemical changes of the blood are without influence upon the occurrence of thrombosis in man. Indeed, in infective and toxic conditions such changes are doubtless the underlying factors. Both the circulatory disturbances and the alterations in the vascular wall to which we attribute

the production of thrombi are the result of damage done to the heart and vessels by bacterial and other toxins. More than this, there is good reason to believe that alterations in the formed elements of the blood, caused directly or indirectly by toxic substances, are of great significance in the etiology of thrombosis. The platelets are in all probability cell-derivatives; and we may well suppose that damage inflicted upon leucocytes and red corpuscles may favour their production, and that, in consequence of abnormal composition of the plasma, the platelets themselves may more readily undergo viscous metamorphosis, and form plugs. In view of recent observations in favour of the origin of platelets from red corpuscles, the studies of Ehrlich, Maragliano, von Limbeck, and others, concerning degenerations and increased vulnerability of these corpuscles in various diseases, are of interest with reference to thrombosis; but it must be confessed that we cannot at present make more than a hypothetical application of these results to the explanation of certain forms of thrombosis. To discuss here further the hypotheses upon this subject would be barren of any useful result.

Increase of Blood-Platelets.—In view of the essential part taken by blood-platelets in the formation of thrombi, it is important to inquire whether thrombosis can be brought into any relation with a pathological increase of these elements. Some observations of the existence of such a relationship are highly suggestive.

Especial difficulties are encountered in the efforts to enumerate the platelets on account of their small size and their viscid consistence, which causes them to clump together. Brodie and Russell give, as the norm, one platelet to 8.5 red corpuscles; or about 635,000 per cubic millimetre. This estimate is considerably higher than that obtained by others, probably, however, by less accurate methods. Van Emden gives as the average for human beings in health 245,000; which corresponds fairly well with the figures of Hayem, Cadet, Afanassiew, Muir, Fusari, and Determann, but is lower than those of Laker and Prus.

There is considerable divergence of statement as to the number of platelets in different diseases. This number is markedly increased in chlorosis (Muir), of which thrombosis is a well-recognized complication. The platelets are increased in post-hæmorrhagic anæmia (Hayem), which is one of the remoter causes of thrombosis. There is evidence that hæmorrhage after childbirth, and in the course of various diseases, favours the occurrence of thrombosis. Several observers have found the platelets reduced in number in pernicious anæmia, which, unlike chlorosis, is rarely, if ever, complicated by thrombosis (Hayem, Birch-Hirschfeld, Beugnies-Corbeau). In purpura hæmorrhagica there is extreme diminution of platelets, sometimes amounting to total absence (Denys, Hayem, Ehrlich, van Emden), which constitutes

the only demonstrated morphological change of the blood in this disease. In febrile infections there is often a correspondence between leucocytosis and the number of platelets. Thus in influenza, pneumonia, erysipelas, meningitis, and septic infections the number of platelets is often increased, in severe cases sometimes diminished; whereas in enteric fever and malaria it is diminished (Hayem, Reyne, Türk, Muir, van Emden). The disappearance of leucocytosis is sometimes followed by increase of platelets. In view of the greater frequency of thrombosis as a sequel than in the course of many acute diseases, the recognition by Hayem of a platelet crisis (crise hématoblastique) is interesting. After the crisis or subsidence of certain infective diseases Hayem observed a rapid and marked increase in the platelets. This was noted after pneumonia and enteric fever. Platelets are said to be often increaesd toward the end of pregnancy and after delivery (Hayem, Cadet). In various cachectic conditions, in tuberculosis, and, in general, in states of bad nutrition, increase is the rule. Dr. Muir finds that in spleno-medullary leucocythæmia the platelets are notably increased, but not in the lymphatic form (art. "Leucocythæmia," Allbutt's "System of Medicine," V, p. 640). In chronic passive congestion, due to heart disease, the platelets are said to be diminished (van Emden). An increase of platelets in various conditions in which they are usually diminished can often be attributed to complications. Upon the whole there is much in support of the view that increase of platelets is an index of lowered resistence of the red corpuscles.

It is fair to say that some of the foregoing statements regarding the condition of the platelets in various diseases need further confirmation, and that in general the subject is difficult and has been insufficiently investigated. Nevertheless we cannot fail to have our attention arrested by a parallelism, in many instances, between disposition to thrombosis and increased number of platelets; although in others no such relationship is apparent. It must suffice to call attention to this parallelism, for we are ignorant of the underlying factors.

It hardly need be said that the mere increase of platelets is insufficient to explain the occurrence of thrombosis. We are brought back here, as elsewhere, to disturbance of the circulation and changes in the vascular walls as the determinants of the localisation of thrombi; while we must recognise changes in the chemistry and morphology of the blood as important predisposing causes.

Localisation.—Thrombosis may occur in any part of the circulatory system. We distinguish therefore arterial, venous, capillary, and cardiac thrombi. Lymphatic vessels may likewise become plugged with fibrin, leucocytes, or foreign material; such as tubercle, cancer, or red corpuscles.

Arterial Thrombi.—The majority of arterial thromboses are caused by some local injury or disease of the arterial wall, or by the lodgment of an

embolus. Especially important are the arterio-sclerotic thromboses of the brain, heart, and extremities.

Here may be mentioned the varying relations of arterial thrombosis to *gangrene* of the extremities. Thrombosis of arteries, as well as of veins, may be secondary to varieties of gangrene which are not caused by primary plugging of the arteries. Senile gangrene is caused either by embolism, which may lead to thrombosis, or by arterio-sclerosis, usually associated with thrombosis. In various infective and chronic wasting diseases gangrene may result from primary arterial thrombosis of the class often called marantic. Many of these thromboses are infective in origin; but we have not sufficient information to warrant the assertion that all are caused by micro-organisms.

Of especial interest is the relation of thrombosis to certain forms of so-called "spontaneous" gangrene which may occur in middle life, or even in the young, and are often preceded by definite symptoms indicative of gradual occlusion of the arteries. Von Winiwarter concluded from his examinations of several cases that the primary disease is an obliterating endarteritis resulting in complete closure of the affected vessels. Zoege von Manteuffel, however, finds that thrombosis participates, in an interesting way, in the gradual occlusion of the arteries. According to him, by the deposition and organisation of successive layers of parietal thrombi, the arteries, which are usually the seat of a primary sclerosis, gradually become filled with vascularised connective tissue. Haga considers this endarteritis thrombotica to be syphilitic. Hoegerstedt and Nemser believe that, in general, the deposition and organisation of parietal thrombi are common and important processes in angio-sclerosis. Von Recklinghausen has described hyaline thrombosis of small arteries in spontaneous and arterio-spastic gangrene.

The *action of infective agents* in the causation of focal and diffuse diseases of the arteries is receiving constantly increasing attention. The occurrence of acute and chronic arteritis as a result of various infective diseases—as enteric fever, typhus fever, acute articular rheumatism, variola, scarlatina, pneumonia, endocarditis, septicæmia, syphilis, tuberculosis, leprosy—is now so well established that it is reasonable to believe that the arterial thromboses complicating or following these diseases are often referable to an infective arteritis.

It cannot be doubted that not a few cases reported in literature as primary arterial thrombosis are to be attributed to embolism which was overlooked. The possible sources of emboli for the aortic system can be usually controlled much more readily than those for the pulmonary arteries; for the latter sources embrace all the systemic veins. These veins may contain mural

thrombi, or in places occluding thrombi, which give no signs of their presence. The possibility that an entire thrombus may be detached and transported by the blood-current, so that its original location cannot be determined, is also to be considered. But, after all has been said, it is carrying scepticism to an unjustifiable extreme to refuse to admit the occurrence of primary arterial thrombosis in infective, cachectic, and anæmic states, under circumstances where the localisation cannot be attributed to arterio-sclerosis or other pre-existing arterial disease. Mr. Jonathan Hutchinson has recently reported observations of rapid thrombosis of arteries without obvious disease of the walls.

The most frequent site of arterial thrombosis is in the extremities, and far more frequently in the lower than the upper. Arterial thrombosis, unlike venous, occurs on the right side as often as on the left. Other situations, more or less common, are the cerebral, pulmonary, coronary of the heart, mesenteric arteries, and the aorta and its primary branches.

Venous Thrombi.—These may result from local causes, such as traumatism, compression, phlebitis, phlebo-sclerosis, varix (266), inflammation or other lesion of surrounding parts, and connection of venous terminals with septic or gangrenous foci.

Vascular thromboses due to general causes are, in the great majority of cases, situated in veins; and to this group the chief medical interest attaches. In special characters of the venous circulation we must seek the explanation of the greater effectiveness of these general causes in veins than in arteries. The physiological peculiarities, partly general and partly local, which come especially into consideration, are—the slower mean speed of the blood in veins than in arteries; the low blood-pressure; the flow from smaller into larger channels; the absence of pulsation; the presence of valves; fixation of the venous wall in certain situation to fasciæ and bone; the existence in some places of wide sinuses and ampullar dilatations; the agency of certain subsidiary forces, such as muscular contraction and movements of the limbs, in assisting the flow in the veins; the composition of venous blood, particularly the higher content of CO_2, and perhaps the functions of the capillaries and small veins in the production and absorption of lymph. It is obvious, without detailed explanation, that some at least of these special characters must render the venous system much more favourable than the arterial to the occurrence, under the general conditions known to dispose to thrombosis, of retardation of the blood-current; eddying motion of the blood, and damage to the vascular wall from impoverished and insufficient blood-supply, or prolonged contact with micro-organisms and toxic substances, the agency of which in the etiology of thrombosis has already been considered.

The best evidence that these mechanical conditions determine the localisation of the majority of thrombi of infective, anæmic, and cachectic diseases

is afforded by the marked preference of such thrombi for situations where these conditions are in the highest degree operative. The tendency of venous thrombi to start from valvular pockets has already been mentioned. It is important to note that thrombi due to general causes, unlike those starting from local septic foci, do not begin in the rootlets, but originate usually in the main venous trunks of a member. The very large veins are unusual primary seats of marantic thrombi. Beginning as a rule in a sinus or medium-sized vein, the thrombus may grow centrally into large veins; as from the femoral into the iliacs and vena cava, and peripherally into small veins, not, however, generally reaching the smallest veins. The favourite starting-point of so-called marantic thromboses of the cerebral sinuses is in the middle of the superior longitudinal sinus at the top of the cranial cavity, whence the thrombus may extend forward, but tends especially to grow toward the torcular Herophili, and into other sinuses and into the cerebral veins. There is, however, no rigid rule in this matter. The plug may begin in other sinuses, or even in the cerebral veins.

In extensive thromboses, such as occur especially in veins of the thigh and leg, it is sometimes difficult to determine the point of origin of the thrombus, and the exact manner of its propagation. Often, however, decisive information can be gained by careful attention to features indicative of the age of thrombi, as already described (p. 119). Thus the autochthonous part of the thrombus is gray, or reddish gray, and firmly adherent; the continued part often red and more loosely attached, and the older parts frequently softened or liquefied in the centre. By observation of such points as these, the common assumption that a thrombus, occupying continuously both large and small veins, began in the most distal veins and grew thence into the larger channels, can often be shown to be erroneous. An occluding thrombus may lead to such disturbances of the circulation as to cause the formation of discontinuous multiple thrombi on both the central and the peripheral sides, and these may become connected by red or mixed thrombi. In short, the modes of extension of thrombi are sometimes complicated, and not readily unravelled.

The so-called law of Lancereaux was enunciated by him in 1862 as an explanation of the common site of thrombi in the cerebral sinuses, and at the summits rather than at the peripheries of the extremities; his rule is as follows:—"Marantic thromboses are always formed at the level of the points where the blood has the greatest tendency to stasis, that is, at the limit of the action of the forces of cardiac propulsion and of thoracic aspiration." There are serious physiological objections to the physical conceptions of the circulation underlying this so-called law, which in any event cannot be accepted in the exclusive form given to it by Lancereaux. Wertheimer has

shown that the effect of thoracic aspiration upon the venous circulation extends to remote parts of the saphenous vein by the side of the tendo Achillis. As the collective sectional area of the veins steadily diminishes from the capillaries to the heart, the average speed of the blood must be greater in the large veins than in the small ones, if the circulation is to continue for any length of time; and this remains true even when the energy of the blood-current is feeble.

Much more satisfactory, it seems to me, is the explanation offered by von Recklinghausen, of which mention has already been made (p. 123). This explanation places the chief emphasis upon the eddying movement (Wirbelbewegung) of the outer lines of flow of the blood-stream when there are counter-currents, or when the blood with retarded flow passes from smaller into larger channels or over obstructions, or especially into spaces relatively too wide for the received volume of fluid. Especially favourable for the appearance of this irregularity of the circulation are the ampullar dilatations just above the insertion of the venous valves, the intracranial sinuses, and the femoral vein near Poupart's ligament, which, in consequence of fixation to bone or fasciæ, cannot readily adjust themselves to a lessened volume of blood, and in which counter-currents are set up by the obtuse or right angles at which blood is received from some of the tributary veins. The trabeculæ which cross the cerebral sinuses may be a contributory factor. Similar irregularities of the blood-flow must occur with feeble circulation in other situations, as in the pelvic venous plexuses, where wide channels are intercalated between smaller ones, in the recesses of the heart, and in aneurysms and varicose veins. Von Recklinghausen has pointed out that the plexus-like arrangement, the entrance of small veins into large ones, and the close apposition of artery and vein render branches of the renal veins in the kidney susceptible to irregular blood-currents.

The greater frequency of venous thrombosis in the left leg than in the right is attributable to the more difficult return-flow from the former, in consequence of the greater length and obliquity of the left common iliac vein and its passage beneath the right common iliac artery. It has been suggested that pressure upon this vein by a distended sigmoid flexure or rectum may likewise contribute to slowing of the blood-current upon this side. The preponderence of thromboses of the left axillary and branchial veins over those of the right is attributed in a similar way by Parmentier; that is, to the greater length and obliquity of the left innominate vein.

As has already been urged, these mechanical disturbances of the circulation are not, by themselves alone, efficient causes of thrombosis. They simply make certain parts of the vascular system seats of election for thrombi. It is quite possible to exaggerate their function in the etiology of thrombosis.

The presence of micro-organisms or other changes in the blood may induce lesions of the vascular wall in any part of the circulatory system; and primary thrombi may be formed in situations apparently the most unpromising, so far as the circulatory conditions are concerned; as for instances in the pulmonary veins and in the venæ cavæ near the heart.

Capillary Thrombi.—The blood in the capillaries remains fluid, even with extensive venous and arterial thrombosis, unless necrosis or gangrene of the tissue ensue, in which case, as in infarctions, the capillaries are always plugged. The interesting fibrinous and hyaline thromboses of the capillaries have already been considered (pp. 115 and 116).

Cardiac Thrombi.—There is no stranger chapter in the history of pathology than the story of cardiac polypi, from the first observation of fibrinous clots in the heart by Benivieni, in the fifteenth century, until the end of the last century. It is full of warnings against the uncritical use of post-mortem findings. The cardiac polyps of the old writers were, for the most part, nothing more than ordinary colourless post-morten clots. Nor has the error of confounding these with genuine thrombi wholly disappeared from medical literature even at the present day. These moist, pale, yellowish, smooth, elastic, uniform, more or less translucent, fibrinous clots, softer or firmer according to their content of serum, non-adherent though entangled with muscular columns and trabeculæ, often showing moulds of the valves or other projecting surfaces with, at least, some red cruor clot at their most dependent parts—such clots, membranous, polypoid, band-like, or filling the right cavities of the heart and sending worm-like offshoots into the vessels, should never be mistaken for the drier, opaque, gray or reddish gray, granular, more friable, usually much smaller, adherent, often centrally softened or stratified thrombi.

Although there is a common impression that these fibrinous clots are found during the death agony, I know of no good reason for such a view. It is much more probable that they are analogous to the buffy coat of clots in shed blood, and are formed after death, when coagulation does not set in until the red corpuscles have settled from the plasma. Liberation of fibrin-ferment, fibrin-content of the blood, sedimentation-time of red corpuscles and coagulation-time,[4] all variable elements, are the leading factors which

[4] By "fibrin-content" is meant the amount of fibrin yielded by the blood, and is not of course to be understood as implying the pre-existence of fibrin in the blood. The rapidity of coagulation is an element which is more or less independent of the total yield of fibrin. Red corpuscles settle from plasma or from serum with varying degrees of rapidity in different specimens of blood. Clots also vary much as to their contraction and the separation of serum. Although in using such an expression as "coagulability of the blood" these factors are often confounded, it is important that they should be distinguished.

determine the production of these colourless clots. Most striking examples of colourless clots are found after death from pneumonia and acute articular rheumatism, where the fibrin-content is high, the sedimentation-time rapid, and the coagulation-time slow. The whole doctrine of death from "heart-clot" in these and other acute diseases is based, in my opinion, upon mistaken interpretation of fibrinous post-mortem clots.

The *fresh vegetations* of endocarditis are not generally included in the consideration of cardiac thrombi. Still they are genuine thrombi, and there is no more favourable situation for the study of the formation of mycotic thrombi than the acutely inflamed heart-valve. The first step is the invasion of bacteria, as a rule directly from the blood in the cardiac cavities, into the endothelial and subendothlial layers. The surrounding cells undergo rapid necrosis with karyorrhexis; and simultaneously are deposited upon the damaged spot masses of conglutinated platelets followed by leucocytes and fibrin, these masses forming the vegetations. Proliferation of the subendothelial and adjacent cells quickly follows, polynuclear leucocytes migrate into the area, and before long new vessels with organisation of the thrombus make their appearance. A process essentially the same may occur not only in the mural endocardium but also in arteries and veins (vegetative arteritis, vegetative phlebitis, p. 128).

Putting aside these endocardial vegetations, it has been customary to consider the conditions leading to cardiac thrombosis as essentially identical with those of peripheral venous thrombsis, but there are differences. Cardiac thrombi are found especially in association with chronic diseases of the heart, lungs, arteries, and kidneys; in all of which, with the exception of pulmonary tuberculosis, peripheral venous thrombosis is uncommon. On the other hand, most of the acute infective diseases, as enteric fever, influenza, pneumonia, which are so important in the etiology of venous thrombosis, are in general of less relative importance in the causation of cardiac thrombosis, although it may occur in these diseases. In cachectic states, especially phthisis and cancer, the conditions as regards the incidence of cardiac and of venous thrombi are more nearly identical, for here thrombi are often enough found in the heart; particularly when there is well-marked fatty degeneration. Cardiac thrombosis stands in no such peculiar relation to chlorosis and gout as does venous thrombosis, although its occurrence in these diseases is not unknown. The great field for cardiac thrombi is afforded by diseases of the valves and walls of the heart, and especially by dilatation of one or more of its cavities with cardiac insufficiency (asystole of the French school); conditions which, in spite of the great retardation of the venous flow, are not often attended by peripheral venous thrombosis, unless in association with diseases known to dispose to the latter.

The seats of election for cardiac thrombi are the auricular appendices and the ventricular apices between the columnæ carneæ; the particular situation varying as the cause may affect the whole heart, on only one side, or one cavity. In cardiac insufficiency from general or local causes these recesses and pockets must offer the best possible conditions for slowing of the blood-current, and especially for the formation of eddies. That there is no actual stasis of the blood is shown by the gray or reddish gray colour of the thrombi.

The familiar *globular thrombi* (végétations globuleuses, of Laennec) are by far the commonest form of cardiac thrombus. Varying in size usually from a pea to a hazel-nut they may attain the size of a hen's egg. They are usually multiple, and neighbouring ones are connected by an adherent subtrabecular thrombotic meshwork or membrane, of which they constitute sessile or pedunculated spheroidal or ovoid projections. Their surface may be smooth, or marked by delicate lines or ribs; and their interior is usually converted into an opaque, gray, or brownish red grumous fluid, so that the whole resembles a cyst with puriform contents. The liquefaction is of the bland variety already described (p. 120). Although the projecting covering of these cysts is often only a thin shell it rarely bursts. These thrombi may, however, be the source of emboli. Hearts containing these thrombi are often the seat of fatty degeneration. Usually no localised mural disease is to be detected with the naked eye beneath these thrombi, although the microscope generally shows degeneration or defect of the endothelium. It is most exceptional for any trace of organisation to be present in these globular thrombi.

Calcification of cardiac thrombi is a rare event. Delépine has described very fully a cardiolith, and has collected reports of similar cases. Some of these are probably phleboliths in or derived from varicose veins which Wagner, Zahn, and Bostroem have described in the wall of the heart, particularly in the septum auriculorum.

Somewhat different as a rule are the *mural thrombi* found on areas of circumscribed disease of the heart wall; as on infarction, fibroid patches,[5] and gummata, and in partial aneurysm. These may be identical in appearance with the ordinary globular cysts; but often they are flat or polypoid, stratified, and more intimately incorporated with the cardiac wall.

Cardiac thrombi may be in the shape of massive or of elongated polypoid formations, occupying a large part of one of the cavities, and extending

[5] It is interesting to note that in 1809, Allan Burns in his classical work on "Diseases of the Heart," in recording his observations on angina pectoris with calcification of the coronary arteries and polypi in the left ventricle, called attention to the relations between disease of the coronary arteries and cardiac thrombosis. He thus anticipated Weber and Deguy, and other recent writers, who have emphasised the occurrence of cardiac thrombi in angio-sclerotic hearts.

even through valvular orifices into adjacent cavities or vessels. One of the cavities, usually a dilated auricle, may be nearly filled with a massive laminated thrombus, as in a case reported by Osler which I examined. There is much resemblance between the clot in these cases and that found in aneurysms.

Apart from endocardial vegetations not much is known of *infective thrombi* in the heart, although it is probable that they occur more frequently than is suspected. In a child dead of scarlatina I found, in association with streptococcal mitral endocarditis, softened thrombi containing streptococci in the right auricular appendix. There are a few scattered reports of the discovery of bacteria in cardiac thrombi. Particularly interesting are the observations of Weichselbaum, of Birch-Hirschfeld, and of Kotlar, of tubercle bacilli in white cardiac thrombi. Birch-Hirschfeld found in a case of extensive genito-urinary and chronic pulmonary tuberculosis a white organised thrombus in the appendix of the right auricle which contained many tubercle bacilli and numerous tubercles. In these and similar cases there is difficulty in determining whether the bacteria are the direct cause of the thrombosis, or are secondary invaders. Kotlar interprets his case as the development of miliary tubercles in an organised thrombus.

As there are unquestionable instances of finding emboli derived from venous thrombi in the right heart, the possibility of a thrombus arising secondarily from such an embolus in this situation may be admitted; but I know of no convincing example.

Ball-thrombi, loose in the left auricle, are rare forms of cardiac thrombi. The first observation which I have found of such a thrombus was published by William Wood in 1814, in Edinburgh. As in other typical cases, the loose thrombus was in the left auricle and there was extreme mitral stenosis. The patient, a girl 15 years old, had the regular symptoms of chronic valvular disease. Death was not sudden. Wood thus describes the appearances: "The substance occupying the sinus venosus of the left auricle, when particularly examined, was found to be of a darkish red colour, in form completely spherical, measuring rather more than an inch and a half in diameter. It felt firm, but elastic; the surface was everywhere smooth and polished, but having a singularly clotted appearance. Rolling loosely in the auricle, it had no connection with surrounding parts. When cut open, after having been kept for some days in diluted alcohol, it was found to consist of a sac, one-eighth of an inch in thickness, formed of an immense number of firm, smooth laminæ, which could be easily separated from each other. Within the cavity formed by this sac was contained a quantity of coagulated blood." Adherent to the wall of the auricle near the mitral valve was a firm, oval

thrombus on the free surface of which was a superficial concavity which formed a "kind of socket for the loose ball to roll in." This last feature is a unique observation.

In 1863, Dr. J. W. Ogle reported a typical instance of ball-thrombus in the left auricle with extreme mitral stenosis, and accompanied the report with an admirable drawing. In 1877 Dr. Wickham Legg reported likewise, to the London Pathological Society, two cases of ball-thrombi in the left auricle with mitral stenosis. He refers to Ogle's specimen which he re-examined, and to a fourth specimen in the museum of St. Thomas's Hospital. One of his cases is unique in the presence of two ball-thrombi in the left auricle. This patient was brought dead to the hospital, and presumably died suddenly in the street. Von Recklinghausen's brief description, in 1883, of two cases of ball-thrombi is quoted in the subsequent German records on the subject as the first observation of this interesting form of cardiac thrombus; although there were much fuller previous accounts of at least four cases, with mention of a fifth, in Scotch and English records extending back as far as 1814; those of Ogle and Legg being certainly very accessible in the "Transactions of the London Pathological Society." Macleod's case of loose thrombus in the right auricle is properly excluded by von Recklinghausen from the class of ball-thrombi. If the conception of a ball-thrombus be simply that of a loose thrombus too large to pass through the valvular orifice, then van der Byl's case, reported in 1858, should be included in this class. He found in a case of sudden death "an irregular, shaggy-looking mass sticking" in the extremely contracted mitral orifice. When floated out in water this assumed a sac-like appearance, was about the size of a pigeon's egg, and completed a broken thrombotic sac in the auricular appendix. This embolus must have been freshly detached, and had not assumed the typical spherical or ovoid shape of the ball-thrombus. There have been later reports of ball-thrombi, by Hertz (two cases), Osler (two cases), Arnold, von Ziemssen, Redtenbacher, Krumbholz, Rosenbach, Stange, and Eichhorst (three cases mentioned without any details), making twenty, without including Macleod's and van der Byl's cases.[6] Of these, fifteen are reported with sufficient details for analysis. This form of thrombus, therefore, although rare, is not so much of a curiosity as has been generally supposed.

[6] I have also not included Schmorl's case, mentioned by Stange, as it is evidently identical with that of Krumbholz, nor Fürbringer's case of numerous globular thrombi, the largest the size of a cherry, in the right auricle, although he reports it as belonging to the group of ball-thrombi. He is evidently under a misconception of the nature of ball-thrombi. There was not the slightest reason why these small bodies, many of them indeed minute, if they were really loose during life, should not have travelled on with the blood-stream.

Three characters, in my opinion, should enter into the definition of a ball-thrombus: (i.) entire absence of attachment and consequent free mobility; (ii.) imprisonment in consquence of excess in the diameter of the thrombus over that of the first narrowing in the circulatory passage ahead of it; and (iii.) such consistence and shape that the thrombus must not of necessity lodge as an embolus in this passage. The third point does not prejudice the question of the possibility of ball-thrombus lodging as an embolus; but it excludes from the group such detached, shaggy, irregular masses (as in van der Byl's case) as must necessarily be caught at once as emboli in the narrowed passage in front. According to this definition a ball-thrombus might, theoretically at least, occur in any circumscribed or sac-like dilatation of the circulatory system; indeed von Recklinghausen considers loose phleboliths and cardiac ball-thrombi as analogous.

All of the cardiac ball-thrombi—as thus defined—hitherto reported, were in the dilated left auricle; and, with one exception, were associated with mitral stenosis. In Stange's case there was aortic stenosis, with slight insufficiency of the mitral valve without stenosis. The agency of mitral stenosis in the production of ball-thrombi is not only that it prevents the escape of detached thrombi which might pass the normal orifice, but also that it favours the formation of thrombi in the left auricle, particularly in the appendix; and doubtless also, through the particular disturbance of the circulation, aids in their detachment, increases the tendency to their rotary motion, and prevents the complete emptying of the left auricle during systole, thus rendering more difficult the lodgment and fixation in the valvular orifice of thrombotic masses which at first may be irregular in shape.

The thrombi have varied in size from that of a small walnut to that of a hen's egg; in Wood's case the thrombus was over an inch and a half in diameter, and in Ogle's the weight was more than four drachms. In ten the shape was spherical; in four ovoid; in one (probably of recent separation) a somewhat irregular flattened hemisphere. In six the surface was smooth and polished; in six marked by granules, lines, ribs, or little depressions; in two smooth and knobbed; and in one (Redtenbacher's) beset with very fine, gray, fibrinous villi. Nine were centrally softened; four solid throughout; and for two there is no statement on this point. The colour was gray or reddish gray; in Wood's "darkish red." In the majority of cases it is said there were adherent thrombi in the left auricle, usually the appendix; and where this is not expressly stated they may have been present. In five cases only was there a rough or projecting spot on the surface of the ball indicative of the previous attachment; and in two this spot was not at all smoothed off: so that the detachment was evidently very recent, possibly indeed during the autopsy, as in one of the two loose balls in Legg's first

case. Krumbholz says that the surface of his thrombus was covered with endothelium. In none, however, was any distinct evidence of organisation detected, for von Ziemssen's statement on this point is too indefinite to be considered.

Ogle, in 1863, clearly recognised the mode of production of a ball-thrombus "by the constant and free agitation of a fragment of fibrinous coagulum separated from some part of the endocardium, and uniformly increased by fresh material at its circumference precipitated from the surrounding blood-stream." Von Recklinghausen has given the fullest and most satisfactory explanation of the spherical shape and smooth surface, in noting that at least some ball-thrombi have a globular shape when first detached; and that irregular bodies, of the consistence of thrombi, rotating in a cavity and growing by successive accretions, assume a spherical shape by a process of moulding, and not by the grinding or breaking off of corners and projections, as was suggested by Hertz to account for the smooth roundness of ball-thrombi. In two or three instances where the ball-thrombus has consisted of a central irregular nucleus enveloped in a concentrically laminated capsule, it has been assumed that the former represents the original detached part, and the latter successive accretions during free rotations in the auricle. While suggestive of such an interpretation, this structure may, however, exist in still adherent globular thrombi. It seems to me probable that most ball-thrombi are smooth and at least approximately spherical when first detached. It is difficult to say how much a thrombus may have grown after its separation.

In nearly all cases that the loose thrombus apparently came from the left auricular appendix, where adherent thrombi were rarely missed when it is expressly stated that they were searched for. In Wood's case the dark red colour, central blood-clot, and polished surface suggest the possibility that the loose body was a separated polypus resulting from hæmorrhage in the wall of the auricle or from a varix; and this opinion is strengthened by the socket-like depression in the adherent thrombus, for it is not clear how such a socket could be formed by a thrombus loose in the auricle; but it might have been the impression left by a polypus attached at some other point.

As regards the clinical significance[1] of cardiac ball-thrombi, Wickham Legg expressed the notion which would probably at first occur to most persons. "A loose thrombus," he says, "in the left auricle would at any time be ready to act as a ball-valve, and stop the circulation in the mitral orifice"; and in this opinion he was strengthened by the presumably sudden death of his patient. Von Recklinghausen, however, who at the time knew

[1] In order to complete without interruption the description of ball-thrombi I introduce here their clinical significance, although the consideration of the symptoms of thrombosis is taken up subsequently.

only of his own two cases and the two of Hertz, in critising a similar opinion expressed by the latter, brought forward several arguments opposed to this notion. The main points of his argument are that instances of sudden death are not infrequent in extreme mitral stenosis without ball-thrombi; that lodgment of the thrombus in the mitral orifice has not been observed, and, even if it were found lying loosely over the orifice at the autopsy, that this would not indicate its position at the moment of death; that the funnel of the stenosed mitral orifice is elliptical in cross-section and shallow, so that a rolling sphere of the consistence of a ball-thrombus could neither completely occlude it nor get wedged in it, nor, if the ball should enter the shallow funnel, is there anything to hold it there, so that the next moment it would roll out. To these points may be added Arnold's argument that the thrombus cannot be horizontally pressed by the auricular contractions against the orifice; for during its systole the dilated auricle does not completely empty itself of blood through the stenosed orifice.

The histories of the cases of cardiac ball-thrombus support in general the position of von Recklinghausen. No symptoms were observed which may not occur in mitral stenosis. Death was gradual in all except four. In only one of these four cases of sudden death was there any conclusive evidence that the thrombus was the cause. This was Dr. Osler's second patient upon whom the autopsy was made in my laboratory by Dr. Flexner. The patient, a woman aged 20, was seen in good condition a few hours before death. At 4.30 a. m. she was found by the nurse very cyanotic, she gave a gasp or two, and died in a few moments. At the autopsy were found marked hypertrophy and dilatation of the left auricle, right ventricle, and to a less extent right auricle; without dilatation or hypertrophy of the left ventricle. The segments of the mitral valve were thickened, adherent, and drawn down by great shortening of the chordæ tendineæ, so as to form the wall of a distinct funnel. There were no fresh vegetations and no œdema. The stenosis was not extreme, the mitral orifice readily admitting the index finger. The other valves and the coronary arteries were normal. An ovoid ball-thrombus, resembling a thick chestnut, measuring $4\times3.5\times3$ ctm., was found, upon opening the heart, occupying with its smaller end and completely blocking the funnel-shaped mitral orifice, from which it was readily removed by the fingers. At one pole of the thrombus was an irregular, roughened spot indicating a former attachment, probably to a thrombus in the appendix. There can be no reasonable doubt that the thrombus in this case was the cause of the sudden death, which is certainly not a common occurrence with such moderate uncomplicated mitral stenosis at the age of this patient. Indeed sudden death is less common in uncomplicated mitral stenosis than in aortic valvular disease; as the former occurs often in young women, and is

usually unassociated with disease of the coronary arteries. In the three other instances of sudden death with ball-thrombus the ages were 21, 22, and 39 years respectively. Only in one of these was the thrombus a perfect sphere; so that it would appear that an oval thrombus is more likely to plug the mitral orifice than a spherical one. This view is strengthened by the fact that of the four observations of ovoid thrombi in three death was sudden. In the light of our case it seems clear that a ball-thrombus may "act as a ball-valve and stop the circulation in the mitral orifice," as suggested by Legg; but it is certain that this is an exceptional occurrence.

Under the name of cardiac *pedunculated polyps* various formations have been described. Some of these are ordinary unorganised or partly organised polypoid thrombi, about which nothing more need be said; but others are very remarkable structures which occupy an entirely exceptional position, not only among cardiac thrombi but among thrombi in general. In the older records some of the latter were described as fibromatous or myxomatous polyps,—two as hæmatoma; but in the later reports most have been recognised as organised thrombi. They are often called true polyps in distinction from the false polyps of the older writers.

The literature of the subject begins with Allan Burns in 1809. References to many of the cases will be found in the papers of Hertz, zum Busch, and Pawlowski. Among the noteworthy observations since Hertz are those of Czapek, Voelcker, Bostroem, and Ewart and Rolleston. I have found records of thirty-three cases, at least twenty of which were well-characterised, organised, pedunculated polyps. Twenty-five sprang from the wall of the left auricle, usually the septum; four from the right auricle; four from the left ventricle.

The following are the more notable features of these curious formations:— In many instances no cause whatever could be found for their occurrence. The hearts containing them were often otherwise entirely normal, with the exception of changes manifestly secondary to the polyp, such as nodular fibroid thickening of the mitral segments and dilatation and hypertrophy of the left auricle and right ventricle. Unlike other cardiac thrombi they are solitary formations, and often unassociated with ordinary thrombotic deposits. The vast majority of these polyps spring from the septum of the left auricle near the fossa ovalis with short pedicle, sometimes narrow, sometimes broad. They are firm or gelatinous, elastic, ovoid or pear-shaped formations, in several instances hanging down into the left ventricle with a constriction corresponding to the mitral orifice. The surface is usually glistening, smooth, and covered by a distinct membrane which often resembles the endocardium. It may present calcific, atheromatous, or pigmented patches; and upon it may be irregular knobs and depressions. The colour

is described as yellowish, gray, dark red or brownish red; the colour often varying in different parts of the polyp. A prevailing dark red colour has been observed in a large number of the cases. In distinction from nearly all other cardiac thrombi, these polyps are more or less organised by connective tissue and vessels; the organisation in some being little marked, in others so far advanced that the structure resembles that of a fibroma or myxoma. The central part is often unorganised or less organised than the base and periphery. In the incompletely organised forms the substance of the polyp is composed of red corpuscles, fibrin, granular detritus, yellow blood-pigment, leucocytes, and other cells between the blood-vessels and fibrous septa. Laminated fibrin may be present in the peripheral layers. Unless ordinary thrombi are likewise present, emboli are usually missed. A further distinction from the ordinary cardiac thrombi is that many of these polyps, by encroaching upon the mitral orifice, are of as much clinical as anatomical interest; the diagnosis during life in these cases being mitral disease, usually stenosis.

We have no satisfactory explanation of these pedunculated polyps. The ordinary causes of thrombosis are generally absent. Their commonest site of origin, the septum of the left auricle near the oval fossa, is not a usual situation for ordinary thrombi. They stand in no demonstrable relation to patency of the foramen ovale or to circumscribed endocarditis in this situation.

Bostroem has suggested that an explanation may be found in the existence of varicose veins which have been observed repeatedly in the septum, usually near the posterior quadrant of the foramen ovale. A difficulty with this explanation is that nine out of ten of the varicosities observed by Wagner, Zahn, Rindfleisch, and Bostroem were on the right side of the septum. In one instance, however, Bostroem found in the left auricle a spherical, dark red polyp, 13 mm. in diameter, attached by a short narrow stem to the septum on the posterior lower margin of the completely closed foramen ovale. This proved to be a varix containing a phlebolith. In another case a similar thrombosed varix had broken from its pedicle on the septum of the right auricle, and was lodged as an embolus in a branch of the pulmonary artery. He suggests this as a possible source of ball-thrombi. Of still greater significance is Bostroem's demonstration in an old museum specimen, labelled "thrombosis of the right auricle (pedunculated cardiac polyp) peripherally organised," of an enormous completely thrombosed varix almost filling the right auricle. In still another case he proved conclusively that a broad-based, nearly spherical polyp, occupying a large part of the right auricle, was a hæmorrhage in the wall of the auricle. Choisy and Nuhn long ago interpreted the polyps, which they observed, as the result of hæmorrhage in the septum of the left auricle.

In the light of Bostroem's interesting investigations, more attention than has been customary should be given to the possibility that pedunculated polyps are the result of hæmorrhage or are thrombosed varices. Most competent investigators, however, have unhesitatingly pronounced the polyps which they have examined to be organised thrombi. It would appear, therefore, that the nature of these formations is not always the same. At any rate the great majority of the typical pedunculated polyps, to which the preceding description applies, occupy a position quite apart from ordinary cardiac thrombi. As already remarked, by no means all of the cases described as true cardiac polyps belong to this peculiar group. Some, as in Krumm's case, are ordinary partly organised thrombi attached to diseased patches of the heart wall.

Association with Certain Diseases.—Thromboses may be divided, as regards their clinical relations, into the following groups: (i.) those resulting from direct injury of vessels, including the penetration of foreign bodies; (ii.) referable to diseases of the vascular wall, as to angio-sclerosis, syphilitic arteritis, aneurysm, varix; (iii.) caused by lesions of neighbouring parts; (iv.) thromboses of arteries and veins whose terminal branches end in septic and gangrenous areas; (v.) complications or sequels of (*a*) infective diseases, (*b*) cachectic and anæmic states, (*c*) cardiac disease, (*d*) certain constitutional diseases; (vi.) idiopathic and primary infective thromboses. Several of these groups, being mainly of surgical interest, will not be considered here. The thromboses embraced in the fifth and sixth groups are of such special medical interest that it is proper in this article to give them particular attention; although it is manifestly impossible within reasonable limits to take up all in detail. Some of them are noticed in other parts of this work.

Enteric Fever.—Cardiac Thrombosis is a rare complication of enteric fever. In 2000 fatal cases of enteric fever in Munich there were only eleven instances of acute endocarditis (Hölscher). Girode, Viti, Carbone, and Vincent have found the typhoid bacillus in endocardial vegetations; and vegetative endocarditis has been produced experimentally by intravascular injections of pure cultures of the typhoid organism combined with injury to the valves. More frequently the endocarditis has been due to secondary infection. In rare instances in the course of enteric fever globular thrombi are formed in the auricular appendages and ventricular apices; and these, as well as the endocardial vegetations, may be the source of emboli.

Arterial thrombosis is a still rarer event, but, in consequence of its gravity, an important one. Bettke, in 1420 cases, found four of gangrene of the extremities; but in 2000 Munich autopsies no instance is recorded, a result in contrast with fifty-nine of thrombosis of the femoral vein in the same

series. Keen, in his admirable monograph, has collected and analysed 115 cases of gangrene associated with enteric fever, and due to plugging of the arteries. In twenty-one cases arterial thrombosis was observed without gangrene, the absence of which is much more common with thrombosis of arteries of the upper extremity than of the lower. The earliest appearance of the gangrene was on the fourteenth day; the latest in the seventh week. In the great majority of cases the thrombus was seated in the arteries of the extremities; and in those of the lower far more frequently than of the upper. In eight out of eleven cases of arterial thrombosis of the lower extremities, collected by Barić, the posterior tibial artery was concerned. In contrast with venous thrombosis the right side is the seat as often as the left.

Other arteries, as the pulmonary, the superior mesenteric, and the cerebral, may become thrombosed. Four fatal cases of typhoidal thrombosis of the middle cerebral artery, or its branches, have been reported (Huguenin, Barberet and Chouet, Vulpian and Osler); and other cases have been recorded in which the diagnosis of cerebral thrombosis was made from the symptoms. In Osler's case, in which Dr. Flexner and I examined the brain, the middle cerebral artery was open; but the ascending parietal and parieto-temporal arteries and their branches were occluded by adherent, firm, mixed thrombi. The adjacent brain substance was studded with punctiform hæmorrhages, but not much softened. Typhoid bacilli were widely distributed in the body.

The arterial thrombosis may be secondary to embolism; but in the great majority of cases it has been reported as autochthonous. In the older records the thrombosis has been usually regarded as marantic; whereas the tendency now is to refer it to an infective arteritis; a view which is probable, although we have few conclusive observations in its support. Rattone and Haushalter claim to have demonstrated the typhoid bacillus in the walls of occluded arteries; and Gilbert and Lion, Crocq, and Boinet and Ramary have produced an acute aortitis experimentally, by injuring the vessel wall and then injecting typhoid bacilli into the circulation. The bacteriological studies are too meagre and unsatisfactory to warrant any definite statements as to the specific cause of arterial thrombosis in enteric fever.

The far commoner venous thrombosis of enteric fever has been adequately considered by Professor Dreschfeld in Allbutt's Syst. Med., vol. i. p. 817; and the points bearing on its causation have been presented under Etiology. Richardson has called special attention to the "marantic" thromboses of intracranial veins complicating enteric fever.

Influenza.—Nearly all of our knowledge of thrombosis in influenza dates from the pandemic of 1889-90, which led to the recognition of countless complications, among which those of the circulatory system occupy a less

prominent place than the respiratory and nervous. *Arterial thrombosis,* although far from common, is still not an extra-ordinarily rare complication or sequel of influenza. It is more common in this disease than in any other acute infection. In a few instances it appeared as early as the third to the fifth day, but in most during convalescence. Over forty cases of arterial thrombosis or of gangrene accompanying or following influenza have been reported. References to many of these will be found in the monographs of Leichtenstern and of Lasker; but their lists are far from complete. In a partial collection of the cases I find that the popliteal artery was occluded in six; the femoral in four; the iliacs, the axillary, the brachial, the pulmonary, and the renal each in two; and the central artery of the retina (embolism being probably excluded) in one. The cerebral arteries were repeatedly invaded. In several instances there were multiple thrombi. Symmetrical gangrene following bilateral plugging was observed in a number of cases. Gangrene was observed in all the cases of occlusion of the arteries of the lower extremities, but not regularly with that of the upper.

It is difficult to say in how many cases the occlusion was due to embolism. Endocarditis is a rare but recognised complication of influenza, and globular cardiac thrombi have also been observed. In the great majority of cases it seems clear that there was primary arterial thrombosis.

Venous thrombosis is a far commoner result of influenza; and has been the subject of a special memoir by Chaudet, and of numerous articles in the medical journals of all countries. Twenty-five cases are recorded in Guttmann and Leyden's collective investigation, and many additional ones are to be found in the vast literature on influenza. Dr. Goodhart, in his article on "Influenza" (Allbutt's Syst. Med., vol. i. p. 683), notes the frequency and the occasional diagnostic value of this complication, which may appear during the course of the disease or weeks afterwards, and in mild as well as severe cases. In the great majority of instances the femoral vein was attacked; but the veins of the upper extremity were thrombosed more frequently than in other acute infective diseases. Leichtenstern notes the acute onset and course in some of the cases. There are records of thrombosis of the cerebral sinuses in influenza. Klebs and Kuskow describe capillary thrombi in the lungs.

Few observers are satisfied with the explanation of either the arterial or the venous thromboses of influenza as marantic. Leyden suggests as a cause increase of blood-platelets from disintegration of leucocytes. Evidences of such disintegration, or of masses of platelets in the blood, have been noted by Klebs, Chiari, and Bäumler. Maragliano observed the onset of necrobiotic changes of the red corpuscles in influenza almost immediately after withdrawal of the blood. French writers for the most part attribute the

thrombosis to infective arteritis or phlebitis (artérite grippale, phlébite grippale). Rendu, however, in his case of arterial thrombosis rejects this explanation; as he found the walls of the thrombosed arteries entirely normal (nothing is said of a microscopical examination), and he attributes the thrombosis to feeble circulation. In his case there was also a thrombus with softened centre in the left ventricle, and the occlusion of the artery may have been due primarily to an embolus. Gerhardt attributes the gangrene in his case to spasm of the arteries, considering it therefore analogous to symmetrical or arterio-spastic gangrene. In support of the more probable view that the thrombosis is the result of some change in the vascular wall, directly referable to infection or intoxication, Kuskow observed with great frequency degeneration, proliferation, and desquamation of the vascular endothelium in influenza. In a fatal case of influenzal phlegmasia alba dolens Laveran found streptococci in the blood. These organisms have often been found in the blood and organs of those dead of influenza.

In a remarkable case of multiple thrombotic vegetations present in large numbers in the pulmonary artery, especially in the left main branch, and also on the pulmonary valves (other valves normal), Flexner in my laboratory found in the thrombus, chiefly enclosed within polynuclear leucocytes, very numerous, extremely delicate bacilli, which were identified as the influenzal bacilli of Pfeiffer. This establishes the occurrence of an acute arteritis and thrombosis due to the bacillus of influenza.

Pneumonia.—The sixteenth century error of mistaking for ante-mortem coagula the firm, yellowish white cardiac clots, intimately intertwined with the columnæ carneæ, and found after death from pneumonia more frequently than from any other disease, has not wholly disappeared at the end of the nineteenth century; for coagulation of blood in the right heart is still occasionally spoken of as a special danger in pneumonia. Genuine ante-mortem thrombi in the cavities of the heart occur in pneumonia, but they are rare; being much less common than in many diseases in which death from "heart-clot" is not mentioned as a special danger. Acute valvular endocarditis is a well-recognised complication of pneumonia. Mention has already been made of coagula in pulmonary vessels directly connected with the inflamed lung (p. 115).

Benedikt, Brunon, Rendu, Leyden, and Blagden have observed gangrene of the extremities consecutive to arterial thrombosis in pneumonia. Blagden's patient was a woman 92 years old. In Leyden's case there was thrombosis of the lower end of the abdominal aorta. Gangrene of the extremities in pneumonia may also be the result of embolism; of this event Osler has observed an instance.

Venous thrombosis, although more frequent than arterial, is scarcely mentioned in text-books as a complication or sequel of pneumonia. Few cases have been reported. Da Costa, in a valuable article on the subject, reports three personal observations, and has collected from the literature six additional ones, and two which are doubtful. In addition to these, I have found reports of cases by Barbanceys (two cases), Lépine, Fabriès, Valette, Mya (two cases), and Lee Dickinson (seven cases), making a total of twenty-three cases of venous thrombosis in pneumonia. The femoral or internal saphenous veins were those invaded, the affection being oftener on the left than on the right side. There were at least three deaths from pulmonary embolism consecutive to the thrombosis. The affection, if one may draw any conclusion from so small a number of cases, is more common in women than in men. Of 367 cases of pneumonia, observed by Dickinson, peripheral venous thrombosis occurred in seven, of which four were in young women, two of these being chlorotic. In several instances of influenzal thrombosis pneumonia had occurred. Laache ranks pneumonia next to influenza and enteric fever as regards the frequency of occurrence of peripheral thrombosis; but this event is far commoner in the last two diseases. The affection occurs during convalescence, rather than in the course of pneumonia; and presents the same general characters as the phlegmasa alba dolens of enteric fever. Da Costa very plausibly attributes it to a primary infective phlebitis. Mya, in one of his cases, found pneumococci in large numbers in the thrombus.

Acute Articular Rheumatism.—There was a time when rheumatic phlebitis ranked in importance next to the puerperal form; but it is now recognised that most of the cases of thrombosis attributed by the older writers to rheumatism had nothing to do with acute articular rheumatism. Schmitt and Vaquez have sifted the reported cases, and they find that, while phlebitis or venous thrombosis is to be recognised as a complication of genuine acute rheumatism, it is a rare one. The infrequency of this event is noteworthy in view of the fibrinous state of the blood and the frequency of acute endocarditis. Gatay has reported a doubtful case with negative result of the bacteriological examination of the thrombus. Legroux reports an instance of thrombosis of the brachial artery without gangrene in acute articular rheumatism.

Appendicitis.—Mention may be made of the occurrence of thrombosis with appendicitis, as this affection is of medical as well as surgical interest. Besides the septic thrombo-phlebitis of the mesenteric and portal veins, thrombosis of the iliac and femoral veins may occur on the left side as well as on the right. The published reports indicate that this is more common on the right side; but in the 131 cases of appendicitis in the service of my

colleague Professor Halsted, with the notes of which Dr. Bloodgood has furnished me, there were four instances of peripheral venous thrombosis, all of the left leg; one being limited to the calf. Three of these were in chronic appendicitis, the operation being between the attacks. Mynter, who has also observed thrombosis of the left femoral vein, attributes it to great prostration and weak circulation. It is interesting to note the analogy of appendicitic thromboses to puerperal thromboses, where we also have septic and suppurative thrombi in veins immediately adjacent to the inflamed organ, and less manifestly infective thrombi in the veins of the lower extremities. It is probable, however, that the latter thrombi in appendicitis, as well as in the puerperal cases, are frequently caused by bacteria, and oftenest by streptococci, which are concerned in both affections with great frequency. In one of Mynter's cases sudden death was probably due to pulmonary embolism following thrombosis of the femoral vein.

Other Acute Infective Diseases.—It would lead too far to continue a detailed inquiry into the association of thrombosis with other acute infective diseases. It must suffice to specify typhus fever, relapsing fever, dysentery, erysipelas, suppurative tonsillitis, diphtheria, variola, scarlatina, measles, Asiatic cholera. In many instances thrombosis, as associated with specific infective diseases, has been due to a secondary septicæmia, streptococci being the commonest secondary invaders. The disposition in or after typhus fever to arterial as well as to venous thrombosis should be especially emphasised. Thrombosis has been added to the growing list of complications of gonorrhœa (Martel, Perrin, and Monteux and Lop).

Tuberculosis.—The consideration of thrombosis directly referable to tuberculous processes adjacent to vessels need not detain us. The occurrence of intimal tubercles, where the evidence is conclusive that tubercle bacilli have penetrated the inner lining of vessels directly from the circulation in the main channel, may be mentioned not only as a cause of thrombosis, but also as an interesting illustration of this mode of infection of the vascular wall. Several instances of endocarditis caused by the tubercle bacillus have been described, and mention has already been made of tuberculous cardiac thrombi (p. 142). Michaelis and Blum have produced vegetative tuberculous endocarditis experimentally, by injuring the valves in rabbits and then injecting tubercle bacilli into the ear veins. Particularly demonstrative of infection taking place through the vascular enothelium are the rare instances of tuberculous foci in the aortic intima, without invasion of the outer coats, and without tuberculosis of neighbouring parts. Two instances of this form of aortic tuberculosis have been observed in my laboratory, and described by Flexner and Blumer. I have recently examined a section, in the possession of Dr. Gaylord, of a superficial tuberculous focus

in the intima of the aorta with an exquisite platelet and fibrinous thrombus containing tubercle bacilli attached to the nodule. A similar case has been described by Stroebe. These rare instances are cited because they furnish conclusive proof that bacteria may penetrate the inner lining of vessels from the main channel, even where the blood-current is forcible; and may set up inflammation of the intima with secondary thrombosis. Hektoen's interesting observations of changes in the intima of vessels in tuberculous meningitis furnish additional evidence along the same lines.

Arterial thrombosis, outside of the forms to which reference has just been made, and which are of pathological rather than clinical interest, is a rare event in tuberculosis. Most common are the instances of thrombosis of the pulmonary artery or its main branches in phthisis. Dodwell mentions an instance of thrombosis of both popliteal artery and vein. Vaquez, in chronic pulmonary tuberculosis, describes an interesting case of thrombosis of the left subclavian, axillary and brachial arteries with gangrene of the arm: he found streptococci in the plug and in the wall of the vessel, including the vasa vasorum, but no tubercle bacilli.

On the other hand, peripheral venous thrombosis in advanced phthisis is a comparatively common and well-recognised ailment. In the great majority of cases veins of the lower extremities, the left oftener than the right, have been plugged; but the thrombus may be in the inferior vena cava, or other veins, or the cerebral sinuses. Dodwell, in his valuable paper on this subject, places the proportion of cases of phthisis with this complication at about 3 per cent. In about 1300 necropsies of phthisical patients at the Brompton Hospital there were twenty cases of thrombosis of veins of the lower extremities (1.5 per cent).

The peripheral venous thromboses of advanced phthisis are usually cited as typical examples of the marantic or cachectic form. Dodwell, however, while recognising enfeebled circulation as a factor, is inclined to refer the thrombosis to some unknown change in the vascular wall set up by a complicating septicæmia. He emphasises the infrequency of venous thrombosis with the acute and the very chronic forms of phthisis, and its relative frequency with an intermediate type with remittent or continued fever. He also noted association with intestinal and laryngeal ulceration in a larger percentage of the thrombotic cases than the average. As is well known, secondary septicæmias, usually streptococcal, are very common in phthisis.

There are several records of bacteriological examination of the peripheral thrombi in phthisis, which show that they may be of mycotic origin. Vaquez found tubercle bacilli, without other micro-organisms, in a thrombus of the left profunda and femoral veins. They were present also in the wall immediately beneath the endothelium, but were absent from the media and

adventitia. Sabrazes and Mongour in two instances found tubercle bacilli both in the plug and in the wall of a thrombosed iliac vein: they were associated with micrococci. More frequently micrococci, presumably pyogenetic, have been found, without tubercle bacilli, in the thrombi and vascular walls: examples of this are recorded by Vaquez. Notwithstanding these suggestive bacteriological findings it would be quite premature to conclude that all the peripheral venous thromboses of phthisis are referable to direct infection of the venous wall by bacteria. In a rather old thrombus of the iliac and femoral veins in phthisis I failed to find any micro-organisms, either by culture or by microscopical examination.

Hirtz has called attention to the occurrence of phlebitis in the initial stage of phthisis. Some cases so reported have appeared to be chlorotic in origin.

Cachectic States.—Of other marasmic or cachectic states, in which thrombosis is somewhat frequent, may be especially mentioned those resulting from cancer, dysentery, chronic diarrhœa, gastric dilatation, prolonged suppurations especially of bone, anæmia from loss of blood, and syphilis. The association of thrombosis with syphilis has been recently discussed by Barbe. Phthisis has just been considered. It is especially in the young and the very old that these conditions are most likely to produce thrombosis. Thromboses of the cerebral sinuses, and of the renal and other veins, in marasmic infants, particularly after diarrhœa, are well recognised. Peripheral venous thrombosis is more often associated with the waxy kidney than with other forms of Bright's disease. The thrombi occasionally found in the renal veins in chronic diffuse nephritis are probably due to local causes, and not to cachexia.

There is a French thesis by Rigollet on thrombosis in malaria, and Pitres, Bitot, and Regnier have likewise called attention to the subject. It is doubtful whether there is any relation between malaria and thrombosis. In over 2000 cases of malaria observed in Professor Osler's service at the Johns Hopkins Hospital no instance of thrombosis was found. (Personal communication by Dr. Thayer.)

Trousseau attached some diagnostic significance to the occurrence of thrombosis in cancer. There have been instances of latent cancer of the stomach in which peripheral venous thrombosis was the first symptom to attract attention, as indeed it was in Trousseau himself who died of gastric cancer. Gouget has reported a case of widespread venous thrombosis, of eight months' duration, which was the only affection observed during life. At the autopsy a small cancer of the stomach was found. Dr. Osler has told me of a personal observation of very extensive multiple thrombosis associated with cancer of the stomach.

The principal seats of cachectic thromboses are the auricular appendages, between the columnæ carneæ of the right heart, in the veins of the lower

extremities, the cerebral sinuses, the pelvic veins, and the renal veins. Lancereaux has strongly urged that this form of thrombosis never occurs in the arteries. Doubtless in not a few reported cases embolism has not been satisfactorily excluded; but older observations of Charcot and von Recklinghausen, and several recent ones, leave no doubt of the occurrence of genuine so-called marantic or cachectic thrombi in arteries, even in the aorta.

While pre-existing vascular disease, particularly angio-sclerosis and varicose veins, are predisposing conditions, these plugs are often seated upon intimæ which show very slight alteration. Indeed competent observers have repeatedly described the vessel wall beneath marantic thrombi as normal. While secondary septic infections often participate in the causation of cachectic thromboses, the view that all have this origin is at present unsubstantiated. It is clear that enfeebled circulation is of importance in their causation; but, for reasons already stated, there must be some additional element, which, in many cases at least, cannot well be other than changes in the composition of the blood. The nature of these changes is not known. Possibly increase of platelets, or a special vulnerability of cells, perhaps of the red corpuscles from which platelets are derived, may be concerned.

Cardiac Incompetency.—I have already had occasion in this article to speak repeatedly of the importance of feebleness of the general circulation in the causation of thrombosis. Thrombi in the heart itself have been considered (p. 139). In this respect attention is called to the occurrence of peripheral venous thrombosis in chronic passive congestion due to cardiac incompetency, chiefly from valvular disease. Especially noteworthy, in view of the slow venous circulation and the frequency of cardiac thrombi in this condition, is the infrequency of peripheral thrombosis. Hanot and Kahn, in reporting an instance of thrombosis of the right subclavian vein, say that they were able to find in the French literature, which is exceptionally rich in clinical contributions to the subject of thrombosis and phlebitis, only five additional observations of peripheral venous thrombosis in cardiac disease. I do not think that this complication is quite so rare as would appear from this statement; for, without any systematic effort to collect cases, I have found records of eighteen additional ones—Ramirez (two cases), Baldwin, Nicolle, Hirschlaff (two cases), Robert, Ormerod, Mader, Huchard (two cases), Cohn (three cases), Cheadle and Lees (three cases reported by Poynton); and I have observed two instances of femoral and iliac thrombosis associated with mitral regurgitation.

The most notable fact concerning these twenty-six cases is that seventeen were thromboses of veins of the neck or upper extremity or both, far more

frequently of the left than the right side; and one of the innominate veins. In one of Cheadle and Lees' cases the innominate, subclavian, axillary, and internal and external jugular veins upon both sides, the left inferior thyroid, and the upper two-thirds of the superior vena cava were thrombosed; and in another of their cases both internal jugulars and both innominates were completely plugged, and there was a mural thrombus in the upper part of the superior vena cava. It may be that femoral thrombosis is more common in heart disease than would appear from these figures; it is less likely to be reported than thrombosis of the neck and arms, and, on account of the œdema attributable to cardiac insufficiency, may more readily be overlooked both at the bedside and the autopsy table. When, however, we consider that Bouchut places the ratio of thromboses of the upper extremity to those of the lower at 1 to 50, the relatively large number of the former associated with cardiac disease is certainly most striking. The clinical histories seem to show that thrombosis is more likely to occur in the cases with tricuspid regurgitation than in others; but it is certainly even then a very rare event. In several cases there was some complication, especially pressure on the veins and tuberculosis. The explanation of the greater frequency of the thrombosis on the left than the right side has already been given (p. 138).

The relative freedom from peripheral venous thrombosis in cardiac disease, in spite of conditions of the circulation apparently favourable to such an occurrence, may perhaps be attributable partly to the reduction in platelets in this condition (which has been noted by van Emden), and partly to the absence of von Recklinghausen's "Wirbelbewegung" (p. 138), an irregularity of the circulation which occurs especially in vessels too wide in proportion to the amount of blood which they receive. Hanot and Kahn refer the thrombosis to a cachectic state developing in the last stages of cardiac disease. Huchard likewise attributes it to cardiac cachexia associated with secondary infection. Cheadle and Lees' three cases are referred by Poynton, who reports them, to rheumatic infection. The bacteriological examination was negative.

As will appear later (p. 244), there is evidence that arterial plugging associated with mitral stenosis is due oftener to primary thrombosis than is generally supposed.

Chlorosis.—The association of thrombosis with chlorosis is of peculiar interest. Professor Allbutt, in his article on "Chlorosis" (Allbutt's "System of Medicine," V, p. 508), has sketched the more essential features, but has referred some points for consideration here. In the older literature there are reports of plugging of the veins in young women which undoubtedly pertain to chlorosis. Thus William Sankey, in 1814, says: "I have met with two cases in young women, not after parturition; both were severe and well

marked; both had obstructed menses." But Trousseau, with his pupil Werner, in 1860 was the first to draw distinct attention to this association. References to the more important records, up to 1898, will be found in the recent article by Schweitzer, from Eichhorst's clinic.

Although thrombosis is not a common complication of chlorosis, it is sufficiently frequent to indicate a special tendency to its occurrence in this disease; a tendency calculated to arrest attention on account of the age and the class of the patients, the obscure causation, and the unexpected and calamitous termination which it may bring to a disease ordinarily involving no danger to life. Some idea of the frequency of chlorotic thrombosis is perhaps afforded by the statements that von Noorden observed 5 instances in 230 chlorotics, and Eichhorst 4 in 243. The list of reported cases was brought by Proby in 1889 to 21, by Bourdillon in 1892 to 32, and by Schweitzer in 1898 to 51. I have found reports of 30 additional cases not included in these lists, and am indebted to Dr. W. S. Thayer for an unpublished personal observation; making a total of 82. (References will be found at the end of this article.) I have also seen 12 other cases mentioned, but without sufficient detail for statistical analysis; and I have come across several references to articles on the subject not accessible to me. Slavic and Italian literature has not been searched, and the American to only a small extent. I have no doubt that mention or reports of over 100 cases of thrombosis chlorotica could be gathered by thorough overhauling of medical books and periodicals. Thirty-one of my cases are from French literature, twenty-five German, eighteen English, three Scandinavian, two American, and one Italian. It would, however, be quite unwarrantable from this literary inequality to infer any difference in the incidence of the affection according to race or country.

The statistical study of these eighty-two cases brings out a number of interesting points, of which some only are directly pertinent to this article. Thrombi in the heart are very rarely mentioned in the post-mortem reports. There were only four instances of primary arterial thrombosis, two being of the middle cerebral arteries (Vergely); one of the pulmonary (Rendu) without thrombosis elsewhere, and one of the right axillary (Tuckwell) with gangrene of the hand and recovery. Dr. Tuckwell reports his case as one of embolism; but it is usually included among the arterial thromboses, and probably with as much or as little right as the others.

All the remaining 78 cases were venous thromboses. There was thrombosis of the cerebral sinuses in 32 cases (39 per cent), 6 (19 per cent) of these being associated with thrombosis of the lower extremities. In four instances thrombi extended from the sinuses into the internal jugular veins. Unquestionably sinus-thrombosis is represented by too high percentage

figures in my list, for the obvious reason that reports of an affection of such gravity and such interest, especially to neurologists, are much more likely to get into print than those of ordinary femoral thrombosis. Still the figures are impressive, and indicate that sinus-thrombosis is not of great rarity in chlorosis; to which malady a leading place among the causes of spontaneous thrombosis of the cerebral veins and sinuses in women must be conceded.

In 51 of the 82 cases there was venous thrombosis of the extremities (62.2 per cent—too low a percentage as already explained); 50 being of the lower and three of the upper, of which only one was limited to the upper extremity. Of the 50 cases of thrombosis of the lower extremities (which are probably involved in at least 80 per cent of all chlorotic thromboses), the process was bilateral in 46 per cent, and unilateral in 54 per cent—34 per cent being left-sided and 20 per cent right-sided. The usual preference of femoral thrombosis for the left side is shown by the beginning of the affection in the left leg in 64 per cent of the thromboses of the lower extremities, in the right leg in 29 per cent, and on both sides simultaneously in 7 per cent. There is in the list one case (Kockel's) with meagre history, in which no mention is made of thrombi outside of the upper part of the inferior vena cava; death ensued from pulmonary embolism. This I have not included among the thromboses of the extremities.

So large a proportion of thromboses involving both lower extremities merits emphasis as a characteristic of chlorotic thrombosis. So again the repeated observations of multiple and successive thromboses, relapses and recurrent attacks (it may be after weeks or after years), all point to the peculiar and widespread tendency of thrombosis in some cases of chlorosis. The most remarkable example of this is Huels' case, in which various large veins of the extremities, trunk and neck became thrombosed in quick succession, until finally only the jugular and right subclavian veins remained free. The patient recovered. In five cases examined after death the inferior vena cava was plugged; and in a few of those who recovered the symptoms indicated extension of the thrombus from the iliacs into this vein.

While the prognosis of chlorotic sinus-thrombosis is extremely bad, Bristowe and Buzzard each report an instance of recovery. Such a possibility has been questioned, but I see no reason to doubt it. Not very infrequently after death in one or more of the intracranial sinuses thrombi are found which had occasioned no recognisable symptoms during life, and no lesions of the brain.

A fatal issue of uncomplicated thrombosis of the extremities is due almost always to pulmonary embolism, which occurs oftenest in the second to the fourth week after the onset, and usually after some movement of the body. In my collection of cases there are thirteen instances of pulmonary embolism

(25 per cent of the fifty-two cases with venous thrombosis outside of the cerebral sinuses). All but two terminated fatally. In some other cases there were symptoms suggestive of embolism; and doubtless emboli lodged in smaller pulmonary arteries without giving any indication of their presence. After making due allowance for the undoubtedly disproportionate representation of embolism of the large pulmonary arteries in published records, this catastrophe remains sufficiently frequent to impart a certain gravity to the prognosis even of simple femoral thrombosis in chlorosis.

There are almost as many hypotheses of chlorotic thrombosis as of chlorosis itself. None of these introduces any factors which have not been considered already under etiology. The principal causes which have been assigned, either singly or in combination, may be grouped as follows: (i.) feeble circulation due to weakness of the heart, sometimes intensified by congenital hypoplasia of the blood-vessels (Virchow); (ii.) alteration of the vascular endothelium, especially fatty degeneration (Eichhorst, Renaut); (iii.) primary phlebitis of unknown causation (Vaquez); (iv.) increase of platelets (Hanot and Mathieu, Buttersack); (v.) some fault in the composition of the blood, variously defined as lowered specific gravity, deficiency of salts (?) (Renaut), presence of extractives derived from muscular activity (Proby), increase of fibrin-ferment (Birch-Hirschfeld); (vi.) secondary infection (Villard, Rendu, Oettinger, von Noorden).

It is not necessary here to discuss all these views in detail. The data for estimating their value have for the most part already been presented in this article. Such primary lesions of the vascular wall as have been noted in the thrombosed veins have usually been trivial, and are common enough without thrombosis. There is at present no bacteriological basis for the infective supposition. Villard's much-quoted observation is unconvincing; in his case a small piece of a peripheral thrombosed vein was excised and examined by Nepveu for micro-organisms with negative result. Villard adds that Bossano found micro-organisms in the blood, but gives no details; and there is no evidence that these micro-organisms may not have come from the skin. Perhaps more weight should be attached to a few observations in which some source of infection, such as furuncle, was present. Proby, Löwenberg, von Noorden, and other observers have examined the thrombi and blood of chlorotics without finding any micro-organisms. Nevertheless von Noorden and others are favorably disposed to the infective hypothesis, on clinical grounds. Sometimes the onset of chlorotic thrombosis is ushered in by a chill or chilly sensations; usually there is fever, which may be well marked; and in general the symptoms are thought by some to indicate infection. It does not seem to me imperative to interpret these symptoms as necessarily indicative of infection by micro-organisms.

There are difficulties with all of the hypotheses which have been suggested. I think that there may be some significance for the etiology of chlorotic thrombosis in the increase of platelets noted by Hanot and Mathieu, and by Hayem; and determined more accurately by Muir.[a] I shall also venture to suggest that there may be some nutritive disturbance of the red corpuscles, in consequence of which they disintegrate more readily from slight causes, and produce the granular material, chiefly platelets, which constitutes the beginning white thrombus; and in support of this opinion I will call attention to Maragliano and Castellino's observations of the lowered resistance of chlorotic red corpuscles. Another element which may enter into the causation is some little understood irregularity of the circulation, other than retarded flow, which is manifested in the venous thrills and hums; and which may in certain situations, where thrombi most frequently form (sinuses, femoral vein), lead to the eddies shown by von Recklinghausen to be of importance in the causation of thrombosis; although I confess that the fullness of the veins in chlorosis does not support this suggestion.

Gout.—Since the publication of the classical paper on gouty phlebitis by Paget in 1866, followed by those of Prescott Hewett and Tuckwell, this affection has been well recognised (see art. on "Gout," Allbutt's "System of Medicine," IV, p. 161). Its causation is unknown. Paget with much reason regards the ailment as a primary phlebitis with secondary thrombosis; and in this he has been followed by most writers on the subject. Although deposition of urates has been found in the sheaths of veins, there is no evidence that gouty phlebitis is caused in this way. Sir W. Roberts, on p. 172 of the article just quoted, ingeniously suggests that the presence of scattered crystals of sodium biurate in the blood may constitute foci around which thrombi may be formed.

Idiopathic Thrombosis.—Paget says that the occurrence of phlebitis in elderly persons without any evident external cause warrants the suspicion of gout; and that this is perhaps the most common form of idiopathic phlebitis. There remain, however, rare instances of apparently spontaneous thrombophlebitis, occurring in previously healthy individuals, which cannot be explained in this way. Daguillon has observed and collected a number of such cases.

[a] Buttersack has recently described the presence in the blood of chlorotics of cylindrical masses of platelets identical with the first form of Litten's blood-cylinders. These he considers to be capillary platelet-thrombi, which have been washed out by the circulating blood. While they may occur in other conditions, Buttersack associates them especially with chlorosis. It remains to be determined whether this cast-like arrangement of platelets is not the result of the mode of preparation of the specimen of blood.

Primary Infective Thrombosis.—There are rare instances of arterial and venous thrombosis, generally widespread, which present the characters of an acute infective disease without anatomical lesions other than the thrombo-phlebitis, or thrombo-arteritis, and the changes consecutive to the vascular obstruction and to the vascular or general infection. The thrombosis may be referable to a primary infective angeiitis, or to a general infection with changes in the blood and circulatory disturbances. The former class of cases may be considered analogous to mycotic endocarditis, the localisation being in the vascular intima instead of in the endocardium. In the latter group, which probably is not strictly separable from the former, the veins or the arteries are plugged with thrombi, which are often extensive and multiple. The venous is more common than the arterial form. Vessels both of the extremities and of the viscera may be invaded. The affection appears as an acute infective fever with the special localisation of the process in the blood-vessels.

As belonging to the group of primary infective thrombo-phlebitides I should interpret a case reported by Dowse. A woman, 43 years old, previously in good health, was suddenly seized with chills, fever, and great prostration, accompanied by the rapid onset of severe pain and œdematous swelling of the right leg. Death occurred after two and a half weeks. At the autopsy the iliac, femoral, popliteal, and deeper veins were found to be filled with mixed, adherent, predominantly red thrombus. The tissues around the thrombosed vessels were suffused with blood.

Osler has reported an instance of the arterial form of primary infective thrombosis. A man, aged 20, who had recovered from typhoid fever two years previously, presented fever, rapid pulse, diarrhœa, and abdominal pain, followed by gangrene of both legs extended to the middle of the thighs. He died about two weeks from the beginning of the illness. At the autopsy was found thrombosis of the femoral and iliac arteries, of the lower two inches of the abdominal aorta, and of two large branches of the splenic artery. The spleen was enlarged, and contained large infarcts, one the size of an orange, which had given rise to peritonitis. There were infarcts also in the right kidney. Numerous micrococci were found in the splenic infarct, and in the exudate covering it. The heart, the intestine, the brain, and the lungs showed no lesions.

Effects and Symptoms.—The lesions and the symptoms produced by thrombi are referable to the obstruction of the circulation caused by the plug, and to the local and constitutional effects of irritative or toxic substances which may be present in the thrombus or vascular wall. It is obvious that these effects must vary with the functional importance of the part supplied by the obstructed vessel; with the rapidity, extent, and completeness of the

obstruction; with the location of the plug in heart, artery, capillary, or vein; with the size of the vessel; with the readiness of establishment of a collateral circulation; with the nature of the thrombus, and with associated local and general morbid conditions. Thus the obstruction of each important vessel produces its own anatomical and clinical picture. The thromboses of certain vessels, as the intracranial sinuses, the portal vein, the femoral vein, are well characterised, distinct affections, which receive separate consideration in medical books. But I know of no modern work which presents in a systematic and thorough way the anatomical and clinical characters of occlusion of each of the important vessels of the body; although scattered through medical literature is a large and to a considerable extent unutilised casuistic material for such monographic treatment. In this article, treating of the subject as a whole, the more general considerations concerning the effects of thrombosis, with special reference to certain common and clinically important localisations which do not receive separate treatment elsewhere in this work, will be presented. Widely different are the effects according as the thrombosis is cardiac, arterial, capillary, or venous.

Of Cardiac Thrombosis.—If the presence of globular cardiac thrombi could be determined during life, it would be generally recognized as an index of grave impairment of the heart's action. But, apart from furnishing emboli, ordinary globular thrombi are not known to occasion any symptoms. There may be instances when during life cardiac thrombi may be suspected as more probable sources of emboli, particularly of those causing pulmonary infarction, rather than either endocardial vegetations or venous or arterial thrombi; but beyond conjecture the diagnosis can hardly go. Gerhardt attributed to the pressure of thrombosed auricular appendages upon the pulmonary artery or aorta murmurs heard over the arterial orifices of the heart; but other causes of such murmurs are commoner and better recognised. The encroachment of massive thrombi and of pedunculated polyps upon the orifices of the heart may occasion murmurs, thrills, and symptoms indistinguishable from those of valvular disease. In three such cases, involving the mitral orifice, von Ziemssen observed gangrene of the feet, which he was inclined to refer to arterial thrombosis rather than to embolism; but this symptom has not the diagnostic value which he assigns to it, for in other cases it was present only exceptionally, and it may occur in ordinary mitral stenosis. Unless the orifices are encroached upon, the mere presence even of large thrombi usually occasions little or no disturbance of the heart, or none which can be distinguished from that of associated valvular or mural disease. The clinical features of ball-thrombi have already been considered (pp. 145 and 146).

Of Arterial Thrombosis.—The effects of arterial thrombosis are so much like those of embolism that it will be convenient to defer the detailed con-

sideration of their manifestations in common to the article on embolism (p. 201), and here to speak only of the more distinctive features and clinical types of arterial thrombosis.

Whether the occlusion of an artery be by a thrombus or an embolus, the result, apart from possibly infective properties of the plug, depends upon the possibility of establishment of an adequate collateral circulation. If the anastomoses are such as to permit the ready development of a collateral circulation, an arterial branch may be plugged without any mechanical effects. In the case of certain visceral arteries, as the terminal cerebral, branches of the splenic, and of the renal, a collateral circulation sufficient to nourish the part supplied by the occluded artery cannot be established, even with a slowly-forming thrombus. In some situations, however, arteries whose abrupt obstruction by an embolus may cause the gravest lesions and symptoms, may be closed gradually by thrombus without serious consequences. This has been observed in thrombosis of various arteries of the extremities, neck, and trunk; as the femoral, the iliac, the carotids, the mesenteric, the cœliac axis, a main division of the pulmonary artery, and even the aorta. But in order to secure whatsoever advantage may accrue from its slower formation, the thrombus must find other conditions favourable for the development of a collateral circulation; and often enough these conditions, of which the most important are integrity of the arterial walls and vigour of the general circulation, are absent. Furthermore, thrombosis is often rapid in attack, and hence, whether the plug be a thrombus or an embolus, the result is frequently the same.

In the differential diagnosis between arterial thrombosis and embolism emphasis is properly laid in the former upon the more gradual appearance of the symptoms of vascular occlusion and pre-existing arterial disease, and upon sudden onset and the detection of some source for an embolus, particularly cardiac disease, in the latter (see "Diagnosis of Embolism," p. 221). But mistakes in diagnosis are sometimes unavoidable; for all the clinical phenomena which attend the one may occasionally be associated with the other form of arterial obstruction. Nor can the distinction always be made, with the desired precision, at the autopsy, although generally this is decisive. Hence cases are reported as arterial thrombosis which are doubtless embolism, and conversely.

Within recent years primary arterial thrombosis, occurring independently of chronic diseases of the arteries, has been recognised as a more frequent and important affection than had been generally supposed since the acceptance of Virchow's doctrine of embolism. Of especial medical interest are the primary arterial thromboses, arising oftener as a sequel during convalescence than as an accompaniment of various infective diseases, particularly

of enteric fever and influenza. The associations and localisation of these thromboses, as well as the prevailing view that they are infective and referable to an acute arteritis, have already been considered.

Arterial Thrombosis of the Extremities.—When, as is usual arteries of the lower extremities are affected, the first symptom is pain in the limb. This is often severe and paroxysmal, and is increased by pressure at certain points in the course of the vessel. The obliterated artery may be felt as a hard, sensitive, pulseless cord; and below it pulsation may be feeble or cease altogether. Before obliteration the pulsations may be of wider amplitude than normal, in consequence of lack of arterial tone (Gendrin, Barié). The leg, especially about the foot and ankle, becomes pale, cold, mottled with blush-red spots, numb and paretic. With loss of tactile sensation there is often increased sensitiveness to painful impressions. There may be diminution or loss of muscular reaction to both galvanic and faradic currents. There may be increased moisture of the skin, and some œdematous swelling of the affected leg. Unless adequate collateral circulation be speedily developed the termination is gangrene. While the extent of the gangrene is in relation to the seat of the obstruction, it varies also according to the collateral circulation; so that with occlusion of the femoral or iliacs it may affect only the foot or even a toe; or with closure of the popliteal or tibial arteries it may extend as high as the point of obstruction. The gangrene is usually dry; but if septic inflammation or closure of the veins occurs it is likely to be moist. Recovery may follow with loss of the gangrenous part; or death may result from exhaustion, from extension of the mortification, from septicæmia and toxæmia.

The rarer arterial thrombosis of the upper extremities may likewise lead to gangrene; but here the chances for restoration of the circulation through the collaterals are much better.

I have already referred to the relations of thrombosis to senile, spontaneous, and other forms of gangrene (p. 135). Heidenhain and Naunyn hold that arterio-sclerotic thrombosis is the usual cause of diabetic gangrene: but further investigations into the causes of this form of gangrene are needed. Thrombosis of the abdominal aorta presents a group of symptoms which will be described under Embolism (p. 243).

The complex of symptoms called by Charcot "intermittent claudication" may be observed with thrombosis of arteries of the lower extremities, or of the iliacs or abdominal aorta; but it is more common with arterio-sclerosis. The term "intermittent claudication" (boiterie) is used by French veterinarians to describe similar symptoms in horses affected with thrombosis of the iliac arteries, which is not a rare disease in these animals. In these cases the lower extremities receive enough blood for their needs during

repose, but not during active exercise. The slighter manifestations consist only in some muscular weakness and numbness of the legs after exercise; but in more severe cases, after walking a quarter of an hour or perhaps less, occur great muscular weakness, numbness, and pains and cramps in the legs, which may become cold, exsanguinated, sometimes cyanosed in the periphery, and almost pulseless. All of these symptoms disappear after repose, perhaps of but a few minutes' duration. Charcot's syndrome has in a number of reported cases been a precursor of arterio-sclerotic gangrene, but it may exist for years without this event. The phenomena are unilateral or bilateral, according to the seat of the arterial obstruction. Spasm of the arteries is evidently an important element in the pathogeny of intermittent claudication.

Other evidences of inadequate collateral circulation with arterial thrombosis of the extremities may be muscular atrophy and so-called trophic disturbances, which are generally the result of traumatism or of some infection in the member whose natural resistance is lowered by the imperfect blood-supply.

Thrombosis of the visceral arteries may produce lesions and symptoms identical with those following embolism, such as sudden death from thrombosis of the pulmonary artery, of the coronaries of the heart, or of the basilar; ischæmic cerebral softening, and infarctions of the lungs, heart, spleen, kidneys, retina, and intestine, with their attendant symptoms.

Thrombosis of the Pulmonary Artery.—It is especially to be noted that thrombosis of the pulmonary artery, both in its principal divisions and in smaller branches, is often entirely latent, both as regards resulting lesions in the lungs and the symptoms. Thrombosis of the main trunk or primary branches may, however, produce sudden or rapid death; or a sub-acute or chronic affection characterised by dyspnœa, cyanosis, hæmoptoic infarctions and incompetency of the heart, as in a case reported by Blachez.

Dr. Newton Pitt believes that thrombosis of the pulmonary arteries is far more frequent than is generally supposed, even going so far as to say "that thrombosis in the pulmonary artery, so far from being very rare, possibly occurs more frequently than in any other vein or artery in the body." This opinion is based partly upon failure to find a source for an embolus; in the right heart or systemic veins, and partly upon absence of folding, fracture, or other appearances of the plug suggestive of an embolus, as well as upon association with general conditions known to dispose to thrombosis. A similar remonstrance against the current interpretation of so many plugs in the pulmonary arteries as embolic in origin was made by Bristowe in 1869. In my experience sclerosis and fatty degeneration of the intima of the pulmonary vessels is not particularly uncommon; and I also believe that pri-

mary thrombosis of the pulmonary arteries, particularly of medium-sized and smaller branches, is more frequent than is usually represented in text-books. Still, for reasons to be considered under Embolism (p. 231), the evidence seems to me in favour of the usually accepted opinion that the majority of plugs found in the pulmonary artery and its main divisions in cases of sudden death are emboli.

Thrombosis of the Coronary Arteries of the Heart.[1] *Cardiac infarction.*— Although the general subject of infarction from arterial occlusion is reserved for the article on embolism, infarction of the heart is caused so much more frequently by thrombosis than by embolism that it is more appropriately considered here.

Thrombosis of the coronary arteries is in the great majority of cases an incident of angio-sclerosis of the heart, an affection of great clinical importance. It may also result from acute or chronic endaortitis near the orifices of these arteries, and possibly from acute inflammation of the coronary arteries. Thrombotic vegetations, springing from the aortic valves, have been known to block the mouth of one of the coronary arteries.

There has been much discussion concerning the existence of anastomoses of the coronary arteries. It has been demonstrated that anastomoses exist between the main trunks of these arteries, the most important being those between the auriculo-ventricular branch of the left coronary and branches of the right coronary in the sulcus on the posterior surface of the heart, forming a horizontal or equatorial auriculo-ventricular circle (Haller), and those between the anterior and the posterior interventricular branches near the apex of the heart, forming a vertical or meridional circle. There are also anastomoses on the surface of the left auricle between branches of the left coronary and those of the left bronchial artery. There are, however, no anastomoses between the branches of the coronary arteries after they have penetrated the myocardium, these intramuscular branches being anatomically terminal arteries.

These anastomoses do not usually suffice for the nutrition of the heart after rapid occlusion either of the main trunks or of intramuscular branches. Thrombosis of one of the coronary arteries may be the cause of sudden death. Barth reports the case of a robust young man, aged thirty, who died suddenly when in apparently the best of health. At the autopsy it was found that the mouth of the right coronary artery was blocked by a thrombus, the size of a pea to a bean, attached to a small atheromatous patch of the aorta, close to the opening of the right coronary. By a singular fatality this first

[1] I regret not to have noticed that this subject had been presented by Sir R. Douglas Powell in Allbutt's Syst. Med., V, p. 899. The paging cannot now be altered.

and only atheromatous patch to be found anywhere in the otherwise perfectly healthy body had formed at the particular point where the small thrombus springing from it stopped one of the streams feeding the very fountain of life.

Porter has shown experimentally that the frequency of arrest of the heart after closure of the coronary arteries is in proportion to the size of the artery occluded; and that when arrest occurs it is preceded by a fall of aortic pressure and an increase of the diastolic intraventricular pressure. This increased intracardiac pressure checks the flow of blood in the coronary veins, and thus interferes with the coronary circulation in the entire heart.

There are, however, many recorded cases which demonstrate that the main trunk of one of the two coronary arteries may be plugged by a thrombus without causing sudden death. In an instance reported by Dr. Percy Kidd the patient suffered from extremely irregular and weak action of the heart, shortness of breath, and paroxysms of dyspnœa; and gradually sank from cardiac failure. The right coronary artery, about three-quarters of an inch from its origin, was blocked throughout by a firm, partly decolourised, adherent thrombus. The left coronary, particularly its descending branch, was greatly narrowed by sclerosis. There were no infarctions or fibroid patches in the heart. Chiari has reported an instance of thrombotic occlusion of the main stem of the right coronary giving rise to an embolus which lodged in the main trunk of the left coronary artery. Sudden death was caused by the latter. In areas supplied by the right coronary were ischæmic infarctions showing reactive inflammation. These, as well as the symptoms and the appearance of the thrombus, indicated that the main trunk of the right coronary artery had been closed for at least several days before death.

If the patient lives long enough, the usual, but not absolutely imperative, anatomical result of thrombosis either of the main trunks or of intramuscular branches of the coronary arteries, is infarction in the area supplied by the occluded artery. As the descending or anterior interventricular branch of the left coronary is by far the most frequent seat of sclerosis and consequent thrombosis, the infarct is most commonly situated in the lower part of the interventricular septum and of the anterior wall of the left ventricle. The size of the infarct corresponds in general to that of the occluded artery; but, as a rule, the infarct occupies only a part, sometimes but a small part, of the area previously supplied by the obstructed vessel. Unlike infarcts in most other situations, those of the heart are not, as a rule, typically wedge-shaped, but are often irregular in outline, and sometimes appear as if several smaller areas of infarction had coalesced: indeed there may be multiple, detached infarcts resulting from occlusion of a single artery.

Both pale, anæmic infarcts and hæmorrhagic infarcts occur in the heart, but the former are the more common. Fresh, anæmic infarcts are swollen, firm, of an opaque yellowish-white colour, and often present in the margin a zone of hyperæmia and hæmorrhage. Microscopically, they are the seat of typical coagulative necrosis; the muscle fibres being devoid of nuclei, indistinctly striated or homogeneous, and of brittle consistence. The term myomalacia cordis, introduced by Ziegler, is not a good designation of the most fresh infarcts of the heart. The infarct usually reaches the endocardium, which then presents a mural thrombus; and it may extend to the pericardium and cause a localised fibrinous pericarditis. A reactive inflammation leading to the ingrowth of granulation tissue appears in the margin of the infarct, which, in course of time, is absorbed and replaced by scar tissue, unless it become infected and suppurate.

Cardiac infarction may be the cause of rupture of the heart, or of a parietal aneurysm; or may result simply in a fibroid patch. It is more common than would appear from the meagre attention usually given to the subject in text-books, and is of much anatomical and clinical interest.

The symptoms associated with coronary thrombosis are those of the angiosclerotic heart, so that it is hardly possible to make a positive diagnosis of thrombotic occlusion of the coronary arteries. Irregular, often slow pulse, shortness of breath, precordial distress, angina pectoris, sudden death, all these may occur from sclerosis of the coronary arteries, either with or without thrombosis. Fibroid myocarditis is often present and directly referable to arterial obstruction; but the changes in the myocardium are probably of much less clinical importance than the underlying disease of the coronary arteries. R. Marie has recently published a valuable monograph on infarction of the myocardium and its consequences, with a full consideration of the previous literature and the addition of many new observations.

Thrombosis of the mesenteric arteries will be considered with embolism of these arteries (p. 237).

Thrombosis of the cerebral vessels will be described in the part of this work treating of diseases of the brain in the next volume of Allbutt's Syst. Med.

Here may be mentioned the interesting observations of recent years concerning the dependence of certain diseases of the spinal cord upon affections of the blood-vessels of the cord, arterial thrombosis being an especially important factor in many of these cases.

Capillary Thrombosis.—In consequence of the abundant anastomoses, it is only when all or nearly all of the capillaries of a part are thrombosed that any mechanical effects result. Such extensive capillary thrombosis is more frequently the result than the cause of necrosis of a part. According

to von Recklinghausen, superficial, often extensive, necrosis of surfaces, as of the skin and mucous membranes, may be caused by widespread hyaline thrombosis of capillaries resulting from the energetic action of thermic, chemical, and even mechanical agents. In frostbites and burns there may be extensive local hyaline thrombosis of capillaries and small vessels. I have already referred to my observations of anuria in swine, caused by extensive hyaline thrombosis of the renal capillaries (p. 116). Although in many cases I have seen similar hyaline thromboses in human kidneys, they were never so extensive as to seem likely to cause recognisable symptoms. Several years ago I drew attention to the presence of hyaline thromboses in capillaries and arterioles in the walls of some fresh gastric ulcers, and since then I have been able to repeat the observation in three or four instances.

Effects of Venous Thrombosis.—Thrombosis is so pre-eminently an affection of veins that chapters in text-books treating of the general subject usually pay scant attention to its occurrence in other parts of the circulatory system. In the veins thrombosis occupies the field of intravascular plugging almost alone, for it is only in the portal system, and in the rare instances of retrograde transport, that embolism enters into consideration; such extraordinary occurrences as embolism of the azygos vein, resulting from thrombosis of the inferior vena cava, reported by Löschner, being mere pathological curiosities.

The direct effects of venous thrombosis, as of arterial, are referable to the mechanical obstacle to the circulation and to the properties of the thrombus. The mechanical effects result from inadequacy of the collateral circulation. The free venous anastomoses in many parts of the body prevent any disturbance of the circulation as a result of venous occlusion by simple or benign thrombi. Such innocuous thromboses are particularly common in the pelvic veins. In some situations veins, whose rapid occlusion may cause serious lesions and symptoms, may be slowly plugged by a thrombus without manifest harm. For example, it is not uncommon to find at autopsy the main trunks of the renal veins completely thrombosed, without consequent alteration of the kidney or corresponding symptoms during life; although we know that ligation of these veins causes hæmorrhagic infarction of the kidney with albuminous, bloody urine.

Frequently, however, the contrast between the effects of ligation and those of thrombosis of veins is in the other direction; the thrombosis being followed by venous congestion, and the ligation of the same veins being without evident disturbance of the circulation. The latter difference is not always easy to explain; but the factors to which we can often appeal with more or less success, in attempting to account for the absence of sufficient collateral

circulation with venous thrombosis, are the extent of the occlusion, general debility, feebleness of the circulation in consequence of coexistent anæmia, infection, cachexia or constitutional disorder, generally high venous pressure and low arterial pressure, lack of muscular movement and perhaps of other subsidiary forces aiding venous circulation, phlebosclerosis, inflammation or some less evident affection of blood-vessels called upon for extra work, and irritative or toxic properties of the thrombus. The importance of these, and perhaps other accessory conditions, in explaining the passive congestion of many venous thromboses in human beings is made evident, not only by the inability to produce similar effects experimentally by correspondingly slight or moderate degrees of venous obstruction, but also by the varying effects of thrombotic processes with the same localisation and extent in different persons and under different conditions. Thus femoral thrombosis may be attended by absolutely no œdema or passive congestion, or may occasion extreme degree of œdema and venous congestion.

The consequence of the passive hyperæmia caused by venous thrombosis is local dropsy. This constitutes the characteristic symptom of uncompensated venous obstruction by a thrombus as local necrosis does that of uncompensated arterial thrombosis. In addition to the œdema, there may be diapedesis of red corpuscles, but this occurs to a perceptible degree only when the obstruction to the venous flow is extreme, or the capillaries unusually permeable. Such hæmorrhages are very rare in peripheral venous thrombosis, but are common with thrombosis of the portal and mesenteric veins, the cerebral veins and sinuses, the splenic, the retinal, and some other visceral veins. Actual necrosis may likewise result from thrombosis of the mesenteric, cerebral, and splenic veins; but, if it occurs at all with thrombosis of veins of the extremities, it is extraordinarily rare, and probably due to complications.

In addition to these effects, due directly to the blocking of the venous circulation, even so-called benign or simple thromboses often set up an acute inflammation in the venous wall and surrounding part; or, as already explained, this inflammation may antedate the thrombosis. These chemical, as distinguished from mechanical, effects consist chiefly in arterial hyperæmia, inflammatory œdema, pain, implication of nerves, and constitutional symtoms, such as chills, fever, and quickened pulse. The occurrence of these irritative or toxic effects, even with the so-called marantic thromboses, is an argument (in addition to those already considered) in favour of the infective nature of many of these plugs, and of their primarily phlebitic origin. But while undoubtedly significant of such an interpretation, it can hardly be considered conclusive; for it is possible that certain thrombi may possess irritative properties not attributable to the presence of micro-organisms or

their products, and that the phlebitis, as well as the periphlebitis, may be secondary. However this may be, the old distinction between benign and infective thrombi no longer appears so sharply marked as was once supposed.

In rare instances the venous medical thromboses associated with anæmic, infective, cachectic, and constitutional diseases are plainly septic, and give rise to phlegmons, and perhaps pyæmia or septicæmia. The suppurative or septic thrombophlebitis, which with its attendant pyæmia was in præ-antiseptic days such a common and formidable wound complication, belongs to the surgeon's domain, or, in puerperal sepsis, to the obstetrician's. (See arts. "Pyæmia" and "Puerperal Septic Disease" in Allbutt's "System of Medicine," I.) To the borderland of medicine and surgery belong certain septic thrombophlebitides of visceral veins, of which the most important medical group, those of the portal system, has been considered by Professor Cheyne (Allbutt's "System of Medicine," I), and by Dr. Davidson in his article on "Suppurative Hepatitis" (Allbutt's "System of Medicine," V, p. 123). Thrombosis of the umbilical vessels, which may occur either before or after birth, may be either simple or septic. The latter is an important affection, the consideration of which belongs to treatises on diseases of infants.

There is perhaps no pathological phenomenon which, on the face of it, appears simpler of explanation than the local œdema consequent upon venous obstruction, but which, the more it is investigated, turns out to be, or at least is made to appear to be, more complicated. The explanation which naturally occurs to one, and which is often given, is that the œdema is due simply to increased filtration of serum from the blood, in consequence of the rise of intravenous and intracapillary pressure resulting from the obstruction to the venous circulation. It is certain that this simple explanation does not suffice, at any rate for most venous thromboses, and that factors other than the mere rise of blood-pressure in the veins and capillaries are concerned; but as to the nature of these other factors there is great difference of opinion. The whole problem is wrapped up with that of the hypotheses of lymph-formation and lymph-absorption, so lively at the present day, into the discussion of which it is impossible here to enter. Corresponding to the two classes of these hypotheses, we have mechanical hypotheses and vital or secretory hypotheses of the œdema of passive congestion. The mechanical explanations are at least easier of comprehension. Cohnheim attributed this form of œdema to increased venous and capillary pressure, combined with increased permeability of the capillary wall due to malnu-

trition.[10] Starling and Cohnstein, with full knowledge of the later work, to which they have made important contributions, are advocates of a similar explanation.

Doubtless several factors, although not all necessarily operative in the same case, are concerned in the causation of the œdema of venous thrombosis. Those which seem to me most apparent are the following: (i.) increased intro-venous and intra-capillary pressure, with consequent increased transudation of serum (not alone sufficient, for tying the femoral vein or inferior vena cava generally causes no œdema); (ii.) increased permeability of the capillary walls, which may be due to various causes, such as stretching from larger content of blood, starvation and asphyxia of capillary endothelium from lack of fresh supply of nutriment and oxygen, and injury from abnormal composition of blood in anæmic, infective, cachectic, and constitutional disease, or from inflammatory irritants; (iii.) diminished absorption of lymph in consequence of lack of muscular movement, of imbibition of the capillary walls with fluid, and especially of retarded capillary and venous flow; (iv.) arterial dilatation from irritative or inflammatory influences emanating from adjacent thrombosed veins, probably also from the asphyxiated tissues, and acting either directly upon the arterial wall, or directly upon vaso-motor nerves, or reflexly (here the conditions resemble those in Ranvier's well-known experiment of tying the inferior vena cava or femoral vein, and producing vaso-motor paralysis by section of the sciatic nerve); (v.) sometimes a watery condition of the blood rendering it easier of filtration. Experiments of Dr. Lazarus-Barlow indicate that changes in the chemical composition of the tissues and tissue-fluids are also a factor in the production of the œdema.[11] The influence of hydrostatic pressure is evident from the greater frequency of œdema with thrombosis of the lower than of the upper extremities, and from the effect of position upon the amount of the œdema. While these various factors can be conceived as essentially physical and chemical in their action, the living capillary wall upon which they act, either directly or indirectly, is to be thought of as something different from a dead animal or artificial membrane.

[10] Cohnheim is sometimes quoted as considering increased pressure a sufficient explanation of mechanical œdema, although in his Allgemeine Pathologie, Bd. I, p. 494, he expressly recognises as an additional factor "unknown influences on the part of the living vessel-wall." As I had the opportunity, when working in his laboratory on a problem concerning œdema, to become familiar with his views on this subject, I may be permitted to say that he often spoke of increased permeability of the capillary wall as an essential factor in the explanation of the œdema of passive congestion.

[11] To these changes, as the cause of alterations in osmotic pressure, Loeb (Pflüger's Archiv, 1898, LXXI, p. 457) assigns the chief importance in the production of œdema.

Opposed to these mechanical explanations are the secretory hypotheses of œdema, of which Hamburger and Lazarus-Barlow are leading exponents. Of especial importance is the work of Lazarus-Barlow upon the œdema of passive congestion. He finds all the physical explanations inadequate; and, upon the basis of interesting experiments, he concludes that a principal factor is increased secretion of lymph by the capillaries incited by starvation of the tissues and accumulation of waste metabolic products. His "Manual of General Pathology" may be consulted for a full presentation of his views and a criticism of the mechanical hypotheses of œdema.

The œdema of phlegmasia alba dolens is by no means all due to venous congestion. Much, sometimes most of it, is an inflammatory œdema spreading from the thrombosed veins. This is evident partly from the hard, brawny, painful, at times warm character of the swelling (œdema calidum); and partly from its location in the part of the extremity nearest the affected veins. The œdematous swelling may begin above and extend downwards, instead of in the usual direction from below upwards. The hydrarthrosis often associated in moderate degree with phlegmasia is probably also referable to an inflammatory serous exudate rather than to passive transudation from venous obstruction. It occurs especially in the knee-joint.

Thrombosis of Veins of the Extremities.—Clinically the most familiar form of venous thrombosis is that of the extremities; the lower much oftener than the upper. Its various sites and clinical associations have already been considered (pp. 136 and 149). The affection may be entirely latent; or may be recognised by a slight or moderate unilateral œdema without general or other local symptoms; or may be in the form of well-marked phlegmasia alba dolens; or rarely may assume a severely infective character, with chills and high fever; or, exceptionally, may lead to phlegmon and pyæmia or septicæmia. There is every transition between the extremes. The latent and milder types occur especially with tuberculosis, cancer, and other cachexiæ; the more severe manifestations with phlebitis of the puerperium, infective diseases, and chlorosis; but there are many exceptions to this rule.

In the more acute and well-characterised cases the general symptoms are chiefly manifest at the onset; and consist in moderate elevation of temperature, rarely preceded by a distinct chill, oftener by chilly sensations and quickened pulse. Increased frequency of the pulse may antedate the rise in temperature, and the pulse may remain rapid after the temperature falls. This disproportion between pulse and temperature is of diagnostic value (Mahler, Wyder, Singer),[12] but it is not always present. These general

[12] Singer (Arch. f. Gynäk., 1898, LVI, p. 218) has made a careful study of the pulse-curve in puerperal thrombosis. A step-like acceleration of the pulse-curve often precedes other manifestations of thrombosis by several days.

symptoms of the initial stage, which may persist for days, are often overlooked; or they are masked by an existing febrile disorder. They are probably present in some degree, even in mild cases, oftener than the clinical records show.

The characteristic symptoms are the local ones in the affected leg. Pain, often paroxysmal, is usually the first to attract attention; but sometimes it is the œdema. The pain may be severe. It is more or less generalised, with especial tenderness in the groin, the inside of the thigh, the popliteal space, and the calf. Often it is first noted and may remain localised in the calf; as is true of the œdema also. There may be sensations of numbness or of "pins and needles." The cardinal symptom, œdema, sometimes descending sometimes ascending, gives rise to the firm, painful swelling of the limb, covered with tense, shiny, smooth, white or mottled skin, marked often by dilated veins, whence comes the name milk-leg or white leg. The œdema in typical phlegmasia alba dolens is hard and elastic, pitting but little on pressure. Occasionally the skin has a more livid, cyanotic hue, or it may be of a brighter red. In the more acute cases the surface temperature is elevated; in others it is often lowered. Muscular movements are naturally restrained, and it is said there may be actual paresis. The thrombosed vein, if accessible to palpation, can often be felt as a hard, tender cord; but it is best not to attempt to gain this information, which in most cases is of little practical importance. The sensation obtained from palpating the vein may be misleading in consequence of the periphlebitis, or of the soft character of the thrombus. Certainly, in view of the manifest danger of detaching an embolus, only the gentlest manipulations are permissible. If the thrombosed vein be superficial, it may sometimes be seen as a line of livid redness beneath the skin. It is not always tender on palpation.

The great and usually the only danger from peripheral thrombosis is fatal pulmonary embolism. It occurs oftenest between the second and fourth weeks, but may occur earlier or later. The danger may be considered to be past at the end of six weeks, if the local symptoms have subsided: although there are exceptional instances of pulmonary embolism at a later period. It is to be noted that pulmonary embolism may result from latent and mild forms of venous thrombosis as well as from those of the well-marked examples; it is, however, rare with the cachectic thromboses of tuberculosis and cancer. Small pulmonary emboli usually cause no lesions or symptoms, yet they may give rise to hæmorrhagic infarction, or embolic pneumonia.

Nervous phenomena are sometimes so prominent as to have led to the recognition of a neuralgic type of phlebitis (Graves, Trousseau, Quenu). There may be even a mild peripheral neuritis associated with the venous thrombosis. This is probably caused by the direct action of inflammatory

irritants spreading from the inflamed veins; but it has also been attributed to thrombosis of small veins in the nerve-trunks, to the bathing of the nerves in the œdematous fluid, and to reflex irritation. Occasional sequels of femoral thrombosis, for the most part very rare, are varicose veins, leg ulcers, persistent chronic œdema, elephantiasis, muscular hypertrophy, muscular atrophy, and club-foot.

There has been much discussion on the possibility of gangrene being caused by thrombosis of the femoral or iliac veins. Cases have been reported in which no other cause of the gangrene was found than venous thrombosis; but with peripheral venous thrombosis this is such an exceptional occurrence that it seems clear that, when gangrene results, complicating factors—such as arterial disease, pressure upon arteries, arterial spasm, great feebleness of the circulation or septic inflammation—must be associated with venous thrombosis. It is true that surgeons are familiar with gangrene after ligation of the femoral vein, but here also the result is exceptional and attributable to some complication. Braune, upon anatomical grounds, attempted to demonstrate that gangrene is to be expected after closure of the femoral vein near Poupart's ligament, but the clinical evidence does not support this view. Galliard has reported a case and has collected from the records others in which gangrene had followed venous without arterial thrombosis.

The thromboses of the upper extremities are usually of shorter duration and milder type than those of the lower; unless referable to some persistent cause, such as the pressure of a tumour. They are often accompanied by some cervical œdema.

Thrombosis of the Inferior Vena Cava.—Since the days of Richard Lower occlusion of the inferior vena cava has been the subject of much experimental and clinical study. There are reports of at least 140 cases of this affection in human beings. The principal records are cited in the monographs of Vimont and Thomas, although the bibliography is by no means complete. Thrombosis of this vein is rarely autochthonous. Usually it is continued from the femoral or pelvic veins through the iliacs, or is due to some abdominal disease, as the pressure of a tumour. It may occur without any symptoms or without symptoms suggestive of the diagnosis. The characteristic symptoms are œdema of both lower extremities and of the abdominal walls, and the development of a typical collateral circulation. When the renal veins are likewise occluded there may be albuminous, bloody urine; but with thrombosis of these veins this symptom is oftener lacking than present. The diagnosis rests especially upon the appearance of dilated anastomosing veins coursing upwards from the groins and flanks over the abdominal walls and lower part of the thorax. These tortuous, varicose veins, sometimes as big as the little finger, make a very striking and characteristic

picture. The superficial veins concerned in carrying on the collateral circulation are the inferior and superior superficial epigastric, the long thoracic, the superficial circumflex iliac, the external pudic, the lumbo-vertebral anastomotic trunk of Braune and numerous unnamed anastomotic veins. The direction of the circulation is of course from below upward. In addition there is a deep collateral circulation through various visceral veins with dilatation of the azygos veins. Sometimes the circulation is almost wholly through the deep collaterals, and there may be little or no dilatation of the visible superficial veins. In fact, in not a few cases, by the absence of visible dilated collaterals, the diagnosis is rendered difficult or impossible. Schlesinger has observed and collected a number of cases where the œdema was in one leg only. This may be due to the previous establishment of a collateral circulation on one side from a former iliac thrombosis, or to unilateral iliac thrombosis with parietal thrombosis of the vena cava, or to congenital duplication of the vena cava.

Thrombosis of the Renal Veins.—This affection is fairly common. It may be an extension of a thrombotic process in the vena cava, or on the other hand the latter may be secondary to renal thrombosis. Marantic thrombosis of the renal veins is not unusual in infants with cerebral symptoms, or exhausted by diarrhœa. In adults thrombosis of the renal veins is observed not very infrequently in chronic Bright's disease, particularly the waxy kidney; and in malignant tumour of the kidney. The renal veins rank among those predisposed to marantic thrombosis. I once made an autopsy on a case of primary genito-urinary tuberculosis in which a caseous mass had broken into a renal vein which contained an adherent grayish-red thrombus extending into the vena cava. Tubercle bacilli were present in the caseous mass and the thrombus. There was acute miliary tuberculosis. The lesions and symptoms which one would expect to find with thrombosis of the main trunk of the renal vein are oftener absent than present. The various collateral veins, communicating through the capsule and along the ureters with the lumbar, diaphragmatic, adrenal, spermatic, and other veins, suffice for adequate return flow. Still a number of cases have been observed with more or less hæmaturia and albuminuria which have been referred to thrombosis of one or both renal veins, and genuine hæmorrhagic infarction may occur.

Thrombosis of the Mesenteric Veins.—Thrombosis of veins in the intestinal wall is often associated with ulcers and other morbid conditions in the intestine. The thrombus may extend into the small mesenteric veins, or the latter may be attacked independently. These small thrombi are important chiefly as a source of infective emboli transported to the liver.

Thrombosis of the large mesenteric veins is less frequent than embolism or thrombosis of the mesenteric arteries. I have reported an instance of

this affection, and have found reports of 31 additional cases with pronounced symptoms, and of a few cases without symptoms referable to the thrombus and without intestinal lesion. The references will be found at the end of this article. The superior mesenteric vein was thrombosed much oftener than the inferior. In many cases with symptoms, the thrombosis was ascending and secondary to inflammation, ulceration or some other disease of the intestine; in some instances it was descending from thrombosis of the portal or splenic vein; in a few it was secondary to enteric fever or some marasmic or cachectic state; in one it was attributed to a calcific plate adjacent to the vein, and in one it followed splenectomy. The symptoms are the same as with occlusion of the mesenteric arteries (see art. "Embolism," p. 237), but as a rule are even more violent in character and rapid in course. They are as follows: sudden onset of very intense, colicky, not definitely localised abdominal pain; distended, tender, tympanitic abdomen; vomiting, which may be bloody; obstipation or bloody diarrhœa; and rapid collapse with cold sweat and subnormal temperature. The diagnosis is likely to be acute ileus, and laparatomy to be performed. Death generally occurs within two or three days. The symptoms may, however, be less violent, and the course less rapid than those mentioned. At the autopsy are found hæmorrhagic infarction and gangrene of the intestine, hæmorrhages in the mesentery, bloody fluid in the peritoneal cavity, and sometimes, although not regularly, peritonitis. The cases without symptoms have been usually thromboses of slower formation, but this does not appear to have been always the case.

In a case reported by Dr. Rolleston, the superior mesenteric vein was filled with softened, canalised clot; and in addition the inferior mesenteric vein, the internal and external iliac veins on both sides, and the splenic vein were completely thrombosed, and a partly occluding thrombus extended into the portal vein. The thrombus in the superior mesenteric vein was regarded as the oldest. There was old and recent inflammation of the intestine, but no intestinal infarction.

Of interest is the relation of thrombosis of the mesenteric veins to portal thrombosis. In several instances of the latter thrombosis of the mesenteric veins occurred without hæmorrhagic infarction of the intestine. Doubtless the explanation is that a sufficient collateral circulation had been established after the portal thrombosis to prevent the usual effects of a subsequent mesenteric thrombosis. That this, however, is not always the case is shown by the sudden or more gradual termination of some instances of portal thrombosis with hæmorrhagic infarction of the intestine, in consequence of the extension of the thrombus into mesenteric veins. This has occurred especially in the more acute cases of portal thrombosis, but it may occur also in those of several months' duration. Acute portal thrombosis may cause

hæmorrhagic infarction of the intestine without mesenteric thrombosis; or the infarction may be over a larger extent of intestine than corresponds to the thrombosed mesenteric veins. On the other hand, the infarcted area may be much smaller than that supplied by the thrombosed vein. The symptoms may be of slower development and of milder type when thrombosis of the mesenteric veins is secondary to portal thrombosis than when it is primary. The sequence of events in Fitz's case is interesting—globular thrombi in the left ventricle, embolism and infarction of the spleen, secondary thrombosis of the splenic vein, extension of the thrombus into the superior mesenteric vein, hæmorrhagic infarction of the intestine terminating fatally. There was no obstruction in the mesenteric arteries.

Pylethrombosis.—The septic variety of thrombosis of the portal vein (suppurative pylephlebitis) having been described (Allbutt's "System of Medicine," I, p. 610, and V, p. 127), it remains to speak here of simple portal thrombosis, often called without much propriety adhesive pylephlebitis. This is a well-characterised, although usually not readily-diagnosed affection. It is caused most frequently by compression either of the intrahepatic branches of the portal vein in cirrhosis, syphilis, or tumours of the liver; or of the main branches or trunk by fibrous perihepatitis, chronic peritonitis, swollen lymph-glands, impacted gall-stones or tumours. Other causes are diseases of the walls of the portal vein, either primary or propagated from some neighbouring focus; extension of a thrombus from the splenic or mesenteric veins; pancreatic disease; gastric cancer; ulcer, or other gastric or intestinal disease; infective and toxic diseases; puerperal eclampsia (Schmorl); marasmus, and traumatism. Sclerosis and calcification of the wall of the portal vein deserve more attention as causes of portal thrombosis than they have usually received. To the 12 cases collected by Spiegelberg and Borrman in which this was the cause, is to be added A. A. Smith's case, in which I made the autopsy. There was extensive calcification and thrombosis of both splenic and portal veins in a man about 60 years old, who died of gastric hæmorrhage. He had previously vomited blood on several occasions. There was rapidly increasing ascites. Calcification of the media of the portal vein may occur without marked affection of the intima. Marantic portal thrombosis is very rare, and, according to Schüppel, occurs chiefly as a terminal event without characteristic symptoms. Nonne, however, in reporting a case of marantic thrombosis from Erb's clinic, interprets several previously reported instances with marked symptoms as belonging to this variety. The thrombus may become organised and the vein converted into a fibrous cord, as in a case reported by Osler.

The symptoms are those of portal obstruction—ascites, hæmatemesis and enterorrhagia, splenic enlargement, dilatation of superficial abdominal veins,

and progressive marasmus. The caprices of venous thrombosis are evident here as elsewhere. Characteristic symptoms may be entirely lacking, or one or more of the important symptoms may be absent. Ascites has been absent or slight, especially in cases with abundant hæmorrhages from the stomach and bowels. In general, however, the rapid onset, the intensity of the evidences of portal obstruction, and especially the quick return of ascites after tapping are characteristic of obliterating portal thrombosis; and by observation of these points a correct diagnosis has repeatedly been made. These acute symptoms are of most diagnostic value when they appear in persons previously in apparent health, as has been observed with phlebosclerotic thrombosis; or in the course of some disease not itself a cause of obstruction to the portal circulation. When, as in cirrhosis of the liver, the symptoms unfold themselves gradually, the diagnosis, is manifestly impossible, or at best no more than mere conjecture.

I have added traumatism as a possible cause of portal thrombosis on the basis of a diagnosis made by Dr. Delafield, while I was resident physician in his service at Bellevue Hospital. A lad, who had received a severe blow on the abdomen, was admitted with extreme ascites which had come on within two weeks after the injury. He was repeatedly tapped, the clear fluid re-accumulating at first with great rapidity after each tapping, afterward more slowly, until in the course of months there was complete recovery. In the meantime enlarged veins made their appearance over the upper part of the abdomen.

Jaundice is not a symptom of portal thrombosis, although repeatedly observed as a complication. The channels for establishment of a collateral circulation are the same as in cirrhosis of the liver, with the exclusion of those which communicate with the portal vein itself, at or beyond the site of occlusion.

Under certain exceptionally favourable conditions recovery may take place; a satisfactory collateral circulation being established, with perhaps opening of channels through the organised thrombus. The usually fatal termination may be from hæmorrhage or exhaustion, sometimes within a few weeks or even days from the onset. I know of no instance, in man, of death within a few hours after occlusion of the portal vein, such as occurs regularly, with great fall of arterial blood-pressure, after ligating this vessel in rabbits and dogs. As already mentioned, hæmorrhagic intestinal infarction may be caused by portal thrombosis (pp. 179 and 180).

There has been much discussion on the occurrence of changes in the liver which can be attributed directly to stoppage of the portal circulation. In the majority of cases of portal thrombosis the liver has been the seat of atrophic cirrhosis, but most modern authors have regarded the thrombosis

as secondary to the cirrhosis. Dr. Samuel West, however, in 1878, took strong ground in favour of the reverse being sometimes the case; and he found support in the experimental results of Solowieff. The later experiments of Cohnheim and Litten have been widely accepted as indicating that obstruction of the portal vein is without effect upon the hepatic structure and functions. Bermant has recently gone over the entire experimental and anatomico-clinical evidence, and has reached the conclusion that stoppage of the portal vein may lead to atrophic cirrhosis. The case which he reports speaks strongly in favour of this view; for only the right branch of the portal vein was thrombosed, and the cirrhosis was limited to the corresponding lobe of the liver. Nevertheless, cases of portal thrombosis, some not of short duration, have been reported by Frerichs, Leyden, Alexander, and others without any alteration in the liver; and I have observed two such cases in which the symptoms of portal obstruction extended over several months.[13]

Thrombosis of the Splenic Vein.—Primary thrombosis of the splenic vein and its radicles is rare. I have seen an instance of autochthonous thrombosis secondary to calcification of the wall of the splenic vein. Thrombosis of veins within the spleen, extending sometimes into the main trunk, is common with infarction, abscess, and certain other morbid processes in this organ. Thrombosis of the main trunk may be caused by suppurative or hæmorrhagic pancreatitis, or by cancer of the pancreas. As has already been mentioned, thrombi may extend from the portal or mesenteric veins into the splenic, as well as from the latter into the former. There is the possibility of thrombosis secondary to retrograde embolism of the splenic vein.

Köster has reported the rare complication of enteric fever with thrombosis of the radicles and main trunk of the splenic vein; the evidence being conclusive that the oldest part of the thrombus was in the spleen. The evidences of occlusion of the main vein appeared at the beginning of convalescence. The spleen was enormously swollen and the pulp of a diffuse reddish-black colour. The capsule and surrounding tissues were suffused with blood. As there were thrombi in the small mesenteric veins near the ulcerated ileum, there was a possibility of retrograde embolism; but Köster thinks it more probable that the process originated within the spleen.

Thrombosis limited to the extra-splenic part of the vein may be completely or nearly compensated by the collateral venous circulation, so that no changes or only a moderate passive congestion occur in the spleen.

[13] Chiari (Centralb. f. allg. Path. u. path. Anat., 1898, IX, p. 854) has recently described endophlebitis, with thrombosis, of the radicles of the hepatic vein. There were symptoms of portal obstruction.

Thrombi occupying intrasplenic veins may cause hæmorrhagic infarction. Dr. Rolleston has observed two instances of anæmic infarcts of the spleen in association with thrombosis of the splenic vein. Litten probably goes too far in attributing most genuine hæmorrhagic as distinguished from pale infarcts of the spleen, to venous thrombosis rather than to arterial embolism.

Extensive necrosis and hæmorrhagic infarction may be caused by torsion of the pedicle of a movable spleen. A perhaps unique instance of this occurrence was observed in the Johns Hopkins Hospital, and has been described by Osler.

Obliteration of the Superior Vena Cava.—Since the admirable studies by Duchek (1854) and by Oulmont (1856) of the causes and symptoms of obliteration of the superior vena cava a considerable number of instances of this condition have been reported. By far the most frequent cause is the pressure of a mediastinal tumour, of swollen lymph-glands, or of an aneurysm. Less common is the growth of a cancer or other malignant tumour into the lumen of the vein. Banti reports a curious case of generalised tuberculosis in which nearly the whole length of the superior vena cava was completely filled by a neoplastic tuberculous mass projecting into the right auricle. The outer walls of the vein were intact. The condition seems to have been analogous to the tuberculous cardiac thrombi already described (p. 142). Primary thrombosis of the superior vena cava is so rare as to be a pathological curiosity. Poynton has reported an instance of thrombotic occlusion of the upper two-thirds of the superior vena cava in association with chronic and acute valvular endocarditis, and in a second case of valvular disease he found a mural thrombus in this vein. In both cases there was tricuspid insufficiency (pp. 157 and 158). The characteristic symptoms are œdema and cyanosis of the upper half of the body—face, neck, arms and thorax—and dilatation of deep and superficial veins, especially marked over the anterior wall of the thorax and upper part of the abdomen. In a case exhibited by Dr. Osler to the Johns Hopkins Hospital Medical Society, the anterior surface of the chest was covered with large, spongy bunches of enormous varicose veins, in one of which a phlebolith could be felt. Other symptoms, which may be present, are œdema of conjunctival and buccal mucous membranes, exophthalmos, watery secretion from the conjunctivæ, nose-bleeding, and such signs of venous congestion of the brain as headache, vertigo, and ringing in the ears, especially on bending over. In the light of the whimsicalities of venous thrombosis it is hardly necessary to add that the symptoms may be less marked, and may deviate from what might naturally be expected.

Thrombosis of the Innominate, Subclavian, and Jugular Veins.—The more important literature of this subject is cited in the papers of Pohl, Hirschlaff, and Helen Baldwin. The occurrence of these thromboses in cardiac disease, and from compression, has already been mentioned (pp. 157 and 158); other rare causes are infection, empyema, acute rheumatism, tuberculosis, marasmus, and traumatism. The symptoms are the usual ones of venous congestion, œdematous swelling, pain in the regions from which the veins convey blood, dilatation of collaterals, and in the case of the cervical veins, recognition of the thrombosed vein by palpation, which, however, should be done with great care.

Thrombosis of the pulmonary veins may be mentioned as a rare source of embolism in the aortic system. It is usually secondary to some pulmonary disease, as gangrene, malignant tumours, abscess, infarction, tuberculosis, pneumonia. It has been observed with extensive emphysema of the lungs (Schmale).

Thrombosis of the cerebral sinuses will be considered in connection with diseases of the brain in the following volume. (Allbutt's Syst. Med., Vol. VIII.)

O. Wyss has described a remarkable instance of extensive hæmorrhagic myelitis caused by widespread hyaline and platelet thrombi in veins within the spinal cord. The thrombosis was secondary to a glioma of the dorsal cord. Rosin has likewise observed thrombosis of veins extending the whole length of the spinal cord, consecutive to a tumour of the cervical cord.

Multiple Thromboses.—Finally may be mentioned the cases in which many veins in different parts of the body become thrombosed, as in Huels's case of chlorotic thrombosis; and Osler's, of thrombosis secondary to cancer of the stomach, already cited (pp. 160 and 156). Erlenmeyer has described as "jumping thrombosis" (springende Thrombose), in distinction from the ordinary creeping form, cases in which the process attacks first one vein and then another, in a different region, until finally various veins in the extremities, trunk, and brain may become plugged.

Treatment.—The treatment of thrombosis of the extremities is about all that needs special consideration in this article. In view of the part played by enfeebled circulation and secondary infections in the causation of thrombosis, prophylactic measures should be directed toward maintaining good nutrition, strengthening the heart's action, and warding off secondary infection, so far as may be, or treating accessible foci of infection antiseptically.

In the absence of any available medicinal treatment known to have any direct control over the process of thrombosis, the general indications for treatment are to secure as speedily as possible an adequate collateral circulation, in order to ward off the danger of tissue-necrosis or gangrene from

arterial thrombosis and the effects of passive congestion from venous thrombosis; and, above all, in the case of venous thrombosis, to guard against the detachment of emboli. These indications are best met by absolute rest, suitable position and immobilisation of the thrombosed extremity, and nourishing diet.

With venous thrombosis of a lower extremity the patient should lie on the back with the limb elevated on an inclined plane, or in a trough well lined with cotton wool. The limb should be kept warm by wrapping in cotton wadding, and hot fomentations of lead-water and laudanum, or some similar preparation, may be applied. If the condition of the heart indicate it, digitalis or other cardiac tonic may be given. At the height of the process the pain may be so intense as to require the use of opium or some of its derivatives.

It is all-important to know what not to do. The patient should be cautioned against moving the leg, especially against any sudden jerk. Palpation of the affected veins should be of the gentlest sort and is better omitted altogether. All unnecessary movements and manipulations should be avoided. Nothing is gained, and harm may be done by resorting, before all danger of embolism is passed, to the old-fashioned treatment of rubbing in mercurial or belladonna ointment. The length of time that the patient should remain quiet in bed will vary according to the severity of the case. Although the thrombotic process does not usually progress after the tenth or twelfth day, it is a general rule that the patient should not be allowed to walk in less than forty days. A large number of the deaths from pulmonary embolism have occurred when the patient first walks, or goes to stool, or takes a bath.

Light bandaging of the lower part of the leg assists the circulation; but, if applied at all, it should be with only minimal compression. After the danger of embolism is passed, massage and bandaging may be employed to advantage, or a long elastic stocking worn.

If gangrene result from arterial thrombosis, the time and site of operation should be determined upon surgical principles.

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EMBOLISM [1]

Definition.—Embolism is the impaction in some part of the vascular system of any undissolved material brought there by the blood-current. The transported material is an embolus. Embolism may occur likewise in lymphatic vessels.

Historical Note.—Rudolf Virchow is the creator of the doctrine of embolism. There is scarcely another pathological doctrine, of equal magnitude, the establishment of which is so largely the work of a single man. Not but that there were foreshadowings of this conception before Virchow, notably by Bonetus and van Swieten in the seventeenth and eighteenth centuries, and by Allibert and François in the early part of the present century. A few observers and experimenters, indeed, anticipated some of Virchow's results. The wonder is that until Virchow's time the idea of embolism remained so foreign to medical thought; so obvious and necessary a corollary does it seem to be of the discovery of the circulation of the blood. Between the years 1846 and 1856 Virchow constructed the whole doctrine of embolism upon the basis of anatomical, experimental and clinical investigations, which for completeness, accuracy, and just discernment of the truth must always remain a model of scientific research in medicine. These discoveries introduced new chapters and necessitated a recasting of many old ones in pathology. A number of important morbid conditions, among which pulmonary embolism and cerebral embolism may be especially mentioned, were now for the first time clearly recognised. Virchow's studies of thrombosis and his demonstration that not all intravascular, ante-mortem clots are formed at the place where they are found, and that infarcts are not the result of inflammation and capillary phlebitis, put an end to the false and to us at present almost incomprehensible ideas then prevailing as to the overshadowing importance of phlebitis in pathological processes. Especially was the doctrine of metastasis, which in old days was one of the most mystical in medicine, greatly expanded and at the same time placed upon an intelligible and firm foundation.

The new fields opened by Virchow have been industriously cultivated by a multitude of workers. The additions to our knowledge have been many and valuable, but they have related mainly to details, and can scarcely be said to have led to new points of view. The works of Bernhard Cohn and

[1] In: Syst. Med. (Allbutt), Lond., 1899, VII, 228-285.

of Cohnheim may be signalised as among the most important of the contributions since Virchow's early publications. Cohn's remarkable book, published in 1860, is extraordinarily rich in anatomical, experimental, and clinical facts, and it is well for any one who believes that he has a new observation or opinion concerning embolism to consult it before venturing on publication; a precaution which has evidently been often neglected by writers on the subject.

Varieties of Emboli.—Substances of the most varied character, solid, liquid or gaseous, may enter the circulation and be conveyed as emboli. Unless some special epithet be used, an embolus is generally understood to be a detached thrombus, or part of it, including under this designation endocarditic vegetations. Other possible sorts of emboli are fragments of diseased heart-valves, calcific masses, bits of tissue, tumour-cells, parenchymatous cells, animal or vegetable parasites, fat, air, pigment-granules and foreign bodies. Emboli of air, of fat, and of parenchymatous cells will be considered separately. An important classification, as regards their effects, is into bland or aseptic emboli and toxic or septic emboli.

Sources of Emboli.—Emboli in the lungs come from the systemic veins, the right heart or the pulmonary artery; those in branches of the portal vein come from the radicles or trunk of this vein; those in systemic arteries from the pulmonary veins, the left heart, or some artery between the heart and the location of the embolus. Sources of aberrant emboli, resulting from unusual modes of transportation, will be considered subsequently (p. 196).

Various features in the structure and disposition of thrombi bearing upon the detachment of emboli have been described in the preceding article. Here may be especially recalled the continuation of an occluding venous thrombus in the form of a partly obstructing thrombus beyond the entrance of an important branch, and the occurrence of softening in the interior of older thrombi; phenomena evidently favourable to the detachment of fragments. Globular thrombi in the right heart, particularly in the auricular appendix, are a fruitful source of the emboli which cause pulmonary infarction in heart disease. Vegetations of the aortic and mitral valves, particularly of the latter, furnish the great majority of emboli in the aortic system. Thrombosis or embolism of an arterial trunk—as of the internal carotid, splenic, femoral—is often followed by the conveyance of fragments of the plug into branches of the artery. When the plug in the main trunk is an embolus, this secondary embolism is described by Cohnheim as "recurrent"—an epithet which has also been applied to retrograde embolism, and, therefore, to avoid confusion, had better not be used in either sense.

The detection of the source of an embolus is often unattended by any difficulty; but sometimes it requires prolonged and painstaking search, and occasionally even such a search is unrewarded. The greatest difficulties are encountered when the source is in some peripheral venous thrombus which has caused no symptoms and is unattended by lesions suggestive of its location. An entire thrombus may be dislocated and transported as an embolus.

Site of Deposit.—Emboli are carried along by the blood-current until they are caught on some obstruction, or become lodged in a channel too narrow to permit their further passage. It is evident that embolism can scarcely occur except in the arterial system, pulmonary and systemic, and in branches of the portal vein. The rare instances of embolism of systemic veins will be considered under aberrant embolism (p. 196). An extremely rare occurrence, of which several instances are recorded, is the blocking of the tricuspid or mitral orifice by an embolus. The result is, of course, sudden death. Very often an embolus is caught at an arterial bifurcation, which it rides with a prolongation extending into each branch (riding embolus). This may happen where the diameter of each branch is greater than that of the embolus. It is not uncommon for several emboli to enter successively the same branch of the pulmonary artery.

Any artery open to the circulating blood may receive an embolus of appropriate size. The course followed by an embolus in its travels is determined by purely mechanical factors, of which the most important are the size, form, and weight of the plug; the direction, volume, and energy of the carrying blood-stream; the size of branches and the angles at which they are given off; and the position of the body and its members. In accord with these principles we find emboli in the lower lobes of the lungs oftener than in the upper; and in the right lung oftener than in the left, the right pulmonary artery being larger than the left. Emboli from the left heart are more frequently carried into the abdominal aorta and its branches than into the carotid or subclavian arteries. The left carotid, arising directly from the aortic arch at its highest point, is in more direct line with the aortic blood-stream than is the right carotid, and is therefore a commoner recipient of emboli. The left common iliac artery is also somewhat more directly in the line of the current in the abdominal aorta, and, therefore, receives emboli somewhat more frequently than the right.

The order of frequency in which emboli are found in the different arteries may be given about as follows:—pulmonary, renal, splenic, cerebral, iliac and the lower extremities, axillary and upper extremities, cœliac axis with its hepatic and gastric branches, central artery of the retina, superior mesenteric, inferior mesenteric, abdominal aorta, coronary of the

heart. There is, however, considerable difference of statement on this point. As a matter of fact this list, like similar ones, does not inform us of the frequency with which the different arteries of the body receive emboli; for it is evident that it is based almost entirely upon embolic manifestations, and not upon the mere presence of emboli. If estimates of frequency be based only on infective emboli, the order would be in several respects different, the hepatic artery, for example, standing higher in the list, and the cerebral lower—sufficient evidence that the customary data for determining the frequency of embolism in different arteries relate only to such emboli as leave behind some record of their presence. Infective emboli, however, do not inform us of the incidence of embolism in different arteries; for these produce abscesses or other lesions in certain special situations, and not in every place where they may lodge; a fact which is brought out clearly in the experimental injections of bacteria into the circulation of animals. It seems to me very probable that of the systemic arteries, those going to the lower extremities must be more frequent receptacles of emboli than either the splenic or the renal; but the smaller plugs in the former usually leave no readily demonstrable record of their presence, whereas in the latter they always do.

Aberrant Embolism.—Certain exceptions to the general rules already stated concerning the sources and direction of transportation of emboli may be grouped under the heading of aberrant or atypical embolism, the latter epithet being the one employed by Scheven to designate paradoxical embolism, and retrograde embolism.

Zahn gave the name "paradoxical embolism," and his assistant Rostan the name "crossed embolism," to the transportation of emboli derived from veins into the systemic arteries without passing through the pulmonary circulation. Cohnheim was the first to note the passage of venous emboli through an open foramen ovale into the aortic system; and since then there have been enough observations of this so-called paradoxical embolism to prove that, although not frequent, it is really of practical importance, and not merely a curiosity. Zahn and Rostan found an open foramen ovale in about one-fifth of their autopsies, which is a considerably smaller percentage than most pathologists, who have investigated the subject, have found. An opening in the form of an oblique slit is certainly very often present in the oval fossa (in 34 per cent of all cases according to Firket), and it has been demonstrated by actual observation that, under certain conditions, this form of opening suffices for the transit of emboli. In three cases an embolus was found by Zahn and Rostan actually engaged in the opening, and two or three similar observations have been made by others.

I have found records of twenty-eight cases of paradoxical embolism, and there is no reason to suppose that this list is complete. The evidence upon which the diagnosis is usually based is an open foramen ovale and the presence in the systemic arteries of coarse emboli, for which the only source to be found is on the venous side or in the right auricle. While in some of the cases there may be room for scepticism as to the venous origin of the arterial embolism, there can be none for Schmorl's observation, in a case of traumatic laceration of the liver, of plugs of hepatic tissue in the left auricle and the main trunk of the renal artery, with an open foramen ovale admitting a finger. Conditions favouring the occurrence of paradoxical embolism are, according to Zahn, increased pressure in the right auricle and lowered pressure in the left. Under these circumstances the opening in the oval foramen is widened, and its walls bulge toward the left auricle. Rostan and Hauser have seen thrombi extending from the right auricle through the oval foramen into the left.

The best explanation of certain tumour metastases without pulmonary implication is by paradoxical embolism. Here, however, there is sometimes another possibility; for, as Zahn has demonstrated, tumour cells not of large size may pass through the pulmonary capillaries. Although the lungs are an excellent filter, their capillaries are certainly so wide that they may permit the transit of emboli too large to pass through capillaries elsewhere in the body.

The first conclusive observation of retrograde transport of an embolus in a human being was made by Heller, in 1870, who found, in a case of primary cancer of the cæcum and ileum, a loose plug of cancerous tissue in a branch of an hepatic vein. The only metastatic growths were in the mesenteric, retroperitoneal, and mediastinal lymphatic glands. Long before Heller, however, the conception of retrograde transport of venous emboli was familiar to pathologists; especially in the discussions of the explanation of metastatic hepatic abscesses in cases where the lungs are not involved and the atrium of infection does not communicate with the portal system. The experimental side of the subject was diligently cultivated. The general trend of opinion among pathologists, however, was opposed to the acceptance of the doctrine of retrograde transport, under conditions occurring in human beings, until the publication of von Recklinghausen's article on the subject in 1885. He reported a convincing observation of embolism of the renal veins with masses of sarcoma, derived from a primary growth of the tibia, and also of retrograde embolism from the left auricle into the pulmonary veins. Since this publication there have been a number of equally conclusive demonstrations of the retrograde transport of venous emboli, and the subject has been taken up again on the experimental side.

Retrograde venous embolism is an interesting, but, so far as at present known, a rare occurrence.

The difficulty of making sure that a suspected thrombotic embolus in a systemic vein is not an autochthonous thrombus is doubtless the reason why most of the reports of retrograde transport relate to emboli of tumour-cells or parenchymatous cells. In addition to Heller's and von Recklinghausen's cases already mentioned, reference may be made to Arnold's observation of masses from a primary mammary carcinoma filling the superior longitudinal sinus, with invasion of the wall of the sinus from within by the new growth, but without any intracranial tumour outside of this wall; or indeed any metastasis elsewhere in the body except in the axillary and cervical lymph-glands: and also to Ernst's case of primary angio-sarcoma of the left kidney, growing into the renal vein, with a loose plug of sarcomatous tissue distending a branch of a coronary vein of the heart without connection with a metastatic growth. Bonome's observation of cancer of the thyroid with metastatic nodules in the liver, developing from plugs in the hepatic veins, should probably also be included in the list, as well as two cases of Bonome, reported by Lui, in one of which a cancerous embolus secondary to cancer of the rectum was found in a branch of the superior mesenteric vein; and in the other a similar retrograde embolus, secondary to adeno-carcinoma of the liver, was met with in the right pampiniform plexus.

To Schmorl's and Lubarsch's cases of emboli of liver-cells in the cerebral and the renal veins may be added two observations from my laboratory, of which one has been reported by Flexner, of clumps of liver-cells in branches of the renal vein in cases with extensive hepatic necroses.

That retrograde transport of ordinary venous thrombi may occur, is demonstrated by Arnold's discovery in a large branch of an hepatic vein of a riding embolus identical in appearance with a thrombus which occupied the right ovarian vein and extended some distance into the inferior vena cava. Cohn accepted, for a limited class of cases, backward conveyance of venous emboli; and in this sense interprets an observation of thrombosis of the superior longitudinal sinus, with a plug in the right axillary vein identical in appearance with an undoubted embolus in the pulmonary artery. Von Recklinghausen has furnished evidence of the retrograde transport of infective emboli into the renal veins.

From these cases it is seen that retrograde embolism of particles of tumour, of tumour-cells, of parenchymatous cells, and of ordinary bland and infective thrombotic fragments has been observed. Experiments have demonstrated that, under certain conditions, light as well as heavy particles may be transported in the veins in a direction contrary to that of the

normal blood-current. The veins in which retrograde embolism in human beings has been found are the hepatic, the renal, the mesenteric, the pampiniform plexus, the coronary of the heart, the cerebral veins and sinuses, the axillary and the pulmonary. Experimental retrograde embolism has been produced in many other veins, including those of the lower extremities. While venous valves, when intact, are undoubtedly a protection against this occurrence, they are often imperfectly developed or insufficient. Emboli have been repeatedly observed in the cerebral veins and sinuses which should be protected by valves in the jugular veins.

Retrograde embolism is usually explained by a temporary reflux of the venous current in consequence of some sudden obstacle to the return flow to the right heart, as may occur with forced expiration and coughing. Whatever increases the pressure in the veins near the heart, and impairs the assistance to the venous stream afforded by the respiratory movements and the suction of the right heart, favours this backward movement. Increased intrathoracic pressure, stenosis of the respiratory passages, spasm of respiratory muscles, distension of the right heart, tricuspid insufficiency, slowing of the heart's beats from vagus-irritation, are among the conditions believed to dispose to retrograde transport.

Ribbert does not accept the reflux theory of retrograde embolism; partly for lack of any positive observation of such backward flow beyond the immediate neighbourhood of the right heart, and partly on account of the difficulty in explaining what becomes of all the blood which would be momentarily pressed back toward the capillaries. His explanation is that in conditions of high venous stasis, emboli, sticking loosely to the venous wall, are not moved forward by the feeble current, but are slowly pressed backward, step by step, by pulse-waves in the veins. For this view he finds support in experiments which he has made. Observations, partly experimental, of Arnold and of Ernst, cannot readily be reconciled with Ribbert's explanation; so that, notwithstanding difficulties needing further elucidation, the reflux theory seems at present the more probable for most cases.

Of a different nature from the preceding form of retrograde transport is the conveyance of emboli by a blood-current reversed from its normal direction in consequence of obstruction of veins by compression or other causes. This kind of retrograde transport from more or less permanent reversal of the normal current is far more frequent in lymphatic vessels than in veins, and plays an important part in the metastases of tumours by means of the lymphatics.

Anatomical Characters.—The appearances observed in embolised vessels vary with the shape, size, consistence, and nature of the embolus, and the duration of its impaction. Approximately spherical emboli, as a rule,

completely close the lumen of the artery in which they lodge. Cylindrical, elongated, or flat emboli are usually caught as riders at an arterial bifurcation; and often at first leave more or less of the channels by their side open. Thrombi several inches long may be washed out of the femoral or other peripheral vein. Such a transported thrombus may be found in the trunk or a primary division of the pulmonary artery, folded two, three, or even four times upon itself, and pressed at different points into several of the main arterial branches at the hilum of the lung, as in an interesting case described by Fagge. In this way an embolus may completely plug a vessel three or four times its diameter. Irregularly-shaped emboli, if of soft consistence, may be pressed into an artery so as to block the lumen completely; but if of firmer consistence they leave at first some space for the blood to flow. Emboli may be of such consistence as to be shattered by impact with the arterial wall, the fragments blocking many or all of the small branches, and producing the same effect as if the plug had been arrested in the main trunk.

An embolus is the starting-point of a secondary thrombus which usually, although not always, completes the closure of the vessel, if this was not effected by the embolus itself, and extends on each side to the nearest branch. The same metamorphoses and process of organisation, with consecutive changes in the vascular wall, occur with emboli and encapsulating thrombi, as described in the previous article for primary thrombi. Non-absorbable emboli or parts of emboli, like foreign bodies, are encapsulated by cells and tissue.

In cases of recent embolism, the plug can generally be recognised as an embolus without much difficulty; but, in those of long standing, the anatomical diagnosis between embolism and thrombosis may be difficult, or even impossible. The criteria for the recognition of a fresh embolus are for the most part sufficiently self-evident. Such a plug lies loosely or is but slightly adherent to the vessel-wall. It often presents a broken or fractured surface which, in fortunate cases, may be made to fit on the corresponding surface of the thrombus from which it was originally broken off. It may be bent or folded, or show the marks of venous valves, or present ramifications which do not correspond to those of the artery in which it lies. It is of course of the first importance to find, if possible, the source of the embolus; and, when this is done, to make a careful comparison between the thrombus and the embolic fragment as to resemblances in structure and appearance.

After the embolus has become adherent and surrounded by a secondary thrombus, some of these differential criteria may still remain for a while; but, as time passes, the anatomical diagnosis becomes increasingly difficult.

The embolus may perhaps still be distinguished from the surrounding thrombus by marked differences in its age and general appearance and structure, possibly by the presence of lime salts. An adherent plug which rides an arterial bifurcation is much more likely to be an embolus than a primary thrombus. In reaching a conclusion, weight must be given to the condition of the arterial wall; whether there be any local cause for thrombosis,—such as compression, aneurysm, arterio-sclerosis; and whether the microscope shows such secondary changes in the arterial wall as generally correspond to the apparent age and character of the adherent plug. The detection of a source for an embolus will be an important consideration. The clinical history may aid in the antomical diagnosis; and all attendant circumstances, especially the existence elsewhere of undoubted emboli, should be taken into consideration. In some situations, as in branches of the renal or splenic arteries, primary thrombosis is so uncommon that the chances are all in favour of embolism.

It is evident from what has been said that in the older cases the anatomical diagnosis must often be based upon a weighing of probabilities, and that sometimes a positive conclusion cannot be reached.

Effects.—Bland or aseptic emboli produce chiefly mechanical effects referable to the obstruction to the circulation; toxic or septic emboli cause also other changes which may be described as chemical or infective. We shall consider first the mechanical effects.

The direct injury which may be inflicted upon the vessel wall by sharp calcareous emboli is, according to Ponfick, a rare cause of aneurysm. Embolic aneurysms, however, stand in much more definite relation to chemical properties of the embolus, as will be shown subsequently (p. 218).

Necrosis; Infarction.—The fate of a part supplied by an artery closed by a bland embolus depends altogether upon whether it is fed within a certain time after the obstruction with enough arterial blood to preserve its function and integrity. An embolus which does not completely plug the vessel may cause no appreciable interference with the circulation; but the closure of the lumen is usually soon effected by a secondary thrombus. The occlusion by a bland embolus of an artery with abundant anastomoses, such as those possessed by the arteries supplying bone, the voluntary muscles, the skin, the thyroid, the uterus, usually causes no circulatory disturbance of any consequence. Even in these situations extensive multiple embolism, or embolism with extensive secondary thrombosis, may cause local anæmia with its consequences.

Sudden death may be the result of embolism of the trunk or a main division of the pulmonary artery, of one of the coronary arteries of the heart, or of the bulbar arteries.

If an adequate collateral circulation be not established within the proper time the inevitable fate of a part, supplied by an embolised artery, is degeneration or death. Local death is the regular result of embolism of branches of the splenic artery, the renal artery, the basal arteries of the brain, the central artery of the retina, and the main trunk of the superior mesenteric artery. It is the usual result of embolism of one of the coronary arteries of the heart, if the patient survive long enough; and it is the inconstant result, depending generally upon accessory circumstances, of embolism of the medium-sized and smaller branches of the pulmonary arteries, of cerebral arteries other than the basal, of the abdominal aorta, iliacs, main arteries of the extremities, and some other arteries. A collateral circulation may be established sufficiently to preserve the life of a part, but not to maintain its full nutrition; under these circumstances it undergoes fatty degeneration or simple atrophy.

When the dead part is so surrounded with living tissue that it can be permeated with lymph, as is usually the case in the viscera, the mode of death is that described by Weigert, and named by Cohnheim "coagulative necrosis." Here the dead protoplasm, and to some extent intercellular substances, undergo chemical changes, believed to be in part coagulative; and actual fibrillated fibrin may appear. If there be enough coagulable material present, the necrotic part becomes hard, dry, opaque, and somewhat swollen. For a time its general architecture, both gross and microscopic, is preserved; but the nuclei and specific granulations disappear early, the former largely by karyorrhexis.

An area of coagulative necrosis resulting from shutting off of the blood-supply is an infarct. Its shape corresponds to that of the arterial tree supplying it, and is, therefore, as a rule, approximately conical, or that of a wedge, the base being toward the periphery of the organ. The wedge-shape is most marked in smaller infarcts; large ones may be roundish or irregular in shape. The size depends upon that of the occluded artery. The colour is opaque, white, or yellowish, unless hæmorrhage is added to the necrosis. We thus distinguish anæmic, pale or white infarcts, and red or hæmorrhagic infarcts; but, in the latter no less than in the former, the essential thing is the coagulative necrosis, the hæmorrhage being merely something added to the necrosis. This was not always clearly recognised, it being supposed at one time that the hæmorrhage was the characteristic feature of infarcts, and that pale infarcts were simply decolourised hæmorrhagic infarcts. The name "infarcts" (from *infarcire*, to stuff), like many other old medical terms, is therefore now used in a sense at variance with its etymological meaning. In some situations, as the kidney and the retina, the infarct is nearly always pale; in others, as the lungs and

the intestine, it is as constantly hæmorrhagic; and in yet others, as the spleen and the heart, it may be either white or red.

Where there is not a sufficient quantity of coagulable substances the area of coagulative necrosis does not become hard; and it may be of much softer consistence than normal, as is the case with the ischæmic necroses of the brain and spinal cord. Necrosis of peripheral parts, as the toes, foot, leg, hand, is not of the coagulative variety; for the dead part is not surrounded by living tissue to furnish the lymph which brings one of the factors essential for coagulation. This peripheral necrosis is called gangrene or mortification, and may be either dry or moist.

Collateral Circulation; Local Anæmia.—As the state of the collateral circulation is the decisive factor in bland embolism, it becomes important to learn the conditions under which establishment or failure of this circulation occurs. This subject is one eminently open to experimental study; but more attention has been given to the anatomical than to the physiological side. In fact many writers seem to assume that the physiological factors can be so readily deduced from the laws of hydro-dynamics that it is only necessary to investigate the size, arrangement, and distribution of the vascular tubes. Nevertheless experience has shown abundantly the danger of accepting anything in the physics of the circulation which has not been put to an experimental test on the living body. The experimental study of the physiological conditions which determine the development of a collateral circulation has demonstrated that this problem is by no means so simple as has been often represented; while some old errors have been corrected and new facts have been added, we are still far from an entirely satisfactory solution or any definite agreement of opinion. It is impossible here to do more than touch upon certain points bearing directly upon the subject in hand.

If an artery with slender anastomoses to its area of distribution, such as the femoral or the lingual in a frog's tongue, be tied, the immediate effect is stoppage of the circulation and anæmia of the part supplied by the occluded vessel, accompanied by contraction of the artery below the obstruction. Almost immediately, or within a short time, the blood begins to flow with greatly increased velocity through arteries arising above the point of ligation, but more rapidly only through those which send blood by anastomosing channels to the anæmic part. At the same time these arteries with quickened flow dilate. Formerly this vascular dilatation and increased flow were attributed to rise of blood-pressure above the ligature, but experiments have shown that in most situations this is a factor of relatively little moment. The rise of pressure cannot of course remain localised, and after ligation of the femoral artery amounts at most to

only a few millimetres of mercury. Evidence of the relatively slight importance of this increased pressure is that the ligated artery actually contracts from the point of ligation to the first branch arising above the ligature (Thoma, Goldenblum); and that the phenomena of dilatation and increased velocity occur only in arteries which send blood to the anæmic area, although others which carry blood elsewhere may arise nearer to the point of obstruction (Nothnagel). Moreover, it is hardly conceivable that increased pressure above the ligature can persist for the days and weeks which may be necessary for the full development of the collateral circulation.

As the increased flow cannot be due to any change in the viscosity of the blood, it must be due to increase of the pressure gradient. Therefore, if it is not the result in any marked degree of rise of pressure above the obstruction, it must be caused by lowered resistance to the stream in the anastomosing vessels. A moment's reflection will show that this is a far more purposeful and better mode of compensation than one brought about exclusively by a rise of pressure which must act upon arteries in no way concerned in the collateral circulation. The difficulty is an entirely satisfactory and complete explanation of the lowered resistance. It seems impossible that it can be due to anything but a widening of the bed of the stream. Von Recklinghausen has pointed out that the stream-bed for the anastomosing arteries is enlarged, inasmuch as after occulsion of the main artery the blood can flow from these collaterals not only in its original bed, but, also, with diminished resistance, into the stream-bed belonging to the closed artery. The pressure gradient is thus increased, and consequently the velocity of the current is quickened in the anastomosing arteries. The cause of the dilatation of these arteries is not so clear. Thoma states as his first histo-mechanical principle that increased velocity of the blood-current leads to widening of the lumen, and eventually, if the increase continues, to growth of the vessel wall in superficies. Admitting this to be true, it can hardly be considered an explanation. As the collateral circulation develops perfectly, and with the same phenomena, after severance of all connection of the part with the central nervous system, it is evident that vaso-motor influences which are under central control are not essential to the process.

Satisfactory as von Recklinghausen's explanation is, as far as it goes, there is evidence that it does not cover all of the facts, and that there is also some mechanism by which the vessels of an ischæmic part are opened wide for the reception of the needed arterial blood. The existence of such a mechanism has been recognised by Lister, Cohnheim, Bier, and others. I must refer especially to the recent papers of Bier for a full

presentation of the evidence on this point, and shall merely mention, as a familiar illustration, the extreme arterial hyperæmia which follows the removal of an Esmarch bandage. This flushing of a previously ischæmic part with arterial blood has been usually attributed to paralysis of vaso-constrictor or stimulation of vaso-dilator nerves, but Bier has shown that it occurs under conditions where this explanation can be probably excluded.

Without following Bier in his somewhat vitalistic conceptions, or speculating regarding the explanation of the phenomenon, we must, I think, admit that deprivation of arterial blood sets up some condition of a part whereby the vessels which feed it are in some way dilated to receive any fresh arterial blood which can reach them. The existence of such an admirably adaptive, self-regulatory capacity must be an important element in the development of a collateral circulation, and it may be remarked that it is a physiological rather than an anatomical factor. Bier believes that this capacity is very unequally developed in different parts of the body; being highest in external parts, and feeble or absent in most of the viscera. He is also of the opinion that the arterioles and capillaries of external parts have the power, by independent contractions, of driving blood into the veins; and that, by contraction of the small veins the capillaries of these parts are in large measure protected from the reception of venous blood.

A possible, but I think not fully demonstrated, variation in the power to lower the resistance to the collateral stream of arterial blood is not, however, the only physiological property which influences the varying effects following obstruction to the arterial supply of different parts of the body. In some situations there are physiological arrangements which seem calculated to increase the difficulty of establishing an adequate collateral circulation. Mall has shown that contraction of the intestine exerts a marked influence upon the circulation through this organ. In the light of his results, it is interesting to note that, immediately after closure of the main trunk of the superior mesenteric artery of a dog, the intestine is thrown into violent tonic contractions and remains in an anæmic, contracted condition for two or three hours; after which the spasm relaxes and the bloodless condition at once gives place to venous hyperæmia and hæmorrhagic infarction, which appears in the third to sixth hour after the occlusion of the artery (Mall and Welch). This intestinal contraction, which under these circumstances is equivalent to arterial spasm, is probably one, although not the sole, reason why, in spite of free anastomoses, occlusion of the arteries supplying the intestine is followed by necrosis and hæmorrhage. That the explanation is not to be found simply in the great length of intestine supplied by a single artery, is evident from the fact that, if the extra-intestinal arteries supplying a loop much more than 5 centimetres in length be suddenly closed, the loop becomes

hæmorrhagic and necrotic (Mall and Welch, Bier). That the conditions are essentially identical in man is proven by the experience of surgeons, who have repeatedly observed the same results after separation of the mesentery close to the intestine over about the same length. The blood can enter at each end of the short loop arteries, whose branches anastomose freely within the walls of the loop with those of the closed arteries; there being a particularly rich arterial plexus in the submucous coat (Heller). But these anastomoses are insufficient to preserve the part; although, with reference to the extent of territory to be supplied, they are large in comparison with some of the trivial anastomoses which in external parts can respond effectively to the call for a collateral circulation to far larger areas. It must be left to future investigations to determine how far the inability of the intestinal vessels to compensate circulatory obstructions of a degree readily compensated in many other situations may be due, as claimed by Bier, to an inherent incapacity to lessen the resistance to the collateral stream, or to contraction of the muscular coats of the intestine, or to other causes. As Panski and Thoma have shown that slowing and interruption of the circulation in the spleen is followed, for several hours, by contraction of the muscular trabeculæ, it is probable that the development of a collateral circulation in this organ meets an obstacle similar to that in the intestine.

The various organs and tissues differ so widely as regards their susceptibility to the injurious effects of lack of arterial blood that local anæmia of equal intensity and duration may in one part of the body produce no appreciable effect, and in another cause the immediate abolition of function and the inevitable death of the part. In general, the more highly differentiated, specific cells of an organ are those which suffer first and most intensely. At one end of the scale are the ganglion cells of the brain, which, after the withdrawal of arterial blood for half an hour, and probably for a much shorter time, cannot be restored to life; and at the other end may be placed the periosteum, the cells of which may be still capable of producing bone two or three days after all circulation has ceased. So susceptible to local anæmia are the ganglion cells of the central nervous system, that not only is embolism of the branches of the cerebral arteries with only capillary communications, even of the minute terminal twigs in the cortex, always followed by necrotic softening, but also embolism of the anastomosing arteries in the pia very often causes softening of at least a part of the area supplied by the plugged artery. In the well-known Stenson experiment, temporary closure of the rabbit's abdominal aorta, just below the origin of the renal arteries, for an hour, results in the inevitable death of the ganglion cells in the central gray matter of the lumbar cord; and this notwithstanding the free anastomoses of the anterior and posterior spinal arteries. Many of the lesions

which pass under the names of myelitis and hæmorrhagic encephalitis present the histological characters of ischæmic necrosis, although often no arterial occlusion can be found.

Perhaps, next to elements of the nervous system, the epithelial cells of the cortical tubules of the kidney are most susceptible to ischæmia. Litten has demonstrated that the temporary ligation of the renal artery of the rabbit for one and a half to two hours is followed invariably by necrosis of many of these epithelial cells. The cells in the walls of the blood-vessels and of connective tissue are relatively insusceptible to temporary slowing or cessation of the circulation.

It is evident from the preceding statements that the nature of the organ or tissue has a very important influence in determining whether local necrosis follows arterial embolism.

I have dwelt in some detail, although within the limited space necessarily inadequately, upon certain physiological characters of the circulation and of different organs and tissues, which appear to me deserving of more consideration than is usually given to them in discussions of the causes of embolic necroses and infarctions. It is, of course, not to be inferred that the number and size of the anastomoses are not of prime importance in determining the mechanical effects of arterial embolism, but, important as they are, they are not the exclusive determinants of the result. There is no single anatomical formula applicable to the circulatory conditions under which all embolic infarcts occur. The nearest approach to such a formula is that embodied in Cohnheim's doctrine of terminal arteries, a name which he gave to arteries whose branches do not communicate with each other or with those of other arteries, although capillaries are of course everywhere in communication with each other. Terminal vessels in this sense are the renal, the splenic, the pulmonary, the central artery of the retina, the basal arteries of the brain, and in general all branches of cerebral and spinal arteries after they have penetrated the brain or the spinal cord, the intramuscular branches of the coronary arteries of the heart, and the portal vein.[2] Cohnheim's teaching was that infarction occurs always after embolism of a terminal

[2] There is some confusion as to the sense in which the words "terminal arteries" should be used, and it must be admitted that later investigations have detracted from the precision given to this term by Cohnheim. Thus some do not recognise the pulmonary artery as terminal, because the lung is supplied likewise by the bronchial and several other arteries whose capillaries communicate with those of the pulmonary artery. But unless we make the extent of a second arterial supply the decisive point in the definition, we should have, for the same reason, to exclude the renal and the splenic arteries from the class of "terminal arteries." Then the conception of arteries which are "functionally" but not automatically terminal, creates still further confusion.

vessel, except of the pulmonary artery, whose capillaries, under ordinary conditions, are numerous and wide enough, after obliteration of an arterial branch, to maintain a sufficient circulation; and of the portal vein whose capillaries communicate freely with those of the hepatic artery. Thoma and Goldenblum have shown that, contrary to Cohnheim's results, no infarction follows embolism or ligature of the frog's lingual artery, which is or can readily be made a terminal artery, provided the tongue be replaced in the mouth after the operation so as to avoid stretching and drying from exposure to the air. It is, therefore, quite possible in some situations for an adequate circulation to be carried on through merely capillary communications, although the conditions are of course less favourable than when there are arterial anastomoses. On the other hand, as we have seen, embolism of anastomosing arteries, such as the mesenteric and the cerebral, may be followed by necrosis or infarction; and it cannot be said that the anastomoses in all of these cases are so unimportant that the arteries are virtually terminal.

We may conclude then that, under ordinary conditions, embolism of an artery having abundant and large anastomoses has no important mechanical effect; that embolism of an artery with few and minute anastomoses, especially embolism of an artery with only capillary communications, is in many situations followed by necrosis, this result being favoured by certain physiological conditions which have been considered; and that embolism of arteries with fairly well-developed anastomoses may in certain situations also cause necrosis. Among the factors influencing the result, other than those relating to the number and size of the anastomoses, are the varying susceptibility of cells to ischæmia, interference with the circulation by contraction of muscular constituents of a part, and perhaps some inherent weakness in the physiological part of the mechanism by which a vigorous collateral circulation is established.

The compensation of sudden occlusion of an artery, by means of the collateral circulation, generally presupposes vessels with fairly normal walls and a certain vigour of the circulation. When the arteries have lost their elasticity, or the general circulation is feeble, or there is some pre-existing obstacle to the circulation such as chronic passive congestion, the development of an adequate collateral circulation is rendered correspondingly difficult, and may be impossible. Hence embolism of arteries of the extremities is often followed by gangrene in the aged, in arterio-sclerosis, in heart disease, and in infective, anæmic, and exhausting diseases. There are some observations which suggest that arterial spasm may co-operate with embolism in causing local anæmia.

The agencies by which a sufficient collateral circulation is established may be thrown out of order to such a degree that embolism of arteries having

even the most ample anastomoses may be followed by necrosis. Foci of cerebral softening have been observed after occlusion of the internal carotid or of one of the vertebral arteries; although the circle of Willis, the largest and most perfect anastomosis in the body, was open, and no vascular obstruction could be found beyond it. Here, doubtless, an important factor in this exceptional occurrence is the rapidity with which nerve cells die when insufficiently fed with arterial blood. Cohn narrates the interesting case of a young woman rendered extremely anæmic by repeated hæmorrhages from cancer of the tongue. In order to control the bleeding the right carotid was tied. The patient immediately, to all appearances, lost consciousness; acquired ptosis of the right, then of the left eye, drawing of the angle of the mouth to the right, and relaxation and almost complete paralysis of the left extremities. The pulse almost disappeared and the face became very anæmic. Respiration was unaffected. The ligature was at once removed, and at the same moment the patient awoke "as from a dream," and the symptoms just mentioned quickly disappeared. She said that she had not completely lost consciousness but was unable to speak, and that her will had lost control over the organs. She had lost so much blood that she died three hours later without again losing consciousness before death. At the autopsy the carotids and all of the cerebral vessels were found open, and there was no change in the brain except anæmia. In this case, the general anæmia was evidently so great that after closure of one carotid, which probably lasted not more than a minute or two, a sufficient supply of blood could not reach the brain through the circle of Willis.

Hæmorrhagic Infarction.—The explanation of the accumulation and extravasation of blood in hæmorrhagic infarcts has been the subject of much speculation and experimental study. It is only in certain situations that infarcts are hæmorrhagic throughout; and, as already mentioned, these are no less necrotic than are the white infarcts. The necrosis and the hæmorrhage are co-ordinate effects of the disturbance of the circulation, neither being caused by the other. Virchow, in his early writings, suggested as possibilities, without definitely adopting any of them, most of the explanations which have since been advanced to account for the apparently paradoxical phenomenon that the occlusion of an artery may be followed by hyperæmia and hæmorrhage in the area of its distribution. Cohnheim, on the basis of experimental investigations published in 1872, came to the conclusion that the hyperæmia which may follow arterial embolism is the result of regurgitant flow from the veins, that the hæmorrhage occurs by diapedesis, and that this diapedesis is the result of some molecular change in the vascular walls deprived of their normal supply of nutriment. Although Cohn, in 1860, had shown con-

clusively, by numerous experiments on various organs, that the hyperæmia and hæmorrhage are not the result of regurgitant flow from the veins, Cohnheim's views were widely accepted until Litten, in 1880, in apparent ignorance of Cohn's work, repeated the experiments of the latter upon this point with the same results. The experiments of Dr. Mall and myself upon hæmorrhagic infarction of the intestine in 1887 convinced us that the blood which causes the infarct is not regurgitated from veins. Cohnheim's results upon the frog as to the source of the blood in infarcts have not been confirmed by subsequent experimenters (Zielonko, Kossuchin, Küttner, Goldenblum, Thoma).

In situations where closure of an artery is followed by hæmorrhagic infarction, tying the veins also, so as to shut off all opportunity for reflux of venous blood, increases the hyperæmia and the hæmorrhage; and it may render an infarct hæmorrhagic which otherwise be anæmic. On the other hand, if all vascular communication of a part be cut off except that with the veins, the part undergoes simple necrosis without hæmorrhagic infarction; and the result is the same even if the artery be cut open, so as to afford apparently the most favourable opportunity for backward flow from the veins. Or, expressed differently, if after closure of an artery all possibility of access of blood to the obstructed area through anastomosing arteries and capillaries be prevented, the veins remaining open, the part dies without hæmorrhagic infarction. Cohnheim was in error in supposing that hæmorrhagic infarction cannot occur where the veins are provided with valves, for it has been shown by Bryant, Köppe, and Mall that the small intestinal veins of the dog have effective valves; yet nowhere can hæmorrhagic infarction be more readily produced experimentally by arterial obstruction than in the intestine of this animal. It is, then, quite certain that the blood which accumulates in the capillaries and small veins, and is extravasated in hæmorrhagic infarction, comes in through the capillary, and, if they exist, the arterial anastomoses, and is not regurgitated from the veins.

It cannot be doubted that the red corpuscles escape by diapedesis, not by rhexis; but our experiments are in entire accord with those of Litten in failing to furnish any support to the prevalent doctrine that the hæmorrhage is the result of changes in the walls of the vessels caused by insufficient supply of arterial blood; in fact they seem to us more conclusive upon this point. If a loop of intestine be completely shut off from the circulation for three or four hours (by which time, after ligation of the superior mesenteric artery, hæmorrhagic infarction begins to appear), and the obstruction be then removed, the blood at once shoots in from the

arteries with great rapidity, and distends the vessels.[1] If, as usually happens, the blood has not coagulated in the vessels, no hæmorrhagic infarction subsequently appears. If, immediately after the circulation has been fully re-established in the loop, the superior mesenteric artery be ligated, the intestine from the lower part of the duodenum into the colon becomes the seat of hæmorrhagic infarction in the usual time; but the infarction does not appear earlier and is not more intense in the part which had been previously deprived of its circulation for three or four hours than in the rest of the small intestine. It is true, as Cohnheim has shown, that re-establishment of a local circulation, after its stoppage for many hours or days, may be followed by hæmorrhages in the previously ischæmic area; but hæmorrhagic infarction after arterial occlusion begins long before it is possible to demonstrate this change in the vascular wall caused by lack of blood-supply.

In a part undergoing hæmorrhagic infarction the circulation is greatly retarded in consequence of the small difference between the arterial and the venous pressures. This result may be brought about by rise of the venous or lowering of the arterial pressure. If the veins are obstructed sufficiently to render the outflow nil, or very small, and the arteries are open, the infarction is intense, and occurs with high intracapillary pressure. In consequence of the free anastomoses of veins this mode of production of an infarct is rare, but it may occur after thrombosis of the mesenteric, the splenic, and the central retinal veins. Its explanation offers no especial difficulties. If the veins are open the arterial pressure must be reduced in order to furnish the conditions necessary for the production of hæmorrhagic infarction. This later cases is the one present in arterial embolism with hæmorrhagic infarction, and is the one especially needing explanation. The intracapillary pressure in this case may vary, but will generally be low. The arterial pressure is so low that the lateral pulse-waves nearly or entirely disappear, so that the force which drives the blood into the capillaries is no longer the normal intermittent one, which experiment has shown to be essential for the long-continued circulation of the blood through the capillaries and veins. This reduction, or absence of lateral pulsation, to which, so far as I know, other experimenters have not called attention, I believe to be the factor of first importance in the causation of hæmorrhagic infarction following arterial embolism.

We are not sufficiently informed concerning the physical and vital properties of the blood and of the blood-vessels to be able to predict posi-

[1] Bier's experimental results concerning the absence of hyperæmia after temporary ischæmia of the intestine do not, according to our experience, apply to prolonged ischæmia, which we found to be followed by intense hyperæmia.

tively what would happen under such abnormal circulatory conditions as those named, and actual observation only can furnish a solution. The difficulties in making such observations under the requisite conditions are considerable. Dr. Mall and I, in examining microscopically, in a specially constructed apparatus, the mesenteric circulation of the dog after ligagation of the superior mesenteric artery, observed that immediately after the occlusion the circulation ceases in the arteries, capillaries, and veins. In a short time the circulation returns, but with altered characters. The arteries are contracted, but may subsequently dilate somewhat; and the blood from the collaterals flows through them with diminished rapidity, and without distinct lateral pulsation. The direction of the current is reversed in some of the arteries. The movement of the blood in the capillaries and veins is sluggish and irregular. The direction of the current in some of the veins may be temporarily reversed, but we were unable to trace a regurgitant venous flow into the capillaries. The distinction between axial and plasmatic current is obliterated. Gradually the smaller and then the larger veins become more and more distended with red corpuscles, and all of the phenomena of an intense venous hyperæmia appear, so that one instinctively searches for some obstruction to the venous outflow. The red corpuscles in the veins tend to accumulate in clumps, and may be moved forward, or forward and backward, in clumps or solid columns. Stasis appears in the veins. This is at first observed only here and there and is readily broken up by an advancing column of blood; but it gradually involves more and more of the veins, and in some becomes permanent, producing an evident obstacle to the forward movement of the blood. The same phenomena of distention with red corpuscles, clumping, to-and-fro movement, and stasis appear gradually in the capillaries. An interesting appearance, sometimes observed in capillaries and veins, is that of interrupted columns of compacted red corpuscles with intervening clear spaces which are sometimes clumps of white corpuscles, sometimes of platelets, sometimes only clear plasma. With the partial blocking of the veins and capillaries, red corpuscles begin to pass through the walls of these vessels by diapedesis; and after a time the hæmorrhage becomes so great that it is difficult to observe the condition within the vessels. The venous outflow is diminished immediately or shortly after the closure of the superior mesenteric artery; it then rises, but later it continuously falls to a minimum.

An experiment which we made shows that the blood for hæmorrhagic infarction need not necessarily enter from the collaterals, and it sheds some light upon the condition of the circulation during the production of the infarct. We ligated all of the vascular communications of the

intestine, with the exception of the main artery and vein, and then tied the intestine above and below, so that the included intestine was supplied only by the main artery and the blood returned by the main vein. Under these circumstances no infarction results. We then by a special device gradually constricted the main artery. In repeated experiments we found that not until the artery is sufficienty compressed to stop the lateral pulsations in its branches—the pressure in these being then about one-fifth of the normal—does hæmorrhagic infarction appear. Precautions were taken to make sure that the flow through the constricted main artery and its branches continued, and that the vein remained open. We have often measured the blood-pressure in branches of the superior mesenteric artery after ligation of this artery and during the progress of an infarction, and have found it to be generally one-fourth to one-fifth of the normal pressure. If the pressure on the arterial side falls below a certain minimum no hæmorrhage occurs in the infarction.

It is evident from the preceding description that the phenomena observed under these peculiar circulatory conditions are in large part dependent upon the physical properties of the blood, especially upon its viscosity and the presence of suspended particles which readily stick together; and differ in important respects from those which would occur under similar conditions with a thin, homogeneous fluid. The pressure gradient from arteries to veins of the ischæmic area is so low that the red corpuscles cannot fully overcome the resistance in the veins and capillaries. They accumulate in these situations, and probably undergo some physical change by which they become adherent to each other and to the vascular wall. The absence of the normal pulse-waves prevents the breaking up of these masses of corpuscles, the longitudinal pulse-waves sometimes observed having little or no effect in disintegrating the masses. In this way numerous small veins and capillaries become blocked, with a resulting rise of intracapillary pressure and diminution of outflow of blood through the veins. Von Frey has shown by interesting experiments that an intermittent pulsating force is necessary to prevent the speedy blocking of veins and capillaries with red corpuscles in carrying on artificial circulation with defibrinated blood through living organs. Kronecker has also demonstrated the influence of a pulsating force in increasing the venous outflow.

The diapedesis is due to the slowing and stagnation of the blood, and to the blood-pressure. Without a certain height of pressure there is no diapedesis; and, with a given retardation and stasis of the blood-current, the higher the intracapillary and intravenous pressure the greater the amount of diapedesis. The matter which needs explanation is that the diapedesis may occur with lower than the normal pressure, and through

vessel walls apparently unaltered. This I attribute to the fact that the red corpuscles, in consequence of the slow circulation, have opportunity to become engaged in the narrow paths followed by the lymph as it passes out between the endothelial cells. Diapedesis is a slow process, and the channels for it are much smaller than the thickness of a red corpuscle. Unless the red corpuscles can get started on the path between the endothelial cells, they cannot traverse it; and unless the circulation is very much slowed, and the outer plasmatic current obliterated, there is no opportunity for the corpuscles to become engaged between the endothelial cells, provided, that is, the vascular wall be normal. With greatly retarded circulation there is opportunity, and when the way in front is blocked by compact masses of red corpuscles, and sometimes by actual thrombi, the only path open to the corpuscles is that followed by the lymph between the endothelial cells. This then becomes the direction of least resistance for their movement.

The reason why infarctions are hæmorrhagic in some situations and not in others offers difficulties chiefly in consequence of our ignorance of the exact circulatory conditions which lead to the production of infarction in different parts of the body. It is generally assumed that these circulatory conditions are everywhere essentially the same; but this is by no means proven. As we have already seen, the physiological conditions which influence the result are various. It may be, therefore, that the requisite intracapillary and intravenous pressure, or some other condition of the circulation essential for the production of hæmorrhagic infarction, is lacking when the infarction is anæmic. In general a high venous pressure favours hæmorrhage in an infarction, and a low arterial pressure opposes it. The pressure in the superior mesenteric and portal veins is higher than in any other veins of the body. Hæmorrhagic infarction of the lung occurs especially with high degrees of chronic passive congestion in which the venous pressure is elevated. Thrombosis of veins seems to be the cause of at least some of the hæmorrhagic infarcts of the spleen. Hæmorrhagic infarction of the kidney may be produced experimentally by ligating the renal veins.

The studies of recent years upon the formation lymph have demonstrated that the blood-vessels in different regions differ markedly in their permeability, those of the intestine being probably the most permeable. It may be that this difference in the constitution of the vessels is an important factor in determining the extent of diapedesis under similar circulatory conditions. As pointed out by Weigert, however, the greatest influence appears to be exercised by the resistance offered by the tissues to the escape of red corpuscles from the vessels. Hæmorrhagic infarction occurs

especially where this tissue-resistance is low, as in the loose, spongy texture of the lungs, and in the soft mucosa and lax submucosa of the intestine. The hæmorrhage is far less in the dense muscular coats of the intestine. The considerable resistance offered by the naturally firm consistence of the kidney is increased by the swelling and hardness resulting from coagulative necrosis of the epithelial and other cells of this organ; so that infarcts in this situation are nearly always anæmic in the greater part of their extent, although often hæmorrhagic in the periphery. The spleen is of softer consistence than the kidney; and here both white and red infarcts may occur, the latter especially with increased venous pressure. Although infarcts of the brain are soft, they are much swollen in the fresh state from infiltration with serum, so as to displace surrounding parts (Marchand). Here also there must be considerable resistance to the passage of red corpuscles through the vascular walls; but it is not uncommon for these softened areas to present scattered foci of hæmorrhage, and sometimes they are markedly hæmorrhagic. The intraocular pressure is probably a factor in making embolic infarcts of the retina anæmic. Embolism of arteries of the extremities with insufficient collateral circulation is often associated with extravasations of blood in the ischæmic areas.

Metamorphoses of Infarcts.—A bland infarct is a foreign body most of the constituents of which are capable of absorption and replacement by connective tissue. The red corpuscles lose their colouring matter, some of which is transformed into amorphous or crystalline hæmatoidin. Polynuclear leucocytes, through chemiotactic influences, wander in from the periphery, the advance guard being usually the seat of marked nuclear fragmentation. This nuclear detritus mingles with that derived from the dead cells of the part. Granulation tissue develops from the living tissue around the infarct. Young mesoblastic cells wander in and assist the leucocytes in their phagocytic work. In the course of time the debris, which becomes extensively fatty, is disintegrated and removed; new vessels and new connective tissue grow in; and finally a scar, more or less pigmented according to the previous content of blood, marks the site of the infarct. In chronic endocarditis, depressed, wedge-shaped scars are often found in the spleen and the kidneys. They are rare in the lungs, not because hæmorrhagic infarcts in this situation usually undergo resolution like pneumonia or simple hæmorrahges, but because pulmonary infarcts generally occur under conditions not compatible with the prolonged survival of the patient. Partly organised infarcts are not uncommon in the lungs. In the brain, ischæmic softening may remain for a long time with apparently little change; but the common ultimate result is a cyst-like structure, which may be more or less pigmented, and is characterised by

a meshwork of delicate neuroglia and connective-tissue fibres, infiltrated with milky or clear serum. Into the finer histological details of the process of substitution of an infarct by scar-tissue it is not necessary here to enter.

Chemical Effects. Metastases.—Embolism and metastasis are sometimes employed as practically synonymous terms; but, in ordinary usage, by metastasis is understood any local, morbid condition produced by the transportation of pathological material by the lymphatic or blood-current from one part of the body to another.

We have already considered the coarser bland emboli in respect of their mechanical effects. Similar emboli, so small as to become lodged only in arterioles or capillaries, produce no mechanical effects unless, as rarely happens, numerous arterioles or capillaries are obstructed. The subject of transportation of pigment granules, and that of metallic and carboniferous dust, producing the various konioses, does not fall within the scope of this article. On account of certain special features, emboli of air, of fat, and of parenchyma-cells are most conveniently considered separately (pp. 222-228). There remain, in contrast to the dead and inert emboli to which our attention has been especially directed, those containing tumour-cells and parasitic organisms, or their products.

Masses of tumour growing into a blood-vessel may be broken off and transported as course emboli, producing all of the mechanical effects which we have described. There have been instances of sudden death from blocking of the pulmonary artery by cancerous or sarcomatous emboli, as in a case reported by Feltz. It is, however, as a cause of metastatic growths that emboli of tumour-cells have their chief significance. In individual cases it is oftener a matter of faith than of demonstration that the metastasis is due to such emboli, for opportunities to bring absolutely conclusive proof of this mode of origin of secondary tumours are not common. There have, however, been enough instances in which the demonstration has been rigorous to establish firmly the doctrine of the embolic origin of metastatic tumours. The evidence is that tumour-metastases are far more frequently due to capillary emboli than to those of larger size. Cancers and sarcomas furnish the great majority of emboli of this class; but in rare instances even benign tumours may penetrate blood-vessels and give rise to emboli, which exceptionally are the starting-points of secondary growths of the same nature as the primary. Mention has already been made of paradoxical and retrograde transport of tumour-emboli, as well as of the possibility of emboli of tumour-cells being so small as to traverse the pulmonary capillaries.

Certain animal parasites, as *Filaria sanguinis*, *Bilharzia hæmatobia*, and *Plasmodium malariæ*, are inhabitants of the blood, or, in certain stages

of their existence within the human body, are frequently found there. According to observations of Cerfontaine and Askanazy, the usual mode of transportation from the intestine of the embryos of trichina is by the lymphatic and blood-currents. Echinococci have been known to pass from the liver through the vena cava; or primarily from the right heart into the pulmonary artery; and emboli from echinococci present in the wall of the left heart may be transported to distant organs (Davaine). *Amœba coli* has been found in the intestinal veins; and, as stated by Dr. Lafleur in his article on "Amœbic Abscess of the Liver" (Allbutt's "System of Medicine," V, p. 156), it is probable that this parasite can reach the liver through the portal vein.

On account of their frequency and serious consequences, infective emboli containing pathogenetic bacteria are of especial significance. Such emboli constitute an important means of distribution of infective agents from primary foci of infection to distant parts of the body, where the pathogenetic micro-organisms, by their multiplication and their chemical products, can continue to manifest their specific activities. These emboli are often derived from infective venous thrombi connected with some primary area of infection. The portal of infection may be through the integument, the alimentary canal, the respiratory tract, the genito-urinary passages, the middle ear, or the eye, with corresponding infective thrombo-phlebitis in these various situations. Or there may be no demonstrable atrium of infection, as in many cases of infective endocarditis, which constitutes an important source of infective emboli. Emboli may of course come from secondary and subsequent foci of infection.

Coarse emboli are by no means essential for the causation of infective metastases, nor is it necessary that there should be any thrombosis to afford opportunity for the distribution of micro-organisms from a primary focus. Bacteria may gain access to the circulation, singly or in clumps; and such bacteria, without being enclosed in plugs of even capillary size, may become attached to the walls of capillaries and small vessels and produce local metastases. In this way infective material coming from the systemic veins may pass through the pulmonary capillaries without damage to the lungs, and become localised in various organs of the body.

We cannot explain the various localisations of infective processes in internal organs of the body exclusively by the mechanical distribution of pathogenetic micro-organisms by the circulation. We must reckon with the vital resistance of the tissues, which varies in different parts of the body, in different species and individuals, and with reference to different organisms. Even the pyogenetic micrococci, which are capable of causing abscesses anywhere in the body, do not generally produce their pathogenetic effects in

every place where they may chance to lodge. They have their seats of preference, which vary in different species of animal and probably in different individuals.

The mere presence of pathogenetic bacteria in an embolus does not necessarily impart to it infective properties. This is true even of emboli containing pyogenetic cocci. I have in several instances observed in the spleen and kidney only the mechanical, bland effects of emboli derived from the vegetations of acute infective endocarditis, and have been able to demonstrate streptococci or other pathogenetic organisms in the original vegetations and in the emboli. As has already been remarked concerning thrombi, the line cannot be sharply drawn between bland emboli and septic emboli, simply on the basis of the presence of bacteria; although of course the septic properties must be derived from micro-organisms.

Infective emboli are capable of producing all of the mechanical effects of bland emboli; to these are added the specific effects of the micro-organisms or their products. These latter effects are essentially chemical in nature, and may occur wherever the emboli lodge, being thus independent of the particular circulatory conditions essential for the production of mechanical effects. The most important of these chemical effects are hæmorrhages, usually of small size, and of an entirely different causation from those of hæmorrhagic infarction; necroses; inflammation, often suppurative, and, in case of putrefactive bacteria, gangrenous putrefaction. The most important function of infective embolism is in the causation of pyæmia. This subject has been most competently presented by Professor Cheyne in Allbutt's "System of Medicine," I, p. 601, who has left nothing which requires further consideration here.

Embolic Aneurysms.—Both the first recognition and the correct explanation of embolic aneurysms, at least of the great majority of cases, belong to British physicians and surgeons. Tufnell, in 1853, called attention to the influence of emboli in causing aneurysmal dilatation. There followed observations by Ogle, Wilkes, Holmes, Church, and R. W. Smith, before the appearance, in 1873, of Ponfick's important paper on embolic aneurysms. Ponfick explained their formation by direct injury to the vessel-wall, inflicted usually by calcareous, spinous emboli; a view which has since been confirmed only by Thoma. In 1877, Goodhart, in reporting a case gave the first satisfactory explanation of the mode of production of most of these aneurysms. He pointed out their association with acute infective endocarditis, and referred them to acute softening of the arterial wall, caused by toxic emboli. Other observations followed; and in 1885 Osler reported a case which, although not embolic, belongs etiologically to the same general category. This was a case of multiple mycotic aneurysms of the aorta due to

infective endaortitis associated with infective endocarditis. In 1886 and 1887 appeared the contributions of Langton and Bowlby, the most valuable in English literature, who fully confirmed and expanded in detail the views first briefly announced by Goodhart. Eppinger, in his extensive monograph on aneurysms published in 1887, presented the results of a minute and careful study of this class of aneurysm, which he calls aneurysma mycotico-embolicum, and reported seven personal observations. Of later papers on the subject may be mentioned those of Pel and Spronck, Duckworth, Buday, and Clarke.

The evidence is conclusive that aneurysms may be caused by the destructive action of bacteria contained in emboli or directly implanted on the inner vascular wall. The usual source for such emboli in relation to aneurysm is furnished by acute infective endocarditis; but as there is every transition from ordinary warty endocarditis to the most malignant forms, and as the same species of micro-organisms may be found in the relatively benign as in the malignant cases, no single type of endocarditis is exclusively associated with these aneurysms. As is demonstrated by Osler's case, the same result may follow a mycotic endarteritis not secondary to embolism.

Eppinger has shown that at least the intima and the internal elastic lamella, and usually a part, sometimes the whole, of the media, are destroyed by the action of the bacteria, when an aneurysm is produced. The site of the aneurysm corresponds to this circumscribed area of destruction, and therefore to the seat of the embolus, and is not above it, as some have supposed. The aneurysm is usually formed acutely, sometimes slowly. It may remain small or attain a large size. Multiplicity and location at or just above an arterial branching are common characteristics of embolic aneurysms. Favorite situations are the cerebral and mesenteric arteries and arteries of the extremities; but these aneurysms may occur in almost any artery. Arteries without firm support from the surrounding tissues offer the most favourable conditions for the production of embolic aneurysms.

Eppinger totally rejects direct mechanical injury from an embolus as a cause of aneurysm in the manner alleged by Ponfick; and Langton and Bowlby are likewise sceptical as to the validity of Ponfick's explanation beyond its possible application to some of his own cases. Certainly the great majority of embolic aneurysms are caused by pathogenetic organisms, and belong, therefore, to the class of parasitic aneurysms rather than to that of traumatic aneurysms. The affection is not a common one.

In this connection mere mention may be made of the interesting and very common verminous aneurysms of the anterior mesenteric artery of horses, caused by *Strongylus armatus*.

General Symptoms.—The symptoms of bland embolism are dependent mainly upon the degree and extent of the local anæmia produced by the

arterial obstruction, and upon the specific functions of the part involved. In infective embolism there are additional symptoms referable to local and general infection. Here the constitutional symptoms usually overshadow those referable to the embolic obstruction and the local lesions.

It is not known that any symptoms attend the act of transportation of an embolus, even through the heart. In some situation there is sudden pain at the moment of impaction of the embolus (embolic ictus). This is more marked in large arteries, especially those supplying the extremities, than in smaller and visceral arteries. This pain has been attributed to various causes; but the most probable explanation seems to me to be irritation, by the impact of the embolus and by the sudden distension of the artery, of sensory nerves and nerve-endings in the vascular wall, present especially in the outer coat. It may be that the Pacinian corpuscles, which are particularly abundant in and around the adventitia of the abdominal aorta, the mesenteric arteries, the iliac and the femoral arteries, are susceptible to painful impressions. Embolism of the arteries named is characterised especially by the intensity of the pain, described sometimes as the sensation of a painful blow, at the moment of impaction of the embolus. Surgeons are familiar with the pain which attends the act of ligation of larger blood-vessels.

Of the pain which follows arterial embolism there are other causes, such as irritation of sensory nerves by local anæmia, altered tension of the part, presence of waste and abnormal metabolic products, structural changes in nerves, inflammation of serous membranes covering infarcts, and so forth.

Some writers have spoken of the occasional occurence of a nervous or reflex chill at the time of the embolic act; but, without denying the possibility of such an occurrence, I think that chills associated with embolism have been due usually to infection rather than to vascular plugging.

Although Stricker has constructed a hypothesis of fever based largely upon experiments interpreted by him as demonstrating that the commotion mechanically set up by emboli causes fever, I am not aware of any conclusive observations which show that fever may be produced in this way in human beings. Independently of the intervention of pathogenetic micro-organisms, arterial embolism may, however, be accompanied by elevation of temperature. Direct invasion of thermic nervous centres is, of course, only a special case in certain localisations of cerebral embolism. Gangolphe and Courmont attribute the fever sometimes observed after arterial occlusion to the absorption of pyretogenetic substances which they find produced in tissues undergoing necrobiosis. Other possible causes of fever may be the reactive and secondary inflammations consecutive to embolism.

Only in external parts, or parts open to inspection, can the phenomena of mortification, or "local cadaverisation," as Cruveilhier designated the results of shutting off arterial blood, be directly observed. Here are manifest the pallor accompanied by patches of lividity, the cessation of pulsation, the loss of turgidity, the coldness, the annihilation of function, the local death. The hæmorrhages which result from arterial obstruction may, however, be evident, not in external parts only, but also by the discharge of blood from the respiratory passages, the intestine, and the urinary tract; as the result of pulmonary, intestinal, and renal infarction respectively. The phenomena following retinal embolism are open to direct inspection by the ophthalmoscope. In parts not accessible to physical exploration the symptoms are referable mainly to the disturbance or abolition of function, and, therefore, vary with the special functions of the part. They will be considered in connection with embolism of special arteries (p. 229).

Diagnosis.—The main reliance in the differential diagnosis of embolism from thrombosis, or from other forms of arterial obstruction, is the discovery of a source for emboli, the sudden onset and the intensity of symptoms referable to local arterial anæmia, occasionally the disappearance or marked improvement of symptoms in consequence of complete or partial re-establishment of the circulation, and to some extent the absence of arterio-sclerosis or other causes of primary arterial thrombosis.

Valuable as these characters are for diagnosis, they are neither always present nor infallible. For pulmonary embolism the source is to be sought in peripheral venous thrombosis or cardiac disease with thrombi in the right heart; for embolism in the aortic system, the usual source is the left heart, the great majority of cases being associated with disease of the aortic or mitral valves. It may, however, be impossible to detect the source, and its existence does not exclude the occurrence of thrombosis or other forms of arterial occlusion.

Nor are the symptoms consecutive to embolism always sudden in onset. An embolus may at first only partly obstruct the lumen of the vessel, which is later closed by a secondary thrombus; or it may be so situated that a thrombus springing from it is the real cause of the local anæmia. For example, an embolus lodged in the internal carotid artery usually causes no definite symptoms, but a secondary thrombus may extend from the embolus into the middle cerebral artery, in which case cerebral softening is sure to follow. On the other hand, the complete closure of an artery may be effected by a thrombus with such rapidity as to suggest embolism.

While the sudden occlusion of an artery by an embolus often causes temporary ischæmia of greater intensity and over a larger area than the

more gradual closure of the same artery by a thrombus, so that when the collateral circulation is fully established the disappearance or reduction of the symptoms may be more marked in the former case than the latter, there may be even in thrombosis very decided improvement in the symptoms with the development of the collateral circulation.

The existence of arterio-sclerosis, of course, does not exclude embolism; but in case of doubt the chances are strongly in favour of embolism in children and young adults with healthy arteries, especially if cardiac disease be present; the most common association in the latter cases being with mitral affections.

Notwithstanding all of these uncertainties, the diagnosis, of embolism, when it produces definite symptoms, can be correctly made in the majority of cases.

Air Embolism.—The majority of cases in which death has been attributed to the entrance of air into the circulation have been surgical operations and wounds about the neck, shoulder, upper part of the thorax and skull, where air has been sucked into gapping veins and sinuses by thoracic aspiration; and cases in which air has entered the uterine veins, chiefly from the puerperal uterus, either spontaneously, as after abortions or detachment of placenta prævia, or after injections into the uterine cavity. Jürgensen has reported cases in which he believes death was caused by the entrance of gas into open veins connected with diseased areas in the stomach and intestine. Gaseous embolism has been assigned as the cause of symptoms and of death in caisson-disease and in divers; and it has been observed in connection with the development of gas-producing bacilli in the body.

A large number of experiments have been made to determine the effects of air introduced into the circulation. These have demonstrated that when the air is introduced slowly and at intervals, enormous quantities can sometimes be injected in a comparatively short time without manifest injury. Thus Laborde and Muron injected into the external jugular vein of a dog 1120 cc. in the space of an hour and a half without causing death; and Jürgensen injected into the left femoral artery of a dog, weighing 43.5 kilo, 3550 cc. in the space of two hours and a half with only slight disturbance of the respiration and of the action of the heart. Under these circumstances the air-bubbles circulate with the blood, pass through the capillaries, and are speedily eliminated. Small amounts of air introduced directly into the carotids, the left heart or thoracic aorta, are often quickly fatal from embolism of the cerebral or coronary arteries.

The sudden introduction of large amounts of air into the veins is quickly fatal. Rabbits are much more susceptible to air embolism than dogs or horses. 50 cc. of air, and even more, can often be injected at once into

the external jugular vein of a medium-sized dog without causing death; nor can a dog be killed by simple aspiration of air into the veins, even when an open glass tube is inserted into the axillary or jugular vein and shoved into the thorax (Feltz). Barthélemy says that as much as 4000 cc. of air must be introduced into the veins of horses in order to cause death.

After death from entrance of air into the veins, the right cavities of the heart are found distended with frothy blood, and blood containing air-bubbles is found in the veins—especially those near the heart, and in the pulmonary artery and its branches. It is exceptional under these circumstances for air to pass through the pulmonary capillaries into the left heart and aortic system.

There are two principal explanations of the cause of death in these cases. According to one, associated especially with Couty's name, the air is churned up with the blood into a frothy fluid in the right heart, and on account of its compressibility this mixture cannot be propelled by the right ventricle, which thus becomes over-distended and paralysed. According to another hypothesis, supported by experiments of Passet and of Hauer, blood mixed with air-bubbles is propelled into the pulmonary artery and its branches, but the frothy mixture cannot be driven through the pulmonary capillaries, so that death results from pulmonary embolism. The paralysing influence upon the heart of obstruction to the coronary circulation from accumulation of air in the right heart and in the coronary veins must also be an important factor, as well as the cerebral anæmia. Probably all of these factors—over-distension of the right heart, embolism of the pulmonary artery and its branches and of the coronary veins, and cerebral anæmia—may be concerned in causing death, although not necessarily all in equal degree in every case.

We have no information as to the amount of air required to cause death by intravenous aspiration or injection in human beings. It seems certain that man is relatively more susceptible in this respect than the dog or the horse; but it is probable that the fatal quantity of air must be at least several cubic centimeters, and that the entrance of a few bubbles of air into the veins is of no consequence. Many authors have entertained very exaggerated ideas of the danger of entrance of a small quantity of air into the veins.

A large proportion of the cases reported in medical records as deaths due to air embolism will not stand rigid criticism. I have had occasion to look through the records of a large number of these cases, and have been amazed at the frequently unsatisfactory and meagre character of the evidence upon which was based the assumption that death was due to the entrance of air into the circulation.

So far as I am aware, the first attempt to make a bacteriological examination and to determine the nature of the gas-bubbles found in the blood under circumstances suggestive of death from entrance of air into the vessels, was made by me in 1891. A patient with an aortic aneurysm, which had perforated externally and given rise to repeated losses of blood, died suddenly without renewed hæmorrhage. At the autopsy, made in cool weather eight hours after death, there was abundant odourless gas in the heart and vessels without a trace of cadaveric decomposition anywhere in the body. It was proven that the gas was generated by an anaerobic bacillus, which was studied by Dr. Nuttall and myself, and named by us *Bacillus aerogenes capsulatus*. This bacillus is identical with one subsequently found by E. Fraenkel in gaseous phlegmons, and with that found by Ernst and others in livers which are the seat of post-mortem emphysema (Schaumleber). It is widely distributed in the outer world, being present especially in the soil, and often exists in the human intestinal canal. Dr. Flexner and I have reported twenty-three personal observations in which this gas-bacillus was found, and since our publication we have met with several additional ones. The only points concerning these cases which here concern us are, that this bacillus not only may produce gas in cadavers, but may invade the living body, and cause a variety of affections characterised by the presence of gas. There is evidence that the bacilli may be widely distributed by the circulation before death, and that gas generated by them may be present in the vessels during life. In most cases, however, in which this bacillus was present, the gas found in the heart and blood-vessels was generated after death. I do not consider that there is satisfactory evidence that similar effects may be produced by the colon bacillus, as has been asserted. There is, however, a facultative anaerobic bacillus, very closely allied to *B. aerogenes capsulatus*, which may also cause gaseous phlegmons and produce gas in the vessels after death.

Our observations have demonstrated that the finding of gas-bubbles in the heart and vessels a few hours after death without any evidence of cadaveric decomposition is no proof that the gas is atmospheric air, or is not generated by a micro-organism. In all such cases a bacteriological examination is necessary to determine the origin of the gas. In many cases reported as death entrance of air into the veins, the evidence for this conclusion has been nothing more than finding gas-bubbles in the heart and vessels after sudden or otherwise unexplained death. In the absence of a bacteriological examination, the only cases which can be accepted as conclusive are those in which death has occurred immediately or shortly after the actually observed entrance of a considerable amount of air into the veins. There have been a number of carefully observed and indisputable

instances in which during a surgical operation in the "dangerous region" life was imperilled or extinguished by the demonstrated entrance of air into wounded veins. After the audible sound of the suction of air into the vein, death was sometimes instantaneous; or it occurred in a few minutes after great dyspnœa, syncope, dilatation of the pupils, pallor or cyanosis, occasionally convulsions, sometimes the detection by auscultation over the heart of a churning sound synchronous with the cardiac systole, and the exit from the wounded vein of blood containing air-bubbles. These very alarming symptoms may disappear and the patient recover.

The evidence for this mode of death would seem to be almost as conclusive for a certan number of the sudden deaths following injections into the uterus, especially for the purpose of committing criminal abortion, and after the separation of placenta prævia. But I am sceptical as to this explanation of many of the deaths which have been reported as due to the entrance of air into the uterine veins. In the reports of Dr. Flexner and myself will be found the description of several cases of invasion of *B. aerogenes capsulatus,* which without bacteriological examination would have the same claim to be regarded as deaths from entrance of air into the uterine veins as many of those so recorded. I have had the opportunity to examine the museum specimen of a uterus of a much-quoted case so reported, and I found in its walls bacilli morphologically identical with our gas-bacillus. Certainly all cases of this kind should hereafter be reported only after a bacteriological examination. Jürgensen's cases of supposed entrance of gas into the general circulation through the gastic and the intestinal veins are undoubtedly instances of invasion, either before or after death, of gas-forming bacilli.

Since Paul Bert's researches, the symptoms and death which occasionally follow the rapid reduction of previously heightened atmospheric pressure upon exit from a caisson or diver's apparatus, have been plausibly attributed to the liberation of bubbles of nitrogen in the circulating blood. This explanation of the phenomena is not, however, free from doubt, and it is difficult to bring conclusive evidence in its support in the case of human beings. Little weight can be attached at present to the reports of finding bubbles of gas in the blood-vessels of those who have died from caisson-disease, for these reports have not hitherto been accompanied by any bacteriological examination to determine the source of the gas.

Ewald and Kobert have made the curious observations that the lungs are not air-tight under an increase of intrapulmonary pressure which may temporarily occur in human beings. They found in experiments on animals that small air-bubbles may appear under these circumstances in the pulmonary veins and left heart without any demonstrable rupture of the pul-

monary tissue; and they argue that this may occur under similar conditions in human beings. The entrance into the circulation of a few minute air-bubbles in this way would doubtless produce no effects. Ewald and Kobert cite two or three not at all convincing published cases in support of the possibility of death resulting from the entrance of air through unruptured pulmonary veins. Very plausible is Janeway's hypothesis that the transitory hemiplegia and other cerebral symptoms, which have occasionally been observed to follow washing-out the pleural cavity with peroxide of hydrogen, or some other procedure by which air or gas may accumulate in this cavity under high pressure, are due to air embolism or gaseous embolism of the cerebral vessels.

Not less remarkable are the experimental observations of Lewin and Goldschmidt concerning air-embolism following injections of air into the bladder and its passage into the ureters and renal pelves. It has not been demonstrated that the same phenomenon can occur under similar conditions in human beings.

Fat Embolism.—Fat embolism, first observed in human beings by Zenker and by Wagner in 1862, is the most common form of embolism; but its practical importance does not correspond to its frequency. It is of greater surgical than medical interest, inasmuch as the severer forms are nearly always the result of traumatism. The usual conditions for its occurrence are (i.) rupture of the wall of a vessel (ii.) proximity of liquid fat, and (iii.) some force sufficient to propel the fat into the vessel.

Fat-embolism probably occurs in every case of fracture of bone containing fat-marrow. When the bone is rarefied, and contains an unusual quantity of fat-marrow, embolism resulting from its injury may be very extensive; as is illustrated by several fatal cases of fat-embolism following the forcible rupture of adhesions in an anchylosed joint. Ribbert has shown that fat-embolism may result from simple concussion of bone, as from falls or a blow. Inflammations, hæmorrhages and degenerations of the osseous marrow may cause it. It may likewise result from traumatic lesions, necroses, hæmorrhages, inflammation of adipose tissue in any part of the body,—of the brain, of a fatty liver, in a word of any organ or part containing fat. Injury to the pelvic fat during child-birth leads to fat-embolism. Oil-globules in the blood may come from fatty metamorphoses of thrombi, of endothelial cells and of atheromatous plaques. The lipæmia of digestion and of diabetes mellitus has not been generally supposed to lead to fat-embolism, but Sanders and Hamilton have observed capillaries filled with oil-globules after death from diabetic coma, and they attribute in certain cases dyspnœa and coma in diabetes to this cause.

In the great majority of cases, fat-embolism is entirely innocuous, and, unless it is searched for, its existence is not revealed at autopsy, and then only by microscopical examination. Plugging of capillaries and small arteries with oil may, however, be so extensive and so situated as to cause grave symptoms and even death. More moderate plugging may aid in causing death in those greatly weakened by shock, hæmorrhage, or other causes. The detection of fat-embolism in the pulmonary vessels may be of medico-legal value in determining whether injuries have been inflicted before or after death.

The deposition of fat-emboli is most abundant in the small arteries and capillaries of the lung, where in extreme cases the appearances of microscopic sections may indicate that considerably over one-half of the pulmonary capillaries are filled with cylinders and drops of oil. In rare instances of extensive injury the amount of fat in the blood may be enormous, so that post-mortem clots in the heart and pulmonary artery may be enveloped in layers of solidified fat. Some of the oil passes through the pulmonary capillaries and blocks the capillaries and arterioles of various organs; those which suffer most being the brain, the kidneys, and the heart. The extent of the embolism in the aortic system varies much in different cases, being sometimes slight, at other times extensive. Probably the force of the circulation determines the amount of fat which passes through the pulmonary capillaries. Oil once deposited may be again mobilised and transferred to other capillaries.

As already stated, it is only in the comparatively rare instances of extensive fat-embolism that effects of any consequence are produced. The fat itself is perfectly bland and unirritating, although it may be accidently associated with toxic or infective material. The lesions and symptoms, when present, are referable mainly to the lungs, the brain, the heart, and the kidneys. These lesions are multiple ecchymoses (which in the lungs and the brain may be very numerous and extensive), pulmonary œdema, and patchy fatty degeneration of the cardiac muscle and of the epithelium of the convoluted tubules of the kidney. Pulmonary œdema, referable probably to paralysis of the left heart, is common with extensive fat embolism of the lungs. Death may undoubtedly be caused by fat-embolism of the cerebral vessels, possibly also by that of the coronary vessels.

The *symptoms* in the extreme cases are quickened respiration, rapid prostration, reddish frothy expectoration, the crepitations of pulmonary œdema, small frequent pulse, cyanosis, and—with cerebral invasion—coma, vomiting, convulsions, and occasionally focal cerebral symptoms. The temperature may either fall or rise. Oil-globules are often found in the urine, but it is still an open question whether these are eliminated through the glomerular capillaries, many of which are often filled with oil.

From the recent investigations of Beneke it appears that the oil is readily disposed of, in small part by saponification, possibly oxidation, and emulsion by means of the blood plasma; but in larger part through the metabolic and phagocytic activities of wandering cells which form a layer around the fat. The saponifying ferment—lipase—which Hanriot has discovered in blood-serum is probably one of the agents concerned in disposing of the fat.

Embolism by Parenchymatous Cells.—This is in general of more pathologico-anatomical than clinical interest, and therefore need not be considered here in detail. As has been shown by Lubarsch, Aschoff, and Maximow, bone-marrow cells, with large budding nuclei, usually undergoing degeneration, may often be found lodged in the pulmonary capillaries after injury to bone, in toxic and infective diseases, in leucocythæmia, and in association with emboli of other parenchymatous cells. I have seen them in large number in capillaries of the liver in a case of spleno-medullary leucocythæmia.

Next in frequency are emboli of liver-cells, which are found chiefly in pulmonary capillaries, but may pass through an open foramen ovale so as to reach capillaries of the brain, kidneys, and other organs. F. C. Turner in 1884 first observed liver-cells within hepatic vessels; and later Jürgens, Klebs, Schmorl, Lubarsch, Flexner, and others noted their transportation as emboli after injury, hæmorrhages, and necroses of the liver, and with especial frequency in puerperal eclampsia. Secondary platelet-thrombi are usually formed about the cells.

Especial significance was attached by Schmorl to the presence of emboli of placental giant-cells (syncytium) in the pulmonary capillaries in cases of puerperal eclampsia; but these emboli, although frequent, are not constant in this affection, and they may occur in pregnant women without eclampsia (Lubarsch, Leusden, Kassjanow).

To the group of parenchymatous emboli may be added the transport of large cells from the spleen to the liver through the splenic and portal veins. I have seen large splenic cells containing pigment and parasites blocking the capillaries of the liver in cases of malaria; and also the well-known large splenic cells containing red blood-corpuscles in cases of malaria and of typhoid fever. The crescentic endothelial cells of the spleen may enter the circulation.

After traumatism and parenchymatous embolism fragments of osseous and medullary tissue may be carried to the pulmonary vessels as emboli (Lubarsch, Maximow). Emboli of large masses of hepatic tissue have been found in branches of the pulmonary artery by Schmorl, Zenker, Hess, and Gaylord as a result of traumatic laceration of the liver. Chorion-villi may be detached and very rarely conveyed as emboli to the lungs (Schmorl), or

by retrograde transport to veins in the vaginal wall (Neumann, Pick). This is much more likely to occur from chorionic carcinoma and moles than from a normal placenta.

So far as known, emboli of marrow-cells, of liver-cells, of normal syncytial cells, and of splenic cells undergo only regressive metamorphoses, which lead to their eventual disappearance. The possibility that without the presence of any syncytial tumor in the uterus or tubes, emboli of syncytial cells may give rise to malignant tumours with the typical structure of those developing from syncytium, seems to have been demonstrated by a case reported by Schmorl; but it can hardly be supposed that the displaced syncytial cells were normal. Emboli of liver-cells manifest a distinct coagulative influence (Hanau, Lubarsch); and in two instances Lubarsch attributed infarcts in the kidney and the liver to thrombi formed around these cells. Marrow-cells and syncytial cells may likewise cause, in less degree, secondary platelet and hyaline thrombi; but it does not appear that these thrombi have the importance in the etiology of puerperal eclampsia which is attached to them by Schmorl. With a few exceptions, no important lesions of the tissues or definite symptoms have been conclusively referred to emboli of these parenchymatous cells.

Although widely different in results, the transportation of tumour cells by the blood-current is a process similar to that of parenchymatous embolism, for which indeed cellular embolism seems to me a preferable designation. Benno Schmidt has found small branches of the pulmonary artery plugged with cancer-cells derived from gastric cancer or its metastases, both with and without growth of the cells into the walls of the plugged arteries. Such cells may reach the lungs by conveyance through the thoracic duct and innominate vein.

Embolism of Special Arteries.—I shall present the salient characteristics of the more important special localisations of embolism, so far as these have not been sufficiently considered in the preceding pages, or do not pertain to other articles in this work. Embolism of the central nervous system will be discussed in the Volume VIII of Allbutt's "Syst. Med." under "Diseases of the Brain and Spinal Cord." The pyæmic manifestations of infective embolism have been described in the articles on "Pyæmia" (Allbutt's "System of Medicine," I, p. 601) and on "Infective Endocarditis" (Allbutt's "System of Medicine," I, p. 626, and V, p. 876).

Pulmonary Embolism.—The effects of pulmonary embolism vary with the size of the plugged vessel, the rapidity and completeness of its closure, the nature of the embolus, and associated conditions. Embolism of large, of medium-sized and small arteries, and of capillaries may be distinguished.

The most frequent source of large emboli is peripheral venous thrombosis, although they may come from the right heart. Sudden or rapid death

follows embolism of the trunk or of both main divisions of the pulmonary artery. It may occur also from embolism of only one of the main divisions or from plugging of a large number of branches at the hilum of the lung.

Death may be instantaneous from syncope. More frequently the patient cries out, is seized with extreme precordial distress and violent suffocation, and dies in a few seconds or minutes. Or, when there is still some passage for the blood, the symptoms may be prolonged for hours or even days before the fatal termination. The symptoms of large pulmonary embolism are the sudden appearance of a painful sense of oppression in the chest, rapid respiration, intense dyspnœa, pallor followed by cyanosis, turgidity of the cervical veins, exophthalmos, dilatation of the pupils, tumultuous or weak and irregular heart's action, small, empty radial pulse, great restlessness, cold sweat, chills, syncope, opisthotonos, and convulsions. The intelligence may be preserved, or there may be delirium, coma, and other cerebral symptoms. Particularly striking is the contrast between the violence of the dyspnœa and the freedom with which the air enters the lungs and the absence of pulmonary physical signs; unless in the more prolonged cases it be the signs of œdema of the lungs. Litten found in two cases systolic or systolic and diastolic stenotic murmurs in the first and second intercostal spaces on the right or left side of the sternum. In prolonged cases the symptoms may be paroxysmal with marked remissions. Recovery may follow after the appearance of grave symptoms. There has been much and rather profitless discussions as to the degrees in which the symptoms are referable to asphyxia, to cerebral anæmia, or to interference with the coronary circulation. Doubtless all three factors are concerned, but the exact apportionment to each of its due share in the result is not easy, nor very important.

The diagnosis is based upon the sudden appearance of the symptoms, with a recognised source for an embolus. It is surprising to find in the larger statistics, as those of Bang and of Bunger, how often the thrombosis leading to fatal pulmonary embolism has been latent. Here the diagnosis cannot always be made; but in many cases it may be suspected, or be reasonably certain: as when the above-mentioned symptoms appear in puerperal women; during convalescence from infective fevers, as enteric fever, influenza, pneumonia; in marasmic and anæmic conditions, as phthisis, cancer, chlorosis; after surgical operations, especially those involving the pelvic organs; and in persons with varicose veins.

Even at autopsies the source for the embolus has sometimes been missed, but this has been due generally to inability or failure to make the necessary dissection of the peripheral veins, or to dislocation of the entire thrombus. Serre has published a series of cases of pulmonary embolism with latent thrombosis, showing the difficulties which may attend the discovery of the

source, and the frequency with which patient search reveals the primary thrombus. The majority of plugs in the trunk or main divisions of the pulmonary artery, found in cases of sudden death, present the anatomical characters of emboli, associated perhaps with secondary thrombi; but there remain a certain number of cases of sudden or gradual death from primary thrombosis of the pulmonary artery, or from thrombosis extending into a main division from an embolus in a smaller branch (see "Thrombosis," p. 167).

Bland embolism of medium-sized and small branches of the pulmonary artery in normal lungs, and without serious impairment of the pulmonary circulation, usually causes no symptoms and no changes in the parenchyma of the lungs. Even in lungs structurally altered, and with serious disturbances of the circulation, such embolism may be without effects. The explanation of the harmlessness of the majority of medium-sized and small pulmonary emboli is that the collateral circulation through the numerous and wide pulmonary capillaries is, under ordinary conditions, quite capable of supplying sufficient blood to an area whose artery is obstructed, to preserve its function and integrity; and that the pulmonary tissue, in contrast to the brain and the kidney, is relatively insusceptible to partial local anæmia.

Often enough, however, medium-sized and smaller branches of the pulmonary artery are occluded by emboli or thrombi under conditions where the pulmonary circulation is incapable of compensating the obstruction, and then the result is hæmorrhagic infarction of the lung. The most common and important of the conditions thus favouring the production of hæmorrhagic infarction is chronic passive congestion of the lungs from valvular or other disease of the left heart. It is especially during broken compensation of cardiac disease that hæmorrhagic infarction of the lungs occurs, sometimes indeed almost as a terminal event. Other favouring conditions are weakness of the right heart, fatty degeneration of the heart, general feebleness of the circulation, pulmonary emphysema, infective diseases.

The source of the embolus causing pulmonary hæmorrhagic infarction is oftener the right heart than a peripheral thrombus. Globular thrombi are often formed in the right auricular appendix and ventricular apex in uncompensated disease of the left heart, particularly of the mitral valve (see "Thrombosis," p. 141). The infarction may be caused also by thrombosis of branches of the pulmonary artery, which are not infrequently the seat of fatty degeneration of the intima and of sclerosis in cardiac disease and in emphysema. Thrombi in larger branches often give rise to emboli in smaller ones.

Pulmonary infarcts are usually multiple, more frequent in the lower than the upper lobes, and occur on the right side somewhat oftener than on the

left; corresponding thus with the distribution of emboli. Their size varies generally from that of a hazel-nut to a pigeon's egg; but it may be smaller or much larger, up to half or even an entire lobe. They are conical or of a wedge-shape, the base being at the pleura. Infarcts are rarely buried in the substance of the lung so as to be invisible from the pleural surface. Typical fresh infarcts are strikingly hard, sharply circumscribed, swollen, upon section dark red, almost black, smooth or slightly granular, and much drier than ordinary hæmorrhages. Examined microscopically, the air-cells, bronchi, and any loose connective tissue which may be included in the infarct are stuffed full of red corpuscles. The capillaries are distended, and in all but the freshest infarcts usually contain, in larger or smaller amount, hyaline thrombi, to which von Recklinghausen attaches much importance in the production of the infarct. Fibrin may be scanty in very recent infarcts, but in older ones it is abundant. The walls of the alveoli in the central part of the infarct are the seat of typical coagulative necrosis with fragmentation and solution of the nuclear chromatin. It is probable that the red corpuscles also undergo some kind of coagulative change, for otherwise it is difficult to explain the extremely hard consistence of the fresh infarct. It is possible that small pulmonary infarcts and very recent ones may occur without necrosis; but the ordinary ones are necrotic, and cannot therefore be removed by resolution; but, if the patient lives long enough and suppuration or gangrene of the infarct does not ensue, are substituted by cicatricial tissue (Willgerodt).

Ever since the first admirable description of hæmorrhagic infarcts of the lungs by Laennec there has been considerable difference of opinion as to their explanation. The doctrine that they are usually caused by emboli, however, gradually gained general acceptance. This explanation has always had opponents, chiefly on the grounds that emboli often occur in the pulmonary arteries without infarction; that infarction is not always associated with obstruction of the corresponding artery; that some have believed that simple hæmorrhages may produce the same appearances, and that until recently attempts to produce pulmonary infarction experimentally have been without positive or at least sufficiently satisfactory results. Hamilton is strongly opposed to the embolic explanation, and attributes hæmorrhagic infarction of the lung to a simple apoplexy, resulting usually from rupture of the alveolar capillaries in chronic passive congestion. Grawitz, likewise, considers that embolism has nothing to do with the causation of pulmonary infarction, which he explains by hæmorrhage from newly-formed, richly-vascularised, peribronchial, subpleural, and interlobular connective tissue consecutive to the chronic bronchitis of cardiac and other diseases. He emphasises structural changes in the lung as an essential pre-requisite for

infarction. Grawitz's attack especially has stimulated investigation which, in my opinion, has strengthened the supports of the embolic doctrine of hæmorrhagic infarction.

The evidence seems to me conclusive that pulmonary infarcts are caused by embolism and thrombosis of branches of the pulmonary artery. In the great majority of cases the arteries supplying the areas of infarction are plugged. Upon this point my experience is in accord with that of von Recklinghausen, Orth, Hanau, Oestreich, and many others. That these arterial plugs are secondary to the infarction is improbable, as hæmorrhages elsewhere, as well as undoubted ones in the lungs, often as they cause secondary venous thrombosis, rarely cause arterial thrombosis. Moreover, there is sometimes an interval of open artery between the plug and the infarct, a relation not observed with the undoubtedly secondary thrombosis of veins connected with the infarct, and not explicable on the assumption that the arterial thrombosis is secondary. The plug often has the characters of a riding embolus. Not a few of the plugs, however, are primary thrombi. The occasional occurrence of pulmonary infarction without obstruction in the arteries has as much, but no more, weight against the embolic explanation as the similar, and I believe quite as frequent, occurrence of splenic infarcts without embolism or thrombosis of the splenic arteries. Both the hæmorrhage and the necrosis of infarcts are essentially capillary phenomena, each being independent of the other; and, undoubtedly can occur, in ways little understood, in various regions, without plugging of the arteries.

The anatomical characters of pulmonary infarcts are essentially the same as those of hæmorrhagic infarcts of the spleen and other parts. The conical shape, the hard consistence, the peripheral situation, the coagulative necrosis are distinctive characters of pulmonary as of splenic infarcts. The necrosis cannot well be attributed to compression of the alveolar walls by the extravasated blood, for the capillaries in these are usually distended widely with blood. It has the general characters of the ischæmic necrosis of infarcts, except that it apparently occurs somewhat later in the formation of the infarct and does not usually reach the periphery; phenomena which may be explained by the relative tolerance of the pulmonary tissue of partial ischæmia, and by a better peripheral circulation than is present in infarcts elsewhere.

Inasmuch as emboli do not ordinarily cause infarction in normal human lungs with vigorous circulation, it is not surprising to find that similar emboli under similar conditions do not cause infarction in the lungs of animals. It is not easy to reproduce experimentally in animals the conditions under which pulmonary infarcts occur in man; yet there have been several valuable contributions in recent years to the experimental production of pulmonary

infarction: these have furnished an experimental basis, which, if not all that is to be desired, still marks a distinct advance for the embolic doctrine of hæmorrhagic infarction of the lung. Pulmonary infarcts, in all essential respects identical with those in human lungs, have been produced by experimental embolism or arterial occlusion by Cohnheim and Litten, Perl, Küttner, Mögling, Grawitz, Klebs, Gsell, Sgambati, Orth, Zahn, and Fujinami. Most of these experimental infarcts have been produced under conditions not very analogous to those of human infarcts; but the essential fact that typical hæmorrhagic infarction of the lung may be caused by arterial plugging has been experimentally established. Into the details of these experiments it is impossible here to enter.

Whether genuine hæmorrhagic infarcts of the lung may ever be caused by simple hæmorrhage from rupture of blood-vessels is perhaps an open question. At present this mode of their production seems to me undemonstrated and improbable, so that I hold that simple pulmonary apoplexies and genuine infarcts should be clearly distinguished from each other. Neither the results of experimental introduction of blood into the trachea (Perl and Lippmann, Sommerbrodt, Nothnagel, Gluziński), nor the appearances of the lungs after undoubted bronchorrhagias, pneumorrhagias, and suicidal cutting of the trachea support the opinion that aspiration of blood from the trachea and bronchi causes genuine hæmorrhagic infarction. In only one of Sommerbrodt's numerous experiments was such infarction observed, and this he regards as accidental. The explanation of this exceptional result is probably the same as in Perl's experiment with thrombosis after venesection and anæmia.

I have seen, in two or three instances, nearly white or pale-red fresh anæmic infarcts in densely consolidated lungs.[1] Even when caused by bland emboli pulmonary infarcts are exposed to the invasion of bacteria from the air-passages; and such bacterial invasion may lead to suppuration or gangrene. Completely cicatrised pulmonary infarcts occur, but they are not common—life being usually cut short by the associated cardiac disease before the infarct is healed.

Hæmorrhagic infarction of the lungs may be entirely latent; often, however, the diagnosis can be made during life. The affection may be ushered in by a chill or chilly sensation, increase of a usually existing dyspnœa, and localised pain in this side. These symptoms are far from constant. The characteristic symptom, although by no means pathognomonic, is bloody expectoration. Profuse hæmoptysis was noted by Laennec, but is very rare. The sputum contains dots and streaks of blood, or small dark coagula; or,

[1] In very rare instances pulmonary infarcts are anæmic in consequence of extreme weakness of the circulation (87).

more frequently, the blood is intimately mixed with the expectoration, which is in small masses and usually less viscid and darker red than that of pneumonia, although it may resemble the latter. Blood may be present in the sputum for one or two weeks or even longer after the onset of the infarction. It acquires after a time a brownish-red tint, and generally contains the pigmented epithelial cells usually seen in the sputum of chronic passive congestion. Circumscribed sero-fibrinous pleurisy is usually associated with pulmonary infarction. Even with infarcts not more than four or five centimetres in diameter the physical signs of consolidation and subcrepitant râles can sometimes be detected; usually in the posterior, lower parts of the lungs. These signs are referable not only to the infarct, but also to the surrounding localised œdema and perhaps reactive pneumonia. There may be moderate elevation of temperature. When the characteristic bloody expectoration, together with signs of circumscribed consolidation, appears in the later stages of cardiac disease, or with peripheral venous thrombosis, there is generally little doubt of the diagnosis. Yet similar expectoration may occur from simple bronchial hæmorrhages in intense passive congestion of the lungs without infarction. The expectoration in cancer of the lungs may resemble that of pulmonary infarction.

The sudden appearance of pain in the chest, cough, and elevation of temperature, immediately after the hypodermic injection of undissolved preparations of mercury, is attributed to pulmonary embolism. The symptoms disappear in a few days without serious consequences. This complication has been rare in the experience of most of those who have employed this treatment of syphilis, but has led some to abandon the method.

The embolic pneumonias and abscesses caused by infective emboli are pyæmic manifestations, and have been considered in the article on "Pyæmia" in the first volume of Allbutt's Syst. Med.

Splenic Infarction.—Anæmic infarcts of the spleen, which are commoner than the hæmorrhagic variety, are not usually in the recent state so pale and bloodless as those of the kidney; for the spleen is much richer in blood than the kidney, and in chronic passive congestion, during which the larger number of infarcts occur, the red pulp contains much blood outside of the vessels. Many of these infarcts can be appropriately described as mixed red and white infarcts. Splenic infarcts vary greatly in size, but in general they are much larger than those occurring under the same conditions in the kidney, as comparatively large arteries in the spleen break up into numerous small terminal twigs. Averaging perhaps two to six centimetres in diameter, a single infarct may occur one-half or more of the spleen. The recent infarcts are hard, swollen, and more or less wedge-shaped, with the base at the capsule, which is often coated with fibrin;

or in older cases is thickened and adherent by fibrous tissue. The great majority are caused by emboli from the left heart or the aorta; but both hæmorrhagic and pale splenic infarcts occur without arterial occlusion; especially in certain acute infective diseases; oftenest in relapsing fever, but also in typhus, enteric fever, cholera, and septicæmia. The causation of the latter is unknown. Ponfick attributes them to venous thrombosis, which may be the cause of the hæmorrhagic infarcts; but it is difficult to understand how it can produce the pale anæmic infarcts. Bland infarcts are mostly absorbed and substituted by pigmented, occasionally calcified, scars, which when numerous may cause a lobular deformity of the spleen.

Splenic infarction is often entirely latent. Of the symptoms attributed to it chills and elevation of temperature belong usually to the accompanying acute or chronic endocarditis. Swelling of the spleen, which pertains to chronic passive congestion, is produced also by infarcts. The most diagnostic value attaches to the sudden appearance of pain in the region of the spleen, perhaps increased by lying on the left side, by deep inspiration, and by pressure; and to a perisplenitic friction rub, which can sometimes be detected. These symptoms are not very certain diagnostic points; but when they occur with some manifest source for a splenic embolus, and perhaps with recognised embolism in other organs, they justify a strong suspicion of splenic infarction.

Renal Infarction.—There have been a few instances, especially after traumatism, of nearly total necrosis of a kidney from thrombosis of the renal artery, combined usually with thrombosis of the vein. Usually plugging of the main artery leads to multiple infarction with intervening intact areas. The capsular arteries suffice for the preservation of at least a narrow outer rim of renal tissue.

Renal infarcts are nearly always anæmic, in the recent state somewhat swollen, and of an opaque pale yellowish colour, with the base of the wedge just beneath the capsule and the apex toward the hilum, most frequently near the boundary between the pyramid and cortex. Three zones can often be distinguished:—the main central yellowish white mass of necrotic tissue; next to this a narrow yellow zone of fatty cells, nuclear fragments, and disintegrating leucocytes; and an outer, irregular, variable rim of hyperæmia and hæmorrhage which belongs partly to the infarct and partly to the surrounding tissue. The hæmorrhage may extend a variable distance into the infarct, and in very rare instances genuine hæmorrhagic infarcts occur in the kidney. Numerous scars from old infarcts may produce a form of atrophic kidney to which the epithet embolic is applicable. Thorel finds that a limited regeneration of the epithelium and even of uriniferous tubules may occur in healing renal infarcts.

Very large infarcts may so stretch the renal capsule as to induce severe pain. In a case diagnosed by Traube an infarct two inches in diameter, projecting well above the surface, caused intense pain and tenderness in the region of the infarcted kidney, with extension of the pain into the corresponding thigh. With the ordinary small infarcts pain is not usually a prominent symptom. The chief sign of diagnostic value is the sudden appearance of blood in the urine in association with disease of the left heart, aortic aneurysm, or other recognised source for a renal embolus. The amount of blood is usually only moderate or evident by microscopical examination of the urine. It is to be remembered that chronic passive congestion of the kidney is itself one of the many causes of hæmaturia.

Infective emboli, which are often capillary in size, cause multiple, often miliary abscesses in the kidney. This is the hæmatogenous variety of acute suppurative nephritis which occurs often in acute infective endocarditis and other forms of pyæmia. Here the pyuria and other renal symptoms are usually of less consequence than those of general infection.

Embolism and Thrombosis of the Mesenteric and Intestinal Arteries.— Thrombosis of the mesenteric veins, which causes lesions and symptoms identical with those following embolism of the mesenteric arteries, has been considered in the preceding article (p. 178). Since Virchow's first description of embolism of the superior mesenteric artery, in 1847, at least seventy cases have been reported of embolism or thrombosis of the mesenteric arteries. The affection, although not common, occurs often enough and is of such gravity as to be of considerable clinical interest. In Watson's collection of cases there are eight which occurred within a single year in Boston. The casuistic literature upon the subject is fairly extensive. The articles of Litten and of Faber contain reports of most of the cases published up to 1875. The principal clinical features were carefully studied by Gerhardt and by Kussmaul in 1863-64. The papers of Watson and of Elliot in 1894-95 refer to about fifty reported cases, of which they have analysed those with satisfactory clinical histories with special reference to surgical treatment. The effects of occlusion of the mesenteric arteries have been experimentally studied by Beckmann, Cohn, Litten, Faber, Welch and Mall, and Tangl and Harley.

The principal conclusions drawn by Mall and myself from our experiments have been stated already in the discussion of the collateral circulation, and of hæmorrhagic infarction following embolism (pp. 205 and 212). It may here be repeated that, according to our experiments, the blood which produces the hæmorrhagic infarction enters by the anastomosing arteries and not by reflux from the veins; that the hæmorrhage cannot be explained by any demonstrable change in the vascular walls, but is the result of retardation and stasis of the circulation and clumping of red corpuscles in the veins and

capillaries, attributable in large part in cases of arterial obstruction to reduction or loss of lateral pulsation of the blood-current; that the ischæmia is increased by the tonic contraction of the intestinal muscle which follows for two or three hours' closure of the superior mesenteric artery; and that the sudden and complete shutting off of the direct arterial supply to a loop of intestine 5 to 10 ctm. in length is followed by hæmorrhage and necrosis of the loop, even when the vessels at each end of the loop are open. These results we obtained by experimentation upon dogs, but there is no reason to suppose that they do not apply to human beings. With the exception of Cohn, the other experimenters explain the infarction by regurgitant flow from the veins and alterations in the vascular walls.

The majority of the cases of hæmorrhagic infarction of the intestine have been due to embolism of the mesenteric arteries, the source of the embolus being usually the left heart, sometimes an atheromatous aorta or aortic aneurysm, and in one instance a thrombus in the pulmonary veins caused by gangrene of the lungs (Virchow). Several cases have been caused by autochthonous thrombosis resulting from arterio-sclerosis, aneurysm, pressure, or the extension of a thrombus from the adjacent aorta. It is probable that a certain number of the cases reported as embolic were referable to primary thrombosis of the mesenteric arteries, as no source for an embolus could be discovered, and the plugs in some of these instances were fresh adherent thrombi. As has been shown in the preceding article, primary thrombi may form in arteries which are free from atheroma or other chronic disease.[5]

In the great majority of the cases the obstruction was in the superior mesenteric artery. The few scattered instances of embolism or thrombosis of the inferior mesenteric artery indicate that this also may, very rarely, cause incomplete hæmorrhagic infarction of the corresponding part of the intestine, but that the collateral circulation here is better, and the lesions likely to consist only in small hæmorrhages in the intestinal mucosa. The inferior mesenteric artery may be obliterated without any manifest disturbance in the structure or function of the part of the intestine supplied by it.

The obstruction may be situated in the main stem or in any of the branches of the superior mesenteric artery. Intestinal infarction has been associated

[5] Litten has reported two cases of hæmorrhagic infarction of the intestine from thrombosis caused by what he calls "latticed endarteritis" (gitterförmige Endarteriitis) of the mesenteric arteries. So far as I can learn he has not furnished the fuller description which he promised in his article of nine years ago. Without such description there is room for the suspicion that Litten has mistaken the latticework markings sometimes seen after detachment of an adherent thrombus for a special form of endarteritis. It does not appear from his article that he has observed this "latticed endarteritis" except after removing adhertn thrombi.

with embolism of the larger branches oftener than with that of the main stem. As the anastomoses through the arterial arches are so free, obstruction of single small branches is without mechanical effects. There have, however, been several instances of intestinal infarction caused by multiple emboli or extensive thrombosis of small branches of the superior mesenteric artery.

Intestinal infarction is not the imperative result of occlusion of the superior mesenteric artery, as infarction is of occlusion of branches of the splenic and renal arteries, and of the basal cerebral. Both the trunk and the principal branches of this artery may be gradually closed without serious effects. Tiedemann and Virchow have found the superior mesenteric artery completely obliterated by old, firm thrombi or connective tissue without any lesions in the jejunum or ileum. The most remarkable case is that of Chiene, who found in a woman sixty-five years old, with aneurysm of the abdominal aorta, complete obliteration of the cœliac axis and both mesenteric arteries, with an adequate collateral circulation through the greatly distended extra-peritoneal anastomosing arteries. In a number of instances plugging of large branches of the superior mesenteric artery has caused no more than hyperæmia and superficial ecchymoses, without genuine infarction of the intestine.

The rapid and complete closure of the superior mesenteric artery, however, is followed with great regularity, probably constantly, by hæmorrhagic infarction of the intestine. There have been several instances in which embolism or thrombosis of the trunk of this artery has caused hæmorrhagic infarction extending from the lower part of the duodenum into the transverse colon (Oppolzer, Pieper, Faber, Kaufmann), as in the experimental cases. More frequently the infarction is in the lower part of the jejunum and the ileum, corresponding to the occlusion of a principal branch or of several branches supplying this region. The infarction corresponds in general to the area of distribution of the plugged arteries, but it may occupy only a part of this area. In several instances a single small loop or several loops with intervening normal intestine have been infarcted.

As already intimated, the infarction may be complete or only partial. When completely infarcted, the wall of the affected intestine is thickened, œdematous, of a dark red colour from infiltration with blood and covered with lustreless peritoneum. The margins of the infarct are often sharply marked but may pass gradually into the normal bowel. The mucous membrane is necrotic, often defective, and may be coated with a diphtheritic exudate. In a few instances the intestine has been gangrenous over considerable areas, without typical hæmorrhagic infarction, or with the hæmorrhagic appearance adjacent to the gangrene. The lumen of the intestine contains black tarry blood. There is bloody fluid in the peritoneal cavity, and usually

a fibrinous, sometimes a fibrino-purulent exudate on the peritoneum covering the infarction; and there may be general peritonitis. The mesentery is succulent and hæmorrhagic, usually in patches, exceptionally in the form of large flat masses of extravasated blood. Areas of fat-necrosis may be present in the mesentery. The mesenteric veins are distended and the mesenteric glands often swollen and hæmorrhagic. Various intestinal bacteria, most commonly the colon bacillus, may make their way into the peritoneal cavity through the necrotic wall. Flexner and I have reported an instance of hæmorrhagic infarction of the jejunum in which evidences of pneumo-peritonitis, supposed to be due to perforation, existed during life. At the autopsy, made six hours after death, a large amount of gas was found in the peritoneal cavity without perforation. *B. aerogenes capsulatus* was present in large numbers in the peritoneal exudate. This case demonstrates the generation of gas in the closed peritoneal cavity. In the intestinal mucosa were gas-blebs which were observed also in one of Faber's cases and in Jürgen's case of intestinal infarction.

The hæmorrhagic infarction is by no means always so completely formed as that just described. There may be no hæmorrhages in the mesentery. The extravasation of blood may be limited to the mucosa, or even to the submucosa, as in one of Ponfick's cases. In an instance of nearly complete thrombosis of the trunk of the superior mesenteric artery, reported by Councilman, there were paralysis, great distension and ecchymoses of the small intestine, but no infarction. Between mere venous hyperæmia with scattered, superficial hæmorrhages, and complete necrosis and infarction, there are all gradations, the controlling factors being doubtless the rapidity and extent of the arterial occlusion and the vigour of the general circulation.

There have been two or three instances in which the anatomical picture of hæmorrhagic infarction of the intestine has been present without discovery of any obstruction in the corresponding arteries or veins. Lycett reports an observation of hæmorrhagic infarction of the small intestine in an infant one month old without discoverable cause.

Hæmorrhagic infarction of the bowel may be insidious in its onset and course; and, in patients profoundly prostrated or with cerebral symptoms, it may occur without the attention of the physician being drawn to any abdominal trouble. Usually, however, the onset is abrupt, and grave intestinal symptoms are present. In the majority of cases, severe colicky pain and abdominal tenderness, either without distinct localisation or most marked near the umbilicus, are prominent and usually the first symptoms. The pain at the beginning is perhaps attributable to the violent, tonic spasm of the intestine which follows sudden occlusion of the superior mesenteric artery. After a few hours this spasm gives place to complete paralysis of

the affected part of the bowel, and then the pain may be referable to peritonitis. The local anæmia, hæmorrhage, and necrosis seem, however, quite sufficient to account for the pain. Vomiting, which often becomes bloody and occasionally fæcal, is also usually an early and persistent symptom. By far the most characteristic symptom, which is present in the majority of cases but not in all, is the passage of tarry blood in the stools, which are frequently diarrhœal, and sometimes have the odour of carrion. In nearly all cases there is hæmorrhage into the bowel, but the blood is not always voided. Symptoms of intestinal obstruction—tympanitic distention of the abdomen, fæcal vomiting and obstipation—are in some cases prominent, and readily explained by the complete paralysis of the infarcted bowel. The subnormal temperature, pallor, cold sweats and collapse, which appear in most cases, are explicable in part by the intestinal hæmorrhage, and in part by the shock of the destructive lesion. The sensation of a palpable tumour, referable to a collection of blood in the mesentery or to the infarcted bowel, has been noted in only three or four cases.

The chief emphasis for purposes of diagnosis is to be laid upon the occurrence of intestinal hæmorrhage, not explicable by independent disease of the intestine or by portal obstruction, in combination with other symptoms mentioned, and with the recognition of some source for an embolus, perhaps of embolic manifestations elsewhere. In the majority of cases the diagnosis has been intestinal obstruction, or acute peritonitis. The symptoms closely resemble those of intussusception, in which hæmorrhage from the bowel, although generally less abundant than with embolism of the superior mesenteric artery, is common. Fortunately the distinction of hæmorrhagic infarction from intestinal obstruction is not of much practical importance; for if the symptoms and condition of the patient warrent it, an exploratory laparotomy is indicated in both conditions. Elliot, by the successful resection of four feet of infarcted intestine, has brought hæmorrhagic infarction of the intestine into the surgeon's domain.

The prognosis is grave; and with complete infarction and necrosis of the intestine it is almost necessarily fatal, unless surgical relief be available. Watson estimates that in about one-sixth of the cases the location and extent of the infarction are suitable for resection of the bowel. It is impossible to say at present to what extent the prognosis of hæmorrhagic infarction of the intestine is favourably modified by the new possibilities of surgical interference. Gordon has successfully resected two feet of infarcted intestine. This and Elliot's case are the only two in which this operation has been performed; so far as I am aware.

When the infarction is incomplete, and is limited chiefly to the inner coats of the intestine, recovery may doubtless take place. Cohn, Moos,

Lereboullet, and Finlayson have reported instances of recovery after symptoms indicative of hæmorrhagic infarction. Packard attributed cicatrical areas found in the mesentery of an old man dead of rupture of the ascending aorta to healed infarction; but no previous history was obtained, and Packard's interpretation does not seem to me to be free from doubt. Death may occur within 20 to 48 hours after the onset, or the duration may be protracted over several days. Karcher has reported the survival of a patient with mitral stenosis for two months after the complete occlusion of the superior mesenteric artery by an embolus, the symptoms being sufficiently characteristic to have permitted a probable diagnosis during life.

Intestinal ulcers due to embolism or thrombosis constitute a distinct class, which has been studied especially by Ponfick, Parenski, and Nothnagel. Parenski relates an instance of operation for intestinal stricture, which at the autopsy was found to be caused by cicatrisation of an ulcer due to embolism of a branch of the superior mesenteric artery. Much more common are ulcers caused by infective emboli lodging in the small arteries and capillaries in the intestinal wall; they are observed especially in acute ulcerative endocarditis and pyæmia. These emboli cause hæmorrhages, necroses, and miliary abscesses with resulting ulceration. The ulcers are usually multiple, sometimes numerous, and situated in the small intestine and cæcum. The intestinal ulcers occasionally associated with degenerative multiple neuritis are referred by Minkowski and Lorenz to thrombosis caused by disease of the small arteries, which has been repeatedly observed in this form of neuritis.

Embolism and Thrombosis of the Thoracic Aorta.—Unless there be some abnormal narrowing or obstruction of the aorta, it is hardly possible for an embolus to lodge in this vessel, except at the ostium or the bifurcation. An exception to this rule may result from the detachment of a large aneurysmal clot, which, as in three cases of abdominal aneurysm reported by Bristowe, may block the aorta at or just below the mouth of the aneurysm.

I know of but three instances of embolism of the mouth of the aorta—two reported by Cohn with instantaneous death, and one by Reid in which the patient lived an hour and a half after the first symptoms of partial obstruction.

In a very few instances the lumen of an atheromatous thoracic aorta has been seriously encroached upon, or even obliterated, by thrombotic masses. Such cases have been reported by Trost, Tewat, Carville, Armet, Chvostek, Jaurand, and Pitt. The thrombus may occupy the ascending, the transverse, or the descending aorta, and may occlude the mouths of the left carotid and subclavian arteries. If there remain a sufficient channel for the blood, as in Pitt's case, there is no resulting circulatory disturbance;

otherwise there may be paralysis, œdema, gangrene of the lower extremities, and, if the left subclavian is obliterated, of the corresponding upper extremity.

Bochdalek and Lüttich have each described an instance of occlusion of the aorta in infants by the extension of an obliterating thrombus from a dilated ductus Botalli. Far more frequent is stenosis or atresia of the aorta at or near the attachment of this duct, due usually to persistence of the isthmus aortæ, as was first shown by Rokitansky. Of this latter condition about 100 instances have been recorded.

Embolism and Thrombosis of the Abdominal Aorta.—Graham in 1814 referred to a museum specimen in Glasgow, which had belonged to Allan Burns, of occlusion of the abdominal aorta just above the bifurcation by old laminated coagulum extending into the iliacs. I have found fifty-nine subsequent reports of occlusion of the abdominal aorta by embolism or thrombosis, and have seen references (which I have not consulted) to six or seven other cases.[6] I have not included in this list the detachment of clots from abdominal aneurysms, although Bristowe's three cases demonstrate that this may occasion the same symptoms. The monographs and articles of Meynard, Cammareri, Selter, Roussel, Charrier and Apert, and Heiligenthal contain references to or reports of forty-seven cases; to these I have added twelve published cases not mentioned by them. The references are at the end of this article.

Three of the patients were living at the time of the reports, and in two fatal cases there was no autopsy. In the remaining fifty-four the plug occupied the lower end of the aorta and extended a variable distance into the arteries below. In thirty-one the plug did not reach higher than the inferior mesenteric artery; in ten the upper extremity lay between the inferior mesenteric and the renals; in three between the renals and the superior mesenteric; in two between the latter and the cœliac axis; in one just below the pillars of the diaphragm, and in seven the length of the plug is not stated. The upper part was often conical; so that, when the plug extended higher than the inferior mesenteric, it was often not obliterating until at or below this artery. In the great majority of cases only the last, or the last two, lumbar arteries were blocked by the thrombus. In several instances a thrombus, either independent or continuous with that in the aorta, occupied the lumbar, the mesenteric, the renal, or other branches of the aorta. In all instances the thrombus extended into the common

[6] I have not included von Weismayr's case (Wiener med. Presse, 1894, p. 1774), as it was reported while the patient was living, and in the discussion some doubt was expressed as to the diagnosis; nor the brief mention made by Teleky, at the same time, of similar observation.

iliacs, and in many into arteries lower down, sometimes even as far as the posterior tibial, the end being usually lower on one side than on the other.

It is difficult, indeed impossible, from the published descriptions, which are only too often incomplete and unsatisfactory, to determine accurately how many of the cases were referable to embolism and how many to thrombosis. Essentially similar cases have been interpreted differently in this respect by different observers. The plug was usually adherent, and only in relatively few cases were its anatomical characters such (or at least so described) as to indicate positively its nature as embolus or primary thrombus. The majority of cases with sudden or rapid invasion of characteristic symptoms were associated with cardiac disease, or disease of the upper part of the aorta; and would, therefore, naturally be interpreted as embolic. Still in many of these no satisfactory source for a large embolus was demonstrated. Some cases not less abrupt in onset were without any affection of the heart or of the aorta above the plug. The sudden appearance of symptoms of obstruction of the aorta, although strongly indicative of embolism, are not decisive upon this point. Barth, in 1848, described a case of obstruction of the aorta by a cylindrical thrombus extending from the superior mesenteric artery to the bifurcation, and leaving only a narrow channel for the circulation of the blood. There were no circulatory disturbances. If this narrow channel had been suddenly closed at one point, as might readily happen, the symptoms would probably have been those of embolism. It is evident that aortic thromboses secondary to only partly obliterative emboli riding the bifurcation of the aorta, or to emboli or thrombi in the iliacs or lower arteries, may occasion symptoms like those of primary thrombosis of the aorta. There are several instances of such secondary thrombosis of the aorta in my collection of cases.

Without much confidence in the accuracy of the classification in several instances, I have divided the fifty-nine cases into forty-five referable to embolism of the aorta at the bifurcation, and fourteen due to thrombosis; of the latter, seven were primary, six secondary to embolism of the iliacs, or possibly the femoral, and one to thrombosis of the arteries of the extremities. The source of the aortic embolus is believed to have been the heart in thirty-five cases; aneurysm of the ascending aorta in one; pressure of a tumour on the aorta in two; atheroma of the thoracic aorta in one; in six it was undetermined. The heart was found to be normal at the autopsy in eleven of the fifty-three cases; and in seven both the heart and the aorta above the plug were normal.

Mitral stenosis existed in twenty cases (two of these being caused by thrombi extending from the left auricle into the ventricle), acute mitral

endocarditis in three, mitral endocarditis, not further defined, in four-mitral insufficiency without stenosis in one, thrombus in the left auricle without valvular disease in one, thrombi in the left ventricle, mostly without valvular disease, in eight, and large aortic vegetations in one.

The most interesting point in the etiology of plugging of the abdominal aorta, so far as it is permissible to draw conclusions from so few instances, is that nearly thirty-four per cent of the cases were associated with mitral stenosis. In many of these the stenosis was extreme. The question at once arises of the source of the embolus in these cases for it cannot be supposed that an embolus large enough to occlude the lower end of the aorta could pass through the contracted mitral orifice. Some of the cases may be explained by a smaller embolus caught at the aortic bifurcation, or in an artery lower down, with secondary thrombosis of the aorta; but the sudden onset of motor and sensory paraplegia and of cessation of pulsation in both femoral arteries in a large number of cases seems to demand abrupt stoppage of the circulation through both common iliacs. A few observers who have realised the difficulty here presented have assumed that a large thrombus had formed in the left ventricle and been detached without any trace behind; for only in two or three of the cases with mitral stenosis was there any evidence of a thrombus in the left ventricle or the aorta above the plug. This explanation must be regarded as purely hypothetical. The coexistence in a number of these cases of infarctions of the spleen, kidney, or brain has seemed to some writers strong evidence in favour of the embolic nature of the aortic plug. It is possible that the explanation even of the cases with acute bilateral symptoms referable to aortic obstruction and associated with marked mitral stenosis may be the lodgment of a small embolus followed by thrombosis of the aorta. Although in the classification above given I have placed nearly all the cases with mitral stenosis under embolism, I am nevertheless not disinclined in spite of the rapid onset of the symptoms, and frequently coexistent infarctions, to interpret many of them as primary thromboses of the aorta. The circulatory conditions with extreme, uncompensated mitral stenosis seem favourable to the occurrence of arterial thrombosis; and, if this view be accepted for the plugging of the abdominal aorta, the question arises whether thrombi frequently present in smaller arteries in association with this form of valvular disease may not oftener be primary than is generally supposed.

In a few cases congenital narrowing of the aorta was noted. In three instances plugging of the abdominal aorta was associated with embolism or thrombosis of arteries of an upper extremity. Coincident thrombosis of the vena cava, iliac, or femoral veins was observed in a few cases. In Jürgens' patient there was hæmorrhagic infarction of the intestine. In

several instances hæmorrhages were found at autopsy in the mucous membranes of the bladder and uterus. Herter, in his experiments in my laboratory with ligation of the abdominal aorta in rabbits, found hæmorrhagic infarction of the uterus to be so common a result of this operation that, when it was desired to keep the animals alive for any length of time, we abandoned the use of female rabbits for Stenson's experiment. It does not appear, however, that in human beings hæmorrhage of the uterus is a common sequel of occlusion of the abdominal aorta.[7] It is probable that if search were made in suitable cases in human beings who have died of aortic thrombosis or embolism, the interesting muscular changes described by Herter in the experimental cases would be found; as similar changes had been previously discovered by Litten in an instance of occlusion of the right iliac and femoral arteries. The most important of these muscular alterations are vacuolisation, proliferation of the sarcolemma nuclei, atrophy, and fatty and pseudo-waxy degenerations.

Plugging of the abdominal aorta has occurred most frequently in the course of chronic cardiac or arterial disease; but in some instances it took place during or after an acute infective disease, as acute articular rheumatism, puerperal fever, erysipelas, during convalescence from enteric fever (Forgues), and after pneumonia (Leyden).

Of the fifty-nine cases thirty were females, twenty-seven males, and in two the sex is not stated. Seventeen were between twenty and thirty years of age, twelve between thirty and forty, eight between forty and fifty, thirteen between fifty and sixty, one was nineteen, one sixty-one, and the ages of seven are not given.[8] Marked atheromatous changes in the arteries were noted in fourteen cases. Occlusion of the abdominal aorta by embolism or thrombosis, therefore, is not especially a senile affection.

When one considers the manifold conditions under which the abdominal aorta may become partly or completely plugged by embolism or by primary or secondary thrombosis, it is evident that there can be no general uniformity of symptoms. The plug may be so situated as to interfere with the circulation in one leg more than in the other. Diversities arise from variations in the collateral circulation in different cases. Still the majority of patients

[7] It may here be mentioned that Herxheimer, Popoff, and Chiari have each described an instance of hæmorrhagic infarction of the uterus after extensive bilateral plugging of the vessels supplying this organ.

[8] In Lüttich's case already mentioned (p. 243) of the thrombosis of the aorta in an infant fourteen days old, a thrombus beginning 4 cm. below the insertion of the ductus Botalli extended into the iliac arteries. Charrier and Apert include in their collection of reports of thrombosis of the abdominal aorta two cases from Alibert's thesis of 1828, one three, and the other three and a half years old, with gangrene of one leg. I have not counted these three cases in my list.

have presented a well-characterised group of symptoms. In the larger number of cases the onset has been acute, in the minority insidious and gradual. The symptoms have often appeared simultaneously in both legs, but there may be a short or a long interval between the invasion of one and that of the other leg. In the more acute cases the leading symptoms are pain in the legs,—sometimes in the loins and abdomen, sudden or rapidly manifested paraplegia, anæsthesia of the legs, absence of femoral pulsation, and phenomena of mortification extending from the feet upward. In several instances the patients, while walking, have been seized with excruciating pain in the legs, and have fallen paralysed to the ground. The pain is often atrocious and more or less paroxysmal. There may be tenderness on pressure over the occluded aorta. In a few cases pain has not been a prominent symptom.

Although the paraplegia has been repeatedly described as instantaneous in its appearance, it is to be inferred from the histories of carefully observed patients that at least a short interval of time and sometimes several hours and even days elapse before it is complete. In forty-four cases in which there are definite statements about the motor power, there was complete or nearly complete paraplegia in twenty-four; incomplete paralysis of both lower extremities, described in some instances merely as weakness, in ten; paralysis of only one leg in five, and no paralysis in five. The paralysis seems to be usually of the flaccid variety, but in some cases the paralysed muscles are stiff. In Barié's patient the paralysed legs were completely rigid, and it may be inferred that a condition analogous to rigor mortis had set in. With complete paralysis the reflexes and electrical excitability are abolished. Paralysis of the bladder and rectum, with retention of urine and involuntary evacuations, was observed in several cases, but not in the majority.

Of the cases with satisfactory histories in only two was there no disturbance of sensation. In some there was only numbness or some reduction of sensation; but in most there was definite anæsthesia, extending in some instances no higher than the knee,—more frequently to the middle or upper third of the thigh, and in two cases as high as Poupart's ligament. There was sometimes complete analgesia, which, however, did not exclude sensations of spontaneous pain in the legs. In many cases, however, there was hyperalgesia, either in the anæsthetic area or above it.

The symptom of greatest diagnostic value is absence of pulsation in the arteries of the lower extremities. In three or four instances it was determined that the abdominal aorta below the naval was pulseless. Wilbur observed excessive aortic pulsation above the obstruction. The legs become cold, and their surface temperature may even fall below that of the room (Browne, Mauz). Absence of bleeding upon incision and of reactive hyper-

æmia after application of heat have been noted. The skin, at first pale, soon acquires a livid mottling, and the superficial veins may be dilated. Œdema of one or both legs and cutaneous hæmorrhages are recorded in some of the histories. If the patient lives long enough gangrene usually ensues, and it may be manifest within twenty-seven to forty-eight hours. Gangrene was bilateral in at least twenty-four cases, and unilateral in seventeen. The extent of the gangrene varied greatly in different cases, being sometimes limited to the foot, sometimes reaching the middle of the thigh, and, in Bell's patient, involving the scrotum. Tympanites, diarrhœa, and albuminuria are common. Exceptional symptoms are the appearance of blood in the urine or stools, hæmatemesis, and priapism. Bedsores appeared in many cases, and may appear within a few days from the onset.

Death may occur within twenty-four hours from the beginning of the attack. Fourteen patients died within the first four days, with collapse and rapid, weak, usually irregular pulse. There may be marked improvement in the initial symptoms either in one or in both legs. The larger number of patients die after a variable interval, which may extend over several weeks or even months, from gangrene, decubitus, and sepsis.

Of the deviations from the type may be especially mentioned incomplete manifestation of symptoms on one or both sides, transitory affection of one leg, limitation of the symptoms to one lower extremity only (four cases), and affection of one leg followed after days, weeks, or months by that of the other (six cases). The two cases reported by Barth and by Jean are considered particularly characteristic of slowly forming thrombosis. Here the first symptoms were chiefly numbness and intermittent claudication, which, after a long interval, deepened into paraplegia without gangrene.

All but three cases terminated fatally, more frequently from the remote effects than from the immediate shock of occlusion of the aorta. The three instances of survival with marked amelioration of all the symptoms are reported by Gull, Chvostek, and Nunez. These cases began acutely with severe pains, paraplegia, disturbances of sensation, coldness and lividity of the lower extremities. The femoral pulse disappeared completely in Gull's and in Nunez's cases, but in Chvostek's it could still be felt, although it was feeble. In Chvostek's patient patches of superficial gangrene appeared; but in the other two cases there was no gangrene. Nunez reports that after a year and a half there was no return of the femoral pulse on either side.

Since the demonstration by Schiffer and Weil, confirmed by Ehrlich and Brieger, Spronck, Herter, and others, that the paraplegia which follows immediately or very shortly after ligation of the abdominal aorta just below the renal arteries in rabbits (Stenson's experiment) is due to ischæmia of the lumbar cord, many have assumed that the same explanation applies to

the paraplegia in human beings after occlusion of the abdominal aorta. If the rabbit's aorta be tied for an hour, and the ligature be then removed, the paraplegia and paralysis of the bladder and rectum are permanent, the gray matter of the lumbar cord undergoes necrosis, and a genuine myelitis affecting chiefly the gray but also the white matter ensues. The same experiment gives negative results with the cat and usually with the dog. In view of the great interest of the subject, it is, to say the least, remarkable how few of the reports of autopsies on persons dead of embolism or thrombosis of the aorta have anything to say about the condition of the spinal cord. Roussel and Heiligenthal observed no macroscopic changes in the spinal cord. In Bell's and Barié and du Castel's cases the cord was microscopically normal, save congestion in the latter. Broca, Legroux, and Malbranc noted with the naked eye changes in colour, from which no definite conclusions can be drawn. The only detailed report of a microscopical examination of the cord is that of Helbing, who found, in the lumbar region of a man who lived thirty-nine days after embolism of the abdominal aorta, degeneration of the anterior and posterior nerve-roots, more marked on one side than the other; and the degenerations in the cord for the most part explicable by the changes in the nerve-roots. The lesions of the cord were quite unlike those found in experimental cases, and are interpreted by Helbing as essentially analogous to those after amputation, and not referable to ischæmia of the cord.

As the matter now stands, there are no direct observations to support the opinion that the paraplegia following embolism or thrombosis of the abdominal aorta in human beings is caused by ischæmia of the cord, so that the old explanation which refers it to ischæmia of the peripheral nerves and muscles has the most in its favor. The question of the possibility of this mode of production of the paraplegia, however, seems to me still open, and it is to be hoped that hereafter fatal cases of this rare condition will not be reported without satisfactory microscopical examination of the spinal cord. The anatomical investigations of Kadyi and of Williamson at least do not exclude the possibility that the lumbar cord in human beings is dependent to a considerable extent for its blood supply upon the lumbar arteries.

The diagnosis of ischæmic paraplegia from spinal paraplegia can generally be made without difficulty by the absence of femoral pulsation, by the coldness and lividity of the extremities, and by the occurrence of gangrene in the former.

Embolism of Arteries of the Extremities.—Of the arteries of the extremities the popliteal and the femoral are the most frequent recipients of emboli. The results of embolism of arteries supplying the extremities are essentially similar to those of arterial thrombosis, which have already been considered (p. 166). The modifications resulting from the sudden advent of embolism

are sufficiently self-evident. There may be severe pain at the moment of impaction and at the site of lodgment of the embolus. The general principles involved in the differentiation of embolism from thrombosis have been presented under Diagnosis (p. 221).

Hepatic Infarction.—As the effects of infective emboli in branches of the portal vein and of the hepatic artery have been considered elsewhere in this work (Allbutt's "System of Medicine," I, p. 601, and V, p. 123), only the possible mechanical effects of hepatic emboli require consideration here. Although the intrahepatic branches of the hepatic artery and of the portal vein are terminal vessels, their capillary communications are so abundant that, as a rule, embolism or thrombosis of the hepatic vessels causes no interference with the circulation in the liver. Experiments of Cohnheim and Litten and of Doyon and Dufourt have demonstrated that complete interruption of the circulation through the hepatic arteries of the rabbit and the dog is followed by necrosis of the liver. Chiari has observed an instance of necrosis of the entire liver caused by closure of the trunk of the hepatic artery beyond the origin of the pyloric branch.

In rare instances, and under circumstances at present not thoroughly understood, a condition somewhat resembling hæmorrhagic infarction may follow plugging, either by an embolus or a thrombus, of branches of the portal vein. Instances of this occurrence in human beings have been reported by Osler, Rattone, Klebs, Lubarsch, Köhler, Pitt, Zahn, and Chiari; the last-named having seen 17 cases, of which 15 were embolic. A somewhat similar condition was observed by Arnold after retrograde embolism of the hepatic vein. Pale wedge-shaped areas have been observed, but in most of the cases there were circumscribed dark red or reddish-brown wedge-shaped, rectangular or irregular areas.

Köhler and Chiari found that the red colour is due mainly to dilatation of the intralobular capillaries, with atrophy of the liver-cells. Genuine coagulative necrosis is not present. The affected areas are patches of circumscribed red atrophy rather than typical hæmorrhagic infarcts. Zahn observed the same condition in a human liver after plugging of portal branches, and reproduced it experimentally by emboli of sterilised mercury injected into mesenteric veins. In his experimental cases the change in the liver did not begin until the eighth day, and was distinct after thirty-five days. It is probable that the areas do not undergo cicatrisation.

Rattone's theory, based upon experiments, that occlusion of branches of both the hepatic artery and portal vein is essential for the production of infarction of the liver, is not supported by the observations in human beings. Klebs, whose two cases followed injury of the liver, as was true also of Lubarsch's observation, attributes the infarction to extensive capillary throm-

bosis. Köhler considers that the essential factor is combination of occlusion of branches of the portal vein with obstruction to the return flow from the hepatic veins. Chiari believes that the second factor, to be added to the plugging of portal branches, is feeble flow through the hepatic artery, from weakness of the general circulation. Wooldridge, by injecting coagulative tissue-extracts into the jugular vein of the dog, caused extensive clotting of blood in the portal vein and its branches, followed by numerous hæmorrhages and necroses in the liver; but the interpretation of these results as actual infarctions does not seem to me certain, inasmuch as these extracts in toxic doses produce a hæmorrhagic diathesis, and may cause necroses in various situations independently of thrombosis. The focal necroses so often met with in the liver in various infective and toxic states do not usually stand in any definite relation to closure of the vessels (Welch and Flexner).

Embolism of the Coronary Arteries of the Heart.—This is far less frequent than thrombosis, but Marie's position, that scarcely more than one or two of the reported cases of coronary embolism are free from all criticism, seems to be too extreme. Metastatic abscesses in the heart are not particularly rare manifestations of pyæmia. To what extent they are caused by coarse infective emboli, or by the lodgment of isolated bacteria, or small bacterial clumps, does not appear to be established. The heart ranks next to the kidney as the most frequent seat of abscesses following intravascular injection of the pyogenetic staphylococci in rabbits.

Virchow, Chiari, Rolleston, Hektoen, and others have published observations of bland embolism of the coronary arteries. I have observed an instance in which the embolic nature of the plug seemed to me conclusively established. A woman, 36 years old, who had presented symptoms of mitral insufficiency, died suddenly after a paroxysm of dyspnœa and precordial distress lasting two or three minutes. I found an entirely loose grayish plug, 4 mm. long, with a rough irregular extremity, completely occluding the descending branch of the left coronary artery near its origin. There was no atheroma at the site of lodgment of the embolus, although there were a few patches in other parts of the coronary arteries. The segments of the mitral valve were thickened, retracted, and beset with both old and fresh vegetations, and globular thrombi were present in the left auricular appendix. There were also fresh vegetations upon the aortic valve. There were infarcts in the spleen and kidneys. There were no fibroid patches or infarction in the myocardium.

The effects of embolism of the coronary arteries are like those of thrombosis, which have already been considered (p. 168).

Embolism and Thrombosis of the Retinal Vessels.—Plugging of the retinal vessels is of general pathological as well as special ophthalmological interest, for it is possible to observe with the ophthalmoscope the circulatory disturb-

ances in the retina. Ischæmia and stasis follow immediately closure of the central artery of the retina by an embolus. Vision is lost with characteristic suddenness. Both the arteries and the veins are narrowed, the latter being often unequally contracted. Subsequently the veins may dilate to some extent, especially in the periphery of the retina, and present ampulliform swellings. An interesting phenomenon is the appearance in the veins of an intermittent, sluggish stream of broken cylinders of red corpuscles, separated by clear spaces; and by pressure on the eye-ball a similarly interrupted current may often be made to flow through arteries and veins. This appearance of interrupted columns of blood is evidently similar to that observed by Mall and myself after closure of the superior mesenteric artery and previously described (p. 212). After a short time the optic papilla becomes pale and gray, and the retina, especially in the neighborhood of the papilla and macula, assumes an opaque, grayish white, œdematous aspect. Hœmorrhages are exceptional. A characteristic ophthalmoscopic appearance is the cherry-red spot in the centre of the macula, caused by the red colour of the choroid shining through. There may be more or less return of the circulation with improvement and even complete restoration of vision: but the prognosis as regards sight is in general unfavourable, as atrophy of the retina and of the optic nerve is likely to ensue. The prognosis is more favourable with embolism of branches of the retinal artery. Here multiple hæmorrhages usually occur.

Thrombosis of the central retinal vein is distinguished from plugging of the artery especially by the abundant hæmorrhages. With occlusion of the central artery the condition is anæmic infarction, and with plugging of the vein hæmorrhagic infarction.

There is some difference of opinion as to the relative frequency of embolism and of thrombosis of the central retinal artery. Of 129 cases collected by Fischer, ninety-one had heart disease; whereas Kern reports that of twelve cases in Haab's clinic only two had demonstrable cardiac disease; and of eighty-three cases, collected from the records, in 66 per cent there was no demonstrable source for an embolus. The latter author, therefore, regards the majority of plugs in the central artery of the retina as primay thrombi. The generally accepted opinion, however, is that embolism is more common than thrombosis of the retinal arteries.

Treatment.—In the preceding pages mention has been made of the surgical treatment of hæmorrhagic infarction of the intestine and of gangrene of the extremities; and under "Thrombosis" the importance of preventing so far as may be the separation of emboli has been emphasised. The general indications in the treatment of embolism are essentially similar to those already considered for thrombosis (p. 184).

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VENOUS THROMBOSIS IN CARDIAC DISEASE[1]

One of the most interesting points of view from which to consider the subject of thrombosis is that of its association with different diseases. The study of such association not only is of clinical interest, but is capable of contributing to our knowledge of the causation of thrombosis, which in many respects is still obscure. Infectious and chronic wasting diseases are those most frequently complicated or followed by vascular thrombosis of medical, as distinguished from surgical, interest; typhoid fever and influenza heading the list among the former, and tuberculosis and cancer among the latter. There are, however, a number of other diseases with which peripheral thrombosis may be associated more or less frequently, and to one of these less generally recognized associations I wish to call attention in this paper.

Although there are scattered reports of a number of instances of the occurrence of venous thrombosis in diseases of the heart, I cannot find that particular attention has been called to this complication either in text-books on these diseases or in special monographs. This is doubtless attributable mainly to the infrequency of the complication, perhaps also in part to a failure to recognize it. By far the largest number of cases have been reported by French physicians.

As will appear from the following reports of cases, there are certain peculiarities of the venous thrombosis of heart disease which render this suject well worthy of investigation. For the clinical histories of the cases from the Johns Hopkins Hospital I am indebted to my colleague, Dr. Osler.

Case I.—*Aortic and mitral insufficiency. Adherent pericardium. Broken compensation. Thrombosis of left innominate, jugular, subclavian, and axillary veins. Death.*—R. H., negress, aged seventeen years, admitted November 26, 1898, died January 16, 1899. Nothing of importance in family history or in personal history, until the occurrence, six years ago, of a severe attack of inflammatory rheumatism, with swelling and tenderness of most of the joints. Since then she has not been strong and has had at times rheumatic pains. In January, 1898, occurred a second attack of articular rheu-

[1] After its presentation before the Association of American Physicians, this paper was published also in the Festschrift in honor of Abraham Jacobi, M. D., LL. D., New York, 1900. I have added to the article in its present form Case V, which has necessitated changes in the statistical figures.

Tr. Ass. Am. Physicians, Phila., 1900, XV, 441-469.

matism, since which she has suffered from shortness of breath on exertion, palpitation, pain in the region of the heart, and some cough. These symptoms became aggravated during the last two months.

Upon admission, patient, who is well nourished, is suffering from respiratory distress. No œdema of extremities. Pulse 112, somewhat irregular, with fair volume and tension. Respirations 40. Temperature 99.5° F. Large veins of neck full and pulsating. Marked bulging of præcordium, and heaving impulse over heart, especially distinct below and outside of left nipple. Marked pulsation in episternal notch. Point of maximum intensity in sixth left interspace, 12 cm. from midsternal line. Relative cardiac dulness begins above in left first intercostal space. Systolic thrill at apex, where on auscultation are heard intense musical systolic and rasping diastolic murmurs transmitted into axilla. In the aortic area both sounds are replaced by a loud to-and-fro murmur, the diastolic portion being especially rough. Second pulmonic sound intensely accentuated. Heart's action irregular and violent. Capillary pulse visible.

At apex of right lung, slight expansion, dulness, prolonged, almost tubular expiration. A few medium-sized moist râles at base of lungs. No tubercle bacilli in sputum.

Liver somewhat enlarged. Urine albuminous, with hyaline and granular casts. Blood count: red corpuscles, 4,524,000; leucocytes, 12,400; hæmoglobin, 65 per cent.

Patient improved somewhat after admission, but her general condition continued much the same. The pulse at times was very intermittent, and there was much tenderness over the præcordial area. The temperature varied from normal to 101° F.

January 14th. For the first time œdema of the left arm is noticed, most marked around the elbow-joint. The right arm is free from swelling. The face and legs are moderately œdematous. Complains of severe headache. Pulse 120, irregular and weak.

16th. Œdema of left arm, which is painful, has increased. Temperature 100.5° F. Pulse very intermittent. Death occurred rather suddenly at 6.30 p. m.

Autopsy by Dr. MacCallum, fourteen hours after death. Body of a girl, rather slenderly built, 162 cm. long. Moderate œdema of ankles and feet. Extensive œdema of left arm, especially about the elbow, the hand being but little swollen. No œdema of right arm and no definite swelling of face or neck.

About 200 c. c. clear yellowish fluid in peritoneal cavity. Surfaces smooth and glistening. Præcordial space greatly enlarged, measuring 16 cm. transversely and 10 cm. vertically. Firm adhesions between parietal pericardium and the pleura, diaphragm, and other surrounding tissues. Left pleural cavity contains over 300 c. c. slightly turbid, yellowish fluid, the left lung being much compressed by this and the enlarged heart. There are many easily torn pleural adhesions. The right pleural cavity contains a small amount of fluid and presents a few light adhesions.

The pericardial sac is obliterated by fibrous adhesions. The heart weighs 720 grammes, and gives the following measurements: right ventricle 8 cm. long, its wall 6 mm. thick; left ventricle 9½ cm. long, its wall 16 mm. thick;

tricuspid orifice 10½ cm., mitral 10 cm., aortic 7 cm. All of the cavities much dilated. Left auricle greatly dilated, reaching nearly to first rib. Tricuspid and pulmonic valves delicate. Mitral orifice very wide; valvular segments, particularly the posterior, thickness and retracted. Aortic valvular segments much thickened, stiff, and curled at their edges, so as to be markedly shortened. No fresh vegetations. Coronary arteries patent and free from sclerosis. The aorta shows yellow streaks of fatty degeneration of the intima, and a few small elevated patches of fresh sclerosis.

The left innominate vein, the left internal and external jugular veins, the left subclavian and axillary veins are occluded by a continuous fresh thrombus mass. The prevailing color of the thrombus is dark reddish. The part occupying the innominate just before the reception of the jugular vein and that filling the well-developed bulb of the internal jugular vein is gray or grayish-red, firmer and more adherent to the wall, therefore older, than the dark-red, softer clot in the distal portions. The thrombus in the jugulars stops somewhat below the level of the larynx. The brachial and other veins of the arm are free from the thrombus. The tissues around the thrombosed veins are œdematous, and freshly swollen lymphatic glands are present in their neighborhood. The corresponding veins of the right side are free from thrombus.

The lungs are dry, tough, and of a salmon-pink color, evidently the seat of chronic passive congestion. The bronchi contain blood-stained mucus. No areas of fresh consolidation. Pulmonic vessels free from thrombi.

The liver is moderately enlarged, and presents typical nutmeg mottling. Spleen also enlarged, firm, dark red, slightly adherent to surrounding tissues; Malpighian bodies distinct. Kidneys swollen, congested, the seat of chronic passive congestion. Gastric and intestinal mucosæ deeply congested, the solitary follicles swollen. No important changes in other organs.

Microscopical Examination.—The swollen lymph glands show marked proliferation of the endothelial cells. The heart muscle is slightly fatty, and shows scattered focal accumulations of small round cells, mainly of the lymphoid type. The kidneys show passive congestion and parenchymatous degenerations, without increase of the connective tissue. The lungs present the usual evidences of chronic passive congestion of moderate degree.

Sections of the thrombosed veins show that the grayish-red part of the thrombus is composed of platelets, fibrin, and leucocytes with entangled red corpuscles. A coral-like arrangement of the platelet masses is indicated, but is not very distinct. Leucocytes are fairly numerous. There are no evidences of organization. The intima and outer coats contain a few leucocytes, and the intima is somewhat swollen, but there are no signs of sclerosis or other chronic affection of the veins. The redder parts of the thrombus are richer in red corpuscles, but here also islands and bands of platelets and fibrillated fibrin are present. A few chains of streptococci are detected in sections stained by Gram's method.

Bacteriological Examination (Dr. Harris).—Plate cultures on agar made with all necessary precautions from the thrombi in the jugular veins showed a considerable number of small, grayish colonies, which were demonstrated to be of *Streptococcus pyogenes*. No other organism appeared in the cultures. *Streptococcus pyogenes* was cultivated also from the lungs. Cultures from

the heart's blood, œdematous tissue in left axilla, the spleen and other organs were sterile.

The principal points of interest in the preceding case are the following: A girl, seventeen years old, with chronic aortic and mitral endocarditis following acute articular rheumatism, and giving rise to insufficiency of both valves, with relative insufficiency of the tricuspid valve, suffered from the effects of broken compensation. During the last days of life painful œdema of the left arm made its appearance, without implication of the right arm. At the autopsy, in addition to the advanced cardiac lesions and their customary secondary effects, an infectious thrombus was found filling the innominate, subclavian, axillary, and lower parts of the jugular vein on the left side. The oldest part of the thrombus occupied the lower bulb of the internal jugular vein and the adjacent part of the innominate vein. The micro-organism concerned was *Streptococcus pyogenes,* which was present in the lungs and the thrombus, but was not found elsewhere.

The three following cases are also from Dr. Osler's service in the Johns Hopkins Hospital:

Case II.—*Mitral stenosis. Thrombosis of left jugular, axillary, subclavian, and innominate veins. Embolism of left popliteal artery. Recovery from effects of vascular occlusion.*—E. O., female, aged thirty-five years, admitted January 4, 1899. History of rheumatism in family. Diphtheria at ten, chorea at eleven years of age, accompanied by paralysis of the right side. Since these attacks patient has not been strong. No history of scarlet fever, pneumonia, nor typhoid fever. Obscure history of repeated attacks of "rheumatism" without definite articular symptoms. Patient has suffered for years from shortness of breath on exertion, indigestion, nervousness, and chronic invalidism. For three weeks before admission has been in bed with epigastric pain and digestive disturbances.

Upon admission patient is very nervous. The point of maximum intensity of cardiac impulse cannot be detected by palpation or inspection, but by the stethoscope is located in the fifth intercostal space, 10 cm. from median line. Area of cardiac dulness not much increased. Very distinct thrill can be felt at the apex, where is heard a rough, intense, presystolic murmur terminating in a short, sharp first sound. No second sound is heard at the apex. Over the body of the heart the valvular sounds are distinct and snapping. The second pulmonic sound is markedly accentuated. Pulse 144, small, irregular both in force and rhythm. Respiration 30. Temperature 99° F.

Medium-sized moist râles are heard behind, over the lower parts of both lungs, where there is also some impairment of resonance.

The absolute hepatic dulness extends from the seventh rib to a point 5½ cm. below the costal margin in the mammary line. The border of the liver can be distinctly felt. There is fairly distinct pulsation of the liver. The epigastric and right hypochondriac regions are somewhat tender to pressure.

There is slight œdema of both ankles. Urine, sp. gr. 1017, contains a small amount of albumin and hyaline and granular casts.

January 12th. The left ankle-joint is swollen, red, and tender.

19th. The left side of the neck is swollen, and painful upon pressure or movement. Temperature 100°. Pulse 124. Respiration 32.

20th. The fulness and tenderness of the left side of the neck have increased, and a sensitive, cord-like body can be felt in the course of the internal jugular vein in its lower part, indicative of thrombosis. The pain and swelling of the left ankle-joint have disappeared. There are evidences of partial consolidation of the right lung below and behind. Moist râles are heard also at the angle of the left scapula. Patient is flighty.

26th. To-day appeared an œdematous swelling of the left arm, extending to the hand. The left arm measures 2 cm. more than the right just above the wrist.

27th. The œdematous, painful swelling is now very marked, and occupies the whole of the left side of the neck, the pectoral region on the left side, the left shoulder, and the left arm to the hand. The œdema has a brawny, indurated character, but there is pitting on pressure. There is no marked difference in the superficial temperature of the two arms. The superficial veins of the arm and neck are distended. On account of the œdema the deeper veins cannot be distinctly palpated. Temperature 101°. Pulse 112. Respiration 40.

31st. The swelling of the left arm is less; that of the neck continues.

February 9th. A cord-like swelling of the left external jugular vein can be traced up to the angle of the jaw. The axillary vein is likewise thrombosed.

26th. The hard œdema of the left arm and neck has continued, at times lessening and then returning. There is œdema of both lower extremities.

March 16th. Pain in the left side and a marked pleuritic friction rub on auscultation.

Soon after this date the general condition of the patient improved, and the œdema of the arm and neck gradually disappeared through the establishment of a collateral circulation.

On November 24th embolism of the left popliteal artery occurred, characterized by loss of pulsation in left popliteal and tibial arteries, sudden pain, numbness, cyanosis, and coldness of the left foot and leg. The history of this embolic attack need not be given in detail. Suffice it to say that a collateral circulation was completely re-established. The patient is still in the hospital.

The diagnosis made by Dr. Osler in this case was mitral stenosis with thrombosis of the left innominate, left internal and external jugulars, left subclavian, and left axillary veins. The location, extent, and persistence of the hard, painful œdema, lasting for nearly three months, make probable the existence of thrombosis of the left innominate and subclavian veins, while that of the jugulars and axillary vein was definitely recognized. The history indicates that the thrombosis started in the lower part of the internal jugular vein. It is to be noted that the onset of the thrombosis was preceded for a few days by a red, painful swelling of the left ankle-joint, and was accompanied by evidences of acute pneumonia and by ele-

vation of temperature, also that during its course acute pleurisy appeared. There is, therefore, much probability in the supposition that the thrombus in this case, as in the preceding, was of infectious nature.

Case III.—*Mitral and aortic insufficiency; general anasarca; thrombosis of the left axillary and brachial veins. Death.*—H. M., aged sixteen years, admitted February 24, 1900; died March 8th. No history of infectious disease except pneumonia at seven years of age. Present illness began in August, 1899, with vomiting and indigestion. Says that he had rheumatism in September, but no definite history of affection of joints was obtained. Repeated attacks of gastric pain and vomiting during the autumn. In January, feet, legs, and abdomen became swollen, and he was confined to bed. The dropsy increased, and a week ago the face and hands began to swell. Continued shortness of breath; digestive disturbance continued.

Examination on Admission.—Patient is propped up in bed; respiration 32, somewhat labored, and irregular. Cyanosis of face and extremities; œdema of face, thorax, upper and lower extremities, penis, and scrotum; marked œdema of left forearm and hands; ascites. Pulse 124, regular in force and rhythm, fair volume, low tension, hyperdicrotic; pulsation of cervical veins.

Distinct præcordial bulging and general heaving in this region. Apex-beat in fifth interspace 11 cm. to left of median line; area of cardiac dulness increased, extending 1 cm. to right of sternum and upward to left second rib. At apex first sound replaced by loud systolic murmur heard far out in axilla; second sound faint. In aortic area both sounds enfeebled, the second sound being accompanied by a faint diastolic murmur traceable down along right border of sternum; second pulmonic sound distinctly accentuated.

Physical signs of a moderate amount of fluid in left pleural cavity are present, also some dulness and impairment of respiratory and vocal sounds on right side below and behind, with a few fine moist râles.

Absolute hepatic dulness begins at sixth rib and is continuous with the abdominal flatness due to ascites, which is marked.

The œdema of the left arm and hand is so much greater than that of the right arm that thrombosis was suspected. Upon palpation the left axillary and brachial veins can be distinctly felt as hard, swollen, somewhat sensitive, cord-like cylinders, which can be made to roll beneath the finger.

Blood Counts.—Red blood-corpuscles, 6,900,000; leucocytes, 14,600; hæmoglobin, 76 per cent; 86 per cent of the leucocytes are polymorphonuclear. Urine contains a small amount of albumin and some hyaline casts; specific gravity, 1027.

After admission the œdema of the left arm and hand continued to increase and reached an extreme degree, so that splits appeared in the corium. The superficial veins were distended. Temperature most of the time a little below normal, only occasionally rising to 99° and once to 100° F.

March 1st. Jaundice appeared. The next day a hemorrhagic eruption appeared over the abdomen. Cheyne-Stokes breathing set in, the sputum became tinged with blood, and death occurred March 8th. Unfortunately, permission could not be obtained for an autopsy.

In the preceding case of uncompensated mitral regurgitation the general dropsy was so great that only the excess of œdematous swelling of the left arm led to examination for venous thrombosis, of which positive evidences were found in the left brachial and axillary veins. Whether other veins were also implicated could not be determined, as no autopsy was permitted.

Case IV.—*Mitral insufficiency; thrombosis of left femoral vein; recovery from effects of thrombosis.*—M. H., male, aged seventy-eight years, admitted December 27, 1898; discharged January 10, 1899. Patient had been in hospital a year ago, suffering from abdominal pain and constipation. At this time mitral insufficiency was recognized. No history of rheumatism or of other infectious disease, except measles and smallpox in childhood. Has suffered of late years from pain in the abdomen, constipation, bronchitis, and increased frequency of urination.

Three days before admission was seized with pain on the inner side of left ankle and inside of upper part of thigh, soon followed by swelling of the left leg and about the ankle.

On admission a rough systolic murmur is heard at the apex, transmitted to the axilla, and heard also over the body of the heart. Systolic whiff over aortic and pulmonic areas. Point of maximum intensity of cardiac impulse in fifth intercostal space 11 cm. to left of median line. Veins of neck full and heaving, but without distinct pulsation. Superficial veins of nose and cheeks dilated; physical signs of emphysema and bronchitis. Pulse 96, regular; respirations 20. Radial and temporal arteries tortuous and sclerotic.

The left lower extremity œdematous from the groin to the foot, the swelling being most marked around the ankle. Superficial temperature of left leg somewhat higher than that of right; superficial veins dilated. An indurated, sensitive cord can be felt in the left Scarpa's triangle, running obliquely downward and inward. The deep lymphatic glands below Poupart's ligament on the left side are somewhat enlarged. The pulsation of the left femoral artery is less distinct than that of the right; slight œdema of the right leg.

Blood Count.—Red blood-corpuscles, 3,800,000; leucocytes, 5000; hæmoglobin, 40 per cent. Temperature remained about normal, occasionally rising in the evening to a little over 99° F. Urine: specific gravity, 1020; acid, faint traces of albumin; no casts.

The œdema of the left leg gradually lessened, and on January 10th patient was discharged at his request with only a little œdema of the extremities.

In the foregoing case there were no marked evidences of disturbed compensation of the mitral lesion, and there was arterial sclerosis. The relationship of the venous thrombosis to the cardiac lesion was not, therefore, so evident as in the three cases first reported, and probably this case does not properly belong in the same category.

For the notes of the following typical, unpublished case, occurring in the service of Dr. James B. Herrick, at the Cook County Hospital, Chicago, I am indebted to the kindness of Dr. H. Gideon Wells, who, when interne at the hospital, observed the patient:

Case V.—*Arterio-sclerosis; mitral and tricuspid insufficiency; fibrous myocarditis and fatty heart; general anasarca; chronic interstitial nephritis; thrombosis of left internal jugular, subclavian, axillary, and brachial veins. Death.*—J. C., negro, aged fifty-three years, admitted January 10, 1898; died July 24, 1898. History of an old syphilitic infection and of excessive use of alcohol. Patient stated that for three weeks preceding admission he had suffered from pain in the chest, cough, increasing difficulty in respiration, and swelling of the legs and ankles, later of the face, with increased frequency of urination.

Examination showed very marked general anasarca, with slight hydroperitoneum and extensive hydrothorax. The cardiac dulness extended 2 cm. to the right of the sternum, and 11 cm. to the left of the sternal border; the base reached to the level of the second costal cartilage. There was a mitral regurgitant murmur. The arteries were hard and tortuous; the pulse in the radial and carotid arteries almost imperceptible. Hepatic dulness extended a short distance below the costal margin; the spleen could not be palpated.

The patient remained in the hospital until his death, six and a half months after entrance. During this time he was generally bedridden and suffered from severe dyspnœa, occasional attacks of præcordial pain, and extensive, general anasarca. The urine was loaded with albumin and contained large numbers of casts. At times the amount of fluid in the pleural cavities was so large as to require paracentesis.

About a month before death it was noticed that the left arm was much more œdematous than the right, although there was more than a moderate amount of fluid in the latter. This condition was observed accidentally, being apparently of gradual development, and the patient experienced no pain referable to this trouble. The œdema remained little changed until the time of death, which was the outcome of a gradual cardiac exhaustion.

Autopsy (Dr. S. M. White).—Body well nourished. Œdema of all parts of the body, most marked in the left upper extremity, penis, and scrotum. Ulcer, size of a dime, covered by a gray, false membrane, on the left leg.

About four litres of bloody, serous fluid in the peritoneal cavity, the walls of which are thick, white, and fibrous. The left pleural cavity contains about one litre of clear serum, with flakes of fibrin; the right a somewhat smaller quantity. A few fibrous adhesions at apices. The pericardial sac contains about 100 c. c. of serous fluid; a few fibrous adhesions bind the left auricle to the aorta.

Lower lobe of the left lung carnified from pressure; general pulmonary œdema; hæmorrhagic infarction in right lobe. Healed tuberculous nodules in the apices and the peribronchial lymphatic glands.

Coronary arteries dilated and atheromatous. Right auricle reaches 4 cm. to the right of the median line. Right ventricle contains a large, adherent, grayish, ante-mortem thrombus. The tricuspid orifice much dilated. The cavity of left ventricle measures 8.5 cm. in length, its walls 1.5 to 2 cm. in thickness; that of the right ventricle 9.5 cm. in length, its walls 5 to 6 mm. in thickness. Aortic valves normal, save for a few yellowish thickenings at the bases. Mitral segments, thickened, retracted; the orifice wider than normal. Endocardium everywhere somewhat thickened. Papillary muscles mottled with yellowish dots and streaks. Myocardium firm, brownish-yel-

low, and contains many grayish-white fibrous areas and streaks. Arteries atheromatous, especially the aorta at its beginning and at the origin of the thoracic branches.

The left subclavian vein is filled with a mixed adherent thrombus, in places grayish, but predominately brownish-black, which occupies also the axillary and brachial veins to the middle of the arm. At the beginning of the left subclavian vein is a yellowish, raised, sclerotic area, about the size of a bean, to which the clot, which here seems to be channelled, is firmly adherent. There is also a thrombus of a brownish-yellow color in the lower end of the internal jugular vein, around which the lymphatic glands are somewhat enlarged and pigmented.

Spleen somewhat enlarged, dark-red, firm. Typical nutmeg liver. Kidneys are the seat of typical arterio-sclerotic nephritis, with adherent capsule, irregular surface, thinned cortex and obscure markings. Other organs and tissues normal.

Microscopical examination of the thrombus in the subclavian vein showed it to be composed of platelets, fibrin, and blood-corpuscles, with a considerable amount of connective tissue growing into it.

In the foregoing case the cardiac affection was associated with arterio-sclerosis and advanced chronic interstitial nephritis, the patient being fifty-three years of age. The excess of œdema of the left arm over that of the right attracted attention a month before death, but it was unattended by pain or other symptoms. The thrombus apparently started from a sclerotic patch in the left subclavian vein and was undergoing organization at the time of death.

Thrombosis of pulmonary vessels, which is not particularly uncommon in uncompensated cardiac disease, is of course not to be included in the same class as peripheral venous thrombosis. I have also excluded from consideration the venous thromboses complicating general arterio-sclerosis and chronic nephritis, even when associated with cardiac hypertrophy and dilatation, unless, as in Case V., the symptoms are clearly referable to cardiac disease. Our autopsy records contain five cases of thrombosis of the femoral and iliac veins complicating arterio-sclerosis and chronic nephritis accompanied by cardiac hypertrophy. In two of these there was atheroma of the aortic valves, with some insufficiency. There is one instance of thrombosis of the superior mesenteric veins associated with small kidneys and cardiac hypertrophy. A case of thrombosis of the iliac and femoral veins on both sides, associated with pulmonary emphysema and hypertrophy and dilatation of the right side of the heart, has also been omitted as not falling under the class considered in this article. For the same reason I have omitted a case in our records of thrombosis of the right femoral vein complicating cirrhosis of the liver with sclerosis, calcification, and insufficiency of the aortic valves, and also instances of thrombi in varicose veins in cases of heart disease.

The arterial thromboses complicating cardiac diseases are of much interest. Doubtless most of those in the systemic arteries are of embolic origin, but there is evidence that some, particularly in cases of extreme mitral stenosis, are autochthonous. This subject, to which I have given some attention in my article on "Thrombosis and Embolism" in Allbutt's "System of Medicine," does not fall within the scope of the present paper.

The only attempts, which I have been able to find, to collect from the records cases of peripheral venous thrombosis complicating diseases of the heart are those by Parmentier (1889),[2] by Hirschlaff (1893), and by Kahn (1896). Parmentier and Kahn each report a single case from Hanot's clinic, and refer to four others which they say are the only ones they can find in French literature. Hirschlaff adds to Parmentier's list two personal observations and the two cases of Robert (1880) and of Ormerod (1889). Peter, in 1873, in his "Lecons de clinique médicale," reports a case and devotes a part of one chapter to an interesting consideration of venous thrombosis in diseases of the heart without adding further observations. Huchard's article (1897), "Cachexie cardiaque et thromboses veineuses," and Helen Baldwin's report of a typical case (1897), the only one which I have met in American literature, deserve especial mention. Without pretence to completeness I have been able to collect reports of twenty-three cases to be added to the five observations already described. I have little doubt that a more diligent search would bring to light other reported cases. I shall present in chronological order abstracts of these twenty-three cases, of some of which the histories are very meagre.

Case VI.—Bouchut (1845). Woman with heart disease succumbed to obliteration of the deep and superficial veins of the left leg. No further details.

Case VII.—Bouchut (1845). Man with heart disease, in whom occurred obliteration of the superior vena cava, jugular, axillary, and deep arm veins. Engorged, painful, hard, venous cords could be felt in neck and arms. Cyanosis and œdema of face, neck, and arms. Innumerable varicose, agglomerated, large veins appeared in neck and over thorax. A satisfactory collateral circulation developed, and the man left the hospital free from cyanosis and œdema.

Case VIII.—Cohn (1860). Woman, sixty-one years old. Stenosis and insufficiency of aortic valves, some thickening of mitral segments, cardiac hypertrophy, and symptoms of non-compensation. For fourteen weeks œdema of left foot and leg, later also of right foot, but here less marked. At autopsy, adherent old thrombi in both iliac veins, extending on the left side half-way down the thigh, and into some of the larger tributaries of the femoral vein. [Cohn reports two other cases of thrombosis of veins of the

[2] The references will be found at the end of this article.

lower extremities with cardiac disease, but in these there was general arterial sclerosis and no pronounced valvular lesion.]

Case IX.—Jolly (1860). Woman with organic disease of the heart had phlegmasia alba dolens of both upper extremities. Death occurred from an ulcero-membranous affection of the intestine. No further details.

Case X.—Ramirez (1867). Boy, aged twelve years. Acute articular rheumatism one year before admission. Aortic and mitral insufficiency, general anasarca, dyspnœa, and other symptoms of extreme cardiac incompetence. Bloody expectoration. Thrombosis of jugular, axillary, and subclavian veins on the right side. The obliterated external jugular vein very evident. Painful œdema of right side of neck and right arm. Death in coma. No autopsy.

Case XI.—Ramirez (1867). Man, aged fifty years. For six months following intermittent fever, dyspnœa, general œdema. Incompletely compensated aortic and mitral insufficiency. Œdema of lower extremities almost disappeared, while that of face and upper extremities persisted. Dyspnœa increased. Painful, hard œdema of left arm and left side of neck appeared, and two large, hard, sensitive cords, formed by the obliterated jugular veins, could be felt.

Autopsy showed thickening and retraction of aortic valves, with relative mitral insufficiency. Great dilatation of all cardiac cavities. Blackish, firm thrombi in left internal and external jugular, subclavian, and axillary veins.

Case XII.—Duguet (1872). Patient, who formerly had acute articular rheumatism, was admitted for dyspnœa, cyanosis, palpitations, and œdema of lower extremities. Three days before death there appeared painful, hard œdema of left arm, and the axillary vein was felt as hard as a cord. Autopsy showed marked stenosis, with insufficiency of the mitral orifice, without fresh endocarditis, with cardiac hypertrophy and dilatation, hydrothorax and hydropericardium, pulmonary infarcts, and grayish-black, non-adherent thrombi filling the left subclavian, axillary, and brachial veins.

Case XIII.—Peter (1873). Woman with mitral insufficiency and obstruction, and with relative insufficiency of the tricuspid valve, suffered from œdema of lower extremities, ascites, dyspnœa, cyanosis, and great congestion of lungs and liver. For past ten days left arm œdematous throughout, with tenderness at certain points; later outer and lower part of neck became swollen and painful, first near the junction of jugular and subclavian veins. The obliterated subclavian [axillary?] and external jugular veins could be felt as hard, cylindrical cords. Venous pulse, formerly present in cervical veins of both sides, is now evident only on the right side. The left radial pulse is almost imperceptible from pressure of thrombosed veins on the arteries. At the end of three weeks collateral circulation was established and œdema of arm had disappeared. General condition otherwise unimproved.

Case XIV.—Robert (1880). Woman, age between thirty and forty years, suffered for eight years with cardiac symptoms following pneumonia, of late palpitation, dyspnœa, cyanosis, œdema of lower extremities and abdominal wall, moderate ascites, pulsation of veins of neck, bronchitis, and

pulmonary congestion. Mitral stenosis and relative tricuspid insufficiency diagnosed. For over a month before death patient had increasing œdema of left arm (right being free) and slight tumefaction of left side of face. Left internal jugular vein felt as hard cord; veins over left pectoral region became distended.

Autopsy.—Extreme mitral stenosis, with hypertrophy and dilatation of the right heart, double hydrothorax, pulmonary infarcts. Thrombosis of left innominate, subclavian, and both jugular veins. The left innominate was notably narrowed at confluence of jugular and subclavian veins, and here and in the lower end of the jugular was a firm, fibroid, adherent thrombus, evidently the oldest part of the clot. The thrombus elsewhere was in places centrally softened. The walls of the left subclavian vein were thickened. The clot in the jugular could be traced to the entrance of the linguo-facial trunk. Lymphatic glands in the neighborhood of the thrombosed veins are enlarged. Superior vena cava free.

Case XV.—Parmentier (from Hanot's clinic) (1889). Woman, aged forty years. For four years, following puerperal infection, cardiac symptoms; for last five months, palpitation, dyspnœa, cough, œdema of lower extremities; and for three weeks before admission painful œdema of left arm and corresponding mammary region; later, slight œdema of right arm. Upon admission: very rapid, irregular heart action; irregular, small, intermittent pulse; marked venous pulsation from systolic reflux, intense dyspnœa, pulmonary râles, and albuminuria. The left upper extremity is tumefied throughout its whole extent by a hard, tender œdema, which extends also to the left mammary region. Symptoms increased in gravity and death occurred four days after admission.

Autopsy.—Extreme mitral insufficiency and dilatation of all cavities of the heart, left hydrothorax, ascites, nutmeg liver. Left subclavian vein and small communicating veins completely obliterated by a reddish thrombus, grayish and most adherent in the middle of the vein, where it is evidently oldest, and where there is partial organization. Upon microscopical examination the coats of the veins were found thickened and the capillaries in the outer coats dilated. The jugular veins were free, and no thrombus was found in other veins of the extremities.

Case XVI.—Ormerod (1889). Patient was admitted for mitral stenosis. At autopsy was found complete obstruction by adherent clot of both innominate veins, internal jugulars, subclavians, anterior and external jugulars, the clot being firmer on right than left side. A projecting end of clot hung into superior cava, but was not adherent there, and ceased at the opening of the azygos. Left auricle and right cavities of heart much dilated. The symptoms of thrombosis, which developed in the hospital, pointed to its commencement in right subclavian vein. No local cause for it could be found. Specimens were presented before the London Pathological Society and no further details are given.

Case XVII.—Hirschlaff (from Leyden's clinic) (1893). Woman. Repeated attacks during last ten years of articular rheumatism. Cardiac symptoms existed for some time before admission. Upon admission, respirations hurried and labored, œdema of lower extremities, ascites, moist pul-

monary râles behind and below, heart's action violent, with diffuse præcordial heaving, cardiac dulness much increased in all directions, loud systolic and diastolic murmurs at apex, feebler systolic murmur, with indistinct diastolic sound in aortic area, distinctly visible venous pulsation; pulse 120, of low tension; enlargement of liver and spleen, moderate albuminuria, diminished excretion of urine. No material improvement followed. Both hands became œdematous. Six days before death there appeared œdema of the left half of the thorax, reaching the middle line, and also of the left supraclavicular fossa; later œdema of left half of face. Pulsation disappeared from the left external jugular, while it persisted in the right. A painful hard cord could be felt in the left supraclavicular fossa, extending upward along the course of the external jugular vein, and a similar one along that of the internal jugular. Erysipelas of the right leg set in after insertion of Ziehl's needles to relieve the œdema, and patient died in collapse.

Autopsy.—Extreme stenosis and marked insufficiency of the mitral valve and slighter insufficiency of the aortic valve; cavities much dilated. Thrombosis of the entire left innominate, internal jugular and smaller tributaries, external jugular, subclavian, and axillary veins. The thrombus is reddish-yellow and oldest in the jugular bulb. The veins of the upper arm contained fluid blood; cerebral sinuses free; red induration of both lungs; small quantities of fluid in both pleural cavities; fresh hyperplasia of spleen.

Case XVIII.—Hirschlaff (1893). Woman, aged fifty-one years. Diphtheria at eighteen; articular rheumatism, without evident sequels, at twenty years of age. For past twenty years epilepsy with periodical swelling of both legs, lasting for months; for last two years persistent œdema of the legs, and for a month before admission palpitation and dyspnœa. Shortly before admission increasing painful swelling of left side of neck and left arm. On admission, marked œdema of lower extremities and of the left side of neck and left arm, slight ascites, slight cyanosis and icterus, systolic pulsation of left external jugular, enlargement of heart, heaving impulse and thrill at apex, loud murmur filling entire period before systole at apex, diastolic murmur in aortic area, dulness and creditant râles over posterior, lower chest; urine diminished, concentrated and slightly albuminous; pulse 108, small, irregular. The veins in the left side of neck and over shoulder became much distended and the œdema increased in extent. Three weeks later the right side of the neck and thorax, and then the face, became œdematous. Pulmonary symptoms. Repeated epileptic attacks occurred, accompanied and followed by extreme cyanosis and dyspnœa. In one of these death ensued a month after admission.

Autopsy.—Cardiac hyperthrophy, extreme dilatation of right ventricle and auricles; tricuspid valve thickened, its chordæ shortened and grown together; extreme stenosis of mitral orifice, insufficiency of aortic valves, on which are fresh vegetations; myocardium flabby, pale, and yellow. Moderate accumulation of fluid in pleural and pericardial cavities; recent and old pulmonary infarcts; chronic passive congestion of liver, spleen, and kidneys. Thrombosis of superior vena cava, left innominate vein, left subclavian and both internal jugular veins. The oldest part of the thrombus occupies the bulb of the left jugular, where it is firm, closely adherent, and partly organized. Tissues around thrombosed veins behind manubrium sterni œdematous. Small thrombus in the left lateral sinus of the dura mater.

Case XIX.—Gatay (1895). Woman, aged twenty-eight years. Ten years ago acute rheumatism and endocarditis, followed by palpitation and articular pains. A few days before admission patient was seized with chills, followed by dyspnœa. On admission, cyanosis, œdema of lower extremities, areas of pulmonary consolidation, disorderly action of heart; pulse small and intermittent; albuminuria; temperature 39.8° C. Four days later hard œdema of left arm, most marked in lower part, appeared. Fluid in wrist-joint. Hard venous cord on inner side of left upper arm was felt.

Autopsy.—Much hypertrophy and dilatation of heart; the right ventricle markedly dilated and tricuspid valve relatively insufficient; mitral valve thickened, retracted, and incompetent; old fibrous plaques on endocardium; no fresh endocarditis; pulmonary infarcts. Left brachial vein swollen and filled with a red, adherent, centrally softened thrombus, 10 cm. long; venous wall above and below thrombus red and thickened.

Case XX.—Kahn (from Hanot's clinic) (1896). Woman, aged fifty-two years. Seven years ago, influenza, followed by some œdema of legs, which soon disappeared. For four months before admission, cough, weakness, œdema of legs, loss of flesh. On admission, cardiac hypertrophy, systolic murmur at apex transmitted into axilla; no murmur at base; pulse 100, small, soft; radials sclerotic; external jugular turgid, but without pulsation; respirations rapid and labored; œdema of lower extremities, emaciation. Ten days after admission painless œdema of right hand and forearm appeared. Temperature, 38.3° C. Subcrepitant râles at base of lungs. The œdema rapidly spread, so as to involve the whole of right arm and corresponding mammary region. There was no pain. The skin was colder than on the left side and somewhat mottled with violet patches. Dyspnœa intense, respiration 42, urine albuminous, sputum bloody, temperature 39° C.; delirium and death in coma about three weeks after onset of thrombosis.

Autopsy.—Hypertrophy of the whole heart, right cavities much dilated, mitral valve indurated, thickened, retracted, insufficient without stenosis; other valves normal, fibrous myocarditis. Fluid in left pleura, pulmonary infarcts, chronic passive congestion of liver and kidneys, spleen swollen and soft. There are five or six enlarged glands near the right subclavian vein, which is completely filled with a reddish, fibrinous, firm, non-adherent thrombus 4 cm. long, extending to the origin of the axillary vein. No thrombi in collateral veins. On microscopical examination, coats of thrombosed vein appear thickened, and capillaries in outer wall dilated.

Case XXI.—Mader (1897). Woman, aged forty-five years. Repeated attacks of articular rheumatism, followed by palpitation, dyspnœa, and œdema of lower extremities. On admission evidences of stenosis and insufficiency of the mitral and tricuspid valves. Marked ascites. Three weeks later patient complained of great tension in veins of arms and, in fact, these became enormously distended, as did also the cervical and upper thoracic veins. Collateral veins could be traced to the epigastric veins. There was vertigo, and the lips became cyanosed. With the establishment of a collateral circulation there was gradual improvement in the symptoms. The diagnosis was thrombosis of both innominate veins, possibly also of superior vena cava, complicating the valvular affections mentioned.

Case XXII.—Helen Baldwin (1897). Girl, aged nineteen years. Three attacks of rheumatic fever, the last seven years ago. Five weeks ago œdema of the feet. A few days before admission, began to suffer from pain in left axilla and left side of neck, also from swelling of the left side of neck. The latter at first would disappear in the erect posture. Amenorrhœa. On admission, great weakness, œdema of both legs, cyanosis, dyspnœa, respirations 40, pupils dilated; pulse 108, small, rapid, and compressible; marked enlargement of heart, double aortic and mitral murmurs, ascites, enlargement of liver, albuminuria, granular and hyaline casts, quantity of urine diminished, sp. gr., 1033. On left side of neck is a hard, tender swelling of lower part of external jugular vein, which is tortuous. There is a hard cord in left axilla, extending for about five inches down the arm. Left arm œdematous and pale. The next day external jugular vein was felt as a cord up to one-half inch of lobule of ear. Œdema of whole left side of neck. Signs of beginning double pneumonia. For five days there was noted a persistently low temperature when measured by thermometer in mouth, whereas that by the rectum was 6 to 7.8 degrees higher. Bloody expectoration on the fifth day. Death six days after admission.

Autopsy.—General œdema, ascites, double hydrothorax, marked hypertrophy of heart, the auricles extremely dilated, chronic changes in all of the valves, the most marked being stenosis and insufficiency, of the mitral valve, the edges of tricuspid valve thickened and curled. Pulmonary congestion and infarcts and early stage of double lobar pneumonia. Chronic passive congestion of abdominal viscera. Firm thrombi fill the left innominate, subclavian, external and internal jugular veins, extending nearly to lobe of ear. Veins of extremities could not be further examined. Enlarged lymph nodes along trachea, not pressing on veins. Small extravasation of blood along left side of trachea and behind the left auricle. On microscopical examination the thrombi were found to be partly organized. There was marked chronic thickening of the intima of the subclavian vein, which was believed to be the starting-point of the thrombus.

Case XXIII.—Huchard (1897). Woman, aged twenty-four years. Seven years ago had articular rheumatism with cardiac complication, followed by mitral stenosis. Painful swelling of left arm appeared during convalescence from an undetermined febrile disease. On admission severe dyspnœa; pulse rapid, small, irregular; expectoration bloody, urine slightly albuminous, no œdema of lower extremities. Painful, hard œdema of entire left arm, with prominence of superficial veins, and hard, sensitive, voluminous, venous cords. Death in coma nine days after admission.

Autopsy.—Double hydrothorax, pulmonary infarcts, slight ascites, nutmeg liver. Heart weighed 450 grms.; buttonhole mitral orifice causing extreme stenosis, slight narrowing of tricuspid orifice, and marked dilatation of right auricle. Large stratified thrombus in left auricle. A few pericardial adhesions. Left brachial vein markedly dilated, and filled in upper part with an adherent thrombus 3 cm. long, starting from a valvular pocket.

Case XXIV.—Huchard (1897). Male with mitral stenosis and thrombosis of veins of left lower extremity. No other details.

Case XXV.—Nicolle and Robineau (1897). Girl, aged sixteen and a half years. Repeated attacks of rheumatism during last four years. Chief symptom on admission, respiratory distress; no œdema. Four months after admission patient felt pain in the left side of neck and head, and a hard, painful cord, 5 to 10 cm. long, was detected in the course of the left external jugular vein. Three days later the thrombus had extended and painful œdema of left side of neck and face appeared. Superficial veins dilated; urine slightly albuminous. Ten days after first symptoms of thrombosis entire left upper extremity became œdematous. Expectoration bloody. Œdema increased, and appeared also in lower extremities. Death occurred a little less than a month after the beginning of the thrombosis.

Autopsy.—Mitral orifice narrowed, numerous hard, papillary vegetations on borders and surface of mitral segments, also on the aortic valves and the free borders of the tricuspid. Chordæ tendineæ of mitral valve shortened. Hydrothorax, many pulmonary infarcts, pneumonia of left lower lobe. Thrombosis of left external jugular vein and branches and of subclavian vein. Thrombus black, rather soft, slightly adherent, unorganized. Venous walls, especially inner coat, thickened. Swollen, hemorrhagic lymph glands surround the thrombosed veins. Tissues of neck very œdematous.

Case XXVI.—Poynton (from service of Dr. Lees), (1898). Girl, aged nineteen years. Very severe attack of rheumatic fever, lasting thirteen weeks, nine months before admission. Swelling of legs and abdomen noticed two months before admission, and a few days before admission left arm suddenly began to swell. On admission great pallor and distress, evidences of advanced organic disease of heart, systolic apical murmur, accentuated second pulmonic sound; pulse 90, irregular in force and rhythm; œdema of legs and thighs, of upper extremities and upper part of chest, the left arm and hand being very much swollen; impairment of resonance and respiratory sounds over bases of lungs, liver large and tender, conjunctivæ icteric, urine somewhat albuminous, temperature subnormal and continuing so throughout illness. Death, preceded by cerebral symptoms and coma, about two weeks after admission.

Autopsy.—Totally adherent pericardium, evidences of old rheumatic endocarditis; aortic, mitral, and tricuspid valves incompetent, and mitral orifice slightly narrowed; cavities dilated, especially right ventricle; weight of heart, sixteen ounces. Pleuræ adherent. Chronic passive congestion of viscera. Adherent firm thrombi filled both innominate and both internal jugular veins, the lower end of left internal jugular being white, narrowed, and very firm. Adherent mural thrombosis in upper part of superior vena cava. Mediastinal tissues œdematous. Brain generally soft and œdematous.

Case XXVII.—Poynton (from service of Dr. Cheadle), (1898). Woman, aged twenty-one years. In childhood scarlet fever, followed by rheumatic fever. Two years ago second attack of rheumatism. Present illness began gradually with weakness, dyspnœa, and œdema of legs and face. On admission anæmia, œdema of legs, face puffy, bronchitic sounds, harassing cough, systolic thrill, loud systolic murmur over front and back, dilatation of heart. Temperature 101° F.; respirations 28; pulse 128, of low tension. Urine albuminous, sp. gr., 1020, contained blood and casts. Liver and spleen enlarged. Irregular pyrexia and sweating continued throughout illness in

hospital. Twelve days after admission pain in wrists and along inside of left forearm. Œdema of face, which had almost disappeared, returned, especially on left side. Irregularity of pulse, orthopnœa, symptoms of renal infarction and pneumonia appeared, and death occurred five and a half weeks after admission.

Autopsy.—Heart weighed 14 ounces, all its cavities much dilated; both ventricles and left auricle hypertrophied; muscle pale; mitral orifice widened; numerous exuberant vegetations of mitral segments, also on endocardium of left auricle and left ventricle; chordæ tendineæ ulcerated through; other valves normal, except slight widening of tricuspid orifice. Pulmonary congestion; pneumonia of left lower lobe; chronic passive congestion of abdominal viscera, with infarcts in spleen and kidneys (microscopically no evidence of interstitial inflammation or chronic nephritis). Left internal jugular, from junction with subclavian vein to angle of jaw, occluded by a thrombus, which was pale and adherent to wall, especially in lower part, where vein was cord-like. Innominate vein and right jugular not thrombosed. Brain normal. On microscopical examination no micro-organisms found in cardiac vegetations or in thrombus. Diplococci, staining by Gram, in pneumonic area. Sections of left internal jugular showed organizing thrombus, without distinct thickening of venous wall. Walls of right jugular normal. (No mention of cultures.)

Case XXVIII.—Poynton (from service of Dr. Cheadle), (1898). Girl, aged nine years. Two years ago scarlet fever, since which heart was affected. For three weeks before admission, thoracic pain and cough, and for one week dropsy. On admission, February 19th, pallor, with some cyanosis; orthopnœa; fingers clubbed; œdema of lower extremities, anterior chest wall and face; some ascites; marked increase of cardiac dulness to right and left; præcordial bulging; epigastric pulsation; systolic and diastolic thrill; double mitral and aortic murmurs; doubtful pericardial friction rub; impaired resonance and respiratory sounds over bases of lungs; scattered bronchitic râles; liver enlarged and pulsating. Temperature 97.4° F.; respirations 30; pulse 100, irregular, weak and small; urine, 1025, contained albumin and blood, without casts. Improvement until March 10th, when pleural friction was heard in left axilla and dulness at left base, without rise of temperature. Again improvement until April 10th, when pulmonary symptoms reappeared and swelling of axillary glands was noticed. Heart more dilated, pulse feebler. 13th: left side of face swollen. 16th: marked œdema of right side of neck, eyelids, and lips; face purple; both sides of neck tense, painful to touch and on movement; temperature subnormal. 17th: right arm began to swell, shortly afterward œdema of left arm and chest; patient apathetic. 18th: drowsiness, cyanosis, sudden dyspnœa, with symptoms of collapse. 19th: tender œdema of right arm extreme. 20th: two firm cords felt in lower part of neck; legs and feet a little swollen; area of cardiac dulness enormous; loud pericardial friction, crepitation over both lungs; urine scanty, slightly albuminous, no blood. Death April 21st.

Autopsy.—Acute sero-fibrinous pericarditis; all cardiac cavities dilated and hypertrophied, the right relatively more than the left. Mitral and tricuspid valves incompetent; fresh vegetations on aortic, mitral, and tricuspid valves. Usual visceral changes secondary to advanced cardiac disease. Ob-

literative thrombosis of superior vena cava in its upper two-thirds, both innominate, subclavian, internal and external jugular, and axillary veins, and the left inferior thyroid vein. Small adherent mural thrombus in left branchial vein. The oldest parts of the thrombus were in the lowest portions of the internal jugular veins and the left innominate, which were white, small, and firm, and adherent to surrounding tissues. Beyond these older thrombi the vessels were bulged with soft clot. The thrombus in the superior cava was soft, pale, non-adherent, except in its upper part.

Cultures and films from pericardial exudate and blood-clot negative: sections of soft clot in superior cava and of thrombus in right axillary showed no micro-organisms. Thrombi were undergoing organization in older parts. Early phlebo-sclerosis, apparently secondary to thrombus, in older thrombosed vessels. Venous wall not thickened where thrombus was fresh and not adherent. Interstitial myocarditis in subpericardial layers and beneath inflamed endocardium.

The most remarkable feature of the foregoing twenty-eight cases of venous thrombosis in heart disease is the location of the thrombi: twenty-four were thromboses of veins conveying blood from the upper extremities or the neck, or both, mostly of the left side, and only four were thromboses of the veins supplying the lower extremities. I do not suppose that these numbers represent the correct ratio between upper and lower venous thrombosis in heart disease, for thrombosis of veins of the lower extremities in this condition is much more likely to be overlooked in consequence of the more common and greater œdema of the lower limbs, and is also much less likely to be reported. How often it is overlooked can be at present only a matter of conjecture, but it is not probable that such thrombosis is at all frequent. In fact, the comparative infrequency of peripheral venous thrombosis in cardiac disease is in itself a matter of interest, in view of the slow, feeble and irregular venous circulation, and of the frequency of so-called marantic thrombi in the heart itself during the failure of compensation. The relatively small liability to venous thrombosis under such conditions of the circulation is one of many evidences that mere slowing of the blood current is not an efficient cause of thrombosis.

Even allowing for a considerable increase in the number of instances of thrombisis of the veins of the lower extremities as the result of more thorough search in cases of heart disease, the relatively large number of observations of thrombosis of the upper veins revealed in my collection of cases still remains most remarkable. Bouchut places the ratio of venous thromboses of the upper extremity to those of the lower at one to fifty. Of sixty-seven cases of peripheral venous thrombosis in our autopsy records at the Johns Hopkins Hospital, only one was of the upper extremities, although several instances of the latter have been observed clinically in the hospital. Moreover, the four instances above recorded of venous throm-

bosis of the lower extremities in heart disease had little in common with the remaining cases. Two were in old persons, with some arterial atheroma, and of two no satisfactory history is given. The thrombosis was on the left side in three and bilateral in one, thus conforming to the rule. As will appear from an analysis of the remaining twenty-four cases, the venous thromboses of the neck and arms in cardiac disease constitute a separate and distinct group, characterized by special features of unusual interest.

Analysis of Twenty-four Cases of Thrombosis of Veins of Neck, Arm and Chest in Heart Disease

Sex.—Seventeen cases were females, five of males, and of two the sex is not stated. While the total number of cases is too small to warrant percentage estimates, there can be no doubt that females are much more disposed to this form of thrombosis than males. Whether this disposition is more than an expression of the greater liability of females to the mitral lesions present at the ages in the cases observed, I must leave an open question. The figures seem somewhat out of proportion to this great tendency.

Age.—One patient was nine years old, 6 were between ten and twenty, 3 between twenty and thirty, 3 between thirty and forty, 2 between forty and fifty, 3 between fifty and sixty, and of 6 the age is not stated. Of the 18 patients with thrombosis of the neck and arms whose ages are stated, nearly one-half (8) were between fifteen and thirty years of age. The youngest was nine and the oldest fifty-three.

Valvular Lesion.—In two cases the exact nature of the valvular lesion is not stated. Of the remaining 22 cases, there was organic disease of the mitral valve in 21; in the exceptional case there was aortic insufficiency with relative mitral incompetence.

The mitral lesion is described as insufficiency in 9 cases, as stenosis in 6, and as stenosis and insufficiency in 6. In the last group there were at least three instances of extreme stenosis. The aortic valves were affected in 10 cases, in all of these there being incompetence, sometimes also with obstruction.

The organic valvular lesion was limited to the mitral valve in 12 cases, to the aortic valve in one, to the mitral and aortic valves in 6, to the mitral, aortic and tricuspid valves in two, and in one case all of the valves were organically diseased.

In all of these cases there was chronic disease of the valves. In five cases there appears to have been a fresh endocarditis engrafted upon the chronic affection, and it is possible that in some other cases this was present, but in the majority of the observations there was not acute endocarditis.

Adherent pericardium was noted in four cases, acute pericarditis in one.

It is evident that the association of thrombosis of the upper veins with valvular disease of the heart is almost, although not wholly, limited to cases of mitral disease, those of mitral stenosis, with or without insufficiency, taking the lead. The preponderance of females and of patients under middle age is thus, at least in great part, explained. That the complication may occur in men in advanced life with general arterio-sclerosis and chronic Bright's disease associated with cardiac disease is shown by Case V.

Relation to Rheumatism.—As is to be expected from its nature, the valvular lesion was most frequently caused by acute articular rheumatism, of which there was a distinct history in a little over half the cases, but other infectious diseases (scarlet fever, pneumonia, influenza, puerperal infection, diphtheria, syphilis, and chorea) also had a share in the causation. In a number of instances the valvular trouble seems to have developed insidiously. There is, therefore, nothing peculiar in the antecedent histories.

Although several observers regarded the occurrence of the thrombosis as a direct manifestation of rheumatism, only in three cases was there any painful swelling of a joint present shortly before or during the attack of thrombosis.

Relation to Cardiac Insufficiency.—In the great majority of cases the thrombosis appeared during a condition of failure, generally extreme failure, of compensation of advanced mitral disease. The frequency with which pulmonary infarction was observed at autopsy is one of the many evidences of this. Relative insufficiency of the tricuspid valve and pulsation of the cervical veins were noted in many of the cases, and very likely were present in some of those in whose histories they are not noted, but it does not appear that these conditions, although contributory, are necessary factors in the causation of the thrombosis.

Location of the Thrombi.—A fact which at once arrests attention is that the thrombosis affected veins of the left side in 22 out of the 24 cases, of which 15 were unilateral and 7 bilateral. In only two cases were veins of the right side alone affected. Bilateral thrombosis is, therefore, more common than unilateral right-sided thrombosis, and unilateral left-sided thrombosis is by far the most common form of the disease. The hypotheses in explanation of this distribution will be considered later.

In 7 cases the thrombosis was apparently limited to the arm veins, in one to veins of the neck, and in 16 cases veins both of the neck and arms were thrombosed. In one case the thrombus was confined to the left subclavian vein, in one to the left internal jugular, and in two to the left brachial. In all the other cases more than one vein was thrombosed, the combination varying in different cases, the most common being continuous thrombosis of the left innominate, internal and external jugular, subclavian, and axillary

veins. The superior vena cava was partly or wholly thrombosed in 6 cases (confirmed by autopsy in four), the innominate in 11 (confirmed by autopsy in 8), the internal jugular in 14 (autopsy in 11), the external jugular in 12 (autopsy in 8), the subclavian in 16 (autopsy in 13), the axillary in 11, the brachial in 6, the inferior thyroid in 1, and the left lateral sinus of the brain in 1.

The commonest starting-point for the thrombus was the lowest part of the left internal jugular (bulb), or of the left external jugular vein and the left innominate or subclavian vein near the entrance of the jugulars. In many cases this was clearly demonstrated by the appearances of the thrombus and the venous wall in these situations. The thrombus may, however, originate in other veins, especially in valvular pockets of the veins in the left arm.

The most extensive thrombosis was that recorded by Poynton (Case XXVIII), in which there was occlusion of the superior vena cava in its upper two-thirds, of both innominate, internal and external jugular, subclavian, and axillary veins, and the left inferior thyroid vein.

The thrombus was generally a continuous one, apparently originating in one vein, whence it was propagated into peripheral veins and also centrally, even into the superior vena cava.

Characters of the Thrombi and Venous Walls.—The thrombi were mixed, the prevailing color being dark red. The older parts were gray or reddish-gray and adherent. The fullest description of the microscopical characters is that which I have recorded under Case I. In a few instances the thrombus was centrally softened, but in most it was solid and completely occluding except at the ends and except in the mural thrombus mentioned in Case XXVIII. The older thrombi were usually more or less advanced in organization. Bacteria were searched for in apparently only three cases, and were found only in my Case I, the organism here being *Streptococcus pyogenes.*

In 7 cases it was noted that the wall of the thrombosed vein was thickened, but this thickening was generally regarded as secondary to the formation of the thrombus, which was two or more weeks old. Only in Helen Baldwin's case and in Case V is it distinctly stated that the appearances indicated phlebo-sclerosis (subclavian vein) antedating the thrombus. In two of Poynton's cases the jugular and innominate veins, where the oldest part of the thrombus was situated, were narrowed, white, and firm, and a similar condition was noted by Robert. Chronic disease of the veins evidently plays only a minor part in the causation of thrombosis in these cases.

Effect and Symptoms.—The anatomical lesions outside of the vessels directly referable to the thrombosis were œdema of the tissues and swelling of the lymphatic glands. The œdema cannot always be explained entirely as the result of venous congestion, but is in part inflammatory, as is true in general of the œdema in phlegmasia. Swollen lymphatic glands, which were sometimes hemorrhagic or pigmented, were often observed in the neighborhood of the thrombosed veins. This swelling was generally acute and evidently secondary to the thrombosis, but Kahn attributed the exceptional localization of the thrombus in the right subclavian vein in his case (XX) to the pressure of previously enlarged glands. Poynton noticed cerebral œdema in one of his cases which had manifested brain symptoms.

The local symptoms are the usual ones of venous thrombosis: pain, tenderness, œdema, the presence of hard, sensitive venous cords, and distention of superficial veins. Often the pain, sometimes the œdema, was the first symptom. The œdematous swelling may be hard and brawny, or softer, as in dropsy. In some cases the pain and œdematous swelling were first manifest in the neck, in others in the arm. Extension of the œdema to the front and side of the upper part of the thorax was repeatedly noted. Occasionally the side of the face corresponding to the thrombosis was œdematous. The extent and distribution of the œdema, while dependent in the first instance upon the extent and location of the thrombosis, were influenced, as is usual in venous thrombosis, by other factors, so that they varied much in cases with the same distribution of the thrombi.

Constitutional symptoms of the thrombosis, if present, could not readily be separated from those of associated conditions. The marked difference between the buccal and rectal temperatures observed in Helen Baldwin's case (XXII) is interesting. Cerebral symptoms, attributed by Poynton to cerebral œdema, were observed in a few cases.

As is illustrated by Case V, the only symptom of the thrombosis may be œdema, usually of the left arm, the patient suffering little or no inconvenience from the swelling, and the affection being recognized sometimes almost accidentally.

Hanot, in 1874, called attention in a short note to the more rapid onset and the longer persistence of œdema of the left arm, as compared with the right, in cardiac affections, and he explained this peculiarity by the greater length and obliquity of the left innominate vein. It would appear, therefore, that œdema limited to or in excess in the left arm in heart disease should not be regarded as positive evidence of thrombosis of veins conveying blood from this extremity. While this is doubtless true, it is desirable, in view of the cases reported in this paper, to search carefully in these instances for other evidences of thrombosis.

Prognosis.—Of the twenty-four cases, twenty ended fatally and four (Case II, VII, XIII, and XXI) recovered. The gravity of the prognosis doubtless mainly results from the circumstance that the occurrence of the thrombosis is in itself an index of extreme failure of compensation of the valvular lesion, being sometimes scarcely more than a terminal event. We know that occlusion of the superior vena cava and its large tributaries, due to other causes, may be completely compensated by the development of a collateral circulation, and there are instances of this even in the present group of cases (VII and XXI), so that it is less the venous occlusion than the condition of the heart and the frequent presence of pneumonia or other terminal infections which makes the issue so unfavorable. In rare instances, thrombosis of the upper veins may occur at a period when the compensation is not badly broken (Case II). Large pulmonary embolism was not observed. Whether pulmonary infarcts, which were frequently present, were attributable to emboli derived from the venous thrombi was not determined. The duration in the fatal cases of thrombosis varied from two days to six weeks.

Causation.—Although five of the cases were reported as instances of rheumatic phlebitis, it does not seem to me demonstrated that even in these cases (XII, XIX, XXVI, XXVII, XXVIII) this was the correct explanation and it is certain that the great majority of cases cannot be explained in this way. It is true that phlebitis, or venous thrombosis, is a genuine, although infrequent, complication of acute rheumatism, and there is some evidence that it may affect veins of the upper extremities somewhat more frequently than does thrombosis due to most other causes, but there is no such enormous preponderance of upper thromboses as in the class of cases now under consideration. As already mentioned, the histories of the cases do not support the view that rheumatism had more than a minor share in the immediate causation of the thrombosis. There is no reason, however, why acute rheumatism, like other infections, may not directly participate in the causation of the venous thrombosis.

French writers (Peter, Parmentier, Kahn, Huchard) attribute the thrombosis to cardiac cachexia combined with circulatory disturbances. They say that this cardiac cachexia (so designated by Andral) is something to be distinguished from asystole—that is, from mere breakage of compensation. They bring this class of thromboses, therefore, into line with that complicating tuberculosis and cancer, and explain the peculiar localization by the particular disturbances of the circulation in cardiac disease. The underlying cause according to this view, is some alteration in the chemical composition of the blood. It is difficult to say how much weight is to be attached to this explanation. In many cachectic conditions there is an increase in the

blood platelets, attributable probably to weakened resistance of the red corpuscles, and some writers have brought cachectic thromboses into relationship with this increase. According to van Emden, the number of platelets is diminished in the chronic congestion of heart disease. I know of no observations concerning the number of platelets in these cases of heart disease with venous thrombosis. I could find nothing in the histories of most of the cases indicating any peculiar cachexia, and I am not inclined to regard this explanation of the thrombosis of heart disease as a satisfactory one.

The first thing which needs explanation is the localization of the thrombosis in the veins receiving blood from the upper part of the body, and especially from the left side. Hanot and Parmentier explain the preference for the left side by the greater length and obliquity of the left innominate vein, so that, like return flow of blood from the left leg, that from the left arm and left side of the neck is more difficult than from the right side, this difficulty being, of course, most in evidence in the venous congestion of uncompensated cardiac disease. Hirschlaff suggests that an additional factor may be the greater frequency of imperfect development and of insufficiency of the valve near the junction of the internal jugular and subclavian veins on the left than on the right side. To these factors I would add pressure, either direct or indirect, on the left subclavian vein from the dilated left auricle and dilated large pulmonary vessels. Popoff noted pressure from this source on the left subclavian artery in mitral stenosis with insufficiency as a cause of relative weakness of the left radial pulse (pulsus differens). I would refer to his article for a consideration of the factors concerned in producing this pressure. A large accumulation of fluid in the left pleural cavity, which was noted in many of the cases, may also contribute to this pressure.

Peter, in 1873, was the first to suggest that the frequency with which the thrombus starts from the lower ends of the jugulars is to be explained by the presence of valves in this situation. I am inclined to lay emphasis upon the readiness with which an eddying or whirling motion of the blood may be set up in heart disease in the lower ends of the jugulars and the adjacent parts of the innominate and subclavian veins. Von Recklinghausen has brought forward strong evidence that this whirling movement (Wirbelbewegung) of the blood is of great importance in determining the localization of thrombi in general. The valves, the bulbous enlargement at the lower end of the internal jugular, the attachment of veins to fascia, and the coming together here at oblique and right angles of currents of blood with different pressures and velocities, seem well calculated to cause in these veins whirling or vertical motion of the blood current, especially in the circulatory conditions of broken compensation of mitral lesions. Most

favorable to this peculiar disturbance of the circulation would be tricuspid insufficiency with systolic reflux of blood into the veins. I would explain, therefore, the special localization of the venous thrombosis complicating cardiac disease, on the one hand by the particular disturbance of the circulation, and on the other by the anatomical disposition and structure of the veins.

These factors, however, explain only why certain veins are the seat of election for the thrombi. The circulatory conditions described must often exist within these veins in uncompensated cardiac diseases, whereas venous thrombosis is a rare complication of heart disease. In the case which first directed my attention especially to this subject, and which I have here reported as Case I, an immediately exciting cause for the thrombosis was discovered by the demonstration of bacteria in the thrombus. This is the only case in the entire list in which micro-organisms were found, but, so far as I can gather, in only three other cases were bacteria especially looked for, and it does not appear that in any of these latter were cultures made from the thrombus. Such cultures are, of course, necessary in order to exclude the presence of bacteria, and, indeed, our experience has been that even a negative result from cultures is not absolutely decisive. Evidence has accumulated in recent years in support of the infectious origin of many thrombi. Dr. Harris and Mr. Longcope, who will report their observations later, have now examined in my laboratory bacteriologically forty-four thrombi, mostly peripheral venous thrombi of the so-called marantic type, and in thirty-four of these have demonstrated the presence of bacteria. As has been shown by Dr. Flexner in my laboratory, terminal infections are not uncommon in heart disease. The histories and autopsies of many of the twenty-four cases now under consideration revealed some infectious process, usually in the lungs, such as bronchitis, pneumonia, and pleurisy. While, therefore, it would be quite unwarrantable, from existing evidence, to refer this class of venous thromboses in cardiac disease positively to infection, this seems to me at present the most probable explanation.

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MILIARY ANEURISM OF A BRANCH OF THE GASTRIC ARTERY [1]

The patient was a man about 50 years of age, who had not been under the observation of a physician before the fatal rupture of the aneurism occurred. His health was not vigorous, but no definite clinical history of his previous condition could be obtained. The patient was seized during the night with profuse vomiting of blood which in a few hours terminated fatally. Gastric ulcer was suspected.

At the *post-mortem* examination the stomach was found filled with dark, partly coagulated blood. On removing this a thick layer of tenacious bloody mucus coated the inner surface of the stomach. No ulceration of the stomach could be detected. It was only after long-continued search, which was rendered unusually difficult by the adherent bloody mucus, that a minute loss of substance, not exceeding 3 or 4 mm. in diameter, was found in the mucous membrane of the posterior wall of the stomach, about midway between lesser and greater curvature and pylorus and cardia. In the floor of this perforation of the mucosa lay a small aneurism about the size of a split pea. The aneurism was of a sub-mucous branch of the coronary artery and it had ruptured at the point nearest the cavity of the stomach so that a fine probe could be passed through the perforation in the mucous membrane directly into the lumen of the artery.

The aneurism was the result of an arteritis. There existed a wide spread *endarteritis obliterans* affecting the medium sized and small arteries over a large part of the body, including those of the stomach, kidneys, spleen, heart and lymphatic glands. Although this condition suggested the existence of syphilis, no further evidence of syphilis could be found at the autopsy. The kidneys were the seat of advanced chronic interstitial nephritis, being small, granular and with fibroid glomeruli. The heart was hypertrophied without valvular lesions and presented patches of fibroid induration.

The case is instructive on account of the comparative infrequency of rupture of miliary aneurism of the stomach with fatal hæmatemesis. The readiness with which such a minute perforation of the gastric mucous membrane might be overlooked at the autopsy is calculated to awaken scepticism regarding certain cases of fatal gastrorrhagia reported without demonstrable lesion of the stomach and therefore attributed to capillary or parenchymatous hemorrhage in persons not affected with cirrhosis of the liver or other conditions causing portal obstruction.

[1] Presentation of pathological specimen and report before the Johns Hopkins Hospital Medical Society, October 22, 1889.

DUPLICATURE OF ARCH OF AORTA WITH ANEURISM[1]

The specimen came from a negro 43 years old, who, for six months before death, had suffered from paroxysmal cough, hoarseness increasing to aphonia, dyspnœa increasing to orthopnœa, pain in the chest and loss of flesh. Nineteen years ago he had acute articular rheumatism, and some years before that pneumonia. On admission he had extreme dyspnœa; inspiration was short and noisy; expiration was much prolonged and rough. His pulse was 32 and regular; respiration, 36; temperature, 97.6° F. There was moderate engorgment of the superficial veins of the neck. Sternal notch was obliterated. Apex beat of the heart was neither visible nor palpable. There was dulness at the level of the third rib and diminished resonance over the sternum at this level. Heart sounds were normal. Coarse and fine râles were audible over the posterior part of both lungs. Breath sounds were rough. The urine contained a moderate amount of albumen, with hyaline and granular casts. The patient died suddenly three days after admission to the hospital.

At the autopsy the lungs were found to be moderately emphysematous with slight dilatation of the bronchi. There were numerous areas of fresh bronchopneumonia in the posterior lobes of both lungs and general pulmonary œdema. The kidneys were small and granular and microscopically showed increase of connective tissue, fibrous glomeruli and atrophied tubules. In the cervical and portal lymphatic glands were encapsulated old caseous nodules. The liver, spleen and alimentary tract presented no noteworthy lesions.

The heart was normal, no changes being present in the valves nor in the size of the heart cavities or the thickness of their walls. On the posterior wall of the ascending aorta, 3 cm. above the valves, is a distinct depression 5 mm. in diameter and 2 mm. in depth, over which apparently normal intima is continuous. At the point where the innominate artery should be given off the aorta divides into two branches, a larger anterior and a smaller posterior branch which joins the anterior branch 2 cm. below the origin of the left subclavian artery. The posterior branch passes behind the trachea, between it and the œsophagus, so that the trachea passes through the ring formed by the two divisions of the transverse arch of the aorta. From the anterior division are given off in their usual position the left common carotid and the left subclavian arteries. The beginning of the posterior trunk is the

[1] Presentation of pathological specimen and report before the Johns Hopkins Hospital Medical Society, February 2, 1891.

Johns Hopkins Hosp. Bull., Balt., 1891, II. 142.

seat of a saccular aneurism about the size of a hen's egg, with a somewhat triangular mouth measuring 2 by 1.5 cm. in diameter. The walls of the opening are smooth and the inner surface of the aneurism only a little irregular and rough. The sac contains fluid and red freshly coagulated blood. There are only a few scattered patches of endarteritis in the wall of the aneurism and elsewhere in the course of the aorta, some of these being atheromatous. From the posterior division of the arch are given off the right carotid and subclavian arteries, the former arising from the sac of the aneurism and the latter a short distance beyond this (*i. e.* further from the heart). Beyond the aneurism the posterior division measures 3½ cm. in length and 1 cm. in diameter.

The chief interest in the specimen is the duplicature of the transverse part of the arch of the aorta. This congenital anomaly, as well as others affecting the aortic arch, can be understood only by a consideration of the embryological development of the aorta and its branches, and from this point of view and from that of comparative anatomy these anomalies are of great interest. Duplicature of the transverse arch of the aorta is to be explained by the persistence after birth of conditions belonging to early fœtal life, which should have disappeared in the normal course of development. The fourth right aortic arch (calling the arch nearest the heart the fifth) persists throughout its course and constitutes the posterior division of the arch in our specimen. In normal development the beginning of the right fourth aortic arch becomes the innominate artery from which ascends the right common carotid, corresponding to the prolongation of the right ascending root of the aorta or the beginning of the third right aortic arch. The transverse part of the right fourth aortic arch (the right fourth bronchial artery) becomes the right subclavian, from which the vertebral is given off, and the descending part of the right fourth arch, which in early development unites with the corresponding part of the left fourth arch to make the aorta descendens, is obliterated. It is in the persistence of this descending part of the fourth right aortic arch that the abnormality essentially consists by which the so-called duplicature of the arch of the aorta is produced, and it is interesting to note that in the amphibia this condition is normal, a right as well as a left aortic arch existing.

The first record of an abnormality in the human being similar to that in our specimen appears to be by Hommel in 1737, but in Hommel's case both the œsophagus and the trachea passed through the ring formed by the anterior and the posterior divisions, whereas in our case only the trachea enters the ring. Since Hommel a number of cases of duplicature of the aortic arch presenting considerable diversity in the exact arrangement and the origin of branches in different cases have been recorded. I have not found any case recorded in which the posterior division was the seat of an aneurism as in the present case.

SUDDEN DEATHS FROM CARDIAC DISEASE[1]

The first specimen was one of thrombosis of the descending branch of the left coronary artery.

The patient was a strongly built, well-nourished German, 55 years old. Five years ago, he had an attack of acute articular rheumatism, and had suffered from sub-acute attacks of rheumatism for several years. He had been a hard drinker. For several months before admission to the hospital, he had suffered from pain in the region of the heart, palpitation, shortness of breath and bloody expectoration. He had paroxysmal attacks of cardiac dyspnœa and pain. He had not noticed any swelling of the feet.

On admission the respiration was quiet. The pulse was 72, small and regular. The arterial wall somewhat stiff. The apex beat of the heart was in the fifth intercostal space below nipple. There was a presystolic thrill, and marked shortness of the first sound. A loud presystolic murmur was heard at apex. Both aortic sounds were clear. The urine contained albumen, hyaline and granular casts. Patient was in the hospital for four weeks, during which he had occasional paroxysmal attacks of dyspnœa, lasting for an hour or more. In the intervals his condition was fairly comfortable. On the morning of November 30th, he was suddenly seized with pain in the chest and shortness of breath, and in a few moments before any assistance could be rendered he was dead.

At the autopsy the essential lesions were found in the heart. The mitral orifice was greatly narrowed, measuring 13 x 8 mm. The chordæ tendineæ of the mitral valve were thickened and shortened; the mitral segments thickened and atheromatous, free from thrombi. The other valves were normal. The heart was greatly hypertrophied and dilated. The hypertrophy and dilatation of the left auricle were most extreme, its wall measuring in places 6 mm. in thickness. The wall of the left ventricle measured 23 mm. and that of the right ventricle 5 mm. in thickness. The heart muscle was firm and of a dark reddish-brown color. On microscopical examination it presented slight fatty degeneration.

The coronary arteries were markedly atheromatous, their walls being irregularly thickened and presenting on the inner surface irregular, elevated, opaque, yellowish white patches. The left coronary artery contained, 3 cm. from its origin, a fresh dark red, almost black, thrombus, adherent to an atheromatous plâque, and about one-half centimeter in length. This thrombus completely occluded the lumen of the artery at this point. It was situated in the descending or vertical branch of the left coronary artery.

[1] Presentation of pathological specimens and report before the Johns Hopkins Hospital Medical Society, December 2, 1889.

Johns Hopkins Hosp. Bull., Balt., 1889-90, I, 34-35.

The aorta throughout its entire extent appeared thickened, dilated, and presented numerous elevated atheromatous patches.

The lungs, liver, spleen, and kidney presented marked chronic passive congestion. The spleen and kidney contained the scars of old infarctions. The large and small bronchi contained muco-pus.

There was an area of old softening involving the cortex of the left second and third frontal convolutions near the anterior central convolution and the adjacent part of the island of Reil.

The chief interest of the case is the explanation of the sudden death of the patient. This is undoubtedly referable to the fresh thrombus which was found attached to an atheromatous patch in the main branch of the left coronary artery. Although marked atheromatous disease of the coronary arteries existed, the circulation in these vessels had not been sufficiently impeded to give rise to fibroid patches in the myocardium. The appearance of the thrombus and the absence of infarction or anæmic necrosis of the heart muscle, are evidence that the clot must have been of recent formation. The cause of the thrombosis was doubtless the irregular atheromatous projecting plâque to which the thrombus was adherent. As is well known, diseases obstructing the circulation of blood through the coronary arteries, such as arterio-sclerosis, thrombosis, embolism of these vessels, are among the most frequent causes of sudden death.

The second specimen was one of complete occlusion of the mouth of the right coronary artery.

The patient, a negro 36 years old, about six months before admission to the hospital began to suffer from shortness of breath on exertion, and palpitation of the heart. Œdema of the lower extremities appeared, but he was unable to do the work of a laboring man until six weeks before admission. Upon admission there were observed severe dyspnœa, general anasarca, pulsation of the veins, increased area of cardiac dulness, the apex beat being in sixth intercostal space in middle line of axilla, and diastolic and systolic murmurs heard most distinctly over base of heart. The urine was scanty, specific gravity 1010 and contained granular and hyaline casts, and some red blood corpuscles and pus cells. For a time he improved under treatment but a few hours before death his pulse became very irregular, small, feeble and compressible, and he died somewhat suddenly.

At the autopsy the heart was found greatly hypertrophied and dilated, the left ventricle being 14 and the right 12 cm. long. The heart weighed 858 grammes. The thickness of the wall of the left ventricle was 25 mm.; that or right ventricle 9 mm. The segments of the aortic valve were much thickened, roughened, retracted, and adherent to each other. The muscular substance of the left ventricle presented several grayish, irregular fibroid patches taking the place of the muscular tissue. The papillary muscles were extensively fibroid. The aorta for a distance of 4 cm. above the valves presented a remarkable nodular thickening of the intima resulting from arterio-selerosis. There were a few small nodules of calcification, but most of

the endarteritis was gelatinous and fresh in appearance. Beyond this circumscribed zone of arterio-sclerosis the aorta presented only a few small patches of atheroma, and in general the arteries of the body were but slightly atheromatous. The coronary arteries of the heart, however, presented a number of atheromatous patches. The most interesting feature of the case was the complete obliteration of the mouth of the right coronary artery. This mouth was involved in the extensive fibrous endarteritis affecting the aorta just above the valves, so that it was impossible to discover any opening from the aorta into the right coronary artery. This artery, however, was present in its normal situation and distribution and its lumen, apparently intact, could be traced nearly to the origin, where even the finest probe could not be made to pass from the lumen into the aorta. The left coronary artery appeared dilated but no large branch of anastomosis, connecting the left and the right coronary arteries, could be discovered. The right coronary must have been supplied with blood from the left artery.

The muscular substance of the heart, save the fibroid growth, was normal in appearance and free from fatty degeneration.

The organs of the body showed evidences of chronic venous congestion, and in the right kidney and ureter were fresh tubercle deposits associated with caseous tuberculosis of the prostate gland.

The case is interesting as showing complete obliteration of the right coronary artery at its origin by arterio-sclerosis of the aorta. Notwithstanding the absence of any large anastomosing branches between the left and the right coronary arteries, sufficient blood reached the regions of the heart, supplied by the right coronary, to nourish these parts and to prevent any fatty degeneration. The fibroid patches were chiefly, in parts, supplied by the left coronary artery.

The third specimen was one of extreme atheroma and thrombosis of the coronary arteries with multiple white infarctions in wall of left ventricle.

The patient was a woman 67 years old who, for twenty years preceding death, had complained of occasional attacks of pain in the region of the heart. During the last three months of life she had suffered from paroxysms of typical angina pectoris, from attacks of extreme dyspnœa, from great restlessness and some mental disorder. The pulse was irregular and feeble. The heart sounds appeared to be normal. Some œdema of the lower extremities developed. The urine contained a small quantity of albumen and a few hyaline casts. During the last few days of life she suffered from great pain and distress in the region of the heart, and she expectorated small dark clots of blood.

At the post-mortem examination the heart was only moderately enlarged, and this enlargement was due chiefly to a considerable deposit of adipose tissue beneath the epicardium. There was general obesity of the body. The left ventricle, at about its middle, measured 1 cm. in thickness. Below this it became gradually thinner, and at the apex measured only 4 mm. in thickness, of which one-half was fat. The average thickness of the right ventricular wall was 5 to 6 mm., of which only 2 mm. represented muscular tissue, the rest being fat. The right cavities of the heart were distended

with coagulated blood, chiefly cruor clots, but some decolorized; but little blood was found in the left ventricle. The aortic valves and the aortic segment of the mitral valve presented several yellowish, fatty and atheromatous patches, but the edges of the valves were delicate and there were no evidences of any change which would interfere with the functions of the valves. There were numerous ante-mortem thrombi attached to the inner surface of the left and of the right ventricles in their lower halves, and filling the appendices of the auricles. Many of these thrombi were globular and had undergone central softening. In the left ventricle they were continuous with areas of necrosis in the ventricular wall, and it was not always possible to recognize the line of separation between the thrombus and the necrotic wall.

The coronary arteries were extremely atheromatous, standing out as rigid tortuous calcified vessels with atheromatous projections on their inner surface. Even the small branches could be traced through the heart wall by means of the calcified beaded thickenings which they presented. Both coronary arteries were greatly narrowed by atheromatous degeneration near their origin. In many places grayish-red thrombi were present in the branches of the left coronary artery, sometimes parietal and sometimes, especially in the smaller branches, occluding. They occurred in situations where there was well marked atheroma. The left coronary artery was more extensively diseased than the right.

A large part of the wall of the left ventricle was the seat of white infarction or anæmic necrosis. These areas of coagulation-necrosis had an opaque, yellowish-white color, a firm consistence and well defined but irregular margins. They projected on the cut surface above the level of the surrounding muscle which, in the immediate neighborhood of the infarctions, appeared depressed, gelatinous, reddish in color and soft. The areas of necrosis were found only in the wall of the left ventricle and in the septum ventriculorum; they occurred chiefly in the part of the myocardium nearest the endocardium, and usually, but not in all cases, reached the endocardium. Sometimes they had more or less of a wedge-shape, but generally they were irregular in contour. They varied from 2 to 6 mm. in thickness, and appeared to have coalesced with each other so as to form a nearly continuous band of coagulation-necrosis in the lower part of the left ventricle. They occurred both on the anterior and on the posterior wall of the ventricle as well as in the septum. The papillary muscles of the left ventricle were affected with coagulation-necrosis throughout nearly their entire extent.

In addition to the infarctions the myocardium of both ventricles was affected by marked fatty degeneration, and presented a characteristic faded-leaf mottling as seen through the endocardium.

The lungs were the seat of chronic passive congestion, of general bronchitis, of œdema; and in the right lung were many firm, black, large, wedge-shaped hemorrhagic infarctions.

The liver, spleen, kidneys and stomach presented the usual appearances of chronic passive congestion.

The aorta and its principal branches were the seat of marked arteriosclerosis, presenting both gelatinous, elevated, fresh plâques and old calcified plates.

Microscopical sections were exhibited showing the appearances of the infarctions in the heart wall. In the necrotic areas the muscular fibres were entirely devoid of nuclei, and presented a homogeneous, hyaline or indistinctly striated appearance. In the edge of the infarction were accumulated between the muscular fibres masses of small irregular particles presenting a nuclear stain and doubtless the result of nuclear fragmentation. Beyond this zone was found an accumulation of leucocytes between the fibres, and a large number of red blood corpuscles. Mixed thrombi, rich in fibrin, leucocytes and blood-plates appeared on the sections attached to the necrotic endocardium. Such thrombi, however, were not limited to the necrotic areas.

In addition to the recent infarctions, the muscular wall of the left ventricle contained a number of old fibroid patches. Along the borders of some of the infarctions genuine granulation tissue, rich in cells and in blood-vessels was present.

AN EXPERIMENTAL STUDY OF GLOMERULO-NEPHRITIS[1]

Of the various processes which make up the pathological anatomy of Bright's disease, perhaps the two which at present awaken the greatest interest and the study of which promises the most fruitful results, are the changes which take place in the glomeruli and atrophy and necrosis of the epithelial cells in relation to interstitial changes. Not that by any means unanimity of opinion has been reached regarding other fundamental questions involving the relationship between the glandular, the interstitial, and the vascular lesions of Bright's disease, but the two processes named have acquired especial prominence within the last few years by the recognition of their frequency and importance.

Alterations of the Malpighian bodies, with which alone the present paper is concerned, were described with much accuracy and fulness by Beer in his excellent treatise on "The Connective Tissue of the Human Kidney in the Healthy and the Diseased State," published in 1859, but until recently little attention was paid to his observations. Klebs, by his description in 1876 of the lesion to which he gave the name of glomerulo-nephritis, incited renewed investigation of this subject. During the last ten years processes embraced under the name of glomerulo-nephritis have been studied by Cornil, Hortoles, Friedländer, Ribbert, Nauwerck, and many others, but we owe to Langhans the most extensive and accurate observations on this subject.

A comparison of the statements of different writers concerning glomerulo-nephritis will show a wide diversity of views, not only as to the interpretation of the facts observed but as to the facts themselves. Without attempting a critical analysis of these divergent views, the following summary of some of the conclusions of different observers will show this to be true.

At present little or no credence is given to Kleb's belief that the essential lesion of glomerulo-nephritis is proliferation of connective tissue cells which he supposed to exist between the capillaries of the glomerulus, although this belief still receives some support from the conception of Hortoles, and of Cornil and Brault, as to the connective-tissue nature of these intercapillary cells.

Langhans, in his publication in 1879, dwelt especially upon swelling, proliferation, and desquamation of the epithelial cells both of the glomerulus

[1] Presented at the first meeting of the Association of American Physicians and Surgeons, Army Medical Museum, Washington, D. C., June 18, 1886.

Tr. Ass. Am. Physicians, Phila., 1886, I, 171-183.

and of Bowman's capsule; whereas in his last article, published in 1885, he regards swelling and proliferation of the endothelium lining the glomerular capillaries as the primary and essential lesion of glomerulo-nephritis, as indeed of all forms of acute nephritis. Similar views are held by Friedländer and by Nauwerck.

Ribbert considers that the only changes are swelling and desquamation of the glomerular and capsular epithelium, changes which he regards as essential to all forms of acute and chronic Bright's disease and as answerable for many of the symptoms. He, as well as Hortoles and Cornil, refers the appearances described by Langhans as proliferation of the capillary endothelium to an accumulation of white blood-corpuscles in the capillaries.

Cornil and Brault assign an insignificant and inconstant rôle to changes in the epithelium of the glomerulus and of its capsule, and find the fundamental lesion of acute glomerulo-nephritis to be an exudation from the glomerular capillaries of inflammatory products composed of white blood-corpuscles, red blood-corpuscles, and an albuminous fluid.

On the other hand, Hortoles and Ribbert deny altogether the occurrence of emigration through the glomerular capillaries, basing this view on the failure to find leucocytes in the capsular space when their presence cannot be explained by emigration from capillaries adjacent to Bowman's capsule. In further support of their view they urge the peculiar structure of the capillaries of the glomerulus.

But it is not necessary to consume time in a further enumeration of the different views which are held upon this subject. Enough have been cited to show that there is room for much more investigation, as well as to bring out some of the leading points which require further study.

In the expectation that light might be thrown upon some of these doubtful points by experiments upon animals, I have made a study of the nephritis produced by acute cantharidin poisoning with especial reference to the alterations induced in the Malpighian bodies. I was led to select cantharidin because several experimenters with this substance have described in cantharidin nephritis notable changes in the Malpighian bodies, and because Cornil bases his description of acute glomerulo-nephritis chiefly upon observations of the kidneys of rabbits poisoned by cantharidin.

My experiments, which have not yet reached their completion, were made upon white rats and upon rabbits. A concentrated solution of cantharidin in acetic ether was used. I injected, subcutaneously, in rabbits usually from one-half to one centigramme of cantharidin, and in rats from one to three milligrammes. When a number of injections were made upon successive days smaller doses were used. The number of injections did not exceed five, and usually not more than two or three.

After the injection of a toxic dose the urine becomes diminished and finally suppressed; it contains albumen, hyaline casts, and a large number of leucocytes and red blood-corpuscles. The kidneys appear swollen, congested, and more succulent than normal.

The microscopical appearances in the rat's kidney will be first described. Here and there foci of infiltration with small round cells, doubtless emigrated white blood-corpuscles, can be found. They are most common around the veins at the base of the pyramid. They are often but not constantly present.

The epithelium of the convoluted tubes is in places normal in appearance, in other places it is swollen, and often the inner part of the epithelial cells is broken off and appears as a granular mass in the lumen of the tubes. Sometimes a large number of epithelial cells are devoid of nuclei, and have apparently undergone coagulation necrosis. In general, the convoluted tubes are wider than normal.

The most marked changes are to be found in the Malpighian bodies. In by far the greater number of these bodies there is between the glomerulus and Bowman's capsule a wide space partly or wholly filled with cells and granular material. These cells may be round or oval, but they are usually polyhedrical in shape. They are much larger than white blood-corpuscles, have granular protoplasm, and oval, vesicular nuclei. They are frequently arranged as a crescentic mass around the glomerulus.

Evidently we have here appearances such as have been often described as glomerulo-nephritis in the human kidney, and naturally one seeks for the same origin of these cells as that assigned for the cells similarly situated in human glomerulo-nephritis, namely, swelling and desquamation, and possibly proliferation of either the capsular or the glomerular epithelium.

The microscopical appearances in the rat's kidney, however, do not admit of this explanation. The epithelium lining the capsule of Bowman is often intact, and can be traced in its normal situation and with its normal appearances around the mass of cells occupying the capsular space. The glomerular epithelium may also preserve its normal position; more frequently it is somewhat swollen and granular, and it may desquamate. Such desquamated glomerular epithelial cells may be mingled with the cells free in the capsular space, but there are no appearances which justify the derivation of the majority of these latter cells from the epithelium of the glomerulus.

Both Cornil and Eliaschoff, whose descriptions of cantharidin nephritis are the best which I have found, and who experimented on rabbits, also came to the conclusion that the cells occupying the capsular space cannot be derived from either the epithelium of Bowman's capsule or that of the glomerulus. They argue that there remains but one other possible source, namely, emigration of white blood-corpuscles from the glomerular capillaries. They

therefore consider the cells in question as white blood-corpuscles, of which the cell bodies and the nuclei are greatly swollen and altered by the action of the cantharidin or of the urine.

So far as the rat's kidney is concerned, this explanation of Cornil and of Eliaschoff cannot be admitted. These authors are in error in supposing that the cells occupying the capsular space, if not originating from the capsular or glomerular epithelium, must come from the capillaries. These cells may be derived also from the convoluted tubes in immediate communication with the Malpighian bodies, and that this is their origin, at least in part, in the cantharidin nephritis of rats can be proven, I believe, beyond question. The cells in the capsular space are identical in appearance with the epithelial cells of the adjacent convoluted tubes. The appearances presented on sections which show the communication between the capsular space and the corresponding convoluted tube hardly admit of any other interpretation than that which I have given. Here it can be seen that the mass of cells in the capsular space is in direct connection with the epithelium of the convoluted tube, and, what is especially demonstrative, there can frequently be found in this mass a group of cells arranged regularly in the form of a ring with a central space, just like the epithelium of a uriniferous tube. Without the explanation given, such an arrangement of the cells is, of course, very puzzling, especially when the Malpighian body is cut so as not to show the connection with the tube. The appearance is as if the epithelial cells lining the mouth of the uriniferous tube (or the neck of the capsule), together with the cells immediately adjacent, had been pushed mechanically into the capsular space. A similarity in appearance between the cells accumulated in the capsular space and the epithelial cells of the convoluted tubes, might be explained by the fact that under normal conditions the epithelium of the convoluted tubes may extend for a variable distance along Bowman's capsule. Such an extension of the tubal epithelium to the capsule is not particularly noticeable in the rat's kidney, and cannot be adduced to explain the peculiar appearances described.

Observations concerning the passage of epithelial cells from the convoluted tubes into the capsular space, have been made by Kölliker[1] and by Argutinski.[2] While discussing the nature of the normal glomerular epithelium, Kölliker says:

"In hardened kidneys the epithelium of the convoluted tubes is not infrequently pressed up into the capsules, so that in many cases a membranous layer is formed which is arranged like a funnel around one end of the glomerulus."

[1] Kölliker, Handb. d. Gewebelehre, Leipzig, 1867, p. 504.

[2] Argutinski, Beiträge zur Normalen und Pathologischen Histologie der Niere, p. 18. Inaug. Diss. Halle, 1877.

Kölliker's observations relate, therefore, to artefacts produced by the action of the hardening fluid. In the cases of cantharidin nephritis which I have studied, the accumulation of tubal epithelium within the capsules cannot be regarded as an artefact, for the same appearances can be seen in sections of the fresh kidney as in sections of kidneys hardened in Müller's fluid, chromic acid, Flemming's solution, picric acid, osmic acid, and alcohol. The change is, therefore, one which occurs during the life of the animal. The same appearances in the Malpighian bodies which I have observed in the cantharidin nephritis of white rats, have been described and figured by Argutinski as occurring in the embolic infarctions experimentally produced in dogs by injecting into the renal arteries plugs of wax. He also speaks of the possibility of producing the same change by forcible injection of fluids into the renal bloodvessels. He therefore assigns as the cause of this phenomenon the pressure exerted by dilated bloodvessels upon the convoluted tubes, whereby the protoplasmatic contents of the latter are forced upward into the capsular spaces.

The following are among the factors which may be adduced to explain the mechanism by which the cells in cantharidin nephritis make their way from the convoluted tubes into the capsular spaces: Obstruction of the uriniferous tubes, both in the cortex and in the pyramid, by desquamated and by necrotic epithelial cells, and by hemorrhages within the tubes, pressure upon the tubes from without by congested bloodvessels and by transuded serum, and cessation of the excretion of urine from the glomeruli. In consideration of these alterations in the kidney, it is comprehensible that swollen and desquamated epithelial cells in the beginning of a convoluted tube might find toward the capsular space the direction of least resistance.

There is, of course, no propriety in designating as glomerulo-nephritis the changes in the Malpighian bodies of the rat's kidney which have been described. The term glomerulo-nephritis, however, is one which is used with much latitude of significance, and embraces nearly all of the changes observed in acute nephritis in the Malpighian bodies and a large number of those found in chronic nephritis. Many of these changes are not proven to be inflammatory.

I am not able to say whether a process similar to that which I have found in the Malpighian bodies of the kidney of the rat poisoned by cantharidin, occurs also in the nephritis of other animals and of man. In the acute cantharidin nephritis of rabbits the capsular spaces also contain granular material and cells, but the cells do not form such compact masses as in the rat's kidney, and more frequently undergo necrosis. I have not been able as yet to reach a positive conclusion as to the origin of these cells. To the descriptions which have been repeatedly given of the cantharidin nephritis

of rabbits, I have to add the almost constant occurrence of necrosis of epithelial cells in certain tubes occupying the boundary zone of the pyramid and the medullary rays. These tubes appear to be terminal portions of the proximal convoluted tubes (Endstückchen, spiral tubes). Hemorrhages within the tubes, particularly those of the pyramid, are not infrequent.

In human glomerulo-nephritis one is not generally at a loss to account for the crescentic mass of cells which frequently occupies the capsular space. The presence of these cells is accompanied with swelling and desquamation of either the glomerular or the capsular epithelium, usually of both, and these changes explain the accumulation of cells in the capsular space.

One of the leading objects in making these experiments on cantharidin nephritis was to determine whether changes were thereby produced in the glomerular capillaries. Friedländer, Nauwerck, and Langhans have called attention to the accumulation of cells in the interior of the glomerular capillaries as a frequent and important lesion of acute and of chronic nephritis. These cells they regard, for the most part, as proliferated capillary endothelial cells. Previous experimenters on nephritis may no mention of alterations in the glomerular capillaries, so far as I have been able to learn.

The technical difficulties attending the microscopical investigation of the glomerular capillaries are considerable. It is often desirable, as recommended by Langhans, that these capillaries should be injected with colorless gelatine, although when they are widely distended with cells, as in some instances of Bright's disease, such a procedure is not necessary. The sections of the glomeruli must be extremely thin, and this is best accomplished by embedding pieces of the kidney either in celloidin or in paraffin, in the latter case cutting the sections, of course, with the dry razor placed at right angles to the specimen.

In some cases of cantharidin nephritis no changes can be detected in the glomerular capillaries; in some instances, however, especially in the rabbit, these capillaries contain a large number of small, darkly staining nuclei, readily distinguished from the larger and paler nuclei of the glomerular epithelium. These nuclei belong for the most part to spherical, granular cells, which I am inclined to interpret as white blood-corpuscles. Positive evidences of proliferation of the capillary endothelium could not be found. Changes in the capillaries comparable in degree to those observed in many cases of nephritis in human beings, I have not been able to find in experimental cantharidin nephritis.

The occlusion of the glomerular capillaries in acute and chronic Bright's disease by granular material and cells, has been most fully described in all of its histological details by Langhans. My own studies of human kidneys are essentially confirmatory of Langhans's descriptions.

Swelling of the endothelium, and accumulation of cells in the glomerular capillaries, are nearly constant lesions in acute scarlatinal nephritis. These changes in the capillaries may be the only marked lesions in the kidney, although, as a rule, there is more or less accumulation of lymphoid cells in the interstitial tissue. I have observed similar accumulation of cells in the glomerular capillaries in acute Bright's disease complicating typhoid fever, and in a number of cases of chronic Bright's disease. The changes in the capillaries are usually accompanied by other lesions of diffuse nephritis.

I would, however, call especial attention to certain cases of Bright's disease which usually pursue a subacute course, in which the accumulation of cells in the capillaries of the glomerulus is the predominant, and sometimes the only evident lesion. The following case may serve as an illustration.

The patient, who had had malaria, was the subject for two months of anasarca. The urine was scanty, albuminous, and contained casts. Death resulted from uræmic convulsions. At the autopsy there was found malarial pigmentation of the spleen and other organs, the heart was considerably hypertrophied, and the kidneys were large, the surface smooth, the capsule non-adherent, and the cortex swollen. The Malpighian bodies were large and pale. Upon microscopical examination of the kidneys, with the exception of the change about to be described, there was very little abnormal. The epithelial cells were normal. Only after careful search could a few patches of infiltration with lymphoid cells be discovered. The Malpighian bodies were rich in nuclei. The glomeruli filled completely the space enclosed by Bowman's capsule. The case seemed a puzzling one, until after the examination of very thin sections it was found that almost everywhere the glomerular capillaries were dilated, and contained a large number of cells, partly resembling white blood-corpuscles, but mostly larger, and of an endothelioid type.

Probably many pathologists have met with kidneys in which the lesions seemed entirely inadequate to explain the symptoms. Doubtless a certain number of these obscure cases belong to the class just described. It certainly is important that a careful examination be made of the condition of the glomerular capillaries.

It is not necessary to dwell upon the importance which attaches to the lesions of the glomerular capillaries which have been described. When one considers the physiological functions of the glomeruli, it is difficult to think of any lesion of the kidney more destructive of its functions than the occlusion of the capillaries of the glomerulus. It is more reasonable to refer the production of albuminuria to changes in the capillary walls of the glomeruli than to desquamation or other alteration of the glomerular epithelium.

Certainly some swelling and desquamation of this epithelium are extremely common, even in cases without renal symptoms.

But while I am disposed to attach such importance to alterations of the glomerular capillaries, we are not justified in asserting, as has been done, that these changes constitute the primary and essential lesion of all cases of Bright's disease. The glomerular lesions are coördinate with the parenchymatous, the interstitial, and the other vascular lesions of diffuse nephritis.

As regards nomenclature, there is not much use in fighting against names which have gained currency, although the term glomerulitis seems to be more suitable than glomerulo-nephritis, and equally expressive. It is customary to include all of the changes of the Malpighian bodies which are not either atrophic or purely degenerative, under the name glomerulo-nephritis; but it is to be borne in mind that this term is used to designate a group of lesions belonging to diffuse nephritis, and not a disease by itself. I would suggest that the form characterized by an accumulation of cells between the glomerulus and Bowman's capsule be designated *desquamative glomerulitis,* and that characterized by accumulation of cells, or other changes in the interior of the capillaries, be called *intra-capillary glomerulitis,* and this without prejudging the question as to the propriety of considering all of these changes as inflammatory.

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DISCUSSION

Dr. Welch.—Experiments have been performed by Guarnieri and Agostinelli which bear upon the points raised by Dr. Jacobi. In a fatal case of cantharidin poisoning in a human being these observers failed to find marked lesions of the kidney, such as had been described by Cornil in his experiments on rabbits. They concluded that these severe lesions occur only when the cantharidin is administered subcutaneously, and not when it is taken into the stomach. This conclusion they confirmed by experiments on rabbits.

It is said that cantharidin acts upon various organs of the body, producing changes especially in the capillary endothelium. I have confined my attention to the kidney, my purpose being not so much to study the action of cantharidin as such, but to investigate certain lesions of the Malpighian bodies.

As to the permanency of the alterations of the glomeruli, this depends upon their character. The accumulation of cells in the capsular space has nothing about it which is irremediable.

Whether or not we are to regard this or some other change of the glomeruli as the necessary starting-point of acute and chronic Bright's disease it is impossible to say positively. 'It seems to me that our present knowledge does not justify us in assigning to any one particular process the origin of the different forms of nephritis. It is sufficient to describe the various processes occurring in Bright's disease, without expressing positive opinions as to the dependence of one process upon another.

I do not wish to be misunderstood in regard to the use of the term glomerulo-nephritis. I do not understand this to indicate a separate disease of the kidney. The term glomerulo-nephritis or glomerulitis is a convenient one to designate all of the changes, not degenerative or purely atrophic which occur in the Malpighian bodies.

I think that too much importance is sometimes attached to mere desquamation of the capsular and of the glomerular epithelium. This desquamation is a very common condition even when there is not much disease of the kidney, and when there have been no marked renal symptoms during life. I question the propriety of attributing albuminuria to changes in the glomerular epithelium. There is more reason to suppose that changes in the walls of the glomerular capillaries are the essential factor in the production of albuminuria. The capillaries of the glomerules differ in structure from the capillaries in other parts of the body, and these differences may explain the fact that normally they do not permit the transudation of an albuminous fluid.

THE CARTWRIGHT LECTURES

ON THE GENERAL PATHOLOGY OF FEVER[1]

LECTURE I

THE NATURE OF FEVER

There is no subject in medicine of more general and varied interest than fever. The practitioner in every department of medicine, the pathologist and the physiologist are equally interested in the investigation of the nature and effects of fever. Even the physicist and the chemist, who are not directly concerned with medical science, have lent their aid to the study of animal heat and its disorders. The history of opinion regarding fever is in great part the history of medicine itself, for no feature of the great systems of medicine from Hippocrates and Galen to the present century so characterizes these systems as the views held concerning the nature of fever. In consequence of the importance of the subject and of the number and ability of those engaged in its investigation, it might be supposed that no chapter in medical science would be better understood than that pertaining to fever. That such is not the case is due to the fact which is becoming more and more evident that the reaction of the animal system which we call fever is dependent upon the most fundamental and essential properties of protoplasm and of nerve energy. In proportion as our knowledge of these properties increases and becomes more accurate, we gain a clearer insight into the complicated processes involved in the production of fever.

I should hardly have selected for this course of lectures a subject where so many problems remain unsolved and which must necessarily be presented in so fragmentary a form, were it not that in all ages the opinions held concerning the nature of fever have controlled measures employed in its treatment. In proof of this, one need not go back to the time when fever was regarded as an almost conscious struggle of an anima with a noxious principle, in which struggle the physician was to interfere as little as possible, or to the time when fever was supposed to result from morbid humors which the physician should aim to eliminate by the production of a critical discharge, or to the period when the treatment hinged upon the belief either in the sthenic

[1] Delivered before the Association of the Alumni of the College of Physicians and Surgeons, New York, March 29, April 5 and 12, 1888.

Med. News, Phila., 1888, LII, 365; 393; 539; 565.

or the asthenic nature of fever. In our own time the treatment of fever is intimately connected with the answers variously given to such questions as whether fever aids in the elimination or destruction of infectious agents concerned in its production; whether increased waste of tissue is a constant condition and a source of danger in fever; what part is played by infection and what part by elevation of temperature in causing the grave symptoms of fever; what in addition to lowering of temperature are the effects of so-called antipyretic measures of treatment?

I need hardly say that the subject of these lectures relates to fever as a condition common to all febrile diseases. Some writers understand by the term fever used in this sense merely abnormal elevation of temperature, others elevation of temperature and the symptoms directly caused by this, and still others a complex of symptoms of which increased temperature is the most prominent but not necessarily the cause of the others. In considering the general pathology of fever it is convenient to adopt the last meaning, although it would doubtless be less confusing if the word fever were applied only to abnormal elevation of temperature.

Increased temperature being the dominant and essential system of fever, all discussions as to the nature of fever centre around the question, How is the febrile rise of temperature produced? It is to the consideration of this question that I first invite your attention. As there are other aspects of fever which I wish to discuss, it will be necessary to present the matter belonging to this division of the subject in as succinct a form as is compatible with clearness. Twelve years ago Burdon-Sanderson[1] brought together in an admirable critical review the results of investigations upon this subject up to that period. Since that time important additions have been made to our knowledge of the mode of production of fever.

In the wonderful preservation of a nearly constant temperature which characterizes in health the warm-blooded animals three factors are concerned, viz., the production of heat within the body, the loss of heat from the body, and the regulating mechanism by which the varying heat production and heat loss are so balanced that the internal temperature remains practically constant. It is theoretically possible that the rise of temperature in fever may be due to the disturbance of any one or more of these factors. It becomes necessary, therefore, to consider the behavior of heat production, of heat loss, and of the regulating mechanism in fever.

We will begin with the consideration of the production of heat in fever. The amount of heat produced by the body is estimated by two methods, one known as direct calorimetry, the other as indirect calorimetry. In the method of direct calorimetry the animal is placed in a closed ventilated box

[1] Burdon-Sanderson: The Practitioner, 1876.

surrounded on all sides by a compartment containing water or air, and the amount of heat discharged from the body is determined by the quantity of heat imparted to the surrounding water or air. If the temperature of the animal remain unchanged during the period of observation, the heat production is equal to the heat loss; if the temperature rise or fall, the amount of heat corresponding to this change of temperature—an amount determined by multiplying the weight of the animal by its specific heat and by the number of degrees of altered temperature—is added to or subtracted from the quantity of heat imparted to the calorimeter. Time will not permit me to enter into experimental details in this connection; it must suffice to say that the method of direct calorimetry necessitates the introduction of a number of corrections which cannot be determined with absolute accuracy, so that the results obtained are of relative rather than of absolute value.

Hitherto the estimation of heat production in fever by determining the entire amount of heat liberated from the body has been made only upon animals in which fever has been artificially produced. The most elaborate researches of this nature are those of Senator[3] and of Wood.[4] The experiments of Wood are of the greater value because he extended his observations over longer periods of time.[5]

In four of the seven calorimetrical experiments of Wood on different fevered dogs comparison can be made of the amount of heat produced hourly in fever with that produced by the same animal when fed and when in a state of hunger. During the period of fever the animal was also in a condition of hunger. I have computed from Wood's tables that the average hourly heat production during seven days described as first and second fever days, is a little over 23 per cent greater than that of the healthy animal during a state of hunger, the minimum excess being 1 per cent and the maximum 55.5 per cent.[5] If a comparison be made of different periods during the existence of fever there are found to be even greater fluctuations in the amount of heat production than these figures would indicate, this amount being sometimes more than double that in hunger and sometimes considerably less than the average production in hunger. Moreover, these experiments show no definite relation between the height of the temperature and the amount of heat produced, nor is it possible to deduce from them any relation between heat production and the different stages of fever, such as the more recent calorimetrical experiments of Wood, Reichert, and Hare[6]

[3] Senator: Untersuchungen über d. Fieberhaften Process, Berlin, 1873.

[4] Wood: Fever, A Study in Morbid and Normal Physiology, Philadelphia, 1880.

[5] In making this computation I have corrected some numerical errors in Wood's tables; these errors are not serious and do not affect his conclusions.

[6] Wood, Reichert, and Hare: Therapeutic Gazette, 1886.

appear to show and which will be described later. An important outcome of these as well as of all similar calorimetrical experiments is that, although the heat production of an animal in fever is greater than that under like conditions of nourishment, it is, as a rule, less than that of the same animal upon a full diet.

There are many reasons which make it important to control the experimental results obtained from animals in fever by corresponding observations of human beings. The agents used in producing experimental fever have been generally putrid fluids or pus, the injection of which causes sometimes diminution instead of elevation of temperature. When fever is thus produced, it is usually of short duration and of only moderate intensity, the rise of temperature being rarely more than four degrees, and sometimes not more than one degree Fahrenheit. Moreover, a large part of the important rôle played by the skin in the regulation of the bodily temperature in man is assumed by the lungs in these animals.

Complete calorimetrical observations of human beings in fever encounter difficulties which have not yet been overcome. The imperfect or incomplete methods employed by Liebermeister[7] and by Leyden[8] in determining the heat production of human beings in fever justify the inference that this production is increased, and, apparently, as a rule, to a greater extent than in animals, but they do not warrant positive conclusions as to the quantity of heat produced.

We turn now to the results regarding febrile production of heat obtained by what has sometimes been called indirect calorimetry. Inasmuch as the heat energy of the body is the result of chemical changes of its proteids, fats, and carbohydrates, it is evident that if we know the kind and the amount and the heat value of the substances consumed in a given time within the body, we can compute their heat production.[9] These chemical changes, so far as their final products are concerned, are processes of oxidation. The heat values of the substances consumed in the body were determined first by Frankland and more recently with accuracy by von Rechenberg, Danilewsky, and Rubner. The investigations of Pettenkofer and Voit have shown that in hunger almost exclusively fats and proteids are oxidized, and that in this condition by determining the amount of oxygen absorbed and of nitrogen

[7] Liebermeister: Handb. d. Path. u. Therap. d. Fiebers. Leipzig, 1875.

[8] Leyden: Deutsches Arch. f. klin. Med., Bd. 5.

[9] The energy resulting from these chemical changes appears partly in the form of heat and partly in mechanical work. As practically all of the internal mechanical work is transformed within the body into heat energy, it is only the external mechanical work which is to be considered in estimating the actual heat production. The influence of this factor in fever will be spoken of later.

and of carbon excreted, we can estimate the quantity of fat and of proteid substances oxidized during the period of observation.

Physicians of past centuries regarded increased consumption of the material of the body in fever as so evident that it needed no especial demonstration, and after Lavoisier made apparent the sources of animal heat, it was accepted almost unquestioningly until the last quarter of a century that fever is essentially a process of increased combustion or oxidation. The immense historical importance of the promulgation in 1863 of Traube's theory, which denied the dependence of fever upon increased production of heat, is that this theory has led to a careful inquiry into the grounds of beliefs hitherto generally accepted, and to the demonstration of the unsatisfactory nature of the evidence hitherto thought to be conclusive.

The striking loss of weight of most fever patients is, as is well known, a fact of great clinical importance. Weber, and Finkler have demonstrated that animals in fever lose weight more rapidly than healthy animals in hunger, and although observations on human beings with reference to this point are not concordant in their results, there can be little doubt that the tendency of fever is to cause a greater loss of weight than can be explained simply by insufficient nutriment. This tendency, however, may be masked by the retention of water within the body as the investigations of Leyden and others have shown. While, therefore, the studies of the loss of weight in fever leave no doubt that there is increased destruction of tissue in this condition, we cannot consider this loss as an accurate measure of the increased destruction, nor, without further knowledge, as an indication of increased oxidation, still less as proof of excessive production of heat.

It was for a long time believed that the excessive excretion of urea in fever afforded satisfactory evidence of increased oxidation and of greater production of heat. We now know, especially from the researches of A. Fränkel,[19] that this is so far from being true that we could explain the excessive elimination of urea better upon the assumption of diminished than of increased oxidation of tissue. In certain pathological conditions, notably phosphorus poisoning, the amount of urea excreted may be increased more than threefold, notwithstanding, or, as Fränkel believes, in consequence of diminished absorption of oxygen and elimination of carbonic acid. It can, moreover, be computed that even without any diminution of the respiratory gases the discharge of urea may be increased without greater production of heat. While, therefore, the enormous increase in the discharge of urea in fever sheds valuable light upon a most obscure subject, the nature of febrile metabolism, it does not, regarded by itself, afford us any information as to the production of heat.

[19] Fränkel: Virchow's Archiv, Bd. 67.

Failing to find satisfactory proof of increased oxidation in the loss of weight of the body, or the excessive excretion of urea in fever, attention was then directed to the elimination of carbonic acid, an excretory product which bears a much closer relation to the production of heat than does urea. Immense importance has been justly attached to the determination of the amount of carbonic acid excreted by an individual in fever. No point in the whole battle-ground of fever pathology has been more hotly contested than whether increased production of carbonic acid is an essential part of the febrile process. The first investigators of this question, Leyden, Liebermeister, Senator, contented themselves with the determination of the amount of carbonic acid eliminated by an individual in fever and in apyrexia. There are several considerations which greatly diminish the value to be attached to the mere estimation of carbonic acid excreted without simultaneous determination of the amount of oxygen absorbed. As has been urged by Senator, and with especial clearness by Pflüger, increased discharge of carbonic acid does not necessarily imply increased production of the same. The discharge of carbonic acid varies, independently of its production, with the rhythm and depth of respiration, and with the temperature and the alkalinity of the blood, all factors which are altered in fever in such a manner as to favor increased liberation of carbonic acid. It is true that the influence of these factors would cause increased discharge of carbonic acid out of proportion to its production only for a limited period, and that the prolonged increase in the amount of carbonic acid discharged in fever, which has been found by several observers, can hardly be interpreted otherwise than in favor of increased production. There is another point which detracts still further from the value of exclusive determinations of the quantity of carbonic acid discharged, and this is that it makes a great difference, so far as the production of heat is concerned, whether the carbonic acid is the result of oxidation of carbohydrates, of fats, or of proteids, a difference amounting, according to Rubner,[11] to 29.5 per cent; or, if only the proteids and fats be considered, to over 20 per cent. In investigations of nutrition it is now known to be of the utmost importance to determine the so-called respiratory quotient—that is, the ratio between the amount of carbonic acid discharged and that of oxygen absorbed. This quotient varies in a definite way with the kind of material oxidized in the body, and an accurate knowledge of it would enable us to draw conclusions as to the substances consumed in fever.

The investigations which have been published within the last few years upon the absorption of oxygen, as well as the discharge of carbonic acid in fever, are to be ranked as most valuable contributions to our knowledge of the subject. The first determination by trustworthy methods of the amount

[11] Rubner: Zeitschrift f. Biologie, Bd. XXI.

of oxygen absorbed and of carbonic acid excreted in fever was made in Pflüger's laboratory by Colasanti upon a guinea-pig, and was published in 1877. Since that time two careful and elaborate researches upon this subject have been made, the one by Finkler, and the other by Lilienfeld."[12]

These experimenters found that in fever there is increase of the amount, both of oxygen absorbed and of carbonic acid excreted. Making comparison with healthy animals under the same conditions of nutrition, Colasanti found that the increase in the absorption of oxygen amounted to 18 per cent, and in the excretion of carbonic acid to 24 per cent; Finkler, whose experiments were made also upon guinea-pigs, found, under varying conditions of external temperature, the average febrile increase of oxygen to be 13.8 per cent, and of carbonic acid 15.3 per cent, and Lilienfeld, who experimented on rabbits, found the average increase of oxygen to be 13.9 per cent. The statement of these averages gives an incomplete conception of the oxidation in fever, as they are derived from all stages of fever, and varying elevations of temperature. No constant proportion was found to exist between the height of the temperature and the amount of oxidation. On the other hand, a relation was observed between the oxidation and the stages of fever, viz., the initial stage with rising temperature, the acme with constant high temperature, and the defervescence with falling temperature. During the period of rising temperature oxidation was increased, and in this stage Finkler found the highest percentages, amounting to 36.6 per cent in the increase of oxygen, and 37.6 of carbonic acid. There were, however, marked fluctuations in this stage, both in the temperature and the amount of oxidation. In the stage of constant high temperature such high percentages were not noticed, and the fluctuations were less marked. The processes of oxidation, according to Lilienfeld, are increased, on the average, less in the acme than in the initial stage of fever.[13] During defervescence of fever the increased oxidation falls, and may sink below the normal. Taking a broad view of these stages, we may say, therefore, that the periods of rising, constant, and falling temperatures in fever, correspond to periods of rising, constant, and falling oxidation, but we must bear in mind that the fluctuations in oxidation are much greater than, and bear no constant relation to, those of temperature; so that, in each period, there are times when oxidation may rise or fall most decidedly without corresponding changes of temperature.

Inasmuch as these experiments have shown that the increased excretion of carbonic acid in fever is accompanied by increased absorption of oxygen,

[12] Colasanti: Pflüger's Archiv, Bd. XIV. Finkler: *Ibid.*, Bd. XXIX. Lilienfeld: *Ibid.*, Bd. XXXII.

[13] In the period of rising temperature there was an increase of oxygen absorbed of 27 per cent, in the acme of 14.9 per cent.

and, as will be explained presently, that the respiratory quotient, if it changes at all, sinks, it is evident that we need not discard experiments in which only the amount of carbonic acid excreted has been estimated by good methods. The most accurate of these experiments are those of Leyden and Fränkel upon fevered dogs.[11] They found that, without exception, carbonic acid is excreted in larger amount in fever than in health under the same nutritive conditions, the excess amounting sometimes to 70 per cent, and in general being larger than in the experiments which have been previously considered. The earlier and meritorious experiments of Senator upon this point did not give uniform results, and he felt justified in concluding that there is no evidence of increased production of carbonic acid in fever. Subsequent experiments with far more accurate methods have demonstrated the incorrectness of Senator's conclusions. It may be well to call to mind that Burdon-Sanderson's deductions, which have naturally had great influence among physicians here and abroad, were based, in great part, upon the data derived from Senator's experiments.

Hitherto, the methods employed in studying the respiratory gases of human beings in fever have not approached in accuracy those used in the experiments described. If the discordant results of Wertheim, which were obtained by methods manifestly very inaccurate, be discarded, all other investigators have observed augmented discharge of carbonic acid in fever of human beings. Leyden found an excess of 50 per cent in the febrile discharge of carbonic acid; and Liebermeister, whose observations were made chiefly on cases of intermittent fever, found an excess of 30 to 40 per cent in the period with rising temperature, and of 19 to 31 per cent in the acme of the fever. During the defervescence of the fever the excess of carbonic acid discharged diminished, and sometimes wholly disappeared. In one instance, in which the determination was made during the rigor of intermittent fever, the carbonic acid excreted was two and a half times the normal amount; an excess so enormous that it was undoubtedly due, in great part, to the muscular movements which attended the chill.

Although we cannot consider these figures as absolutely accurate, they indicate clearly that in human beings, as well as in animals, fever is characterized by increased oxidation, and apparently that, as a rule, in man the excess of oxidation is greater than in the experimental fever of animals. This was to be expected, as it is difficult to produce experimentally in animals anything approaching in intensity the well-marked fevers of human beings.

As the result of these laborious researches we may consider it established that increased oxidation is a part of the fever process. It has been claimed that this augmented oxidation is simply the result of the elevation of tem-

[11] Leyden and Fränkel: Virchow's Archiv, Bd. 76.

perature, but it can be proven that this is not true. Pflüger has demonstrated that the processes of oxidation are more active at high than at low temperatures of the body, and he has also established the increment of oxidation which corresponds to each degree of rise of temperature. By means of these data Finkler has computed that in guinea-pigs the febrile elevation of temperature of 1° C. could cause an increase of the absorption of oxygen of only 3.3 per cent. Moreover, Lilienfeld found decided increase in the processes of oxidation before there is any marked elevation of temperature, and all the experiments have rendered it quite evident that there is no such relation in fever between the height of the temperature and the energy of oxidation, as would be expected if the augmented oxidation were merely the result of the increased temperature.

There is no reasonable doubt that the more energetic oxidation which we find to be an essential part of the process of fever indicates increased production of heat. Exactly what amount of heat production corresponds to the increased oxidation we cannot know until the kind and the quantity of substances oxidized in fever have been determined. It is to be regretted that no experiments have been made in which the amount of nitrogen excreted has been determined at the same time with the estimation of the oxygen absorbed, and of the carbonic acid discharged. These data would enable us to form some estimate, although not an accurate one, of the amount of heat production corresponding to the oxygen absorbed, unless very different laws from those in health control the oxidation processes of fever.

Mention has already been made of the importance of determining in fever the respiratory quotient, or the ratio between the carbonic acid discharged and the oxygen consumed. A few words will make this clear. It is well known that under ordinary circumstances in health not all of the oxygen consumed reappears in the carbonic acid discharged. This indicates that a part of the oxygen absorbed is used in other oxidations than those resulting in the production of carbonic acid. According to the extent of these other oxidations, therefore, the respiratory quotient must vary. It is probable that these oxidations, of which carbonic acid is not a product, result at least in part, in the formation of water, which is, therefore, one of the excretory products of the body, as has been urged especially by Austin Flint. The influence of various circumstances upon the respiratory quotient has been studied, but what especially concerns us here is that in hunger this quotient sinks, which is to be expected from the fact that in this condition almost exclusively fats and proteids are oxidized. We evidently possess in the determination of the ratio of carbonic acid discharged to the oxygen consumed a means of reaching a conclusion as to a cardinal point in the pathology of fever, viz., whether the processes of oxidation in fever conform

to the laws which govern them in health, and particularly whether, as has been often asserted, unusual or incomplete products of oxidation are formed to any considerable extent in fever. Colasanti and Lilienfeld found that the respiratory quotient in their fevered animals did not vary from that of healthy animals under similar nutritive conditions. Finkler observed that the respiratory quotient fell in fever somewhat more rapidly than in hunger, and this he explains by the more active oxidation in fever. All three experimenters reached the conclusion that the substances oxidized are the same in fever as in health, and that other than the normal products of combustion are not formed in fever in any considerable amount. That the metabolism in fever does differ in at least one important respect from that in hunger, is evident from the excessive amount of urea excreted in fever, but considerable variations in the disintegration of albuminous material may occur without much change in the respiratory quotient.

The only determinations of the febrile consumption of oxygen and discharge of carbonic acid in man are those of Wertheim and of Regnard. Both investigators found a decided diminution of the respiratory quotient. The method employed by Wertheim was so defective that no confidence can be placed in his results. The experiments of Regnard [15] are presented with great neatness, but his results on other points differ so much from those obtained by trustworthy physiologists and by better methods, that we cannot accept his conclusions as to respiratory quotient in fever without confirmation. Regnard found in all fevers which he studied a most marked diminution of the respiratory quotient. If this were true it would follow that in fever a much larger part than in health of the oxygen consumed is employed in other oxidations than those yielding carbonic acid. This would confirm the widely accepted belief that water and products of incomplete oxidation are formed in excessive amount in fever.

From the unfortunate discrepancy of these results it is evident that the knowledge which we now possess of the processes of oxidation in fever is not sufficient to enable us to form from them an accurate estimate of the heat production. In hunger, from one-fourth to one-third of the absorbed oxygen is available for combination with hydrogen to form water, the remainder uniting with carbon to form carbonic acid (Regnault and Reiset). If in fever the same ratio exists, then the excess of heat production would be proportionate to the excess of oxygen absorbed, assuming that the substances oxidized are the same in both conditions; if, however, as Regnard's experiments indicate, a larger proportion of oxygen is available in fever for the oxidation of hydrogen, then the increment of heat production would be still

[15] Regnard: Recherches Exp. sur les Variations Pathologiques des Combustions Respiratoires. Paris, 1878.

greater, for the same amount of oxygen produces more heat when employed in the oxidation of hydrogen than in that of carbon. It is also to be considered that the same quantities of hydrogen and of carbon in their oxidation yield varying amounts of heat according to the chemical compounds in which they are contained, and we cannot say positively whether the compounds oxidized are the same in fever as in health under like conditions of nutrition. Upon the whole the weight of evidence is in favor of the view that the excess of heat production in fever is approximately proportionate to the increase in the consumption of oxygen, but it would be rash to assert this positively. It is evident that in fever ordinarily a much smaller amount than in health of the energy resulting from chemical processes is transformed into external mechanical work, so that relatively more remains in the form of heat.

In connection with this discussion of the possibility of unusual sources of heat in fever may be mentioned an hypothesis which has been advanced with much ingenuity by Dr. Ord.[18] This hypothesis is based upon the assumption, which is probable enough, that there are in the body chemical processes in which heat energy is transformed or rendered latent. These processes are thought to be chiefly those concerned in the building up of tissue. It is argued that inasmuch as the construction of tissue is manifestly in abeyance in fever, the amount of heat in the body may be increased not only by disintegrative processes, but also by "the persistence in the form of heat of energy which should have taken another form." That these building up processes influence decidedly the amount of heat produced in the developing ovum has been demonstrated by d'Arsonval's calorimetrical determination that the egg during incubation absorbs heat, notwithstanding the consumption of oxygen and the excretion of carbonic acid. This fact, which might have been predicted, certainly does not justify us in refusing to attach any calorimetrical value to the determination of the respiratory gases and the urinary nitrogen. From the little we know of these constructive processes in human beings we should infer that the amount of energy in the form of heat which they appropriate bears only a very small ratio to the total heat energy set free by heat-producing processes, so that their cessation would not bring a large increment to the heat of the body. Moreover, these constructive processes are also in abeyance, although doubtless to a less extent, in starvation, with which experimental fever is usually contrasted as regards heat production and heat loss. It is not probable that any extraordinary difference in the behavior of the processes of tissue-building in fever and in starvation can occur without affecting the respiratory quotient. For the present, therefore, we cannot attach any great importance, so far as the

[18] Ord: British Medical Journal, 1885, II.

increase of heat energy in fever is concerned to the inactivity of heat-absorbing processes.

We have gone over now the evidence which, in my judgment, establishes the fact that there is increased production of heat in fever. The same conclusion is reached also by the study of the loss of heat from the body in fever. That fever is accompanied by increased production of heat and by more active combustion, has been in all ages the belief of the majority of physicians. This belief, however, has been rather instinctive than based upon actual demonstration. It has been contested by investigators of great ability, and on the ground of scientific observation. For these reasons, and on account of the importance of the subject, it has seemed to me desirable to present to you the exact evidence, although many of its details, I fear, may have wearied you. We have learned, moreover, certain facts concerning febrile thermogenesis which the mere observation of fever patients does not render so apparent. We have found that there is no definite relation between heat production and the height of the temperature, so that we may have excessive thermogenesis with low as well as with high temperatures. There appears to be, however, a relation between the stages of fever and heat production, this being in spite of remarkable fluctuations greatest in the initial stage, and least in defervescence.

Although for reasons which have been mentioned, and others might have been adduced, we can attach hardly an approximative value to figures which purport to give the actual heat production in fever, still, unless far more serious errors than seems possible in here in the methods of direct and of indirect calorimetry, we can draw one important conclusion. This is that while an individual in fever produces more than he would in health under similar conditions as to food and muscular movements, he does not produce necessarily in fever more heat than he would in health on a full diet. And it is certain that he usually produces far less heat in fever than he often does under circumstances which normally increase heat production, such as a cool environment and muscular exercise. That one in health, with little or no change of temperature, may produce twice or more the quantity of heat which he produces in fever, makes it plain that it is impossible to explain febrile rise of temperature simply on the basis of increased thermogenesis, or what probably comes to the same thing, of increased oxidation. That in health vastly increased heat production may occur with comparatively little change of temperature is, of course, due to the fact that the dissipation of heat is proportionately increased. It is self-evident, and, so far as I know, has never been disputed that in fever the equilibrium is so disturbed that heat loss does not correspond to heat production as it should in health. This disturbance of equilibrium can be brought about in various ways, and

it is only by the determination of the actual heat production and heat loss in fever that we can say in what direction the balance is disturbed.

We have found that the production of heat is increased in fever when the comparison is made with like conditions of nourishment and of environment. It is obvious that the total loss of heat cannot equal the total production of heat during the period of febrile rise of temperature.

As is well known, most of the heat of the body is liberated from the skin and from the lungs; from the former by radiation and conduction and by the evaporation of moisture, and from the latter by evaporation of moisture and warming the respired air. It has been estimated that in man about eighty per cent of the total heat dissipation is from the skin.

The method of direct calorimetry, already described, has been applied only to animals for the determination of the total heat loss in fever. Here Wood's experiments are the best which we possess. Leyden and Liebermeister have furnished calorimetrical data which, although unsatisfactory in many respects, indicate the general direction of febrile heat loss in human beings. All of these experiments show that more heat is dissipated in fever than under like conditions in health. The fluctuations of heat loss during a febrile paroxysm are so great that the statement of an average for the entire period has little significance. Such an average, according to Wood's results on fevered dogs, would fall between twenty to thirty per cent excess of heat loss as compared with the loss in health under like conditions of food. The dissipation of heat in fever, however, may be at times more than double the normal amount, and again may sink below the norm. We have not sufficiently accurate estimates either of the total amount of heat produced or of that dissipated during a febrile attack to enable us to strike a balance between the two. Some persons have been so impressed with the large amount of heat lost during certain periods of fever, that they have concluded that there must be far greater excess of heat production than previous investigations have shown to be probable. They suggest that there are sources of febrile heat of which at present we have no idea. Such conclusions seem to me quite unwarranted, when we consider the behavior of heat-loss, not for a limited time but throughout the different stages of a paroxysm of fever. We have already seen that we obtain no satisfactory conception of febrile production of heat unless we follow it during the stages of fever, and this is no less true of heat dissipation. The observation of the condition of the skin as regards temperature and moisture must in all ages have afforded an insight into the general behavior of heat dissipation during the different periods of fever. It does not require any instruments of precision to make plain the fact that a cold, dry skin, such as we observe during a febrile chill, liberates less heat than normal, or that a hot, moist skin, such as we are

likely to find at the defervescence, loses more heat than normal. Not quite so evident is the direction of heat loss during the hot stage or acme of a febrile paroxysm or fastigium of a continued fever. Here the skin usually appears hot and dry. The ordinary impression that more heat than normal is dissipated during this stage is supported by calorimetrical experiments. There can be no doubt that the elevation of the cutaneous temperature which we observe in the hot stage of fever causes an increase in the amount of heat lost by radiation and conduction. Similar elevations of cutaneous temperature in health, such as those caused by muscular exercise, are accompanied by increased moisture of the surface. Not only is visible perspiration usually absent during the hot stage of fever, but the invisible perspiration is, as a rule, relatively although not absolutely diminished, as Leyden has shown. The dryness of the skin, therefore, is a factor which in the hot stage of a fever tends to lessen heat dissipation. Clinical observation, however, shows that fevers differ markedly from each other as regards perspiration during the hot stage, the skin being sometimes bathed in perspiration without any depression of temperature. It would undoubtedly be of great interest to possess trustworthy data as to the exact loss of water from the surface of the body in different fevers and at different stages of fever. We cannot place much reliance upon the indications afforded by Weyrich's hygrometer, which has been repeatedly used for this purpose. More is to be expected from the method employed by Peiper[17] in studying insensible perspiration under physiological conditions.

The general impressions regarding febrile loss of heat derived from clinical observations, are supported by calorimetrical experiments. The dissipation of heat is least during the initial stage of fever, and greatest during the period of defervescence. During the hot stage or fastigium heat dissipation exceeds the normal, but usually, on account of the dryness of the skin, not so much as one might infer simply from the impression of heat received by the hand when placed upon the skin.

During the initial period the loss of heat, although on the average less than in the following stages, is usually greater than normal. If, however, the rise of temperature be rapid the heat loss falls below the normal amount. As there is now increased production of heat, there is evidently a glaring disproportion between the two factors, heat production and heat loss, and under these circumstances the febrile attack is likely to be ushered in by a chill. During the febrile chill all the efforts of nature combine to produce in the shortest time the greatest possible elevation of temperature. Not only is heat loss reduced to a minimum, but heat production is excited to the utmost.

[17] Peiper: Zeitschr. f. klin. Med., Bd. 12.

During the period of defervescence, on the other hand, the relation between heat loss and heat production is reversed. This is, of course, most apparent when the fever terminates by crisis with rapid fall of temperature. Then the loss of heat is excessive, being sometimes threefold that in the normal state, and the production is relatively and often absolutely diminished.

It is of importance to remember that there are continual and irregular fluctuations in the dissipation of heat during the different stages of fever. These fluctuations bear no definite relation either to the momentary production of heat, or to the height of the internal temperature. We deal in ordinary life so much more with units of temperature than with units of heat that it is difficult for us to keep constantly in mind the fact that no inference can be drawn as to the height of the internal temperature from the knowledge of the momentary heat production and heat loss. If the heat loss fall behind heat production the temperature of the body rises, and it can remain at this elevated point with either diminished or increased heat production so long as the heat loss equals heat production.

No correct conception of the condition of the heat-regulating mechanism in fever can be obtained without taking into consideration these irregular variations in the discharge of heat, and it is a merit of Senator and his pupils to have emphasized particularly this point. These variations are made apparent not only by calorimetric measurements and direct observation, but also by the studies which have been made of the cutaneous temperature in comparison with the internal temperature in fever. Hankel's law that the difference between the temperature in the axilla and that of the surface of the body in the febrile condition is less than in the normal condition manifestly does not hold for the chill, in which it has been proven that the superficial temperature falls while the internal temperature rises. Jacobson, Wegscheider, Schülein,[15] find that there constantly occur in the course of most fevers changes of the superficial temperature, which stand in no relation whatever to alterations of the internal temperature. Schülein thinks that he has discovered some facts in this regard which are available in diagnosis. However this may be, these observations indicate that contraction and dilatation of the cutaneous vessels are constantly occurring, and without any regularity, in fever. These irregular variations in the calibre of the bloodvessels are also apparent to the eye in the vessels of the rabbit's ear during fever. When it is considered, furthermore, that these irregularities of cutaneous circulation vary decidedly in different situations, no further proof is needed that the mechanism which regulates the discharge of heat from the surface of the body is profoundly disturbed in fever.

[15] Jacobson: Virchow's Archiv, Bd. 65. Schülein: *Ibid.*, Bd. 66. Wegscheider: *Ibid.*, Bd. 69.

These alterations in cutaneous circulation are such striking phenomena that it is perhaps not surprising that two great medical authorities should have based upon them exclusively theories of fever, Traube assuming excitation and Marey paralysis of vaso-motor nerves as the primal element in fever. We need not discuss these theories, now generally abandoned in their exclusive form. From what has been said concerning the loss of heat in fever, it is evident that we cannot explain febrile rise of temperature solely by the behavior of heat dissipation any more than we can explain it solely on the basis of increased heat production. In rejecting Traube's theory that fever is the result solely of retention of heat we must still recognize the fact that decrease in the dissipation of heat, at times absolute, at other periods relative, is a factor of the utmost importance in the febrile process.

From whatever point of view we consider the question we cannot avoid the conclusion that it is the mechanism which controls the relation of heat production to heat loss, which is disturbed in fever.

Heat production is increased in fever, but if the regulating mechanism were normal, then the discharge of heat would be proportionately increased and the temperature not be materially affected. Nor would the force of this argument be changed if febrile thermogenesis were twice as energetic as we suppose it to be.

The loss of heat is increased in fever, so that on this ground alone we should be obliged to assume increased heat production. But, even if it were proven that heat dissipation is diminished, as has been recently claimed again by Rosenthal,[19] and that fever is the result of heat retention alone, it would still be necessary to admit that the regulating mechanism is at fault, for Pflüger has demonstrated that when this is normal, changes in the temperature of the skin are attended by such changes in heat production that the internal temperature remains within wide limits unaltered.

I repeat then that the conclusion is forced upon us that the fever-producing agents must act either directly or indirectly upon the mechanism regulating the harmonious relation of heat loss to heat production.

That the heat-regulating mechanism, although profoundly disturbed, is not entirely paralyzed in fever, is proven by the effect of heat and cold upon fevered individuals. Although Colasanti believed that his fevered guinea-pig had lost all power of heat regulation under varying external temperatures, a similar conclusion has not been reached by others who have investigated this question.

We can best describe the condition of heat regulation in fever as unstable or ataxic. External cold stimulates to some extent the heat production of an individual in fever, but by no means as much as it does in health. A

[19] Rosenthal: Deutsche med. Wochenschrift, 1888.

person in fever is not able to maintain his bodily temperature under the influence of heat and cold to the same degree that he can under normal conditions. Liebermeister, as is well known, held that heat regulation in fever is simply adjusted for a higher point, although he admits not perfectly adjusted. Experience shows that this so-called adjustment is so unstable that it does not seem proper to compare it with that to normal temperatures in health, so that it is not clear what deep meaning lies in Liebermeister's idea.

We cannot imagine the heat-regulating mechanism to be other than a nervous one.

Some years ago this was about as far as the theory of the mechanism of fever could be carried. All paths led to this mysterious nervous apparatus, and beyond this nearly all was speculation. We stood, as has been said, before imposing processes veiled in the deepest obscurity. Since then the veil has been lifted here and there and we have caught glimpses of the nature of these processes. I refer particularly to the results of researches which have brought to light a more immediate and direct dependence upon nerve energy, than had been supposed, of chemical processes concerned in the disintegration and construction of tissue, and therefore, in the production of heat.

With one side of the nervous mechanism concerned in temperature regulation, the classical investigations of Claude Bernard have made us tolerably familiar. This is the vaso-motor nervous apparatus presiding over the circulation of blood in the superficial parts of the body, and thereby controlling in great measure the discharge of heat. That the important part taken by the perspiration in the dissipation of heat is likewise under nervous influence, has been demonstrated by Luchsinger. The facts concerning this side of the regulation of heat are too well known to require elucidation on this occasion.

Heat regulation, however, is effected not only by variations in the elimination of heat, but also by changes in the production of heat. Familiar as the fact is, it can never cease to arouse our admiration that the temperature of the body remains the same in cold and in warm atmospheres. Man has become so dependent upon clothing that in the naked condition his capacity of preserving his normal temperature in a cold environment is much less than that of most animals. Pflüger has demonstrated that the heat regulation under varying external temperatures is accomplished by changes both in heat production and in heat loss, so that in a cold atmosphere more heat is produced and in a warm atmosphere less heat, provided the external temperature is not so high or so low as to make it physically impossible to preserve the body temperature. It is evident that this is the most rational and

economical method of retaining the internal temperature of the body. To regulate the body temperature simply by variations in the discharge of heat, as was formerly supposed to be the method, would be, as has been said, like regulating the temperature of our rooms summer and winter by opening and shutting the windows without controlling the source of heat.

A heat-producing or thermogenic apparatus, therefore, is no less a part of the heat-regulating mechanism than is the heat-discharging or thermolytic apparatus, to use the terms employed by Foster. As the thermogenic apparatus is less generally understood it is not permissible to dismiss its physiology in this connection so briefly as I have the thermolytic, although our knowledge of the former is very imperfect.

I can assume that the convincing reasons are known to you which have led physiologists to conclude that most of the animal heat is produced in the muscles and the glands, and that the muscles have the larger share in this function. It is also well known that stimulation of secretory and motor nerves causes not only visible physical alterations in the glands and muscles, but also production of heat. This sort of dependence of heat production upon innervation has been long admitted. It may, however, not be so generally known that there are reasons to believe that nervous impulses control chemical changes which result in the production of heat independently of visible physical alterations of the tissues; in other words, that heat production or thermogenesis is at least in considerable part under the immediate and direct control of the nervous system. The idea is not a new one, and was advocated especially by Claude Bernard. Recent discoveries, however, have given it unexpected support.

This subject of the relation of innervation to thermogenesis is most pertinent to the pathology of fever, but it is essentially a physiological one, and as I wish to confine to a single lecture what I have to say concerning the theory of fever, it is impossible for me to do more than summarize the most essential points belonging here. This I can do the more readily as Dr. MacAlister,[20] in his admirable Goulstonian Lectures on the "Nature of Fever," which were delivered last year, has clearly and forcibly presented the main facts.

The larger part of these facts relates to the chemical changes and heat production of muscles under varying conditions.

That a large part of the chemical changes in a muscle in the condition which we call repose is under the influence of the nervous system, is made apparent by the great diminution in its consumption of oxygen and formation of carbonic acid, which follows the separation of the muscle from all connection with the central nervous system. This is conclusively shown by

[20] MacAlister: The Lancet, 1887, I.

the experiments of Bernard, Pflüger, von Frey, and others. It is, of course, possible, and it has generally been supposed that under these circumstances it is simply the withdrawal of motor impulses which lowers the heat-producing energy of the muscle.

Far more suggestive as regards the point under consideration are the results of investigation which have been carried on in Ludwig's laboratory by Meade Smith, MacAlister, and Lukjanow. These experimenters have shown that heat production and contraction are in a measure independent properties of the muscle. By various influences the thermogenic property may be so impaired that a stimulus causes contraction with scarcely any development of heat. The laws governing the restoration and the fatigue of the thermogenic function differ from those controlling the mechanical function. These researches, upon which I here only touch, have made it extremely probable that there are in the muscle chemical processes resulting mainly in the production of heat and chemical processes causing mainly contraction, and that these processes, although coördinate, are not identical. A new light is shed upon the meaning of the term chemical tonus of muscle, which has for some time been used by some physiologists. Great caution is properly exercised by Ludwig and his pupils in the interpretation of these interesting results. They do not infer from them, necessarily, the existence of so-called thermic of calorific nerves. They suggest that it is possible to explain the phenomena upon the supposition that there are in the muscle two kinds of material, thermogenic and contractile, and the nervous impulses acting upon these may pass through the same set of nerves.

Proof of the existence in connection with muscles of thermic in distinction from motor nerves, would be afforded if we could succeed, after paralysis of the motor nerves, in exciting by nerve stimulation the thermogenic function of the muscle. We possess, in curare, a drug which paralyzes the terminations of the motor nerves. Meade Smith attempted by its aid to determine whether possible thermic nerves may be differentiated from motor, but he reached no positive conclusion on this point. There are, however, on record some observations which suggest the possibility that in moderate doses curare may leave intact thermic nerves after the suspension of the function of motor nerves. When an animal is profoundly under the influence of curare the internal temperature falls, and the processes of oxidation are greatly reduced. The animal is no longer able to resist the changes of external temperature, its own temperature rising and falling like that of a cold-blooded animal when exposed to heat or cold. This effect of curare poisoning is another proof of the dependence of heat production upon nervous influences. Claude Bernard in his early researches on the action of curare noted elevation of temperature soon after its administration. Voison and

Liouville[21] observed after subcutaneous injections of curare in man rigors, perspiration, headache, and elevation of temperature to 104.7° F. They attribute to curare the power of producing all of the essential phenomena of fever. Fleischer[22] noticed in dogs and in rabbits rise of temperature after curare injections, and the same was observed in a rabbit in one case by Högyes.[23] Recently Mosso[24] claims that an animal may be placed so far under the influence of curare as to paralyze completely the voluntary muscles, and the internal temperature either remain normal or rise. He infers that these moderate doses of curare, although sufficient to paralyze the motor nerves, must have left intact the thermic nerves. That rise of internal temperature is not due to retention of heat, he thinks is evident from the normal or elevated temperature of the skin. Mosso is strengthened still further in his conclusion as to the existence of thermic nerves, by finding that after complete paralysis of the motor nerves by curare injections of strychnine cause an elevation of rectal temperature, which may amount to three degrees centigrade. Under these circumstances strychnine produces no spasms or other visible mechanical effect upon the muscles. Mosso brings forward a number of other experiments (decidedly open to criticism) intended to demonstrate the existence of nerves directly controlling heat production, but those which I have mentioned are by far the most striking. It seems to me that the natural interpretation of these experiments is in favor of the view that there are nerves controlling heat production in the muscle distinct from motor nerves. Far more conclusive as to this point than thermometric observations would be calorimetric experiments determining the heat production of animals under varying doses of curare.

This whole line of experimentation directed toward the differentiation of the mechanical and the chemical functions of muscle is certainly most suggestive, but so long as the interpretation of the results is not perfectly clear, we should be very guarded in drawing far-reaching conclusions. I cannot refrain, however, from pointing out that, as mentioned by MacAlister, all of these thermogenic phenomena may be found eventually to depend upon nerves whose chief function, on the one hand, is the disintegration, the metabolism of tissue, and, on the other hand, the restoration, the anabolism of tissue. From the study of the electrical changes which stimulation of the pneumogastric nerve produces in the heart muscle, Gaskell concludes that this nerve puts the heart in a condition of relative rest during which the energy of the muscle is increased. During this period there is reason to

[21] Voison and Liouville: Virchow u. Hirsch's Jahresbericht, 1866, I, p. 330.
[22] Fleischer: Pflüger's Archiv, Bd. II, p. 441.
[23] Högyes: Arch. f. exp. Path. u. Pharm., Bd. XIV, p. 136.
[24] Mosso: Virchow's Archiv, Bd. 106.

believe that the material of the muscle, which, when disintegrated, gives rise to heat and mechanical work, is in the process of restoration. Hence Gaskell speaks of the pneumogastric or inhibitory nerve of the heart as anabolic—that is, it directs the restorative, formative, anabolic processes in the muscle. On the other hand, the accelerator nerve of the heart induces the opposite electrical changes in the heart muscle. Gaskell describes this nerve as katabolic—that is, its stimulation causes disintegration of the muscle materials, and liberates energy in the form of heat and of mechanical work. If it be found that similar inhibitory and accelerator nerves preside over the chemical changes in the voluntary muscles and other tissues of the body, then Gaskell's induction as to the existence of anabolic and katabolic nerves must be regarded as one of the most important and profound in modern physiology. Thermo-excitory nerves we should then rank as katabolic, thermo-inhibitory as anabolic.

These investigations tending to demonstrate the independent existence of thermogenic properties in the muscles and possibly of nerves directly controlling thermogenesis, have prepared us for the consideration of the relation of the central nervous system to the heat-producing properties of the body. Here you will willingly permit me to confine my remarks to the more essential and best established facts, without entering into a full discussion of one of the most perplexing subjects in the physiology of the nervous system.

The clinical basis of the doctrine that lesions of the central nervous system influence directly the temperature of the body was laid by Sir Benjamin Brodie, who reported the well-known case of fracture of the cervical vertebrae and injury of the spinal cord followed within a few hours by a rise of temperature to 111° F. measured between the scrotum and the thigh. Since then many similar instances have been reported. It is well to remember, in framing theories on the basis of these cases, that there are also on record not a few instances in which apparently similar injuries of the same parts of the spinal cord have been followed by equally striking fall of temperature.

The experimental basis for the acceptance of an influence of the nervous system on temperature was laid by Bernard, in his celebrated experiments on the effects of division of the sympathetic nerve in the neck. Bernard interpreted the increased temperature of the ear following this operation as referable not only to the larger amount of blood in the part, but also to increased tissue metamorphosis and consequent heightened heat production. The latter part of this interpretation is not generally accepted. It may be said here that the common idea that an organ or tissue simply because it receives a larger supply of blood indulges in more active metabolism is opposed by the investigations of Pflüger, who finds that the amount of oxygen taken up by the cells depends in a far higher degree upon the state

of their innervation at the time than it does upon the supply of oxygen. The demand of the tissues for oxygen is not increased simply because the supply is greater. The arguments upon which Pflüger bases this line of reasoning, although not without opposition, would dispose of the idea that when any considerable increase of heat production in the muscles occurs this can be explained simply by vasomotor changes. I mention this here, because the opinion has been advanced that a large part of the increased production of heat in fever and after certain injuries to the nervous system is referable simply to vasomotor changes in the muscles.

In 1866 Tscheschichin[25] published experiments which he interpreted as indicating the existence in the brain of centers which, when irritated, moderate the production of heat, and which he called heat-moderating or heat-inhibitory centres, and in the spinal cord of centres which when stimulated excite the production of heat, heat-excitive centres. These conclusions were not justified by the experiments, but they have been widely accepted.

I may here say that, in this connection, I use the term heat centre as a convenient and generally adopted one. There is a proper reaction against the prevailing misuse of the word centre for all sorts of little understood localization of nervous functions. It would undoubtedly be more accurate to use some such expression as thermically active region instead of heat centre.

It is not easy to reconcile the clinical fact that in human beings lesions of the spinal cord may be followed at once, or in a very short time, by extraordinary elevations of temperature with the results of experiments on animals. That the rise of temperature in human beings is not due to inflammatory fever is apparent from the rapidity with which it follows the injury. It cannot be explained by vasomotor lesions, for the paralysis of the vasomotor nerves accelerates the discharge of heat from the surface of the body. The high temperature can be explained on Tscheschichin's assumption. The lesion either stimulates the spinal thermogenic centers or removes the influence of the thermo-inhibitory centres. These clinical observations are the strongest support which has been found for the belief in the existence of centres in the spinal cord which accelerate heat production. Complete section of the cervical part of the spinal cord in a dog or rabbit is, under ordinary conditions, always followed by a rapid fall of the internal temperature and diminished oxidation. These varying results in man and in animals have been explained by supposing that after section of the cervical cord, on the one hand, the discharge of heat is increased by dilatation of the superficial bloodvessels, in consequence of vasomotor paralysis; and, on the other hand, the production of heat is increased by withdrawal of thermo-inhibitory

[25] Tscheschichin: Reichert und Du Bois—Reymond's Archiv, 1866.

cerebral impulses. If, as ordinarily happens in dogs and smaller animals, the first factor predominates then, in consequence of sinking of the internal temperature, the heat-producing processes are so reduced that the influence of the second factor is not manifest. The attempt has been made to test this explanation by placing the animal in a warm atmosphere. If thereby the heat discharge be reduced to a minimum, it is found that the internal temperature of the animal often rises more rapidly than that of a normal one under the same external conditions. Here thermometric observations are not conclusive as to the point to be tested, for the more rapid rise can be explained simply by failure of the heat-regulating mechanism. Wood's calorimetric experiments seem to show that there is greater heat production, under these circumstances, in the animal with cut cord. These experiments admit of various interpretations, but if they be regarded as establishing the assumption from which we started, then it is evident that in man and in large animals the increased heat production after injury of the cord would not be so readily overcome by the increased discharge of heat from the surface, for, in proportion to its volume, a large animal has less surface than a small one. The interplay, therefore, of these opposing tendencies might cause different results, according to the size of the animals.

Tscheschichin found that a transverse section made at the junction of the pons and medulla oblongata is followed, in a short time, by rise of internal temperature. As the superficial temperature is also elevated, he concludes that there is no retention of heat; moreover the section is made above the dominant vasomotor centre. Wood has shown by means of the calorimeter that after this operation there is actual increase in the production of heat. He, as well as Tscheschichin, interprets the experiment as indicating thermo-inhibitory centres above the lower border of the pons. Bruck and Günter[26] repeated and modified these experiments under Heidenhain's directions. Out of seven cases in which they separated the pons from the medulla, they observed in only two rise of temperature; of eleven cases in which they punctured the pons with a needle, in five they noted increased temperature. Heidenhain thinks these experiments indicate heat-exciting rather than heat-moderating centres, and it must be admitted that the evidence is not conclusive in support of either view.

By far the most interesting and conclusive experiments, showing the influence of the central nervous system on thermogenesis are those of Isaac Ott, followed by Richet, Aronsohn and Sachs, Baginsky, and Girard.[27] The

[26] Bruck and Günther: Pflüger's Archiv, Bd. III.

[27] Ott: Journal of Nervous and Mental Diseases, April, 1884; Medical News, July, 1885. Therapeutic Gazette, Sept., 1887. Richet: Arch. de Phys., 1884. Aronsohn and Sachs: Pflüger's Archiv, Bd. XXXVII. Baginsky and Lehman, Virchow's Archiv, Bd. CVI. Girard: Arch. de Phys., 1886.

observations of Ott, Richet, and Aronsohn and Sachs were made independently and at about the same time, but Ott was the pioneer. The experiments of Aronsohn and Sachs are reported with especial fulness and detail. These investigators found that if the skull of a rabbit be trephined at the junction of the coronal and sagittal suture, and a needle be passed vertically down so as to puncture the anterior part of the caudate nucleus near its median convexity, there follows a rise of temperature, which may amount to three degrees or more, and which may persist for two or three days. The rapidity and the duration of this elevation of temperature vary somewhat with the depths of the puncture, parts immediately beneath the caudate nucleus being also thermically active. Puncture of the overlying cortex or medullary substance has no such effect upon temperature. With the exception of some increase in the frequency of the respiration and of the pulse, the animal after puncture of the anterior median part of the caudate nucleus presents no abnormal symptom other than the rise of temperature.

I have several times repeated this experiment and always with the result described. That the pyrexia induced by puncture of the caudate nucleus is not due to vasomotor changes causing retention of heat, is proven by Richet's and Ott's calorimetric experiments, and by the determination by Aronsohn and Sachs that the consumption of oxygen and the elimination of carbonic acid, and urinary nitrogen are increased. Aronsohn and Sachs and Girard find that electrical stimulation of the anterior median part of the caudate nucleus causes the same thermic phenomena as the puncture, and they, therefore, conclude that this region contains a thermo-excitor heat centre. This is the natural interpretation of their experiment, although Baginsky and Ott regard the centre as thermo-inhibitory on grounds which cannot be considered convincing.

Ott claims that there are four cerebral heat centres, one about the corpus striatum, the second in the caudate nucleus, the third in the anterior inner end of the optic thalamus and the fourth near the median line between the optic thalamus and the corpus striatum. The greatest rise of temperature he found after injury of the thalamic centre.

No adequate demonstration has been afforded of any influence of the cerebral hemispheres upon thermogenesis. Corin and van Beneden[25] find that pigeons, after removal of their cerebral hemispheres, exhibit no change of temperature, no failure of the heat-regulating mechanism, and no alteration in the excretion of carbonic acid.

I have endeavored to present to you the main physiological facts bearing upon the relation of the nervous system to thermogenesis. It must be ad-

[25] Corin and van Beneden: Arch. de Biol., 1887.

mitted that we are left to surmise as to the interpretations of many of the facts, and particularly as to their connection with each other. But certain important points come out clearly. We have found evidence of the existence in the body of chemical processes resulting chiefly in the production of heat energy. We have learned that these processes are under the direct control of the nervous system, and possibly of nerves distinct from those now recognized as motor or secretory. We have seen that there are regions in the central nervous system which are doubtless in some way connected with these nerves, and through them control the chemical processes resulting in the production of heat.

The bearing of these facts upon the theory of fever is evident. The study of heat production and of heat loss in fever has led us, by arguments which need not be repeated, to the conclusion that the pyrogenic agent must in some way act upon the heat-regulating mechanism. The study of this mechanism, more particularly of its thermogenic side, affords some insight into the manner in which the fever-producing agent may affect the regulation of heat. The main difficulty in the neurotic theory of fever has been to understand how by any action of the fever-producing agent directly upon the nervous system the chemical processes leading to heat production could be stimulated. I have dwelt thus at length upon the innervation of thermogenesis to show that this difficulty has been in great part overcome.

To some it seems more reasonable to suppose that the pyrogenic agent circulating in the blood acts directly upon the tissues, altering and stimulating their chemical changes. This is the haemic theory, which, in some form, has always stood over against the neurotic theory of fever. Although it may at first glance appear simpler, the haemic theory is really the more complicated, for it has already been set forth that we cannot explain fever simply by increased heat production, so that even if the primary effect of the fever agent were upon the heat-producing processes there must be a secondary influence upon the nervous system, for heat dissipation is no less disturbed than heat production.

If an animal be thoroughly curarized so that no impulses from the nervous centres can reach the muscles, the great heat producers, then it is found to be impossible to produce febrile elevation of temperature by the injection of pyrogenic agents. This fact, first demonstrated by Zuntz, is justly held to weigh heavily in favor of the neurotic theory of fever.

Contrary to the results of Murri,[29] I have not been able to induce rise of temperature or check its fall by the injection of pyrogenic agents into the jugular veins of dogs whose spinal cords have been cut in the lower

[29] Murri: Teoria della Febbra, Fermo, 1874.

cervical region. In these experiments I have employed various pyrogenic agents, and especially pepsin and papoid. One specimen of the latter which I used possessed very striking pyrogenic properties.

The pyrexia produced by puncture of the caudate nucleus in the manner already described, possesses all of the essential properties of fever, regarded as abnormal elevation of temperature. In this experimental condition there are increased production of heat, increased dissipation of heat, excessive elimination of urea and of carbonic acid, and excessive absorption of oxygen. The breathing and the pulse are increased in frequency. The elevation of temperature (usually after a brief fall) begins within half an hour after the puncture, attains a febrile height and persists sometimes for days. As no observations exist as to the heat regulation of these animals, I have made experiments on rabbits after puncture of the caudate nucleus, by placing them in a cold environment and in a box heated to various temperatures, and I find that their power of temperature regulation is less than that of normal animals.

These animals, in a word, present all of the essential symptoms of fever, and I do not know why we should not call the condition fever. If so, we must admit that injury to a circumscribed definite region of the brain is capable of causing fever. This experiment, therefore, is of the greatest importance in support of the neurotic doctrine of fever. It indicates, of course, that we may have fever of purely nervous origin, without any pyrogenic agent in the blood. This experimental evidence is supported by the clinical cases collected by White in "Guy's Hospital Reports," 1884. It is to be hoped that by careful thermometric study of focal brain and cord lesions a more accurate idea may be reached than is now possible of the topography of the thermically active regions in the central nervous system of man.

Admitting the dependence of fever upon the nervous system, I do not regard as particularly profitable with our present knowledge the discussion as to whether febrile thermogenesis is excited by the withdrawal of thermo-inhibitory impulses or by the stimulation of thermo-excitory nerves or nerve centres. If we regard, and there are forcible arguments for doing so, possible heat-inhibitory nerves as anabolic, and the heat-exciting nerves as katabolic, then inasmuch as the formative or anabolic processes are manifestly in abeyance in fever, we can reasonably infer that the function of the heat inhibitory nerves or centres is impaired. The phenomena of the febrile chill in which both the contractile and the thermogenic properties of muscle are stimulated, speak strongly in favor of direct irritation of the heat-exciting nerves in fever. We might infer, therefore, that both sets of nerves or nerve centres are affected.

But my aim in this lecture has been not so much to construct a theory of fever, a theory which, although it may be useful, must necessarily be largely speculative if it be coherent and rounded but to bring before you the main facts concerning heat production, heat loss, and heat regulation in fever, and to point out the physiological basis on which their solution is to be expected.

Lecture II

The Effects of Increased Temperature of the Body

In the last lecture I endeavored to bring before you the main facts which we possess bearing upon the explanation of febrile rise of temperature. After a review of our knowledge concerning heat production, heat dissipation, and heat regulation in fever, we were led to the conclusion that neither the changes hitherto observed in the production of heat nor those in the loss of heat suffice to explain febrile temperatures. Such an explanation seemed possible only upon the assumption that the fever-producing agents act either directly or indirectly upon the nervous mechanism controlling the relations to each other of the production and the discharge of heat. We then turned our attention to the relations of the nervous system to these processes, and found that the investigations of recent years have enabled us to obtain a much clearer conception than was formerly possible, of the manner in which the complicated heat relations in fever may be brought about by an action upon the nervous system. We found even substantial experimental basis in support of clinical facts which show that circumscribed lesions of certain parts of the central nervous system may induce directly febrile disturbances of animal heat.

To carry the subject further, to consider whether pyrogenic agents act primarily or only secondarily upon the processes concerned in heat production or upon those concerned in heat dissipation, or upon the apparatus regulating the relations to each other of these two sets of processes, to discuss whether these agents act directly upon the central nervous system, and if so upon what part; or upon the peripheral nerves or their terminations, or upon the tissues; to follow out more fully than we have done hitherto the themes here suggested would lead us with our present knowledge into a sea of speculation. We should find only here and there a faint light of fact to guide us. Even upon foundations as insecure as this speculations have their legitimate uses. A good hypothesis is a most valuable incentive to scientific work. It is not my purpose, however, to carry you with me further in this direction, although I realize that a single lecture has been far from sufficient for a thorough exposition of this subject.

After dismissing the considerations bearing upon the so-called theory of fever, there still remains a host of questions properly belonging to our subject. It is evidently impossible, even if it were desirable, that these lectures should include a discussion of all of these questions. I have, therefore, selected certain ones, partly because they seem to me of immediate interest and partly because I have given some attention to their study.

In the present lecture I wish to present to you some observations concerning the relation of elevation of temperature to other disorders of fever, and as to the question, How far increased temperature is a source of danger in fever?

Here I may repeat that the word fever is used as a convenient name for a group of symptoms commonly associated together in febrile diseases. The association of these symptoms, however, is so loose that we regard only the dominant one—the increased temperature—as the essential criterion of the existence of fever. It saves circumlocution to adopt this somewhat vague and common signification of the term fever, although I think it would be an improvement to confine the term to abnormal elevation of temperature. The literature of fever is full of misapprehensions resulting from the various meanings attached to the word by different authors.

All of the bodily functions may be disordered in fevers. The various symptoms or classes of symptoms which are so commonly associated as to be regarded by many as belonging to the febrile process are, in addition to heightened temperature, increased frequency of the pulse and other circulatory disturbances, increased rapidity of respiration, muscular weakness, lessened secretions, disordered nutrition and digestion, and nervous symptoms.

What is the connection, if any, between these symptoms and the elevation of temperature? What degrees of elevated temperature are dangerous to life, and in what does the danger consist? This subject can, at least, claim the interest that attaches to the questions of the day. The various opinions which have been held by clinicians on these points are too well known to you to require an historical review. I need only remind you that until within a few years the views advocated with especial force for nearly thirty years by Liebermeister have prevailed, although not without, considerable opposition. According to these views, the chief source of danger in uncomplicated essential fevers is the elevation of temperature, and the main indication for treatment is the reduction of temperature. Above all, it was urged with apparently convincing arguments that the weakness of the heart, which is undoubtedly one of the gravest dangers of fevers, is the direct effect of prolonged high temperature, and is manifested anatomically by parenchymatous or fatty degeneration of the cardiac muscle. Liebermeister sharply defined

his position when he said, "A man whose temperature measures continuously 104° (40° C.) or more surely dies in consequence of the elevation of temperature, one in a few days, another after a somewhat longer time, according to the resistance of the individual." "If his temperature reaches 108.5° (42.5° C.) or more, then is he irrecoverably lost."[30]

At the present moment there is a decided reaction against these views, a reaction which in some quarters goes to the extent not only of denying that there is danger in febrile temperatures which do not exceed a very high point, but of asserting that the elevation of temperature is a beneficient provision, a most important *vis medicatrix naturae,* which should not be checked by the interference of the physician. This reaction of opinion is plainly due, in great part, to the disappointment which has followed the high hopes raised by the discovery of a number of drugs which are admirable antithermic agents and, nevertheless, do not exert over febrile diseases that controlling influence which had been anticipated.

These questions, you may say, are clinical ones, and not much edification is to be expected from their discussion by a pathologist. So far as the propriety of the use of antipyretic agents or of any other mode of treatment in fever is concerned, it is true that the decision must be reached at the bedside and cannot and never should be controlled by the results of experimental pathology. But an appeal has properly been made to experimental pathology to shed light upon such questions as the effects of heat upon the functions of the whole body and of its various organs, and upon the causes of parenchymatous and fatty degenerations. The arguments advanced in support of the view that all of the characteristic symptoms of fever are directly dependent upon the increase of temperature and that high temperature is the chief source of danger, are derived no less from experimental pathology than from clinical observations.

Three methods have been employed to determine the effects of increased temperature in fever: one is to study the effects of external heat upon man and animals; the second is to examine in different fevers and in different cases of the same fever the relation of the temperature to the other symptoms, and to the general condition of the patient; and the third is to note the influence of reduction of temperature upon these symptoms. Each method has its limitations.

The condition produced by exposure to external heat, even if it be called thermic fever, is something quite different from ordinary fevers, and we cannot transfer the results obtained by this method directly to the explanation of febrile phenomena. On the other hand, in the clinical study of fevers it is very difficult and often an arbitrary matter to separate the effects of in-

[30] Liebermeister: Volkmann's Sammlung, No. 31, p. 240.

creased temperature from those of other factors nearly always present. Hence we find no agreement of opinion among physicians as to what symptoms or lesions in fever are referable to the heightened temperature, and what are due to infectious or other conditions often present. Even the frequent or constant association of certain symptoms with elevated temperatures and their subsidence or disappearance by reduction of temperature do not justify us in inferring that the high temperature is the cause of the symptoms, for both may be coördinate effects of the same cause, and the so-called antipyretic treatment may influence other conditions as well as the temperature. As has been frequently said of late, the high temperature may be rather an index of the severity of the disease than a source of danger in itself.

In hyperpyrexia and in many cases of insolation there can be no doubt that the high temperatures, as such, are the main elements of danger. But both of these conditions have important points of distinction from ordinary febrile processes. In hyperpyrexia there is probably almost complete paralysis of heat regulation, and we shall find that an analogous condition with similar dangers sometimes develops in animals artificially heated. The cases of insolation in which the high temperature is so dangerous are analogous to the condition which may be produced in animals by brusque elevation of the bodily temperature through exposure to heat, and which differs from that resulting from more gradual increase of temperature.

The most direct way of determining the influence of heat upon the body is to raise the internal temperature by the external application of heat. Here we are not disturbed by the presence of other factors, such as infection, which render doubtful so many of the conclusions derived from clinical observations as to the effects of high temperatures. For the solution of many problems it is evidently irrelevant whether the source of heat be within or without the body.

These experiments, if properly conducted, are calculated to shed much light upon many questions relating to the effects of febrile temperatures.

According to the testimony of all experimenters, a mammalian animal, artificially heated, dies when its internal temperature reaches 111.2° F. (44° C.) or 113° F. (45° C.). Death is preceded by convulsions and immediately or soon after death rigor mortis appears. At the moment of death the irritability of the heart and muscles ceases. Death seems to be due to heart paralysis, and the cause of this is usually set down as heat rigor, but this is not probable as death generally occurs at a temperature several degrees below that at which rigor of the heart muscles appears.

It is generally argued that temperatures several degrees below those which are fatal must exert toxic effects, and this conclusion seemed to be substantiated by the majority of experimenters, who found that animals whose tem-

peratures were artificially raised to 105° F. (40.5° C.) or 107° F. (41.7° C.), or even to a lower point, manifested signs of illness. These latter results, however, are opposed to those obtained by Rosenthal, and especially Naunyn,[31] who points out that the conditions in most previous experiments were not favorable, as the animals were generally placed in small, dark, poorly ventilated metallic boxes. Naunyn succeeded in keeping a rabbit alive for thirteen days with an average temperature of 106.7° F. (41.5° C.).

Following Naunyn's example, I have had constructed a wooden box, three feet long, two feet high, and two feet broad, which fits closely within a double-walled galvanized iron box. The wooden box is provided with a perforated movable bottom, which allows the urine to escape. The space between the two walls of the iron box measures three inches across, and is filled with water, which, therefore, surrounds the inner box on all sides, except at the top, which is left open. The dimensions of this apparatus are somewhat larger than those of Naunyn's heating-box. A folded woollen blanket was drawn over each end of the box, so as to leave uncovered at least one-third, and generally more of the top. A rose burner placed underneath served to heat the box. At first a thermo-regulator was employed, but this was found unnecessary, as the temperature of the room varied but little, and there was no difficulty in keeping a sufficiently constant temperature in the box. The experiments were made upon rabbits, and only a single one was placed in the box at a time. Corrected thermometers were used. The temperature of the box was taken a short distance above the bottom, and that of the rabbit at a depth of three to four inches in the rectum. This occasion does not seem an appropriate one to describe these experiments in detail with their protocols. I shall take another opportunity for that, and at present give only a general account of those results which relate to the subject before us.

In the box described I have succeeded in keeping for three weeks two large black rabbits, the one with an average rectal temperature of 107.3° F. (41.8° C.), the other with an average temperature of 106.6° F. (41.4° C.). The rectal temperature fluctuated usually between 105.5° F. (40.8° C.) and 108° F. (42.2° C.), scarcely ever sinking below 105° F. (40.5° C.), but occasionally rising as high as 109.5° F. (43.1° C.). The temperature of the box varied between 96° F. (35.5° C.) and 106° F. (41.1° C.). The rabbits lay most of the time stretched out, breathing very rapidly. They took their food greedily, and did not appear ill. At the end of the experiment the first animal was removed from the box, and appearing perfectly well for ten days afterward it was used for another experiment; the second animal was killed at the end of the experiment, and presented marked fatty degeneration of

[31] Rosenthal: Zur Kenntniss der Wärmeregulirung u. s. w., Erlangen, 1872. Naunyn: Archiv f. exp. Path. u. Pharm., Bd. 18.

the heart, liver, and kidneys. Both animals lost weight while in the box.

In these and similar experiments the rabbits were given only moist, green fodder, and were allowed to drink plenty of water, which they took eagerly. It is important for the success of the experiment that the temperature should be gradually, and not suddenly, raised.

Different rabbits offer varying degrees of resistance to the effects of high external temperature. It has seemed to me that black and gray rabbits surpass, in this respect, white rabbits. The same temperature of the box does not produce, in all cases, the same rectal temperature in different animals, or in the same animal at different times. No factor is of more importance in determining the effects of external heat than the animal's power of temperature regulation. Failure of this power is manifested by a sudden rise of internal temperature, which may quickly attain a point incompatible with life. This event may take place without any alteration in the box temperature. The degree of internal temperature at which this paralysis of heat regulation occurs varies in different animals. One may be able to hold his temperature, for a short time, from further rise at as high a point as 109.5° F. (43.1° C.); in another, after the temperature has reached 107.6° F. (41.5° C.), there may occur, without any change in the box temperature, a sudden, and often fatal, elevation of temperature. In general, temperatures between 108° F. (42.2° C.) and 109° F. (42.8° C.) may be regarded as critical temperatures for these animals. One is forcibly reminded by these sudden and dangerous elevations of temperature of the occurrence of hyperpyrexia in certain fevers of human beings, and there is reason to believe that this, too, is caused by paralysis of heat regulation.

It seemed to me of some practical interest to determine what effect upon the rabbit's power of resisting high temperature is exerted by exhausting influences, particularly by anaemia. For this purpose rabbits which had been moderately bled, and others which had been used for some other experiments, were placed in the hot box. It was found that these animals are, although not without occasional exceptions, unmistakably less resistant to the effects of high temperatures than are robust animals. They succumb sooner, and at lower box temperatures.

We may now consider what inferences may be drawn from these and similar experiments as to the effects of high bodily temperatures. It seems clear that a considerable part of the current arguments based upon experiments concerning the injurious effects of high temperatures must be revised in the light of Naunyn's experiments, and of those which I have briefly related. Because an animal may be killed by raising its temperature to 111° F. (43.9° C.), or 113° F. (45° C.), it does not follow that an increase of temperature up to within 4° or 5° F. of this fatal point involves danger

to life, or even any serious disturbance of the functions of the body. Although experiments in hot-air chambers show that in man brusque elevations of the temperature by only a few degrees give rise to serious symptoms, Krishaber[31] found that by habituation his temperature could be raised to 106.5° F. (41.4° C.), or 107.2° F. (41.8° C.), without much discomfort. As small animals generally succumb more readily than large ones to artificial heating, it is not likely that the power of resistance in human beings is less than that found to exist in rabbits, and there is reason to believe that it is greater.

We cannot transfer directly to human beings the highest temperature at which we found rabbits can exist without serious discomfort save increased respiration. A rabbit's temperature is normally considerably higher than that of man, and apparently slight causes suffice to produce marked fluctuations. The normal rectal temperature of the rabbits used in my experiments was generally between 102° F. (38.9° C.) and 103° F. (39.4° C.). The highest average temperature at which a rabbit was kept for three weeks in the hot box exceeded, therefore, by 4° to 5° F. the average normal temperature. Such an increase would not correspond to a high febrile temperature in man. We can, however, with equal, and probably greater propriety, compare this temperature with that at which death surely occurs in a condition bordering on heat rigor. This temperature (111° to 113° F.) is probably about the same for man as for rabbits and other mammalians. From this point of view the inference may be drawn, although, of course, with much reserve, that human beings may tolerate temperatures of 107° F. (41.7° C.), or even higher, for a considerable time. This inference is supported by clinical observations, especially in cases of relapsing fever.

As already pointed out, the condition produced by artificial heating is not directly comparable with that in fever. In the former the loss of heat from the body is reduced to a minimum: the superficial temperature is three or more degrees higher than the internal, so that the average temperature of the whole body is higher than in fever with the same internal temperature. We cannot say, therefore, but that man may tolerate considerably higher internal temperatures when the elevation is brought about under conditions in which the discharge of heat is not checked than when the temperature is forced up by stopping heat dissipation. This would be proven if confidence could be placed in the enormous elevations of temperature reported by Teale and others. In these cases, however, even if authenticated, it is probable that heat is abnormally distributed in the body, and we cannot infer that the internal temperature is uniformly raised to such paradoxical heights.

[31] Krishaber: Gaz. Méd. de Paris, 1877.

It is of the utmost importance to bear in mind that, as my experiments have shown, not only do animals differ in their power of tolerating high temperatures of the body, but this resistance may be weakened by various depressing causes. Nothing would be more irrational than to conclude, because one individual in a certain condition can tolerate very high temperatures, another in a different condition possesses the same power. In fevers we have various factors, particularly infection, which we may well believe can lower the tolerance of high temperatures. That in some fevers, particularly relapsing fever, this does not appear, or only partially, does not disprove that in another fever, such as typhoid or pneumonia, the system may be placed by other factors of the disease in such a condition that even moderately high temperatures are injurious. It does not seem to me proper in these cases to lay, as some seem inclined to do, the sole stress upon the element of infection. This is in all likelihood the determining factor, but the practitioner cannot shut his eyes to the possibility that under its influence the high temperature, as such, is a source of danger to his patient.

With these restrictions I shall surely not be misunderstood when I assert that temperatures which are ranked as high febrile temperatures do not in themselves, independently of other factors, exert any such injurious influence as has been usually attributed to them.

Our attention up to this point has been directed to the effects of high temperatures upon the general condition of the body. It is of importance for the proper understanding of fever to determine the influence of heat upon the structure and functions of the various organs. To what extent can the febrile disorders of respiration, of circulation, of secretion, of nutrition, of innervation be attributed directly to the elevated temperature? These are questions which can be answered better by experimental methods than by clinical observation, for the latter has to deal with the effects of heat complicated by other circumstances whose influence cannot be accurately determined. The one method, however, should be made to control the other.

The most striking immediate effect of heat upon an animal is increased frequency of respiration. When a dog or a rabbit is placed in an atmosphere of 100° F. (37.8° C.), it at once begins to pant and the respiration may run up to 150° or more. The causation of this increased respiration, to which the name heat dyspnoea has been applied by Ackermann,[33] has been repeatedly investigated. Goldstein[34] in Fick's laboratory found that by applying to the carotid arteries tubes through which hot water is flowing the respirations may be greatly increased in frequency. Goldstein's experiment is usually cited as the crucial one, showing that the increased breathing is

[33] Ackermann: Deutsches Archiv f. klin. Med., Bd. II.

[34] Goldstein: Würzburger Verhandl., 1871.

due to the effect of the heated blood upon the respiratory centres in the medulla oblongata. Sihler,[35] working in the Biological Laboratory of the Johns Hopkins University, however, has demonstrated that the increased respiration of an animal exposed to heat is due to two causes, warmed blood and stimulation of the skin by the heat, and that probably skin stimulation is the more important factor. Some of Sihler's criticisms of Goldstein's experiments have been met by Gad and von Mertschinsky[36] who have made it evident that increased temperature of the blood stimulates the respiratory centres, or increases their irritability. Section of the vagi does not check heat dyspnoea, so that this does not result primarily from the action of the increased temperature upon the terminal pulmonary expansion of these nerves. The removal of afferent impulses form the skin by section of the spinal cord does, however, exert so marked an influence that it cannot be doubted that heat stimulation of the skin is an important element in the causation. I have convinced myself of the correctness of Sihler's explanation by observing that in the hot box at temperatures of 90°-95° F. (32.2°-35° C.) rabbits often preserve their normal temperature, and still their breathing is markedly increased, and that, on the other hand, upon taking them out of the box the respirations may sink before the internal temperature begins to fall. In one striking experiment the respirations fell immediately to about normal upon removing from the hot box a rabbit whose skull had been trephined on each side of the median line, and the optic thalami punctured with a needle.

We cannot transfer directly to human beings the results of experiments on heat dyspnoea in animals, because in the latter respiration has a far more important function in temperature regulation than in the former. To keep cool a dog pants under circumstances when a man sweats. As heat regulation is largely influenced by the cutaneous temperature, it is not improbable that in man heat stimulation of the skin is less prominent than the warmed blood acting upon the respiratory centres in increasing the frequency of respiration in fever.

Inasmuch as disturbances of the heart and of the circulation in general are among the most important symptoms of fever it is natural that much attention should have been given to the study of the effects of heat upon the organs of circulation. The supposed injurious effects of prolonged high temperatures in fever have been usually attributed especially to some toxic action of heat upon the heart.

[35] Sihler: Journal of Physiology, II, and Studies from the Biological Laboratory, Johns Hopkins University, Baltimore, II.

[36] Gad and v. Mertschinsky: Virchow u. Hirsch's Jahresbericht, 1881, Bd. I, S. 197.

That the pulse-rate is quickened by artificially heating rabbits and dogs has long been known. The positive demonstration that this acceleration is due to the direct action of the heated blood upon the mammalian heart itself was first given by my colleague, Prof. Martin.[37] By conducting through the dog's heart, isolated physiologically by the ingenious method which he devised, Martin proved that the heart "beats quicker when supplied with warm blood and slower when cold blood is supplied to it; also, that the rate of beat depends much more upon the temperature of the blood in the coronary arteries than on its temperature in the right auricle or ventricle." These experiments make it unnecessary to recur to any action of the heated blood upon extrinsic cardiac nerves or nerve centres in order to explain the quickened pulse of fever. Moreover, Fick[38] found that the nervous centres of the heart and bloodvessels are unaffected by heating the blood flowing through the carotid arteries in the manner adopted by Goldstein in his experiments on heat dyspnoea.

Prof. Martin has kindly permitted me in this connection to mention certain unpublished results of experiments which he is now conducting upon the effects of heat and cold on the isolated heart. As these results are pertinent to our subject I gladly avail myself of this privilege. The table of an experiment which I have examined shows that the isolated cat's heart beats regularly and more and more rapidly as the temperature of the blood is gradually raised to 111.2° F. (44° C.). At this point the beats become irregular, but are restored to their normal rhythm by feeding the heart with cooler blood. The temperature of about 111° F. (43.9° C.) appears to be a critical one for the isolated heart. Above 111.2° (44° C.) to 113° (45° C.) the pulsations become slower instead of quicker as the temperature is raised. At 122° F. (50° C.) the heart's action ceased, but the heart was made to beat again by supplying it with cooler blood, showing that the cessation was not due to heat rigor. This interesting experiment teaches among other things that very high temperatures may produce results differing not only in degree but also in kind from those of temperatures only a degree or two lower.

We may consider it then established that increased frequency of the pulse in fever is referable to the direct action of the warmer blood on the nervomuscular substance of the heart itself. Clinical observation of cases of fever makes it evident that there may be and often are present other circumstances which influence the rapidity of the heart's pulsations, circumstances which

[37] Martin: The Direct Influence of Gradual Variations of Temperature upon the Rate of Beat of the Dog's Heart, Philosophical Transactions of Royal Society, part II, 1883.

[38] Fick: Pflüger's Archiv, Bd. V.

in themselves may slow or may quicken the pulse. Large series of statistics, therefore, are required to bring out the ratio between the pulse-rate and the temperature in fever and even then for any given temperature the maximum and the minimum pulse-rates lie so far apart that the statement of the average increase in the frequency of the pulse for each degree of rise of temperature, such as has been computed by Liebermeister, has very little value.

Not only is the pulse-rate quickened in fever, but there are often other and more serious circulatory disturbances. In the fever produced in rabbits by injection of the swine plague bacillus I find a reduction of the blood-pressure measured in the carotid artery, and others have obtained similar results in the artificial fevers of animals. The determination of the blood-pressure in fevers of human beings by means of Basch's sphygmomanometer has given, in the hands of different experimenters[39] such contradictory results, that no conclusion can be drawn, unless it be the very probable one that the blood-pressure varies, being sometimes high, sometimes low, and sometimes normal in fever. That the arterial tension is often reduced is made evident by the marked dicrotism of the pulse wave. This dicrotism, however, characterizes particularly septic and typhoid types of fever and is absent during the chill of intermittent fever and often in exanthematous and some other fevers, so that we cannot consider the blood-pressure and arterial tension as having any such definite relation to fever as does the pulse-rate.

It has been observed by Paschutin, Senator, and Mendelson,[40] that the blood pressure rises with increasing bodily temperature, produced by exposure to heat. Mendelson found that the pressure begins to sink as the temperature approaches a point incompatible with life. In these experiments the animals were subjected to rapid elevations of temperature. I find that when a rabbit is gradually and cautiously heated in the hot box used in my experiments, the rise of temperature is less marked, and may not surpass even for temperatures of 107° F. (41.7° C.), the normal limits of variation which may be found in the blood-pressure of the same animal examined at different times. These measurements, however, are not very conclusive, for, as has been already remarked, rabbits which have been operated upon do not stand well artificial heating.

I have observed that the rhythmical contractions of the bloodvessels of the rabbit's ear are feeble or absent when the temperature is much elevated by

[39] Von Basch, Zadek, Arnheim, Wetzel.

[40] Paschutin: Ludwig's Arbeiten, 1873. Senator: DuBois-Reymond's Archiv, 1883, Supplant-Band. Mendelson: On the Renal Circulation during Fever, Amer. Journ. Medical Sciences, October, 1883.

artificial heating; whereas, it will be remembered that in experimental septic fever these contractions are irregular and exaggerated.

Upon the whole, I think that we are justified in concluding that the variations of arterial tension in fevers are much less dependent upon increased temperature than upon other factors, such as infection.

But the corner-stone of the doctrine which teaches that a chief source of danger in fevers is the elevation of temperature is not the effect of increased temperature upon the pulse-rate or the arterial pressure, but it is the belief that prolonged high temperature exerts a directly paralyzing influence upon the heart. The main support of this belief is not the admitted fact that extremely high temperatures paralyze the heart, for these critical temperatures lie far above the ordinary high temperatures of fever, and in a region where all admit the dangers of the excessive internal heat. The stately superstructure has been built up chiefly on the basis of experiments showing that when the internal temperature of animals has been maintained for some time at a high point by exposure to external heat, parenchymatous or fatty degeneration of the heart muscle ensues. It is true that all experiments are not in accord upon this point, and that, as a rule, pathological anatomists have not given adherence to the doctrine that parenchymatous degenerations are chiefly dependent upon high temperature, still this doctrine has gained a wide acceptance among clinical men, and is advocated with especial force by Liebermeister. I have therefore, thought it desirable in my experiments to give especial attention to this question.

Among previous experimenters on artificial heating of animals, Iwaschkewitsch, Wickham Legg, and Litten may be mentioned as finding parenchymatous or fatty degeneration of the heart, liver, and kidneys; and Walther, Obernier, and Naunyn as obtaining only negative results.

It is not necessary here to enter into a criticism of these different experiments, which are of very unequal value. Litten's [1] experiments on the one side, and Naunyn's [2] on the other, appear to be the most carefully conducted. Litten, whose experiments are those usually cited, kept guinea-pigs in a double-walled metallic box which was at a constant temperature of 98.8° F. (37° C.) with dry air, or of 96.6° F. (36° C.) with moist air. He never failed to find fatty degeneration at the end of thirty-six to forty-eight hours. The liver was first affected, and then the heart and kidneys, which become fatty by the second or third day. The animals did not survive longer than five or six days, and by that time the fatty degenerations had reached an extreme degree. Von Recklinghausen [3] urges with apparent justice against

[1] Litten: Virchow's Archiv, Bd. 70.

[2] Naunyn: Op. cit.

[3] Von Recklinghausen: Handb. d. Allg. Pathologie d. Kreislause u. d. Ernährung, p. 512, Stuttgart, 1883.

these experiments that the enforced inactivity of the muscles and the imperfect ventilation may have had as much to do in causing the degenerations as had the high temperature. These objections find support in the experiments of Naunyn, who, making use of a much larger and better ventilated heating box than Litten failed to find any parenchymatous or fatty degeneration in his rabbits after they had been exposed for two weeks to higher temperatures than Litten employed.

As my experiments confirmed in other respects Naunyn's results, I was quite unprepared to find that my rabbits, after a variable period of artificial heating quite constantly presented fatty degeneration of the heart, liver, and kidneys, and sometimes of the diaphragmatic and intercostal muscles. I never found the degeneration at so early a period as did Litten. It was not until the rabbit had been kept for at least a week with an average rectal temperature of 106° F. (41.1° C.) that the degeneration was noticed, and then only in moderate degree. The higher and the less fluctuating the internal temperature, the more certain was the degeneration to appear. I could reckon upon obtaining rabbits with well-marked fatty degeneration of the heart by keeping them for ten days with a rectal temperature between 107° F. (41.7° C.) and 108° F. (42.2° C.). I am not prepared to account for the discrepancy in this respect between Naunyn's and my experiments. The box used was larger than that employed by him, and every care was taken to keep it well ventilated by leaving at least one-third and often one-half of the top open.

I do not think that my experiments altogether do away with the force of von Recklinghausen's criticisms. The fact that in these experiments the degeneration made its appearance at the end of a week or ten days, and in Litten's in forty-eight hours, to say nothing of Wickham Legg finding it at the end of twelve hours, would suggest that if the rabbits were heated in a still larger and better ventilated apartment, the degeneration might not occur at all, or might be deferred to a much later period. In my opinion, however, even if full allowance be made for this line of argument we must still admit that prolonged high temperature is a factor in the causation of fatty degeneration.

That it is not the sole factor no one can doubt. As is well known, fatty degeneration is produced by anaemia and by a variety of poisons, and even in fevers most pathologists are convinced that it bears a closer relation to the kind and degree of infection than it does to the height of the temperature. It is more frequently absent than present in pneumonia, even where there have been symptoms of heart failure.

The kind of degeneration present in my rabbits was fatty and not parenchymatous. Probably all who make many post-mortem examinations will

agree with von Recklinghausen, that altogether too liberal use has been made of the diagnosis of parenchymatous degeneration, and not sufficient account has been taken of the anatomical changes of the parenchyma produced by post-mortem chemical changes, such as acid formation, etc.

In order to determine what influence is exerted by infection combined with high temperature, I inoculated a rabbit which had been in the hot box for four days, with the bacilli of swine plague. These bacilli, if not identical with, are closely allied to those of rabbit septicaemia, and are extremely virulent for rabbits. In thirty-six hours the animal, which had remained at a high temperature in the box, was dead, with characteristic lesions of the disease, and the most extreme fatty degeneration of the heart and other organs was found. As in other experiments the degeneration had not made its appearance at this early date, there can be no doubt that the infection was an important element in the causation. That it received powerful support in the high temperature however, is proven by the fact that little or no degeneration of the heart is observed after infection with this organism when the animal is kept at ordinary temperatures.

Admitting, then, that high temperature aids in the causation of fatty degeneration of the heart in fever, the question arises, What do we know of the effects of this degeneration upon the functions of the heart? I will say nothing of the growing tendency to transfer a large part of the classical symptomatology of Quain's fatty heart to other conditions, particularly to disease of the coronary arteries and chronic myocarditis; we are concerned at present only with the occurrence of this degeneration in fever. Have we not been somewhat hasty in assigning to degeneration of the heart's muscle so large a share in the production of heart failure in fevers? One cannot look at a muscular fibre in which the striated substance is all replaced by fatty globules, and suppose that its functional activity was unimpaired; but into what serious errors should we fall if we attempted to deduce from the anatomical changes in the liver cells or the renal epithelium the corresponding functional disturbances? Certain it is that symptoms which are usually considered those of heart failure are often enough present in fevers without finding at the autopsy any degeneration of the heart; and, on the other hand such degeneration may be discovered without any history of these symptoms, although, of course, the two are often associated.

In the face of these doubts it seemed desirable to determine, if possible, experimentally the damage inflicted upon the cardiac functions by the presence of fatty degeneration of the heart muscle. That this degeneration may exist without apparent injury is rendered probable by the fact that a rabbit which has been kept for three weeks in the hot box at a high temperature, and in which there is every reason to suppose that fatty degeneration has

occurred, may present no symptoms of heart paralysis, and when removed from the box appear and remain perfectly normal. An instance has already been mentioned where one rabbit at the end of three weeks was killed and presented marked fatty degeneration of the heart; and another, which had possessed a higher average rectal temperature, was removed from the box at the end of the same period, and appeared for ten days perefetly normal, when it was used for another purpose. That this degeneration can be recovered from is, moreover, rendered probable by clinical experience, and is universally admitted.

Once in teasing out, in a warm room, a bit of fatty heart muscle from one of the rabbits, I made a curious observation. Near the edge of the cover glass, where there was a slight current in the physiological salt solution, rhythmical contraction was observed in a group of muscle-fibres. This interesting spectacle could be watched under the microscope for ten minutes. These contracting fibres were filled with fatty globules, and only here and there, and then indistinctly, could any trace of striation be detected. This observation teaches that a fatty degenerated muscular fibre is capable of contraction, but, of course, warrants no further conclusions.

Far more important than any inferences which can be drawn from such observations is the measurement of the actual blood-pressure in animals whose hearts have undergone fatty degeneration. This I have done in three instances. The rabbit was removed from the box at the end of ten days to two weeks, and the pressure in the carotid artery was measured by a mercury manometer attached to Ludwig's kymograph. In no instance was the blood-pressure found to be lower than that normally present in rabbits. In an experiment recently performed, the average pressure was 125 mm. of mercury; the pulsations were regular; the heart responded to stimulation of the vagi in an entirely normal manner. After such stimulation the pressure in one case rose to 176 mm. of mercury. Immediately after the measurement of the blood-pressure the rabbit, as in the previous instances, was killed, and marked fatty degeneration of the muscular fibres was found. In many of the fibres the striation could not be made out, and only fatty globules were visible; in others, which also contained fatty granules, the striation was distinct. The degeneration involved the whole muscular substance of the heart. A similar appearance in a human heart would be considered to indicate well-marked fatty degeneration.

These experiments show that a rabbit's heart which has undergone marked fatty degeneration from exposure to heat, may perform its functions to all appearances, and for the time being, in a perfectly normal manner.

There is at least one consideration which should make us cautious in drawing far-reaching conclusions from these experiments. There are dis-

eases of the heart—I need only refer to lesions of the coronary arteries—in which the functions of the organ are performed for a longer or shorter time, apparently in a perfectly normal way, and then heart failure suddenly appears. It is probable that here too the blood pressure would be found normal at a certain period of the disease, and still it would be an error to suppose that the lesion does not damage the heart.

Whatever force there may be in this analogy, I still think that these experiments, as well as careful pathological and clinical observations, necessitate some revision of the current opinions concerning the significance of fatty degeneration of the heart in fever.

So much time has been devoted to a consideration of the effects of heat upon the respiration and the heart that the limits of the present lecture will permit hardly more than a summary of the effects exerted by heat upon other functions and organs of the body. On account of the great clinical importance of the subject it seemed desirable to treat with especial fulness the influence of increased temperature on the heart.

What part has increased temperature in producing febrile consumption of tissue? In the first lecture mention was made of Pflüger's experiments showing that animals with elevated temperature, produced by exposure to heat, absorb more oxygen and excrete more carbonic acid than at the normal temperature. This is in conformity with the general law that within certain limits cell activity is more energetic at high than at low temperatures. It was also shown in the first lecture that only a comparatively small part of the increased oxygen absorption and carbonic acid elimination in fever can be referred to the immediate effects of high temperature. It has not been demonstrated that the respiratory gases in human beings are increased by artificial elevation of temperature. Indeed Voit[“] was unable to find any such effect of increased temperature in human beings on the respiratory gases as both he and Pflüger observed in animals.

Inasmuch as increased disintegration of nitrogenous material is such a prominent disorder in fever, much attention has naturally been given to determining how far this can be explained by elevated temperature. That it cannot all be so explained is proven by the interesting observation of Sydney Ringer, that excessive elimination of urea antedates the rise of temperature in intermittent fever, and Naunyn has found the same to be true of the septic fever of dogs. The experiments which have been made to determine the influence of artificial heating on the amount of urea excreted by man and by animals have yielded contradictory results. A number of these experiments are of little or no value, because no attention was

[“] Voit: Zeitschrift für Biologie, Bd. XIV.

given to establishing beforehand nitrogen equilibrium. Schleich's [45] experiments may be mentioned as, perhaps, the most accurate of those showing an increase in the urea excreted under the influence of exposure to heat. The more recent experiments of Simanowsky [46] were made in Voit's laboratory upon a dog with especial precautions as to the establishment of nitrogen equilibrium. He failed to find any increase in the excretion of urea as the result of exposure to external heat. While then this question must be left at present *sub judice,* there can be no doubt that only a part at least of the excessive disintegration of nitrogenous substance in fever can be assigned to the influence of the increased temperature.

The loss of weight exhibited by animals kept for a long time in a hot atmosphere is usually explained by the excessive evaporation of water from the body. In many of my experiments the rabbits were freely supplied with food and water, and still the loss of weight was very noticeable. I am inclined, therefore, to attribute to the increased temperature under these conditions a decided influence upon the consumption of tissue.

Senator [47] found the urine of rabbits artificially heated to contain more albumen than is ever found in the urine of healthy rabbits. This observation I have not been able to confirm on the rabbits in my experiments and probably this difference is to be explained by the more rapid and intense heating employed in Senator's experiments. Senator explains the heat albuminuria by the rise of arterial pressure in the renal vessels, but this is not in conformity with the interesting experiments of Mendelson,[48] who found by means of Roy's oncometer that both in thermic and in septic fevers of dogs the kidney is anaemic, while the general blood-pressure is elevated.

No satisfactory explanation has yet been offered of the diminution of perspiration which distinguishes fever so strikingly from the condition produced by exposure to high external temperatures. Luchsinger's assertion that this is the result of lessened irritability of the sweat centres in the spinal cord remains to be proven, and at the best is not a satisfying explanation.

Bokai,[49] in a recent experimental research on intestinal peristalsis in thermic and in septic fevers, comes to the conclusion that the constipation of fever is to be explained by the heated blood stimulating the nerves inhibiting intestinal peristalsis. If this should be confirmed, then it would be proven that at least three symptoms of fever, the quickened respiration and pulse and the constipation are direct effects of elevated temperature.

[45] Schleich: Arch. f. exp. Path. u. Pharm., Bd. IV.
[46] Simanowsky: Zeitschr. f. Biologie, Bd. XXI.
[47] Senator: DuBois-Reymond's Archiv, 1883, Supplement-Band.
[48] Mendelson: Op. cit.
[49] Bokai: Archiv f. exp. Path. u. Pharm., Bd. 23.

When we consider the important nutritive changes in the muscles accompanying increased thermogenesis, we shall be inclined to attribute in part, at least, to these alterations and the associated abnormal innervation, rather than to increased temperature, the muscular pains and weakness which form such an early and frequent complaint in many fevers.

The investigations hitherto published of changes in the blood produced by increased temperature within febrile limits are not of sufficiently definite and satisfactory nature to warrant any consideration on the present occasion.

Nor am I acquainted with any experimental evidence (save Bokai's work already mentioned) that increased temperature is concerned in the production of the digestive disorders of fever. It has already been said that the rabbits with high internal temperatures in the hot box ate greedily, but these voracious animals cannot be considered favorable subjects to test this question.

Especial emphasis has been laid by Liebermeister and those who accept his teachings upon the dependence of the nervous symptoms of fever, particularly the so-called typhoid symptoms, on the elevation of temperature. There is, however, abundant clinical evidence to disprove this doctrine. Reference need be made only to relapsing fever, and especially to the aseptic fever described by Genzmer and Volkmann, in which there is entire absence of the whole group of so-called nervous symptoms. Moreover, Liebermeister's opinion in this respect is not supported by adequate experimental evidence. Unless the temperature of the brain or of the entire animal be brusquely raised to a high point by coarse methods, no disturbance of the cerebral functions is noticed until the temperature reaches a critical point, beyond which further increase is likely to prove rapidly fatal. At this critical point the animal, which before has lain quietly, becomes very uneasy, and if the temperature rise higher it has convulsions and coma and dies.

I have endeavored to bring before you in this lecture the experimental evidence relating to the effects of increased temperature upon the general condition of the body and upon the functions of its various organs. I have given account, as briefly as possible of some experiments which perhaps shed additional light upon this important subject. In the course of this lecture emphasis has repeatedly been laid upon the necessity of controlling the results of the experimental method by clinical observation, and here and there I have endeavored to institute this control. Further than this I shall not attempt to set before you the clinical evidence regarding the effects of increased temperature in fever. There are those here more competent than I to deal with this side of the question. We may feel assured that when all the facts are before us and are properly interpreted, there can be no lack of harmony between the results of experimental and those of clinical investigations.

Lecture III

THE ETIOLOGY OF FEVER

We considered in the last lecture the experimental evidence concerning the effects of increased bodily temperature. An advantage of the experimental over the clinical method of investigating this subject is that it enables us to study the effects of heat upon the whole body and its various functions without the intervention of disturbing factors, such as infection, which complicate the clinical analysis of febrile phenomena with reference to this question.

We found that animals may be kept at high febrile temperatures for at least three weeks without manifesting any serious symptoms. The only functional disturbances which could be attributed directly to the influence of the elevated temperature were increased frequency of respiration and quickened pulse. The rapid respiration was found to be due partly to stimulation of the skin by external heat and by the warmed blood, and partly to the action of the warmed blood on the respiratory centres. The quickened pulse could be positively referred to the effect of the warmer blood upon the heart itself. No definite relation could be established between the variations of arterial tension which occur in fever and the height of the temperature.

Although the experiments narrated showed that prolonged high temperature is an element in the causation of fatty degeneration of the heart, they also indicated that other factors, such as infection, are concerned in the production of this lesion. Moreover, experimental evidence was found in support of clinical facts showing that this alteration may exist without serious interference with the functions of the heart, so that the conclusion seems justified that failure of the heart's power in fever is less an effect of high temperature than of other concomitant conditions.

Of the other disturbances in fever we learned that the increased consumption of tissue can be explained only in relatively small part by the elevation of temperature. The lessened perspiration, the renal disorders, and the digestive disturbances (with the possible exception of constipation) are referable also chiefly to other causes than the increased temperature. Both experimental and clinical observations strongly support the view now widely accepted that the disturbances of the sensorium which constitute so prominent a part of the group of so-called typhoid symptoms, are dependent in far higher degree upon infection or intoxication than upon the heightened temperature.

Although no attempt was made to analyze in detail the clinical evidence relating to the effects of high temperature, attention was called to the fact

that the absence of all serious symptoms in many cases of relapsing fever, and in the so-called aseptic fevers in spite of prolonged high temperatures, strongly support the conclusions derived from the experimental study of the effects of heat upon man and animals. Even in fevers, such as typhoid fever and pneumonia, where the height of the temperature is undoubtedly a most important index of the severity of the disease, there exists no such parallelism between the temperature and the nature and the severity of the other symptoms as we should expect if these symptoms were caused by the increased heat of the body.

It was emphasized that the results of experimental investigations should not be permitted to control the treatment of fevers, more particularly the use of so-called antipyretic agents. These agents, whether hydrotherapeutic or medicinal, influence, as is well known, many functions besides reducing the temperature. I need only refer to the powerful influence of cold baths upon the circulation and the nervous system, and to the action of antipyrin and other antithermic drugs upon the nervous system.

Reasons were given for assigning to hyperpyrexia and insolation a position separate from other febrile conditions in the discussion as to the effects of elevated temperature.

Before leaving this subject of the effects of increased temperature, I wish to call attention to one consideration which should perhaps influence our opinion on this much disputed question. Is it a matter of indifference, so far as the effects of febrile temperatures are concerned, in what manner the increase of temperature is brought about? We have seen that heat regulation, heat production, and heat loss are disturbed in fever; but, as experience shows, not always in the same manner or the same degree. In one case the incoördination of the regulating mechanism may be most apparent, the temperature fluctuating strangely up and down; in another case the heat-producing processes are excited to the utmost; and in another the circulatory changes in the skin, the vasomotor disturbances, are the most prominent phenomena. Now this varying interplay of the factors which cause febrile rise of temperature doubtless corresponds to varying conditions of innervation, of structure and of function of certain tissues of the body. May we not reasonably suppose that these varying conditions of the tissues directly associated with the rise of temperature may influence their tolerance of increased body heat? We have not the experimental or the clinical data which would enable us to give a definite answer to the question here propounded, and it would lead me too far from the theme of the present lecture to attempt to sift the equivocal evidence which might be gathered. I suggest this question, however, as one worthy of more attention than it has hitherto received.

I wish now to invite your attention to some considerations concerning the etiology of fever. In this era, when etiological studies occupy the foremost rank in medical science, it will naturally be expected that a discussion of the general pathology of fever, even though it does not aim at completeness, will not leave wholly untouched the etiological aspect of the subject.

The general etiology of fever relates mainly to a consideration of the agents producing fever, the so-called pyrogenic substances. It is, moreover, only certain general characters of these agents which can be properly considered here. Most of the questions which at present engage so prominently the attention of physicians concerning the specific causes of individual fevers belong, of course, to the special etiology of fevers, and therefore do not lie within the limits of our subject. But even with these limitations we cannot in treating of the general etiology of fever consider the febrile processes so much in the abstract as we have done hitherto. We must come into closer contact with the individual forms of fever.

At the start it should be said that probably in no instance are we acquainted with the actual substance or substances upon which the febrile disorder of animal heat immediately and directly depends. We deal here, as elsewhere in medicine, not with direct but with remote causes. But in no department of etiology have we advanced nearer the proximate causes than in many of the infectious fevers. To be convinced of the immense progress which has been brought about by the etiological study of fevers, let one glance over some of the older books on fevers, such as Percy's or Selle's,[50] with their endless divisions into symptomatic genera and species, and their barren speculations. Percy, for instance, describes no less than one hundred and fifteen different kinds of fever.

In all ages it has been customary to divide fevers into two great groups, viz.: those which are secondary to some local cause, usually an inflammation, and those which cannot be explained by the presence of any local lesion. The explanation of the symptomatic seemed so much clearer than that of the essential fevers that attempts have repeatedly been made to place all fevers in the symptomatic group. It is a curious fact that the two methods which have been of the greatest service in the study of fevers, each, when first introduced, led to an entire misconception of the nature of fever. Boerhaave, who was the first to make any extensive use of the thermometer at the bedside, supposed that this instrument indicated a reduction of the bodily temperature during the febrile chill. He therefore taught that increased frequency of the pulse and not the elevation of temperature is the constant and essential symptom of fever. If we except de Haen's correction, which never

[50] Percy: Die gesammte Fieberlehre, Pesth, 1820. The original is in French.
Selle: Rudimenta Pyretologiae Methodicae, Berolini, 1773.

became widely known, it was not until the middle of the present century that Boerhaave's error was overthrown. A no less serious misconception sprang from the study of the pathological anatomy of fevers in France during the early part of the present century. The exaggerated ideas of the immediate followers of Bichat as to what can be accomplished by pathological anatomy led them to the belief, for a long time widely accepted, that there is no such thing as an essential fever, that all fevers are symptomatic of some local disease. This error of Broussais, one of the most influential and eloquent medical teachers of this century, is plainly traceable partly to the fact that his autopsies were chiefly of typhoid fever, and partly to the belief that the lesions found at the autopsy suffice to explain all of the manifestations of the disease during life. But we need not stop to trace the fate of the various attempts to overthrow the doctrine of essential fevers. I have mentioned one attempt chiefly on account of the suggestive lessons it conveys rather than from a desire to enter into historical details which I have hitherto purposely avoided.

The division of fevers into symptomatic and essential fevers is one of undoubted practical utility, and is not likely to be abandoned. But it cannot truthfully be said that this popular classification has been of much assistance in advancing our knowledge. Close inspection shows that the boundary lines between the two groups of fevers are vague and shadowy. Probably no one any longer believes that traumatic fever, the principal type of the symptomatic group, is due to increased production of heat in the seat of inflammation, which, acting like a furnace, was once thought to warm the whole organism, or to the irritation of nerves connected with the inflamed region. The opinion of Billroth and of Weber is now generally accepted, that traumatic fevers are caused by the absorption of pyrogenic substances from the inflamed district. Symptomatic fevers as well as essential fevers, therefore, are dependent upon the presence within the blood of fever-producing agents. Many essential fevers, moreover, resemble the symptomatic ones in the existence of inflammation, or necrosis at the portal where there is reason to believe that the pyrogenic agents gain access to the general circulation. A distinction in these cases cannot be based on the ground that in symptomatic fevers only chemical substances, although possibly the products of bacteria, enter the circulation, and in essential fevers microörganisms invade the blood, for such a distinction would place cholera and possibly tetanus and typhoid fever among the symptomatic fevers. These considerations show how vague and unsatisfactory are the distinctions between symptomatic and essential fevers. Still, similar criticisms can be made of many of our artificial classifications which nature is under no compact to observe, and we should undoubtedly be put to great inconvenience if we attempted to

dispense with the epithets symptomatic and essential as applicable to different forms of fever. There are, however, other points of view which seem to me more fruitful in the study of the etiology of fever than those embodied in these distinctions. I refer to the differences in the nature of fever-producing agents, concerning which our knowledge, although still very imperfect, has been materially increased within recent years. And here again we are greatly indebted to the results of experiments upon animals.

Much light has been shed upon the causes of a certain class of fevers by a series of experiments, which received their impulse from the important studies of Alexander Schmidt and his pupils upon the physiology of the blood. A particular direction was given to these experiments by the often repeated observation that fever and other injurious effects may follow the transfusion of blood, especially when the blood of one species of animal is transfused into an animal of another species. In order to test the supposition that these bad symptoms are due to an excess of fibrin ferment Köhler [51] injected into the vessels of animals blood made rich in fibrin ferment and fibrino-plastic substance, and found that this blood when injected in large amount into the jugular vein causes sudden death by rapid coagulation of the blood in the right heart and pulmonary arteries, but when injected in smaller amount or in a different manner produces a typical febrile attack bearing a close resemblance to that following the injection of putrid fluids. Angerer [52] then found that a similar fever, although less intense and more gradual in its development, may be produced by the injection of blood into the peritoneal cavity or the subcutaneous tissue, or even by an extravasation of blood. Although in these experiments it was believed that fibrin ferment is the pyrogenic agent, Edelberg [53] was the first to produce fever and other symptoms of intoxication by the injection of this ferment isolated according to Schmidt's method.

In the light of these experiments it was to be expected that other ferments would be examined with reference to their pyrogenic power. Schmiedeberg [54] discovered that injections of histozyme into the blood of dogs produced high fever associated with general illness, and particularly with diarrhoea. The ferment to which Schmiedeberg has given the name histozyme he believes to be present normally in small amount in the body, and to be concerned in the dissociation of the nitrogenous constituents of the tissues. He concludes from his experiments that an excessive accumulation in the

[51] Köhler: Ueber Thrombose und Transfusion, u. s. w. Inaug. Diss., Dorpat, 1877.

[52] Angerer: Klin. u. Exp. Untersuch. üb. d. Resorption v. Blutextravasate, Würzburg, 1879.

[53] Edelberg: Arch. f. exp. Path. u. Pharm., Bd. XII.

[54] Schmiedeberg: *Ibid.*, Bd. XIV.

body of this normal ferment gives rise to fever with increased metamorphosis of nitrogenous materials. Schmiedeberg thinks it probable that the fibrin-ferment solutions employed by Edelberg in his experiments contained also histozyme, and that the pyrexia was due to the latter substance.

Following these observations concerning the pyrogenic power of fibrin-ferment and histozyme comes the discovery of von Bergmann and Angerer[55] that injection of pepsin and of trypsin into the blood of dogs causes a well-marked fever with characters like those of the other ferment intoxications described. A valuable calorimetrical study of pepsin and trysin fevers has been made by Wood, Reichert, and Hare.[56] These authors, as well as Ott,[57] have demonstrated that it is not the pepsin and the trypsin ferments themselves which constitute the pyrogenic agents, but some contaminating substance, which seems to be a peptone. That peptones artificially prepared contain poisonous principles has been known for some time, and Brieger[58] has succeeded in isolating a crystallizable poisonous ptomaine, called pepto-toxin, from commercial peptone and from that formed by the artificial digestion of fibrin. This ptomaine, however, is not identical with the pyrogenic agent found by Ott and by Wood and his colleagues in commercial pepsin. To this list of pyrogenic substances obtained from impure ferments may be added leucin, and, according to Ott, papayotin and neurin which produce marked fever when injected into the blood in small quantity. The substance sold under the name of papoid possesses marked pyrogenic power when its filtered aqueous solution is injected into the blood. This substance contains principles belonging to the peptone or albumose group. Dr. Mall, Fellow in Pathology at the Johns Hopkins University, has isolated from commercial papoid a bacillus, which in pure cultures exerts a powerful peptonizing action on fibrin and on connective and elastic tissues. The bacillus itself is not pathogenic, but an albumose or some similar substance produced by its activity, has pyrogenic power when injected into the blood.

It does not appear that any one has actually isolated the pyrexial agent from the various ferments employed in these experiments. Certainly no such agent has been obtained in a crystalline form, which is the test of its purity, if we except Brieger's pepto-toxin, the pyrogenic capacity of which has not been established. It has been alleged that the fever-producing agent is the same in all these ferment intoxications, but this has not been proven nor does it seem probable.

[55] Von Bergmann u. Angerer: D. Verhältniss d. Fermentintoxication. Festschrift: Würzburger Universität, 1882, I, 135.

[56] Wood, Reichert, and Hare: Therapeutic Gazette, 1886.

[57] Ott: Journal of Physiology, VIII.

[58] Brieger: Ueber Ptomaine, Berlin, 1885.

On better grounds it has been urged by von Bergmann and Angerer, that all of the substances in the group of pyrexial agents now under consideration, cause fever by producing the same change in the blood. These authors claim that this change is the formation in the circulating blood of an excessive amount of fibrin ferment, which leads either to coagulation or to stasis in the capillaries, particularly those of the lungs and of the intestines. One of the main arguments for this view is the fall of blood pressure which von Bergmann and Angerer observed after injections of pepsin and of pancreatin, but this fall can be explained in other ways than by supposing that the pulmonary capillaries are occluded, and, moreover, Wood, Reichert, and Hare find that the blood pressure often rises in the course of pepsin fever. It does not seem to me that we are any more able to explain in exactly what manner the pyrogenic substances act in this class of fevers than in other fevers. The idea, however, that the liberation of fibrin ferment in abnormal quantity is capable of causing fever, finds support not only in experiments which have been mentioned, but also in the fact that injections of haemoglobin solutions, and of large quantities of water into the blood, produce fever.

But you, perhaps, by this time have asked yourselves what bearing all of these experiments with various pyrogenic substances have upon the etiology of human fevers. They have, in my judgment, an important bearing on this subject. However, obscure may be the explanation of the mode of action of these substances, however doubtful may be their exact chemical composition, they have certain common characteristics which are calculated to shed light upon the causation of some obscure febrile disorders of human beings. In the first place, the members of this group of pyrogenic substances, if not identical with certain physiological ferments, are readily produced by them, quite independently of the action of bacteria or other microorganisms. In the second place, some of these substances are present normally in small amount in the body, and if their elimination is impeded, or their formation is excessive, there is reason to believe that they become efficient causes of fever. In the third place, these pyrogenic substances may be produced, again without the action of bacteria, in extravasated blood, or by the abnormal disintegration of tissues, and if they are absorbed from these sources in such a condition, or in so large an amount that nature cannot render them harmless, they are capable of producing fever. It is customary to call the morbid condition produced by the absorption of these substances, ferment intoxication in analogy with the term putrid intoxication, applied to the diseases caused by the absorption of the products of putrefactive bacteria. The term ferment intoxication seems to me to imply more than our knowledge warrants, but it is not of much use to contend against names which have gained currency.

It is probable that some of the pyrogenic agents in this group belong to the class of leucomaines, but our present information regarding these bodies does not justify any positive statement on this point.

Although the etiology of individual fevers, does not belong to our subject, I cannot forbear calling your attention to certain febrile conditions which seem to be produced by the accumulation of substances that are either normal constituents of the body or are the result of chemical processes, differing but little from physiological ones.

To this category probably belongs the so-called aseptic fever, first described by Genzmer and Volkmann.[59] These surgeons have established the fact that there are traumatic fevers not caused by the absorption of septic material, and that severe injuries and wounds which pursue an entirely aseptic course, are not infrequently associated with considerable elevation of temperature. This aseptic fever is usually to be observed with extensive wounds or injuries in which there is much lacerated tissue or extravasated blood to be disintegrated and absorbed. It occurs not only with wounds correctly treated by antiseptic methods, but also with subcutaneous injuries, particularly fractures of the large bones, where there can be no suspicion of the action of bacteria. Aseptic traumatic fever differs by such marked characteristics from septic fever, that there can be no doubt that the two types of fever are etiologically distinct. Aseptic fever has no prognostic significance; its only symptoms are the elevation of the temperature, which may mount to 104° (40° C.), or even 105.8° (41° C.), and the increased frequency of the pulse. The entire absence of all the intoxication symptoms of septic and infectious fevers, such as the benumbed sensorium, the dry tongue and skin, the lessened secretion of urine. I have already referred to in confirmation of the belief that these symptoms are not dependent upon the rise of temperature. Genzmer and Volkmann assign as the cause of aseptic traumatic fever, the absorption of substances resulting from the disintegration of the wounded tissues and of the extravasated blood, and state that these substances probably do not differ markedly from those produced by physiological tissue metamorphosis. This explanation certainly has received decided support by the experiments which I have described in this lecture, a large part of which have been performed since the publication of Genzmer and Volkmann's article. It has been suggested that aseptic traumatic fever is a reflex neurosis, and this suggestion cannot be absolutely rejected as a possible explanation, but for various reasons, which cannot here receive further consideration, the usually accepted explanation is the more probable one.

[59] Genzmer and Volkmann: Volkmann's Sammlung, No. 121.

An instructive case of ferment intoxication has been reported by Cramer.[60] There existed in a young woman a cyst, the size of a goose's egg, between the fibres of the semitendinosus muscle. The cyst was developed from a cavernous angioma, and was filled with dark fluid blood. The patient had had fever for almost two years up to the day of the operation. The cause of the fever could not be discovered. Immediately after the removal of the cyst the fever stopped and did not return. In this case the cavernous structure of the cyst wall accounts for the ease with which we must suppose a considerable quantity of pyrogenic substance was continuously absorbed from the bloody contents of the cyst. The results of Angerer's experiments, already mentioned, enable us to explain the source of the fever in this case.

Another instance may be cited in which fever is probably to be explained by the accumulation within the body of products of normal metabolism. More or less fever appears to be a constant accompaniment of the agonizing method of treatment known as the Schroth cure. In this treatment the patient is kept for a number of successive days on dry food with scarcely any fluids. Both Bartels and Jürgensen,[61] who have investigated the nutritive changes of individuals under this treatment, believe that the body becomes so poor in water that some of the products of regressive metamorphosis cannot be carried out of the system. This certainly seems very probable, and, if true it affords in the light of recent experiments an explanation of the accompanying fever.

I believe that good reasons can be adduced in support of the opinion that the febrile conditions sometimes associated with leucocythaemia profound anaemias and chlorosis belong to the group of fevers we are now considering. It is probable that some of the obscure ephemeral fevers are also to be included here. But to consider these febrile disorders in detail would lead us into the domain of special etiology upon which we have already perhaps encroached too far. My purpose has been to bring before your attention only a few clinical examples in illustration of the experimental results.

I think that you will agree with me in the conclusion that experimental and clinical evidence justify us in recognizing as a distinct group of pyrogenic agents substances which have no necessary connection with microorganisms and which are either not foreign to the healthy organism or are readily formed by unorganized ferments from normal or abnormal constituents of the body. These substances may be described as homologous in distinction from the heterologous agents concerned in the production of septic and infectious fevers.

[60] Cramer: Verhandl. d. Deutschen Gesellschaft f. Chirurgie, 13th Congress, 1884.

[61] Jürgensen: Deutsches Arch. f. klin. Med., Bd. I.

A class of pyrogenic agents of far greater clinical importance than those previously considered is formed by the products of microörganisms which in themselves are not pathogenic. A considerable number of bacteria which when inoculated in pure culture into the body are not capable of further invasion or of multiplication produced in culture fluids and in dead animal or vegetable material poisonous substances often of great virulence. Exception may be taken to the description of these organisms as non-pathogenic, inasmuch as the products of their activity are poisonous, but the epithet pathogenic is usually assigned by bacteriologists only to such microorganisms as are capable of multiplication within the body. If we called all of the microorganisms pathogenic which produce poisonous ptomaines we should have to include in this category a far larger number of the known species of bacteria than has hitherto been customary.

The best known and most important of the fevers produced by chemical products of saprophytic bacteria are those grouped under the name putrid intoxication. Until the introduction of the modern era in bacteriology by Koch nearly all of the experimental work on the etiology of fevers related to the causation of the septic and putrid fevers. It is instructive with our present knowledge to follow the experiments on this subject from the period of Gaspard, Magendie, and Sedillot up to recent times. What light has been shed upon the mass of contradictory and perplexing results of experiments with putrid fluids by the recent chemical and biological studies of putrefactive processes? Some of the putrid substances experimented with undoubtedly contained parasitic microorganisms, and others contained only obligatory saprophytes. Some were rich in poisonous ptomaines, and others were nearly devoid of them. The whole doctrine of the parasitic nature of infectious fevers seems to have hinged in the minds of some upon the determination of the question whether septic and putrid fevers are produced by the absorption of chemical substances, or by the invasion of pathogenic bacteria. The ideas concerning putrid intoxication dominated at one time the whole field of fever etiology, and were applied not only to septicaemia but to typhoid fever, typhus fever, yellow fever—in fact, to nearly all infectious fevers. Nor have the echoes of this period even now entirely died out.

Panum was the first to isolate from putrid materials some chemical substance or substances in tolerable purity, certainly free from bacteria. This substance, when injected into animals, produced symptoms of putrid intoxication. Subsequently, von Bergmann and Schmiedeberg isolated from putrefying yeast a poisonous crystalline substance, their celebrated sepsin. For a time the opinion prevailed that this sepsin is the source of all putrid intoxications. Thanks to the investigations of Nencki and others, and par-

ticularly of Brieger, we now know that many alkaloidal substances can be separated from putrefying materials. Some of these so-called cadaveric alkaloids or ptomaines are poisonous, fever-producing, others are harmless. There is no reason to suppose that the list of the ptomaines of putrefaction has been exhausted, nor is it necessary to believe that all of the poisonous constituents of putrefying materials of an alkaloidal nature.

Most of the bacteria concerned in ordinary putrefactive processes are purely saprophytic. They are incapable of multiplication in the living animal tissues. In a mixture of putrefactive bacteria it is not, however, uncommon to find genuine pathogenic or parasitic bacteria. It was from such sources that the bacilli of mouse septicaemia and of rabbit septicaemia (Koch) were obtained. The bacillus of malignant oedema is also often found in the early stages of post-mortem decomposition.

There is, of course, no doubt that the absorption of the chemical products of putrefaction may produce fever with septic symptoms, quite independently of the penetration and multiplication within living tissues of bacteria.

Here belong certain cases usually described as septic, in which fever and other bad symptoms subside upon the thorough cleansing and disinfection of a foul wound, or of a puerperal uterus. The majority of cases of septicaemia are not to be included here, for they depend upon the invasion of pathogenic bacteria. But, excluding the cases of genuine septicaemia, there remain the putrid intoxications which result from the absorption of poisonous substances produced in necrotic or disintegrating tissues, or exudations, or extravasated blood, by the action of purely saprophytic bacteria. The ideas which I have expressed on this subject are now so generally admitted that they require no further elucidation.

It is probable that fever, with symptoms of intoxication, although generally of a much milder nature than in the class of cases just considered, may be produced by abnormal fermentations and putrefactions caused by saprophytic bacteria in the alimentary canal. But here the essential morbid conditions seem to be abnormalities in the gastric and intestinal contents, due partly to the character of the ingesta, but chiefly to alterations of the digestive juices. Fermentative and putrefactive bacteria are normally present in the intestinal canal, and have abundant opportunities to gain access to this situation. The number, however, which can multiply and thrive there is quite limited, for under normal conditions, according to Escherich, only such bacteria can multiply to any extent in the intestinal canal as are capable of growing with little or no oxygen, and of deriving their nourishment from the anaërobic fermentation of the food supplied to them in this situation. Suitable conditions for the excessive multiplication of putre-

factive or fermentative bacteria may, however, be furnished by abnormalities of the gastric or intestinal contents.

Of a far more serious nature are the putrid or ptomaine intoxications which result from the ingestion of substances which have undergone outside of the body putrefaction, or changes which lead to the formation of poisonous ptomaines. To this group of cases belong at least many of the instances of poisoning which have been caused by eating certain kinds of meat, sausage, fish, cheese, etc. In some of these instances poisonous ptomaines have been isolated from the suspected substances, but we know scarcely anything of the microorganisms which are concerned in their production.

It is important to bear in mind that it is not stinking putrefaction alone which gives rise to poisonous products. Brieger has found that such products may be absent in very advanced decomposition, and that in general the most virulent products are formed in the early stages of putrefaction. We know, furthermore, that putrefactions and fermentations differ in the character of their products. There are differences according to the kind of bacteria present, according to the substances decomposed, and according to various other conditions, such as the presence of oxygen, the temperature, etc. This is not the proper occasion to discuss these details.

Enough has been said to prove that we are justified in recognizing as a second class of pyrogenic agents substances which are the products of bacteria in themselves not pathogenic. These pyrogenic agents may be formed on or within the body, or they may be produced outside of the body. I would not by any means have you infer that it has been proven in all of the special examples which I have mentioned, that the bacteria involved are not pathogenic, or capable of multiplication within the living tissues. We have not sufficient knowledge to assert or to deny this in every instance, but I do not think that it is likely exception will be taken to the classification which I have adopted for most of these cases. As has repeatedly been mentioned, our purpose here is not an analysis of individual cases of fever, but an attempt to classify systematically the various pyrogenic substances.

We come now to the third and most important group of fever-producing agents, the pathogenic microorganisms. So overshadowing is their importance that it has been claimed that they are the sole causes of fever. In contrast with former times it is no longer the symptomatic fevers whose etiology is clearest. We have much more definite ideas as to the mode of production of some of the essential fevers which were once the most obscure, than we have of symptomatic fevers. It does not seem to me worth while to go over the chain of evidence which establishes the doctrine that the infectious fevers are caused by microorganisms. There is probably no one who has thoroughly investigated the subject, and is competent to form an opinion

on it, who does not to-day admit that a number of infectious diseases have been proven to depend upon specific microorganisms, and that it is a logical inference that all infectionus diseases are caused by parasitic organisms.

It is not germane to our subject to enter into a morphological or biological description of the different species of pathogenic organisms which are causes of febrile diseases. The only question which concerns us in this consideration of the general etiology of fever is how the microorganisms produce fever. Are they themselves the pyrogenic agents, or do they produce chemical substances which are pyrogenic? A number of other possibilities might be mentioned. These and similar questions have suggested themselves to investigators since the beginning of any knowledge of parasitic microorganisms. Our information is far from sufficient to enable us to answer these questions in a positive manner, and still we are not left wholly to vague surmises in attempting to form some sort of an opinion.

That bacteria can produce mechanical effects by plugging up capillaries and in other ways is certain, but the wide differences presented by the various infectious diseases cannot be reconciled with the idea that pathogenic bacteria act chiefly by mere mechanical interference with the fluid and the solid constituents of the body. Notwithstanding the fact that Stricker and Albert succeeded in producing fever by the injection of starch granules into the blood, probably no one will be inclined to attribute the pyrogenic activity of bacteria in any considerable extent to occlusion of bloodvessels.

In a certain number of infectious diseases, particularly of animals, bacteria are present in such enormous number in the blood and tissues that some are inclined to refer the disastrous effects of the organisms to the withdrawal of oxygen and other nutritive pabulum from the cells of the body. So far as the appropriation of oxygen is concerned, this idea is not supported by the results of most of the examinations of the blood in cases of anthrax. This explanation was more popular in the early days of bacteriology than it is at present, and at the best its value is limited, for it cannot be applied to a large number of infectious diseases, such as cholera or typhoid fever where the circulating blood is not largely invaded by the parasites. Furthermore, it is not clear how the appropriation by bacteria of nutriment intended for the tissues would help us to explain the production of fever.

It has been suggested that the increased temperature in infectious fevers may be explained by the heat produced by oxidation or other chemical changes in the microorganisms themselves. But this is not at all a satisfactory explanation. Not only is the quantity of heat which can come from this source in all probability very small compared with that constantly produced in the body, but such an explanation of febrile rise of temperature is

not in harmony with what we know concerning the mode of production of fever (see Lecture I).

The failure to explain the pathogenic power of bacteria in these and similar ways led to the supposition that the morbid activity of pathogenic bacteria is exerted chiefly by means of injurious chemical products. The demonstration of such products leaves no room for doubt as to the correctness of this supposition for some infectious diseases. This explanation is probable for most such diseases, but experience has shown that it is particularly dangerous to indulge in hasty generalization in this department of medical science.

Sterilized and filtered cultures, particularly old cultures, of various pathogenic bacteria are capable of producing fever and other symptoms when injected into the blood or tissues. This, of course, makes it evident that the bacteria in question give rise to poisonous substances. It is necessary to distinguish between the intoxication produced by the injurious products of bacteria and the infection caused by multiplication of the microorganisms within the body. That this distinction may be readily overlooked is shown by the recent experiments with the inoculation into animals of pure cultures of the typhoid bacillus. Small quantities of these cultures may be inoculated without any apparent effect; if, however, larger quantities are injected into the veins or the peritoneal cavity of a rabbit, the animal dies in a short time and the characteristic bacilli are found in the blood, spleen, and elsewhere. It was supposed by Fränkel and Simmonds,[62] to whom we owe this latter observation, that actual infection took place, but it has been demonstrated by Sirotinin and by Beumer and Peiper[63] that under these circumstances no multiplication of the injected bacilli occurs, and that the same results may be obtained by the injection of sterilized typhoid cultures.

The isolation in a chemically pure state of the poisonous products of pathogenic bacteria encounters great difficulties, and we owe to Brieger[64] nearly all that has been accomplished in this direction. Two substances which he has obtained from cultures of pathogenic bacteria are of great interest. Brieger isolated from pure cultures of the typhoid bacillus a very poisonous ptomaine or toxine, as he prefers to call this group of substances. He has given to it the name typhotoxine. It may be somewhat significant that he failed to find typhotoxine in a culture which had stood for twenty-four hours at a temperature of 102.2° F. (39° C.). The injection of typho-

[62] Fränkel and Simmonds: Die Aetiologische Bedeutung des Typhus-bacillus, Hamburg und Leipzig, 1886.

[63] Sirotinin: Zeitschrift f. Hygiene, Bd. I, 465.
Beumer u. Peiper: *Ibid*, p. 489.

[64] Brieger: Untersuchungen über Ptomaine, Berlin, 1886.

toxine into guinea-pigs produced great muscular weakness, diarrhoea, increased frequency of pulse and of respiration, and death. Nothing is said as to the effect upon the temperature of the animal.

A toxine has been isolated by Brieger in a crystalline form from an impure culture of the tetanus bacillus. This substance, called tetanin, produces, when injected into animals, the characteristic symptoms of tetanus.

It is evident that these important discoveries render far more definite than was formerly possible, the belief that bacteria produce fever by means of their chemical products.

A dangerous influence exerted by poisonous ptomaines is that under their agency the power of the body of resisting the invasion of various microorganisms may be impaired or overcome. Thus, Wyssokowitsch has shown that the immunity of some animals against certain species of bacteria may be destroyed by ptomaine poisoning.

In order to observe the effects upon the temperature, I have injected into rabbits sterilized cultures of the typhoid bacillus. Injections of very small quantities of these cultures produce no effects, somewhat larger amounts cause a rise of temperature without other marked symptoms, still larger quantities produce increased temperature, diarrhoea, weakness, and other manifest symptoms of severe illness, but the animal may recover; relatively large amounts are followed by fall of temperature, grave illness, and death. I have also obtained results similar to those of Sirotinin, who inoculated two rabbits with the same amount of a typhoid culture. In one rabbit fever developed and the animal recovered; in the other, the temperature fell after the injection, and the animal died. This certainly does not indicate that the rise of temperature in itself is an unwelcome attendant of intoxication with the poisonous products of bacteria. My experiments certainly showed that the animals were more likely to die after injection of typhoid cultures when the temperature fell than when it rose, independently of the quantity of material injected. One is reminded here of the very malignant cases of typhoid fever reported by Fräntzel, and others, in which the temperature throughout a great part of the disease was subfebrile, or even at times subnormal.

In no disease is the dependence of the febrile paroxysm upon the presence of bacteria so apparent as in relapsing fever, where, according to the statements of most, although not of all, observers the spirilla appear in the blood at the beginning of a paroxysm and disappear at the end. Whether or not, here and in malaria, the pyrogenic agent is a chemical product of the microorganisms causing the disease, we do not know.

I must content myself with having brought before you evidence showing that at least in some of the infectious fevers the specific bacteria produce

pyrogenic substances. We have no right to say that this is the only way in which pathogenic bacteria can cause fever.

We have considered now three groups of agents concerned in the production of fever, viz.: first, unorganized ferments and other relatively homologous substances; second, ptomaines and other chemical products of saprophytic microorganisms; third, pathogenic microorganisms and their chemical products.

It is not to be understood that these groups correspond to sharply defined classes of fever-producing agents. The same substance may be produced by the action of unorganized ferments, as well as by saprophytic bacteria or by parasitic bacteria; hence, we may find the same fever-producing agent in each of the three groups. As has already been mentioned, our knowledge does not justify us in regarding these various substances as the immediate and direct pyrogenic agents. The epithet pyrogenic is applied to them only by a certain latitude of signification. It is possible that these various substances, which we are in the habit of describing as pyrogenic, may produce in the body some common change which gives rise to the real fever-producing agent. This is the view of von Bergmann and Angerer, who believe that this common change is a liberation of fibrin ferment by destruction of leucocytes. While we cannot consider this view as more than an hypothesis, it is, nevertheless, well to remember that apparently heterogeneous substances, which are usually designated as pyrogenic, may produce similar changes which are to be regarded as the real source of the febrile disorder of animal heat. But, notwithstanding these limitations and these elements of uncertainty, it seems to me that some such classification as that suggested of the agents producing fever is more useful than that usually employed in the discussions of the etiology of symptomatic and of essential fevers.

There is one point which must be impressed upon every one who makes many experiments with pyrexial agents. This is, that once in a while a substance of undoubted pyrogenic power causes a fall instead of a rise of temperature. This occurs frequently when the substance is injected in large quantity and under these circumstances there is usually produced a condition of collapse. But in exceptional cases the same dose which will cause in one animal a rise of temperature may give rise in another animal of the same species to a distinct reduction of temperature. In these latter cases there must be some idiosyncrasy on the part of the animal. Aronsohn [65] refers this unusual phenomenon to some peculiarity of the heat centers in the brain, and he draws an interesting parallel between this contrary effect of pyrogenic substances and the exceptional cases in which antipyretic drugs give rise to elevation instead of lowering of temperature.

[65] Aronsohn: Deutsche med. Wochenschrift, 1888.

The causes of fever which we have thus far discussed, have been substances which exert a pyrogenic effect when introduced into the circulation. We suppose that these substances act in some way upon the nervous system, but whether or not this action is a primary one it is impossible to say. Even if we assume, as is often done, that these substances incite directly in the blood and tissues chemical changes which lead to increased production of heat, we must still have recourse to some action upon the nervous system, as has already been sufficiently set forth in the previous lectures.

It cannot be doubted that fever may be caused by other agencies than pyrogenic substances present in the blood or tissues. The effects of exposure to external heat have already been considered. We found experimental evidence in support of the view ably advocated by H. C. Wood, that in typical cases of thermic fever or sunstroke, the strain placed upon the heat-regulating centres by exposure to excessive heat results in paralysis of these centres with rapid elevation of the internal temperature.

The cause of the elevation of temperature in tetanus is not altogether clear. In this disease the temperature may vary but little from the normal, but it is not uncommon to find excessive elevations of temperature toward the termination. Temperatures of 113° F. (45° C.), or more, have been recorded. The idea would naturally suggest itself that the rise of temperature is due to the tetanic muscular spasms, which we know to be accompanied by production of heat. Leyden was led to adopt this explanation by the results of experiments made upon animals. He succeeded by producing violent tetanic contractions of the muscles of a dog, in raising the internal temperature in the course of one hour and a half from 103.3° F. (39.6° C.) to 112.6° F. (44.8° C.). Clinical observations, however, do not support the supposition that the hyperpyretic temperatures of tetanus are dependent upon the muscular contractions. In spite of violent and prolonged tetanic spasms, the internal temperature may remain normal or be but slightly elevated. There is a decided similarity between the hyperpyrexia of tetanus and that which occurs in rheumatism and some other diseases, particularly in affections of the central nervous system, and it certainly seems probable that in all of these cases there is a profound disturbance of the heat-regulating centres. As the elimination of urea in tetanus is not excessive, we find additional reason to separate tetanic hyperpyrexia from ordinary febrile conditions. Recent investigations of the etiology of tetanus, have rendered it certain that at least some forms of this disease are caused by infection with a special microorganism. This has been demonstrated not only in the tetanus of animals but also in that of human beings. The tetanus bacillus has been found wide-spread in the ground in Germany, and I find it abundant in the ground in Baltimore and its neighborhood. In experimental tetanus, the

bacillus, which has not yet been obtained in perfectly pure cultures, develops chiefly in the tissues near the seat of innoculation, and does not invade other parts of the body and the blood to any great extent. This indicates that the symptoms are referable chiefly to poisoning by some chemical products of the specific microorganism. As has already been mentioned, this view is sustained by Brieger's discovery in cultures containing the tetanus bacillus of a peculiar ptomaine which he has called tetanin, and which produces tonic spasms of the muscles. It is, therefore, reasonable to believe that the hyperpyrexia of tetanus is caused by the action of poisonous products of the tetanus bacillus on the nervous centres concerned in temperature regulation. Our present knowledge, however, does not warrant us in asserting that all forms of tetanus in human beings are of an infectious nature.

In the first lecture of this course, evidence was presented to show that pyrexia may be caused by affections of the nervous system without the agency of any pyrogenic substance. It may jar upon the sensibilities of some to call this form of pyrexia fever; but this hesitation can be due only to the idea that symptoms which are referable to infection or intoxication are essential to the conception of fever. In my judgment, we shall be led into confusion if we attempt to incorporate into our definition of fever, more than properly belongs to the febrile disorder of animal heat, and from this point of view there can be no impropriety in designating as fever, the pyrexia dependent directly upon affections of the nervous system.

It is not necessary to repeat here the conclusive experimental evidence for the existence in the nervous system of centres or regions which control the dissipation of heat and the chemical processes concerned in the production of heat. Those who are not much impressed by experiments upon animals, can hardly fail to be convinced by the clinical evidence which demonstrates that lesions of the nervous system may cause elevation of temperature, which cannot be referred to the action of any pyrogenic substance. Such evidence must, of course, be collected from cases where the fever cannot be explained by inflammation, bed-sores, or other lesions which can give rise to absorption fever. W. Hale White,[68] in the interesting article already referred to, has collected a number of cases of tumor, hemorrhage, softening, sclerosis, injury and functional disturbance of the spinal cord and brain, in which the pyrexia or hyperpyrexia is to be explained only by the lesion of the nervous system. The number of such cases might be considerably increased. These cases show that lesions of the cervical part of the cord, of the pons, of the corpus striatum, and of the neighboring white matter, are most likely to be associated with high temperature, but the cases hitherto reported hardly justify

[68] W. Hale White: The Theory of a Heat Centre from a Clinical Point of View. Guy's Hospital Reports, 42, 1884.

positive statements as to the exact situation in man of thermically active nerves or regions in the brain and spinal cord. As might be expected, not only focal lesions, but also diffuse diseases such as occur in general paralysis of the insane, locomotor ataxia, multiple sclerosis may give rise to pyrexia which sometimes assumes the form of temperature crises. It is in harmony with what we know of other disorders of the nervous system, to find that not only demonstrable anatomical lesions, but also functional disturbances may produce nervous pyrexia. Such functional disturbance furnishes the most probable explanation of the singular and erratic elevations of temperature which have been occasionally observed in hysteria.

A question which merits more consideration than it is possible to give to it on the present occasion, relates to the possibility of the occurrence of fever as a reflex neurosis. The advance in our knowledge of the etiology of traumatic and inflammatory fevers, has pushed aside almost wholly the old doctrine of irritative fever. There are, however, cases of fever where still the simplest, and apparently most rational, explanation of the causation, is peripheral nerve irritation. As examples may be mentioned, the fever resulting from teething in children, that sometimes accompanying the passage of gall-stones or urinary calculi, and that occasionally following the insertion of a catheter into the urethra. It must be admitted that the evidence on this point is not conclusive. Especially is there lack of satisfactory experimental evidence. Electrical irritation of the exposed sciatic nerve is, under ordinary circumstances, followed by a moderate fall of temperature, although Ott[47] finds that in atropinized cats such irritation is followed by a decided rise of temperature. But these experiments cannot be held to weigh for or against the doctrine of irritative fever. Observations on human beings indicate that peripheral nerve irritation, if ever a cause of fever, is so only in certain situations and under certain forms of stimulation, and in certain individuals. In infants temperature regulation is more labile than in adults, so that it may be that nerve irritation can more readily disturb the temperature in the former than in the latter. The chief controversy as to the question now before us, has been as to the explanation of certain forms of urethral or catheter fever. It cannot be doubted that a large number, probably most, of the cases of so-called urethral fever, are instances of genuine absorption fever. Even if we exclude all cases with diseased kidneys, or with cystitis or other inflammatory disease of the urinary passages, there remains a certain number of cases in which the gentle insertion of a disinfected catheter is followed by distinct febrile reaction. It seems unwarrantable to assume that in all of these cases the catheter has caused a laceration of the urethra

[47] Ott: Therapeutic Gazette, August, 1887.

through which pyrogenic substances are absorbed. What is the nature and whence the source of these substances? In the cases now under consideration, they can be sought only in the normal urine, and of their existence there no proof has been afforded. In these cases it is certainly very difficult to understand how the fever can be interpreted as due to the absorption of some pyrogenic agent, and failing this explanation, the idea that the fever is dependent upon nerve irritation is most plausible.

I have now presented to you an imperfect survey of the general etiology of fever. The attempt has been made to classify the leading causes of fever, but it cannot be claimed that every variety of fever can be assigned to one of these groups of causes. Our knowledge of the etiology of special fevers is still too imperfect to warrant any such generalization. This is an attractive field for much patient investigation. I need only remind you of the uncertainty which still pertains to the causation of many of the fevers of warm countries. There is reason to believe that there remain yet to be differentiated etiologically, specific types of fever which occur among us, and particularly in our Southern States. It may be, that increasing knowledge will necessitate the recognition of varieties of pyrogenic agents entirely distinct from any with which we are now familiar. It is certain that future investigations will add clearness and precision to our ideas of the nature and mode of action of causes of fever which, at the best, we can now understand only imperfectly.

I cannot conclude this course of lectures without saying a few words on a subject which must engage the attention of every one who gives much thought to the nature of fever. What is the significance of fever, is a question which thrusts itself upon us no less than it has upon physicians in all ages. Unfortunately, we cannot to-day, any more than could our predecessors, give other than a speculative answer to this question. There have been in all ages enlightened physicians who have held the opinion that fever is a process which aids in the elimination or destruction of injurious substances which gain access to the body. Under the influence of ideas which sought in increased temperature the origin of the grave symptoms of fever, we have in recent times in great part lost sight of the doctrine once prevalent, that there may be in fever a conservative element. There is much which speaks in favor of this doctrine. The real enemy in most fevers, is the noxious substance which invades the body, and there is nothing to prevent us from believing that fever is a weapon employed by nature to combat the assaults of this enemy. The doctrine of evolution indicates that a process which characterizes the reaction of all warm-blooded animals against the invasion of a host of harmful substances, has not been developed to so wide an extent, and is not retained with such pertinacity without subserving some useful

purpose. This is a point of view from which many pathological processes can be regarded with advantage. Even suppuration, which one does not generally look upon as a beneficent provision, is a most important instrument of nature in forming a barrier against general infection of the body with certain microorganisms. It is impossible with our present knowledge, to say in exactly what way fever accomplishes a useful purpose. There are facts which suggest that in some cases of fever the increased temperature as such may impair the vitality or check the virulence of pathogenic microorganisms, but there are many circumstances which make it difficult to suppose that this is the agency by which fever usually exerts a favorable action.

The supposition seems to me more probable that the increased oxidation of fever aids in the destruction of injurious substances. According to this view, the fever-producing agents light the fire which consumes them. It is not incompatible with this conception of fever, to suppose that the fire may prove injurious also to the patient and may require the controlling hand of the physician. Time will not permit me to elaborate further the ideas here suggested. In the course of these lectures some facts have been presented and others might be drawn from clinical and experimental observations which favor the hypothesis that fever is in a certain sense a conservative process. Unproven and intangible as the hypothesis may seem to some, no apology is needed for bringing to your attention a conception of fever in favor of which much can be adduced, and which, if true, is of fundamental importance, both theoretically and practically.

HYPERTHERMY IN MAN[1]

An even more remarkable case has been reported than that described by Dr. Jacobi. It was reported by Dr. W. J. Galbraith, of Omaha, Neb., in an article entitled "A Remarkable Case," and published in the "Journal of the American Medical Association," March 31, 1891. The temperature in this case was observed by Dr. Galbraith to rise to 151° F., while the nurse's record shows it to have reached 171° F. The patient was a married woman, twenty-six years of age, who is said to have had repeated attacks of peritonitis during the period of observation of the high temperature, and to have passed *per vaginam* over one thousand pieces of bone, which were believed to come from a dead foetus of extra-uterine pregnancy. Dr. Galbraith's description of the case is most graphic. At first, entirely skeptical, he refused at the first call even to see the patient in consultation, but personal examination later made a complete convert of him. Suspecting some deception, he says the following test was made: "The patient was placed in a chair, all clothing removed, and a careful examination made of her month and axillary region, every possible precaution taken in order to prevent any deception, and holding the end of the thermometer so that it could not be tipped in any way, we again proceeded to take her temperature; but, gentlemen, the result was the same; the thermometer under the axilla registered 137° F., while that under the tongue registered 131° F."

There was nothing in the pulse or the general condition of the patient to indicate any elevation of temperature. Especially constructed and carefully tested thermometers were used.

So far as one can judge from the description of Dr. Galbraith's case, and the same is true of Dr. Jacobi's case, there was no apparent mode of deception. Still, Dr. Jacobi must pardon me if, with the greatest respect for his skill as an observer, I express complete skepticism as to the trustworthiness of these observations. I do not undertake to explain in what way deception was practised, but there is no doubt in my mind that there was deception. Such temperatures as those recorded in Dr. Galbraith's and Dr. Jacobi's cases are far above the temperature of heat-rigor of mammalian muscle and are destructive of the life of animal cells. They could not be present even in

[1] Remarks on a paper by A. Jacobi, before the Association of American Physicians, Washington, D. C., May 31, 1895.

Tr. Ass. Am. Physicians, Phila., 1895, X, 189-191.

the integument alone for any length of time without leaving behind manifest lesions where they existed. I consider them to be physical impossibilities under the conditions described.

[Addendum. When making the preceding remarks I was not aware that Dr. Galbraith's case had already been thoroughly discredited by subsequent developments. A physician—Dr. Bridges—who happened to be present when I was speaking, immediately afterward told me that he was familiar with the case, having been an interne in the hospital where this woman was admitted, and where she attempted again to practise deception, which was detected. Two articles relating to the case, published since Dr. Galbraith's article, have come to my notice, and I believe that Dr. Bridges referred to a third article, in which his experiences were narrated; but this last one I have not seen. One article is by Dr. J. E. Summers, Jr., in the "Omaha Clinic," September, 1891, and is entitled "Omaha's Remarkable Case of High Temperature—an Undoubted Hysterical Fake." The patient's temperature had continued to oscillate from several degrees below normal to any point below 150° F., with symptoms interpreted as those of peritonitis. On May 19, 1891, Dr. Summers performed abdominal section, and, save the presence of old adhesions about the uterine adnexa, found no evidences of peritonitis or of the previous existence of an extra-uterine pregnancy. Several pieces of bones which had been removed from the vagina, and had been attributed to a macerated foetus, were sent to Dr. Billings, at the Army Medical Museum, where they were pronounced to be "portions of the sternum of some bird, probably a chicken; also one of the long bones nearly complete, and a portion of the skull of a chicken or some bird about the same size. Other fragments are of larger bones than those of a fowl; in fact, they resemble splinters of ordinary beef or mutton bones. You may be positively certain that none of the fragments of bones have come from any organism developed in a human female." Before sending the specimens Dr. Summers had himself come to the conclusion that the bones were not those of a human foetus, but had been placed in the genital passages by the woman herself. These bones are still preserved in the Army Medical Museum, where I have seen them. The patient had "never been able to make her temperature go up," as she expressed it, when Dr. Summers tested it.

A second article was published in February, 1892, in the same journal, by Dr. C. T. Poe, entitled "A Chronic Malingerer." Dr. Poe describes his experience with this patient two years previous to the publication of Dr. Galbraith. Dr. Poe narrates a remarkable attempt on the part of the patient to represent that she had recently been delivered of a child, although examination precluded the possibility of this, and he exposed her in the attempt to palm off on him a temperature of 112° F. Here the trick was the simple

one of heating the thermometer with a hot-water bottle in the bed. It may be stated that in the fall of 1889 this versatile malingerer attended a course of lectures in the Woman's Medical College at Chicago. There were many other interesting phenomena of malingering presented by this patient. I am not aware that any explanation has been given of the precise method by which she deceived Dr. Galbraith. The points in the case most interesting to me are not the extraordinary height of the temperature, but the entire good faith, with which Dr. Galbraith, one of the most experienced and best-known surgeons in Omaha, reported the case, and the apparent thoroughness of the tests to which he subjected the patient.]

ADAPTATION IN PATHOLOGICAL PROCESSES[1]

Grateful as I am for the personal good-will manifested by my selection as President of this Congress, I interpret this great and unexpected honor as an expression of your desire to give conspicuous recognition to those branches of medical science not directly concerned with professional practice, and as such I acknowledge it with sincere thanks.

All departments represented in this Congress are working together toward the solution of those great problems—the causes and the nature, the prevention and the cure, of disease—which have always been and must continue to be the ultimate objects of investigation in medicine. It is this unity of purpose which gives to the history of medicine from its oldest records to the present time, a continuity of interest and of development not possessed in equal degree by any other department of knowledge. It is this same unity of purpose which joins together into a single, effective organism the component parts of this Congress, representing, as they do, that principle of specialization and subdivision of labor which, notwithstanding its perils, has been the great factor in medical progress in modern times.

Medical science is advanced not only by those who labor at the bedside, but also by those who in the laboratory devote themselves to the study of the structure and functions of the body in health and disease. It is one of the most gratifying results of the rapid advance in medical education in this country during the last few years, that successful workers in the laboratory may now expect some of those substantial rewards which formerly were to be looked for almost exclusively in the fields of practical medicine and surgery. We already have abundant assurance that the steady improvement in opportunities and recompense, and other material conditions essential for the prosecution of scientific work in medicine, will enable this country to contribute to the progress of the medical sciences a share commensurate with its great resources and development in civilization.

The subject of "Adaptation in Pathological Processes," which I have selected for my address on this occasion, is one which possesses the broadest biological, as well as medical, interests. It is this breadth of scientific and practical interest that must justify my choice of a theme which involves

[1] President's address before the Congress of American Physicians and Surgeons, Washington, D. C., May 5, 1897.

Tr. Cong. Am. Phys. & Surg., N. Haven, 1897, IV, 284-310.

many technical considerations and many problems among the most obscure and unsettled in the whole range of biology and of medicine.

I shall employ the epithet "adaptive" to describe morbid processes which bring about some sort of adjustment to changed conditions due to injury or disease. In view of the more technical and restricted meaning sometimes attached to the term "adaptation" in biology, objection may be made to this broad and general application of the word in pathology; but no more suitable and convenient epithet than "adaptive" has occurred to me to designate the entire group of pathological processes whose results tend to the restoration or compensation of damaged structure or function, or to the direct destruction or neutralization of injurious agents. Processes which may be described variously as compensatory, regenerative, self-regulatory, protective, healing, are thus included under adaptive pathological processes. These processes are, in general, more or less advantageous or useful to the individual; but for reasons which will be stated later the conception of pathological adaptation and that of advantage to the individual are not wholly coextensive.

Within the limits of an address I cannot hope to do more than direct attention to some of those aspects of the subject which seem to me to be of special significance. Although most striking examples of adaptation are to be sought in comparative and vegetable pathology, what I shall have to say will relate mostly to human pathology. My purpose is not to point out the beauties or the extent of adaptations in pathological processes, but rather to say something concerning the general mechanism of their production and the proper attitude of mind regarding them, and to illustrate the general principles involved by a few representative examples.

It has been contended that the conception of adaptation has no place in scientific inquiry; that we are justified in asking only by what means a natural phenomenon is brought about, and not what is its meaning or purpose; in other words, that the only question open to scientific investigation is How? and never Why? I hope to make clear by what follows in what light I regard this question, and in this connection I shall simply quote Lotze, who, beginning as a pathologist, became a great philosopher: "Every natural phenomenon may be investigated not only with reference to the mathematical grounds of its possibility and the causes of its occurrence, but also as regards the meaning or idea which it represents in the world of phenomena."

The most wonderful and characteristic attribute of living organisms is their active adaptation to external and internal conditions in such a way as tends to the welfare of the individual or of the species. Of the countless physiological examples which might be cited to illustrate this principle, I

select, almost at random, the preservation of the normal temperature of the body in warm-blooded animals under varying external temperatures and varying internal production of heat, the regulation of respiration according to the need of the tissues for oxygen, the influence of the load upon the work performed by muscles, the accommodation of the heart to the work demanded of it, the response of glands to increased functional stimulation, the adjustment of the iris to varying degrees of illumination, the influence of varying static conditions upon the internal architecture of bone.

The most striking characteristic of these countless adaptations is their apparent purposefulness. Even if it be true, as has been said by Lange, that "the formal purposefulness of the world is nothing else than its adaptation to our understanding," it is none the less true that the human mind is so constituted as to desire and seek an explanation of the adaptations which it finds everywhere in organic nature. From the days of Empedocles and of Aristotle up to the present time there have been two leading theories to explain the apparent purposefulness of organic nature—the one, the teleological, and the other, the mechanical theory. The teleological theory, in its traditional signification, implies something in the nature of an intelligence working for a predetermined end. So far as the existing order of nature is concerned, the mechanical theory is the only one open to scientific investigation, and it forms the working hypothesis of most biologists. This theory, in its modern form, seeks an explanation of the adaptations of living beings in factors concerned in organic evolution. What these factors are we know only in part. Those which are most generally recognized as operative are variation, natural selection, and heredity. That additional factors, at present little understood, are concerned seems highly probable. The acceptance of the explanation of physiological adaptations furnished by the doctrine of organic evolution helps us, I believe, in the study of pathological adaptations.

As the word "teleology" has come to have, in the minds of many, so bad a repute in the biological sciences, and as I desire, without entering into any elaborate discussion of the subtle questions here involved, to avoid misconceptions in discussing subjects whose ultimate explanation is at present beyond our ken, I shall here briefly state my opinion that all of those vital manifestations to which are applied such epithets as adaptive, regulatory, regenerative, compensatory, protective, are the necessary results of the action of forms of energy upon living matter. The final result, however useful and purposeful it may be, in no way directly influences the chain of events which leads to its production, and, therefore, the character of the result affords no explanation whatever of the mechanism by which the end, whether it appear purposeful or not, has been accomplished. In every case the ulti-

mate aim of inquiry is a mechanical explanation of the process in question. Notwithstanding valuable contributions, especially within recent years, toward such mechanical explanations, we are still far removed from the attainment of this aim.

The knowledge of the fact that the living body is possessed of means calculated to counteract the effects of injurious agencies which threaten or actually damage its integrity must have existed as long as the knowledge of injury and disease, for the most casual observation teaches that wounds are repaired and diseases are recovered from. It is no part of my present purpose to trace the history of the numerous speculations or even of the development of our exact knowledge concerning the subjects here under consideration. I cannot refrain, however, from merely referring to the important rôle which the conception of disease, as in some way conservative or combative in the presence of harmful influences, has played from ancient times to the present in the history of medical doctrines. Whole systems of medicine have been founded upon this conception, clothed in varying garb. There is nothing new even in the image, so popular nowadays, representing certain morbid processes as a struggle on the part of forces within the body against the attacks of harmful agents from the outer world. Indeed, Stahl's whole conception of disease was that it represented such a struggle between the anima and noxious agents. What lends especial interest to these theories is that then, as now, they profoundly influenced medical practice and were the origin of such well-known expressions as *vis medicatrix naturae* and *medicus est minister naturae*.

It is needless to say that there could be no exact knowledge of the extent of operation or of the nature of processes which restore or compensate damaged structures and functions of the body or combat injurious agents, before accurate information was gained of the organization and workings of the body in health and in disease. Although the way was opened by Harvey's discovery of the circulation of the blood, most of our precise knowledge of these subjects has been obtained during the present century, through clinical observations and pathological and biological studies. In the domain of infectious diseases wonderful and hitherto undreamed-of protective agencies have been revealed by modern bacteriological discoveries. Here, as elsewhere in medicine, the experimental method has been an indispensable instrument for discoveries of the highest importance and for the comprehension of otherwise inexplicable facts. Very interesting and suggestive results, shedding light upon many of the deeper problems concerning the nature and power of response of living organisms to changed conditions, have been obtained in those new fields of experimental research called by Roux the mechanics of development of organisms, and also in part designated

physiological or experimental morphology. Although we seem to be as far removed as ever from the solution of the most fundamental problem in biology, the origin of the power of living beings to adjust themselves actively to internal and external relations, we have learned something from these investigations as to the parts played respectively by the inherited organization of cells and by changes of internal and external environment in the processes of development, growth, and regeneration.

In physiological adaptations, such as those which have been mentioned, the cells respond to changed conditions, to meet which they are especially fitted by innate properties, determined, we must believe, in large part by evolutionary factors. In considering pathological adaptations the question at once suggests itself whether the cells possess any similar peculiar fitness to meet the morbid changes concerned; whether, in other words, we may suppose that evolutionary factors have operated in any direct way to secure for the cells of the body properties especially suited to meet pathological emergencies. Can we recognize in adaptive pathological processes any manifestations of cellular properties which we may not suppose the cells to possess for physiological uses? This question appears to me to be of considerable interest. I believe that it can be shown that most pathological adaptations have their foundation in physiological processes or mechanisms. In the case of some of these adaptations, however, we have not sufficiently clear insight into the real nature of the pathological process not into all of the physiological properties of the cells concerned to enable us to give a positive answer to the question.

While we must believe that variation and natural selection combined with heredity have been important factors in the development and maintenance of adjustments to normal conditions of environment, it is difficult to see how they could have intervened in any direct way in behalf of most pathological adaptations.

An illustration will make clear the points here involved. Suppose the human race, or any species of animal, to lack the power to compensate the disturbance of the circulation caused by a damaged heart-valve, and that an individual should happen to be born with the exclusive capacity of such compensation. The chances are that there would arise no opportunity for the display of this new capacity, and it is inconceivable that the variety would be perpetuated through the operation of the law of survival of the fittest by natural selection, unless leaky or clogged heart-valves became a common character of the species. When, however, we learn that the disturbance of circulation resulting from disease of the heart-valves is compensated by the performance of increased work on the part of the heart, and that it is a general law that such prolonged extra work leads to growth of

muscle, we see at once that this compensation is only an individual instance of the operation of a capacity which has abundant opportunities for exercise in normal life, where the influence of natural selection and other factors of evolution can exert their full power.

In a similar light we can regard other compensatory and functional pathological hypertrophies—indeed, I believe, also to a considerable extent the pathological regenerations, inflammation, and immunity, although here the underlying factors are, of course, different.

We may, however, reasonably suppose that natural selection may be operative in securing protective adjustments, such as racial immunity, against morbific influences to which living beings are frequently exposed for long periods of time and through many generations.

These considerations help us to explain the marked imperfections of most pathological adaptations as contrasted with the perfection of physiological adjustments, although I would not be understood to imply that the absence of the direct intervention of natural selection in the former is the sole explanation of this difference. The cells are endowed with innate properties especially fitted to secure physiological adaptations. No other weapons than these same cells does the body possess to meet assaults from without, to compensate lesions, to restore damaged and lost parts. But these weapons were not forged to meet the special emergencies of pathological conditions. Evolutionary factors have not in general intervened with any direct reference to their adaptation to these emergencies. Such fitness as these weapons possess for these purposes comes primarily from properties pertaining to their physiological uses. They may be admirably fitted to meet certain pathological conditions, but often they are inadequate. Especially do we miss in pathological adjustments that co-ordinated fitness so characteristic of physiological adaptations. So true is this that the propriety of using such terms as compensation and adaptation for any results of pathological processes has been questioned.

A heart hypertrophied in consequence of valvular lesion does not completely restore the normal condition of the circulation. Experience has shown that a kidney hypertrophied in consequence of deficiency of the other kidney is more susceptible to disease than the normal organ. What an incomplete repair of defects is the formation of scar-tissue, and with what inconveniences and even dangers may it be attended in some situations! If we look upon inflammation as an attempt to repair injury, and, therefore, as an adaptive process, with what imperfections and excesses and disorders and failures is it often associated! How often in some complex pathological process, such as Bright's disease or cirrhosis of the liver, can we detect some adaptive features, attempts at repair or compensation, but these overshadowed by disorganizing and harmful changes!

It is often difficult to disentangle, in the complicated processes of disease, those elements which we may appropriately regard as adaptive from those which are wholly disorderly and injurious. There are usually two sides to the shield, and one observer from his point of view may see only the side of disorder, and another from a different point of view, only that of adaptation.

The conception of adaptation in a pathological process is not wholly covered by that of benefit to the individual. I understand, as has already been said, by an adaptive pathological process one which in its results brings about some sort of adjustment to changed conditions. This adjustment is usually, wholly or in part, advantageous to the individual; but it is not necessarily so, and it may be harmful. The closure of pathological defects by new growths of tissue is a process which must be regarded as adaptive. But one would hardly describe as advantageous the scar in the brain which causes epilepsy. A new growth of bone to fill in defects is often highly beneficial; but what grave consequences may result from thickening of the skull to help fill the space left by partial arrest in development of the brain in embryonic life or infancy! We see here, as everywhere, that "Nature is neither kind nor cruel, but simply obedient to law, and, therefore, consistent."

In turning now to the more special, but necessarily fragmentary, consideration of a few of the pathological processes in which adaptation, in the sense defined, is more or less apparent, I shall have in view the answers to those two questions, What is the meaning of the process? and How is it caused? which confront us in our investigation of all natural phenomena. At the outset it must be admitted that our insight into the nature of many of these processes is very imperfect, and that here answers to the world-old riddles Why? and How? are correspondingly incomplete and liable to err.

Although almost all of the elementary morbid processes, even the degenerations and death of cells, may, under certain conditions of the body, serve a useful purpose—the pre-eminent examples of pathological adaptation, in the sense of restoration or compensation of damaged structure or function, or the direct destruction or neutralization of injurious agents, are to be found among the compensatory hypertrophies, the regenerations, and the protective processes. To this last ill-defined group I refer parasiticidal and antitoxic phenomena, and some of the manifestations of inflammation, and perhaps also of fever. In the last analysis these protective processes, no less than the others mentioned, must depend upon the activities of cells.

As it is manifestly impossible, within the limits of a general address, to attempt a detailed consideration of any large number of these adaptive pathological processes, and as such consideration would necessarily involve the

discussion of many technical and doubtful points, I have thought that my purpose would be best served by the selection of a few representative examples.

The compensatory hypertrophies afford admirable illustrations of certain fundamental principles regarding adaptations in pathology which I have already stated. The hypertrophy secures a functional adjustment, often of a highly beneficial character, to certain morbid conditions. This useful purpose is attained by a succession of events determined from beginning to end of the necessary response of cells and tissues, in consequence of their inherent organization, to the changed conditions. Given the changed conditions, on the one hand, and the organization of the cells, on the other, the result must follow as surely as night follows day, and this final result influences the preceding series of events no more in the one case than in the other. That the cells possess the particular organization determining the manner of their response to these changed conditions, and, therefore, the beneficial character of the result, is dependent upon innate properties whose fitness for the purpose doubtless has been largely fixed by evolutionary factors, operating, however, mainly in behalf of physiological functions and not directly toward pathological adjustments. In correspondence with this view we find that our knowledge of the manner of production of the compensatory hypertrophies of various organs and tissues stands in direct relation to our knowledge of the physiology of the same organs and tissues.

Those compensatory hypertrophies into the mechanism of whose production we have the clearest insight are referable to increased functional activity, and are, therefore, spoken of as work-hypertrophies. This has been proved for the muscular hypertrophies and compensatory hypertrophy of the kidney; but the demonstration is not equally conclusive for the compensatory hypertrophy of other glands. I know, however, of no instance in which this factor in the explanation can be positively excluded.

The relationship between increased functional activity and hypertrophy is so evident in many cases that there is strong presumption in favor of this explanation of those glandular compensatory hypertrophies which have not as yet been clearly referred to the class of functional hypertrophies. The very occurrence of compensatory hypertrophy of an organ may direct attention to the fact that it is endowed with definite functions, and the conditions under which the hypertrophy occurs may shed light upon the nature of these functions. I need only remind you of the significance, from this point of view, of the compensatory hypertrophy of the thyroid, adrenal, pituitary, and other glands with internal secretions. I fail to see why Nothnagel should consider *a priori* improbable the occurrence of compensatory hypertrophy of one sexual gland after loss of the other, even before sexual ma-

turity, or why Ribbert, who has apparently demonstrated experimentally such an occurrence, should find it necessary to seek the explanation in reflex nervous influences or mere hyperaemia. The so-called secondary sexual characters and the changes following castration, including the influence upon a hypertrophied prostate, point to important, even if little understood, functions which for the present we can perhaps best attribute to so-called internal secretions of these sexual organs.

The name compensatory hypertrophy is sometimes applied to growths of tissue that merely take the place of another kind of tissue which has fallen out, as, for example, the growth of adipose tissue around a shrunken kidney or pancreas, or between atrophied muscle-fibres. Here there is only compensation of space, but no compensation of structure or function. Such hypertrophies and growths are described better as complementary than compensatory.

Familiar examples of pathological hypertrophies from increased work are the hypertrophy of the heart from valvular disease and other causes, that of the muscular coats of canals and bladders behind some obstruction, and that of one kidney after loss or atrophy of the other.

In order to understand fully the manner of production of work-hypertrophy of a part resulting from some morbid condition, it is essential to know the nature of the disturbances induced by the underlying morbid condition, how these disturbances excite increased functional activity of the part which becomes hypertrophied, and what the relation is between this greater activity and the increased growth of the part.

It is impossible on this occasion to go through the whole list of compensatory hypertrophies with reference to the application of these principles. In no instance can the requirements stated be completely met in the present state of our knowledge. It will suffice for an understanding of the principles involved, and it is only with these that I am now concerned, if I take a concrete example. I select the classical and best studied one—compensatory hypertrophy of the heart. I trust that I shall be pardoned for selecting so commonplace an illustration, as the main points involved must be familiar to most of my audience; but it is possible that the application made of them may not be equally familiar. The only matters essential to my present line of argument are the mechanism of production of the hypertrophy and the general character of the adaptation thereby secured.

The heart, like other organs of the body, does not work ordinarily up to its full capacity, but it is capable of doing at least three or four times its usual work. The excess of energy brought into play in doing this extra work is called conveniently, although not without some impropriety, "reserve force." It has been proved experimentally that this storehouse of

reserve power is sufficient to enable the healthy heart, at least that of a dog, to accommodate itself at once or after a few beats to high degrees of insufficiency or obstruction at its valvular orifices without alteration in the mean pressure and speed of the blood in the arteries. But even so tireless and accommodating an organ as the heart cannot be driven at such high pressure without sooner or later, becoming fatigued, and consequently so dilated as to fail to meet the demands upon it. If it is to continue long the extra work, it must receive new increments of energy.

The cardiac muscle is far less susceptible to fatigue than the skeletal muscles, but that it may become fatigued seems to me clear.

Leaving out of consideration some doubtful causes of cardiac hypertrophy, such as nervous influences, the various morbid conditions which lead to this affection are such as increase either the volume of blood to be expelled with each stroke, or the resistance to blood-flow caused by the pressure in the arteries or by narrowing at one of the valvular orifices, or both. Unless some regulating mechanism steps in, each of these circulatory disturbances must increase the resistance to contraction of the cardiac muscle, and it is evident that the heart must do extra work if it is to pump the blood through the arteries with normal pressure and speed. It is, however, no explanation of this extra work simply to say that it occurs because there is demand for it. Increased work by the heart in cases of disease of its nutrient arteries would often meet a most urgent demand on the part of the body, but here the heart flags and fails.

The physiologists have given us at least some insight into the mechanism by which the heart responds through increased work to the circulatory disturbances which have been mentioned. These disturbances all increase the strain on the wall of one or more of the cavities of the heart; in other words, increase the tension of the cardiac muscle, in much the same way as a weight augments the tension of a voluntary muscle. Now it is a fundamental physiological law that with a given stimulus greater tension of a muscle, within limits, excites to more powerful contraction, and thus to the performance of greater work. It seems clear that this law applies to the muscles of the heart, as well as to voluntary muscle. We do not know precisely how increased tension facilitates the expenditure of greater muscular energy.

Another well-known fact in the mechanics of muscle is of importance in this connection. With increase of muscular tension under a given stimulus a point is reached where the extent of contraction is diminished, although the mechanical work done, determined by multiplying the height to which the load is lifted by the weight of the load, is increased. This law applied to the heart, whose contractions are always maximal for the conditions present at any given time signifies that, with increased resistance to the

contraction of the muscular wall of one of its cavities, this cavity will empty itself during systole less completely than before. In other words, dilatation occurs, and, as has been shown by Roy and Adami, to whom we owe important contributions on this as well as on many other points relating to the mechanics of the heart, dilatation regularly antedates hypertrophy. This primary dilatation, however, is not to be looked upon as evidence of beginning heart-failure, for, as these investigators have pointed out, it is within limits only an exaggeration of a physiological condition, and can be subsequently overcome by hypertrophy, which, in consequence of increase in the sectional area of the muscle, lessens the strain upon each fibre, and thereby permits it to shorten more during contraction. If this result is completely secured, we have simple hypertrophy. More often the dilatation remains, and must necessarily remain, and we have eccentric hypertrophy, which secures, for a time at least, adequate, but I do not think we can say perfect, compensation.

The weight of existing evidence favors the view that the power of the heart to adapt its work to the resistance offered resides primarily in its muscle-cells, and not in intrinsic or extrinsic nervous mechanisms, although doubtless these latter in various ways, which cannot be here considered, influence and support this regulating capacity. Nor can I here pause to discuss the influence of blood-supply to the cardiac muscle upon the force of ventricular contraction, although Porter has demonstrated that this is important.

In tracing the steps from the primary morbid condition to the final hypertrophy, we have thus far had to deal mostly with known mechanical factors. We now come to the question, How does increased functional activity lead to increased growth?

Inasmuch as greater functional activity is regularly associated with a larger supply of blood to the more active part, the view is advocated by many that the increased growth is the direct result of this hyperaemia, and one often encounters, especially in biological literature, this opinion expressed as if it were an indisputable fact. There is, however, no conclusive proof of this doctrine, and many facts speak against it. The examples from human pathology commonly cited to support the doctrine that local active hyperaemia incites growth of cells are, so far as I am able to judge, complicated with other factors, such as injury, inflammation, or trophic disturbances. Transplantation-experiments, such as John Hunter's grafting the cock's spur upon the cock's comb, sometimes adduced in this connection, are not decisive of this question, for here a new circumstance is introduced which some suppose to be the determining one for all morbid cell-growth, namely, the disturbance of the normal equilibrium between parts. Local active hyperaemia may exist for a long time without evidence of increased growth

in the congested part. To say that the hyperaemia must be functional is at once to concede that it is not the sole factor. Experiments from Bizzozero's laboratory, by Morpurgo and by Penzo, indicate that local hyperaemia due to vaso-motor paralysis, or to the application of heat, favors cell-multiplication in parts where proliferation of cells is a normal phenomenon or is present from pathological causes, but that it is incapable of stimulating to growth cells whose proliferating power is suspended under physiological conditions, as in developed connective tissue, muscles, and the kidneys.

It has been usually assumed that the way in which local hyperaemia may stimulate cell-growth is by increasing the supply of nutriment to cells. The trend of physiological investigation, however, indicates that the cell to a large extent regulates its own metabolism. If the cell needs more food, of course it cannot get it unless the supply is at hand, and in this sense we can understand how a larger supply of blood may be essential to increased growth; but this is a very different thing from saying that the augmented blood-supply causes the growth.

It is by no means clear that the question as to the influence of increased blood-supply upon cell-growth is identical with that of increased lymph-supply. The experiments of Paschutin and of Emminghaus, from Ludwig's laboratory, nearly a quarter of a century ago, indicate that local hyperaemia due to vaso-motor paralysis does not, as a rule, increase the production of lymph; and more recent experiments, although not wholly concordant in their results upon this point, tend to the same conclusion. Functional activity, however, has a marked influence in increasing the quantity and affecting the quality of lymph in the active part. Our knowledge of the physical and chemical changes in working muscles and glands enables us to conceive why this should be so, for all are now agreed that the formation of lymph is due not simply to filtration from the blood-plasma, but also to diffusion, and some believe likewise to active secretion by the capillary endothelium. Doubtless arterial hyperaemia is essential to the maintenance of the increased flow of lymph in working organs.

There are difficulties in the way of supposing that increased supply of lymph in itself furnishes the explanation of cell-growth, and especially of that which characterizes hypertrophy of muscles and glands. Pathologists have frequent opportunities to study the effects of all degrees of increased production and circulation of lymph associated with venous hyperaemia. A kidney or a muscle may from this cause be subjected for months and years to an excess of lymph-flow, but there is no demonstration of any consequent hypertrophy or hyperplasia of renal epithelium or muscle-cell. It is true that the chemical composition of the lymph is not the same as that of lymph resulting from increased function, and it is possible that in this chemical

difference lies the kernel of the whole matter. It may also be urged that in venous hyperaemia there are circumstances which restrain or prevent growth. Nevertheless, if overfeeding, merely in consequence of increased supply of nutriment, were the real explanation of work-hypertrophies, one would expect to find some evidence of this in the class of cases mentioned.

Ribbert has recently given a new shape to the doctrine that local hyperaemia excites growth. While rejecting the usual explanation that it does so by supplying more food, he contends that distention of the blood vessels and lymph-spaces, by mechanically disturbing the mutual relations of parts, removes obstacles to growth. This theory cannot be advantageously discussed until the fact is first established that uncomplicated local hyperaemia does incite growth.

As the matter now stands, it seems to me that any satisfactory explanation of the cell-growth causing work-hypertrophies must start from physical or chemical changes in the muscle- or gland-cell itself directly connected with the increased function. These changes are the *primum mobile,* and, however important increased supply of blood or lymph may be in the subsequent chain of events, it is not the determining factor. The whole problem is part of the general one of the causes of pathological cell-growth, to which I shall have occasion to refer again.

It is interesting to note that not all kinds of excess of functional activity lead to hypertrophy. A heart may beat for years faster than normal without becoming hypertrophied. Small movements of muscle, often repeated, do not cause hypertrophy. It would appear that the amount of work done in each functional act must attain a certain height in order to stimulate growth. On the other hand, if the muscle be stretched beyond certain limits, it does not hypertrophy; on the contrary, it may atrophy, as may be seen in greatly distended canals and cavities with muscular walls. This behavior is also in accordance with physiological observations.

The compensatory hypertrophy of muscle seems to be due mainly to increase in the size of cells, although there are observations indicating that they may also multiply. That of most glands is referable to increase both in number and size of cells. Within four or five days after extirpation of a kidney karyokinetic figures may be found in increased number in the cells of the remaining kidney.

The general character of the adaptation secured by compensatory hypertrophy of the heart is sufficiently well-known. I wish to point out certain of its imperfections. I shall not dwell upon the well-known abnormal conditions, with their remote consequences, of the systemic or pulmonary circulation, which are present during the stage of compensation, nor shall I speak of the various circumstances which may interfere with the establishment of compensatory hypertrophy.

The muscle of a hypertrophied heart is sometimes compared to that of the blacksmith's arm, and the statement is made that there is no reason inherent in the muscle itself why the one should fail more than the other. This may be true, but it is not self-evident. Exercise may influence in various ways the nutrition, function, and growth of muscle as well as of other parts. Mere increase in bulk is a coarse effect. Quality may be improved as well as quantity. The biggest muscle is not necessarily the best or the most powerful. As every trainer knows, various conditions under which work is done influence the result. Increase in the reserve energy of the heart, secured by judicious exercise—and this is the main factor in endurance—probably cannot be attributed mainly to hypertrophy; indeed, enlargement of this organ from exercise is often a serious condition. Much more might be said in this line of thought, but I have indicated why it seems to me unjustifiable to assume, without further evidence, that the condition of the muscle in pathological hypertrophies is necessarily identical in all respects with that in physiological hypertrophies.

There is an important difference in the working-conditions between most hypertrophied hearts and the normal heart. Although the maximal available energy of a hypertrophied heart during compensation is greater than that of the normal heart, clinical experience shows that in the majority of cases the energy available for unusual demands—that is, the so-called reserve force—is less in the former than in the latter. Sometimes, especially when the hypertrophy has developed in early life, the hypertrophied heart is at no disadvantage in this respect. As pointed out with especial clearness by Martius, the significance of this alteration in the ratio normally existing between the energy expended for ordinary needs and that available for unusual demands, is that it furnishes an explanation of the greater liability of the hypertrophied heart to tire upon exertion. Fatigue of the heart is manifested by dilatation of its cavities, and when this dilatation from fatigue is added to that already existing in most cases, relative insufficiency of the mitral or tricuspid valve is likely to occur, and the compensation is, at least for a time, disturbed. The circulation through the coronary arteries, whose integrity is so important for the welfare of the heart, is impaired, and a vicious circle may be established. Notwithstanding the valuable contributions from the Leipzig clinic as to the frequency of various anatomical lesions in the muscle of hypertrophied hearts, it does not seem to me necessary to have recourse to them as an indispensable factor in the explanation of the breakage of compensation; but I shall not here enter into a discussion of the general subject of the causes of failure of compensation.

I have described with some detail, although very inadequately, the manner of production of compensatory hypertrophy of the heart, in order, by this

representative example, to make clear what seem to me to be certain general characteristics of many adaptive pathological processes, and I beg here to call attention especially to the following points. As has been emphasized by Nothnagel and others, no teleological idea or form of language need enter into the explanation of the mechanism of the process. The final result is the necessary consequence of the underlying morbid conditions. We have satisfactory mechanical explanations for essential steps in the process, and there is no reason to assume that other than mechanical factors are concerned in those vital manifestations which at present we are unable to explain by known physical and chemical forces. The properties of the cells which determine the character of their response to the changed conditions are none other than their well-known physiological properties. The adaptation finally secured, admirable as it is in many respects, and perhaps adequate for long and active life, is generally attended with marked imperfections, and strictly speaking, is not a complete compensation. It does not present that co-ordinate and special fitness which we are accustomed to find in physiological adaptations, for the explanation of which so much has been gained by the study of the factors concerned in organic evolution.

It may be argued that under the circumstances no better kind or degree of adaptation can be conceived of than that which actually occurs, and that the operation of evolutionary factors, with especial reference to the adjustment of the organism to the conditions causing cardiac hypertrophy, could not secure any better result. I think that it is not difficult to conceive how improvements might be introduced. It is, however, permissible to suppose that the introduction into the workings of the organism of some better mechanism to compensate the morbid conditions, might be at the sacrifice of more important physiological attributes of the body. More perfect pathological adaptations might in many instances involve a deterioration of the physiological characters of the species. It is often the case that the more highly organized living beings lack some capacity possessed by those lower in the scale of organization to resist or compensate injury and disease. This is notably true of the power to regenerate lost parts. It is, however, along the lines of improvement in the physiological characters of the individual or species that the opportunity often lies for securing increased resistance to disease or better pathological adaptations.

It would be interesting to continue our consideration of the compensatory hypertrophies by an examination of those of glandular organs from points of view similar to those adopted for the heart. For the kidney, at least, the materials are at hand for such a purpose; but, as I desire, in the limited time at my disposal, to touch upon other varieties of pathological adaptation, I must refer those interested especially to the investigations of Grawitz and

Israel, Ribbert, Nothnagel, and Sacerdotti as to the conditions underlying compensatory hypertrophy of the kidney. I can likewise merely call attention to the interesting researches of Ponfick upon the most wonderful of the compensatory hypertrophies in higher animals, that of the liver. Ponfick, as is well known, has demonstrated that after removal of three-fourth of this organ new liver-substance, with normal functions, is recreated from the remainder and to an amount nearly equalling that which was lost.

The chapter of pathological adaptations in bones and joints I shall leave untouched, notwithstanding the admirable illustrations which might be drawn from this domain.

There is no more fascinating field for the study of pathological adaptations with reference to the mechanical factors involved than that furnished by the blood vessels, as has been shown especially by the brilliant researches of Thoma. With wonderful precision can a vessel of system of vessels adjust itself to changes in the pressure, velocity, and quantity of blood, and thereby serve the needs of the tissues for blood. Under pathological, as well as physiological conditions, this adjustment may be brought about not only through the agency of vaso-motor nerves and the physical properties of the vascular wall, but also, when the necessity arises, by changes in the structure of the wall.

The changes in the circulation introduced by the falling out of the placental system at birth are essentially the same as those resulting from amputation of an extremity, and the consequent alterations in the structure of the umbilical artery are identical with those in the main artery of the stump after amputation. The closure of the ductus Botalli and the ductus venosus soon after birth. and, still better, transformations of vessels in the embryo, furnish physiological paradigms for the development of a collateral circulation. Many other illustrations might be cited, did time permit, to show that in the processes of normal development, growth and regressive metamorphosis of parts, both before and after birth, and in menstruation and pregnancy, changed conditions of the circulation arise analogous to certain ones observed under pathological circumstances, and that the mode of adjustment to these changes by means of anatomical alterations in the vessels may be essentially the same in the physiological as in the morbid state. I see in these facts an explanation of the relative perfection of certain vascular adaptations to pathological or artificial states, as may be exemplified by changes in a ligated artery and by the development of a collateral circulation. The mechanisms by which the adjustments are secured have, in consequence of their physiological uses, for reasons already explained, a special fitness to meet certain pathological conditions. That this fitness should be greater in youth than in old age is in accordance with laws of life, indicated with

especial clearness by Minot in his interesting studies on "Senescence and Rejuvenation."

But these mechanisms are not equally well adapted to meet all morbid changes in the vessels. Although Thoma's interpretation of the fibrous thickening of the inner lining of vessels in arterio-sclerosis and aneurism as compensatory, or, as I should prefer to say, adaptive, is not accepted by all pathologists, it seems to me the best explanation in many cases. But the adaptation, if it be such, is here usually of a very imperfect nature, and it is not surprising that it should be so, when one considers the improbability of any mechanism developing under physiological conditions which should be specially fitted to meet the particular morbid changes underlying aneurism and arterio-sclerosis.

I shall not be able to enter into a consideration of the mechanical factors concerned in adaptive pathological processes in blood vessels, although perhaps in no other field are to be found more pertinent illustrations of the views here advocated concerning pathological adaptations. The whole subject has been studied from the mechanical side most fully and ably by Thoma, whose four beautifully simple histo-mechanical principles are at any rate very suggestive and helpful working-hypotheses, even if it should prove, as seems to me probable, that they are too exclusive. I shall call attention in this connection only to the inadequacy of the old and still often adopted explanation of the development of a collateral circulation. The rapidity with which a collateral circulation may be established after ligation of a large artery, even when the anastomosing branches are very small, is known to every surgeon. This was formerly attributed to increase of pressure above the ligature; but this rise of pressure has been shown to be too small to furnish a satisfactory explanation, and Nothnagel has demonstrated that there is little or no change in the calibre of arteries coming off close above the ligature unless they communicate with branches arising below the ligature. Von Recklinghausen several years ago suggested a better explanation. The bed of the capillary stream for the anastomosing arteries is widened by ligation of the main artery, inasmuch as the blood can now flow with little resistance from the capillaries of the anastomosing branches into those of the ligated artery. The result is increased rapidity of blood-flow in the anastomosing vessels. According to one of Thoma's histo-mechanical principles, increased velocity of the blood-current results in increased growth of the vessel-wall in superficies—that is, in widening of the lumen. The tension of the vessel-wall, which is dependent on the diameter of the vessel and the blood-pressure, is, according to Thoma, thus increased; and, according to another of his principles, this greater tension results in growth of the vascular wall in thickness. The changes in the walls of the anastomosing

vessels seem to me best interpreted as referable to a genuine work-hypertrophy, a conception which has already been advanced by Ziegler.

The pathological regenerations constitute a large group of adaptive morbid processes of the highest interest. Their study has become almost a specialized department of biology, and occupies a very prominent place in the extensive literature of recent years relating to experimental or physiological morphology. It has revealed in unexpected ways the influence of external environment upon the activities of cells, as is illustrated in a very striking manner by Loeb's studies of heteromorphosis.

Although the capacity to regenerate lost parts must reside in the inherited organization of the participating cells, there are observations which seem to indicate that in the lower animals this capacity may exist independently of any opportunity for its exercise during any period of the normal life of the individual or species or their ancestors, including the period of embryonic development. This is the inference which has been drawn from Wolff's observation, that after complete extirpation of the ocular lens with the capsular epithelium in the larval salamander, a new lens is reproduced from the posterior epithelium of the iris. There are other observations of similar purport. The acceptance of this inference, however, seems to me to involve such difficulties that we may reasonably expect that further investigations will afford more satisfactory explanations of these curious and puzzling phenomena of regeneration. Of much interest and significance are the so-called atavistic regenerations, where the regenerated part assumes characters belonging not to the variety or species in which it occurs, but to some ancestral or allied species. For these and other reasons Driesch refers the pathological regenerations to what he calls the secondary self-regulations, by which term he designates those adjustments of artificially induced disturbances which are brought about by factors foreign to the normal development and life of the individual.

The view advocated by Barfurth seems to me more probable, that the pathological regenerations depend upon cellular properties pertaining to the normal life of the organism. This view is supported by the fact that, with a few probably only apparent exceptions, the regenerations conform to the law of specificity of cells. The pathological regenerations occurring after birth can be referred to the retention in greater or less degree of formative powers possessed by the cells pre-eminently in embryonic life. These powers in general tend gradually to diminution or extinction as the individual grows older, although in some cells, such as the covering epithelium of the skin and mucous membranes, this loss of regenerative power with advancing years is scarcely manifest. Even after the cessation of growth the regenerative capacity is not wholly in abeyance under physiological con-

ditions. Bizzozero has studied and classified the various tissues of the body according to the activity of their physiological regeneration.

In general, the more highly differentiated and specialized a cell, the less is its capacity for regeneration; but we now know that such differentiation is attended with less sacrifice of its regenerative power than was once supposed. Even such highly specialized cells as those of striped muscle are capable of regeneration. Indeed, the nerve-cells seem to be the only ones incapable of proliferation, and even this is not certain, for there are competent observers who claim that these cells may multiply, although there is no evidence that in the higher animals they can give rise to functionally active new nerve-cells. The ease with which a part of the nerve-cell, namely, its axis-cylinder process, can be regenerated is well known.

The cell-proliferation in regeneration is attributed to the removal of resistance to growth in consequence of the defect resulting from loss of tissue. It has been pointed out, especially by Ziegler and by Ribbert, that not only cells in the immediate neighborhood of the defect multiply, but likewise those at such a distance that it is difficult to suppose that the latter have been directly influenced by the loss of tension in the tissues caused by the defect. Ziegler refers the proliferation of the distant cells to compensatory hypertrophy, and Ribbert attributes it to hyperaemia resulting from the presence in the defect of foreign materials, such as extravasated blood, exudation, and necrotic tissue.

We are brought here, as we were in the consideration of the compensatory hypertrophies, to one of the most fundamental and important questions in pathology—the causes of pathological cell-growth. The interpretation of many pathological processes as adaptive or not, hinges often upon opinions held concerning the underlying causes of cell-proliferation. The main question at issue is: How far is one willing to go in attributing cell-growth to primary defects in the tissue, and interpreting the growth as for the purpose of regeneration or filling up a defect? Differences of opinion upon this subject are illustrated by the different interpretations of the cell-proliferations in acute and chronic inflammations, some pathologists considering these to be essentially regenerative and compensatory; others regarding them, at least in large part, as directly incited by inflammatory irritants and not to be ranked wholly with the regenerative processes.

The doctrine of Virchow was long accepted without question, that inflammatory cell-growth is the result of the action of external stimuli, the so-called inflammatory irritants, upon the cells, which are thereby directly incited to grow and multiply. The attack upon this doctrine has been most vigorously led by Weigert, who denies absolutely the power of any external agencies to stimulate directly cells to proliferation. He considers that to

concede such a bioplastic power to external agents is equivalent to the acceptance of a kind of spontaneous generation of living matter.

Weigert's views upon this subject have undoubtedly had a most fruitful influence upon pathology. It has been such an influence as a good working-hypothesis, whether finally demonstrated to be true or not, has often had in the development of science. In putting to the test of actual observation Weigert's hypothesis, we have been led to recognize the frequency and the importance of primary injuries to cells inflicted by external agencies. Not only various degenerations and necroses of entire cells, but more subtle and partial damage of cytoplasm and nucleus have been made the subject of special study. It has been recognized that our older methods of hardening tissues reveal often only very imperfectly the finer structure of cells, and new and better methods have been introduced which enable us to detect more delicate lesions of cell-substance which formerly escaped attention, as is well illustrated in recent studies in neuropathology. Weigert's postulate of some primary injury to the tissues as the immediate effect of mechanical, chemical, and other external agencies, which were formerly regarded as the direct stimuli of cell-growth and multiplication, has been fulfilled in many instances where such damage had previously been overlooked or unsuspected. It is his belief that in cases where we cannot now detect such primary injury more thorough search and better methods will enable us to do so. One may, of course, reasonably cherish such an expectation; but at the same time we must recognize the fact that morbid cell-proliferations occur under circumstances where we cannot at present associate them with any demonstrable injury to the tissues—indeed, in some cases where our insight into the structure of the part seems to be so clear and satisfactory that one is very reluctant to admit the existence of an undetected damage to the cells.

Perhaps the most important modification of former pathological conceptions, resulting from the belief that cell-growth is caused by primary defects and injuries of tissue, relates to the chronic interstitial inflammations or fibroid processes. The older view that in these processes the active and essential feature of the disease is the new growth of connective tissue, which strangled the more highly organized cells of the part, has been replaced to a large extent by the opinion that the primary and most important lesion is the degeneration, atrophy, or necrosis of the more specialized cells, whose place is taken by the new growth of interstitial tissue. In many instances, as in fibroid patches in the myocardium, and in many scleroses of the central nervous system, this latter conception forms the best and most natural interpretation of the facts. There are, however, great difficulties in explaining all chronic interstitial inflammations by this doctrine, and I must take side with those who admit the occurrence, for example, in the kidney and in the liver,

of primary interstitial inflammations characterized by proliferation of the connective tissue and endothelial cells.

Indeed, it seems to me that Weigert's formula is too narrow to cover all of the observed facts concerning cell-proliferation. Essential features of the theory that cells cannot be directly stimulated to growth by external agents were present in Boll's doctrine of border warfare between neighboring cells. Weigert's presentation of this theory is in a far more acceptable shape than that of Boll. A still more comprehensive statement of the general theory is that cells are incited to growth through removal of obstacles to growth in consequence of some disturbance in the normal relations or equilibrium of the cells with surrounding parts. The capacity to proliferate must be present in the cells, but with the cessation of growth this capacity is rendered latent or potential by the establishment of definite relations or an equilibrium between cells and neighboring parts, including under the latter not only adjacent cells, but also basement-substance, lymphatics, blood vessels, tissue-juices, chemical substances, etc. It is evident that under these circumstances in only two ways can the cells be incited to growth, either by removal of resistance or obstacles to growth, or by an increase in the formative energy resident within the cell, and that in either way energy must be used, whether it be employed to remove obstacles to growth, or to increase the proliferative forces within the cell.

It appears to me by no means an easy matter to decide in all cases in which of the two ways mentioned cell-proliferation is brought about. Removal of obstacles to growth, not only in the way indicated by Weigert, but also by other disturbances in the neighborhood-relations of the part, and very probably by the presence of definite chemical substances, may be the explanation of all pathological cell-growths. Certainly it would not be easy conclusively to disprove this view. Nevertheless, I fail to comprehend the inherent difficulties which some find in admitting the possibility of forms of energy, acting from without, directly increasing the formative energy of the cell; in other words, directly stimulating the cell to growth and multiplication. If such a possibility be admitted, the natural interpretation of some examples of cell-proliferation is that they are directly caused by the action of external forces, in the sense advocated by Virchow.

Students of the problems of pathological cell-growth must take into consideration not only the facts of human and allied pathology, but also those which are so rapidly accumulating in the domain of experimental embryology and morphology, to the importance of which I have repeatedly referred in this address. I would call attention especially to the observations from this source as to the influence of various changes of environment, particularly of definite chemical, thermic, and mechanical changes in surrounding

parts, upon the direction of movement and of growth of cells. The use at present made of chemotactic phenomena in explaining the direction of movement of cells in human pathological processes is only a very limited and inadequate application of these important observations concerning tactic and tropic stimuli. We shall probably come to realize more and more the operation of these factors in determining cell-movements and cell-growth in human pathology. We already have evidence that different kinds of leucocytes not only possess different specific functions, but also respond in different ways to definite tactic stimuli. The long-standing problem of the lymphoid cell in inflammation approaches solution along these lines of investigation.

A burning question, and one of perennial interest, relating to our subject is: How far are we justified in regarding acute inflammation as an adaptive or protective morbid process? There is fair agreement as to the essential facts of observation, but regarding their interpretation there are wide differences of opinion, and when one considers the complexity of the process and its still unsolved riddles, it is not hard to see why this should be so. Much depends upon the point of view, and in this respect there can be recognized a certain antagonism between the purely clinical and the purely pathological and experimental views, an antagonism, however, which must be reconciled by a fuller knowledge of the subject.

It is not likely that the purely clinical study of inflammation would ever lead to the idea that the general tendency of this process is advantageous to the patient. The more severe and extensive the inflammatory affection, the more serious, as a rule, is the condition of the patient. The surgeon sees his wounds do well or ill according to the character and extent of inflammatory complication. Measures directed to the removal of inflammatory exudation, such as the evacuation of pus from an abscess or an empyema, are the most successful methods of treatment, and the rules are embodied in ancient surgical maxims. How can one conceive of any purpose useful to the patient served by filling the air-cells of his lung with pus-cells, fibrin, and red corpuscles in pneumonia, or bathing the brain and spinal cord in serum and pus in meningitis? If nature has no better weapons than these to fight the pneumococcus or meningococcus, it may be asked, "What is their use but to drive the devil out with Beelzebub?"

But the pathologist and bacteriologist sees another aspect of the picture. An infectious micro-organism has invaded the tissues, where it multiplies and where its toxic products begin to work havoc with the surrounding cells, and by their absorption to cause constitutional symptoms and perhaps damage to remote parts. Is the destructive process to go on without any defence on the part of the body? There are attracted to the injured part

an army of leucocytes from the blood vessels, and perhaps other cells, from the neighboring tissues, and it has been conclusively shown that these cells can pick up foreign particles and remove them, and that they contain substances capable of destroying many micro-organisms. At the same time serum accumulates in and around the injured area, and this may aid by its chemical properties in destroying bacteria, in diluting poisons, in flushing out the part. Fibrin may appear, and some think that this may serve in some situations as a protective covering. If these agencies, hostile to the invading micro-organism, gain the upper hand, the débris is cleared away by phagocytes and other means, and the surrounding intact cells, which had already begun to multiply, produce new tissue which takes the place of that which had been destroyed. The victory, however, is not always with the cells and other defensive weapons of the body. The struggle may be prolonged, may be most unequal, may cover a large territory, and the characters and extent of the inflammation furnish an index of these different phases of the battle.

Such in bald outlines are two divergent views of inflammation.

I do not see how we can fail to recognize in that response to injury which we call inflammation, features of adaptation. Inflammation may be in some cases the best response to secure the removal or destruction of injurious agents, but we cannot look upon it as the most perfect mode of protection of the body against invading micro-organisms. One may inoculate into three animals, even of the same species, but possessed of different individual resistance, the same quantity of the same culture of a pathogenic microorganism and obtain sometimes the following results: The first one will present no appreciable inflammatory reaction whatever, and no evidences of any other disturbance, and examination will show that the micro-organisms have quickly disappeared. The second one will develop an extensive local inflammation and survive, but after a long illness. The third one will offer little resistance to the micro-organism, which rapidly multiplies without causing marked inflammation, invades the blood or produces toxaemia, and quickly destroys the life of the animal. Now, it is evident that the best protective mechanism is that brought into action by the first animal, but that the inflammatory reaction set up in the second one is better than the absence of reaction and of other defences in the third animal.

I can scarcely do more on this occasion than to indicate some of the points of view from which it seems to me that we can best approach the study of inflammation as an adaptive process. With inflammation, as with other adaptive processes, any useful purpose subserved affords no explanation of the mechanism of the process. We should guard against all ideas which introduce, even unconsciously, the conception of something in the nature of an intelligent foresight on the part of the participating cells. The response

of these cells in inflammation is a necessary and inevitable one, determined by their innate properties. Our efforts should be directed, in the first place, toward as near an approach as possible to a mechanical explanation of inflammatory processes by a study, on the one hand, of the properties and mode of action of the causes of inflammation, and, on the other hand, of the nature and source of the cellular properties concerned. We may properly inquire whether these properties fit the cells to counteract the effects of injury, and if so, whence comes this fitness. Has the fitness those attributes of relative perfection which we find in most physiological adaptations? Is the character of the response to injury in inflammation such as to indicate that the agencies concerned have acquired through evolutionary factors a special fitness to meet the pathological emergencies? Are all or only a part of the manifestation of the inflammatory processes adaptive?

It cannot be doubted that there are innate properties of certain cells, called into action in inflammation, such as those manifested in the attraction of leucocytes and other cells by definite chemical substances, the capacity of cell-proliferation from causes connected with injury, the power of phagocytosis and other bactericidal properties, which may be adapted to counteract the effects of injurious agents. When these forces bring about the prompt destruction or removal of the injurious substances and the defect is quickly repaired, the adaptation is complete and unmistakable. When, however, the inflammatory irritants and their destructive effects persist, and the proliferation of cells and accumulation of inflammatory products become excessive and occupy large areas, the features of adaptation are not so easily recognized. The mere occupation of territory by inflammatory products is often a serious injury and it can be regarded as an adaptive feature only when they fill some artificial defect. Such occupation may be in itself enough to counteract any useful work in which these products may be engaged.

We can reasonably seek in the relations of the body to the outer world an explanation of the development of certain properties of cells which serve a useful purpose in mechanical and other injuries. These properties find application also in the normal life of the organism. Their exercise in response to injury imparts to inflammation important adaptive or protective characteristics, but I fail to see in this process any such special fitness as would justify extravagant statements which have been made, to the effect that inflammation ranks among the adaptations of living beings by the side of digestion and respiration.

I have endeavored in this address to present certain general considerations concerning pathological adaptations. It has been possible to bring under consideration only a small part of an immense field, and this very

inadequately. We have seen that in the sense in which adaptation was defined we can recognize in the results of morbid processes frequent and manifold evidences of adjustment to changed conditions. These adjustments present all degrees of fitness. Some are admirably complete; more are adequate, but far from perfect; many are associated with such disorder and failures that it becomes difficult to detect the element of adaptation. The teleological conception of a useful purpose in no case affords an explanation of the mechanism of an adaptive process. I have suggested that the adaptability of this mechanism to bring about useful adjustments has been in large part determined by the factors of organic evolution, but that in only relatively few cases can we suppose these evolutionary factors to have intervened in behalf of morbid states. For the most part, the agencies employed are such as exist primarily for physiological uses, and while these may be all that are required to secure a good pathological adjustment, often they have no special fitness for this purpose.

The healing power of nature is, under the circumstances present in disease, frequently incomplete and imperfect, and systems of treatment based exclusively upon the idea that nature is doing the best thing possible to bring about recovery or some suitable adjustment, and should not be interfered with, rest often upon an insecure foundation. The agencies employed by nature may be all that can be desired; they may, however, be inadequate, even helpless, and their operation may add to existing disorder. There is ample scope for the beneficent work of the physician and surgeon.

HYDROPHOBIA[1]

Of the many subjects suitable for the Report of the Chairman of this Section I have selected *hydrophobia,* on account of the numerous and important contributions to its pathology and etiology during the past four years, and especially because the time has come when we can form an intelligent estimate of the value of the Pasteurian inoculations against hydrophobia. Although these inoculations constitute the central point about which controversy has waged, it is not to be forgotten that Pasteur's discoveries and the investigations aroused by them have shed much light in many directions upon the nature of one of the most mysterious and fatal diseases. Whatever had been the outcome of Pasteur's antirabic treatment, his researches upon hydrophobia would still have remained an important scientific contribution to our knowledge of the disease.

We are still insufficiently informed concerning the pathological anatomy of hydrophobia. I have had opportunity to make post-mortem examination of three cases of hydrophobia in human beings. In one case serial microscopical sections were made of the medulla oblongata and pons from the second cervical nerve upward. The lesions consisted in small hemorrhages, in accumulations of small round cells in large numbers, both in the perivascular lymph spaces, and in scattered foci in the neuroglia between the nerve elements, and in thrombi, composed of hyaline material and of leucocytes, in small blood vessels. These lesions were microscopical, and their extent and distribution could be determined only by the examination of a large number of sections from different parts. The lesions were especially well marked in and near the nuclei of origin of the spinal accessory, pneumogastric and glosso-pharyngeal nerves, and in the motor nucleus of the trigeminus. Cases have been reported in which even more extensive lesions than these have been found; their intensity depending apparently in large measure upon the duration of the disease. While it can not be claimed that these lesions are peculiar to hydrophobia, or by themselves suffice for its diagnosis, it is incorrect to suppose that hydrophobia is a disease without demonstrable anatomical lesions which bear a manifest relation to the symptoms of the affection.

[1] Report of the Chairman of the Section on Anatomy, Physiology and Pathology, before the Medical and Chirurgical Faculty, Baltimore, April 26, 1889.
Tr. M. & Chir. Fac. Maryland, Balt., 1889, 162-180.

Far more important than the additions to our knowledge of the pathological anatomy of rabies following Pasteur's discoveries, are the contributions to a better comprehension of the causation of the disease. Before Pasteur's publications on hydrophobia, dating from 1881, about all that we knew of the virus of rabies was that it was contained in the salivary glands and their secretions, and that infection often followed the bites of rabid animals. We knew that after characteristic symptoms appeared, the disease was uniformly fatal; but we possessed no positive means of diagnosis. Hence it was impossible to secure trustworthy statistics of the mortality among those bitten by rabid animals; for we could not determine accurately how many of the animals were rabid. There obtained among a few an unwarrantable scepticism even as to the existence of such a disease as hydrophobia.

We now possess positive means of diagnosis of hydrophobia by the inoculation of animals, particularly of rabbits; so that the last vestige of doubt as to the existence of the disease must disappear. We have now valuable information concerning the properties of the rabid virus, its distribution in the infected body, the manner of its transmission, the singular differences in its action, according to the mode and seat of its inoculation, and the means of producing immunity against its destructive action on the body.

Although there is no reason to doubt that the infectious agent of rabies is a micro-organism, no actual demonstration of this organism has yet been made. If fluids containing the rabid virus be filtered through substances impenetrable to particulate matter, the filtrate is free from infectious properties. In the Pathological Laboratory of the Johns Hopkins University, we have had opportunity to study the effects of the rabid virus upon a series of rabbits, the original material having been obtained from the medulla oblongata of a man dead of hydrophobia. We were able abundantly to confirm the statements of Pasteur and others as to the behavior of these animals when inoculated in succession with the virus of rabies. We endeavored by cultures and by staining re-agents to demonstrate some specific micro-organism; but with entirely negative result. A repetition of the methods indicated by Fol, failed to confirm his statements as to the presence in the nervous centres of a demonstrable species of bacteria. But while we are not acquainted with the specific organism causing hydrophobia, we know many of its properties.

The virus of rabies is destroyed by comparatively low temperatures, exposure for one hour to a temperature of 50° C. (122° F.) sufficing for this purpose. It is killed in a short time by drying, certainly within four days when exposed in thin layers capable of rapid desiccation. It is said to be destroyed by exposure to the direct rays of the sun, even when under conditions preventing elevation of temperature. According to Babes, the virus is

more resistant to the action of corrosive sublimate and carbolic acid than most bacteria; but it loses its infectious properties after exposure for three hours to the action of 0.1 per cent sublimate, or of 1 per cent carbolic acid solution. Galtier has pointed out a fact of practical importance, that the virus of rabies may be demonstrated after forty-four days, and perhaps longer, in the cadavers of buried animals. An easy means of preserving the virus is to place the brain or cord of the infected animal in pure glycerine, which may be diluted with water, and which should be occasionally changed. In cases in which persons are bitten by animals suspected of rabies, the animal should be secured and watched, and if it dies, the nervous centres should be removed and preserved in dilute glycerine for subsequent inoculation of rabbits, whenever such inoculation can not be performed at once by a competent person.

It has been ascertained that the certainty of infection with rabies depends largely upon the part of the body and the character of the tissues into which the virus is inoculated. The disease develops always and with the shortest period of incubation after inoculation of the virus into the brain, or upon its surface. Those who have asserted that the same group of symptoms may follow the intra-cranial inoculation of substances other than rabid virus, have fallen into serious error. Equally certain in the effects are inoculations of the virus into the eye, although here the period of incubation is less definite. Inoculations into the substance of nerve trunks appear to be uniformly successful in rabbits, but somewhat less certain in dogs, although even in the latter animal inoculation into the pneumogastric nerve does not fail. Intra-venous injection does not produce the disease in ruminants unless large quantities of the virus are used; but it is a ready means of conferring immunity upon these animals. The same mode of injection succeeds often in dogs, and usually in rabbits, in producing the disease; but it may fail in both classes of animals. Especial importance attaches to the behavior of subcutaneous injections of the virus of rabies. Dogs often resist infection from the injection of considerable quantities of the most intense virus into the subcutaneous tissue. Indeed, Pasteur finds that the more intense the virus, and the larger the quantity injected subcutaneously, the less likely is the dog to develop rabies, and the more certain is it to acquire immunity. Ferran's super-intensive method of producing immunity in human beings, is to inject at once the strong virus into the subcutaneous tissue. Although he has done this in over 400 cases without injury, the method does not rest upon a safe basis so far as experiments upon dogs are concerned; for these animals sometimes contract the disease after this mode of inoculation. Infection is more likely to follow injections into the muscular tissue than into the subcutaneous connective tissue. Of course the in-

jection of the virus into the subcutaneous tissue by means of a hypodermic syringe can not be considered analogous to inoculation by means of bites which wound the skin and subcutaneous tissues. Di Vestea and Zagari have shown that while simple subcutaneous injections are often unsuccessful in producing rabies, the application of the virus to the divided ends of nerve filaments in a cutaneous wound is generally efficacious in causing the disease. Although deep and severe bites of rabid animals are the most dangerous, hydrophobia may result simply from a mad dog licking an abrasion or scratch. Intra-peritoneal injections of the rabid virus produce the disease in rabbits, and guinea-pigs, if considerable quantity of the virus be used.

As regards the distribution in the body of the infectious material of rabies, it has been demonstrated by Pasteur that in human beings or animals which have died of hydrophobia, the virus is contained most abundantly in the central nervous system, and especially in the medulla oblongata and brain. It is found also in the nerves near their exit from the brain and cord, but less constantly and in less amount in the peripheral nerves. The virus is probably always present in the salivary and lachrymal glands, and sometimes in the pancreas, but it is usually absent from the blood, kidneys, spleen and liver. Only exceptionally is it present in the mammary glands and the milk. It is very rarely transmitted to the foetus through the placenta. We see, therefore, that the virus is very unequally distributed in the body, and that its chief habitat is the central nervous system.

A point of much interest is the manner in which the virus is conveyed from the seat of inoculation to the central nervous system. The chief possibilities which present themselves are transmission by the blood-current, by the lymph-current, and along the nerve trunks. There is evidence that the virus may be conveyed in each of these three ways. The production of the disease by intra-venous and by intra-peritoneal injections of the virus, speaks for the first two modes of transmission. But there are considerations which favor the view that the usual mode of transmission is along the nerves. Inoculations made directly into nerve trunks are more certain to produce rabies than either intra-venous or intra-peritoneal injections, and by the first method a smaller quantity of the virus suffices. The symptoms of rabies, which are chiefly nervous, frequently bear a certain relation to the seat of inoculation in the order of their development. Thus when the inoculation is made into the anterior extremities or the head, the first symptoms are bulbar, whereas, when the inoculation is into the posterior extremities or tail, spinal symptoms, especially paralysis of the posterior extremities, appear first. No such regularity in the sequence of symptoms is observed after intra-venous injections. In a large proportion of cases of hydrophobia in human beings, the first symptoms are referable to disturb-

ances in the nerves in or near the injured part, and paraplegia or the paralytic form of rabies is most likely to follow bites in the lower extremities. By killing animals at the proper period, it has been ascertained that after inoculation in the head or anterior part of the body the virus makes its appearance in the medulla oblongata sooner than in the posterior part of the spinal cord, while the reverse holds true when the inoculation is made in the tail or the posterior extremities. The virus propagates itself in steps, as it were, along the spinal cord. Roux and Bardach have found the virus present in the nerves of a bitten extremity when it has been absent in the corresponding nerves of the opposite side; whereas, the reverse of this has never been observed. Di Vestea and Zagari have succeeded, in rabbits, by making resections of the spinal cord, and keeping the divided ends separated by a plug of antiseptic cotton in preventing the virus from extending from one segment of the cord to the other, so that, after intra-cranial inoculations, the upper segment contained the virus and the lower did not, and after inoculations into the sciatic nerve, the virus was prevented from passing from the lower to the upper segment. Division of a nerve trunk above the point of inoculation may retard, but does not prevent the development of the disease, but here there is the possibility of the propagation of the virus along anastomotic nerve filaments. It must be admitted that the facts and experiments which have been mentioned speak strongly for the view that the virus passes along the nerves, although we have no information as to how this is accomplished, and it is not worth while to consider the theories which have been framed to explain this interesting and curious phenomenon.

One of the most important discoveries of Pasteur in this subject, is that the virus of rabies may undergo changes in certain of its properties by transmission through a series of animals of the same species. The principal change is an increase of virulence, characterized by a shortened period of incubation of the disease. This change is brought about by the transmission of the virus through a long series of rabbits, each one being inoculated beneath the dura mater with an emulsion made with the medulla oblongata of the preceding rabbit which has died of hydrophobia. When a rabbit is inoculated beneath the dura with the medulla of a dog dead of rabies, the so-called rabies of the street (*rage des rues*), the period of incubation of the disease is usually between 15 and 20 days, and apparently never less than 11 days. By inoculating intra-cranially rabbits in series, beginning with this first rabbit, the period of incubation is gradually reduced to seven and finally to six days, at which it remains indefinitely. In the series of rabbits employed by Pasteur for his preventive inoculations, the period of seven days had been reached before the 80th passage, and at the time of the 178th passage, the period of incubation had been for a year 6 days in at

least two out of three of the rabbits. The virus from the medulla of rabbits with this uniformly short period of incubation of 6 or 7 days is spoken of as fixed virus (*virus fixe*). The time required for obtaining the fixed virus may be very much shortened by employing young rabbits and by inoculating several at a time, selecting for successive inoculations from each group the one presenting the shortest period of incubation. In this way Hogyes obtained the fixed virus in the 16th passage, about five months after the beginning of the successive inoculations.

If the medulla of a rabbit which has died of inoculation with the fixed virus be preserved in a dry atmosphere, its virulence progressively diminishes, as is indicated by the lengthening of the period of incubation. The loss of virulence is rapid in proportion to the temperature at which the medulla is kept. The infectious properties, as a rule, disappear at the end of a fortnight if the temperature be from 23° to 25° C. (73.6°—77° F.), and sooner than this if the medulla be of small size.

The question arises whether these changes in virulence depend upon alterations in the quantity or in the quality of the infectious agent. We judge of the degree of virulence mainly by the length of the period of incubation after the intra-cranial inoculation of a rabbit. It has been shown experimentally that this period may be progressively lengthened by dilution of the virus inoculated, and this fact may be put in evidence in favor of a quantitative change to explain varying degrees of virulence. On the other hand, fixed virus would seem to differ qualitatively from the virus of rabies of the streets, for no matter how prolonged the period of inoculation may be rendered by dilution of the fixed virus, or in other words, by diminution in the quantity of the infectious agent, if this rabbit develops rabies, its medulla always contains the fixed virus—that is, when inoculated intra-cranially into another rabbit, its period of incubation is 6 or 7 days, which is shorter than ever occurs with the virus from the rabies of the street. Pasteur is inclined to attribute the progressive loss in virulence of the rabbit's medulla preserved in a dry atmosphere, to a gradual diminution in the quantity of the infectious material, rather than to any change in its quality.

It is a significant fact, which should be remembered in judging the results of Pasteur's treatment, that there is a period of so-called latent development of the virus in the central nervous system. In rabbits inoculated with the fixed virus, the period of inoculation is six or seven days, but as early as the fourth day the virus has been found in the medulla oblongata. Doubtless, therefore, in human beings the virus is present in the central nervous system for a period before any characteristic symptoms of rabies appear, so that it may readily happen that treatment is begun too late, even when undertaken before there are manifestations of the disease. Careful obser-

vation has shown that in rabbits this period is not, strictly speaking, a latent one, but it is accompanied by elevation of temperature, increased frequency of respiration, slowing of the pulse rate and loss of weight, symptoms which point to an action of the rabid virus primarily upon the heat centres and upon the vagus.

It is customary to divide rabies according to its clinical manifestations into two forms, furious or convulsive rabies and dumb or paralytic rabies. A third form, however, should also be distinguished—namely, mixed rabies, which represents a combination of convulsive and of paralytic rabies. The most common form of rabies in human beings is furious or convulsive rabies, but paralytic rabies also occurs in man, especially after bites on the lower extremities, and is more common, according to recent reports, than was formerly believed. In dogs, furious rabies is the predominant variety, whereas, in rabbits, paralytic rabies is the more common, and in Pasteur's series it became the sole form after inoculation with the fixed virus. A careful study of the symptoms, however, renders less sharp the distinction between furious and paralytic rabies, for in either form it is often possible to distinguish a stage of excitation and a stage of paralysis, but in the furious form the stage of paralysis is short and may be wanting; whereas, in the paralytic form, the stage of excitement is of short duration, and may be characterized only by acceleration of the breathing, elevation of temperature and symptoms referable to irritation of the vagus nerve. There is probably no difference in the quality of the virus causing the two clinical forms of hydrophobia, the distinction depending rather upon the nature of the animal infected, and the seat of inoculation, possibly also upon the quantity of virus inoculated. The only observation in favor of differences in the character of the virus causing the two varieties of rabies are those of Helmann, who claims to have a virus which will produce in rabbits invariably furious rabies, and another virus which produces the customary paralytic rabies, but these observations have not been confirmed, are not free from objections, and are not in harmony with the observations of Pasteur and others, who find that the virus of rabies of the street, which is generally furious in character, produces paralytic rabies in the rabbit, and that the latter causes furious rabies in the dog, there being occasional exceptions to these rules. The occasional occurrence of paralytic rabies in human beings who have not been subjected to treatment after the bite of a mad dog, disproves the assertion of Peter that paralytic rabies is only rabies of the laboratory, and when it has occurred in persons treated by Pasteur's method, it can be attributed only to the anti-rabic inoculations and not to the bite of the animal, an assertion which, moreover, can be positively disproven by experiment, as will be explained subsequently.

There can be no doubt whatever that it is possible to render animals immune against rabies both before and after inoculations which would otherwise cause the disease. The independent and careful experiments of Ernst in this country are free from all partisan bias, and have fully confirmed the statements of Pasteur and others upon this point. The methods employed by Pasteur for protective inoculation against hydrophobia have been so often and so fully described in medical and other journals, that it is not necessary to repeat the description on this occasion. The method is based upon the injection subcutaneously (sometimes in certain animals into the blood) first of attenuated virus contained in the medullae, dried for a certain period, of rabbits dead after inoculation with the fixed virus, and then of stronger and stronger virus contained in medullae dried for shorter periods, until strong or the strongest virus is reached. These inoculations are most effective in preventing the disease when undertaken soon after the reception of the poison, and with a large quantity of virus and with the speedy employment of material containing the strongest virus (*virus fixe*). Animals may be rendered immune by a single injection into the blood or into the subcutaneous tissue of a large quantity of strong virus, whereas dogs which are bitten by mad dogs and which do not develop the disease, as may happen, are not usually left immune, evidently because not sufficient quantity of the virus has been received. Dogs which have once been rendered immune against rabies preserve this immunity for at least two years, and doubtless for a longer period.

The experiments of von Frisch are often quoted in opposition to the validity of Pasteur's conclusions. Von Frisch claimed that it is impossible to produce immunity after the virus of rabies has been received in a manner certain to produce the disease. He urged that Pasteur's experiments demonstrated the possibility of producing immunity only before and not after the reception of the rabid virus. In this latter assertion he was in error. Von Frisch's failure to produce immunity after the reception of the strong virus was due partly to his selection of rabbits for his experiments, and partly to imperfect methods of preventive inoculation. On account of their extreme susceptibility to the rabid virus, and of the short period of incubation after intra-cranial inoculations, rabbits are much less suitable animals for these experiments regarding immunity than dogs. But even in rabbits immunity may sometimes be produced if the preventive inoculations be undertaken speedily after the reception of the virus, and be according to the intensive method. Pasteur and others have shown that in a large proportion of cases the development of rabies may be prevented in dogs even after subdural injection of the strongest virus, if preventive inoculations by the intensive method be begun not later than the second day after the reception of the poison. Bardach succeeded in this way in saving 60 per cent of the dogs

inoculated beneath the dura mater. This test is evidently the most severe one to which Pasteur's preventive treatment can be subjected, one far more severe than is required to meet the ordinary channels of infection with rabies in human beings, in whom the period of incubation is longer and the virus is received in less intense form and in situations from which infection is slower and less certain. It must be admitted, therefore, that Pasteur's treatment rests upon a satisfactory experimental basis, and one which forms a complete justification of the application of the treatment to human beings bitten by rabid animals.

We have no positive knowledge as to the manner in which immunity is caused by the Pasteurian vaccination against rabies, any more than we have as to the causation of immunity in other diseases. Pasteur is inclined to attribute the immunity to the action of some substance, which he calls "*matière vaccinale*," contained in the inoculated material, but not identical with the micro-organism causing rabies. That immunity against infectious diseases may be secured by the injection of chemical substances produced by the growth of specific bacteria, was demonstrated by Salmon and Smith in the case of hog cholera, and has been since demonstrated by Roux and Chamberland for malignant oedema, and by Wooldridge for anthrax. It has not yet been found possible to prove the correctness of Pasteur's supposition in the case of rabies, and although there are arguments in its favor, it is hardly worth while for us to consider further a question at present in so hypothetical a state.

Encouraged by the results of his experiments upon animals, Pasteur, in July, 1885, first applied to a human being his method of preventing hydrophobia by successive injections of the virus contained in the rabbit's medulla subjected to drying for different periods, the medulla being taken from rabbits which had died after inoculation with the fixed virus.

During the years 1886, 1887, and the first half of 1888, there have been treated under Pasteur's supervision, either by the simple or by the intensive method of vaccination, 5374 persons who have been bitten by animals either proven or suspected to be rabid. The mortality from hydrophobia, including even the cases which developed within a day after the cessation of treatment, was for 1886 1.34 per cent; for 1887, 1.12 per cent; for the first half of 1888, 0.77 per cent. If the fatal cases which developed within a fortnight after the end of treatment, and in which there is reason to believe that the inception of treatment was too late, be excluded, the mortality for 1886 falls to 0.93 per cent; for 1887, to 0.67 per cent; and for the first half of 1888, to 0.55 per cent. From May 1, 1888, to May 1, 1889,[2] there were

[2] I have endeavored to bring the statistics of this paper up to the date of its publication (July, 1889), and have therefore added certain statistics which have appeared since the time the paper was read in April, 1889.

treated at the Pasteur Institute, in Paris, 1673 persons bitten by dogs, either rabid or suspected to be rabid. Of these 6 died during treatment, 4 in less than a fortnight after treatment, and 3 died later than a fortnight following the cessation of treatment. Only the last 3 cases, therefore, are to be counted as failures. If all the deaths, both during and after treatment, be included, which would be illogical, the mortality equals 0.78 per cent; if only the deaths after treatment be reckoned, the mortality becomes 0.42 per cent; and if only those occurring more than a fortnight after the end of treatment be estimated, the death-rate sinks to 0.18 per cent. This mortality may be somewhat increased by subsequent deaths, as sufficient time has not elapsed for full completion of the returns. Pasteur, in a recent letter to Sir H. Roscoe, says that up to the end of June, 1889, over 7000 persons have been treated in his laboratory, and that the general mortality applicable to the whole number of the operations was 1 per cent.

Doubtless a considerable number of cases are included in the foregoing statistics of persons subjected to treatment who have not been bitten by animals actually rabid. How large is this number, it is impossible to say; but even if ample allowance be made for this class of cases, the results of the treatment can hardly be interpreted otherwise than in favor of its efficacy.

It is possible, however, to select from the reports only those cases in which the animal inflicting the injury has been actually proven to be rabid. This proof is the most exact which can be furnished, and consists in the results of the inoculation of animals with the brain or cord of the animal, or in the development of hydrophobia in persons or animals bitten at the same time as those treated. Pasteur's statistics, which are published monthly, are arranged in tables which embrace: *A*—Persons bitten by animals proven to be rabid: *B*—Cases in which the existence of rabies in the animal is certified by a veterinarian: *C*—Cases in which there is reason to suspect rabies in the animal, although the evidence furnished in the foregoing classes was not obtained.

If the cases be analyzed according to this classification, we obtain the following results: Since the beginning of his operations in July, 1885, up to the end of the first half of 1889, there have been treated under Pasteur's supervision 6950 patients. There were bitten by animals suspected, but not proven to be mad, 1187, of whom 12, or 1.01 per cent, died; by animals pronounced rabid by veterinarians, 4686 persons, of whom 44, or 0.94 per cent, died; and by animals proven experimentally to be rabid, 1077 persons, of whom 15, or 1.39 per cent, died. The similarity of the results in the three classes shows that the second and third groups must contain a large number of cases in which the wounds were inflicted by rabid animals. If we exclude from the preceding statistics those who began treatment a fortnight or more

after being bitten, we find the death-rate in Class *C* to be 5, or 0.42 per cent; in Class *B*, 31, or 0.66 per cent, and in Class *A*, 11, or 1.2 per cent.

The most convincing presentation of the case is to select the results of treatment in persons bitten on the head and face by animals proven to be rabid. In all statistics purporting to give the mortality from the bites of rabid animals, by far the largest death-rate is afforded by the bites on the head and face. I have collected from Pasteur's reports for 1887 and 1888, those bitten on the head and face by animals proven experimentally to be rabid. There were 72 cases, with 4 deaths from rabies during treatment, and 3 following treatment. Of the latter, one was seized three days after the end of treatment, and it is therefore reasonable to suppose that in this case the treatment was begun too late. If this case and those dying during treatment be excluded, there remain 67 cases bitten on the head or face by animals proven to be rabid, with 2 deaths, a mortality of 3 per cent. I was not able to obtain the data for an analysis of all of the cases in this group since the beginning of Pasteur's treatment; but after collecting these cases, I have met the statement that the total number of persons bitten on the face and neck by animals proven to be rabid is 540; of whom 21 died, leaving a mortality of 3.89 per cent; but how many of these are fairly attributable to failure of the treatment does not appear. These cases undoubtedly belong to both Class *A* and Class *B*.

Unless it can be shown that the mortality following the bites of rabid animals is as small as that derived from the foregoing statistics, no other conclusion can be drawn than that Pasteur's treatment is efficacious; for we can dismiss as unworthy of consideration all attempts to cast doubt upon the truthfulness of the statistics published by Pasteur. Notwithstanding the out-cry of those who assert that nothing can be proven in medicine by statistics, it is apparent that Pasteur could have proceeded in no other way than he has done, in order to demonstrate the value of his treatment, and that the statistical method is the only one applicable to this demonstration, although we are to keep in mind all possibilities of error belonging to the method.

There are various careful collections of statistics which show that a conservative estimate of the average mortality of persons bitten by rabid animals is about 15 per cent (Lablanc, Dujardin-Beaumetz, Horsley). The results of different statistics on this point vary widely, as is to be expected from the fact that they include generally in large but variable numbers bites from animals not proven to be rabid. On this point Pasteur's statistics have the merit of greater accuracy. It is logical to suppose that the statistics with large mortality include a greater proportion of bites from actually rabid animals than those with small mortality.

All agree that bites on the head and face by rabid animals furnish the highest mortality. This is given by Brouardel as 88 per cent. If we place it at 60 to 80 per cent, we are likely certainly not to exaggerate the mortality.

If now we contrast with these moderate estimates of the mortality following the bites of rabid animals, the results obtained by Pasteur's method of treatment, there is left no room for doubt that this treatment has been proven to be efficacious, and has saved already hundreds of lives. I call attention especially to the convincing character of the results in persons bitten on the head and face by animals proven to be rabid.

The Pasteurian treatment, as is apparent from the preceding statistics, has a certain number of failures to record. It is not therefore unfailing, although if we compare its results with those obtained by methods of medical treatment in various diseases, it takes a very high rank, perhaps second only to vaccination in small-pox. The death from hydrophobia in two instances of persons over two years after treatment, casts a certain shadow upon the results, but can not invalidate the general conclusions as to the efficacy of the treatment.

It is most encouraging that the results of the treatment have improved with each successive year of its application. This is attributable to improvements in the methods, and is even more strikingly illustrated in the statistics of some others than in those of Pasteur, but I have preferred in this article to consider only the results obtained under Pasteur's immediate supervision. Essentially similar results, however, have been obtained in various places, chiefly in Russia, Italy and South America. The principal improvement in the method, as first applied by Pasteur, is in the elaboration of the so-called intensive method of preventive inoculation which is applicable to severe cases, especially to those bitten in the head or face and by wolves. In some anti-rabic institutes the intensive method has entirely superseded the simple method.

It is a sufficient answer to the assertion that has been made that Pasteur's intensive inoculations are dangerous, in that they may actually produce the disease, that the mortality from rabies is strikingly smaller after the application of the intensive method than after the simple treatment. There is, furthermore, a method of demonstrating experimentally that those who may die from rabies after preventive inoculations have not contracted the disease by means of the inoculations. These inoculations are made with the fixed virus, of which the period of incubation in rabbits after sub-dural injection is six or seven days; whereas those treated were bitten by animals affected with rabies of the street, the virus of which after sub-dural inoculation of rabbits has a period of incubation of fifteen to twenty days. As has been already mentioned, even if the period of incubation of the fixed virus

be lengthened by dilution or attenuation of the virus, or if it be used to kill another animal as a dog, the virus as obtained from the brain or cord of the latter animal is still fixed virus, and will destroy rabbits with a period of incubation of six or seven days. Now, in all instances in which the brain or cord of a human being dying of rabies after the Pasteurian treatment has been used to inoculate rabbits, it has been found to contain virus with the period of incubation of rabies of the street, and not fixed virus, or in other words, not the kind of virus which was used for the preventive inoculation.

We are not to forget that the measures which are of first importance in preventing hydrophobia must be directed against the development and extension of the disease in dogs; for if canine rabies could be eradicated, there need be no fear of the disease, at least in this country and in eastern Europe. These measures consist in good dog laws, and their efficient application. A proper tax-rate upon dogs, their muzzling, and the destruction of stray and ownerless dogs, are the principal measures. It may be well also to enforce quarantine measures against dogs imported from countries where rabies is prevalent. In most parts of Germany these preventive measures are thoroughly enforced, and the result is an almost total disappearance of rabies; whereas in France similar measures are not carried out, and rabies is consequently alarmingly prevalent. I do not know of any data which enable us to determine the extent of prevalence of rabies in this country; but so far as can be judged by general impressions, it does not seem to be common with us. Its occurrence at all, however, is sufficient reason for the enforcement of those measures which have been found most efficient in its prevention.

CIRRHOSIS HEPATIS ANTHRACOTICA.[1]

I have placed under the microscopes sections of a liver showing a peculiar form of cirrhosis associated with the deposition of coal pigment. The specimen of liver together with portions of other organs were sent to me recently by Dr. Unger, of Mercersburg, Pa., for microscopical diagnosis. All that I have been able to learn of the history of the man from whom the specimens were obtained is as follows: He was a German, about 70 years of age, who had lived for many years as a farmer in the neighborhood of Mercersburg, Pa. He is said to have worked as a weaver in Germany, but nothing more definite concerning his occupation or life in that country could be learned. The place where he lived in Pennsylvania is not particularly smoky. His health was good until about two years ago when he began to suffer from vomiting, loss of appetite and severe pain in the abdomen. Accumulation of fluid in the peritoneal cavity necessitated repeated tappings by which serous fluid was withdrawn. The patient grew very weak and emaciated.

The autopsy was made by Dr. Unger, and on account of special external circumstances was necessarily hasty and incomplete. Only the abdominal organs were examined and Dr. Unger as regards these, was chiefly interested in the character of the new growth which was found. The peritoneum was found much thickened and presented many nodular masses, mostly of small size. The omentum was thickened and retracted into a hard, nodulated, cord-like mass. The mesentery was likewise thickened and retracted. A number of small, hard, whitish, circumscribed nodules were found in the superficial part of the liver. Pieces of the liver, omentum and peritoneum were sent to me for examination. Sections of the nodular tumors showed them to be carcinomata, presenting a fibrous stroma rich in cells and irregular alveoli filled with polyhedrical and cuboidal cells. The primary origin of the cancer was not determined, although doubtless a more complete autopsy would have revealed it.

The most interesting feature of the case, however, is the condition of the liver. Of this organ several pieces hardened in alcohol were sent. On the cut surface as well as through the capsule of the liver can be seen with the

[1] Delivered before the Johns Hopkins Hospital Medical Society, December 15, 1890.

Johns Hopkins Hosp. Bull., Balt., 1891, II, 32-33.

naked eye numerous small black specks and small streaks. These little black lines and dots are present everywhere throughout the liver scattered irregularly at intervals not more than 0.5 to 1 mm. apart. They are irregular in size and shape. They are not present in the cancerous nodules nor more abundant in their neighborhood than elsewhere. Some of the pieces of liver which were sent do not contain any cancerous nodules. Around many of the black specks the tissue has a grayish color. The prevailing color of the liver substance between the black deposit is yellowish brown.

On microscopical sections the little black spots and streaks, sometimes lying in a grayish tissue, sometimes in the yellowish brown liver substance, can be seen distinctly with the naked eye. By microscopical examination the black foci are seen to be due to the deposit of black granules in all respects identical with the coal pigment found in the lungs. The granules are of a pure black color, vary in size from granules about one-quarter the diameter of a red blood corpuscle to very minute granules, occur sometimes in large conglomerate masses evidently composed of a close aggregation of granules, and are sometimes quite regularly round, but may be slightly irregular and angular in shape. They occur both free and enclosed in cells. They remain unchanged when the sections are treated with concentrated sulphuric acid as well as with boiling glacial acetic acid, hydrochloric acid, nitric acid, aqua ammoniae or concentrated liquor potassae. Compared with the coal pigment found so often in the lungs and bronchial glands absolutely no points of difference can be detected and I have therefore no hesitation in saying that they are coal particles.

The particles of coal pigment are not distributed uniformly throughout the liver as is the case with malarial pigment but occur in scattered areas. There are in some places small deposits of the pigment between unchanged liver cells. These deposits between liver cells are generally within round or irregular cells lying against the capillary walls and sometimes appear to be contained in Kupfer's cells. The black pigment is never within the hepatic cells. As a rule the pigment lies within bands and nodules of dense fibrous tissue, and it is the character of these fibrous areas and the relation to them of the coal pigment that make the unusual feature of the case.

These fibrous areas differ in distribution and in appearance from the formation of fibrous tissue in ordinary hepatic cirrhosis. The fibrous areas are sharply circumscribed. They never completely surround a lobule. They occur most frequently in the interlobular tissue, but they are also often formed around the central vein as well as at any point in the interior of the lobule. They vary in size. Some are not larger than a group of five or six liver cells, others occupy nearly the entire field of the microscope with

Zeiss objective A, ocular 3. The majority are much smaller than this latter dimension, averaging about one-sixth to one-eighth the diameter of a liver lobule. Five to eight such nodules can usually be seen in each field of the microscope with Zeiss A, ocular 3. The shape of the fibrous patches varies, but there is a general tendency to assume a round or oval shape. Many of the patches, however, are long and narrow following the course of the interlobular vessels or the rows of liver cells. The fibrous areas are in general composed of dense sclerotic fibrous tissue poor in cells, these cells being chiefly elongated connective tissue cells closely applied to the fibres and cells containing black pigment. Some of the areas, especially the smaller intralobular ones are composed of a hyaline indistinctly fibrillated material poor in cells. In the interlobular fibroid formations can be seen very much compressed interlobular veins, branches of the hepatic artery with thickened walls resulting from an obliterating endarteritis leading in some instances to complete obliteration of the vessel, and bile ducts. The bile ducts are few and there appear to be no so-called newly formed bile ducts so often observed in ordinary cirrhosis. All of the fibroid formations, whether intralobular or interlobular, contain in large amount black coal pigment, both free and in round oval, and elongated, sometimes branching cells. With the exception of the comparatively few small deposits seen between normal liver cells, the coal deposits are found only in the fibroid masses and the growths of fibrous tissue do not occur except in association with the pigmentary deposits. There can be seen on careful examination unmistakable evidences that the new growth tissue is referable directly to the deposition of coal pigment. Where the pigment is surrounded by normal liver cells, it is present only in comparative small amount. There are places where a clump of the pigment is surrounded by two or three homogeneous liver cells devoid of nuclei or by a little hyaline or finely granular material replacing two or three immediately adjacent liver cells, and places where a small area of nearly homogeneous basement substance containing a mass of coal pigment has taken the place of not more than five or six liver cells in the interior of a lobule and all transitions exist between these small areas and the larger ones. The appearances indicate that small deposits of the coal pigment do not injure the surrounding liver cells, that larger deposits lead to a death of the immediately adjacent liver cells, and as a result of this loss of liver cells, a new growth of dense fibrous tissue is developed.

The histological picture is quite different from that of ordinary hepatic cirrhosis. Instead of interlacing bands of connective tissue more or less completely surrounding lobules or groups of lobules, we have in the present instance sharply circumscribed, round, oval and elongated discrete areas of

sclerotic, at times nearly homogeneous, fibrous tissue, containing such masses of coal pigment as to appear in places almost uniformly black. Different as are the appearances from ordinary cirrhosis, there is manifestly a close analogy between the changes in this liver and those occurring in indurative anthracosis of the lungs. In both is found the same formation of circumscribed bands and nodules of dense fibrous tissue, colored black, with coal pigment.

This anthracosis of the liver has no relation to the presence of the secondary cancerous nodules in the liver which are entirely free from pigment.

Besides the changes mentioned there is no other lesion of the liver save a considerable bile pigmentation of the liver cells.

The presence of a small amount of coal pigment in the liver is not particularly uncommon. Instances have been reported by Arnold, Soyka, Weigert and others. We owe to Weigert and to Arnold especially the establishment of the especial conditions leading to this occurrence. Whereas under ordinary conditions the bronchial lymphatic glands form an effectual filter against the entrance into the blood of coal pigment inspired into the lung, Weigert has shown that adhesions and destructive inflammations may open the way for the passage of this pigment from the glands directly into adjacent blood vessels, and it is probable that similar alterations in the lungs may lead to the same result. Arnold has pointed out the frequent association of emphysema of the lungs with the presence of coal pigment in the spleen, liver and elsewhere. It is unfortunate that in the present case we have no clue as to the condition of the lungs or of the bronchial glands, but we can hardly be mistaken in assuming that some abnormal condition existed which permitted an unusually free entrance into the circulating blood of coal pigment from these situations. I have repeatedly had the opportunity of confirming the observations both of Weigert and of Arnold, but I have never before seen a liver containing such a large amount of coal pigment as the present one, which is speckled everywhere with black dots and streaks. Ordinarily the presence of coal pigment in the liver is not associated with any important lesions referable to the deposition of the pigment. Careful examination, however, will often reveal atrophied liver cells and a small quantity of dense fibrous tissue poor in cells around coal deposits of considerable size, but as far as I can learn, this is the first instance recorded of a peculiar form of wide-spread cirrhosis of the liver dependent upon the presence of coal pigment, and I propose to designate the condition cirrhosis hepatis anthracotica.

From the description already given, it is clear that the primary change leading to the cirrhosis is the atrophy and death of liver cells. Whether we are to attribute this cell death to a mechanical or to a chemical action of

the pigment deposits cannot be positively determined, but the former seems the more probable view. Still, as pointed out by Weigert, the coal particles inhaled may carry with them substances of an irritating nature, which may give to the particles an injurious action which the pure carbon granules themselves would not possess. Although occasionally the coal particles were present immediately around and in some places appeared to be within the capillary vessels, there was no such obstruction of the blood vessels by coal pigment as would explain the death of liver cells.

THE PATHOLOGICAL EFFECTS OF ALCOHOL[1]

Introduction.—In considering the action of alcohol upon the living body, it is convenient and customary to distinguish between the physiological, the pharmacological, and the pathological action or effects of this agent, although in a broad sense all marked deviations from the normal condition produced by alcohol are pathological. Inasmuch as previous articles in this book have treated of the composition and relative toxicity of the constituents of alcoholic beverages, and of the action of alcohol on the digestion, the circulation, the respiration, and the nervous and muscular activities, this article is intended to be a concise statement of the pathological effects of alcohol and of alcoholic drinks in the more restricted sense of the term "pathological," and especially of those effects which are characterized by demonstrable anatomical changes in the body.

It may at the outset be stated that the injurious effects of alcohol upon the body are represented only in part by known anatomical lesions, for we are still ignorant of the anatomical basis of many of the morbid manifestations produced by this substance. With improvements in methods of microscopical investigation our knowledge in this respect has materially increased, and from still more refined methods further advance in the same direction may be expected.

The questions of primary importance concerning the effects of alcoholic beverages relate to the action of ethyl alcohol, which is the chief harmful constituent of such drinks, although the effects of other possible ingredients, such as the flavoring essences and the higher alcohols, and the influence of concentration of the alcohol are by no means to be ignored. In this article, by the word "alcohol," unless otherwise specified, ethyl alcohol is to be understood.

Our sources of information concerning the morbid effects of alcohol are experiments upon animals and observations upon human beings. The experimental method has the advantages that the conditions can be better controlled and are less complicated, and the results, therefore, are generally clearer of interpretation than in the case of observations on human beings, but great caution should be exercised in applying directly to human beings the conclusions derived from animal experiments.

[1] In: Physiological Aspects of the Liquor Problem, Bost. & N. Y., 1903, II, 349-374.

I. Results of Experimental Investigations

Alcohol in sufficient quantities is a poison to all living organisms, both animal and vegetable. Our chief interest in this connection is with those experimental results which shed light upon the pathological-anatomical effects of alcoholic drinks upon human beings. During the last fifty years many experiments to elucidate this subject have been made upon animals, most frequently upon rabbits, dogs, and swine. Different sorts of alcohol and of alcoholic drinks in varying doses and for varying lengths of time have been administered to animals in different ways, the best and most commonly employed method being injection into the stomach through a soft rubber tube passed down the gullet.

An elaborate experimental investigation, extending over four years, of the pathological effects of alcohol upon rabbits has been made in behalf of the Physiological Sub-Committee of the Committee of Fifty by Dr. Julius Friedenwald in the Pathological Laboratory of the Johns Hopkins University and Hospital. Reference will be made to conclusions derived from these experiments, which have hitherto been published only in part.

The symptoms of acute alcoholic intoxication in the animals named resemble so closely those in human beings that the experimental method would seem adapted for the study of anatomical changes which may be produced under these circumstances. On the other hand, most experimenters record unsatisfactory, although not wholly negative, results in their attempts to reproduce experimentally the characteristic symptoms and lesions of chronic alcoholism as observed in human beings.

Experimental Acute Alcoholic Intoxication.—Inasmuch as the symptoms of acute alcoholic intoxication in animals, as well as in man, are referable almost entirely to the nervous system, it is not surprising to learn that the only significant anatomical changes produced by this condition are of the nerve cells and their processes. Hyperaemia of the stomach with increased secretion of mucus is also often present, especially when the alcohol is given in a concentrated form. The nervous changes are of such a nature that they can be detected only by the delicate modern methods introduced by Golgi, Nissl, and Marchi for the study of the microscopical characters of the nervous system, and hence our knowledge concerning them dates back scarcely a decade. Berkley's paper published in 1895 and preceded only by the brief articles of Vas in 1894, and of Dehio in 1895, which were based upon examination of a small material, is the first systematic and elaborate study by modern methods of the changes of the central nervous system in experimental acute and chronic alcoholic intoxication. Dr. Berkley's examinations were made, in behalf of the Committee of Fifty, upon the brains and spinal cords of rabbits used in Dr. Friedenwald's experiments. Another

valuable investigation of the influence of acute alcoholic poisoning on nerve cells is that conducted under Dr. Hodge's direction for the Committee of Fifty by Colin Stewart, and published in 1896. Among later investigators of this subject may be mentioned Marinesco (1897), Jaccotet (1897), Carrara (1898), H. Braun (1899), and Kleefeld (1901).

Two different kinds of lesion of the nerve cells have been found in acute poisoning of animals by alcohol, the one, revealed by the Golgi method, being of the cellular processes, and the other, shown by Nissl's stain, being of the body of the cells. The former, described as "the moniliform change," is characterized by the appearance of irregular swellings or varicosities in the course of the protoplasmic processes of some of the nerve cells, associated with partial loss of the delicate bud-like or spinous projections normally present on these processes. The other change, designated "chromatolysis," is the disintegration of the small, stainable granules, known as the Nissl bodies, which can be demonstrated by certain methods of hardening and staining within normal nerve cells. It is not within the scope of this article to describe the finer histological details of these lesions.

The extent and the intensity of these changes in the nerve cells depend upon the depth of the alcoholic intoxication. Nerve cells altered in the ways described have been found in the cerebral hemispheres, the cerebellum, the medulla oblongata, the spinal cord, and the sympathetic ganglia, but even in extreme degrees of the lesions it is only a minority of the cells which are affected. Kleefeld claims that the moniliform change occurs almost instantaneously, and may be found within a few minutes after the entrance of toxic doses of alcohol into the circulation. Stewart found beginning chromatolysis in nerve cells of a cat killed in fifty minutes by the injection of a large dose of alcohol into the abdominal cavity. The most extensive changes have been found in animals subjected to repeated, profound intoxication.

There is considerable difference of opinion concerning the interpretation of these changes and their relation to the symptoms of alcoholic intoxication, but the weight of evidence favors the view that they cannot be satisfactorily utilized to explain the symptoms. The same changes occur from various causes and under a great variety of conditions which have nothing in common with the phenomena of alcoholic intoxication. They do not represent any serious or permanent damage to the nerve cells, but are readily recovered from after disappearance of the causative factor. It has even been questioned whether these changes are really of a degenerative nature, some authors being inclined to refer them to abnormal movements of protoplasm or other manifestations of cell life.

Experimental Chronic Alcoholism.—Since the publication in 1851 of the important work by Magnus Huss on chronic alcoholism many experiments

have been made to determine the effects upon animals of the long-continued use of alcohol. The most extensive and prolonged series of experiments of this nature hitherto made is that for the Committee of Fifty by Dr. Friedenwald in the pathological laboratory of the Johns Hopkins University and Hospital. The details of these experiments will be published elsewhere. Most of the one hundred and twenty rabbits used in these experiments received daily, through a soft rubber stomach tube, from five to eight cubic centimetres of alcohol largely diluted. These quantities sufficed to induce within half an hour a drunken stupor which lasted from three to five hours, the animal generally appearing well on the following day.

Dr. Friedenwald observed, as other experimenters have done, marked individual variations in susceptibility to the injurious effects of the continued use of alcohol. While the tolerance of any given animal could not be positively foretold, young rabbits, pregnant females, and those weighing under one thousand grammes were the most susceptible. Certain individuals were found to be so resistant that they seemed capable of tolerating daily intoxicating doses of alcohol for an indefinite period. Thus, one rabbit was given alcohol for over four years, receiving in this time over four litres of absolute alcohol without permanent ill effects; others were fed with alcohol for three and a half and for three years. These animals had the best of care and were kept under excellent sanitary conditions. On the other hand, some of the rabbits died from acute intoxication after a few doses, and the majority succumbed after shorter or longer periods of time, with gradual loss of weight and exhaustion. If especial care was taken to lessen or to intermit the dose of alcohol when the animal began to lose weight, it was found possible later to increase the dose and to keep a considerable number of the rabbits alive for an indefinite period. Under favorable conditions the animals tended to gain in weight when taking alcohol, especially during the early period.

As regards the pathological effects, there have been considerable differences between the results reported by various experimenters. Some of the earlier experimenters found practically no anatomical changes in animals to which intoxicating doses of alcohol had been fed for weeks or months. The experiments of Dujardin-Beaumetz and Audigé (1879-1884) on swine, extending over three years, which are among the most elaborate and painstaking investigations of this subject ever made, yielded practically negative results, so far as pathological lesions are concerned. On the other hand, the more recent experimental researches, although not altogether in accord, have in general been more fruitful in positive results.

While these discrepancies are at present partly inexplicable, some at least may be accounted for by differences in the animals selected for experimenta-

tion, by variations in the quantity, quality, and mode of administration of the alcohol, by the duration of the experiments, by the technique employed in the microscopical examinations, and by the concentration of attention upon changes in special organs.

It is to be noted that in most of the experiments the amount of alcohol given at a single dose sufficed to produce marked symptoms of intoxication, this quantity being in ratio to the body weight generally much greater than that taken by heavy drinkers. No systematic experiments have been made to determine the pathological effects upon animals of the long-continued use of alcohol in quantities so small as to produce no manifest symptoms of intoxication; but in view of the comparatively meagre results in the experiments with moderately intoxicating doses, it seems improbable that experiments of the former character would yield positive results.

Naturally the attention of the experimenters has been drawn mainly to the examination of those organs which are known to be most frequently affected in man in cases of chronic alcoholism, namely, the stomach, the liver, the kidneys, the heart and blood-vessels, and the nervous system.

Stomach.—Congestion of the gastric mucous membrane and increased secretion of mucous are among the most common conditions noted by the various experimenters. Haemorrhages, erosions, and actual ulceration of the stomach have also been repeatedly recorded. Several experimenters have reported degenerative changes in the cells of the gastric tubules and chronic interstitial inflammation of the mucous membrane.

There is evidence that some of these alterations, especially the more profound ones, are attributable to administration of the alcohol in too concentrated a form and sometimes to mechanical injuries inflicted by the stomach tube.

In Friedenwald's experiments on rabbits there was frequently observed during life a gradual reduction in the amount of free hydrochloric acid in the gastric contents. In some cases hyperaemia, increased secretion of mucus, and fatty degeneration of the epithelial cells of the gastric tubules were found, but in many instances, even after the prolonged use of diluted alcohol, the stomach appeared entirely normal, both to the naked eye and under the microscope.

As a rule, no pathological changes were present in the intestine.

Liver.—Inasmuch as the long-continued excessive use of alcoholic drinks is by far the most common and important cause of cirrhosis of the liver in human beings, the attention of experimenters has been directed especially to the condition of this organ in chronic, experimental alcoholic poisoning.

Of the various anatomical changes noted by the different experimenters, fatty metamorphosis of the liver cells is the one most frequently recorded.

This change is not usually present in an extreme degree, and it is not generally associated with loss of the cellular nuclei or other evidences of death of cells. It readily disappears after cessation of the administration of alcohol. Hyperaemia of the liver is not uncommon.

Actual necrosis or death of the liver cells, either singly or in groups, occasionally occurs, but this, at least in marked degree, is exceptional.

An increase in the number of lymphoid cells in the interlobular tissue has been found by a minority of the experimenters. It was noticed in varying degree in some of Friedenwald's experiments, but its occurrence was inconsistent and rather exceptional.

Genuine cirrhosis of the liver has not been satisfactorily reproduced by the experimental use of alcohol. It was present in one of the rabbits of Friedenwald's early experiments, but as this was an isolated instance of its appearance, it is not certain that it was attributable to the alcohol. The few experimenters who have reported successful results in this regard have probably mistaken mere accumulations of lymphoid cells for early stages of cirrhosis, or have not excluded changes due to accidental infections, particularly from unintended injuries of the stomach. This failure to produce experimetally cirrhosis of the liver by the use of alcohol cannot be attributed in Friedenwald's series to the too short duration of the experiments. It lends support to the opinion held by many that in human beings alcohol acts only indirectly in leading to cirrhosis of the liver, or that special predisposing or associated conditions must be present in addition to the action of the alcohol.

Kidneys.—Most of the experimenters have not noted serious anatomical changes in the kidneys, but von Kahlden in a careful research lays especial emphasis upon lesions of this organ in dogs. He describes fatty degeneration and necrosis of the renal epithelium, hyperaemia of the veins and capillaries, haemorrhages, and transudation of an albuminous fluid, and considers that with longer duration of the experiments a chronic interstitial nephritis would appear as a result of these grave lesions.

Seven of the rabbits in Friedenwald's series of experiments had marked albuminuria, associated in five cases with casts. Fatty degeneration of the epithelium of the convoluted and Henle's tubules was common, although not constant. In a few instances there was necrosis of the epithelium, and atrophy of the glomeruli. On the other hand, a number of the rabbits showed no changes in the kidneys after long-continued use of alcohol. An actual chronic interstitial nephritis was not produced.

Heart, Blood-Vessels, and Blood.—In Friedenwald's experiments fatty degeneration of the muscle of the heart was found in most of the rabbits which died from chronic alcoholic intoxication, but was absent in those which were killed after cessation of the use of alcohol.

In these experiments, as well as in those of others, now and then a sclerotic or atheromatous patch was found on the inner surface of the aorta or other blood-vessel. This lesion was present, however, too inconstantly to be attributed with any certainty to the action of the alcohol, especially as similar changes occasionally are found in animals which have not received alcohol. Pétrov, however, describes progressive sclerosis of blood-vessels in experimental alcoholism.

Fatty degeneration of the endothelial cells and sometimes of the smooth muscle is found with sufficient frequency in the blood-vessels of different organs to be ascribed to the effect of the alcohol.

Often the distribution of the blood does not differ materially from the normal, but there may be hyperaemia of certain organs, most commonly of the stomach, liver, kidneys, and brain.

Friedenwald noted in many instances a considerable reduction in the percentage of haemoglobin. In those chronic intoxications which terminated fatally there was usually, during the last month or so of life, a distinct anaemia, with reduction in the number of both red and white corpuscles. Fatty degeneration of leucocytes may occur.

Nervous System.—The more recent experimental studies of the pathological effects of alcohol have been concerned especially with the condition of the central and the peripheral nervous system. In animals, dead from chronic alcoholic poisoning, changes of the nerve cells have been found identical with those described under "Experimental Acute Alcoholic Intoxication" (p. 414). There is reason to think that these changes belong, even in the chronic cases, to the more immediate, acute effects of alcoholic poisoning, for in Friedenwald's experiments they were often absent in animals which did not die, but were killed in the course of the experiments, and they were not observed in animals allowed to live a few days after the alcohol was stopped.

Of other lesions of the brain and spinal cord ascribed to chronic alcoholism in animals Afanassijew and Braun describe fatty and vacuolar degeneration of nerve cells: Braun also describes a vacuolar rarefaction of the medullary substance, fatty degeneration of the myelin, and the appearance of fatty granular cells along the blood-vessels, and Berkley alterations in the calibre and walls of the blood-vessels and the peri-vascular lymphatics, and accumulations of leucocytes: Small haemorrhages are occasionally found. None of these changes is constant. Some of the rabbits of Friedenwald's experiments which were killed after daily intoxication with alcohol for over two years showed practically no lesions of the nervous system.

In view of the importance of peripheral neuritis in the pathology of chronic alcoholism in man, much interest attaches to the observations of

Spaink, and later of Braun, who found both in rabbits and in dogs subjected to chronic poisoning with alcohol degenerations of various peripheral nerves. Only in the more chronic cases was this degeneration, which is characterized especially by breaking-up of the myeline, well marked. These experimenters claim to have observed in these animals most of the nervous, muscular, and other symptoms characteristic of chronic alcoholism in man. Further confirmatory investigations are needed before these results can be unhesitatingly accepted, especially as similar extensive changes in the peripheral nerves were not observed in Friedenwald's experiments.

Other Organs.—Although hyperaemia, oedema haemorrhages, and actual inflammation of the lungs have been described as results of alcoholism in animals, there is no good reason for this interpretation. Doubtless in many cases these lesions, when found, were attributable to the accidental escape of alcohol into the windpipe. There is no satisfactory evidence that alcohol, administered by the stomach, acts injuriously upon the lungs of animals. In Friedenwald's rabbits a diffuse, fine deposition of fatty granules in the epithelial and interstitial cells of the testicles was often observed. More profound changes in these organs, even atrophy, induration, and softening, are described by Bouin and Garnier as the result of alcoholic poisoning of white rats for eight to eleven months; but these observations need confirmation before acceptance. The same caution is applicable to Sodokow's statements concerning changes in the ovules and spermatozoa.

Experimental Investigations of the Influence of Alcoholism upon Resistance to Infection.—There have been at least a dozen experimental investigations published concerning the influence of alcohol upon susceptibility to infection, the first extensive series of experiments being that of Dr. Abbott, published in 1896, and made in behalf of the Committee of Fifty. These various experiments are in remarkable accord, nearly all showing that animals intoxicated by alcohol are more susceptible to bacterial infection or to toxines than are normal animals. Roos, however, found no increase in susceptibility to the tubercle bacillus of guinea pigs fed with wine, and Kögler, under Gruber's direction, noted a favorable influence of alcohol upon the survival of animals treated with this agent during the stage of acute collapse produced by intraperitoneal injection of killed cultures of *Bacillus prodigiosus*. Deléarde has found that the process of experimental immunization is unfavorably influenced by alcohol.

These researches furnish an experimental basis for the generally recognized lowering of resistance to many infectious diseases manifested by alcoholic patients. They are not however, decisive as to the usefulness of alcohol in the treatment of infectious diseases in human beings, for the amount of alcohol used in experiments proportionately to body weight far surpasses

that generally given for therapeutical purposes, and the question is one which must be answered by clinical experience.

In this connection may be mentioned the unfavorable influence of alcohol upon pregnant females observed by Friedenwald in his experiments. Of twenty pregnant rabbits fed with alcohol seventeen aborted, and of these eight died soon afterward of septicaemia. Nearly all of the young which were born at full term died a few days after birth. Laitinen reports a similar experience with pregnant guinea pigs intoxicated with alcohol.

SUMMARY OF THE PATHOLOGICAL CHANGES IN EXPERIMENTAL ALCOHOLISM

1. There are no satisfactory experimental data to determine the pathological effects upon animals of alcohol or of alcoholic beverages taken for a long time in quantities which produce no marked symptoms of intoxication. In most of the experiments the amount of alcohol administered at a dose, in proportion to body weight, considerably exceeded that usually taken even by heavy drinkers.

2. Animals exhibit marked individual differences in their susceptibility to the injurious effects of the prolonged administraton of intoxicating doses of alcohol. While certain individuals succumb quickly, others may be kept alive under these circumstances for at least four years without presenting any serious anatomical lesions attributable to the alcohol. Between the extremes there are all gradations in susceptibility, young animals and pregnant ones being generally the most susceptible.

3. In acute experimental alcoholism there can be demonstrated certain delicate changes in the nerve cells, which readily disappear after stopping the alcohol.

4. The experimental reproduction in animals of certain of the more characteristic diseases of human beings, attributable to the abuse of alcohol, such as cirrhosis of the liver, chronic Bright's disease, and arterio-sclerosis, has not been satisfactorily attained. The most common pathological condition noted in experimental chronic alcoholism of animals is a fatty metamorphosis affecting especially the cells of the liver, the heart muscle, and the kidneys. This lesion soon disappears after stopping the use of the alcohol. Death or necrosis of limited groups of cells in the liver and kidneys may occur, but is inconstant, and, according to most experimenters, is exceptional. More common is an acute or chronic catarrhal gastritis, but this, is often absent or but slight. Changes in the central nervous system, similar to those in acute alcoholism, as well as certain additional ones, may be present in experimental chronic alcoholism. There may also be degenerations of the peripheral nerves. Hyperaemia and small haemorrhages may occur, especially in the stomach, the kidneys, and the brain. In view of considerable

differences in the results reported by different experimenters, and of many still unsolved problems, additional experiments upon the pathological effects of the long-continued use of alcohol and of alcoholic drinks are needed.

5. Alcoholic intoxication increases the susceptibility of animals to many infections, and influences unfavorably the process of immunization. Pregnant rabbits or guinea pigs repeatedly intoxicated by alcohol are likely to abort, and to die soon afterward from some accidental infection. Many of their young die a few days after birth.

II. Alcohol as a Cause of Human Diseases

It is universally recognized that alcoholic intemperance is the direct or the contributory cause of an immense amount of sickness and disability, and of a very large number of deaths, concerning which, for obvious reasons, mortality returns furnish only imperfect and partial statistical information.

According to Vacher the Registrar-General's Reports for England and Wales show during the twenty years from 1881 to 1900 a total of 110,215 deaths due to chronic alcoholism, delirium tremens, and cirrhosis of the liver, these being the only causes of death, registered in the reports, which directly represent the mortality from alcoholic intemperance. These deaths correspond to an average death-rate per million living for the twenty years from these three diseases of 188.45, that among the male population between 226.7, and that among the female population 152.6. A large majority of these deaths occurred between twenty-five and fifty-five years of age, when men and women should be at their best. During the twenty years there was an increase in the mortality from each of these diseases, but only in the case of chronic alcoholism was this very remarkable. The three causes of death included in these statistics by no means represent the total mortality from alcoholic intemperance, for the agency of alcohol in the causation or the fatality of Bright's disease, diseases of the heart and blood-vessels, apoplexy, paralysis, insanity, pneumonia, tuberculosis, and other diseases is not recorded in these or in most other mortality returns.

For the last twelve years the official mortality reports from the larger Swiss cities contain data concerning alcoholic excess as a contributory as well as a direct cause of death. The statistics (cited from Delbrück) from the fifteen largest Swiss cities for the eight years from 1891 to 1898 show that in 6.4 per cent of all deaths of persons over twenty years of age alcoholism was either the direct cause or a contributory cause. The percentage is 10 for men over twenty years old. Different places and countries, of course, show marked differences in the mortality from intemperance. Switzerland ranks among countries with a medium consumption of alcohol.

Individual predisposition and also predisposition of special organs of the

body are important factors in the etiology and pathology of alcoholism. It is a matter of common experience that many persons drink beer, wine, and spirits in moderation throughout a long life without apparent impairment of the general health. There are, however, others so extremely susceptible to the action of alcohol that they are intoxicated by quantities so small as to be without manifest effect upon most persons. In some individuals, also, the symptoms of intoxication assume an unusual so-called pathological type. Unusual susceptibility to the toxic influence of alcohol, as well as a morbid craving for alcoholic liquors in increasing quantities, have been attributed in many instances to an inherited or acquired degeneracy or instability of the nervous system, but the opinions of authorities are much divided as to the relative importance to be attached to this factor in the causation of alcoholism. The periodical excessive drinking which characterizes dipsomania is now generally regarded as a manifestation of a disease which some physicians consider to be analogous to epilepsy. Of the injurious effects of the continued use of even small quantities of alcoholic liquors upon infants and children Demme and others have brought abundant evidence.

The importance of predisposition is further illustrated by the familiar fact that some persons after a relatively short period of immoderate indulgence in alcoholic liquors present the symptoms and lesions of chronic alcoholism, whereas others under the same conditions, or perhaps even more intemperate, are affected only after a much longer interval or, it may be, not at all. Evidence of predisposition on the part of organs is furnished by the remarkable differences in the manifestations and the localization of alcoholic diseases in different persons, so that in one the kidney, in another the liver, in another the heart, and in still another the brain is the organ chiefly damaged by alcohol. These differences can be explained only in part by the kind and concentration of the alcoholic beverages used.

There being no constant and definite relation between the amount of alcohol consumed and its pathological effects, it is difficult to make statements which shall be both precise and truthful concerning possible pathological effects of what is ordinarily called "moderate drinking." This subject is one concerning which widely divergent views have been expressed even by those whose opinions are authoritative in medicine. Its scientific investigation encounters peculiar difficultes, and at present the established facts are too few to permit secure, broad generalizations. The increasing recognition, especially within recent years, of the importance of this matter, is sure to lead to more exact knowledge concerning it, but it will probably be a considerable time before an entire agreement of medical opinion in this regard is reached.

A difficulty at the beginning is encountered in attempting to define moderation in drinking. What is moderate for one person may be immoderate for

another. The discussion of this fundamental aspect of the subject belongs to the consideration of the physiological and the pharmacological action of alcohol, and has been presented in other articles, particularly in Dr. Abel's "Review of the Pharmacological Action of Ethyl Alcohol," which were published in the book on "Physiological Aspects of the Liquor Problem." There it has been pointed out that the closer analysis of the physiological effects of alcohol, especially upon the nervous centres, has led many to adopt, in comparison with earlier standards, a considerable reduction in the quantity of alcohol which may be properly designated as "moderate," that is, the quantity which may be habitually taken without bad results of any kind. It may here be said that increased knowledge of the pathological effects upon the body of the continued use of alcoholic beverages has drawn many physicians who have carefully studied the subject to a similar conclusion, the demonstration of the causative relation of beer-drinking to diseases of the heart and arteries having been of especial influence upon medical opinion in this regard. Alcoholic diseases are certainly not limited to persons recognized as drunkards. Instances have been reported in increasing number in recent years of the occurrence of diseases of the circulatory, renal, and nervous systems, reasonably or positively attributed to the use of alcoholic liquors, in persons who never became really intoxicated and were regarded by themselves and by others as "moderate drinkers." Strümpell believes that the daily consumption of three to four litres of beer will eventually act injuriously upon the heart. No precise figures are available concerning the frequency with which alcoholic indulgence in its lesser degrees causes disease. It is well established that the general mortality from diseases of the liver, kidney, heart, blood-vessels, and nervous system is much higher in those following occupations which expose them to the temptation of drinking than in others.

The bodily injury inflicted by alcoholic abuse may be entirely latent until it is made manifest by some accessory circumstance. Thus delirium tremens, neuritis, and other nervous manifestations of alcoholism often make their first appearance as an accompaniment or sequel of some acute febrile disease, such as pneumonia, or of traumatism, loss of blood, emotional shocks, or other affection. Or the bad effects of immoderate drinking may be unsuspected until they influence unfavorably the course and outcome of some infectious disease or of a surgical operation.

Alcoholism, as pointed out by Strümpell, represents the summation of injuries inflicted upon the tissues of the body by alcohol, each injury being perhaps minimal in amount but the total constituting serious disease. It is not necessary to consider here the various theories concerning the mode of action of alcohol as a poison, or the extent to which it does injury by acting

directly as such upon the cells, or indirectly through nutritive or other disturbances. In one way or another most of the organs and tissues of the body may become the seat of morbid changes attributable to the poisonous action of alcohol. For the purposes of this article it is not necessary to attempt more than a brief specification of the more characteristic and common pathological effects of alcohol. None of the lesions of either acute or chronic alcoholism is absolutely pathognomonic of this condition, but in many cases of death from chronic alcoholism the anatomical changes in their entirety are sufficiently characteristic to establish a probable diagnosis without knowledge of the history of the case.

The poisonous effects of alcohol may be referred to the following classes of morbid change, which may occur either singly or in combination: (1) disturbances of function, (2) irritative effects marked by hyperaemia, with which may be associated haemorrhages and transudation of serum, (3) cellular degenerations of various kinds, (4) production of new connective tissue, (5) abnormal metabolism, characterized especially by increased formation of fat or deposit of fat in abnormal situations. When brought directly in a concentrated form into contact with the tissues alcohol is an inflammatory irritant. The most important and characteristic pathological action of alcohol is that of a cellular poison. It is probable that the new growth of fibrous tissue in certain alcoholic diseases, especially in cirrhosis of the liver, is consecutive to a primary degeneration or death of cells, although this opinion is disputed.

In the rare instances of *fatal acute alcoholic poisoning,* when a large quantity of strong spirit is taken at once, no characteristic lesions are found after death. There may be redness and inflammation of the stomach and congestion and haemorrhages in the brain, the lungs, and perhaps other organs, but these changes are not invariably present, and they are in no way diagnostic. We have experimental evidence, which has already been presented, that acute alcoholic intoxication causes certain changes of a transitory nature in the nerve cells, and similar changes have been found in human beings in the acute cerebral disorders of alcoholism.

CHRONIC ALCOHOLISM

Alimentary and Respiratory Tracts.—Chronic catarrhal inflammation of the stomach is a common affection of alcoholic patients, but the lurid descriptions and pictures of the drunkard's stomach in certain popular or pseudo-scientific "temperance" tracts and books are drawn from the imagination and not from nature. There may also be intestinal catarrh, but usually no marked lesions are found in the intestine, except in cases of cirrhosis of the liver. Catarrh of the pharynx, larynx, and bronchi is common in alcoholic patients.

Liver.—Cirrhosis of the liver, although not the most common, is the most characteristic pathological-anatomical condition produced by alcohol. The liver is hard and nodular, and usually reduced in size, although it may be larger than normal. The microscope shows a new growth of connective tissue between the liver lobules and atrophy of liver cells, which may also be fatty. The immoderate use of alcohol is the cause of probably over ninety per cent of the cases of hepatic cirrhosis, and some think that it is the sole cause. This disease is the result especially of drinking strong spirits, being rare in beer drinkers, although not so infrequent in France from excessive use of wines. The disease is sometimes called "the gin-drinker's liver." Cirrhosis of the liver was found by Formad in only six of 250 postmortem examinations on confirmed drunkards who had died suddenly from the effects of alcohol. Although other statistics show a much higher percentage of cases, this disease is upon the whole a relatively infrequent form of chronic alcoholism, except in regions where excessive drinking of strong spirits prevails. Deposition of fat in the liver cells is common in alcoholism, and large fatty livers, as well as cirrhotic livers, are found in drunkards.

Pancreas.—With or without cirrhosis of the liver, chronic interstitial inflammation of the pancreas may be the result of alcoholic intemperance. In eight of thirty cases of this disease studied by Opie there was a history of alcoholic excess, but in three of these cases the affection was only indirectly, if at all, referable to the use of alcohol.

Kidneys.—There has been much discussion concerning the effect of alcohol upon the kidneys. Large hyperaemic kidneys are found with great frequency in those who drink beer to excess, but this is a condition of functional hypertrophy rather than of actual disease, the kidneys being called upon for extra work in eliminating the excessive amount of fluid taken into the circulation. The evidence, however, is strong that alcoholic excess is injurious to the kidneys. The observations of Glaser made in 1891 have since been repeatedly confirmed, that the urine, even after a single alcoholic excess, often contains abnormal elements, such as leucocytes, casts, and crystals of oxalate of lime and of uric acid, indicative of transient irritation or even slight inflammation of the kidneys. The experimental evidence upon this subject furnished by von Kahlden and by Friedenwald has already been cited (p. 418). Although some English authors, following Anstie and Dickinson, deny any causative relation of alcoholic abuse to Bright's disease, Strümpell regards renal disorders as the most common of all the pathological effects of alcohol. The weight of authority and of evidence supports the view that excessive indulgence in alcoholic liquors, fermented as well as distilled, is an important cause of chronic Bright's disease, especially of the small, granular kidney. Strümpell describes also a form of acute nephritis

which may rarely result from the long-continued use of alcohol, and occasionally passes into the chronic form.

Heart.—Disorders of the heart are among the most important manifestations of chronic alcoholism, these depending not so much upon any direct injury inflicted upon the heart by alcohol as upon associated conditions resulting from alcoholic abuse. Bollinger and Bauer in Munich were the first prominently to call attention to the frequency of hypertrophied and dilated hearts in those who drink large quantities of beer. This so-called "Munich beer-heart," which is commonly associated with the "beer-kidney," is probably the result mainly of the extra demand upon the heart for work in propelling the excessive volume of fluid in the vessels. The compensation thus established is likely sooner or later to be broken, and then appear serious symptoms referable to cardiac insufficiency. Other causes of hypertrophy of the heart in alcoholic patients are sclerosis of the arteries and chronic Bright's disease. Chronic myocarditis, or new growth of fibrous tissue in the muscle of the heart, although sometimes ascribed to the direct action of alcohol on the heart, is rather the result of disease of the arteries of the heart.

Fatty degeneration of the heart muscle may be caused by alcoholic excess, but a more important condition clinically is the overgrowth of adipose tissue upon the surface and in the substance of the heart, which is found particularly in association with the general obesity of some cases of chronic alcoholism. This latter condition may interfere seriously with the normal action of the heart.

Blood-Vessels.—Alcohol is usually regarded, and probably correctly, as one of the causes of sclerosis or atheromatous degeneration of the arteries, a disease of great clinical importance and attended by varied symptoms and organic lesions according to the particular arteries chiefly affected. In this way alcoholic excess may stand in a causative relation to cerebral disorders, such as apoplexy and paralysis, and also to diseases of the heart and of the kidneys. Dilatation of the veins, particularly about the nose and face, are, together with acne rosacea, familiar manifestations of chronic alcoholism, although they may occur quite independently of this condition.

Nervous System.—The special toxic action of alcohol is, in the first instance, upon the higher nervous centres, a fact which is manifest enough in the familiar symptoms of a drunken fit. Although the special affinity of alcohol for the nervous system has long been known, the most interesting and important clinical and pathological studies of alcoholism in recent years have related to this subject, and have added materially to our knowledge. These researches have shown that the relationship of alcohol to mental disorders and other disturbances of the nervous system is in many instances less

simple and direct than was formerly and is still often represented. A problem of fundamental importance, as yet awaiting final solution, is the determination of the part to be assigned to underlying inherited or acquired constitutional defects of the body, chiefly of the nervous system, in the causation and the pathology of the various disorders of the nervous system caused by or associated with alcoholic excess. That this part is a very important one cannot be questioned, but the limits to be assigned to it are at present uncertain. Both the general and the statistical statements current in many medical as well as popular writings upon the causative relation of alcohol to insanity, to epilepsy, and to certain other nervous diseases are often of little value with reference to the question of causation of these diseases in previously normal persons by alcoholic poisoning.

It is important to know that the immoderate drinking of alcoholic liquor may be the first symptom of some disease which, when later recognized, is erroneously ascribed to alcohol as the cause. It is furthermore established that many of the mental and nervous disorders of alcoholism, while they are attributable to the toxic action of alcohol, are dependent in large measure upon an underlying psychopathic constitution, excessive indulgence in alcohol rarely producing certain of these disorders in persons of normal constitution. Inebriety in the parents or more remote ancestors ranks among the important causes of this inherited instability of the nervous centres. After making the necessarily large, but not precisely definable allowance for the share of inherited or acquired organic or constitutional defects in the étiology of the nervous manifestations of alcoholism, there still remain cases enough in which alcoholic poisoning is the cause of serious disease of the brain, spinal cord, and nerves in persons of previously normal constitution, so far as can be ascertained.

Much has been done in recent years by psychiatrists in the careful analysis of the precise psychical defects characteristic of the various alcoholic psychoses, and in this way the features particularly distinctive of the mental disturbances due to alcoholic poisoning have been more sharply defined than was formerly the case. Investigations of this nature have been made by Wernicke, Kraepelin, Bonhoeffer, Cramer, and others on delirium tremens, alcoholic neuritis, with the corresponding cerebral and spinal diseases, especially chronic alcoholic delirium or Korsakow's psychosis, acute hallucinatory mania, the "pathological" drunken paroxysm of chronic alcoholics, attended often with acts of violence, and alcoholic epilspsy, but it is not within the scope of this article to attempt a consideration of these interesting results.

Correspondingly sharp anatomical definitions of the various alcoholic diseases of the nervous system are still lacking. The pathological lesions of

the brain found with greater or less frequency in cases of chronic alcoholism are thickening, opacity, and adhesions of the membranes, chronic haemorrhagic pachymeningitis, transudation of serum, atrophy of the cerebral convolutions, a granular condition of the ependyma, atheromatous arteries, and increase of neuroglia in the superficial layers of the cortex. These lesions belong to chronic alcoholism as such rather than to any one of the special alcoholic diseases of the brain. In the acute alcoholic psychoses, of which delirium tremens is the most common and familiar type, the modern histological technique, particularly the Nissl and the Marchi methods, have revealed changes in the nerves and the nerve cells of the brain and spinal cord, but the functional significance of these alterations is not at present well understood.

Since the investigations of Leyden and of Mocli about twenty years ago, alcoholic neuritis has been recognized as an important, although not very common, manifestation of chronic alcoholism. The paralyses, disturbances of sensation, ataxia, and other symptoms of the disease had been previously noted. Recent studies, particularly those of Oppenheim, Gudden, and Cole, have led to the important conclusion that peripheral neuritis is only one part of an affection which may implicate the nerve cells and their processes throughout the whole nervous system. In some cases the peripheral neurones, in others the central neurones are chiefly affected, but the degeneration may affect in a single case various groups of neurones in the brain and in the spinal cord and ganglia, including widely distributed peripheral nerves. The lesion in all cases is primarily a degenerative one. The results of these researches bring into close relationship various alcoholic diseases of the brain, the spinal cord, and the peripheral nerves, especially delirium tremens, Korsakow's psychosis, and multiple neuritis. The underlying condition is a toxaemia induced by alcoholic excess. It is especially in this group of affections that the cooperation of various contributory or exciting causes, such as pneumonia, tuberculosis, or other infection, shock, surgical injury, privation, etc., is most apparent. The patient may have been addicted to alcoholic excess for years, but the introduction of one of these accessory causes suddenly gives rise to the outbreak of one of these disorders of the nervous system.

In this connection may be mentioned various disturbances of vision which are often associated with chronic alcoholism and which are referred by Uhthoff mainly to changes in the optic nerves or their terminations.

The excessive use of absinthe and other cordials and liqueurs is particularly injurious to the nervous centres, for here the flavoring essences in varying degree, as well as the alcohol, are poisonous to the nerve-cells. Epileptic disorders may be caused by the immoderate use of this class of alcoholic liquors.

Disorders of Metabolism.—One of the symptoms of chronic alcoholism, most common in beer-drinkers, is obesity. Adipose tissue may appear in situations where it is not normally present, the most dangerous localization in this regard being between the muscle fibres of the heart. Much of the fine, molecular fat deposited in the hepatic and other cells is the result of abnormal metabolism of the fats rather than of a true fatty degeneration. An excess of fatty particles in the blood of drunkards has been observed.

The use of alcoholic liquor, especially in the form of the stronger wines, and heavy beer or porter is a well-recognized cause of gouty manifestations in those predisposed by inheritance to this disease.

Strümpell was the first to call attention to the influence of beer in interfering with the oxidation of sugar in the body. He observed in certain cases that the drinking at once of as much as 1½ to 2 litres of beer was followed by a transitory alimentary glycosuria. These observations have since been confirmed and extended. Strümpell recognized a special form of diabetes mellitus due to alcohol, and he brings the three conditions—obesity, gout, and diabetes—into a group of correlated alcoholic disorders of metabolism.

Lowered Resistance to Disease.—A much larger number of the victims of alcoholic intemperance die of some infectious disease than of the special alcoholic affections. Attention has repeatedly been called in this article to the lowering of the resistance of alcoholic patients to many infectious diseases, and the experimental data bearing upon this point have been summarized. This lowered resistance is manifested both by increased liability to contract the disease and by the greater severity of the disease. Physicians generally recognize the graver prognosis of pneumonia, cholera, erysipelas, and other infections in persons who habitually drink to excess than in others.

The belief was once widely held that those who indulge freely in alcoholic liquors thereby acquire a certain degree of protection from tuberculosis, but this opinion is now completely discredited. Alcoholism, if it does not actually predispose to tuberculosis, as some believe, certainly furnishes no protection against it. The course of tubercuIous disease in alcoholic patients is often more rapid than usual.

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OSTEO-FIBROMYOMA OF THE UTERUS[1]

Sections from the different pieces which were sent show a variety of tissues.

Smooth Muscle.—This is present in considerable amount, although not predominating in these pieces. It occurs especially around masses of bone, and around areas of soft connective tissues; in places, making a kind of capsule for these structures. It is, as usual, in irregular interlacing bundles, and is the seat of considerable hyaline degeneration.

Bone.—True bone is present, showing bone corpuscles, with canaliculi, typical basement substance, lamellae and Haversian canals, with marrow substance. The lamellae are arranged around the marrow spaces with more or less regularity. Some of the bone seems to be formed by a direct metamorphosis of connective tissue, and is, therefore, so-called osteoid. But there are places which show osteoblasts, forming bone in the usual way.

The tissue within the marrow spaces varies. It is well supplied with blood-vessels. In some places it is dense, fibrous tissue, in others more delicate tissue, and in the latter case may contain large numbers of lymphoid cells. Particularly abundant in the marrow are large cells, filled with granules, which may be fine droplets of fat. Adipose-tissue cells occur, but are few.

Embryonic Types of Connective Tissue.—There are large areas, in some pieces composing most of the tissue, of a delicately fibrillated tissue, very rich in cells. These cells are predominantly young connective-tissue cells, but there are also lymphoid and plasma cells, and eosinophiles. Thin-walled blood-vessels are fairly abundant. This embryonic tissue is apparently of soft consistence. In addition, in connection with this tissue, and also independently, are areas of soft mucoid tissue, with large, elongated and branching connective tissue cells. In one set of sections this embryonic tissue occupies all except a narrow, peripheral rim, which is composed of smooth muscle. There are hyaline and necrotic changes in these tissues.

Ordinary Adult Fibrous Tissue.—This is present in connection with the bone and other tissues.

Degenerations.—There are extensive areas of degeneration: (a) Calcification both of muscle and hyaline connective tissue, (b) hyaline and necrotic

[1] Report on a pathological specimen. In: Osteo-Fibromyoma of the Uterus, by George B. Johnston, Richmond, Virginia.
Am. Gynaec. & Obst. J., N. Y., 1901, XVIII, 307-308.

changes have affected considerable areas, (c) actual disintegration of the necrotic areas, with fatty metamorphosis and deposit of cholesterin crystals.

Diagnosis.—Histologically, Dr. Randolph's designation of the tumor as osteo-fibromyoma is unobjectionable.

Remarks.—The tumor must, I think, be referred to embryonic remnants, and there is no objection to considering it as a teratoid formation, although not a very complex one. Besides the bone and smooth muscle, there is a great deal of peculiar embryonic connective tissue in the growth, partly mucoid in character, and partly more cellular, and this tissue is quite unlike any found in ordinary myomatous tumors.

MEDULLARY FORM OF SARCOMA OF THE STERNUM, WITH METASTASES IN THE LYMPHATIC GLANDS[1]

I am indebted to Dr. D. F. Unger, of Mercersburg, Pa., for this specimen. I extract the following points from Dr. Unger's history of the case:

Mrs. S., aged 32 years, weight 120 pounds, mother of three children, had previously enjoyed good health. Parents are healthy. On September 2, 1892, she called my attention to a small, deep seated, firm swelling just above the sternal notch. This gradually increased in size. On November 30, 1892, an operation was performed by a surgeon in Philadelphia, who regarded the affection as a tubercular adenitis. The operation consisted in curetting the growth above the sternum, trephining the sternum about 1½ inches from the top, curetting through this opening, passing a tube from the upper to the lower opening and washing through this canal with a solution of bichloride of mercury and peroxide of hydrogen. Following this, the suprasternal growth increased in size so as to form an irregularly elevated, somewhat nodular firm mass about 6 cm. in diameter, adherent to the skin, and involving for a short distance the tissues over the upper anterior surface of the sternum. In the latter situation the skin ulcerated over a small area. The openings made by the operation did not close but became filled with grayish, soft tissue. Examination of the patient on February 1, 1893, showed a swelling projecting about ½ inch at the right margin of the sternum, at the level of the first and second intercostal spaces. This swelling increased so as to touch the opening made in the middle of the sternum and to reach the margin of the suprasternal tumor. February 14 were noticed several swollen and somewhat painful lymphatic glands just above the middle of the right clavicle. After this there developed enlargement of other cervical and of axillary glands, and several nodules could be felt beneath the skin of the upper part of the thorax in front. The right arm became slightly oedematous and the veins over the right shoulder distended. Dullness on percussion, and absence of respiratory sound over the upper part of the right side of the chest were determined. General itching of the skin became a most troublesome symptom. The pulse became accelerated, respirations increased in frequency, and an irregular fever developed, the temperature running from 98° to 103° F. A note made on July 1, 1893, records increase in the number and size of enlarged lymphatic glands on both sides of neck and in the axillae, and the presence of many nodules feeling like marbles beneath the skin of upper part of the thorax on both sides. These nodules are movable and not painful, except when they first appear. Cough became trouble-

[1] Report of a case before the Johns Hopkins Hospital Medical Society, December 4, 1893.

Johns Hopkins Hosp. Bull., Balt., 1893, IV, 103-105.

some only during the last two months of life, and was attended with little expectoration. During the last two months of life the pulse ranged from 120 to 130, the respiration from 30 to 45, and the temperature from 98° to 102°. Urine diminished in amount, but was free from sugar and albumen. The patient became weaker and weaker and more emaciated, and died apparently from exhaustion on September 2, 1893, just one year from the date attention was called to the first swelling above the sternum.

The autopsy was made by Dr. Unger, from whose notes I extract the following:

The anterior mediastinum is occupied by a large, firm, irregularly nodular tumor mass, so closely adherent to the sternum that it is necessary to remove most of the tumor with the sternum. The tumor consists in part of swollen and adherent lymphatic glands. It presses upon the vena cava superior, the arch of the aorta, the arteria innominata, the trachea and the base of the heart, but the caliber of these channels does not seem to be much diminished. The glands at the bifurcation of the trachea and at the root of the lungs are also the seat of new growth. The tumor on section is grayish white, with more opaque yellowish white areas, which in some places are softened and breaking down.

The right pleural cavity contains 4 pints of clear serum, and the left 1 pint of the same fluid. The right upper lobe is adherent to the costal pleura, and is closely incorporated with the tumor behind the sternum, which seems to have grown continuously into it. This lobe is consolidated throughout with diffuse and nodular masses resembling in structure the tumor and presenting areas of necrosis. The right middle lobe is filled with tumor nodules of similar appearance. The lower lobe is compressed. The left lung is adherent only at its upper part. In the anterior edge of the left upper lobe is a separate tumor nodule the size of a marble. The rest of the lung appears normal. Pericardium and heart normal, likewise the spleen, liver, kidneys, abdominal lymphatic glands. Inguinal glands not enlarged.

Dr. Unger sent to me specimens from this case removed at autopsy. I had previously, during the life of the patient, examined microscopically a small piece of tissue excised from the suprasternal tumor and found it to be a sarcoma composed of variously shaped cells, including giant cells of the type found in giant-celled sarcoma.

The specimens from the autopsy were preserved in alcohol, and consisted of the sternum with adherent tumor, of parts of the lungs containing tumor nodules, of lymphatic glands from the mediastinum, neck and axillae, and of detached pieces of tumor. For convenience of transportation the sternum has been divided transversely through the middle piece. The ribs are severed close to the sternum.

The upper part of the sternum, consisting of the manubrium and adjacent half of the gladiolus, is covered posteriorly by a large, irregular, adherent, firm tumor mass, extending to the upper margin of the bone and laterally to

the right 4 cm. beyond the margin of the sternum and to the left a little beyond the margin. Parts of this tumor mass have been cut away. The remaining part measures 8 cm. in length from above downwards, 7 cm. laterally and 4 cm. in thickness. The free surface of the tumor is irregularly lobulated. To the right margin of the tumor is attached a piece of lung measuring 4 x 6 x 3 cm., which is completely invaded by the new growth and inseparably incoroporated with the tumor behind the sternum.

There is a defect in the manubrium 2 cm. below the top near the median line. This defect, 1 cm. in diameter, is surrounded by bone to the left, and is continuous to the right, with an outgrowth of the tumor through the bone. It corresponds to the opening made during life by the trephine. On the anterior surface of the manubrium are two detached firm tumor nodules, the larger measuring 2 cm. in length and 8 mm. in breadth.

In order to determine the relation of the tumor to the sternum the bone was sawed through to the median line and the tumor partly cut through in the same plane. This section shows that the manubrium throughout nearly its whole extent is invaded by the new growth, which has caused perhaps some general enlargement of the bone, but has not materially altered the normal size and shape so that from external examination the extent of involvement of the bone would not be suspected. The manubrium measures 5.3 cm. in length, 5 cm. in width, and 2.5 cm. in thickness at the level of the clavicular articulations.

Throughout an area of considerable extent the osseous substance is entirely replaced by a grayish white or yellowish white tissue of medium consistence, in places rather soft. This area begins on the posterior surface just below the center of the manubrium and extends downwards for 2 cm. Its verticle length on the anterior surface of the bone measures 1.5 cm. It occupies over this extent the entire thickness of the right half of the manubrium, and in the left half occupies the posterior part of the bone leaving bone substance only in front and on the left margin. The hole made with the trephine, now filled with the new growth, corresponds to the central part of this area in which no bone substance is present.

Above and below this area of complete destruction of bone the spongy texture of bone can be made out, at first very much rarefied, and gradually becoming near the upper and lower ends of the manubrium more nearly normal in arrangement. The soft part of the tumor replacing bone merges gradually into the part where plates of bones are present. Throughout the manubrium the marrow spaces, much dilated near the soft area, are filled with grayish white tissue of the same general appearance as that in the tumor. This filling up of the medullary spaces with new growth renders the cancellous tissues of the manubrium markedly different in aspect from the

normal appearance in the adjacent middle piece of the sternum. The whole manubrium on section has a nearly uniform, solid, grayish white appearance, in which the bony plates can be more readily appreciated by the touch than by the eye. The cartilage between the first and second pieces of the sternum and the remainder of the sternum are normal.

The tumor on the posterior surface of the sternum is directly continuous with that part of the new growth in the manubrium which occupies the area in which the bone is entirely gone. At the upper and lower margins of this area the periosteum on the posterior surface of the manubrium can be traced as a grayish fibrous band outwards over and into the post-sternal tumor for a distance of 2 to 3 cm., giving the impression of a growth from the interior of the bone pushing the periosteum out and then breaking through it. Above and below this apparent outgrowth of the tumor from the bone the tumor has developed to the extent already indicated, and has come into contact with the periosteum, from which, however, it can be separated without difficulty.

To the right of the sternum the tumor has grown laterally and forwards so as to form a projecting mass 4 cm. in width, filling the first intercostal and part of the second intercostal spaces. This is the swelling which was recognized during life at the upper part of the right margin of the sternum.

Upon section the prevailing aspect of the tumor is firm and grayish white, with some denser grayish fibrous bands running through it. In many places can be seen more opaque yellowish white areas of coagulation necrosis. These areas are irregular in size and shape, some being 5 or 6 mm. in diameter. In three places these areas are softened and broken down so as to form little cavities with friable, necrotic contents and irregular walls.

The consolidated upper lobe of the right lung presents in general a similar appearance, diffuse growth and circumscribed, often coalescing nodules of grayish white firm tissue, in places necrotic. The swollen lymphatic glands, some as large as a pullet's egg, and the separate tumor nodules over the sternum are likewise of a nearly uniform grayish white color, with areas of firm coagulation necrosis, and in a few places with areas of broken down necrotic tissue. The pigmented bronchial lymphatic glands are similarly affected. In places the new growth has extended through the capsules of the lymphatic glands and involved the surrounding tissues.

The microscopical examination reveals essentially the same structures in the main tumor in and attached to the sternum and in the metastases. The grayish white, fresher parts of the growth are composed of cells and scanty stroma. The cells are of various shapes, small round cells with deeply staining single nuclei, larger cells of an epithelioid habitus, fusiform cells, giant cells, and cells with deeply staining, large, irregular budding nuclei,

such as occur normally in the marrow of the bones. In places one or the other of these various forms of cells may predominate, but in general they are mixed together. The stroma is in places scanty, the tissue being composed mostly of cells; in other places it is more abundant, and it may form dense bands of sclerotic fibrous tissue with few cells. There is no regularity in the arrangement of the cells, especially no suggestion of an alveolar arrangement. The giant cells are present both in the sternal tumor and in the metastases. They are not abundant, but are seen here and there in all of the sections. They are large protoplasmic bodies with large multiple nuclei, usually clumped in the central part of the cell. None are seen with a mural arrangement of the nuclei or suggestive of tubercle giant cells. Allied to these giant cells are large round and oval cells with deeply staining, often very irregular large nuclei, some ring-like, some like the letter S, and many budding (*cellules à noyau bourgeonnant*). These cells are abundantly present. Transitional forms suggest the development of the giant cells from the cells with the budding nuclei. In the more opaque yellowish areas the appearance is that of typical coagulation necrosis, absence of nuclei or presence of fragments of nuclei. These areas are usually dense and somewhat fibrous in appearance, but, as already mentioned, some are disintegrated into a structureless detritus. The margins of the necrotic areas show the same structure as in the rest of the tumor, or may be more fibrous in texture. In no places are seen tubercles of appearances indicating tuberculosis. Staining for tubercle bacilli and for other bacteria fails to show any bacteria.

The appearances described establish the diagnosis of sarcoma. The possibility that the growths are syphilitic was considered. The areas of coagulation necrosis are not unlike those which occur in gumma, but the structure of the surrounding parts and other clinical and anatomical characters cannot well be reconciled with the diagnosis of syphilis. Areas of coagulation necrosis of the character present in this specimen are not uncommon in some kinds of sarcoma.

The sarcoma is of the mixed-celled type with cell elements belonging to the marrow of the bones. Giant cells of this type and large cells with large, irregular, budding nuclei occur more frequently in sarcoma of bone than in any other kind of sarcoma. The relation of the tumor to the manubrium sterni cannot well be explained otherwise than upon the supposition that the tumor originated in this bone, a view confirmed by the histological structure. The most natural interpretation is that the tumor sprang from the marrow of the bone, but tumors of similar structure may spring from the periosteum. The relation of the periosteum to the tumor as already described cannot be considered conclusive proof of the central origin of the tumor, as a similar anatomical arrangement may occur with primary tumors of the periosteum

and secondary invasion of the bone. While therefore I am inclined to the view that the growth originated in the medullary part of the bone, I do not think that the possibility of a periosteal origin can be positively excluded.

There are several points of especial interest which suggest themselves in connection with this case.

It is interesting that there has been no new production of bone coincident with the extensive destruction of bone. This type of sarcoma in the long bones is likely to contain newly formed bone, but it does not always, and when originating in the short bones it is less likely to do so.

The main tumor topographically belongs to the group of tumors of the anterior mediastinum, and the present case is one of unusual origin of such tumors.

The extensive secondary involvement of lymphatic glands in this case is an unusual feature of sarcoma. This involvement was limited to the glands within the thorax and in the neck and axillae. At one time during life Hodgkin's disease was suspected. The numerous discrete nodules over the sternum and thorax occurred in situations where there are no preexisting lymphatic glands. These metastases were probably of lymphatic origin and invaded the fasciae and muscles, which were replaced by the new growth.

Giant celled sarcoma is ranked as a comparatively benign type of sarcoma, and is not likely to metastasize. The present tumor cannot be considered as a typical giant celled sarcoma like the ordinary epulis. The giant cells were less numerous and the rest of the tumor was richer in cells, especially in small round cells, than an ordinary epulis. It is however, a somewhat arbitrary matter as to what proportion of giant cells is necessary to establish the diagnosis of giant celled sarcoma. In the present case the giant cells were of the regular medullary type, and although not very abundant, they were present in fair number both in the primary growth and in the metastases. More numerous were the large marrow cells with budding nuclei, which appear to merge into the giant cells. The histological evidence of malignancy, however, was expressed in this case by the abundance of such cells as are found in common forms of rapidly developing mixed celled sarcoma.

The occurrence of the necrotic areas and the occasional disintegration of these areas are not so rare in sarcoma, especially sarcoma of the bones, as to need especial emphasis.

Several cases of primary sarcoma of the sternum have been recorded, and nearly the whole sternum has been successfully excised for this disease, but this bone is not a common seat of primary sarcoma.

DIFFUSE INFILTRATING CARCINOMA OF THE STOMACH[1]

I. Abstract of Clinical History by F. R. Smith

Dr. Welch has requested me to give a brief history of the case from which the specimen came. The man came into the hospital in the beginning of April, but had been under observation in the dispensary sometime before, complaining of indigestion, with flatulence and pyrosis, which had lasted for six months. He absolutely denied that he had ever vomited; then he corrected himself and said that he did not vomit but spat up a good deal of bitter stuff. On asking him if he ever vomited in large quantities he said no.

The family history of the patient is negative, except that the family fear that his sister may have a similar trouble, for which reason they have allowed the autopsy. His personal history is entirely negative. He has no long history of indigestion. Up to four or five months before coming into the hospital he had been a thoroughly healthy man, a very moderate drinker, and had no venereal disease and had lived a very regular life.

His occupation, that of a tailor, had been a sedentary one. The symptoms that he complained of were slight pain in the epigastric region and loss of appetite. When the stomach was empty he complained more of an uncomfortable feeling than of pain. The pain was rarely sharp. He went to St. Joseph's Hospital in December and was treated he said, for indigestion. While there he caught cold and had a swollen gland under the left clavicle. When he came into the dispensary the epigastric region was examined and nothing whatever was found. Dr. Finney was asked to look at this gland in the left axilla, and after examining it and hearing the man's symptoms, he made the diagnosis of carcinoma of the stomach. He was seen by Dr. Osler about a fortnight afterwards. Dr. Osler said he felt something indefinite in the epigastric region but he would not positively say anything about its size, except that it was probably a very small lump. The man came to the dispensary from January to April. All his symptoms grew worse, and he developed swollen glands under the other clavicle, and then after a few weeks, there was a distinct lump or ridge in the epigastric region. This grew larger and the patient became more and more distressed,

[1] Report of a case before the Johns Hopkins Hospital Medical Soc, May 15, 1893.

Johns Hopkins Hosp. Bull., Balt., 1893, IV, 98-99.

He came into the hospital April 4. The ridge was then very distinct and was found to occupy the right hypochondrium and extended as low down as the umbilicus. The stomach tube was inserted and brought up some blood. It distressed the patient so very much that it was not tried again. Two attempts were made to dilate his stomach with bicarbonate of soda and tartaric acid. He had hardly swallowed the tartaric acid when he vomited, and therefore the outlining of the stomach was always somewhat unsatisfactory. This ridge-like mass extended, when the stomach was distended as well as could be, slightly below the umbilicus. It was said in the note to feel something like a rolled-up omentum. The resonance of the tumor suggested that it might be connected with a cavity. Dr. Finney's diagnosis was confirmed by Dr. Osler. Although suffering some pain, the patient was fairly comfortable, but he gradually grew worse. The patient lost weight very rapidly and the tumor increased in size. The only other thing of interest in the case was that one morning he complained of great pain in the left leg, which was swollen and very painful to the touch and which made him take to his bed. The inguinal glands on that side seemed to be enlarged, but no thrombosis of the vein could be felt. The leg got better, but he gradually sank, and at his own desire he went home. The same night he was taken very ill and died in the morning.

II. Pathological Report

This case was diagnosed during life as one of carcinoma of the stomach. If it were only that, perhaps it would not be worth while to exhibit it here, but it is a form of carcinoma of the stomach not very common, although you will find it described in the literature. The interest of the case is due also to the fact that the disease can be readily confounded with fibrosis or cirrhosis of the stomach, so that the literature of the subject of cirrhosis of the stomach is of very little value so far as cases are reported as fibrosis of the stomach, induration of the pylorus, etc., without microscopical examination. In other words, a large proportion of the older cases to be found in the literature reported as cirrhosis of the stomach are in reality this disease, viz., diffuse cancer of the stomach. At the autopsy the parts around the stomach were the seat of marked fibroid induration. The transverse colon, the mesentery, the duodenum and the pancreas were all more or less matted together. I exhibit here the entire stomach. You will observe that the size and the shape of the organ are about the size and shape of the kidney. The cavity of the stomach is reduced to an extremely small capacity. The walls are enormously thickened; the mucous membrane is everywhere intact; no ulceration and no nodular growth. It is entirely a diffuse disease involving all of the coats and all of the parts of the stomach. The thickening is univer-

sal, but is somewhat greater towards the pylorus than at the fundus. Examining more carefully, we find that certain coats of the stomach are very much thickened. The grayish, more translucent, muscular coat is extremely hypertrophied and makes up one-third to one-half of the entire thickness of the walls of the stomach. The peritoneum is smooth and glistening and distinctly thickened, but not extremely so. The submucous coat of the stomach is enormously thickened, is extremely dense and fibrous in character, and looks as though it was the primary seat of the disease. The mucous membrane is a very thin line, and is distinctly atrophied. The firm consistence and unyielding character of the walls of the stomach cause it to remain open on incision. There is nothing at all suggestive of a tumor; there is no circumscribed or lobulated new growth. Cirrhosis of the stomach consists in a fibrous overgrowth in the walls without cancerous involvement. This condition, which cannot be distinguished by the naked eye from cirrhosis, is really cancerous, as determined by the microscope. The microscope shows the following condition of things: The mucous membrane is an extremely thin membrane indeed. The tubules can be made out, but they are very much altered in size and broken up in general arrangement. You can make out rows of cells suggesting a tubular arrangement, and that is about all. The muscularis mucosae is extremely hypertrophied and is everywhere provided with nests of cancer cells running down in strands connecting the mucous membrane with the submucosa. The submucous coat is the seat of large cancerous alveoli. The cancer cells are to be found in all of the coats of the stomach. They are present in the mucous membrane where they have a tendency to conform more or less to the tubular arrangement of the mucous membrane, but they are different from the cells which belong normally to the tubules of the stomach. Many of them are very large, irregular cells, with large deeply staining vesicular nuclei. Similar clumps of cells extend in bands and alveoli through the muscularis mucosae, and form the largest masses in the submucosa. The alveoli containing cancer cells extend into the muscular coats along the septa and between individual fibers. There is no coat of the stomach which has escaped. This is the type of infiltrating cancer as distinct from the one which grows in the form of a circumscribed tumor. Here the infiltration is uniform throughout the walls of the stomach. This type of cancer is found also in the ovary, which is then like a very large ovary, the regular outlines being preserved. There is such a thing also as infiltrating cancer and sarcoma of the serous membranes, which spread out flat like a pancake and do not form tumor masses. I have seen one in the meninges of the brain which was simply a uniform thickening, preserving accurately the normal appearances of the dura mater so far as shape was concerned. We have no positive information as to which coat of

the stomach is primarily involved in this case. The general idea is that the growth originates in the mucosa. One would almost be tempted to think that there was a uniform involvement of the tubules and that everywhere they tended to grow down through the muscularis mucosae and into the submucosa. I have alluded to this form of carcinoma in the article in Pepper's System of Medicine on Cancer of the Stomach and called attention to the danger of confounding it with cirrhosis of the stomach. The growth in this instance was primary in the stomach. The only secondary nodules present are in the neighboring lymphatic glands.

I was particularly interested in this case, because some years ago I made an autopsy on a somewhat similar one, also a case of diffuse infiltrating carcinoma of the walls of the stomach, but it was secondary. The woman, about 40 years of age, had double carcinoma of the ovary, of that form in which we have this exaggeration of the normal shape. There was marked ascites in that case, and the fluid was withdrawn during life. From the character of the fluid I ventured a diagnosis of carcinoma involving the peritoneum. No operation was done in the case. There was no suspicion during life that the stomach was involved. We found in the stomach a uniform enlargement of all the walls without ulceration of the mucous membrane, and with extreme narrowing of the lumen of the stomach. I have placed under the microscope a section of this stomach for your inspection. The peritoneal coat is thickened, the muscular coat considerably hypertrophied, and the submucous coat shows interlacing bands of fibrous tissue. The mucous membrane in this case, instead of being atrophied, is hypertrophied. There is a marked lengthening of the gastric tubules and a marked hypertrophy of the muscularis mucosae in this case. It looks like a diffused fibroid induration of the organ, and would correspond to descriptions of fibroid induration of the stomach or cirrhosis of the stomach. It, however, contains nests of cancer cells. In this case the involvement was from the peritoneum and secondary. The type of the cancer was that of carcinoma of the ovary. We have three diseases which can produce gross alterations in the stomach, indistinguishable from each other to the naked eye: cirrhosis or fibroid thickening of the stomach, primary infiltrating carcinoma of the stomach, and secondary infiltrating carcinoma of the stomach.

SYRINGO-CYSTOMA[1]

The case is a perfectly typical one of the Jacquet-Darier group of cases. In general there has been such a remarkable uniformity in the reported cases referred to this group that it is quite improbable that, as claimed by Möller, some are of endothelial and others of epithelial origin. While a considerable number of authors (since the report of the first case by Kaposi in 1868 as a lymphangioma) have adopted the hypothesis of endothelial origin (some as a lymphangioendothelioma and others as haemangioendothelioma), I believe that the epithelial nature of the tumors has been demonstrated.

I also believe that the evidence is very strong that tumors of the Jacquet-Darier type originate from sweat ducts or the "Anlagen" of sweat ducts. It is true that actual connection of the epithelial strands and cysts with preexisting sweat glands has been missed by most of the investigators, and it may be exceptional, but there are now several well authenticated reports where such a connection has been recognized, as for example in cases reported by Blaschko, Neumann, Joseph and Deventer, Fiocco, Winkler, Dohi, Landsteiner and Matzenuer, Stockmann and others, so that this side of the evidence is fairly strong. Dohi's observation is interesting of narrow epithelial, tube-like connection of cysts with the interpapillary epithelial processes, such connections resembling sweat ducts and being probably such. Then weight is to be given to Török's argument, who made the first thorough study of the histogenesis of these tumors, that the absence or rare occurrence of sweat glands in the area of the tumor, in contrast to their presence in the adjoining skin, is indicative of the transformation of preexisting sweat tubules into the tumor elements.

I attach, however, even greater importance in support of the sweat gland theory of histogenesis of these tumors to the resemblance between the epithelial strands, nests and cysts and the tubules of sweat glands, and your sections show this resemblance very well. There is a manifest resemblance between the narrow, often wavy or twisting strands of epithelium connected with the cyst and the tubules of the sweat glands, but most significant, and it seems to me conclusive, is the presence in many of the cysts and tubular

[1] Report on a Pathological specimen of R. L. Sutton, Kansas City, October 18, 1911. [Quoted in article by R. L. Sutton and C. C. Dennis: J. Am. M. Ass., Chicago, 1912, LVIII, 333-336.]
Unpublished.

strands of the double row of epithelial cells, the outer row being flat and the inner row cubical, precisely with the arrangement so characteristic of the cellular lining of the sudoriparous tubules. Of course this arrangement is not in all places apparent in consequence of the pressure of the contents of the cyst, of proliferation of cells and other obvious causes, but it can be recognized in so many places that it cannot be doubted that it is a characteristic histological feature of this class of tumors. I do not see how this can be interpreted otherwise than as evidence of the origin of the tumor from sweat glands.

Much more problematical, it seems to me, is the decision of the question as to whether the tumor springs from previously normal sweat ducts or from congenital or acquired defects of the sweat glands. In favor of the congenital theory is the occurrence of so many instances of the affection in early life and especially its occurrence in several members of the same family, a point emphasized by many of those who have reported cases, as Quinquad, Stockmann, Elschnig, Gassmann, Winkler, Csillag and others. Of much interest are Schidachi's experiments in which he succeeded in producing similar cysts, even with epithelial strands, by occlusion of the sweat ducts.

Now as regards the relation of these tumors of the Jacquet-Darier type, to which such a confusing multiplicity of names have been given, and the benign multiple cystic epithelioma of Brooke and Fordyce, I am inclined to hold them apart. I cannot weigh the value which has been attached to the clinical points, especially the difference in location, but in Brooke's type of tumor connection of the growth with the epidermis, with hair follicles and outlets of sebaceous glands is usually very evident.

In your sections I see the two cysts to which you refer in your letter lying close to a sebaceous gland, but I fail to make out any connection between the two, and, so far as I know, Hartzell is the only one who claims to find connection. His case is so poorly described and the photographs so poor that I do not think it can be satisfactorily interpreted. It may be, as you surmise, that it is a combination of the two types (Jacquet-Darier and Brooke). Hartzell speaks of the tube-like structures being lined with cylindrical epithelium, and does not seem aware of the importance of the two layers of cells in the true syringo-cystomata.

In Brooke's tumor the outer row of cells is cylindrical, whereas in the Jacquet-Darier tumor it is flat. Of course the occurrence of colloid degeneration in both types of tumor, with the resulting cysts, points to analogies, which are all the closer from the fact that horn cysts have occasionally been found in the upper layers of syringo-cystoma, such keratinisation being of course a marked feature of the Brooke's tumor, although, as Csillag has

demonstrated, the colloid cysts and the horn cysts in the benign cystic epithelioma have not the same origin.

In spite, however, of such apparent analogies and even transitions I hold with the majority of authors that syringo-cystoma is histogenetically distinct from benign cystic epithelioma, the former originating from sweat tubules, either fully developed or congenital rest, and the latter from the basal cells of the epidermis, hair follicles and sebaceous glands.

As you perhaps know, Pick and some others object to regarding the so-called syringo-cystadenomata as true adenomata, the question being whether there is any thing of the nature of a true secretion. If the hyaline or colloid material in the cysts is merely the result of cellular degeneration the propriety of such names as cystoma or cyst adenoma would be questionable, but Stockmann has apparently shown that in some instances the cysts and tubules contain genuine secretion, so that I see no particular objection to calling the Jacquet-Darier tumor a syringoma, or syringo-cystoma, or hydrocystoma or the like. Still strictly speaking it is a benign cystic epithelioma, although the latter name had better be reserved for the Brooke-Fordyce type of tumor.

I have found Stockmann's article in the "Archiv für Dermatologie und Syphilis," 1908, Bd. XCII, Hft. I, a good one. You will find there references to Schidachi's experiments and other authors to whom I have referred.

CHRONIC JAUNDICE WITH XANTHOMA MULTIPLEX[1]

I hope that a careful histological study will be made of specimens of the xanthomatous lesions in this case, as the subject is one offering many unsolved problems. My attention was directed a few years ago to xanthoma through the opportunity of examining sections sent to me by Dr. Pollitzer of New York, whose specimens were utilized by Unna in his description of generalized xanthoma. The specimens which I examined were of ordinary xanthoma palpebrarum. There appear to be at least three, and probably more, clinical types of disease which have been called xanthelasma or xanthoma, namely, xanthoma vulgare of the eye lids, an extremely common and unimportant affection, juvenile xanthoma multiplex, and generalized xanthoma of adults, most frequently secondary to jaundice and diabetes mellitus, but occurring also without any apparent cause. Unna makes a sharp histological difference between the common form of palpebral xanthoma and generalized xanthoma. According to him, in the former the fat, which gives the yellow color to the lesion, is of a peculiar character and lies in extracellular masses within the lymphatic spaces and vessels, there being no true xanthoma cells. I am not aware that Unna's views, which are not in accordance with those usually accepted, have been confirmed. Waldeyer in his first publication and most other investigators following him find the fat in small granules or droplets within large cells believed to be derived from connective tissue cells or endothelial cells, these fatty cells being the so-called xanthoma cells. Later Waldeyer suggested that these cells may come from his plasma cells or Toldt's embryonic fat forming cells, and this view has had a number of advocates. Dr. Pollitzer finds evidence in his sections of palpebral xanthoma that the characteristic cells containing fat are derived from striped muscle, partly displaced through congenital abnormality into the corium. Virchow objects to the designation "Xanthelasma" or "Xanthoma," as not based upon histological characters, and has proposed, as a substitute, fibroma lipomatodes, but this suggestion seems to have met with little success. There is a rare form of lipoma which bears considerable anatomical resemblance to certain of the larger neoplasms which have been described as xanthomata. I examined such a specimen some years ago. It was a lobulated and encapsu-

[1] Remarks on a case of Dr. Osler and report of pathological specimen, before the Johns Hopkins Hospital Medical Society, February 4, 1901.
Johns Hopkins Hosp. Bull., Balt., 1901, XII, 220-221.

lated subcutaneous tumor, the size of a hen's egg, removed from the groin of a young man, and believed at the operation to be an ordinary lipoma. On section it presented a uniform, yellow surface, and microscopically it was composed entirely of vascular stroma and large cells filled with minute granules or droplets of fat. After removal of the fat single, or occasionally multiple, round or oval nuclei with nucleoli were found usually about the middle of cells filled with a finely porous or reticulated protoplasm. There was a stroma around individual cells or groups of cells. I interpreted the tumor as composed of embryonic adipose tissue. There were no adult adipose-tissue cells with single, large oil drops. I mention this tumor on account of its histological resemblance to certain xanthomatous tumors, but otherwise it has no relation to xanthoma, as it was the only new growth and was in the subcutaneous tissue. It is highly probable that a variety of distinct affections have been described under the name of xanthoma.

CHRONIC PERITONITIS WITH COMPLETE OBSTRUCTION, CAUSED BY NUMEROUS CONSTRICTIONS OF A PREVIOUSLY UNDESCRIBED CHARACTER, THROUGHOUT THE INTESTINE[1]

I. Abstract of Clinical History by Miles F. Porter

History.—Dr. L. A. H., aged 35, married, had an attack of pneumonia 21 years previously, followed by empyema for which a rib was resected and drainage instituted. Complete recovery followed, but the diseased chest still remained considerably contracted. He drank excessively throughout 1903, but now is a total abstainer. In December, 1906 (six months before admission), after a full meal of sausage, he was taken with very severe abdominal cramps and vomiting, for relief from which he took $\frac{3}{8}$ grain of morphine hypodermically. The pain was worse in the lower abdomen, and especially on the right side, and some tenderness, localized over the painful area, followed. This attack caused him to quit work for one day. Six weeks later he had a similar attack, accompanied by vomiting of a light, bright green-colored fluid and a more severe one followed on March 28, 1907. The bowels were constipated. A few days before coming to the hospital he had a formed putty-colored stool. No elevation of temperature was present during these attacks. The patient stated that his abdomen was sore when he was jolted; he complained of accumulation of gas in the stomach, which was relieved by belching or the use of the stomach pump. He frequently vomited bright green-colored fluid and complained of a metallic taste in the mouth. It was very difficult to get the bowels to move; the stools were not formed.

Examination.—The patient was a fairly well nourished man of good color, and of dark complexion. His abdomen was rather retracted and boogy. An indistinct mass was felt in the pelvic region, both on rectal and on abdominal palpation. Examination of the chest was negative. The pulse was 62; the temperature, 97.6° F. The blood picture was normal. The urine was normal in character but reduced in amount, only 18 ounces being passed in the 24 hours. Bacteriological examination of the vomitus showed a bacillus which culturally and microscopically gave characteristics of *Bacillus typhosus.* The Widal reaction was positive. There was no reaction to two injections

[1] Report on a specimen of Miles F. Porter, August 14, 1907.
J. Am. M. Ass., Chicago, 1908, LI, 719-722.

of old tuberculin of 5 and 10 mg., respectively. Permeability of the intestinal tube was demonstrated by the charcoal test. No clinical diagnosis could be made other than that of a low grade, wide-spread peritonitis with incomplete obstruction of the bowels.

Operation.—An exploratory laparotomy with the patient under ether anaesthesia was done two days after admission to the hospital. Practically universal close adhesions were found between contiguous bowel surfaces. There was some fluid. Very little adhesion between the visceral and the parietal peritoneum was found. The appendix was freed and removed, but presented nothing abnormal. The bowel adhesions were fairly completely broken up. The small intestine seemed abnormally short and nowhere constricted, but on the contrary unusually large in its transverse diameter, and on palpation felt as though it were filled with angle worms. Attempts to empty sections of the bowel by stripping were ineffectual. The surface of the bowel was grayish white, and the non-adherent surfaces perfectly smooth. An incision was made into the ileum. There was no escape of faeces or gas. The bowel seemed full of mucous membrane arranged in accordion-like folds. A probe could not be made to pass in either direction; but the finger could be made to pass in either direction by carefully working the folds aside. It was concluded that the case was hopeless, even temporary relief being out of the question. The incisions in the ileum and the abdominal wall were closed.

Just previous to the operation the patient's pulse was 70, and temperature 97.6° F. Twelve hours after the operation his pulse was 102 and his temperature 98.2° F. Sixteen hours after the operation a catheter was inserted and the bladder found empty. Only eight ounces of urine were secreted during the three days that intervened from the time of operation until his death. There was no vomiting for 20 hours after the operation, when it commenced again and continued until death. At first the vomitus was green, but later became dark brown in color. The temperature gradually rose to 102° F., while the pulse rate increased and became more feeble in quality, and death occurred from a gradual failure, 72 hours after operation.

Autopsy.—About two hours' time intervened between the time of death and the autopsy. Both the wound in the abdomen and that in the intestine were found to be healing normally. There was no evidence of recent peritoneal infection. The stomach presented nothing abnormal except some adhesions to the abdominal wall. The whole of the small intestine and all of the large intestine except the rectum were covered by a layer of grayish white, rather strong, plastic material about $\frac{1}{16}$ of an inch in thickness, which could be stripped off, leaving the underlying peritoneum looking, to the naked eye, normal. This membrane was smooth on the free surfaces of the bowel but

ragged where it had been adherent. The adventitious coat did not reduce the transverse diameter of the bowel, but shortened it by actual measurement by 70 to 80 per cent. Closely placed parallel incisions around the bowel would allow it to be drawn out to its normal length, as would stripping off the false membrane. Mesentery and omentum were normal. The liver, spleen, and peritoneal surface of the bladder were covered, as were the bowels, by this membrane, but not diminished in size. Transverse section of the bowel shows its lumen to be occluded by transverse folds of mucous membrane.

II. Pathological Report

Gross Appearances.—The specimen, which had been preserved in formalin and alcohol, was a portion of the small intestine, evidently jejunum, which had been severed from the mesenteric attachment except at one end, where a small piece of the mesentery was retained.

The specimen measured 21 cm. in length opposite to the mesenteric border, and 15 cm. in length along the mesenteric border. For a distance of 13 cm. from one end the intestine had been cut open along the mesenteric margin, the remaining 8 cm. being unopened. The unopened part of the intestine measured 10 cm. in external circumference, was not collapsed and felt from the outside as if filled with a rather elastic and moderately firm material. The transverse section presented by the cut end of this solid, unopened part of the intestine showed no recognizable lumen, but in its place a complicated mass of folded mucous membrane. Only with difficulty and after much twisting and turning could a metallic probe be passed from the lumen corresponding to the opened part of the intestine through the lumen of the unopened part; after inserting the probe this latter part was cut open opposite to the mesenteric attachment, when it was seen that the obstruction was due entirely to the infoldings of the intestinal wall occurring at short intervals and kept in place by an organized false membrane attached to the peritoneal surface. This false membrane covered the entire peritoneal surface of the intestine, but over the opened part of the specimen, as stated in Dr. Porter's letter accompanying the specimen, "closely placed parallel incisions around the gut, made through the false membrane," had permitted this part of the intestine to be stretched to its normal length and had effaced the involutions of the intestinal wall, so that here the lumen was free from obstruction and the mucous surface showed no especial abnormality. It was evident that by a similar procedure the same result could be obtained in the remaining part of the specimen. There were no contents found in the lumen of the obstructed intestine after opening it as described.

As has already been stated, the entire peritoneal surface of the intestine was covered with a false membrane. This membrane, which was from 0.5 to 1 mm. in thickness, was grayish in color, of firm consistence, almost cartilaginous in translucence over most of its extent and smooth over the greater part of its free surface, although careful inspection showed that much of this surface was finely granular or slightly shaggy, as would result from a thin coating of fibrous exudate on an organized fibrous membrane. No remnants of fibrous threads or bands projected from the free surface of the false membrane. This dense and nearly uniform false membrane, consisting apparently of organized fibrous tissue with superficial fibrinous exudate, was attached to the underlying wall of the intestine by fibrillated connective tissue, which was evidently also of new formation. This attachment was in general so loose that there was no difficulty in peeling the dense false membrane off from the intestine, the surface thus exposed appearing smooth in consequence of the delicacy of the severed threads of tissue. The attachment of the false membrane was firmer and more intimate over the intestine situated between the infoldings of the wall, while it was very loosely attached directly over these infoldings. No tubercles could be seen with the naked eye in the outer covering of the intestine or elsewhere.

In this examination the greatest interest attached to the infoldings of the intestinal wall which have filled up and obstructed the lumen of the bowel. As these infoldings had been entirely obliterated in the opened part of the intestine by numerous transverse incisions through the false membrane they could be studied only in the 8 cm. of the intestine which had not been cut open previous to the reception of the specimen. The folds were the result of a sharp bending inward of all the coats of the intestinal wall from a direction parallel to the long axis of the intestine to one perpendicular to this axis, much as if a contraction of a narrow band of the circular muscular coat had occurred and persisted or been held in place. These segmental, transverse constrictions of the intestinal wall followed each other longitudinally at short intervals, as many as eight being present in a length of 8 cm. of intestine. Each of the infoldings extended as a rule transversely nearly around the circumference of the intestine, but some were shorter. There was a certain alternating arrangement of the folds such that the shallower part of one fold fitted in between the deeper parts of adjacent folds, whereby a spiral-like arrangement of the intestinal ridges on the mucous surface resulted. This arrangement suggested that each infolding corresponded to the course of the larger vessels which run transversely round the bowel, and in many of the folds it was possible to see these vessels in the lax tissues bridging the depressions. The depth of the folds averaged from 1 to 2 cm., the tendency was for each fold to become shallower in its course and to dis-

appear before it had completely encircled the bowel. The thickness of the folds was about 1 cm., the adjacent muscular coats on each side of a fold being nearly in apposition in the deeper part of the depression and separating slightly above, so as to approximate a V-shape. Between successive folds the lumen appeared of normal dimensions, but this lumen was evident only on stretching the intestine longitudinally as the folds were so close together and so deep as to obstruct it completely. The dense false membrane which covered the outer surface of the intestine did not follow the involution of the intestinal coats into the folds, but it extended bridge-like over the depressions, and it was evident that it was these bridges of false membrane which kept the folds in place. By incising these bridges transversely over the folds the latter were readily obliterated on stretching the bowel longitudinally. There was little evidence of the constrictions on inspection of the outer wall of the unopened intestine, which appeared merely invested in a uniform grayish coat of false membrane; still, careful inspection showed frequent slight external furrows corresponding to the constrictions. The delicate loose connective tissue already noted as present beneath the denser part of the false membrane was, however, present in the depressions, stretching between the adjacent sides of an infolding. It was evident that the existence of the constrictions or folds described must have caused an extraordinary shortening of the intestine. By actual measurement of the part of the intestine in which the constrictions were in place (not having been obliterated by transverse cuts through the false membrane) there was found to be a shortening of from 70 to 80 per cent of the normal length. The inner or mucous surface of the intestine showed no abnormalities other than the ridges resulting from the constrictions. Vulvulae conniventes were high and numerous as in the jejunum. There was no ulceration, necrosis or haemorrhage to be detected with the naked eye. The small tag of mesentery which still remained attached to one end of the intestine was moderately rich in adipose tissue and contained two or three small lymphatic glands, free from any abnormality.

Microscopical Examinations.—The mucous membrane was well preserved and appeared entirely normal. The submucosa also was free from any pathological change. The circular muscular coat appeared somewhat thicker in the part of the intestinal wall included in the constrictions than in that between these, but this was probably due to the obliquity of the section of the muscle in the former situation. The spaces between the muscular bundles of the circular coat appeared rather wider than normal. The longitudinal muscular coat also appeared somewhat thicker near and in the depressions, but the same explanation probably applies here also. The coat was in places moderately invaded by new connective tissue extending in from the

peritoneal surface. The existence of the constrictions was sharply defined on the microscopical sections by abrupt change of the direction of the mucous, submucous and muscular coats, the angle of the bend being almost a right angle, but with its apex rounded off. The distance between the muscular coats on each side was about 2 or 3 mm. at the angle and became less as they approached the point of union of the muscle at the bottom of the constriction. The peritoneum was entirely replaced by organizing exudate and connective tissue. The original subperitoneal tissue could be made out as a layer firmly connected with the longitudinal muscle. Over this was, first, a layer of richly vascularizing fibrillated connective tissue, containing many fibroblasts, plasma cells and lymphocytes. This layer was very lax, with wide meshes and numerous blood vessels over and between the layers of the infoldings of the subjacent coats, whereas it was denser and more intimately connected with the adjacent tissues between the successive constrictions. This layer passed gradually into a dense layer of organizing connective tissue of a rather sclerotic or, in places, hyaline appearance, containing fibers and long fibroblasts, disposed mostly parallel to the longitudinal axis of the intestine, leucocytes and developing capillaries. In this layer, old fibrin in process of substitution by connective tissue was enclosed. On the free surface was a fibrinous exudate, in places old, dense and hyaline in character, and in other places fresh with fibrillated fibrin and many polymorphonuclear leucocytes, with fragmenting nuclei. The layer described under the gross appearances as "false membrane" consisted mainly of the organizing connective tissue and exudate. Corresponding to the constrictions in the intestinal wall the denser part of the organizing exudate stretched across the interval between the walls of a fold, and did not follow the intestinal wall as if bent abruptly inward. The subjacent delicately fibrillated, very vascular, lax, newly formed connective tissue extended down in long threads which appeared to be stretched and which ran perpendicularly from the under surface of the dense membrane into the depressions, which were thus occupied by this lax tissue with wide meshes. Corresponding to the tops of many of the constrictions the denser texture of the bridges of false membrane extended down for perhaps 3 or 4 mm. as a wedge-shaped mass from the under surface of a bridge into the depression, the apex of the wedge lying in the center of a depression. No tubercles were seen in any of the sections. Sections stained for bacteria (for tubercule bacilli, Gram's stain, and methylene blue) showed various bacilli and cocci on the surface of the exudate, but these resembled bacteria found on the surface of the mucous membrane, and were probably the result of postmortem contamination.

Pathological Diagnosis.—Chronic organizing peritonitis of unrecognized etiology. Intestinal obstruction resulting from numerous transverse infold-

ings or constrictions of the intestinal wall, these being held in place by bridges of dense, organizing false membrane.

Interpretation of Findings.—After completing the foregoing examination and description I received from Dr. Porter two other parts of the intestine from the same case. These were both of small intestine. One measured 48 cm. in length, and the folds had been largely obliterated by transverse cuts through the false membrane. The other piece was still unopened. The appearances and pathological changes in these parts were identical with those already described, the same obstruction from infoldings of the intestinal wall existing as in the specimen already described.

The mode of production of intestinal obstruction in this case is most remarkable and quite unfamiliar to me, and, so far as I am aware, previously unrecorded, although I have not searched the literature. The peritonitis was of the organizing, proliferative type, associated with fibrinous exudation. It was probably the primary lesion. Anatomical features of interest relating to the peritonitis were the uniformity of the false membrane enveloping the bowel, the absence of fibrous adhesions to any notable extent, the laxity of the layer of connective tissue connecting the dense false membrane with the intestinal wall where the constrictions occurred, and the bridging of the tops of the constrictions by the dense false membrane of such a nature that when these bridges were cut through around the bowel the constrictions could be completely obliterated and the intestine restored to its normal length and appearance, save for the evidences of peritonitis. Most remarkable were the extent of intestine, implicated in this unusual form of intestinal obstruction, all of that submitted for examination being similarly affected, the great shortening of the intestine in length resulting from the myriads of transverse constrictions, and the symmetry and regularity of the segmental constrictions entirely unlike the nicks and puckerings of the intestinal wall resulting from peritoneal adhesions.

It is evident from the description that the dense false membrane was responsible for keeping the constrictions in place. A further question is whether it was also responsible for their original production. If it be assumed that in process of organization of a progressive fibrinous exudate a false membrane, composed partly of connective tissue, was formed, that this surrounded the bowel uniformly, and was firmly adherent around the bowel at intervals, then it would seem that contraction of this false membrane in a longitudinal direction in consequence of the growth of cicatricial tissue would draw the intestinal wall into transverse folds at the situations where the contracting membrane is loosely attached. Mr. Brödel, who contributed the drawings, has called my attention to the possibility of explaining such a disposition of the false membrane and the situation and regularity of the

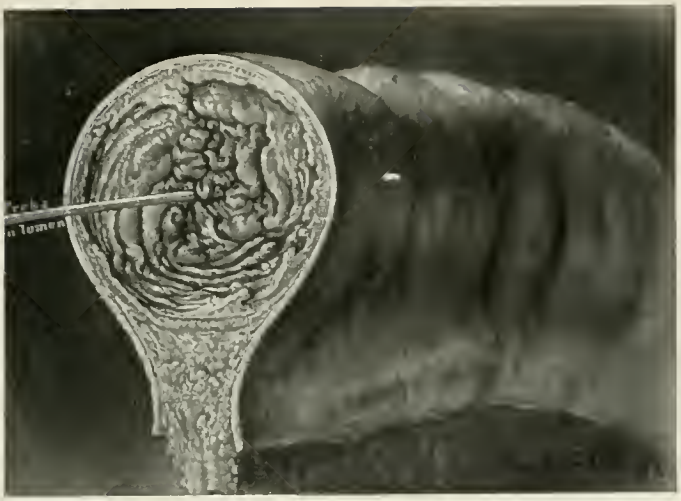
constrictions by taking into account the arrangement of the intestinal vessels. On an injected and moderately distended small intestine slight transverse furrows can be seen, each corresponding to the course of the artery which passes from the mesenteric border over the side of the intestine, these arteries alternating as they pass now to one, now to the other, side of the intestine.

As already noted, the constrictions seemed to correspond to the situation of these arteries. The suggestion is advanced, therefore, that the situations where the false membrane was loosely attached and where, therefore, the constrictions occurred, correspond to these arterial furrows, and that the constrictions themselves were due to contraction in a longitudinal direction of the organizing false membrane which was firmly adherent to the intestinal wall between the furrows. The distinguishing feature of the process in accordance with this view and as seems supported by the histological characters described, is the peculiar mode of organization of a peritoneal exudate whereby the resulting membrane is firmly adherent in places to the intestinal wall and only loosely adherent in intervening places. As already noted, the fibers and fibroblasts in the organizing membrane had a prevailing direction parallel to the long axis of the intestine, and this arrangement may account for preponderance of contraction in this direction.

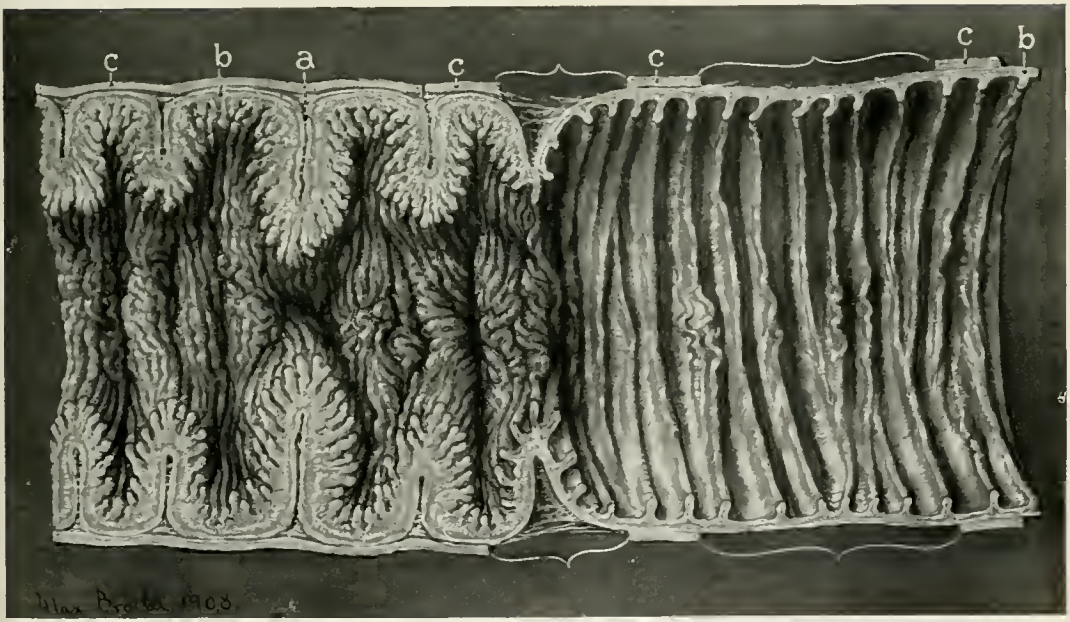
The mechanical explanation which is offered is advanced as an hypothesis without strong proof. Other hypotheses have suggested themselves which take into account the participation of muscular contraction during life in producing the constrictions. In the stage of chronic peritonitis represented in this case, at which the acute exudate is far removed by intervening newly formed connective tissue from the muscular coats, there is no reason to assume paralysis of these coats during life.

While it is apparent that the anatomical condition in this case was in no sense intussusception, the possibility may be entertained that muscular contractions causing the bowel contractions may have been such as would initiate intussusception, but that the dense false membrane covering the intestine was an obstacle to the production of actual intussusception.

Nothing was found to indicate the cause of the peritonitis by examination of the specimen sent me.



Unopened piece of gut, enveloped in a false membrane. The shallow circular furrows on the surface are located at the region of the infolding of the gut wall. The cut end of the gut shows the lumen practically obliterated by folds of intestinal mucous membrane. A probe forced through the folds demonstrates the difficulty of locating the lumen.



Intestine opened longitudinally, showing infoldings (*a*) of the intestinal wall (*b*), occurring at short intervals and kept in place by an organized false membrane (*c*), attached to the peritoneal surface. On the right, the intestinal wall (*b*) has been unfolded to its normal length by cutting the false membrane (*c*). The brackets indicate the extent of unfolding.

IDIOPATHIC PHLEGMONOUS GASTRITIS[1]

I recall a case of diffuse phlegmonous gastritis which I examined at autopsy several years ago at Bellevue Hospital, New York. The patient was a man beyond middle life, with a history of chronic alcoholism. Abdominal pain, vomiting, and fever were among the symptoms, the diagnosis during life being acute peritonitis. The walls of the stomach were nearly one centimetre in thickness and were diffusely affected, although the pyloric region was the most thickened. The thickening was most marked in the submucosa, which presented a yellowish-white, rather firm appearance. There was no tumor or large ulceration, but small drops of pus could be squeezed in many places from the surface of the mucosa as through a sieve, and also from the incised wall of the stomach. There was diffuse seropurulent peritonitis.

The microscope showed an immense diffuse infiltration of the submucous coat with leucocytes, chiefly polymorphonuclear. In scattered foci were small submucous abscesses. Lines of pus cells extended up between the gastric tubules and opened upon the free surface. The accumulation of pus cells was most abundant in the inner layers of the submucosa near the muscularis mucosae but the outer layers were also infiltrated, and strands of pus cells extended through the muscular coats, the intermuscular and subserous layers of connective tissue being considerably thickened by purulent infiltration. The peritonitis appeared to be secondary to the phlegmonous gastritis. I did not at the time of the autopsy examine for the presence of bacteria, but I have since done so, and have been able to discover in the microscopical section numerous streptococci.

Phlegmonous gastritis was described by Brinton under the peculiar name of "suppurative linitis," and I recall that in my student days we were expected to know about it under this latter designation.

[1] Report of a case, during remarks on a paper of Francis P. Kinnicutt, before the Association of American Physicians, Washington, D. C., May 1, 1900. Tr. Ass. Am. Physicians, Phila., 1900, XV, 133.

THE EFFUSION OF CHYLE AND OF CHYLE-LIKE MILKY, FATTY, AND OILY FLUIDS INTO THE SEROUS CAVITIES[1]

I have brought with me and here present a specimen of the fluid from a case of chylous ascites. The specimen was recently sent for my examination by Dr. McNamara, of New York, who has at different times withdrawn by tapping several quarts of similar fluid, exactly like milk in its optical properties, from the abdominal cavity. The patient is a boy, whose clinical history does not render clear the cause of the affection.

Save here and there a stray leucocyte or red blood corpuscle, the only morphological elements to be seen microscopically in the fluid are extremely minute granules, so minute that they cannot be recognized as fatty globules. This granular matter can be dissolved in ether, and on evaporating the ether drops of oil remain. No filaria are present.

Those who will look through the literature relating to chylous effusions, will perhaps be surprised to find that the pathology of the affection is involved in considerable doubt and differences of opinion. Quincke advanced the subject by distinguishing clearly between chylous and fatty hydrops, a distinction of much importance, although often lost sight of. The microscope enables us to distinguish between these two affections, as in fatty hydrops there are larger oil globules, and also fatty granular corpuscles and lymphoid and other cells in various stages of fatty degeneration.

There are many writers who entirely reject the view that the chyle-like effusions in the peritoneal and the pleural cavities are due to the escape of chyle from the chyle vessels. They argue that in such cases postmortem examination has not furnished satisfactory demonstration of the existence before death of rupture of chyle-containing vessels, that the chemical constitution of the fluid differs in some respects from that of chyle, notably in the absence of sugar, and that similar effusions are to be found in parts of the body where no chyle-containing vessels exist.

Notwithstanding these objections, it seems to me to have been demonstrated that the chyle-like effusions in the serous cavities of the abdomen

[1] Presentation of specimen and remarks on a paper of Samuel C. Busey, before the Association of American Physicians, Army Medical Museum, Washington, D. C., September 18, 1889.

Tr. Ass. Am. Physicians, Phila., 1889, IV, 102.

and chest are in reality the result of the escape of chyle by rupture of the lacteal vessels or of the thoracic duct. In many instances cancerous and tuberculous masses obstructing large numbers of the lacteals at the root of the mesentery have been found, with plain evidences of damming back of chyle and rupture of lacteal vessels. I do not think that the mere occlusion of the thoracic duct, still less obstruction to the venous flow in the subclavian veins, is followed by serious interference with the flow of lymph or chyle. I have found the thoracic duct completely occluded by a tuberculous thrombus in a case of acute miliary tuberculosis, without any such effect. Straus has shown in his interesting paper that the ingestion of substances like butter, which are absorbed by the lacteals, causes a corresponding change in the composition of the chylous effusion. In Whitla's case the guarantee that the perforation found in the thoracic duct occurred during life, is furnished by the character of the hole and by the dissection of the skillful anatomist, Redfern.

CATHETERIZATION OF THE URETERS IN THE MALE[1]

I recall a case in New York in which I made an autopsy—a case in which a serious mistake was made which would have been avoided had this method of determining the presence or absence of the kidneys been used. The patient was a vigorous young German girl who had atresia of the vagina. An effort had been made to reach the uterus by cutting through this closed vagina. They opened the canal up to a certain distance and then abandoned the attempt. Then they found a mythical tumor on the left side. Various diagnoses were made as to the nature of that tumor. The prevailing opinion was that it was connected with the left ovary, and, indeed, that was the opinion of one of the most distinguished surgeons of New York. Dr. Lusk, who saw the case, made a correct diagnosis of movable kidney. The case was operated upon before the class at Bellevue Hospital and the kidney removed. There was nothing the matter with the kidney other than it was movable. The kidney was brought at once over to my laboratory. It was a very large, succulent kidney. I happened to have made an autopsy a few days before on a man who had only one kidney, and the appearance of the kidney was impressed upon my mind; the thick cortex and the beautiful markings of the cortex, the normal structure greatly exaggerated but perfectly healthy. This kidney looked so much like the one just mentioned that I surmised at once that it was the only kidney the patient had and suggested that, to the horror of the surgeon. The patient lived 11 to 13 days, voiding no urine. For 7 or 8 days there were no symptoms to occasion alarm. During the last 48 hours uraemic symptoms manifested themselves and the patient died. The autopsy showed that the patient had but one kidney, and that had been removed by the surgeon. The operator was very frank in bringing the case to the notice of the medical profession and published it in all its details in one of the medical journals in 1881 or 1882. He discussed at that time all the methods that his ingenuity could suggest as to the possibility of recognizing the presence of a second kidney. I do not know that he at that time even thought of the possibility of catheterizing the ureter. I remember that he discussed the advisability of pressing on the ureter on one side and determining in that way whether the other was present. This is simply one case which shows that there is a practical use for this procedure.

[1] Remarks on a paper of James Brown, before the Johns Hopkins Hospital Medical Society, Baltimore, December 17, 1894.

Johns Hopkins Hosp. Bull., Balt., 1895, VI, 16.

PRIMARY ECHINOCOCCUS CYSTS OF THE PLEURA[1]

I have examined the sections of the cysts. I am of the opinion that the cysts are degenerated echinococcus cysts. The gross appearances of the specimens which you showed me were like those of echinococcus cysts. The microscopical characters of the fresh teased material and of sections of the hardened specimens seem to be best explained upon the assumption that the cysts are much degenerated hydatids. Cholesterin crystals and fatty detritus, such as were present in these cysts, are common in degenerated hydatids. No organized tissue is present in the walls of the cysts. These walls, as shown in the sections, present an outer, thin, hyaline membrane, with irregular inner surface continuous with fragments and shreds of a structureless material which occupies a considerable part of the interior of the cysts on the sections. There are scarcely any intact cells in the sections: here and there a few are attached to the outer wall and a few nuclear fragments are seen in the interior, but there is nothing indicative of suppuration, or of previously organized tissue, nor is there any suggestion of fibrin or inflammatory exudate in the sections.

As no hooklets can be detected, I have looked carefully for the characteristic lamellation of the cuticular layer of echinococcus cysts. I think that there are suggestions of such lamellation in the parallel striae occasionally seen in some of the more coherent and hyaline membranous fragments attached to the wall and in the interior of the cysts, but they are not so distinct as to be convincing.

It is well known that echinococcus cysts may perish and undergo complete disintegration. Davaine, Leuckart, Neisser and others have described such degenerative changes in the dead cysts. In some of these cases nothing but the hooklets remain to establish the diagnosis. Sterile echinococcus cysts occur, and should these undergo similar degeneration, it is evident that not even hooklets would be present to aid in the diagnosis.

[1] Pathological report taken from a letter to Charles Cary and Irving P. Lyon and published.

In: Primary Echinococcus Cysts of the Pleura. Report of a Case of Primary Exogenous Echinococcus Cysts of the Pleura, Showing Hyaline Degeneration of the Cuticle without Lamellation, with Notes from the Literature, by Charles Cary and Irving P. Lyon.

Tr. Ass. Am. Physicians, Phila., 1900, XV, 371-373.

In your case the degeneration has not reached a stage in which the gross appearances of echinococcus cysts have been obliterated, but the characteristic physical and microscopical features do not seem to me reconcilable with any other sort of cysts than much degenerated echinococcus cysts. As already mentioned, the large amount of fatty detritus and of cholesterin crystals within the cysts is in favor of the diagnosis of degenerated hydatids.

Echinococcus cysts, of course, receive their nourishment from the tissues in which they are embedded, and impairment of this nutrition tends to the production of sterility and degeneration of the cysts. In your case the partial and small attachment of the cysts to the pleural membrane must have favored these results of imperfect nutrition, and in this way I should explain at least in part, the sterility of the cysts and their degenerated condition (April 1, 1900).

In my previous letter I did not speak particularly of the outward curling of incised echinococcus cysts. This physical property is well known, and is demonstrable readily in fresh, undegenerated cysts. As it depends upon the integrity of the parasite, it, of course, is likely to disappear after the parasite dies and undergoes degeneration, as certainly occurred in your case, assuming it to be a bladder-worm. It would not be contended, of course, that the absence of this property would exclude the diagnosis of a degenerated echinococcus cyst.

As I wrote you, I attach more importance in explaining the sterility of the cysts, and the evidence of death and degeneration of the parasite, to the comparatively limited attachment of the cysts to the surrounding living structures, and their consequent feeble nutrition Most of the instances of pleural echinococci have been of single or few large cysts, firmly attached in their circumference. The topographical relations of the cysts in your case are rather peculiar and unusual (April 5, 1900).

MALARIA[1]

Definition

Malaria comprises the diseases caused by the specific protozoan parasite called *Haematozoön malariae*.

The name "malaria," derived from the Italian *mal' aria* and signifying "bad air," was applied originally to the miasm or poison which was supposed to produce the disease. It is now used to designate the disease itself, and is the most convenient term for this purpose.

The most characteristic malarial manifestations are intermittent or remittent fever, certain forms of the disease described as "pernicious," and a chronic cachexia with enlarged spleen and anaemia. The parasite discovered by Laveran is invariably present in malaria and produces from the haemoglobin of the red blood corpuscles the brown or black pigment granules which are characteristic of the disease.

Synonyms

Malarial fever; Intermittent fever; Chills and Fever; Fever and Ague; Paludism or Paludal fever; Swamp or Marsh fever; Miasmatic fever; Periodical fever; Autumnal fever.

Names derived from localities where the disease has prevailed with especial intensity have sometimes been used; as, Walcheren fever, Batavia fever, Hungarian fever, African fever, Panama fever, Chagres fever.

Special names have been applied to certain types or manifestations of malaria; as, remittent fever, bilious remittent fever, hemorrhagic remittent fever, congestive fever, dump ague, black-water fever, black jaundice.

History

There are few diseases which can be traced so surely and continuously as malaria in medical writings from ancient times to the present. Various types of malarial fever are described by Hippocrates, Celsus, Galen, and other ancient writers, although it is often impossible to determine the precise characters of many of the fevers described by these authors.

Celsus and Galen divide intermittent fevers into quotidian, tertian, quartan, semi-tertian, and irregular. They recognized intermittent fevers with long intervals. The nature of their semi-tertian fever (hemitritaeus) has

[1] In: Syst. Pract. M. (Loomis), N. Y. & Phila., 1897, I, 17-154.

given rise to much discussion. Certain forms of intermittent fever were believed by Galen to have their seat in the spleen, others in the liver. The influence of marsh effluvia and of seasons of the year in the causation of certain of these fevers was recognized. Various symptoms were discriminated as to their prognostic significance, often with much acuteness of observation. A passage in Celsus clearly alludes to the type of malarial fever now called aestivo-autumnal fever.

The Arabian physician Rhazes described the so-called subintrant malarial fevers. No important advance beyond the knowledge of Celsus and of Galen concerning malarial fevers was made until toward the end of the sixteenth century, when Mercatus in his work on malignant fevers described various forms of pernicious paroxysms in association with intermittent fever, particularly with the tertian type.

The introduction of cinchona bark from Peru into Europe by the Countess del Chinchon and her body-physician, Juan del Vego, in 1640, gave great impetus to the study of malarial fevers, and, indeed, in its revolutionizing influence upon medical doctrines this event marks an epoch in the history of medicine.

In the latter half of the seventeenth and the beginning of the eighteenth century there appeared a voluminous literature regarding malarial fevers. The most notable of the works upon this subject of this period are those of Sydenham, Richard Morton, Torti, Ramazzini, and Lancisi. These works remain to this day the great classics upon malaria. They contain the fundamental clinical and therapeutical facts and many etiological data relating to this disease. Morton and Lancisi demonstrated clearly the relation of malaria to marsh miasm. Sydenham pointed out the differences between vernal and autumnal intermittent fevers. Especially complete and keen in analysis is the nosography of Torti,[2] whose classification of the malarial fevers, particularly of the pernicious and mixed forms, has been followed by most subsequent authors. The diagnostic as well as the therapeutic value of the preparations of Peruvian bark was recognized, and assisted materially in the discrimination of the malarial fevers from the other so-called essential fevers. It is interesting to note the relative accuracy of diagnosis and of description of the group of malarial fevers from the latter half of the seventeenth century onward, in contrast to the confusion which existed regarding the other essential fevers until the discrimination of the latter by the pathological-anatomical studies of the present century.

The military and colonial enterprises of England in the eighteenth century served to extend the knowledge of the geographical distribution of malaria,

[2] Torti: Therapeutice specialis ad febres quasdam perniciosas, etc., Mutinae, 1712.

particularly in tropical climates, the works of Pringle and of Lind containing especially noteworthy observations on this point. But the great mass of the very extensive literature on the epidemiography of malarial diseases which has been so industriously collected and ably analyzed by Hirsch[3] belongs to the present century.

The significance, as regards malaria, of the active studies in morbid anatomy of the first half of the present century relates to the clear differentiation of typhoid fever from malarial and other fevers rather than to the actual contributions to the pathology of malaria, although these were not lacking. The occurrence of enlarged spleens, so-called fever cakes or ague cakes, and even the dark color of the organs in association with malarial fevers, had been occasionally observed by the older writers, notably by Lancisi, but the intimate relation of these alterations to malaria was not established until during the first half of the present century.

Audouard (1808, 1812, 1818) emphasized congestion and enlargement of the spleen as the essential anatomical lesion of malarial fever. Bailly (1825) noted in a series of autopsies on cases of pernicious malarial fever observed in Rome in 1822 the dark color of the cortical gray matter of the brain and the congestion of the cerebral meninges and substance. He laid especial emphasis upon evidences of supposed inflammation of the central nervous system and of the stomach and intestine. These anatomical observations, together with those of Nepple (1828, 1835), and, to a less extent, of Maillot (1835), were interpreted in favor of Broussaisism, which at this period exerted such a pernicious influence upon medical practice.

Valuable contributions to the pathological anatomy of malarial fevers, especially of the remittent type, were made in the United States during the fourth decade of this century by Stewardson in Philadelphia, Swett in New York, and Anderson and Frick in Baltimore. Stewardson demonstrated the bronzed color of the liver in remittent fevers, and regarded this as the characteristic anatomical criterion of the disease. His observations were confirmed and extended by the other writers named. Alonzo Clark in 1855 demonstrated that the bronzed color of these livers is due to the presence of granules of yellow, brown, and black pigment, which he regarded as derived from the coloring matter of red blood-corpuscles. The monumental work of Daniel Drake on "The Principal Diseases of the Interior Valley of North America" (1850, 1854) contains a large amount of valuable information, based upon personal observation and research, as to the distribution and characters of the malarial fevers in the then Western States of this country.

In the light of recent discoveries it is interesting to note the ingenious arguments advanced by John K. Mitchell in his work "On the Cryptogamous

[3] Hirsch: Handbuch der historisch-geographischen Pathologie, Stuttgart, 1881.

Origin of Malarious and Epidemic Fevers," published in 1849, in favor of the doctrine of contagium animatum. This book deserves to rank with the more frequently quoted work of Henle relating to the same line of argument. At about the same period Bassi and Rasori in Italy also advocated the parasitic theory of malaria.

The discoverer of the malarial pigment is Heinrich Meckel, who found and described the pigment in 1848 in the blood and organs of the dead body of an insane patient. He was, however, ignorant of the relation of this pigment to malaria. The next report concerning the pigment was in 1849 by Virchow, who observed it in the body of a man who had suffered from chronic malaria. There soon followed the observations of Heschl, Planer, A. Clark, Tigri, Frerichs, and others, fully establishing the relation of the pigment to malaria. The source of the pigment was regarded by Meckel and Virchow as in the spleen, and this doctrine was elaborated by Frerichs. Planer (1854) was the first who saw the pigment in the fresh blood of living patients, and he suggested that the pigment may be formed in the circulating blood—a view which was more fully presented and advocated by Arnstein (1874) and by Kelsch (1875).

There is no doubt that some of the pigmented bodies which are now recognized as parasitic organisms had been seen by earlier observers without knowledge of their true nature. Thus Meckel noted the presence of pigment granules in colorless, hyaline bodies devoid of definite nuclei. He, and more particularly Virchow and Frerichs, observed pigment in fusiform and curved bodies in the blood, which, although interpreted as endothelial cells of splenic origin, in all probability were, at least in part, the crescentic forms of the parasite. Some of the larger pigmented spherical organisms must have been seen and mistaken for pigmented leucocytes.

In November, 1880, Laveran discovered the parasitic nature of these and previously unrecognized forms in the blood of malarial patients, and thereby introduced a new era into our knowledge of the malarial diseases.

The discovery of the malarial parasite has furnished an unfailing means of diagnosis of malarial diseases, has materially advanced our knowledge of their pathology, has led to a better understanding of their clinical phenomena and various types, has furnished important data for prognosis, and has led to improvements in methods of treatment.[4]

[4] The so-called *Bacillus malariae* described in 1879 by Klebs and Tommasi-Crudeli, which for a short period had a certain vogue, chiefly with Italian writers, never rested upon satisfactory observations which indicated that it bore any relation to malaria, and it deserves no more consideration than the palmella of Salisbury and the other alleged malarial organisms described before Laveran's discovery.

Parasitology

historical

In 1879, A. Laveran, a French military surgeon, stationed at the time in the province of Constantine, Algeria, began to study the pathological anatomy of malaria, and at once directed his attention to the much discussed question of the origin of the pigment. He observed in the blood of malarial patients certain pigmented bodies different from the melaniferous leucocytes, but he was uncertain as to their nature until, on November 6, 1880, he discovered that some of these pigmented bodies threw out long flagella endowed with such active lashing movements as to convince him, as they have convinced every one who has since then seen them, that they are living parasites. Laveran published his observations in a note to the Académie de Médecine in Paris, presented November 23, 1880. This was followed by the publication of several notes in 1880 and 1881, and in the latter year appeared a small monograph by Laveran on the parasitic nature of malaria.[5]

In these various early publications Laveran describes (1) pigmented crescentic and ovoid bodies; (2) spherical, transparent bodies, sometimes free, sometimes applied to the surface of red blood corpuscles, the smallest about one-sixth of the diameter of a red blood corpuscle and containing only one or two fine pigment granules, these representing an early stage of development of (3) larger, pigmented, spherical bodies averaging 6 μ in diameter, but sometimes larger than a red blood corpuscle, and containing numerous, often moving, pigment granules; (4) bodies similar to the last mentioned, but beset with actively motile flagella; (5) free motile flagella; and (6) swollen spherical or deformed bodies 8-10 μ in diameter, containing pigment, and regarded as cadaveric forms of spherical parasites. Laveran noted amoeboid movements of the spherical forms, grouping of the small spherical bodies together and the occurrence of small, colorless, motile bodies, without specific characters, which he suggested may perhaps represent the first phase of development of the parasitic elements. He regarded all of the forms as different stages of development of the same species of organism, and considered the free flagella, which he believed were formed within the spherical bodies and escaped by rupture of the enveloping membrane, as the most characteristic and perfect stage of development of the parasite.

[5] Only occasional references to the voluminous literature on the parasitology of malaria are given in this article. A full table of references to the works treating of malarial fever since the recognition of its parasitic origin up to and partly including the year 1895 will be found in The Malarial Fevers of Baltimore, by William Sydney Thayer, M. D., and John Hewetson, M. D. (The Johns Hopkins Hospital Reports, V, 1895).

Laveran communicated his results to his colleague Richard, stationed in Philippeville, Algiers, who in February, 1882, published a communication confirming Laveran's observations and adding certain points of importance. He describes the development of the parasite from small, perfectly transparent bodies contained in otherwise normal red blood corpuscles. This clear body grows larger, forms pigment out of the haemoglobin of the enveloping red corpuscle, which thereby becomes gradually decolorized and reduced to a mere colorless shell-like rim, which finally ruptures and sets free the parasite. This now generally accepted view as to the intracorpuscular development of the parasite, which was first announced by Richard, was, however, in the following year abandoned by him in favor of Laveran's view that the parasites develop either free in the plasma or in close attachment to the surface of red corpuscles or in depressed spots on the surface. Richard observed amoeboid movements of the parasites, and noted spherical bodies with a central block of black pigment from which delicate lines radiated so as to produce rosette forms.

Laveran continued to publish brief communications in 1882 and 1883, and in 1884 he published a larger work[6] presenting his observations and views in detail. In this work he describes more fully the forms already mentioned, and he notes the occurrence of segmenting forms, which, however, he interpreted as forms of degeneration, not of reproduction.

The observations of Laveran and of Richard were made by microscopical examination of the fresh blood. In 1883 and 1884, Marchiafava and Celli published in a number of articles the results of their studies of stained specimens of dried malarial blood. With the exception of small, spherical stained bodies in the red blood corpuscles, which they thought might be micrococci, they interpreted the various other stained and usually pigmented bodies found in the red corpuscles of malarial patients as probably degenerative changes. As a matter of fact, the coccus-like dots were probably in part Ehrlich's degenerations, whereas their drawings show that the supposed degenerative forms were in reality the actual parasites, which in many of their phases were accurately depicted, although not recognized as such.

In 1885, Councilman and Abbott in the organs from two cases of pernicious comatose fever found and described small pigmented hyaline bodies in and outside of red corpuscles, most abundantly in capillaries of the brain.

In 1885, Marchiafava and Celli, as the result of the examination of fresh malarial blood, came to a correct interpretation of these bodies and described them fully and accurately. They emphasized especially the amoeboid, unpigmented, transparent intracorpuscular bodies, to which they gave the

[6] Laveran: Traité des Fièvres palustres, Paris, 1884.

inaccurate name of plasmodia, which has been widely adopted. They described clearly the intracorpuscular development of the parasite, the formation of pigment out of the blood coloring matter, the consequent changes in the blood corpuscles, and they pointed out the probable reproductive nature of the segmenting bodies, which they described more fully and accurately than had been done by Laveran and Richard.[1]

The publications of Marchiafava and Celli attracted wider attention than had those of Laveran, and from the year 1885 up to the present time there has been a steady flowing stream of literature upon the various questions connected with the parasitology of malaria.

Immediately following the confirmation of Laveran's discoveries by Italian observers came similar confirmation from Sternberg, Councilman, and Osler (1886-87), and somewhat later by James (1888) and Dock (1890), in this country, and within a few years numerous reports from various parts of Europe, America, Asia, and Africa demonstrated the invariable association of Laveran's parasites with all cases of malarial fever. There are no observers of any prominence who, with sufficient opportunity and training for such examinations, have failed to recognize the parasites in cases of malaria, nor is there now any authoritative voice of dissent from the acceptance of the parasite as the specific cause of this disease.

Since the fundamental researches of Laveran, Richard, and Marchiafava and Celli (1880-85) other observers have greatly extended our knowledge as to many details concerning the structure and life history of the parasite and its relation to various types, phenomena, and lesions of malaria, although not a few important questions still remain unsettled. The most important of these later discoveries are due to the demonstration by Golgi (1885-86) of a definite relation between the cycle of development of the parasite and the different stages of malarial fever, and to the recognition by Golgi (1885-86) of the two varieties of the parasite belonging respectively to quartan and to tertian fever, and by Marchiafava and Celli and Canalis (1889) of the variety or varieties belonging to aestivo-autumnal fever. These observations have led to two schools of doctrine—the one, headed by Laveran, holding to the unity of a pleomorphic malarial parasite, the other, headed by Golgi and other Italian writers, upholding the plurality of malarial parasites. The latter doctrine has the larger number of supporters.

[1] Marchiafava and Celli claim for themselves the discovery of the intracorpuscular amoeboid forms with and without pigment, and of the segmenting forms, but as is apparent from the review of Laveran's and Richard's preceding publications, this claim cannot be admitted. Marchiafava and Celli, however, described and interpreted these phases of the parasite far better than Laveran, and to them belongs the credit of demonstrating the intracorpuscular development of the parasite.

Dock (1890-92) was the first to differentiate the three principal varieties of the malarial parasite in the United States, and recently Thayer and Hewetson[8] have published a thorough study of the malarial fevers of Baltimore with careful descriptions of these varieties.

Investigations concerning the intimate structure of the malarial parasites have been made especially by Celli and Guarnieri, Grassi and Feletti, Romanowsky, Sacharoff, Mannaberg, Antolisei, Bastianelli and Bignami, and others.

The results of these later studies concerning the malarial parasites will be considered in various parts of this article. They are fully and systematically presented in the recent monograph of Thayer and Hewetson, already cited.

NOMENCLATURE

Various names have been suggested for the malarial parasite. Among these may be mentioned *Oscillaria malariae* (Laveran), *Plasmodium malariae* (Marchiafava and Celli), *Haematomonas malariae* (Osler), *Haematophyllum malariae* (Metehnikoff), *Haemamoeba malariae* (Grassi and Feletti), *Haemococcidium malariae* (L. Pfeiffer), *Haemosporidium malariae* (Danilewsky), *Haematozoön* or *Haemocytozoön malariae* (Osler and various authors).

Of these names, *Plasmodium malariae* has gained wide currency, but it is on zoological grounds singularly inappropriate, and there is no reason why it should be perpetuated.

The name *Haemosporidium malariae* has much to recommend it, but it has not been generally adopted. Upon the whole, the name *Haematozoön malariae,* which expresses nothing as to the zoological classification of the parasite, and which has been adopted by many writers, may be provisionally accepted until more precise knowledge is reached concerning the zoological position of the parasite. Haemocytozoön is more precise, but the other term has the advantage of greater brevity.

ZOOLOGICAL POSITION OF THE MALARIAL PARASITE

The malarial parasite belongs to the class of Protozoa, under which name are grouped the unicellular organisms with the physiological characters of animals. Bütschli divides the Protozoa into the orders—Sarcodina, Mastigophora, Sporozoa, and Infusoria. Grassi and Feletti classify the malarial parasite among the Sarcodina, subdivision Rhizopoda, and adopt the name *Haemamoeba malariae.* Antolisei considers that the parasite belongs to the Gymnomyxa, or, more precisely, the Proteomyxa of Ray Lankester. The great majority of authors classify the malarial parasite among the Sporo-

[8] *Op. cit.*

zoa, which are divided by Balbiani into the groups Gregarinida, Sarcosporidia, Myxosporidia, and Microsporidia. Under the Gregarinidae are included the Coccidia, with which some writers group the malarial parasite. Kruse makes under the Gregarinidae a special family which he designates as Haemogregarinidae, and to which he refers the malarial parasite and similar haemocytozoa in lower animals. Danilewsky suggests forming a new group under the Sporozoa to be called Haemosporidia, in which he places the malarial and similar haematozoa, and Labbé calls the group Gymnosporidia.

As we know nothing of the malarial parasite in the outer world, it is evident that our knowledge of its life history is incomplete, so that any attempt at zoological classification must be regarded as only provisional. Such information as we possess favors classifying the parasite among the Sporozoa, but it possesses characters which do not enable us to fit it exactly into any of the existing subdivisions of the Sporozoa, so that the suggestions of Kruse and of Danilewsky of establishing a new subdivision of the Sporozoa or of the Gregarinidae to include the malarial parasite and similar organisms in birds seems to be a good one, and the name Haemosporidia for this new subdivision appears to be appropriate. According to this classification, the malarial parasite may be called *Haemosporidium malariae.*

METHODS OF INVESTIGATION

The methods for demonstrating and studying the malarial parasite will be described under the heading "Diagnosis." It may here be stated that generally the most useful procedure is the examination of thin layers of fresh blood with an oil-immersion objective. The description of the parasite which is to follow is based mainly upon this method. This procedure may be advantageously combined with the examination of stained specimens. For the study of the finer details of structure this latter method is indispensable.

GENERAL MORPHOLOGY AND BIOLOGY

The malarial parasite is a unicellular, protozoan organism which develops within the red blood corpuscles, and therefore belongs to the group of Haemocytozoa. As will be described subsequently, organisms closely resembling the malarial parasite have been found in the blood of birds. The numerous attempts to cultivate artificially the malarial parasite have hitherto been unsuccessful, nor has this organism been recognized in the outer world. Our entire knowledge of it is derived from its study in human beings.

Three varieties of the parasite have been differentiated. These varieties are that of quartan fever, that of tertian fever, and that of aestivo-autumnal

fever. This last variety it is proposed by the writer to call *Haematozoön malariae falciparum*. Before considering the justification of this division and the special characters of each of these varieties it is desirable to describe the more important characters common to all varieties of the malarial parasite.

The cycle of development of the malarial parasite embraces a vegetative and a reproductive phase. Its duration varies from 24 to 72 hours, according to the variety of parasite.

The vegetative phase begins in the form of small, colorless, amoeboid, hyaline bodies, 1-2 μ in diameter, within the red blood corpuscles.[9] These amoeboid bodies increase in size, and, with the occasional exception of the aestivo-autumnal variety, they develop within them a variable number of dark pigment granules, situated, as a rule, near the margin of the parasite. The pigment increases in amount and in the coarseness of the granules as the organisms continue to develop. It occurs in the form of irregular grains and of fine rods, which may be in active motion within the parasite.

Having attained a certain stage of development, which differs as regards the size of the organism in the different varieties, the parasite gradually ceases its amoeboid movements, assumes a spherical or oval shape, and becomes somewhat sharper in contour. In this condition it may continue for a while to grow. When it has reached its full size it may completely fill the red blood corpuscle or may occupy only a small part of it, these differences depending mainly upon the variety of parasite. The parasite now may be called the full-grown or adult form.

[9] As has already been mentioned, Laveran believes that the forms of the parasite which have, since the publications of Marchiafava and Celli, usually been regarded as within the red corpuscles, are attached or applied (accolés) to the outer surface of the corpuscles. Mannaberg (1893) has again raised this question by his statement that many of the amoeboid forms, particularly in their younger stages of development, are attached to the corpuscles, often in little niches or indentations on the surface. There is no doubt that the organism may be situated as described by Mannaberg. Marchiafava and Celli, who had previously noted this appearance, interpreted it as indicating the extrusion of the parasite from the red blood corpuscle. It is, in fact, often very difficult to determine with precision whether the organism is on the surface of or within the corpuscle, but the evidence is that the majority of the younger forms are intracorpuscular. Marchiafava and Bignami (1894) describe in the following words their conception of the manner of penetration of the youngest forms into the corpuscle: "The youngest amoebae, the offspring of sporulation, by virtue of the viscidity of their protoplasm adhere to the surface of, and by their movements bury themselves in, the contour of the red corpuscle. In this position the parasite attacks the external strata of the corpuscle as a means of nourishment, and after altering these layers is able to penetrate within, and thus becomes entirely endoglobular."

Coincidently with these stages of development the enveloping red blood corpuscle may undergo various changes, which are of significance in distinguishing the varieties of parasite from each other. The corpuscle may become swollen and pale, or shrunken, or brassy green in color, or otherwise deformed, or it may appear unaltered, as will be described in considering the varieties of the parasite.

The subsequent stages in this cycle of development belong to the reproductive phase, which is shorter in duration than the vegetative. The first evidence of this reproductive phase is the collection of the pigment into a mass of granules or a solid block situated usually at or near the centre, but sometimes near the periphery, of the organism. These bodies with clumps of pigment may be designated, in accordance with Thayer and Hewetson's suggestion, as the presegmenting forms (*corpi con blocchetto* of the Italian writers).

Coincidently with or following this gathering of the pigment into a clump, sometimes without a definite collection of the pigment, the process of segmentation begins. In its most typical form segmentation is ushered in by the appearance of delicate lines radiating from the periphery toward the centre. Eventually the substance of the spherical organism is divided into a variable number of round or oval bodies called spores. The enveloping red corpuscle, which now may be reduced to a narrow pale rim, bursts and the spores are set free, or the corpuscle may have disappeared before the process of segmentation is completed. The pigment remains behind, and is quickly engulfed by phagocytes. Sometimes in the aestivo-autumnal variety segmentation occurs in organisms entirely devoid of pigment. These segmenting bodies are called also sporulating forms.

The free spores speedily invade fresh red blood corpuscles, where, as the small, colorless, amoeboid, hyaline bodies already mentioned, they begin again the cycle of development. The direct transformation of the motionless[10] round spores into the small, hyaline, amoeboid bodies has been very rarely observed, but there is no reason to suppose that there exists any stage intervening between these two forms.

In the complete sporulating cycle of development which has been described we can distinguish, therefore, the following forms of the parasite: (1) unpigmented, amoeboid, hyaline bodies; (2) pigmented, amoeboid, hyaline bodies; (3) full-grown or adult bodies; (4) presegmenting bodies; (5) segmenting or sporulating bodies; and (6) spores.

[10] Plehn claims to have observed that the spores are actively motile and flagellated, but this statement is opposed to the observations of all others.

As already mentioned, in the aestivo-autumnal variety this cycle may be completed without the appearance of pigment. These bodies are to be thought of, not as separate and distinct forms, but simply as successive stages of development with all transitions from the youngest to the most advanced. Especially can no sharp distinction be drawn between bodies (1) and (2) and between bodies (3) and (4). The recognition, as a distinct form, of the body designated as presegmenting is of less practical importance for the quartan and tertian varieties than for the aestivo-autumnal.

The name "plasmodium" was applied by Marchiafava and Celli originally to the unpigmented, amoeboid forms. It is frequently employed to designate both the pigmented and the unpigmented amoeboid bodies, as well as the parasite in all of its forms. These amoeboid bodies may be called, in general, hyaline forms or amoebae.

As will be explained subsequently, it is only the quartan variety which is found in all its forms with equal frequency in the peripheral circulation and in the blood of internal organs; whereas segmenting tertian parasites are more abundant in the spleen and bone marrow than in the peripheral vessels, and the aestivo-autumnal parasite develops mainly in the internal organs, its segmenting forms being extremely rare in the peripheral circulation.

Each of the forms of the parasite which have been described as developing within the red blood corpuscles may also be found free in the plasma. They probably escape by rupture of the enveloping corpuscle, a process which one can often witness when examining the fresh blood microscopically. Extracorpuscular mature forms may possibly segment in the usual way, but there is no evidence that forms in the earlier stages may complete their cycle of development free in the plasma.

The important discovery was made by Golgi that all of one generation of the parasite form a group, the members of which develop approximately at the same time, and that a definite relation exists between the phases of development of the parasite and the stages of malarial fever. The onset of a paroxysm corresponds to the ripening of one generation of the parasite. A few hours or shortly before the paroxysm segmenting forms appear, and enable the observer to predict the approaching paroxysm. The spores which are set free by the act of sporulation invade the red blood corpuscles and start a fresh generation, which pursues during the paroxysm and the subsequent apyrexia so regular a development that in typical cases the experienced observer can tell approximately by examination of the blood the stage of the disease—that is, the time which has elapsed since the last paroxysm and the time when the next paroxysm may be expected.

It is not, however, always the case that the parasite develops with the regularity expressed by Golgi's law, and especially in the aestivo-autumnal fevers irregularities are very common. The simultaneous occurrence of two or more generations in different stages of development may render difficult the interpretation of the phases observed, although even here careful observation will enable the observer to draw correct conclusions in tertian and quartan fevers.

It has not been satisfactorily demonstrated that there occurs any other cycle of development of the malarial parasite in human beings than that which has been described, although the possibility of such an occurrence is by no means disproven. Canalis (1889) believes that he has found evidence that a second, slower cycle of development of the aestivo-autumnal parasite occurs, which is represented in certain of its phases by bodies of the crescentic group, to be described subsequently; and this view, with certain modifications, has been accepted by Golgi, Antolisei and Angelini, Grassi and Feletti, and Sacharoff. This doctrine is, however, opposed by many observers, and it does not at present rest upon sufficient evidence.

It seems necessary to suppose, on the basis of clinical evidence, that the malarial parasite may remain for months in a latent condition in the human body, and then begin to develop again, causing a relapse of the fever. As such relapses may occur in forms of malaria in which crescents do not appear, there must be in these cases some resistant organism other than bodies belonging to the group of crescents. We know nothing as to the nature of these resistant bodies. The hypothesis is advanced by Bignami that they may be spores which are enclosed within leucocytes and other cells, and which have become surrounded by a resistant membrane and have lost their usual staining properties.

Besides the forms which have already been described as representing phases of the regular sporulating cycle of development of the malarial parasite, there occur other forms which cannot at present be referred to any cycle of development. These other forms are—(1) crescentic bodies and fusiform, oval, and round bodies belonging to the same group; (2) flagellate bodies and free flagella; and (3) degenerative forms.

The crescentic and flagellate bodies, from their size and remarkable appearance, are the most striking forms of the parasite, and from the beginning have attracted much attention. Their significance, although there are many hypotheses concerning it, is not understood.

(1) The crescents develop only from the aestivo-autumnal parasites, and will therefore be described in connection with these. They are never formed from quartan and tertian parasites.

(2) *Flagellate bodies,* on the other hand, may form from each variety of the parasite, tertian, quartan, or aestivo-autumnal. The weight of evidence is that they do not exist in the circulating blood, but develop after the blood has been withdrawn from the body, usually within ten to twenty minutes, sometimes earlier. Some observers have found them frequently, others only rarely. They are frequently found if the blood is examined at the right stage of the disease and time is allowed for their development. Councilman showed that they are more commonly found in blood aspirated by a hypodermic needle from the spleen than in the peripheral blood. They develop in tertian and quartan fevers from the mature, full-grown extracorpuscular forms—in tertian especially from swollen forms larger than the red blood corpuscles. They are therefore found most frequently a short while before and during the paroxysm. In infections with the aestivo-autumnal parasite the flagellate bodies develop from round bodies belonging to the group of crescents, and do not occur in definite relation to the stage of the fever. Rarely intracorpuscular bodies may develop flagella.

The spherical bodies which become transformed into the flagellate bodies are always or nearly always pigmented. Marchiafava and Celli state that they once saw an unpigmented flagellate body. These bodies may be somewhat smaller or larger than the red blood corpuscles, the size varying to some extent with the different varieties of the parasite, as will be explained later. The process of development of the flagella may be studied under the microscope. The pigment granules, which at first (aestivo-autumnal variety) may have been in repose, usually begin to dance about within the organism, often in a lively way. In the aestivo-autumnal variety they usually gather in the central part, but in the others they may be near the periphery or irregularly distributed. The spherical body may acquire an oscillatory or jerking movement. Projections may be formed and retracted at the periphery, and the whole edge may acquire a vigorous undulating movement. These changes are attributed to the movements of the flagella within the body or in its peripheral layers, and have been graphically compared by Richard to the struggles of an animal to get free. Suddenly the flagella shoot out from the periphery, and with their active lashing movements produce a violent commotion among the red blood corpuscles and other small particles which may be in their neighborhood.

The flagella are pale and thin, and present often at their extremities and along their course small olive shaped swellings which may change their position. Here and there a pigment granule is occasionally seen in a flagellum. The flagella vary in size, number, and position. Their length may be three or four times the diameter of a red blood corpuscle or not more than half that size. One to six may be attached to the spherical body. They may project from one side or from any part of the circumference of the body.

Their movements may be somewhat rhythmical; they may become slow or even cease, and again start up.

Flagella may become detached and move about freely among the red blood corpuscles. On account of their pallor such free flagella would usually be overlooked were it not for the commotion which they produce among the red blood corpuscles. The motion of the flagella may be observed on the slide for half an hour, sometimes longer.

These flagellate bodies are the most startling forms of the malarial organism, and no one who sees them doubts for a moment that he is looking at a living parasite. It is not surprising that they attracted in an especial manner the attention of Laveran, who, as already mentioned, regarded the flagella as the most characteristic and perfect form of development of the parasite. Subsequent studies have not, however, tended to confirm the conception of Laveran as to their significance. As has already been made clear, the flagellated bodies do not belong to the regular sporulating cycle of development of the malarial parasite in the human blood. The most prominent theories as to their significance are the following:

(*a*) They are forms of degeneration or appearances belonging to the death agony of the parasite. In support of this view it is urged that the flagellate bodies do not belong to any known cycle of development; that they are developed only outside of the human body; that they are developed from mature forms which are known frequently to undergo undoubted degeneration, such as hydropic swelling, vacuolation, and fragmentation, and which may already show beginning evidences of degeneration; that nuclear substance is absent from the flagella; and that similar appearances of extrusion of motile filaments in other unicellular organisms are known to zoologists and are interpreted as degenerative.

(*b*) Sacharoff, from the study of their structure on stained specimens, believes that the flagella are extruded chromatin filaments derived from perverted karyokinetic nuclear division. He regards the process as degenerative.

(*c*) Dock suggests that the flagellate bodies "represent resting states of the organism, capable of existing independently, perhaps even of reproducing themselves, but also able, under favorable circumstances, of reproducing the typical growth of the parasite."

(*d*) Mannaberg's opinion is that the flagellate bodies may represent a state belonging to the saprophytic existence upon which the mature forms of the parasite enter soon after the blood is withdrawn from the body. On account of unsuitable conditions of environment they are unable to continue this existence in the blood outside of the body and soon perish. A similar view is advanced by Manson, who suggests that the flagellate bodies repre-

sent the first stage, and the detached flagella, in search of their appropriate host, represent the second stage of life of the parasite outside of the body. Manson [11] conjectures that the mosquito is the extracorporeal host of the malarial parasite, and he reports observations of Ross showing the development of flagellate forms in the stomach of mosquitoes fed on malarial blood.

There are arguments for and against each of these theories. Reluctant as one may be to consider such striking forms as the flagellate bodies as phases of degeneration, the existing evidence seems upon the whole to be more in favor of this hypothesis than of any other which has been advanced. Still, if Sacharoff's observation as to the presence of nuclear material in the flagella be correct, the objection of Grassi and Feletti, that the flagella are incapable of reproductive development because the nucleus of the parasite does not divide and enter them, would be overthrown and the hypothesis of Mannaberg and Manson would become more probable. It is evident from the description of these bodies that the use of the word "flagella" to designate the motile filaments is of doubtful propriety, but it is the term commonly employed.

(3) There are various bodies, often seen in the examination of malarial blood, which are undoubtedly *degenerative forms* of the parasite, and others which are probably degenerative, although opinions concerning the latter are divided. The more common signs of degeneration of the parasite are vacuolation, pseudo-gemmation, fragmentation, deformities of shape, particularly swelling, granular condition of the protoplasm, certain alterations in the arrangement and appearance of the pigment, disappearance of nuclear material, defects and irregularities in staining, and changes in the refraction of the organism. These various degenerative changes produce forms too numerous to describe in detail. They have often been misinterpreted and described as special forms of the parasite, some of them, particularly certain vacuolated and budding forms, as special modes of reproduction.

Degenerations may occur in any form of the parasite, but they are particularly common in the extracorpuscular forms. Mannaberg describes the disintegration of young intracorpuscular forms, with disappearance of their nuclei. Fragmentation of forms extruded from the blood corpuscles can sometimes be watched while examining fresh blood under the microscope. As a rule, only a certain number of the mature forms actually enter into reproductive segmentation, and many of the spores or segments perish. If all segmented and the offspring survived, the number of the parasites after a

[11] Manson: The Goulstonian Lectures on the Life History of the Malaria Germ Outside the Human Body (The British Medical Journal, 1896, March 14, 21, 28). Manson lays much emphasis upon supposed analogies between the malarial germ and *Filiaria sanguinis*. Only future investigations can determine the correctness of Manson's hypothesis.

few paroxysms would become enormous. As a matter of fact, degenerations of full-grown parasites are often observed. An interesting form of such degeneration, found most frequently in the mature forms of the tertian variety, is the appearance of swollen, pigmented, so-called hydropic bodies, often much larger than red blood corpuscles, and sometimes containing vacuoles. Round bodies simulating spores are sometimes seen in these vacuoles, but on properly stained specimens they are devoid of the nuclear material of genuine spores. Pseudo-gemmation, or the appearance of sarcodic buds on the surface of the organisms, is doubtless a form of degeneration. Such buds may become separated, in the form of hyaline balls, from the parent organism. These evidences of degeneration may appear also in crescents and bodies belonging to this group and in flagellate bodies. From the latter small hyaline balls with a flagellum attached may break off and move around actively. Such bodies might be mistaken for flagellated spores.

There is no good evidence that the malarial parasite ever multiplies by budding [12] or by simple cell division. The only form of multiplication which has been demonstrated is that of sporulation, also called segmentation, already described, although it cannot be denied that other forms of reproduction may exist.

Various interesting degenerative changes are produced by the influence of quinine. These will be fully described under TREATMENT, *Action of Quinine on Malarial Parasites* (page 146, Vol. I, Syst. Pract. M. [Loomis] 1897).

As the malarial parasite passes its vegetative life mostly within the red blood corpuscles, it is evident that it finds its food in this situation. This food may be appropriated both by intussusception and by diffusion. Evidence of intussusception is found in the occasional presence of fragments of the corpuscular substance within the body of the amoeboid forms. Doubtless diffusion is the more important mode of nutrition of the parasite.

The question has been raised whether the parasite may develop in other cells of the body than the red blood corpuscles. Nearly all forms of the parasite have been found enclosed in cells, chiefly leucocytes, splenic or medullary cells, and endothelial cells. As such included parasites often present evidences of degeneration, these appearances have been generally interpreted as referable to phagocytic destruction of the parasites, and such they unquestionably usually are. Golgi and Monti have, however, recently

[12] Celli and Guarnieri for a time believed that spherical bodies of the crescentic phase may multiply by the formation of buds (gemmation), but they subsequently abandoned this view and adopted the now generally accepted opinion that these budding forms are degenerative. The "buds" are now devoid of the structure of genuine spores.

published observations intended to show that the aestivo-autumnal parasite may develop within endothelial and other cells, as will be explained in considering this variety of parasite.

The malarial parasite in the condition in which it exists in the human body is very susceptible to injurious agencies. It is quickly killed by the addition of distilled water and of dilute acids and alkalies. Under ordinary conditions it does not long survive in blood withdrawn from the body. Under certain special circumstances it has been kept apparently alive from two to four days, possibly for a week. Sacharoff observed amoeboid movements in aestivo-autumnal hyaline bodies which had been for a week in the intestinal canal of leeches kept on ice, and he obtained a positive result by inoculating himself with malarial blood preserved in this way for four days in leeches. The tertian and quartan parasites were found to be less resistant than the aestivo-autumnal. Ripe bodies may segment in blood outside of the body, but no further development or multiplication of the parasites has been positively observed in the various attempts made to preserve or cultivate them. The parasite does not continue to develop and multiply in the human body after death.

Of course no inferences can be drawn from these observations as to the resistance of the parasite in its natural condition in the outer world. As to what this natural condition is we can only speculate. Grassi and Calandruccio have thought that certain species of amoebae which they have observed in malarial districts might be the extraparasitic form. The failure of artificial cultivations and certain analogies drawn from the zoological characters of the parasite have led to the prevalent theory that the malarial parasite passes at least a part of its existence as a parasite in animal or vegetable organisms. Mention has already been made of Manson's hypothesis that the mosquito may be a host for the malarial parasite. That the germ is capable of entering upon some resistant phase of development seems highly probable in view of the evidence that malaria can be contracted from the air. There is no evidence that the malarial parasite is eliminated from the human body in a condition capable of infecting another individual or the locality. The disease, however, can be transmitted by inoculating into healthy individuals, either subcutaneously or intravenously, blood from a malarial patient.

UNITY OR PLURALITY OF THE MALARIAL PARASITE

As has already been mentioned, there are two schools of doctrine as to the malarial parasite—the one led by Laveran holding that the malarial parasite is a single species with pleomorphic characters, the other believing that there are three or more species, or at least varieties, of malarial parasites.

The observations upon which the latter doctrine is based originated with the Italians, and have been supported by investigations in this country and elsewhere.

Golgi in 1885 and 1886 first differentiated the parasite of quartan fever from that of tertian fever, and Marchiafava and Celli and Canalis in 1889 and 1890 differentiated the variety of parasite characteristic of aestivo-autumnal fever.[13] There is much difference of opinion as to the number of aestivo-autumnal parasites. All adherents of the doctrine of plurality agree that there are at least three varieties of malarial parasite—namely, the quartan, the tertian, and the aestivo-autumnal—distinguished from each other by morphological and biological characters to be subsequently described. The discovery by Golgi of the definite cycle of development of the malarial parasite and the recognition of several distinct varieties have done much to bring order out of the earlier chaotic condition when a multitude of parasitic bodies were described without knowledge of their significance or relations to each other. There remain, however, many unsolved problems which it may be expected that further investigations will clear up.

In opposition to the doctrine of plurality it is urged by Laveran that all of the so-called varieties of the parasite may be explained simply as phases of a single pleomorphic organism influenced by various conditions of environment, such as locality, season, individual predisposition, and various unknown circumstances. He contends that the characters upon which a

[13] Marchiafava and Celli on the one hand, and Canalis on the other hand, have conducted a polemic as to which of them belongs the credit of first distinguishing the aestivo-autumnal parasite. The differentiation of this parasite was not made all at once, and with the same precision in all details, as in the case of Golgi's sharp separation of the quartan and tertian parasites. Golgi from the beginning of his researches (1885-86) suggested that the crescentic bodies belong to a special cycle of existence different from that of the tertian and quartan organisms, and noted their occurrence in irregular malarial fevers. Councilman in 1887 emphasized the association of crescents with remittent fevers and malarial cachexia. Golgi in February, 1889, definitely expressed the opinion that in addition to the malarial fevers caused by the quartan and the tertian parasites we must recognize another type of fever associated with unpigmented amoeboid forms and crescents. On September 13, 1889, appeared a preliminary communication of Marchiafava and Celli, which must be regarded as furnishing the first clear and sharp description of the essential differential characters of the aestivo-autumnal parasite, with especial emphasis on the occurrence of unpigmented organisms. On October 10, 1889, appeared the preliminary communication of Canalis, in which likewise the essential characters of this parasite were discribed, and greater emphasis was laid upon its relation to the crescents than had been done by Marchiafava and Celli. The full publication of Canalis anticipated by a short time the complete article of Marchiafava and Celli on the aestivo-autumnal parasite.

division into separate varieties is based are insufficient for such a purpose and inconstant; that one so-called variety under certain conditions may be transformed into another; and that there is no definite, necessary relation between the types of fever, such as quartan, tertian, quotidian, irregular, continued, and the form of parasite present. The variations of the malarial parasite can be explained, he thinks, in large part by the varying rapidity of development. He emphasises the view that malaria with all its diverse manifestations is nevertheless clinically and anatomically one disease, and has always been so regarded. He argues that the experimental production of malaria by inoculation does not support the doctrine of plurality.

In considering the force of these objections it must be admitted that so long as we are unable to cultivate the malarial parasite artificially, and are ignorant of its life history and the conditions of existence outside of the human body, the possibility must be admitted that under certain conditions, at present unknown, one variety may be transformed into another. But, on the other hand, the existing evidence—and it is already considerable—goes to show that under the conditions which we can at present control and study each of the three principal varieties of the parasite preserves its identity and is not transformed into another variety; that is to say, there is no evidence that a quartan parasite ever becomes metamorphosed into a tertian, or either of these into an aestivo-autumnal parasite.

The principal arguments in support of this doctrine of plurality may be summarized as follows:

(1) Each well-established variety of parasite presents morphological and biological characters which suffice for its identification.

(2) Each variety of parasite corresponds to definite types of fever. Genuine quartan fever can be produced only by the quartan parasite. As will be explained in the clinical part of this article, other types of fever may be caused by more than one variety of parasite, and much complexity may result from multiple and mixed infections and various irregularities; but all of this does not prevent the recognition of certain fundamental types of fever especially characteristic of each variety of the parasite.

(3) Cases of pure infection with one variety of parasite have been carefully studied for weeks and months without any indication of the transformation of one variety into another (Calandruccio, Grassi and Feletti). Opportunities for such study are exceptional. The appearance of a second variety of parasite in localities where there is opportunity for renewed infection cannot of course be interpreted in favor of the metamorphosis of one variety into another.

(4) In certain localities only one or two of the varieties of the parasite are met with. In a few places only the quartan, or more frequently only the

tertian, parasite is observed; in most places where malaria is mild and infrequent only tertian, and occasionally quartan, parasites, with entire absence of aestivo-autumnal parasites, are found. Instances of this localized distribution of the parasites, which manifestly is a strong argument in favor of the doctrine of plurality, will be subsequently mentioned (page 99, Vol. I, "Syst. Pract. M." [Loomis], 1897).

(5) Strong arguments in favor of the constancy of the varieties of the malarial parasite are furnished by the experimental production of malaria. Gerhardt in 1882 and 1883 (reported in 1884) was the first to produce malaria experimentally by the subcutaneous injection of blood obtained from malarial patients. At this time the malarial organism was not generally recognized. Since these first experiments similar ones have been repeated, usually in the manner of intravenous injections of malarial blood, with positive result in over thirty cases. The experiments before 1889 were made without determination of the exact variety of parasite injected and found in the experimental case. In 1889, Gualdi and Antolisei, without full knowledge of the critical nature of the experiment, injected two patients intravenously with 3 c. c. of blood from a patient suffering with quartan fever and possessing quartan parasites. In each of the inoculated individuals irregular fever with aestivo-autumnal parasites developed. These two cases are constantly adduced as a main support of the doctrine of mutability of the varieties of the parasite, but unjustly so, for it was subsequently determined that the patient from whom the blood was obtained had previously suffered from irregular fever, and he subsequently developed characteristic aestivo-autumnal organisms, so that the experimenters themselves later expressed the opinion that at the time of the inoculation the patient furnishing the blood had combined quartan and aestivo-autumnal organisms, the latter being overlooked. In view of the uniform results yielded by the numerous subsequent experiments in support of the doctrine of immutability of the varieties of the parasite there can be little doubt that this later opinion of Gualdi and Antolisei is correct. It has been found regularly since these experiments that if blood containing only the tertian or the quartan or the aestivo-autumnal parasite be injected intravenously into a person unaffected with malaria, the variety of parasite injected, and only that variety, appears in the blood of the experimental case. When two varieties of parasite are injected, or when the malarial blood is injected into a patient already affected with a malarial organism other than that injected, then it usually happens that one variety supplants the other, most frequently the one injected supplanting that already existing in the inoculated individual. For such displacement of one organism by another we have numerous examples in bacterial infections.

The bearing of the inoculation experiments upon the determination of the periods of incubation of malaria will be considered in the clinical part of this article (pages 97, 98, Vol. I, " Syst. Pract. M." [Loomis], 1897).

These already numerous inoculation experiments, showing the identity of the parasite in the experimental case with that in the blood used for injection, furnish the strongest existing arguments in favor of the plurality of the malarial parasites.[14]

Whether accepting this doctrine, we shall designate the different types of the malarial organism as separate species or separate varieties is with our present knowledge a matter of secondary importance and of individual judgment. If it be admitted that under no existing circumstances one type is transformed into another, then we are justified in speaking of separate species of malarial parasites. As at present we can study only a small part of the conditions which surround the entire life-history of the parasite, it seems to the writer preferable to designate the different types as varieties rather than species.

CLASSIFICATION

We have already had occasion repeatedly to mention the division of the malarial parasites into three principal varieties—the quartan, the tertian, and the aestivo-autumnal. No further subdivisions of the quartan variety has ever been suggested. Nor has any attempt been made to subdivide the tertian parasite originally described by Golgi; but, as it has since been found that the aestivo-autumnal parasite—or, according to some observers, one form of this parasite—may likewise produce tertian fever, the latter form of the aestivo-autumnal organism is designated by Marchiafava and Bignami as malignant tertian or aestivo-autumnal (summer-autumn) tertian, and the former called mild or vernal (spring) or genuine tertian or Golgi's tertian parasite. This so-called aestivo-autumnal or malignant tertian is, however, in no sense a subdivision of the tertian parasite originally described by Golgi, which remains a well-differentiated, separate variety. When the name " tertian organism " is used without any epithet, it is always this variety which is meant.

The name " parasite of aestivo-autumnal fever," introduced by Marchiafava and Celli and already adopted by many writers, leaves much to be desired. It is intended to indicate that this form of the parasite is the cause of the malarial fevers prevailing in summer and autumn. This application, however, is correct only for certain localities, chiefly those warmer regions where severe as well as mild types of malaria occur. In localities

[14] Di Mattei: Contributo. allo Studio della Infezione Malarica Sperimentale nell' Uomo e negli Animali, Arch. per le Scienze Mediche, XIX, N. 4, 1895.

where the prevailing type of the disease is mild at all seasons the summer and autumn malarial fevers are caused generally or exclusively by tertian or quartan parasites. Even in the warmer situations where the aestivo-autumnal parasite is common, not all of the summer-autumn fevers are caused by this parasite, but often a large proportion are caused by the ordinary tertian parasites. In subtropical and tropical regions the aestivo-autumnal parasites may occur in winter and spring fevers. It is evident that the epithet "aestivo-autumnal," as applied to a special variety of malarial parasite, is sufficiently designative for many localities, as, for example, the southern parts of the United States and Central and Southern Italy, but it is not so for all.

The term "parasite of aestivo-autumnal fever" does not at once suggest the relation of the parasite to a definite type of malarial fever, and is therefore out of harmony with the designations "parasite of quartan fever" and "parasite of tertian fever." But it is characteristic of a large proportion of the fevers caused by aestivo-autumnal organisms that they do not correspond to any definite type, but are notably irregular. Hence these organisms were designated by Golgi and by Sacharoff as the "parasite of irregular malarial fevers." But the objection to this latter name is that aestivo-autumnal organisms may cause typical quotidian and tertian fevers. Indeed, this is the only form of malarial parasite which, it is believed, may complete its cycle of development in twenty-four hours, and thus when present in only a single group or generation may cause quotidian fever.

As leading characters of the aestivo-autumnal organisms are their small size, their slight formation of pigment, and the ring-like shape of the amoeboid forms, they are sometimes spoken of as the small malarial organisms (*forme piccole*), or the unpigmented, colorless, or slightly pigmented organisms, or the ring-like annular organisms. They are also called the organisms of grave or pernicious malaria, although they may likewise cause mild types of the disease.

As it is to the group of aestivo-autumnal parasites that the crescents exclusively belong, these parasites have been described as the semi-lunar variety. They may be designated as crescent-producing. *Haematozoön falciparum* is suggested by the writer as a suitable technical name for this variety of parasite.[15]

[15] The name *Haematozoön falciforme* suggested by Antolisei and Angelini is objectionable, as it implies that the shape is always falciform, and is applicable only to the crescentic forms. The adjective "falciparum" (*falx*, "sickle," *parire*, "to bring forth," "to produce"), on the other hand, indicates that the property of forming crescents is a distinctive character of the organism, and it is therefore applicable to the variety of the parasite which possesses exclusively this property.

The three varieties of the malarial parasite may therefore be technically designated—(1) *Haematozoön febris quartanae;* (2) *Haematozoön febris tertianae;* (3) *Haematozoön malariae falciparum.* The name aestivo-autumnal parasite, as the more commonly used and generally understood designation, will, however, continue to be used, as well as the term "*Haematozoön falciparum,*" in this article for the last named variety.

There is no difference of opinion, except among the unicists, that the aestivo-autumnal organisms form a variety or group which is to be differentiated from both the quartan and the tertian organisms even more sharply than the tertian and the quartan are differentiated from each other. But the question as to the unity or the plurality of the aestivo-autumnal organisms is still an open one, and is the most important unsolved problem relating to the divisions of malarial parasites. Its solution is attended with unusual difficulties, but we may reasonably expect that they will be surmounted by future investigations.

In distinction from the quartan and the tertian organisms the aestivo-autumnal are often irregular and atypical in their cycle of development. Some, it is believed, may complete their cycle in twenty-four hours, others in forty-eight or a longer period: their tendency to develop simultaneously in well defined generations is far less marked than is the case with tertian and quartan organisms, so that several or all phases of development of aestivo-autumnal forms may be observed in the internal organs at the same time. The occurrence of multiple groups of the parasite is common. Forms appear which pass through their amoeboid, mature, and segmenting phases without any formation of pigment within the parasite. The development takes place largely in the internal organs. The development of crescents occurs at a variable period after the onset of the disease, but rarely in less than a week. Corresponding to these variations and irregularities the types of fever with which aestivo-autumnal organisms are associated are various and irregular.

The attempt has been made to deduce certain laws controlling these variations and apparent irregularities, and to subdivide the aestivo-autumnal organisms into certain varieties or subvarieties, but there is little agreement of opinion as to this subdivision.

The following are the principal divisions of the malarial parasite which have been proposed, the essential differences in these various divisions relating, of course, to the different views held concerning the aestivo-autumnal organisms:

I. Marchiafava and Celli (1889) recognized a short cycle of development of the aestivo-autumnal parasite, unaccompanied by development of pigment, and a longer cycle with formation of a few pigment granules. Mar-

chiafava and Bignami (1891) make two varieties of this parasite—viz. the amoeba of aestivo-autumnal quotidian, with twenty-four-hour cycle, and the amoeba of aestivo-autumnal tertian, with a forty-eight-hour cycle—*Amoeba febris quotidianae* and *Amoeba febris tertinae aestivo-autumnalis.* The latter variety is the malignant tertian organism of these authors. The main differences between these varieties, according to Marchiafava and Bignami, relate to the length of the cycle of development, but there are claimed to be also minor morphological and biological differences to be mentioned subsequently (pp. 503 and 504).

These authors, therefore, make four different varieties of the malarial parasite. They divide the malarial fevers into two main groups:

1. Mild malarial fevers which prevail in winter and spring. These are—

(*a*) Quartan fever (with its varieties of double and triple quartan). This caused by the *Amoeba febris quartanae* (Golgi), which completes its life cycle in seventy-two hours.

(*b*) Tertian fever (with double tertian and rarely certain subcontinued fevers). This is caused by the *Amoeba febris tertianae* (Golgi), which completes its life cycle in forty-eight hours.

2. Severe or aestivo-autumnal fevers, including the pernicious and most of the subcontinued fevers. This group comprises—

(*a*) Aestivo-autumnal quotidian fever (to be distinguished from quotidians of tertian and of quartan origin), caused by the *Amoeba febris quotidianae,* which completes its cycle in twenty-four hours. This is the only variety of malarial parasite which can complete its life cycle in so short a period as twenty-four hours.

(*b*) Aestivo-autumnal or malignant tertian fever, caused by the *Amoeba febris tertianae aestivo-autumnalis,* which completes its cycle in forty-eight hours. Most of the pernicious cases belong to this variety, the remainder to the aestivo-autumnal quotidian variety.

II. Canalis (1889) does not subdivide into varieties the aestivo-autumnal parasite, which he calls the "semilunar variety," but he considers that it has two cycles of development: (*a*) a rapid cycle with the usual phases of amoeboid, mature, segmenting forms and spores, and (*b*) a slower cycle associated with the development of crescentic bodies, which he considers to be reproductive and to represent one phase in this second cycle. A similar view is held by Antolisei and Angelini.

III. Grassi and Feletti (1890) regard the crescent-producing forms as an entirely separate species, which they call *Laverania malariae,* and which they distinguish both from the directly spore-forming unpigmented aestivo-autumnal forms, which they call *Haemamoeba immaculata* and from similar

rapidly developing, but pigmented, aestivo-autumnal parasites, without crescents, which they call *Haemamoeba praecox.* Their classification of the malarial parasite is as follows: (*a*) *Haemamoeba malariae,* identical with the quartan parasite; (*b*) *Haemamoeba vivax,* which is identical with the tertian parasite of Golgi; (*c*) *Haemamoeba praecox,* a form of the aestivo autumnal parasite, giving rise to quotidian fever; (*d*) *Haemamoeba immaculata,* similar to the preceding, but without development of pigment; (*e*) *Laverania malariae,* the crescent-producing variety, giving rise to irregular fevers.

Sacharoff formerly regarded the crescents as belonging to a separate species of malarial parasite, and adopted the following classification: (*a*) *Haemamoeba febris quartanae* (Golgi), (*b*) *Haemamoeba febris tertianae* (Golgi), (*c*) *Haemamoeba praecox* (Grassi), (*d*) *Laverania* (Grassi). Recently (1896) he holds that all variations of the aestivo-autumnal parasite are modifications of a single variety due, mainly, to the development of the parasite within nucleated red blood corpuscles.

IV. Mannaberg (1893) accepts Marchiafava and Bignami's division of aestivo-autumnal parasites into quotidian and tertian, and also adopts Grassi and Feletti's division into pigmented and unpigmented quotidian parasites. He does not, however, consider the crescents as belonging to a species or variety distinct from these, but considers them as developing from each of these three divisions of aestivo-autumnal parasites. He has a peculiar view as to the origin of the crescents from conjugation of cells, and regards them, therefore, as forms of syzygia. He divides the malarial parasites into two groups—the *first group,* with sporulation and without syzygia, comprising (*a*) the quartan and (*b*) the tertian parasites of Golgi; the *second group,* with sporulation and with syzygia, comprising (*a*) the pigmented quotidian parasite, (*b*) the unpigmented quotidian parasite, and (*c*) the malignant tertian parasite.

V. Golgi (1893), an admirable and successful investigator of the malarial parasites, does not consider the semilunar forms as belonging to a species or variety distinct from the ordinary sporulating aestivo-autumnal parasite, He attempts no subdivision of the aestivo-autumnal parasite. His conception of the mode of development of this parasite differs in essential points from that of Marchiafava and Bignami and of most other investigators, as will be explained in considering the special characters of the aestivo-autumnal parasite.

The following statement of Golgi's classification of the malarial fevers is quoted from Thayer and Hewetson's work on "The Malarial Fevers of

Baltimore," already cited.[16] Golgi divides the malarial fevers into two groups:

(1) Fevers the pathogensis of which is connected with parasites which have their principal habitat in the circulating blood where, by preference, they accomplish the phases of their cycle of existence.

(2) Fevers the pathogenesis of which is connected with parasites which have their chief seats in the internal organs, particularly the bone marrow and the spleen, where, by preference, they accomplish their cycle of existence in conditions of relative stability.

(1) The fevers of the first group are unquestionably associated with different species or varieties of the parasite—viz. (*a*) the quartan parasite; (*b*) the tertian parasite.

(2) "To the second group belong the fevers which appear clinically under multiform types, very often irregular, of which for the present it is impossible to make a grouping based upon an ascertained biology or cycle of development of the parasite. . . . . We are dealing in these cases with generations of parasites which, occurring in the parenchyma of organs in different stages of development, give origin, at periods of a certain regularity or in a more or less continuous succession, to colonies of young forms which, in large or small numbers or in insignificant quantity, may escape into the blood current, permitting one to discover by microscopical examination of the blood the presence of the small endoglobular amoebae." Golgi refers to the crescents as "forms the biology of which has not yet been well determined."

VI. Thayer and Hewetson (1895) were likewise unable to confirm Marchiafava and Bignami's subdivision of the aestivo-autumnal parasite into a quotidian and a tertian variety. They say: "We have been unable to trace a constant length of the cycle of development, and we have been unable further to separate two or more types of the [aestivo-autumnal] parasite depending either upon the length of the cycle of development or upon any other morphological or biological differences. We believe that the length of the cycle varies greatly in different cases, lasting usually from twenty-four hours, or even a little less, to forty-eight hours or more. After the infection is five days or a week old certain of the organisms, instead of segmenting, pursue a further growth, developing into the hyaline, refractive, ovoid, and crescentic bodies." They do not feel justified in making any positive statement as to the significance or capacity of reproductive development of the crescentic bodies.

[16] The writer wishes to acknowledge his indebtedness to this excellent monograph for much valuable assistance in the preparation of this article.

The question has been raised whether in tropical regions, where pernicious types of malaria are common, any form of malarial parasite different from those already mentioned occurs. The observations of Vandyke Carter, Dock, van der Scheer, Plehn, and others show that the same parasites are found in India, Panama, Java, and other tropical countries as elsewhere. The negative reports which have been published are referable doubtless to insufficient training in such examinations on the part of the observers. The fact that a large part of the tropical malarial fevers are caused by aestivo-autumnal organisms which appear in the red blood corpuscles as small, pale, feebly staining, delicate, diaphanous, often unpigmented amoeboid rings of hyaline protoplasm, difficult to detect in many cases, and sometimes scanty or at times even absent, will account for many of these negative observations.

The singular distribution of the haemoglobinuric type of pernicious malarial fevers in certain definite localities suggests the possibility that this may be caused by a special type of organism. The sporadic cases of malarial haemoglobinuria examined in Italy have shown, however, ordinary aestivo-autumnal organisms. Plehn [17] found in cases of black-water fever occurring on the West Coast of Africa small, annular amoeboid forms, staining with great difficulty and never pigmented, in the red blood corpuscles. "Out of the amoeba there develops by thickening of the peripheral zone an oval or egg-shaped body, with well staining double contour. In course of time this divides into five or six small oval forms, staining at one pole, which, when they are set free, move about with great rapidity in the blood. These probably develop into the amoeboid forms." The organism never attained a size larger than one-quarter of the red blood corpuscle. Crescents were occasionally found. Plehn seems to regard this organism as allied to, but not identical with, the aestivo-autumnal parasite described by Italian writers. Although his description presents certain peculiarities of the parasite which he observed in the pernicious malarial haemoglobinuria and other pernicious fevers of the West Coast of Africa, especially the constant absence of pigment, the extremely small size, the sporulation in the blood, and the apparently motile spores,[18] nevertheless it is not sufficiently complete and satisfactory to justify the inference that the organism differs from forms of the ordinary aestivo-autumnal parasite as previously observed.

From the preceding review of the various investigations and opinions concerning the divisions of varieties of the malarial parasite, especially of the

[17] Plehn: Ueber das Schwarzwasserfieber an der afrikanischen Westküste, Deutsche med. Wochenschrift, 1895, Nos. 25, 26, 27.

[18] It may here be mentioned that Plehn considers that the spores of all varieties of the malarial parasite are flagellated—a view which has not been confirmed by other observers.

aestivo-autumnal form, we may draw the conclusion that whereas the separation into quartan, tertian, and aestivo-autumnal varieties rests upon a sound basis of fact, the various attempts to further subdivide the aestivo-autumnal group have not as yet been sufficiently successful to justify our acceptance at the present time of any of these subdivisions. There is, however, some reason to believe that this last group, as at present constituted, may comprise varieties which will hereafter be satisfactorily differentiated from each other.

We will now consider the special characters of each of the three varieties of the malarial parasite.

1. THE PARASITE OF QUARTAN FEVER (*HAEMATOZOÖN FEBRIS QUARTANAE*)

In most malarial regions this is the rarest form of the malarial parasite, but there are certain places (none of these have been recognized in this country) where it is the prevailing variety. Being particularly common in the neighborhood of Pavia in Italy, the quartan parasite was the first to be differentiated and described by Golgi (1885-86), to whose masterly description nothing of essential importance has been added by subsequent investigators, with the exception of certain details of intimate structure.

The quartan parasite completes its cycle of development in seventy-two hours and entirely within the circulating blood. The youngest forms of the parasite are small, amoeboid, when at rest discordial, hyaline bodies, within the red blood corpuscles. They are about one-fifth to one-fourth the size of the red blood corpuscles. The central part of the body may appear paler than the peripheral. These unpigmented, youngest forms are found during and for several hours after the paroxysm; they may begin to appear two hours before the paroxysm. The very earliest forms are not to be distinguished from the youngest tertian parasites, but as they begin to develop they present a sharper outline and somewhat more refractive appearance, and their amoeboid movements are more sluggish and restricted than those of the corresponding stages of the tertian organism. These movements become more active on the warm stage of the microscope. The presence of more than one parasite in a red blood corpuscle is sometimes observed.

Shortly, or within twelve to eighteen hours, after the paroxysm pigment granules appear within these hyaline bodies, which continue to increase slowly in size, and for a while to exhibit lazy amoeboid movements. The pigment appears in the form of brownish or black rods and grains, which are coarser and darker than those seen in tertian parasites. The rod form of pigment is less common than in the tertian organism. These pigment granules are arranged generally in the peripheral part of the parasite, and they present only a sluggish movement in comparison with the active motion

of the pigment in the tertian parasite. With the gradual increase in size of the hyaline bodies and in the amount of contained pigment the red blood-corpuscles enclosing them may appear unchanged, or often they become a little smaller, more refractive, and deeper in color, which may be somewhat greenish or coppery in tint. There is not that tendency to decolorization and swelling of the infected red blood corpuscles which is noticed in the case of the tertian parasite, although in the more advanced stages of development there is usually some loss of color in red corpuscles containing quartan organisms.

In the process of development the amoeboid movements cease, and the parasite appears as a quiescent, pigmented, spherical, or ovoid body occupying perhaps one-half to two-thirds of the red corpuscles. Such bodies are usually seen within forty-eight hours after the paroxysm. These bodies continue to grow, and when they have reached their full development in sixty to seventy hours after the paroxysm they are somewhat smaller than the normal red blood corpuscles. These full-grown forms are spherical or ovoid, refractive, hyaline bodies, with nearly or quite motionless dark pigment granules of variable size, but coarser than in the tertian parasite, and with a tendency to peripheral arrangement, but at times irregularly distributed. Around these bodies a thin layer of the colored, refractive substance of the red blood corpuscle can usually still be seen, or the haemoglobin may be entirely removed, so that only a delicate, thin, colorless rim or line surrounding the parasite is all that is left of the original red blood corpuscle. In unstained specimens these latter forms often appear to be free in the plasma, and are sometimes spoken of as free bodies, which may also occur.

In six or eight to ten hours before the febrile paroxysm the first phases of reproduction begin to appear. These are ushered in by the gradual withdrawal of the pigment from the periphery toward the centre of the body. The pigment in this process is often arranged in definite radial striae. Such regular stellate arrangements of the pigment as are seen in this stage of the quartan parasite are rarely, if ever, observed in the tertian (Thayer and Hewetson). Finally the pigment is concentrated into a central mass of granules or a solid block of coalesced pigment, less frequently into two or more collections, and the organisms assume a somewhat more refractive and slightly granular appearance.

At the same time or soon afterward radial divisional striae begin to appear in the periphery, and quickly extend to the central part of the parasite, whereby the substance of the spherical organism becomes divided into six to twelve ovoid or pear-shaped segments arranged with characteristic and exquisite regularity around the central mass of pigment like the petals of a daisy (rosettes of Golgi). In each of the segments can be seen a small round

glistening body which represents the nucleus or nuclear material. The pyriform segments assume rapidly a round or oval shape, and become separated from the central mass and from each other. The delicate enveloping membrane, which may not be recognized on unstained specimens, derived from the red blood corpuscle ruptures, or it may previously have disappeared, and the small round or oval bodies, each provided with a bright nucleiform dot, are set free in the plasma. These bodies are the so-called spores. Simultaneously with this process of sporulation young amoeboid hyaline bodies, formed directly from the spores, make their appearance in the red blood corpuscles, and the cycle of development is completed and another cycle is begun.

Segmenting or sporulating forms of the parasite may appear six or eight hours before the paroxysm, and are most abundant shortly before and during the onset of the paroxysm. It is of course not to be understood that all of the parasites of one group pass through their developmental phases and mature at exactly the same moment. One parasite of the group may be several hours in advance of another, but this does not interfere with the recognition of distinct groups or generations, each standing in definite relation to a paroxysm, or with the establishment of Golgi's law that the onset of each paroxysm corresponds to the maturation of one group of organisms.

The cycle of development of the quartan parasite it attended with fewer irregularities than that of any other variety of the malarial parasite. Nevertheless, certain irregularities may occur. As pointed out by Antolisei, segmentation may occur exceptionally in pigmented bodies considerably smaller than the usual full-grown forms, containing less pigment and filling only a part of the red blood corpuscle. Here the segments do not usually exceed four to six or eight. The accumulation of pigment in the segmenting forms may be peripheral, or distributed between the spores, or otherwise irregular.

As the quartan parasite completes its development entirely within the circulating blood, there is no appreciable difference at any stage between the splenic and the peripheral blood as regards the number and variety of the parasitic forms observed. Moreover segmenting forms of the quartan parasite are often seen in small number in the blood at a period before the total number of organisms is sufficiently large to produce by their ripening a paroxysm, whereas segmenting tertian parasites are very rarely seen in the peripheral blood without the occurrence of a paroxysm in relation to the segmenting forms.

Not all of the mature forms proceed to sporulation. Some, especially those which may have escaped from the red corpuscles, swell up, become transparent and larger than a red blood corpuscle, and present irregularly distributed and actively moving pigment granules. These swollen, hydropic

forms are probably sterile. It can often be seen in examining these bodies in fresh blood that the pigment becomes quiescent, the outlines of the body become irregular and indistinct, and evidently cadaveric forms result. Or these bodies may break up into a number of fragments which become misshapen and indistinct, or the whole body may become vacuolated. Bodies more or less resembling spores, but without the nuclear structure of spores, may appear in these vacuoles.

As may occur with any variety of the malarial parasite, the mature forms of the quartan parasite, instead of sporulating, may develop into flagellate bodies in the manner already described. These bodies are smaller and contain coarser pigment than the flagellate forms of the tertian parasite. Degenerated and flagellate forms are less common in quartan than in tertian infections.

Not only may mature forms degenerate in the ways described, but forms in earlier stages of development may be liberated from the red corpuscles and likewise degenerate.

The phenomena of phagocytosis are observed with regularity during and for some hours after the paroxysm in quartan as well as in other malarial infections. The pigment set free by the process of sporulation is taken up by phagocytes. Extracorpuscular organisms, particularly the various degenerated forms, are engulfed by phagocytes. The assault on the flagellate bodies by leucocytes can be watched with interest on the slide of fresh blood. The leucocytes can also be seen to take up segmenting bodies and spores when the specimen of blood is kept for a while. The details and the significance of these phagocytic phenomena will be considered subsequently (page 519).

The intimate structure of the quartan and other malarial parasites, as revealed by methods of staining, will also be described subsequently.

Two or more groups of quartan parasites are often present in the blood at the same time, causing double and triple quartan infections. On account of the regularity in the development of the quartan parasite, anticipating, retarding, and irregular fevers are less common in quartan than in the other malarial infections. Careful examination of the blood enables the observer to recognize the presence of two or more groups of the parasite by noting the simultaneous occurrence of bodies in noticeably different stages of development; as, for example, during the paroxysm the association of segmenting and young hyaline bodies with half-grown pigmented bodies.

II. THE PARASITE OF TERTIAN FEVER (*HAEMATOZOÖN FEBRIS TERTIANAE*)

This variety of the malarial parasite is common in most malarial regions. Where only mild types of malaria occur it is, as a rule, the prevailing, and sometimes the sole, variety observed. The tertian and the quartan parasites

cause most, or in some places all, of the winter and spring intermittents, but they, and especially the tertian parasite, may cause in districts of even severe malaria not a few of the malarial fevers of summer and autumn, although the more severe and irregular of these latter fevers are caused chiefly by the aestivo-autumnal parasite. The tertian parasite may, however, produce severe, as well as mild, types of malaria.

The tertian parasite was differentiated from the quartan and described in its essential characters by Golgi in 1886 and 1889. Other observers, particularly Antolisei (1889-90) and Bastianelli and Bignami (1890), have added to, and in some points corrected, Golgi's first description.

The chief points to be emphasized in this description of the tertian parasite are those which distinguish it from the quartan parasite. Unlike the quartan parasite, certain stages of development of the tertian—namely, those concerned with sporulation—take place by preference in the spleen and the bone marrow, although segmenting forms are seen also in the peripheral blood. The cycle of development is completed in forty-eight hours.

During the paroxysms or shortly after it small, unpigmented, hyaline, amoeboid bodies are found within the red blood corpuscles, of which they are about one-fifth to one-fourth the size. Usually one hyaline body is found, but not very infrequently two or more are present, in a single blood corpuscle. The tertian amoebae, especially in their pigmented stage, change their shape and position within the corpuscles much more actively than the quartan amoebae, these movements being vigorous at ordinary room temperature. Several branching pseudopodia are sent out, often reaching nearly or quite the periphery of the corpuscle, and are retracted. All sorts of shapes may thus be assumed by the parasite, which with its long branching processes may seem to pervade nearly the whole corpuscle. By the union of two pseudopodia the shape may be that of a ring enclosing a bit of the corpuscular substance. The tertian amoebae are paler, less sharply outlined, than the quartan. In a short time fine reddish brown or yellowish brown rods and granules of pigment, varying somewhat in size, appear in the margins of the amoebae. Pigment granules often collect in the bulbous ends of pseudopodia, and the intervening parts of the pseudopodia may be so thin and delicate as to be readily overlooked, so that the appearance may be that of several distinct bodies within one red blood corpuscle. Careful examination will, however, detect the fine connecting processes or the retraction of the apparently separate bodies into the substance of one parasite. Two or more parasites may, however, be present occasionally within one red corpuscle. The pigment is in finer grains and rods, and of a lighter, somewhat different, tint in the tertian, than in the quartan parasite. It is also in much more active movement in the tertian amoebae. This movement is

not altogether like the Brownian or molecular motion, and is probably due to intrinsic protoplasmic movements or currents.

With the continued growth and increased pigmentation of the amoebae the infected corpuscles as a rule become distinctly swollen and paler than normal— a change which may be already indicated even with quite small pigmented forms, and which is one of the most distinctive characters of the tertian parasite. Occasionally the enveloping corpuscle is not noticeably swollen or altered, and exceptionally it may even shrink and acquire something of the brassy appearance commonly seen with red corpuscles infected with aestivo-autumnal parasite.

On the day of apyrexia the parasite, now with somewhat sharper contour and more richly pigmented, may attain a size equalling one-half to two-thirds that of the infected blood corpuscle. The amoeboid movements have become more sluggish, but they persist in stages of development corresponding to which forms of the quartan parasite have become quiescent. The pigment continues in active motion.

The fully developed parasite is about the size of a normal red corpuscle, sometimes a little smaller, sometimes somewhat larger, and it is therefore smaller than the swollen corpuscle in which it is contained. It is nearly or quite spherical in shape, and without amoebic movements. The pigment for a while preserves its marginal arrangement or less frequently is irregularly distributed. The expanded red blood corpuscle enveloping the parasite becomes still paler.

These fully grown forms change into the presegmenting bodies by the collection of the pigment, which has already become quiescent into a mass of granules or into a solid block situated usually in or near the center or sometimes near or at the margin. As with the other varieties of the malarial parasite, the pigment with the development of the parasite becomes coarser, and the delicate rod-like forms of pigment become relatively less numerous. These spherical bodies with central pigment clumps are more refractive than is the parasite in preceding stages of development. Stained specimens show that in these presegmenting bodies there appear multiple, deeply staining chromatin granules, which represent nuclear substance, and which are the first indication of the inception of sporulation.

This phase of segmentation presents more variation than is observed in the quartan parasite. Sometimes it begins with the appearance of radial striation extending from the periphery to the center, and proceeds by a division of the substance of the parasite into twelve to twenty or even more segments arranged in a rosette form around the central clump of pigment. A little later the pigment clump is surrounded by a group of small round bodies, which are the spores. More commonly, without the formation of

such regular figures, the protoplasm breaks up into a mass of fourteen to twenty or more spores. Sometimes one sees an outer and inner ring of spores concentrically arranged around the central mass of pigment. The larger number of segments or spores formed by the tertian as contrasted with the quartan parasite is an important differential characteristic.

The modes of segmentation described correspond in the main to Golgi's second type of segmentation. His first mode of segmentation of the tertian parasite has not been noted by other observers. It is as follows: After the collection of the pigment in the centre the organism is differentiated into a peripheral zone sharply separated from a central body containing the pigment. The peripheral ring becomes radially striated, and then divides into fifteen to twenty small hyaline segments. The central pigmented body does not segment, but remains behind after the separation of the spores. Golgi's third variety of segmentation is now generally recognized as a process of degenerative vacuolation.

Sometimes the segmenting bodies show, instead of one central accumulation of pigment, two or more clumps excentrically placed, or the pigment may be concentrated in the periphery or distributed between the spores or otherwise irregularly arranged.

The spores are set free by rupture of the enveloping membrane derived from the red corpuscles, or this membrane may have disappeared before the segmentation is completed. The individual spores are somewhat smaller than those of the quartan parasite. They usually show a refractive nucleiform dot, which is, as a rule, less distinct than in the quartan spores.

Coincidently with sporulation the young colorless, amoebae, formed from the spores, make their appearance in the red blood corpuscles and start on a fresh cycle of development.

The segmenting bodies may make their appearance several hours before the paroxysm. They are most numerous shortly before and during the onset of the paroxysm. They may be scanty in the peripheral blood, for the process of sporulation takes place largely in the internal organs. The red corpuscles containing mature and presegmenting bodies accumulate especially in the spleen and the bone marrow, and there the organisms complete their reproductive development. During most of the period of apyrexia no noticeable difference is observed in the number and kinds of parasites between the peripheral blood and that withdrawn by hypodermic syringe from the spleen. But shortly before and during the paroxysm far more ripe and sporulating forms are found in the splenic than in the peripheral blood.

Precocious segmentation into five to ten spores may occur in bodies, sometimes containing only a grain or two of pigment, which have not attained a size exceeding one-half to two-thirds that of the red blood

corpuscles, the usual size of a segmenting body being about that of a red corpuscle, but sometimes considerably larger. Such immature forms of segmentation are associated by Bastianelli and Bignami with anticipating fevers, but Mannaberg and Thayer and Hewetson, although not inclined to discredit this interpretation, were unable to convince themeslves of this relation.

Partly developed and mature tertian parasites are often seen free in the plasma. Swollen, transparent, extracorpuscular forms which may attain the size of large leucocytes, and which contain scattered dancing pigment granules, are generally considered to be degenerative or incapable of reproductive development. These so-called hydropic forms are considerably larger and paler and more common than the similar forms of the quartan parasite. These swollen, richly pigmented forms are very common in tertian infections. In general, the various forms of degeneration which have already been described, such as fragmentation, vacuolation, pseudo-gemmation, are more common with the tertian than the quartan parasite. Flagellate bodies are likewise more common. They are, as a rule, larger and contain finer pigment than the quartan flagellates. They develop chiefly from the round, swollen, extracorpuscular forms with scattered pigment, although flagella have been observed to develop from forms still surrounded with a distinct layer of hemaglobin containing substance of the red blood corpuscle. Flagellate bodies are most abundant in blood withdrawn from the spleen shortly before and during the paroxysm. Phagocytosis occurs with the same regularity and with similar phenomena in tertian as in quartan infections.

Infection with two groups of tertian parasites (double tertian), as described for quartan infection, is more common than with a single group, especially in the later period of the malarial season in the spring and in summer and autumn. The resulting type of fever is quotidian. In some cases there seem to be several irregularly distributed generations causing remittent or subcontinued fevers. It is not necessary to attribute the presence of two or more groups of the same variety of parasite to corresponding multiple infections from without. There is evidence that certain members of a group may, in their development, lag behind or advance beyond others of the same group, and in course of time by further multiplication may constitute a separate group capable of causing its own paroxysms of fever. It is remarkable, however, that the second group should be separated in its cycle of development by such definite intervals from the first as we usually observe in quotidian fevers of tertian origin. Genuine mixed infections with malarial parasites, the most frequent combination being that of the tertian and of the aestivo-autumnal parasites, are not very uncommon.

The length of the cycle of development of the tertian parasite may occasionally be noticeably shorter than forty-eight hours, perhaps only forty hours or less, or, on the other hand, it may be longer than the normal period. This may explain the anticipating and the postponing fevers.

III. THE PARASITE OF AESTIVO-AUTUMNAL FEVER (*HAEMATOZOÖN FALCIPARUM*)

This was first clearly differentiated from other varieties ot the malarial parasite by Marchiafava and Celli (1889), and was subsequently more fully described by the same authors and by Canalis (1889-90). (See footnote, page 481.) The extensive literature concerning the parasitology of malaria during the last six years has been concerned to a large extent with this variety, but we are still far from possessing so full and accurate knowledge regarding the characters and development of *Haematozoön falciparum* as regarding those of the quartan and tertian parasites. Such knowledge is much to be desired in view of the frequency of the aestivo-autumnal parasite in regions, such as the southern part of the United States, where the more severe types of malaria occur, and of the almost exclusive association of this parasite with pernicious malarial fevers.

Chief reasons for the difficulty in investigating the entire life history of *Haematozoön falciparum* are that it develops mainly within the internal organs and often in multiple groups, and that the later reproductive phases of development are met with in the circulating blood only very exceptionally. Under the *Classification* of the malarial parasites we have already presented the more important opinions which have been advanced concerning possible subdivisions of the aestivo-autumnal variety (page 484 *et seq.*).

The youngest forms of this parasite are small hyaline bodies, about one-sixth the diameter of a red blood corpuscle, which make their appearance in the blood corpuscles during or shortly after the paroxysm. It is not uncommon to find two or more hyaline bodies in a single corpuscle. The aestivo-autumnal hyaline bodies are in general the smallest forms of the malarial parasite which are observed in the red blood corpuscle. The youngest forms may be quiescent, but as they develop they manifest amoeboid movements resembling in their activity those of the tertian amoebae.

The young aestivo-autumnal amoebae may not be readily distinguishable from the similar forms of the quartan and tertian parasites. Particularly characteristic, however, the young hyaline forms of *Haematozoön falciparum* when in repose and in stained specimens is the ring shape. The appearance in fresh specimens is that of a somewhat refractive, clear, hyaline ring, usually thicker on one side, surrounding a small round central, or oftener excentric, shaded part, or sometimes two or three such parts, through which the color of the red corpuscle shows. In stained specimens the ring appears

thinner than in fresh specimens, and the central or oftener excentric part is unstained, while a minute deeply stained granule is situated in the outer ring.

The study of the further development of these forms, especially on stained specimens, has demonstrated that these apparently annular bodies are not actual rings, as some have supposed, enclosing a bit of the red corpuscle, but that the clear area which does not stain is a transparent part of the organism, which, as will be subsequently explained, some regard as the nucleus. Actual rings, however, as has already been mentioned, may be formed by the junction of pseudopodia, which thereby enclose some of the corpuscular substance, but such is not the explanation of the typical annular appearance of the aestivo-autumnal hyaline bodies. It is not uncommon to find free hyaline bodies in the blood plasma.

These hyaline bodies may, while under observation, become somewhat expanded and paler and lose their annular appearance, and again resume the ring shape. While the very smallest intracorpuscular hyaline bodies may present no amoeboid movements, as they grow larger these movements become active. Hyaline bodies are occasionally observed to change their position within the corpuscle without change in their shape. Manifold shapes are assumed during the amoeboid movements.

Usually in the course of development a few very fine dark reddish brown or black pigment granules appear in the outer layer of the hyaline bodies. They may be situated near the periphery or on the inner margin of the ring near the clear part. Sometimes the pigment does not appear until shortly before a paroxysm. The presence of many bodies containing a considerable number of grains of pigment is generally indicative of an impending paroxysm. The pigment granules are at first very minute and few, and may be readily overlooked. The granules of pigment increase in number and size, but it is one of the characteristics of the aestivo-autumnal amoebae that the formation of pigment is, as a rule, scanty and in fine grains. Often only one or two very fine pigment granules are seen in the periphery or on the inner edge of the refractive border of the hyaline bodies. Usually about six or seven granules of pigment are developed in the hyaline bodies. The pigment generally shows but little motion in contrast with that in the tertian amoebae.

The aestivo-autumnal amoeboid forms do not generally grow larger than one-quarter to one-third the diameter of the red blood corpuscle, and they may remain smaller. The infected red corpuscles may appear otherwise normal. They do not become swollen and decolorized in this stage, as is the case in the tertian infections. On the other hand, they often become shrunken, creased, or otherwise deformed, and present a deep brassy color (*globuli rossi ottonati* of the Italian writers). Sometimes the haemoglobin separates

from a part or the whole of the outer part of the stroma of the corpuscle and collects around the enclosed hyaline body. These changes in the red corpuscles, which are particularly characteristic of the aestivo-autumnal variety, although not absolutely limited to it, are to be regarded as degenerative or necrobitic. Marchiafava and Celli and some others have thought that the parasite within these profoundly altered corpuscles is also dead or incapable of further development. Bastianelli states that sporulation forms are not observed in the brassy corpuscles, but this statement is opposed to observations of Marchiafava and Bignami and others. The view that parasites within profoundly altered corpuscles are incapable of further development is by no means proven, and is opposed to the natural interpretation of many observations.

As the time for the onset of a paroxysm approaches, the hyaline bodies gradually cease their amoeboid movements, assume a spherical or ovoid shape, become somewhat more refractive and homogeneous, and present a small collection of quiescent or but slightly moving pigment granules at about the centre or often near the periphery. This pigment usually fuses into a single small, black, round or irregular mass or block, or there may be two such blocks.

These round, refractive bodies with pigments blocks or collections of pigment granules (*corpi con blocchetto*) are the presegmenting bodies, and when they are present the onset of a paroxysm, within at most a few hours, may generally be safely predicted. These bodies are much smaller than the corresponding forms of the quartan and tertian parasites. They do not generally exceed one-quarter or one-third of the size of the corpuscle, although they may be considerably larger. They are surrounded with haemoglobin containing substance of the corpuscle, which is often of a brassy color.

The next phase of development is that of sporulation, but the segmenting forms are found in the peripheral blood only most exceptionally, save in some pernicious cases, in which they may in rare instances be even abundant. Sacharoff observed in the Transcaucasus sporulating forms in the blood, and on this account, but apparently without sufficient reason, he regards this form as a special variety. For a few hours before and during the early stage of the paroxysm very few parasitic forms of any kind are to be found in the circulating blood, and at this period they may be entirely absent, in marked contrast to quartan infection. During this period the presence of pigmented leucocytes in the blood may aid in the diagnosis. In tertian infections an analogous condition is found, but not in the same degree. The disappearance of the parasites from the blood is believed by most authorities to be due to their deposition in internal organs, especially the spleen and the bone marrow, and is attributed to the profound changes in the red blood corpuscles

containing them, these changes rendering the corpuscles virtually foreign bodies which, like other foreign particles, are caught and retained especially in the spleen and the bone marrow.

Blood withdrawn by puncture of the spleen at this time will, with rare exceptions, show abundant intracorpuscular and free round bodies with central or peripheral pigment, and also segmenting forms. In certain cases segmenting forms are few in the spleen, but abundant in certain other internal organs, as has been shown by postmortem examinations. These sporulating bodies are smaller than those of the quartan and tertian parasites, and occupy, as a rule, only a relatively small part of the corpuscle, which is always altered in appearance, being shrunken and brassy colored or more frequently decolorized. They may appear to be free or may be actually free. In pernicious cases they are present in large, often enormous, numbers in the internal organs, especially in the spleen and bone marrow, and in some types of pernicious fever in the capillaries of the brain and in those of the intestinal mucosa. This varied distribution of the parasites in internal organs is in relation with the types of pernicious fever. The stage of sporulation occupies a rather long period and takes place in successive groups. This circumstance is believed to explain the long duration of the paroxysm in aestivo-autumnal fevers. In pernicious cases sporulation seems to be going on continually in the vascular areas of certain internal organs.

In aestivo-autumnal infections the process of sporulation is in general similar to that of the tertian parasite, but it is more irregular and variable and the spores are much smaller. The number of spores formed by a segmenting aestivo-autumnal organism is extremely variable. There may be not more than six to ten spores, or even fewer; often there are ten to twenty, and the number may exceed thirty. Some segmenting forms are much larger than others. Golgi has observed exceptionally very large ones containing as many as forty to fifty spores. There are slight differences often to be observed in the finer structure between the aestivo-autumnal spores and those of the quartan and tertian parasites, as will be described when we consider the intimate structure of the malarial parasites.

The young hyaline bodies of the new generation may be found in the blood in the early part of the paroxysm, but often they do not make their appearance until several hours after the beginning of the paroxysm or during its decline.

Not all of the aestivo-autumnal amoebae develop pigment. Sporulation may occur in bodies, usually of small size, entirely devoid of pigment. As a rule in these cases both pigmented and unpigmented forms occur, but cases of aestivo-autumnal malaria have been observed, especially in tropical climates, in which only unpigmented bodies could be found at any stage of the fever before the appearance at a later period of crescentic bodies which always contain pigment.

As has already been mentioned (page 487) Grassi and Feletti regard the parasites which do not develop pigment as belonging to a distinct variety (*Haemamoeba immaculata*), but it is difficult to reconcile this view with the frequent association of pigmented and unpigmented forms, the frequent transitions from one to the other as regards the quantity of pigment developed, and the absence of any points of distinction other than the presence or absence of a variable, but generally small, amount of pigment. Still further researches, especially of the grave tropical malarias, may perhaps demonstrate the existence of a distinct unpigmented variety of the parasite.

There is considerable uncertainty as to the length of the cycle of development of *Haematozoön falciparum*. This uncertainty is due to the manner of development of the parasite, usually in multiple groups, in the internal organs, the most characteristic reproductive phases being absent from the circulating blood. So far as one can judge from the study of these phases in connection with the different types of fever with which they may be associated, the length of the cycle of development may vary from twenty-four hours or less to forty-eight hours or more.

Haematozoön falciparum may be associated with typical quotidian fever or with tertian fever, and in some of these cases the blood shows apparently only one group of organisms. As already mentioned, Marchiafava and Bignami believe that there are two distinct varieties or subvarieties of the aestivo-autumnal parasite, the one a true quotidian organism, with a cycle of twenty-four hours' duration, and the other their so-called malignant or summer-autumn tertian variety, with a cycle of forty-eight hours' duration; and this division has been accepted by some other authors. This distinction is based mainly upon the apparent duration of the cycle of development—in the quotidian about twenty-four hours, and in the malignant tertian forty-eight hours, more or less—but there are claimed to be other differences of a minor character relating to the pigmentation, the size, and the amoeboid movements of the organisms.[19] The differential diagnosis is said to be pos-

[19] The following are the biological and morphological differences between the aestivo-autumnal quotidian and malignant tertian parasites, according to Marchiafava and Bignami (On Summer-Autumn Malarial Fevers, translation, p. 83, The New Sydenham Society, London, 1894): Duration of cycle development in the quotidian, about twenty-four hours, in the summer tertian, forty-eight hours, more or less; in the quotidian sporulation on rare occasions is completed before the amoebae have become pigmented—this is not observed in the summer tertian; the fine granules of pigment in the periphery of the summer tertian are sometimes endowed with oscillatory movements—this is not noticed in the quotidian; in the same relative stage of development the tertian amoeba is usually larger than the quotidian, the adult pigmented tertian forms may be one-third of the size of the red blood corpuscles, and the forms of segmentation may be one-half or

sible only with the adult forms. The differential characters claimed to exist between the quotidian and the tertian varieties of the aestivo-autumnal parasite are, for the most part, only such as one would expect with a malarial parasite developing more rapidly in some cases than in others, and they, at least so far as at present formulated, scarcely suffice for a distinction into two well defined varieties.

Thayer and Hewetson, while confirming Marchiafava and Bignami's recognition of quotidian and tertian fevers caused by the aestivo-autumnal parasite, emphasize the occurrence of intermediate types of fever, and in general the essential irregularity of the fevers caused by this organism. They were unable to distinguish any morphological or biological differences between the parasites associated with these various types of fever. Although unwilling to commit themselves to a positive conclusion, they are "inclined to believe that the irregularity of the febrile manifestations is due chiefly to the tendency on the part of the parasite to irregularities in the length of its cycle of development (this variability being dependent, perhaps, upon the malignity of the organism or upon the resistance of the individual affected); to the fact that the period of time required for the sporulation of one group of organisms is materially greater than in the regular infections, owing to the fact that the arrangement of the parasites in definite sharp groups, sporulating nearly at the same time, is much less distinct than in the tertian and quartan intermittents; to the fact that, frequently, organisms in all stages of development are present at one time, segmentation occurring almost continuously."[20]

Golgi also considers that Marchiafava and Bignami's division into quotidian and tertian aestivo-autumnal organisms is based upon insufficient evidence, and that the duration of the cycle of development of the aestivo-autumnal parasite is indeterminate, or at least has not as yet been accurately ascertained. This cycle is probably, he thinks, longer than is supposed by Marchiafava and Bignami. This form of parasite, according to Golgi, is characterized by the fact that it develops entirely in the internal organs, and that the forms, chiefly of the earlier stages of development, which appear in the circulation, although they are found there at certain periods of the dis-

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two-thirds of it; in the tertian the amoeboid movements are maintained longer, even in the adult pigmented forms, and the motion is more lively than in the quotidian during the pigmented phase; the duration of the non-pigmented amoeboid phase in the tertian is relatively long and may exceed twenty-four hours; the young forms of the new generation in the tertian usually appear in the blood several hours after the beginning of the paroxysm, which is much later than in the quotidian.

[20] Op. cit., pp. 151, 153.

ease in practically all cases, are, in a sense, accidentally present in this situation, being washed into the circulation from their foci of development, as nucleated red blood corpuscles may be conveyed from the bone marrow into the blood current in certain anaemias. Golgi at first thought that the forms present in the circulation degenerate, but he does not now deny that they may lodge in internal organs and there develop into segmenting organisms. Marchiafava and Bignami with much reason vigorously contest Golgi's conception of the "accidental" nature of the presence of aestivo-autumnal organisms in the circulating blood, although they also believe that a large part of the parasites develop wholly in the internal organs, and that sporulation occurs only most exceptionally in the circulating blood.

The two most important and original points in Golgi's doctrine concerning the aestivo-autumnal parasite are that groups of the parasitic organisms are variously distributed in vascular areas in the internal organs, and there develop more or less independently of each other, "with relative stability," and that a large number of the organisms develop within leucocytes, endothelial cells, and other tissue cells. All phases of development, according to Golgi, are found within these cells. The spleen and the bone marrow are situations preferred by the parasite, but the capillaries of the liver, of the brain, of the lungs, of the intestinal mucosa, may also contain them enclosed within cells.

A. Monti [21] has recently described these intracellular forms in pernicious malaria, and he confirms the observation of many others that cells containing parasites frequently degenerate and die. He finds apparently intact parasites not infrequently within cells, particularly endothelial cells.

It is contended by Marchiafava, Bignami, and Bastianelli that the intracellular inclusions of the parasite, upon which Golgi bases his doctrine, are simply the well known phagocytic phenomena, and that such enclosed parasites belong chiefly to the later stages of development (presegmenting and segmenting bodies and spores), and that, instead of developing, they degenerate within the cells. The young amoeboid bodies, which, according to Golgi's doctrine, should be frequently found within cells, they found only with comparatively infrequency within phagocytes, and then almost always within their corpuscular hosts, which had been swallowed by cells. They admit the possibility of some development of intracorpuscular parasites which have been taken up by phagocytes, but not of free parasites within cells.

As with the other varieties of the malarial parasite, the aestivo-autumnal do not all mature and segment. Extracorpuscular forms are common, and

[21] A. Monti: Bollettino della Società medico-chirurgica di Pavia, 1895.

it is more particularly these forms, deprived of the protective covering of the red blood corpuscles, which degenerate. Adult and presegmenting bodies and bodies of the crescentic phase frequently become swollen and pale or vacuolated or fragmented, or throw off buds, or present other degenerative changes which have been described.

Phagocytism in the aestivo-autumnal, as in all malarial infections, is a phenomenon of much importance, as will be subsequently explained.

The frequency with which two or more groups of parasites in different stages of development are found in aestivo-autumnal infections has already been repeatedly emphasized. Marchiafava and Bignami believe that even in the pernicious fevers there are not generally present more than two groups of the aestivo-autumnal parasite, and that the short cycle of development and the prolonged period of sporulation suffice to explain the simultaneous presence of parasites in notably different stages of development. Combined infections with the aestivo-autumnal parasite and one of the other varieties occasionally occur.

It is important to bear in mind the discrepancy which characterizes aestivo-autumnal malaria between the number of parasites in the blood and the number in the internal organs. In the majority of cases the more severe the infection the greater the number of parasites found in the circulating blood, but there are so many exceptions to this that the number of parasites in the blood cannot be considered a trustworthy index of the number within the body. Pernicious cases have been repeatedly observed where the splenic blood examined during life or the internal organs examined after death contained enormous numbers of aestivo-autumnal parasites, although the blood of the finger showed very few. The organisms may be few even in the spleen when they are abundant in the cerebral capillaries or in some other situation. As will be explained subsequently, the varying symptoms and types of pernicious malaria can be explained in large part by the varying distribution of the parasites in internal organs.

It is evident from the description which has been given of the aestivo-autumnal parasite that this variety is characterized especially by its great activity in multiplication, and it will appear from the consideration of the clinical features of the infections caused by this parasite that other most important characteristics are its virulence, greater than that of other varieties, and its greater resistance to quinine.

There is a group of bodies of crescentic, fusiform, oval, or round shape, presenting certain common and peculiar characters, which develop only from *Haematozoön falciparum*. The crescents are the most typical of these bodies, which may be designated, therefore, as bodies of the crescentic (or semilunar) phase or group. They merit special consideration.

Bodies of the Crescentic Group.—When a malarial fever caused by *Haematozoön falciparum* has lasted a week or more bodies of the crescentic or semilunar phase are likely to appear in the blood. They are very rarely found in the blood in the latter part of the first week. If the fever is treated with sufficient doses of quinine during the early part of the first week, crescents do not appear, but the administration of quinine after the fever has lasted much longer than a week does not prevent their appearance. They may persist in the blood two weeks or more after all other forms of the parasite have disappeared. In such cases they are often unassociated with any febrile manifestations or any symptoms which can be definitely referred to their presence. If a relapse of the fever occurs, then the young hyaline bodies already described are always present. The crescents themselves are very resistant to the action of quinine. Councilman in 1887 called attention to the occurrence of crescentic bodies as characteristic of the irregular and remittent forms of malarial fever and malarial cachexia.

There was for a time much doubt as to the origin of the crescents, but Marchiafava and Celli's demonstration in 1886 of their intracorpuscular development has been abundantly confirmed by the later studies of Canalis, Bastianelli and Bignami, and others. The early intracorpuscular stages of development of the bodies of the crescentic group are rarely seen in the circulating blood, except in certain pernicious cases, but they can often be found in the splenic blood. Bastianelli and Bignami have found these early phases so abundantly in the bone marrow that they consider that they develop by preference in this situation.

Certain of the intracorpuscular spherical forms of *Haematozoön falciparum* with collected pigment granules, instead of continuing their regular cycle of development into segmenting forms, are transformed into the young bodies of the semi-lunar phase. This transformation takes place only after a number of febrile paroxysms; that is to say, only after the parasite has repeatedly passed through its regular sporulating cycle of development.

The young bodies of the crescentic group occupy perhaps one-quarter of the red corpuscle. Their shape is round, oval, or fusiform. They present a characteristic homogeneous, refractive appearance, being more refractive than the presegmenting bodies with central blocks of pigment. They contain dark pigment, usually in the shape of fine rods, sometimes collected in a mass, but oftener irregularly distributed. In the fusiform bodies the pigment is often arranged along the longitudinal axis of the spindle. The haemoglobin is frequently retracted into a denser stratum around the bodies. These bodies increase in size without a correspondingly large increase in the amount of pigment, and, as will be explained later, without a corresponding increase in their chromatic or staining substance—a point which distin-

guishes the direction of crescentic development from that of the regular sporulating development.

It is some time after these young semilunar bodies have begun to form in the bone marrow and spleen before the adult crescents appear in the circulating blood. These completely developed typical crescents are on the average 8-10 μ long, and in the middle 2-3 μ broad. They do not often exceed in length one and a quarter or one and a half times the diameter of a red corpuscle. They present a characteristic, homogeneous, refractive appearance. An outer double-contoured border can sometimes be seen, especially after treatment with certain reagents, and this is interpreted by Laveran, Mannaberg, and many authors as evidence of a distinct enveloping membrane; but the weight of evidence is opposed to the view that the crescents, any more than any other form of the malarial parasite, possess a membrane other than that which pertains to the enveloping red corpuscle. The outer refractive margin of the crescents, as pointed out by Antolisei and Angelini—who interpret it as a cuticular envelope derived from the red blood corpuscle—may be slightly colored by haemoglobin, and it may show evidence of this presence of blood coloring matter by the staining with eosin. On the typical crescent shaped forms a fine line can often be seen stretching like a bow across the concavity, its attachment at each end being within the extremities of the horns. This line is derived from the red blood corpuscle within which the crescent has developed, and represents the outer contour of the partly or completely decolorized corpuscle. This contour of the corpuscle can sometimes be detected also on the convexity of the crescent, and parts of the corpuscle still containing haemoglobin may occasionally be seen on the margin of the crescent, or the whole crescent may be surrounded with haemoglobin containing corpuscular substance. Similar evidences of the partly or completely decolorized enveloping blood corpuscle can frequently be seen on the margin of the round and oval bodies.

Bodies of the crescentic group are always pigmented. The pigment is very dark in color, often black, and mostly in fine rods. In the typical crescents the pigment, which is without movement and in fine rods and grains, is usually collected in the middle, sometimes in a single clump or in two clumps, often in a coronal shape. Mannaberg emphasizes the frequency with which the pigment is arranged in two adjacent clumps near the centre, presenting a figure-of-8 shape. In the immature crescents the pigment is often scattered, or is arranged longitudinally, as it often is in the fusiform bodies. The amount of pigment varies; it is often considerable. In certain pernicious fevers young crescents with scattered pigment may be abundant in the blood. In the oval and round bodies the pigment is usually concentrated in the centre, often in the form of a circle, but it may be distributed

throughout the body. Ovoid, round, and fusiform bodies may be changed into typical crescents, and, on the other hand, crescents may change into fusiform, oval, and round bodies. The appearance of a fusiform or ovoid body may be presented when a crescent is seen from the convex side.

From the round bodies flagellate forms may develop in the manner already described. The aestivo-autumnal flagellate bodies develop only from round bodies of the crescentic group. They are smaller than the tertian flagellates, resembling rather the quartan. The process of transformation of crescentic bodies into oval and round forms, and the development of flagella from the latter, can sometimes be observed in studying the fresh blood microscopically. Councilman once observed a rapid undulatory movement of a body presenting the general appearance of a crescent.

Crescents and the other bodies belonging to the same phase not infrequently become vacuolated or contain or throw off from the margin little hyaline balls (pseudo-gemmation), or disintegrate or present other degenerative changes. Danilewsky has observed crescents of unusually large size, as much as 20-22 μ long and 4-6 μ broad.

The biological significance of the crescents is unknown. These bodies do not belong to the regular sporulating cycle of development of the parasite, and there is no positive proof of their capacity for further development.

Dr. Thayer in a personal communication to the writer reports a valuable experiment made by himself which demonstrates the incapacity of crescents when inoculated into the blood of healthy individuals to develop or to cause any symptoms. The blood was taken from a patient who had had acute aestivo-autumnal fever, which was arrested by administration of quinine. Crescents persisted in the blood. For seven days the blood was examined without finding hyaline bodies or any form of the malarial parasite other than crescents. Seven days after the disappearance of the hyaline bodies a hypodermic syringeful of blood containing crescents in considerable number was withdrawn from the median basilic vein of the patient and immediately injected into the corresponding vein of a healthy man. No elevation of temperature or other symptoms followed the injection, nor did crescents or any parasitic forms make their appearance in the blood, which was examined daily for two weeks and at intervals for over a month. In the inoculation experiments of Gualdi and Antolisei and others in which it is stated that the blood contained only crescents and infection with *Haematozoön falciparum* followed in the inoculated individual, it is probable that hyaline bodies were present in the blood used for the inoculation in such small number that they escaped detection.

The following are the principal views which have been advanced regarding the interpretation of the crescents:

1. Laveran regards the crescentic bodies as encysted forms from which the flagella develop. There is no proof that these bodies are encysted.

2. Canalis and Antolisei and Angelini believe that they have found evidences of sporulation in the crescents and the ovoid and round bodies belonging to the crescentic phase. Grassi and Feletti and Sacharoff likewise believe that these bodies may sporulate. Golgi considers them capable of reproductive development in long cycles, and brings them into special relation with relapses and with fevers of long intervals. Most observers have been unable to find genuine sporulation or other evidences of reproduction in these bodies.

3. Grassi and Feletti consider that the crescents belong to a separate species which they call *Laverania,* and of which they represent a regular phase of development. The sporulating hyaline bodies with which the crescents are usually associated constitute, according to these writers, different species. This view is not generally accepted, and is opposed to the observed facts.

4. Mannaberg regards the crescents as encysted syzygies formed by conjugation of two aestivo-autumnal parasites and capable of reproduction by segmentation. His view is unconfirmed by any other observer, and is improbable. It fails to explain the ovoid and round bodies which belong to the same phase of development, and it cannot be reconciled with the appearances noted in the steps of development of the crescents, as has been shown by Bastianelli and Bignami.

5. Councilman suggests that the crescents may be of the nature of spores. Several authors have called attention to a resemblance between these bodies and the falciform spores of coccidia, but there are such essential differences between the two that the apparent resemblance is only of the most superficial character.

6. Bastianelli and Bignami have described the crescents as deviate and sterile forms. This has been interpreted to mean that they regard the crescents as degenerative forms—a view held by Kruse and some others—but in their latest publication [22] they suggest that these bodies are a rudimentary phase of a second developmental cycle which cannot be completed within the human body, but requires for its continuation some new environments in the outer world. They call attention to the occurrence of two cycles of development in several unicellular parasites, especially the coccidia, which, after passing through several generations in the ordinary parasitic life, enter upon forms belonging to a second cycle. The forms of this second

[22] Bastianelli and Bignami: Studi sulla Infezione Malarica, Bullettino della R. Accademia Medica di Roma, Anno XX, 1893-94.

cycle remain sterile, degenerate, and die, unless the parasite can escape from its host and find its appropriate new conditions of life. Manson independently also has advanced the hypothesis that the crescents are intended for the continuance of the life of the species in the external world. It has already been mentioned that a similar view has been suggested also regarding the significance of the flagellate bodies, and that Manson believes that the mosquito may serve as the host for this second cycle of development.

DIFFERENTIAL DIAGNOSIS OF THE VARIETIES OF THE MALARIAL PARASITE

An inexperienced observer may possibly mistake for the unpigmented intracorpuscular hyaline forms of the malarial parasite the vacuoles which occasionally are present within red blood corpuscles or the clear spots which may result from certain deformities in the shape of the corpuscles. These vacuoles and clear spots may be distinguished in the fresh specimen by their sharp outlines, the absence of amoeboid changes of shape and difference in refraction often suggestive of an empty space or hole, and which can be described less readily than it can be appreciated by actual observation. The absence of definite staining readily distinguishes these vacuoles from the hyaline bodies of the parasite in stained specimens.

There are occasionally seen in red corpuscles in stained specimens of the blood, especially in anaemic conditions, small stained dots which do not bear much resemblance to forms of the malarial parasite, but which should be known to the observer in order to avoid the possibility of mistake. They are believed by some to be the result of degenerative changes in the corpuscles, and by others to be remnants of nuclear chromatin derived from the originally nucleated condition of the red corpuscle.

Blood plates can be mistaken only for free spores or very small extracorpuscular hyaline bodies. In general no attention should be paid as regards diagnosis to bodies free in the plasma which resemble blood plates. In fresh specimens it is practically impossible to diagnose free spores with any certainty. Clumps of blood plates have been mistaken for sporulating bodies, but they can be readily distinguished from the latter by the absence of pigment.

For the sake of convenience the principal characters which enable us to distinguish each of the three varieties of the malarial parasite, and which have already been described in detail, will here be summarized. For modifications and amplification of these general statements the reader must consult the detailed descriptions already given.

1. *Duration of the Cycle of Development.*—In the quartan parasite, seventy-two hours; in the tertian, forty-eight hours; in the aestivo-autumnal, irregular, varying from twenty-four hours to forty-eight hours.

2. *Amoeboid Hyaline Bodies.*—In their earliest stages often indistinguishable from each other. Later, those of the quartan parasite, sharply outlined, somewhat refractive, sluggishly amoeboid, with development of dark brown or black, relatively coarse pigment granules, which have but little motion. Amoeboid movements cease in a relatively early stage of development of the pigmented hyaline body.

Those of the tertian parasite, pale and indistinct, actively amoeboid, with development of reddish brown, actively motile, relatively fine pigment granules, which tend to accumulate in the bulbous swellings at the extremities of the delicate branching pseudopodia. Amoeboid movements continue in late stages of development of the pigmented amoebae.

Those of the aestivo-autumnal parasite, small, somewhat refractive, in repose ring shaped, actively amoeboid, with development of a few very fine dark reddish brown or black, only slightly motile, pigment granules, or sometimes without pigment throughout all phases of the sporulating cycle of development.

3. *Fully Developed Hyaline Bodies.*—Those of the quartan parasite are somewhat smaller in size than the normal red blood corpuscle, and are usually surrounded by a border of the colored refractive substance of the enveloping red blood corpuscle.

Those of the tertian parasite attain the full size of a normal red blood corpuscle and lie in swollen decolorized red blood corpuscles. Swollen, extracorpuscular, transparent bodies with dancing pigment granules are common.

Those of the aestivo-autumnal parasite do not generally exceed one-quarter to one-third the size of the red blood corpuscle. The enveloping corpuscle is often shrunken and brassy. They contain much less pigment than the quartan and tertian forms, and sometimes none at all.

4. *Presegmenting Bodies.*—In the process of collection of the pigment into a mass or block in the centre or excentrically, the pigment granules often assume a more regular stellate arrangement in the quartan than in the tertian forms. The differential points between the three varieties in this stage relate to the same differences in size, in the amount of pigment, and in the condition of the infected corpuscles as have been mentioned under the preceding heading. The presence in the blood of quartan and tertian presegmenting bodies is associated with that of sporulating forms, whereas with the aestivo-autumnal presegmenting bodies sporulating forms are almost always missed in the circulating blood.

5. *Sporulating Bodies.*—Those of the quartan parasite in equal proportion in the peripheral and the splenic blood. They are somewhat smaller than in the red corpuscles, and present typical rosette forms with a division

into six to twelve ovoid or pyriform segments, each segment becoming an oval or round spore containing a bright nucleiform dot.

Those of the tertian parasite are more numerous in the splenic than in the peripheral blood. They are as large as the red blood corpuscle, and present less regularity in segmentation than the quartan parasite. They segment usually into from fourteen to twenty spores, which are a little smaller and with less distinct nucleiform dot than those of the quartan organism.

Those of the aestivo-autumnal parasite are found only most exceptionally in the circulating blood in ordinary cases. They are abundant in certain internal organs, including, as a rule, the spleen. They do not generally exceed one-third to one-half the size of the red blood corpuscle. They segment irregularly, the number of spores being sometimes six to ten, sometimes ten to twenty or even more. The spores are smaller than those of the quartan and the tertian parasites. The stage of sporulation is a prolonged one.

6. *Behavior of the Infected Corpuscles.*—These often become somewhat shrunken and deeper in color in the quartan infections; swollen and decolorized in the tertian; and shrunken and brassy, sometimes with retraction of haemoglobin from the outer part of the corpuscle, in the aestivo-autumnal.

7. *Crescentic Bodies.*—Crescents and bodies of the crescentic phase appear only in infections with the aestivo-autumnal parasite.

8. *Pigmented Leucocytes.*—Most abundant during and shortly after the paroxysm, they usually disappear during the period of apyrexia in quartan and tertian infections, whereas it is not uncommon to find them in all periods of aestivo-autumnal infections.

The Intimate Structure of the Malarial Parasite

The first systematic study of the finer structure of the malarial parasite was made by Celli and Guarnieri (1888-89). This was followed by similar investigations by Grassi and Feletti, Romanowsky, Sacharoff, Mannaberg, Antolisei, and Bastianelli and Bignami. The small size and the but slightly differentiated appearance of most forms of the parasite, and the difficulty of obtaining clear differential stainings, obscure the insight into their intimate structure.

Little detail of structure can be made out in unstained specimens. The substance of the parasite presents in general a homogenous, colorless, hyaline appearance. In the amoeboid hyaline bodies of the quartan and tertian parasites, particularly in the larger forms, an area of variable size in the centre, or more frequently excentrically placed, may sometimes be differentiated by its clear, pale appearance from the more refractive outer zone.

This area corresponds to the unstained structure interpreted by many observers as the nucleus in stained specimens. Occasionally two or more such clear spaces can be seen. Sometimes in the larger amoeboid and the mature forms a finely granular appearance of the protoplasm can be detected. It is particularly characteristic of the aestivo-autumnal parasite that the young intracorpuscular hyaline bodies show, when at rest, a clear space surrounded by a ring of protoplasm, usually thin and delicate on one side and thicker on the other. This clear space appears unstained on stained specimens. The mature forms in which the pigment has collected into one or more clumps appear uniform in structure in fresh specimens, or may perhaps present a slightly granular appearance. Within the spores, especially distinctly in those of the quartan parasite, a bright body can often be distinguished, which represents the nucleus or a nucleiform material.

The methods for staining the parasites are described under "Diagnosis," (page 139, Vol. I, "Syst. Pract. M." [Loomis], 1897). These methods are useful, not only for the study of the finer structure, but also for the ready detection of the unpigmented young hyaline forms, particularly of the aestivo-autumnal parasites, which may, without very careful observation, escape recognition on fresh specimens, whereas the presence of pigment at once attracts attention in the fresh specimens to the other parasitic forms.

On suitably stained specimens the intracorpuscular young hyaline bodies show a stained outer part, an unstained, usually excentrically placed, internal part, and one or more deeply stained round or elongated particles situated, as a rule, near the border of the stained and unstained parts. The constant unstained part is not to be confounded with vacuoles which may occasionally be present. There have been various interpretations of the structures thus differentiated. Celli and Guarnieri designated the stained part as ectoplasm and the unstained part as endoplasm. The deeply staining particles they interpreted as the beginning differentiation of a nucleus, which they thought they could recognize in larger forms as a definite, stained or pale body within the endoplasm. Grassi and Feletti do not recognize a division of the protoplasm into ectaplasm and endoplasm, and in this they are followed by most observers. The clear unstained part they interpret as a relatively large, vesicular nucleus, and the deeply staining particles as nucleoli from which may proceed a delicate reticulum of chromatin connecting them with the nuclear membrane which they assume to exist. The rest of the bladder-like nucleus is filled with clear nuclear juice. Although not all of these details in the structure of the nucleus, such as the membrane and the reticulum, have been observed by subsequent investigators, Grassi and Feletti's interpretation of the unstained part as a nucleus and of the deeply staining particle as a nucleolus or a concentration of nuclear chromatin has

been adopted by Celli and Sanfelice, Romanowsky, Sacharoff, and Mannaberg, and has been widely accepted.

Bastianelli and Bignami, while not denying that this interpretation is applicable to the quartan and tertian amoebae, adopt a different view as to the structure of the aestivo-autumnal amoebae, which they have studied with great care. They differentiate in the latter an outer colored, chromatic cytoplasm in the form of a stained ring, usually thicker on one side, and an inner uncolored, achromatic cytoplasm, which is all of the clear part enclosed by the ring. The deeply staining chromatic particle they find in the chromatic and not in the achromatic cytoplasm. Often there are two particles, each at opposite points in the ring. This particle is the only representative of nuclear material in the parasite, and they interpret it as fulfilling the functions of a nucleus. They consider that the rapidity of development and multiplication of these aestivo-autumnal parasites prevents the formation of a definite nucleus in a resting stage, such as is described for the quartan and tertian forms.

According to Grassi and Feletti and Romanowsky, the nucleus and nucleolus can be found in all stages of the regular cycle of development of the parasite. The nucleus divides directly—or, according to Romanowsky, by karyokinesis—to form multiple nuclei just before sporulation, each nucleus then entering into the structure of a spore.

The evidence, however, is in favor of the view that at a certain stage of development the nucleus and the nucleolus disappear as differentiated structures, the latter to reappear in multiple form shortly before sporulation. Mannaberg was the first to demonstrate this clearly in his studies of the structure of the tertian parasite. He observed that as the amoebid bodies approach their mature form, and then become the presegmenting bodies, the deeply staining particle (nucleolus) disappears, and later the clear, previously unstained part (nucleus) stains diffusely, so that there is in this stage no definite differentiation of structure in the parasite, although the outer part, as a rule, stains more deeply than the central part. He, however, speaks of the outer part, which contains pigment granules, as the "plasma part," and the inner part, into which the pigment does not penetrate, as the "nuclear part." He attributes the deeper and more diffused staining of the parasite in this stage to the solution of nuclear chromatin into the protoplasm. The first evidence of sporulation on stained specimens is furnished by the appearance of numerous small, deeply staining granules of chromatin in the periphery of the protoplasm. These are the forming nucleoli, which increase in size and around each the general protoplasmic substance, during the process of segmentation, divides, so that each segment or spore is a cell composed of a nucleiform, deeply staining body surrounded by its pro-

toplasmic envelope. In the quartan and tertian spores a clear unstained part later is usually differentiated around the chromatin granule, and the nucleus now resembles that seen in the young amoeboid hyaline bodies within the red corpuscle.

Bastianelli and Bignami likewise demonstrated the disappearance of the deeply staining nucleiform body in the forms of the aestivo-autumnal parasite containing collected pigment (presegmenting bodies), and soon afterward the appearance of diffuse staining in the previously achromatic cytoplasm, so that in this stage no sharp differentiation of structure can be made out within the parasite, which is richer in chromatic material than before the disappearance of the nucleiform body. The first sign of sporulation is the formation of multiple nucleiform chromatin granules in the periphery and the development of spores proceeds in the manner already described, save that the aestivo-autumnal spores are composed only of a deeply staining nucleiform body immediately surrounded by cytoplasm. The presence of the small, clear, unstained part, which with the chromatin particle is interpreted as the nucleus, often seen in the tertian and quartan spores, is rarely observed in the aestivo-autumnal spores.

It is evident from this description that the spores of the malarial parasite possess a definite structure, a most important feature being the presence of a deeply staining body which serves the function of a nucleus. The recognition of this structure renders it possible to distinguish from genuine spores the various pseudospores which have been at times erroneously interpreted as phases of reproduction of the parasite, and which belong to the category of degenerative forms. Although Antolisei has described a double contour, which he interprets as a membrane, about the spores, this observation has not been confirmed, and the spores are to be regarded as naked, thus belonging to the class of gymnospores. Some have objected to the designation of these segments as spores, but this nomenclature is in accordance with that employed by zoologists for similar bodies formed in a like manner in certain other unicellular organisms.

It is evident from the preceding description that investigators are not wholly agreed as to what structure in the malarial parasite shall be called the nucleus, some applying this name to an unstained part containing the deeply staining chromatin particle, others regarding the chromatin granule itself as the only representative of the nucleus. There is, however, general agreement that this deeply staining particle or body is an essential constituent of the nucleus, and that the presence of a nucleus or of a nucleiform body in the parasite has been demonstrated. This demonstration fulfills the important biological condition that something performing the functions of a nucleus belongs to every cell capable of reproduction, and it has served to

remove any lingering doubt which may have been entertained as to the recognition of these bodies as parasitic organisms

It is interesting to note that during the regular cycle of development there is a continual increase in the amount of staining or chromatic substance from the small hyaline body to the sporulating bodies, and that the cell becomes multinucleated just before segmentation occurs. As the chromatic substance is to be regarded as endowed with especial functional activity, these changes are highly significant.

The mature crescents, as a rule, stain feebly and diffusely, or often only at the poles, and perhaps also along the margin. Near the middle one or two deeply stained granules, often covered up by the pigment, may be present, but they are not constant. Mannaberg finds often a narrow stained band in which are two or more deeply stained granules, stretching across the middle of the crescent. Bastianelli and Bignami find that the young developing bodies of the crescentic phase stain diffusely and less intensely than the bodies with a central block of pigment which develop into segmenting forms. Whereas in the forms of the parasite which develop into sporulating bodies there is a continual increase in the chromatic substance as the bodies continue to develop, in the development of the semilunar bodies there is no correspondingly large increase of staining substance. With rare exceptions these observers found no chromatin granules in these developing crescentic bodies, nor did they ever find in any body of this group those changes of structure, such as the appearance of several chromatin granules, which indicate sporulation.

Laveran, Celli and Guarnieri, and, with especial emphasis, Mannaberg, consider that the crescents are enveloped in a double contoured membrane. A number of other observers have also adopted this view. We do not consider that any definite membrane, which can be regarded as a part of the parasite itself, has been satisfactorily demonstrated around the crescents or around any form of the malarial parasite. A double contour can sometimes, but not regularly, be seen in the periphery of the crescents, but this alone cannot be considered as proof of the existence of a membrane. The manner in which little hyaline pieces (pseudo-gemmation) can sometimes be seen to form at the margin of the crescentic bodies speaks against the presence of an actual membrane.

THE MALARIAL PIGMENT

The question as to the origin of the malarial pigment, which was so long discussed without conclusive result before the discovery of the malarial parasite, has been definitely settled by this discovery. The pigment is formed by the parasite out of the haemoglobin of the blood corpuscles by

what may be regarded as a process of digestion. The pigment occurs in the form of little granules, which may be fine or coarse, and of distinct rods and spicules, which may be as much as 1 μ long. Such rods often present a certain superficial resemblance to deeply stained bacilli. The pigment may occur in the form of extremely fine dust-like particles not easy to detect. It may be fused into black blocks. The color varies from a yellowish brown or rusty, reddish brown to black. Laveran speaks of fire red and even light blue pigment, and Rosenbach observed a greenish hue of the pigment. The malarial pigment is somewhat loosely ranked by pathologists among the melanin pigments. The differences in the characters of the pigment belonging to the different varieties of the malarial parasite have already been sufficiently described. The deposition of the pigment in the various organs will be described under the "Pathological Anatomy" (page 83, Vol. I, "Syst. Pract. M." [Loomis], 1898).

Since the examinations of malarial pigment by Meckel and by Frerichs it has been known that concentrated sulphuric acid and hydrochloric acid do not alter it, and that it disappears upon the addition of strong alkalies and of chloride of lime. Kiener observed that the pigment is dissolved by ammonium sulphide.

The demonstration of the origin of the malarial pigment from the blood coloring matter at once raised the question whether, like many pigments of haematogenous origin, it contains iron demonstrable by our microchemical tests. A statement by Perls as long ago as 1867, that pigments in the spleen of intermittent fever respond to the test for iron, has given rise to much confusion. It is not wholly clear that Perls examined the malarial pigment, but, if he did, there can be no doubt that he mistook for the true malarial pigment other pigments which are abundantly present in certain organs of those dead of malaria, and which respond to the chemical tests for iron (haemosiderin). It has been shown by Neumann, Bignami, Stieda, Dock, and others that the pigment formed directly by the malarial parasite does not contain iron in a combination which will respond to our ordinary microchemical tests for this element. This, of course, does not prove that it may not contain iron in some combination, such as that in haemoglobin, which cannot be demonstrated by our microchemical reactions. As has been pointed out by the writers named, the organs of those dead of malaria, particularly the spleen, the liver, and the bone marrow, contain a large amount of haemosiderin, the presence of which is doubtless to be explained by the extensive destruction of red blood corpuscles in malaria. There is no evidence that haemosiderin is formed directly by the malarial parasite. Marchiafava (1889), however, has advanced the hypothesis that the black pigment may be formed not only within the malarial parasites, but also

within the leucocytes out of red corpuscles altered by the action of the parasite. He thus explains the intense melanosis of the spleen, liver, and bone marrow in certain aestivo-autumnal pernicious infections where the parasites appear only slightly pigmented. Bignami [23] comes also to the conclusion, from his extensive examinations of malarotic organs in malaria, that the black pigment without microchemical iron reaction may have this double origin, being formed either within the malarial parasite without an intermediate haemosiderin stage or within cells out of haemosderin derived from destroyed red corpuscles. The objection to this conclusion of Bignami is that haemosiderin is found in the liver, spleen, and bone marrow very commonly in anaemias, but that the black pigment, without microchemical iron reaction, which characterizes malarial infections, does not appear under these conditions. It is possible that the malarial parasite may produce some chemical change in the substance of the red blood corpuscle which permits the transformation of the specifically altered haemoglobin into black malarial pigment within certain cells of the body. This, however, is a pure hypothesis.

PHAGOCYTISM

The presence of malarial pigment in leucocytes and other cells has long been known. Since the observation of phagocytic phenomena in malaria by Laveran, Marchiafava and Celli, and Metchnikoff, important studies of this subject have been made, especially by Guarnieri, Golgi, Bastianelli, and Marchiafava and Bignami.[24] These investigations have shown that phagocytosis is a common and important phenomenon in malaria, although there is much difference of opinion as to the interpretation of some of the observed facts. Some assign to the phagocytes no higher rôle than that of scavengers charged with the collection and removal of the pigment and débris resulting from the activities of the malarial parasites and from the death and disintegration of the parasites themselves. The amount of slag which is produced in severe cases of malaria in the form of pigment, dead and disintegrating red blood corpuscles, and degenerated and broken up parasites is so large that even this office of scavengers becomes an important one. But Metchnikoff, Golgi, and some others believe that the phagocytes devour large numbers of intact, healthy parasites in certain phases of their development, and that in this contest between cell and parasite is to be found the most important agency for the defence of the body. The arguments for and against

[23] Bullettino della Reale Accademia Medica di Roma, Anno XIX, fasc. II, p. 230, 1893.

[24] Especially valuable are the articles of Golgi, Il fagocitismo nell' infezione malarica, Riforma Medica, 1888, and of Bastianelli, I leucociti nell' infezione malarica, Bull. della R. Accademia Medica di Roma, 1892.

this latter conception are essentially similar to those which are adduced as to the phagocytic theory in bacterial infections, the main difficulty being to determine to what extent fully active and virulent parasites are taken up and destroyed by phagocytes, and, even admitting the occurrence of this mode of disposal of the parasites, whether or not it is the most essential and the predominant factor in their destruction. That malarial parasites, as well as bacteria, may perish in the blood plasma without incorporation within cells cannot be doubted, as we have direct observations demonstrating this.

The cells which assume the functions of phagocytes in malaria are the leucocytes, the endothelial cells of the walls of the blood vessels, and large cells, found especially in the spleen, the bone marrow, and the liver, and called by Metchnikoff "macrophages." Of the leucocytes the large mononuclear, the polymorphonuclear, and the transitional forms act as phagocytes. The small lymphocytes and the eosinophils have never been observed to contain pigment or débris in malaria. Of the leucocytes it is the large mononuclear forms which are the most active and important phagocytes within the body in malaria, but, as has been pointed out by Thayer and Hewetson, the polymorphonuclear leucocytes are the ones which can be observed to be active in the fresh blood during examination under the microscope. It is the latter which pick up the pigment and the extracorpuscular and degenerated parasites, and which attack the flagellated bodies in the fresh blood withdrawn from the body, so that there may be a notable difference between the blood examined immediately after its withdrawal from the body and that examined at a later period as regards the number of polymorphonuclear leucocytes containing foreign elements. Endothelial cells containing pigment, parasites, or fragments of parasites or of red corpuscles are rarely seen in the circulating blood withdrawn for microscopical examination: but the study of microscopical sections of organs of those dead of malarial infections shows that the endothelial cells lining the capillaries and small blood vessels, especially those of the spleen, bone marrow, and liver, in certain cases also of the brain, intestine, and other parts, manifests extensive phagocytic activities. So too the macrophages, although they have repeatedly been found in the circulating blood, are met with chiefly in the splenic blood and in the microscopical examination of organs of those dead of malaria. These macrophages, which may attain an enormous size and are frequently destitute of nuclei, and therefore necrotic, are mononuclear cells derived probably in part from mononuclear leucocytes and certain fixed cells of the pulp of the spleen and bone marrow. Their contents may be varied, consisting sometimes within one cell of pigment, intact or degenerated parasites, and red blood corpuscles and entire smaller phagocytes.

Dock has counted as many as twenty parasites within one phagocyte in the spleen. Under "Pathological Anatomy" (page 83, Vol. I, "Syst. Pract. M." [Loomis], 1897), will be described the appearances of these various phagocytes as seen in sections of the different organs of the body.

The foreign elements which are found within these phagocytes in malaria are—(1) malarial pigment; (2) yellowish or reddish-yellow pigment derived directly from disintegrated red corpuscles (haemosiderin); (3) red corpuscles, sometimes intact, but usually more or less altered and fragmented; (4) malarial parasites, either free or enclosed within red corpuscles, which are usually altered, such parasites appearing sometimes intact, often degenerated and fragmented; (5) particles which are probably often derived from the disintegration of parasites, but which do not present appearances sufficiently characteristic to enable one to determine their origin. It has already been mentioned that a phagocyte may be enclosed by a macrophage. Leucocytes either with or without pigment may be thus enclosed. As phagocytes and other cells often degenerate and become necrotic and disintegrated in malaria, it is evident that from this source may be derived material for inclusion within living cells.

First in order of frequency are phagocytes containing malarial pigment. In the examination of malarial blood obtained from the peripheral circulation the only form of phagocyte which is to be seen with any frequency in the perfectly fresh specimen is the melaniferous leucocyte. Leucocytes containing clearly recognizable parasites are rarely, if ever, seen in the freshly drawn specimen of peripheral blood. Macrophages containing definite parasitic forms may occasionally be found in this situation. Both mononuclear and polymorphonuclear leucocytes may contain the pigment, but in the perfectly fresh specimen the former preponderate. The pigment is found most frequently in the form of blocks and coarse granules, corresponding to that set free by the process of sporulation, but sometimes the pigment within the leucocytes is in fine rods and grains, such as belong to the earlier stages of development of the parasite. The inference is a probable one that in the latter case the leucocyte may have enclosed the parasite.

As has already been stated, in the fresh blood removed from the body and examined for a while under the microscope the polymorphonuclear leucocytes can be seen to engulf pigment and certain parasitic forms—viz., extracorpuscular forms, especially degenerated and fragmented forms, segmenting form and spores, and altered red corpuscles—and especially do they attack the flagellate bodies, as has been demonstrated by Thayer and Hewetson. Such enclosed parasitic forms, with the exception of the spores, can be seen rapidly to become indistinct and unrecognizable within the leucocytes.

From the examination of the fresh circulating blood alone one obtains a very inadequate conception of the extent and nature of the phagocytic processes in malaria. A fuller idea of these processes can be derived from the study of blood withdrawn by puncture of the spleen, where phagocytic phenomena are far more active than in the circulating blood; but it is especially in the microscopical examination of the organs of those who have succumbed to a malarial attack that the best opportunity is offorded to learn the extent of phagocytosis in malaria. Here one finds abundantly leucocytes, endothelial cells, and macrophages containing pigment, parasitic forms and altered red blood corpuscles.

Parasites in their later stages of development, especially when they are free, are frequently taken up by phagocytes—in their early stages rarely, unless they have become extracorpuscular or the corpuscle containing them is degenerated. Sporulating forms, and somewhat less frequently forms with collected pigment (presegmenting bodies), are the ones most commonly found in a recognizable condition within the phagocytes. It is stated by Bastianelli and Bignami that the bodies with pigment blocks (presegmenting) are found most frequently within macrophages, and sporulating forms within polymorphonuclear leucocytes. Pigmented amoebae they found rarely, and red blood corpuscles containing unpigmented amoebae very rarely, within phagocytes. Bastianelli gives the following as the order of frequency in which the various parasitic elements are found within phagocytes: (1) pigment; (2) sporulating forms and spores; (3) red corpuscles, normal or decolorized, containing sporulating forms or bodies with central pigment blocks; (4) brassy and decolorized red corpuscles containing plasmodia (hyaline bodies in the amoeboid stage); (5) free bodies with central pigment clumps; (6) more rarely free amoebae or red corpuscles of normal appearance containing parasites in the amoeboid stage. According to the observations of the writer, free bodies with central pigment clumps occupy a higher place in this scale than that assigned to them by Bastianelli. Crescents enclosed in phagocytes may be found even in the circulating blood. The various bodies within phagocytes often lie in an area surrounded by a clear zone like a vacuole.

Golgi (1887-88) discovered that phagocytosis occurs in quartan and tertian infections with a definite periodicity which stands in relation to certain phases in the cyclical development of the parasite, and therefore to certain periods of malarial fever. This is readily understood when one considers that it is especially the free pigment and the mature and segmenting parasites and the degenerative forms which are taken up by phagocytes. The pigment is liberated by the process of sporulation which, as has already been explained, occurs shortly before and during the early stages of the paroxysm.

Corresponding with this, Golgi found that pigmented leucocytes are present in the circulation during the paroxysm and for a short time afterward, and that they disappear from the circulation during the apyrexia. This periodicity in the appearance of melaniferous leucocytes and of other phagocytes can be observed regularly in quartan and tertian infections. There are frequently indications of it also in aestivo-autumnal infections, but on account of the irregularities in the cyclical development of *Haematozoön falciparum*, of the prolonged period of sporulation, of the frequent occurrence of multiple groups of parasites, and of the presence at all periods of degenerated red corpuscles, this periodicity in the occurrence of phagocytosis is often obscured or is not manifest at all. Pigmented leucocytes may be found in many cases of aestivo-autumnal infection during all periods of the disease, although they are more numerous during the paroxysm and shortly afterward. In the severe prolonged cases they are generally abundant, and they may persist in the circulation for several days after cure is effected. As long as crescents are present pigmented leucocytes may be found.

Parasites which, to all appearances, are normal are found within phagocytic cells. What is the fate of such enclosed parasites? That many degenerate and die cannot be questioned, for these degenerative alterations can be directly observed in progress under the microscope in examining fresh blood, and in studying malarial blood and tissues one frequently encounters evidences of this fate of the parasites. It is claimed, however, by Marchiafava, Bignami and Bastianelli that enclosed spores, although prevented from further development, may survive for a long time within leucocytes and other cells, and that such latent spores may after an indefinite period be set free and cause by their development a relapse of the fever.

Attention has already been called to Golgi's belief that the aestivo-autumnal parasite may, and to a considerable extent does, develop within the leucocytes and endothelial cells of internal organs, in ordinary cases chiefly of the spleen and bone marrow. He adduces a number of considerations in support of this view, but the objective evidence he and his pupil, A. Monti, find in the detection of the frequent presence of this parasite, apparently intact and in all stages of development, within these cells. In opposition to Golgi, however, it is claimed by Marchiafava, Bignami and Bastianelli that early phases of development of the parasite are rarely seen within the cells, and that, therefore, the much more commonly enclosed late phases cannot have developed within the cells from young parasites. Golgi also brings to his support the observation, made by all who have studied the subject, that many of the cells containing parasites degenerate and die, as is made evident especially by the loss of their nuclei. He interprets this as meaning that in the conflict between cell and parasite the latter often comes

off the victor. Further investigations are needed to determine to what extent Golgi's doctrine as to the intercellular residence and development of *Haematozoön falciparum* is correct. Certainly the greatly preponderating number of intact aestivo-autumnal parasites observed in examining the organs of those dead of pernicious malaria are found within free red blood corpuscles in the vessels of internal organs.

The theory of Metchnikoff that the essential factor in the resistance of the body to the malarial parasite resides in the activities of phagocytes is opposed by many considerations. The most important factors in determining the gravity and the course of a malarial infection are the degree and quality of virulence possessed by the parasite, on the one hand, and the resistance of the individual receiving the parasite, on the other hand. There is no evidence that phagocytic functions are in abeyance in severe and pernicious cases of malaria. On the contrary, we find here often enormous numbers of parasitic enclosures within phagocytes. There is no proof that spontaneous recoveries from malaria are associated with an increase of phagocytic activity. Inasmuch as phagocytes regularly attack degenerated and fragmented parasites, and as we know that such degenerations occur frequently within parasites free in the plasma, it is permissible to suppose that many of the parasitic forms found within phagocytes were already impaired in their vitality before they were engulfed by cells. After the administration of quinine, which directly injures the malarial parasite, a distinct increase in the number of phagocytes has been often observed. Certainly quinine does not stimulate the leucocytes to swallow the parasites. Here the increase in the phagocytes must be attributed to the increase in the number of damaged parasites.

There is evidence that the blood plasma may exert a parasiticidal effect upon the malarial organism, as well as upon other protozoa (Faggioli), when the parasite has escaped from the protective covering of the red blood corpuscle. The period when the largest number of malarial parasites are destroyed is that of sporulation and of free spores, and it is during this phase of the life history of the parasite that quinine acts most effectively. We may, at least provisionally, adopt a theory to explain natural resistance to the malarial parasite similar to that which many accept regarding resistance to bacteria—viz. that the parasites are destroyed by parasiticidal substances contained both in the plasma and within leucocytes and other phagocytic cells. The substances injurious to the parasite are in the last analysis furnished to the plasma by the cells, and are in a more concentrated or potent form within the cells than in the fluids. This theory assigns to the phagocytes a higher rôle than that of mere scavengers. They are endowed in especial degree with the power of destroying the parasite, but this power is shared by the plasma.

PATHOGENESIS

The discovery of the malarial parasite has placed within our reach the means of solving many problems concerning malaria which we could not formerly even attack with any hope of success. Already we have attained a satisfactory understanding of not a few previously unexplained manifestations of malaria, and other formerly obscure malarial phenomena have been brought at least within the range of our comprehension. Much still remains to be elucidated, but we cannot doubt that further studies will continue to throw fresh light upon what remains obscure.

In the description of the symptoms and lesions of malaria attention will frequently be called to their relations to the parasite, and in this connection only certain salient points, relating more particularly to pathogenic properties of the parasite, require consideration.

The mere presence of the malarial parasite in the body is not sufficient to cause symptoms. The organisms must have multiplied to a certain point before their presence is manifested by recognizable symptoms. The bearing of this fact upon certain malarial phenomena, more particularly upon the varying periods of incubation as determined by experimental inoculations of malarial blood and upon fevers with long intervals, will be considered in the clinical part of this article.

It may be stated as a general rule, which was first formulated by Golgi, that the larger the number of organisms present in the body the more severe are the manifestations of the disease; but the number of the organisms is by no means the only factor which determines the gravity of the disease. The variety of parasite which is concerned in the infection is a factor of fundamental importance. The quartan variety produces the mildest attacks, the tertian is more virulent than the quartan, and the aestivo-autumnal variety is the most virulent of all, and is the one which is almost exclusively associated with the pernicious attacks. These variations in virulence are best explained upon the assumption that the malarial organism produces toxic substances of varying virulence according to the variety of parasite. There is also clinical evidence that one and the same variety may vary in virulence, so that, for example, some aestivo-autumnal parasites are more virulent than others.

In seeking an explanation of the varying clinical characters of malarial infections we have to reckon not only with the number, the varieties, and the virulence of the parasites, but also with several other factors, such as predisposing conditions on the part of the individual infected, the occurrence of multiple groups of the parasite, the distribution of the organisms in internal parts, the circulatory and other anatomical disturbances induced by the parasites.

Periodicity is the most striking clinical characteristic of malarial fevers, and the explanation of this phenomenon has exercised the minds of pyretologists from ancient times. It is true that intermittence is not limited to fevers of malarial origin, but regularity of rhythm in the occurrence of the paroxysms is especially characteristic of malaria. One of the most interesting additions to our knowledge resulting from the discovery of the malarial parasite is the demonstration by Golgi, which has been abundantly confirmed, that this rhythm in the malarial paroxysms corresponds to a rhythm in the development of successive generations of the parasite.

The onset of each paroxysm corresponds to the ripening and sporulation of a generation of parasites and the setting free of a new brood.[25] Exactly what the connection is between this act of sporulation, with the liberation of a fresh brood of young parasites, and the cause of the febrile paroxysm, is not definitely known. It was at first suggested by Golgi (1887) that the paroxysm is due to the invasion of the red blood corpuscles by the new group of parasites, but it was shown by Antolisei (1890) that the paroxysm depends rather upon the act of segmentation than upon the invasion of the blood corpuscles by a new generation of organisms, for quinine, administered before a paroxysm in sufficient quantity, may, by destroying the fresh brood, completely prevent the invasion of the red corpuscles, but it cannot prevent the segmentation and the impending paroxysm. The view is now widely held, and seems plausible, that in the act of sporulation and of liberation of the spores chemical poisons are set free, and that these poisons, by their action on the nervous centres concerned in the production of fever, cause the

[25] The old idea that the periodicity of malarial fevers depends upon the periodical production in the blood of a *materia peccans* is thus confirmed. It is interesting in this connection to note the line of argument presented by Griesinger in his admirable and suggestive article on the malarial diseases (Virchow's Handb. d. spec. Path. u. Therap., Bd. II, Abth. 2, 2te Auflage, p. 41, Erlangen, 1864): The cause of the periodicity of the fever cannot, therefore, be referred to the disposition of the nervous system to rhythmical vital actions, as many have formerly done, but it must, at least according to our present although very incomplete knowledge concerning the causes of heat, be attributed to something periodically occurring in the blood, which is connected with the increased production of heat. It has been formerly conceived that a certain substance, a *materia peccans*, appears periodically in the blood and incites the febrile heat and reaction: this material requires for its production and complete development sometimes longer, sometimes shorter, periods, and herein lies the cause of the rhythm of the fever. . . . . As an explanatory hypothesis this conception accomplishes more than the later attempts at explanation. . . . . The continuous morbid process which causes the poisoning incites periodically changes in nutrition or in the blood which arouse the nervous apparatus to abnormal manifestations.

febrile paroxysms. This toxic theory of malaria has been elaborated especially by Baccelli.

The fact that the malarial parasite resides in, feeds upon, and destroys the red blood corpuscles furnishes an entirely satisfactory explanation of two of the most characteristic and important manifestations of malaria—the melanaemia and the anaemia. The malarial pigment, for which we formerly had no adequate explanation, is formed as an undigested residue within the body of the parasite by metabolic processes directly out of the haemoglobin of the infected red blood corpuscle. Various stages of the formation of the pigment within the parasite can be seen. The liberation of this pigment, its inclusion by phagocytes, its deposition in various internal organs, have all been described, and will be further considered under the "Pathological Anatomy" (page 83, Vol. I, "Syst. Pract. M." [Loomis], 1897). The relations of the biological characters of the parasite to malarial anaemias and to haemoglobinuria will be fully considered in the anatomical and clinical parts of this article (pages 93, 116, 125, and 130, Vol. I, "Syst. Pract. M." [Loomis], 1897).

The ways in which the red blood corpuscles may be altered by the action of the malarial parasite are various. The extent of these changes varies with the variety and the virulence of the parasite. They are least in quartan infections, greatest in the aestivo-autumnal. The infected blood corpuscle may appear otherwise normal. It may be swollen or shrunken or variously deformed. It may divide into two or more pieces. It may be partly or completely decolorized, or the haemoglobin may separate from the stroma and be dissolved in the plasma, or may be concentrated around the parasite. Especial significance in the aestivo-autumnal infections attaches to that alteration in the corpuscle which has been repeatedly referred to as the brassy change, on account of the resemblance in the color of the shrunken corpuscles to brass, sometimes compared also to copper or old gold. Nor are the corpuscles which are actually infected by the parasite the only ones which may be altered. Uninfected corpuscles may also be changed in appearance, and may be destroyed, especially in cases of haemoglobinuria.

These changes in the red blood corpuscles, which must be regarded as degenerative and destructive cannot be brought wholly into parallelism with the development of the malarial pigment. In fact, the most profound lesions and the greatest destruction of the red corpuscles occur in infections with the aestivo-autumnal parasite, which is characterized by the small amount or even the entire absence of pigment. To explain many of these changes we must have recourse again to the theory that toxic substances are produced by the parasite and directly damage the blood corpuscles.

These alterations in the red blood corpuscles not only explain the malarial anaemias and the haemoglobinuria with their concomitant symptoms and lesions, and the accumulation of malarial and other pigments in certain organs, but they are utilized, although less conclusively, to explain certain other malarial phenomena. We know from physiological observations that the physical integrity of the red blood corpuscles is an important condition in the maintenance of their circulation within the blood current. It is reasonable to suppose that corpuscles as profoundly altered as are many of those infected with the malarial parasite will circulate with difficulty, and will tend to accumulate in certain situations where local conditions of the circulation favor the lodgement of foreign particles which get into the circulation. Many writers, therefore, attribute to these alterations in the physical properties of the infected red blood corpuscles the accumulation of the parasites within the vessels of certain internal organs, more particularly the spleen, the bone marrow, the liver, and the brain, and they explain the absence of such accumulation in quartan infections by the comparatively slight lesions of the infected corpuscles, and the large accumulation in tertian, and still more in aestivo-autumnal, infections by the more serious damage inflicted upon the infected red corpuscles by the varieties of the parasite causing these latter infections. Doubtless these factors—changes in the infected red corpuscles and local conditions of the circulation—are important in determining the localization of the parasites in certain internal parts, but with our present knowledge we cannot explain the varying distribution of the parasites observed in different cases exclusively by their aid, any more than we can adopt a similar explanation for the localization of the microorganisms in other infections.

The localization of the parasites in some cases, more particularly in aestivo-autumnal infections, within definite vascular areas of internal organs stands in relation to corresponding symptoms and lesions. The comatose and the choleriform types of pernicious malaria are associated with an accumulation, which may be enormous, of the parasites in the capillaries and small vessels of the brain and of the stomach and intestine respectively. Other special localizations of the parasites will be mentioned in the subsequent part of this article. In these cases capillaries and other small bloodvessels may be partly or completely plugged with parasites, chiefly within red blood corpuscles. Swollen, degenerated, and desquamated endothelial cells, pigment, macrophages, and other phagocytes contribute to this occlusion of the vessels. Genuine thrombi also occur.

Serious disturbances of the circulation must result from such extensive plugging of the vessels. It is not easy to determine how far these mechanical disturbances of the circulation are responsible for symptoms and lesions

with which they are associated. Marchiafava and Bignami and others regard them as the essential cause of the grave nervous symptoms in comatose pernicious fever, and of other symptoms and of lesions. Many years ago Frerichs likewise attached much importance in the causation of cerebral symptoms to accumulations of pigment and the formation of coagula within the cerebral vessels. It appears, however, to the writer that, aside from certain general pathological considerations and analogies with similar conditions in other diseases, this mechanical explanation is inadequate, and that here too the toxic products of the parasite are operative. The promptness with which the grave cerebral symptoms may subside after administration of quinine is not easily reconcilable with the theory that they are due to plugging of the vessels.

Even the focal necroses which are common in the liver in pernicious cases, and may occur in the spleen, the kidneys, and elsewhere, are best interpreted as due to the toxic products of the parasite, rather than as the result, as is claimed for the liver by Guarnieri, of plugging of the bloodvessels. These necroses do not differ from those observed in diphtheria, typhoid fever, and streptococcus and other infections, and that they may be purely toxic in origin has been demonstrated by Welch and Flexner.[26]

The capillary hemorrhages which have been observed in the brain in the comatose form of pernicious fever, and which may occur elsewhere, may be referred to the hyperaemia and stasis resulting from plugging of the vessels. The interesting fact has been observed that in these capillary haemorrhages the extravasated red corpuscles are without parasites, while the neighboring bloodvessels are filled with red corpuscles containing parasites. The explanation of this which is given by Marchiafava and Bignami and adopted by others is that the corpuscles containing parasites on account of their greater adhesiveness stick to the walls of the vessels and thus are prevented from escaping. The writer offers another explanation as the more probable. The examination of these small haemorrhages shows that they are the result of diapedesis, and not of actual rupture of the vessels (rhexis). It is not difficult to comprehend that red corpuscles altered by the invasion of parasites would not participate in the process of diapedesis, whereas it is not easy to understand why they should not escape from ruptured vessels.

It is evident from what has been said that, while occlusion of vessels and consequent disturbances of the circulation are common in severe malarial affections, and are doubtless of importance in causing some of the lesions and symptoms, the more important and characteristic symptoms and lesions are, in the opinion of the writer, with our present knowledge, better explained

[26] The Johns Hopkins Hospital Bulletin, March, 1892.

by the toxic theory of the pathogenic action of the malarial parasite than by any mechanical theories which have yet been offered.

We have, however, no positive demonstration of the existence of specific malarial toxins. The investigations as to the toxicity of the urine of malarial patients will be described on page 123 (Vol. I, "Syst. Pract. M." [Loomis], 1897). They have not led to any positive results as to the detection of specific malarial poisons.

It is a very old conception that the febrile reaction of the malarial paroxysm is conservative in the sense that this response of the body to the presence of pyogenic agents in some way aids in the elimination or destruction of injurious substances. This conception is not altogether without support from the parasitological study of malaria. The fever begins at the time of the birth of a new generation of parasites. These young organisms before they have entered the red blood corpuscles are, of all phases of development of the parasite, in the most vulnerable condition, as has been shown by investigations of the action of quinine. That a large number of them perish during the febrile paroxysm seems to be demonstrated, at least in quartan and tertian infections, by the contrast between the number of sporulating forms and the number of succeeding infected corpuscles. Especially suggestive of increased potency of parasiticidal agencies during the febrile paroxysm are cases, especially of quartan or tertian infection, in which, after a sharp paroxysm, the symptoms and the parasites disappear, perhaps permanently, but often to return after a long interval as a recrudescence of the fever (page 121, Vol. I, "Syst. Pract. M." [Loomis], 1897).

SIMILAR HAEMATOZOA IN THE LOWER ANIMALS

Great interest attaches to the presence in the blood of certain lower animals of protozoan parasites closely resembling the malarial parasite. Attention was first called to this resemblance by Danilewsky (1885-86), who described more fully certain forms which were previously known, and added the discovery of new forms, especially that of haematozoa in birds which bear close resemblance to the human malarial parasite. Since Danilewsky's first publications there have been a number of investigations on this subject by Kruse, Celli and Sanfelice, Grassi and Feletti, Laveran, Labbé, and others.

In the blood of frogs, turtles, lizards, and some other cold-blooded animals haematozoa presenting some points of resemblance to the malarial parasite are not uncommon. Of these the best studied and most interesting is *Drepanidium ranarum* (Lankester), identical with Gaule's "Würmchen," in the blood of frogs. It is, however, certain haematozoa in birds which bear such close resemblance to the malarial parasite that their identity with

the latter has been assumed by Danilewsky and Grassi and Feletti, who speak of the existence of malaria and of malarial parasites in these animals. Most of the observations thus far reported have come from Russia and Italy, but the parasites have been found in birds also in Germany and France, and recently in the United States.

In birds thus infected have been found forms similar to those of the malarial parasite in man—viz. unpigmented and pigmented hyaline bodies (which, however, in distinction from similar bodies in man, manifest little or no amoeboid movement), sporulating forms, crescents, and flagellated bodies. The bird's haematozoa are also parasites of the red blood corpuscles, from which they produce black pigment: they pass through the same stages of development as the latter, and the same diversity of views exists as to the origin and significance of the crescents and flagellated bodies. The name HAEMOPROTEUS was introduced by Kruse to designate these so-called malarial parasites of birds, and various other names have also been suggested. Grassi and Feletti adopt the same names and the same classification for these parasite of birds as for the human parasites (page 487). There are differences between the haematozoa found in different species of birds, and in the same species apparently different varieties of the parasite have been observed, but there are at present no definite classification and no certainty as to the number of varieties which may exist.

Although these haematozoa of birds evidently belong to the same class of organisms as the malarial parasite, there are several reasons which indicate that they are not identical with the latter. They present certain morphological and physiological differences which it would lead too far here to describe. Although found thus far chiefly in birds from malarial regions, it is not proven that they may not exist in birds elsewhere. The inoculation of uninfected birds with the blood of birds containing the parasites has been, in a large preponderance of the experiments, unsuccessful in the result. The inoculation of birds with blood from human beings affected with malaria, and the inoculation of human beings with the blood of birds containing the haematozoa, have been uniformly without positive result (Di Mattei). Large doses of quinine have no influence upon the parasites in birds. The presence of the haematozoa in birds is usually without recognizable disturbance of the health of the birds, although it may cause a chronic or an acute affection. While, then, we must admit a close relationship between certain haematozoa of birds and the human malarial parasite, the existing evidence is opposed to their identification.

SO-CALLED PARASITIC BODIES IN EPITHELIOMA[1]

Under the microscope are specimens of carcinoma which show various intracellular formations apparently identical with some, at least, of the bodies which a number of recent observers have described as sporozoa or similar parasites. There are also sections of an epithelioma of the penis, made from pieces which had been placed immediately after removal in Fleming's solution, which are particularly rich in these intracellular bodies. These bodies correspond in appearance and behavior with coloring agents to many of those described by Sjöbring and by Siegenbeck van Heukelom. Most of them appear as round or irregular masses, sharply differentiated from the protoplasm of the cancer cell enclosing them by a higher refraction index and by deeper staining with eosin and safranin. They vary in size from minute globules to masses which occupy the greater part of the cell. They occasionally lie in a vacuole within the cell. They sometimes contain one or more particles which stain deeply with haematoxylin. Round or irregular particles, staining deeply with haematoxylin, are sometimes found within cancer cells presenting normal nuclei. Some of the inclosed bodies are pale and do not stain deeply with any of the dyes employed, but are more or less sharply differentiated from the surrounding protoplasm. These pale bodies are usually about the size of leucocytes, or somewhat smaller, and frequently contain nuclear masses resembling fragmented nuclei. It is not easy to give an accurate description of all the various bodies or formations which may be found in the cells of an epithelioma more or less sharply differentiated from the surrounding protoplasm.

These and similar enclosures in cancer cells must be familiar to all who have made a careful study of epithelioma and, while their nature cannot always be satisfactorily determined, it is entirely premature and unwarranted, on any evidence as yet brought forward, to regard them as sporozoa of other forms of parasites.

Many of these bodies so far as flat celled epithelioma is concerned, can be explained, (1) as masses of keratine, a part of the protoplasm having undergone in a circumscribed area the keratine metamorphosis, while the rest remain granular; (2) as irregular masses of eleidin or kerato-hyalin; (3) as

[1] Report of remarks before the Johns Hopkins Hospital Medical Society, Baltimore, October 6, 1890.

Johns Hopkins Hosp. Bull., Balt., 1889-90, I, 97-98.

included leucocytes undergoing degenerative changes, with or without fragmentation of nuclei; (4) as scattered nuclear fragments derived from the preceding.

Just as epithelioma is essentially an atypical growth of epithelium, so it is not surprising to find various atypical metamorphoses of the epithelial cells, such as partial transformation of the cell protoplasm into kerato-hyaline and into keratine.

THE PARASITE OF CANCER[1]

Dr. Gaylord has brought before us something more than the mere description of the so-called cell enclosures observed in hardened specimens of cancer. Of the enclosures hitherto described in preserved material the only ones which present anything like a definite organization and which, it seems to me, have not been altogether satisfactorily explained are the bodies first accurately described by Thoma and Sjöbring, and subsequently noted by most of those who have studied the subject. These bodies in English and American writings are often designated without much propriety as "Plimmer's bodies." No conclusive evidence that these bodies, still less that any other of the various enclosures, are parasites, has been furnished, and it now seems evident that no further progress in the search for parasites is likely to be made by the examination of hardened material with our present methods.

Under these circumstances it is important to turn to the examination of fresh material and to make attempts to cultivate parasitic organisms, provided such exist in cancer and other malignant tumors. This direction of study has therefore been followed in recent years by several investigators, and it is especially his results along these lines which Dr. Gaylord has reported. As regards artificial cultures, it is certain that no forms of bacteria demonstrable by existing methods are directly concerned in the causation of cancer, and, notwithstanding the stronger claims made in behalf of Blastomycetes, I am glad to learn that Dr. Gaylord rejects these claims and takes a position in this regard opposed to that of Sanfelice, Roncali, Plimmer, Leopold, and others. He interprets as protozoa the bodies which he regards as parasites.

Leaving out of consideration the occasional and accidental presents of cultivable bacteria and yeasts in cancer, I question whether what is called by Dr. Gaylord and other investigators as the cultivation of protozoa or of sporozoa from cancers should be so designated, and it does not appear that secondary cultures carried on from generation to generation have in any instance been secured.

[1] Remarks on a paper entitled, The Parasite of Cancer with Demonstrations, by Harvey R. Gaylord, before the Johns Hopkins Hospital Medical Society, Baltimore, April 15, 1901.

Johns Hopkins Hosp. Bull., Balt., 1901, XII, 295-296.

There is not much agreement among different observers either in the description or the interpretation of the various bodies regarded by them as parasites to be seen in fresh cancerous material or fluids, or in such material kept free from bacterial contamination, whether mixed with some cultural fluid or not. Dr. Gaylord lays especial emphasis upon the presence in cancers and other conditions of homogeneous, yellowish, spherical bodies resembling droplets of fat but without the usual reactions for fat, and he considers that he finds evidences of multiplication of these bodies and of their passing through a definite cycle of development which he describes. He is, I trust, prepared for a considerable degree of skepticism following this announcement of his results, and it is desirable that this should be the attitude of mind until we are in possession of more evidence than has as yet been furnished in favor of the parasitic hypothesis. It is, however, incumbent upon pathologists to make a careful study of all that can be seen in the microscopic examination of fresh, macerated, and preserved cancerous material, and whatever else may be the outcome of such studies, they will have furthered our knowledge of cellular degenerations and metamorphoses. Unless there are those present who on the basis of such study are prepared to discuss Dr. Gaylord's findings, it does not seem to me worth while to discuss them in detail.

Dr. Gaylord has presented an instance of multiple nodules in the lungs of an adenocarcinomatous nature following the intravenous injection of cancerous ascitic fluid. With this exception and one or two more doubtful cases his experimental results, so far as the reproduction of malignant tumors is concerned, are, like those of other investigators in the same line, negative.

EXHIBITION OF ANIMAL PARASITES[1]

These parasites were collected from domestic animals in Baltimore, during the previous two years as opportunity offered, no attempt being made to have the collection complete. The interest in animal parasites has been overshadowed of late years by the study of the pathogenic bacteria, but nevertheless the *entozoa* are of great interest and importance and deserve our careful attention.

1. From the horse:

Spiroptera megastoma (or *Filaria megastoma*). The stomachs show the honey-combed submucous tumors, with ulcerated mucosa, containing the large-mouthed maw-worms. This parasite is not very rare in the horses of this region, but in none of the cases in which it was found, was there evidence that it had materially damaged the usefulness of the animal.

Strongylus armatus. Here are several specimens, gross and microscopical, of verminous aneurism of the anterior mesenteric artery. The presence of the palisade worms in the bloodvessels causes interesting histological changes. This parasite with the resulting aneurisms is common in horses of this region. In one instance it had caused fatal colic.

Gastrophilus equi. Here is a stomach, the mucous membrane of which near the cardia is completely covered with bots.

2. From the cow:

Actinomyces bovis. Although this is a vegetable parasite, the opportunity is taken to show a number of specimens of actinomycotic tumors from the jaws and other parts of the cow. On account of the absence of any satisfactory laws regulating the inspection of meat in this state, the number of cattle affected with actinomyces brought to Baltimore and slaughtered here for the market is unusually large and there is rarely any difficulty in procuring specimens of this disease. Attempts have been made to cultivate the organisms according to the directions given by Boström but without success. No instance in which the actinomyces has been found in human beings has been recorded.

Cystirercus taeniae mediocanellatae. This parasite was found once in the heart-muscle of a cow.

Strongylus micrurus. A number of cases of verminous bronchitis and pneumonia in calves due to this parasite have been observed and here are microscopical sections of the lungs so affected.

Filiaria labiato-papillosa (Alessandrini). This worm was found free on the peritoneal surface of a cow without causing any apparent injury.

[1] Report of remarks before the Johns Hopkins Hospital Medical Society, Baltimore, March 17, 1890.

Johns Hopkins Hosp. Bull., Balt., 1890, I, 72-73.

3. From the sheep:

Taenia expansa. This parasite was found in the small intestine. It is quite common.

Strongylus contortus. The parasite was found in large numbers in the stomach of several sheep which had died at Druid Hill Park without other apparent cause of death.

4. From the hog:

Echinococcus. Echinococci were found in several hogs which had been born and reared in the neighborhood of Baltimore, but this parasite is not common in this region. Sections of the liver are shown illustrating every stage of development of this bladder worm from cysts smaller than a pea up to cysts as large as an orange. Here are specimens of the taenia echinococcus produced by feeding the cystic worms to a dog.

Cysticercus cellulosae. The pork measles has been found in only a few instances.

Echinorhynchus gigas. This worm is common in the swine of this region and appears to be common throughout the United States. The ulcerated and necrotic patches in the inner wall of the small intestine caused by the attachment of the thorn-headed worm, bear some resemblance to the necrotic foci resulting from hog cholera. In only one instance had the gut been actually perforated by this worm.

Trico-cephalus crenatus. This parasite was very common in the caecum.

Ascaris suilla, believed by many to be identical with *Ascaris lumbricoides*. It was not very often met with. In one case the small intestine for a distance of 40 cm. was found packed full of ascarides, but there were no evidences of intestinal obstruction and it is questionable whether this accumulation of the worms, so as apparently to obstruct the gut, is not a post-mortem occurrence.

Sclerostoma pinguicola (Verrill), believed to be identical with *Stephanurus denatus* (Diesing), although this identity is not absolutely certain. This interesting worm was found in the abdominal adipose tissue and in the liver. The presence and mode of migration of this parasite in the liver of swine have not hitherto been described. *Sclerostoma pinguicola* was found in the livers of eleven swine, and, while not very frequent, cannot be considered a rarity in this situation. It is found, often in large numbers, in the main trunk and branches of the portal vein, which then usually contain parietal or occluding thrombi in which the worms are imbedded. The real habitat of the worm is, however the connective tissue around the portal vessels. In this tissue it burrows its way, producing inflammatory masses of new connective tissue rich in leucocytes. On section of the liver, nodules and bands with sinous cavities containing a brownish or reddish white purulent fluid are observed. Similar nodules are also visible projecting on the surface of the liver. In these sinous cavities the parasite may be found, or it may be absent, having made its way to other parts. The worm finds its way into the portal vessels by ulceration from the peri-portal tissues through the walls of the vessels, and in several instances the worm could be demonstrated partly without the vein. Before actual penetration into the vein there occurs a bulging inward of the vessel wall on which forms a thrombus composed primarily of blood platelets. One of the most interesting his-

tological changes produced by the invasion of this parasite into the liver is an extensive new growth of the mucous glands in the walls of the bile ducts. This new growth occurs in the areas of newly formed connective tissue in the neighborhood of the parasites. Actual adenomatous formations of undoubted parasitic origin are produced in this way. The same alteration has been recently described and pictured by Schaper in connection with distomatosis of the liver ("Deutsche Zeitschrift für Thiermedicin," Bd. VI, p. 1). On section of the worms, as found in the liver, leucocytes with well stained nuclei, resembling those in the fluid of the cavities containing the worms, can be seen in the intestinal canal of the worm, but whether this can be interpreted as evidence that the pus cells produced by the presence of the worm actually serve as its food is uncertain. Sometimes the lesions of the liver, which have been described were extensive, the surface and interior of the organ presenting a large number of parasitic foci, and it would seem as if such an extent of the disease must be injurious but no cases were observed in which the death of the animal could be attributed to the presence of *Sclerostoma pinguicola*. The parasite as found in the liver and as found in the well known foci in the abdominal fat tissue is identical. Here are instances in which the main trunk of the portal vein as it enters the liver is completely occluded by a thrombus containing the sclerostomata.

Strongylus paradoxus. This strongyle is extremely frequent in the bronchi of the swine in this region. Its presence was found to be the direct cause of death in three pigs. In these cases the trachea and bronchi contained an almost incredible number of strongyles, so that on sections of the lung, the medium-sized and small bronchi appeared filled with worms. *Strongylus paradoxus* is usually associated with some bronchitis and often with broncho-pneumonia, but it may be present, even in large numbers, without either bronchitis or pneumonia. In fact in one of the fatal cases in which the strongyles appeared to fill the medium-sized and small bronchi and were present in enormous numbers in the trachea and large bronchi there was no trace of pneumonia and scarcely any bronchitis. The animals suffered from extreme dyspnoea and the heart pulsated so violently as to be visible at a distance and to communicate its motion to the entire thorax. At the autopsy the right ventricle was hypertrophied. The favorite habitat of the worms when present only in moderate number is in the bronchi in the posterior part of the caudal lobes, and sometimes their number is so small that considerable searching is required to detect them. There is usually a little muco-pus in the thrombi where the strongyles are lodged even when there is no general bronchitis. The adjacent lung parenchyma is often emphysematous or on the other hand it may be simply atelectatic or it may be the seat of a broncho-pneumonia. Frequently there is a broncho-pneumonia of the ventral lobes when the worms are to be found only in the posterior parts of the caudal lobes. The broncho-pneumonia associated with *Strongylus paradoxus* appears as a brownish or grayish red consolidation in which the individual lobules and lobulettes can be felt and seen as nodules. The affected part is not much swollen and there is generally no pleuritic exudation. On microscopical section the air cells contain leucocytes, epithelioid cells, sometimes fibrin and red blood corpuscles and frequently ova of the strongyles. These ova are often partly or completely enclosed within giant

cells By a combination of Weigert's fibrin stain and picrocarmine very beautiful pictures in which the ova are stained blue and the cells red and yellow with picrocarmine can be obtained. A very instructive lesson in embryology is furnished by the ease with which all stages of development of the ova from the simple cell up to the developed embryo worm can be followed in these preparations.

5. From the dog:

Taenia cucumerina. This is by far the most common tape-worm of the dogs used for experiment in the laboratory, being found in sixty per cent of these animals.

Taenia serrata. Here are specimens produced by feeding dogs *Cysticeri pisiformes* from the rabbit.

Taenia echinococcus was found only in dogs artificially fed with the echinococcus from the hog.

Eustrongylus gigas. Here is a specimen of this worm, 95 cm. long, found free in the peritoneal cavity of a dog. It has been found three times in this situation in dogs used for experiment in the laboratory.

Strongylus of dochmius trigonocephalus (*Uncinaria trigonocephala*). This parasite was found in the small intestine in seventy per cent of the dogs used in the laboratory, a much larger proportion than has hitherto been observed. The head of the worm was often found imbedded in the mucous membrane and surrounded by a small extravasation of the blood. Sometimes scanty, it was, in many cases, found in large numbers. Positive evidence that the parasite was the cause of anaemia in the animals could not be found. It was occasionally met with in the stomach as well as in the small intestine.

Tricocephalus depressiusculus. This worm appears to be a constant inhabitant of the dog's caecum.

Ascaris marginata (doubtless a variety of Ascaris mystax). This parasite was found in only a few cases. It was found both in the stomach and in the small intestine.

Filiaria immitis. It was not met with in any of the dogs used in the pathological laboratory and is not common in this region. It, however, occurs here and it has been observed occasionally in the biological laboratory of the Johns Hopkins University.

6. From the rabbit:

Coccidium oviforme. This parasite was present in one-third of the rabbits used for experiment in the laboratory. Coccidia are also common in the intestines of rabbits. There are small, opaque, grayish white patches, suggesting somewhat a superficial necrosis, on the surface of the mucous membrane of the small and large intestine. These patches contain large numbers of coccidia, often enclosed in epithelial cells.

Cysticercus pisiformis. It is common in the peritoneal cavity. Here are specimens which illustrate the nodules and scars caused by the migration of this parasite through the rabbit's liver.

7. From the rat:

Cysticercus fasciolaris. It was found in the liver.

8. From the cat:
Taenia drassicollis. This worm was found in the intestines.

No instance of *Distoma* in the animals examined was discovered and in general distomatosis of domestic animals appears to be rare in this region. Through the kindness of Professor Brooks, I am in possession of a number of living water snails, many of which are infested with cercaria and living specimens of those interesting forms in the life history of Distoma are exhibited under the microscope. These snails were obtained in the neighborhood of Baltimore, so that opportunity for infection with distomata is present here.

INTESTINAL AND HEPATIC ACTINOMYCOSIS, ASSOCIATED WITH LEUKAEMIA[1]

I. Abstract of Clinical History by Thomas S. Latimer

History.—W. H. Thomas, colored male, aged 21, single, a day-laborer, was admitted to the City Hospital, Baltimore, November 17, 1895. The patient claimed to have always been well until the previous eight months, during which several attacks simulating appendicitis, but without operative treatment, occurred. On admission he complained of headache, loss of appetite and obstinate constipation, with frequent nose bleed, an irregular fever, slight chills and sweats, not requiring continuous taking to bed.

Examination.—The patient was anaemic. There was slight enlargement of the axillary and post cervical lymphatic glands. The chest examination was negative except for a feeble heart-beat. The pulse was 120 per minute, weak and easily compressible. On abdominal examination, no tenderness or lump in the region of the appendix was made out. Upon repeated examination, the spleen could not be felt. His liver, however, was found greatly enlarged, extending well below the margin of the ribs, felt smooth and firm and was somewhat tender on palpation. No fluctuation could be found. Because of a tentative diagnosis of deep seated hepatic abscess, the liver was aspirated in several places but without result. No microscopical examination of the small particles that were found clinging to the aspirator was made. Blood examination showed red blood cells, 3,200,000, white blood cells, 246,000. A differential white blood count showed:

Polymorpho-nuclear neutrophilic leucocytes	58	per cent.
Polymorpho-nuclear neutrophilic leucocytes	5	" "
Large mononuclear and transitional leucocytes	4	" "
Small mononuclear leucocytes	3	" "
Myelocytic leucocytes	30	" "

The haemoglobin was 25 per cent. No malarial parasites were found.

Subsequent Course.—The patient had an irregular morning and evening temperature that varied between 97.6° and 104° F. respectively. The patient only suffered discomfort when lying on the right side or during

[1] Report of a pathological specimen.

In: A Case of Intestinal and Hepatic Actinomycosis in Man, Associated with Leukaemia, by Thomas S. Latimer, Baltimore.

Tr. Ass. Am. Physicians, Phila., 1896, XI, 332-335.

manipulation of the liver. The liver continued to increase steadily and uniformly in size, with no localized area of tenderness, fluctuation or enlargement. The patient became unable to lie on the right side. He was uncomfortable after eating and his bowels continued constipated. At first a slight general anasarca developed, which rapidly increased, together with an ascites, so that respiration became considerably embarrassed. The dyspnoea was greater than was fairly to be accounted for by the interference with the movements of the diaphragm. The ascites was tapped several times to relieve the dyspnoea. Oedema of the lungs greatly increased the dyspnoea. There was no intestinal disturbance except a tendency to constipation without increase of pain on defecation. Any disease of the appendix was completely masked by the condition of the liver, ascites and oedema of the abdominal wall. In spite of all treatment, the patient's strength steadily diminished until February 10, 1896, when he died, apparently from asthenia.

Diagnosis.—Myelogenous leukaemia with enlarged liver due to diffuse leukaemic infiltration. No suspicion of actinomycosis was entertained.

Autopsy (by N. G. Keirle and John Rurah).—Autopsy about five hours after death; body that of a medium sized man; with general anasarca; oedema greater on the left side of the body, the face and arms especially. Skin pitted on pressure everywhere; the abdomen much distended with fluid; thin watery fluid ran from the nose and mouth. The muscles were pale and bloodless. The abdomen contained a large quantity of pale, straw-colored fluid; there were numerous adhesions; both the parietal and visceral layers of the peritoneum generally thickened; intestines bound together by peritoneal adhesions; omentum very adherent and without fat. Liver extended some 10 cm. below the margin of the ribs. Along the costal margin to 7 cm. of the median line was a dense, firm mass of organized inflammatory tissue 3 cm. in thickness. At the lower part of the same, pus escaped, on cutting out the mass from a cavity that could not be well determined, as it was all closed in by thick walls of inflammatory tissue. Just below the liver about 25 c. c. of greenish pus escaped from an abscess at that point. Spleen was slightly enlarged; weight 350 gm; surface bluish gray; capsule slightly thickened. Kidneys were somewhat swollen (moist) with cloudy swelling. The entire ascending colon and the hepatic half of the transverse colon were massed in inflammatory tissue. The ascending colon, for 6 cm. in its middle could not be removed. The appendix was involved in a mass of inflammatory tissues just above the brim of the pelvis; bile duct, patent; the liver weighed 3260 gm. Left pleural cavity contained 500 c. c. of pale, yellowish fluid; no adhesions. There was no effusion on the right side; but a few adhesions, that broke up easily, between visceral and parietal layer of the lower lobe and the diaphragm. The right lung was pushed up to the

fourth rib in front, but extended in the back to the tenth rib. The left lung was slightly pigmented, upper lobe crepitated, was somewhat emphysematous, and oozed white frothy fluid on section. Lower lobe did not creditate in the lower half, and oozed a thin sanious fluid on section. Pieces sank in water. The right lung showed changes similar in character to those existing in the left lung. The heart showed no important alteration.

II. Pathological Report of Liver

The liver was the only part submitted to me for examination. It had been incised, but was complete. It was preserved in alcohol.

Macroscopic Examination.—The liver presents an irregularly globular shape, measuring 22 x 18 x 12 cm. The right lobe, which is much enlarged, is occupied throughout nearly its whole extent by a mass measuring 12 x 16 cm. This mass extends for a short distance also in the left lobe. It extends throughout the whole thickness of the liver, from the lower to the upper surface, but it occupies a larger transverse area in the lower two-thirds than in the upper third of the organ.

The inferior surface of the right lobe, with the exception of a narrow margin of liver-substance on the right side, is entirely occupied by the new growth, which here was apparently continuous with an abscess formation extending downward along the ascending colon. This inferior surface and the posterior margin of the right lobe are connected with a dense mass of fibrous adhesions, in which are included the hepatic vessels, the right adrenal gland, and the hepatic flexure of the colon.

The diaphragm is firmly adherent to the superior surface of the right lobe of the liver, and has been removed with the liver. The mass of new growth in the liver has penetrated through the liver substance on the upper surface, but has not penetrated through the adherent and thickened diaphragm.

Upon section it is seen that a definite fibrous capsule of dense consistence and grayish color surrounds the mass in the liver, separating it from the surrounding brownish red parenchyma of the liver. This fibrous capsule is complete except in certain areas on the inferior surface of the liver or of the new growth, where the opaque, yellowish characteristic foci of the mass come to the surface, and were evidently in connection with the subhepatic abscess. This relation and the general topography afford presumptive evidence that the morbid process invaded the liver from below by continuity.

Upon section the mass presents in exquisite manner the characteristic honeycombed appearance of a chronic actinomycotic tumor. There are spaces and interlacing trabeculae. The spaces often anastomose. They vary in shape and size on section, some being round, others oval, others more or less cylindrical. They contain a soft yellowish white purulent material,

which can be squeezed out readily, and in which can be detected abundantly the small yellowish granules of the colonies of actinomyces. The immediate margins of the spaces are of an opaque, yellowish white, necrotic appearance. The spaces vary from 1 to 6 or 8 mm. in diameter.

The trabeculae are in general broad and interlacing and of firm consistence and translucent gray color, like fibrous or granulation tissue.

Microscopic Examination.—For the study of the histological structure, staining with haematoxylin and eosin was used; for the details of the structure of the parasite, Gram's, Weigert's, and Mallory's stains were found most serviceable.

The microscopical sections show interlacing bands of fibrillated connective tissue, rich in long fusiform cells. Between these fibrous bands there are dense accumulations of cells. In the immediate neighborhood of the actinomyces the cells are closely packed together and there is little or no basement substance. These cells are predominately polymorphonuclear leucocytes; in other words, the parasitic colonies lie for the most part in purulent foci. Outside the areas of actual pus there is granulation tissue in varying stages of formation, from a tissue composed almost exclusively of granulation cells and leucocytes to a tissue rich in basement-substance and with elongated cells. In the fibrous trabeculae are bloodvessels with thick muscular walls and containing an excess of leucocytes, among which are many mononuclear forms. Adjacent to the liver parenchyma the fibrous tissue is dense and contains numerous rows of compressed liver cells, presenting the appearance of the so-called newly formed bile ducts. Here and there are mucous glands derived from those in the walls of the bile ducts, but now without evident connection with bile ducts, and apparently hypertrophied and proliferating so as to simulate adenomata. The capillaries of the liver contain an excess of leucocytes, mononuclear cells predominating.

The colonies of actinomyces are rarely single, more frequently they are conglomerated into irregular masses, which may be 1 to 2 mm. in diameter. These colonies in general present a central, looser part of tangled fine filaments and slender rods, with, at times, deeply staining coccus-like bodies, and a more densely woven ring of fine filaments nearer the periphery, from which the filamentous branching threads radiate outward. These radiating threads often extend out among the surrounding pus cells and are often devoid of any bulbous swellings or club-like extremities.

It is not found easy to demonstrate satisfactorily the clubs which are frequently found at the extremities of the threads in cases of actinomycosis. The stain recommended by Mallory is most suitable for this demonstration. By this stain there could be demonstrated around some, although not around most, colonies a deeply stained red, almost homogeneous, peripheral zone,

into which the blue threads could be traced. This red margin clearly belonged to the parasite and not to the surrounding cells, from which it was often separated by a narrow space. The outer surface of this red border was often somewhat irregular and indented, and in general the impression was gained that this outer zone, which stained by Mallory's method deeply red, consisted of the coalesced material which composes the club-like swellings at the extremities of the threads in most cases of actinomycosis. I am inclined to interpret the failure to demonstrated sharply defined clubs in this case, and the appearance of a diffuse, homogeneous, peripheral substance, with the staining reactions of the clubs, to postmortem changes. That the clubs may become indistinct or even disappear in consequence of postmortem changes has been demonstrated by Weigert.

But only some of the colonies showed this homogeneous marginal zone. Many were entirely devoid of such a zone or of any suggestion of clubs. It is now well known that actinomyces colonies are often devoid of characteristic club-like swellings. In this case, as in that reported by Mallory, there are numerous bacilli belonging to the actinomyces, scattered among the cells independently of the colonies. Clumps of streptococci were also observed in small number, so that there was mixed infection with actinomyces and streptococcus.

The mass in the liver, therefore, presents macroscopically and microscopically the typical structure of an actinomycotic tumor. As has already been stated, the evidence is that the parasite gained access to the liver and generated the new growth at the inferior surface of the organ. The process gradually extended so as to invade most of the right lobe and a part of the left lobe of the liver.

Although I have not had the opportunity to examine other parts from this case, there can be little or no doubt, in the light of the clinical history and the observations made at the autopsy, and in similar cases, that the portal of entry of the parasite was the intestine, and in all probability the starting point was actinomycotic appendicitis (possibly colitis), whence the morbid process extended upward in the tissues along the ascending colon to the right hypochondrium, and invaded the liver at its lower surface.

PREVENTIVE MEDICINE

MODES OF INFECTION[1]

Mr. President and Gentlemen, Fellow-Members of the Medico-Chirurgical Society.—When honored by the invitation to deliver the Annual Address before this Society, it seemed to me appropriate to select a subject relating to that department of medicine in which the most important discoveries have been made in recent times. The far reaching advances in our knowledge of the causation of infectious diseases have opened up new fields of view in so many and in so various directions, that I have been somewhat in doubt as to what phase of the subject it would be most profitable for us to consider on the present occasion.

The time has gone by when much profit is to be derived from the discussion of that very general and hackneyed theme, the germ theory of disease; for the doctrine thus expressed is no longer a theory, and there is, doubtless, no one competent to form an opinion on the subject who does not believe that certain infectious diseases are caused by microorganisms, and that it is a logical inference that the other diseases of this class are produced by parasitic organisms—although there may be differences of opinion as to how far this doctrine has been proven for individual diseases.

I have thought that it might be of interest to pass in review certain fundamental ideas concerning infectious diseases, and to note how far these ideas have been modified or expanded by recent discoveries.

Many of these ideas are by no means of recent origin, for from the earliest times onward much attention has been devoted to the investigation of epidemic diseases, and particularly of their causation. The conceptions of contagium and of miasm are almost as old as the history of medicine itself. Ancient writers have recorded their belief in the existence of infected localities, and in the conveyance of epidemic diseases by means of the drinking water and of the air. Individual predisposition to infection, as well as predisposition according to time and to place, are not modern ideas, as is shown by such historical terms as *genius epidemicus, constitutio pestilens.* The science of epidemiology is much older than that of bacteriology, and has taught us much concerning the causation and development of infectious diseases.

The question arises: Has our knowledge concerning the origin and spread of infectious diseases been widened and has it become more exact since the

[1] Annual address delivered before the Medical and Chirurgical Faculty of Maryland, Baltimore, April 27, 1887.

Tr. M. and Chir. Fac. Maryland, Balt., 1887, 67-87.

discovery of the living contagium of many of these diseases? While granting the vast scientific importance of this discovery, it is in itself only the confirmaton of the faith of far-seeing minds of past generations. The mere demonstration of that which was previously a reasonable supposition does not offer a new point of view.

It is proper for us to inquire whether the investigation of the microorganisms causing infectious diseases, and the study of the characteristics and life histories of these parasites, of the media and conditions of their growth and of the means of their destruction, have added materially to the knowledge which was already afforded us by the epidemiological study of these diseases. Have we thereby gained a clearer conception of such terms as miasm, contagium, and miasmatic contagium? Have we a deeper insight into the conditions under which a virus is transmitted from an infected to a healthy person, and of the conditions of infection through the air, the drinking water and other media? Can we form any more definite ideas of what is meant by individual predisposition to an infectious disease and by such terms as predisposition in time and in place?

Even if we were obliged to answer all of these questions in the negative, not one particle would be detracted from the importance of further pursuit of bacteriological studies, for experience has shown that nothing is more short sighted than to estimate the value of scientific discoveries according to their immediate practical utility. And, moreover, the questions which I have raised relate to only a few out of many practical aspects of these studies; but if, as I believe to be true, it can be shown that light has been shed upon some of the most interesting and obscure problems concerning infectious diseases, by the studies of the living organisms causing these diseases, then it is apparent that the results of these studies are of more immediate interest and of interest to a much wider circle than would otherwise be the case.

Our knowledge in the directions indicated is but fragmentary. The title "Modes of Infection" under which I wish to gather together some of these fragments has been selected as a convenient one to cover most of the thoughts which I desire to present to you. The intention, however, is not to consider exhaustively all possible modes of infection, but chiefly to dwell upon such points relating to the causation of infectious diseases as have been most illuminated by recent investigations, particularly in bacteriology.

There is now tolerable unanimity of opinion as to the meaning attached to the terms infections and infectious diseases. Most recent authorities understand by infection the condition produced by the entrance and multiplication of pathogenic microorganisms within the body. An infectious disease is one which is caused by the invasion and reproduction within the body of pathogenic mieroorganisms. To define an infectious agent as a

specific poison capable of indefinite multiplication is only to express obscurely the idea just conveyed, for we know and can conceive of no poison capable of indefinite multiplication except a living organism. The analogies formerly drawn from the fermentation and the putrefaction of organic substances, and still preserved in the designation zymotic diseases, have lost all force as an opposing argument since it has been shown that these processes are produced by living organisms. In the absence of any other probable, I may say even conceivable, hypothesis, to refuse to accept the doctrine of a *contagium vivum* as applicable to all infectious diseases because it has been demonstrated only for certain of these diseases, is about as reasonable as to reject the law *omnis cellula e cellula* because this has not been proven for every cell or every species of cell.

We should be by no means justified to substitute in the foregoing definition of infection instead of pathogenic microorganisms, bacteria or fissure fungi. It is true that most of the infectious agents with which we have become acquainted are bacteria, but the malarial parasite is a notable exception to this. There are grounds for believing that the specific organisms of some of the infectious diseases may belong to low forms of animal or vegetable life other than the bacteria. Our means for demonstrating the presence of bacteria are comparatively satisfactory, but this cannot be said of most of the other protozoa, and it is perhaps in consequence of this imperfection of our methods of investigation that so many infectious diseases have resisted successfully our efforts to discover their efficient causes.

It is gratifying, after so much strife, to be able to record this agreement of opinion as to the definitian of infection and of infectious diseases in general. It is customary to classify infectious diseases etiologically into contagious, miasmatic, and miasmatic contagious diseases. As to the significance of these terms, and particularly as to the real nature of the so-called miasmatic contagious diseases, there exists great confusion. As the epithets miasmatic, contagious, and miasmatic contagious meet us upon every hand in our investigations of infectious diseases, as they relate to conceptions which lie at the very foundation of our knowledge of the subject, it is manifestly of the utmost importance that their meaning should, if possible, be rendered clear and precise. I question, however, whether these terms any longer suffice for the classification of infectious diseases, although, as Pettenkofer has said, the ideas contagium and miasm are so bred into our flesh and blood that we would as soon think of parting with them as with one of our limbs even after it had become useless.

Originally the distinction between contagium and miasm was sharply defined. There are two attributes which essentially characterize the ordinary conception of contagium, viz. multiplication within the diseased body, and

capability of transmission from the diseased to the healthy body. The latter attribute implies, of course, the elimination of the contagious principle in an active state from the diseased body. On the other hand a miasm is produced outside of the body. According to the belief of many writers it does not multiply within the body, and all agree that it is not eliminated from the body in a condition capable of producing infection. Especial emphasis in framing these distinctions was laid, in the case of a contagious disease, upon the origin of the virus within the body (endogenous), and in the case of a miasmatic disease, outside of the body (exogenous). These ideas concerning contagium and miasm answered well enough for the typically contagious diseases such as syphilis and the exanthematous fevers, and for the typically miasmatic disease, malaria. But confusion began during the middle third of the present century when the origin and spread of Asiatic cholera were carefully studied. It was found impossible to classify this disease under either of the two existing divisions. It has in common with the contagious diseases the characteristic that persons affected with cholera may convey the disease to localities previously free from it, and may prove the starting points of wide spread epidemics. Cases sometimes occur of which the only natural interpretation is that they have originated from contagion. On the other hand, in infected localities the disease often develops in those who have never seen a cholera patient, much less come into contact with one, while those in attendance upon such patients as a rule are no more liable to the disease than others living in the same locality. Similar observations were made with reference to typhoid fever.

There arose the contest, not yet ended, between the contagionists who held that these diseases are to be ranked as contagious, and the localists who regarded them as miasmatic in origin, and to explain certain peculiarities introduced the new conception of a portable miasm. The majority, however, sought refuge under a new cover. The class of miasmatic contagious diseases was formed, and in this amalgamated group were placed cholera, typhoid fever, yellow fever, and several other infectious diseases not conveniently classified elsewhere.

Various meanings have been and still are attached to the term miasmatic contagious diseases. Some understand by a miasmatic contagious disease one which is propagated sometimes by a contagium and sometimes by a miasm—that is, sometimes by a virus produced within the diseased body, and sometimes by a virus produced outside of the body. Others hold the opinion that for the production of cholera, typhoid fever, and other diseases of this class, two viruses or microorganisms are necessary, one derived from a person affected with the disease, and the other derived from the soil, or at least from some external source. But the view which has gained the most

adherents, and which is the prevalent one at the present time, is that a patient with typhoid fever or with cholera throws off from his body a poison, a microorganism, which at the time of its discharge is not capable of producing the disease, but which under favorable circumstances undergoes outside of the body some unknown metamorphosis by which it acquires this power. This last view is the one which is accepted in most of the text books on medicine published within recent years in this country and in Europe, and I presume that it embodies the belief on the subject of most practitioners of medicine.

One of my main objects in the present address is to direct your attention to what seem to me weak points in this hypothesis, and to endeavor to explain in a more natural and satisfactory manner the peculiarities of the so-called miasmatic contagious diseases, at least so far as two leading representatives of this group, viz. cholera and typhoid fever, are concerned. The discovery of the microorganisms which are in all probability to be regarded as the specific causes of cholera and of typhoid fever, and the investigation of their properties, should have led, it might be supposed, to a general revision of the widely accepted doctrine of miasmatic contagious diseases; but this has not been the case—at least among clinical writers, who apparently see no reason why the actually discovered germs, as well as those previously surmised, may not undergo the assumed matamorphosis outside of the body which renders them capable of infection. This is still the reasoning of Liebermeister in his work on "Infectious Diseases," published in 1885, in which he accepts the cholera and the typhoid bacilli as the agents of infection.

Let us now examine in detail the arguments which are brought forward in support of the miasmatic contagious doctrine as previously defined.

In the first place, it is urged that a metamorphosis such as is assumed to occur in the agents of infection after their elimination from the body of a cholera or a typhoid fever patient, has its analogy in the well known instances of alternation of generation; and usually the ordinary tape-worm is cited, the ova of which, as is well known, first develop into cysticerci, and only these, when swallowed, are capable of giving rise to mature tape-worms.

The argument by analogy, however, instead of supporting the miasmatic contagious hypothesis, is directly opposed to it. In the class of organisms to which the typhoid and the cholera germs belong, no instance is known of any organism after its discharge from the body acquiring infectious properties which it did not previously possess, or of its undergoing any transformation at all resembling that assumed to occur. On the other hand, we know of some pathogenic organisms which are rendered more virulent by their passage through the body of an animal susceptible of the disease; and, in general, bacteriologists are inclined to regard as especially potent bacteria

which are fresh from the bodies of infected animals. Where it is aimed to produce intoxication by means of ptomaines, as can be done by cultures of the typhoid and of the cholera bacilli, then it is true that old cultures, as would naturally be supposed, are the most effective; but there is no reason to believe that ptomaine intoxication plays any rôle in the primary infection with the typhoid or the cholera germs; or, if it did, where are the ptomaines likely to be more abundant than in fresh typhoid and cholera stools?

Before we knew as much as we now do about the properties of bacteria, the transformation hypothesis now under criticism could be advanced with some show of reason; but at present our information upon this and similar points is by no means scanty, and in the absence of any pertinent analogy for such an occurrence, the assumption seems entirely unwarrantable that the specific organisms of cholera or of typhoid fever acquire new or increased virulence after their removal from the body. Inoculation experiments upon animals with the cholera spirilla lend no support to this assumption.

In the second place, it is urged in support of the miasmatic contagious theory that the specific germs of these diseases cannot be eliminated from the body in a condition capable of causing infection; otherwise those who are in proximity to the patients must frequently become infected, as in cases of smallpox or of typhus fever. This is, evidently, the argument which has the greatest weight. It is to explain the absence, or at least the infrequency of any direct communication of cholera and of typhoid fever from one person to another, that the hypothesis under consideration was constructed.

It is, of course, apparent that the specific germs of cholera and of typhoid fever must be discharged from the body in a very different way and must have very different properties from those of the contagium of smallpox and similar diseases. It is because our ideas of what characterizes a contagium are derived from our observations of such highly contagious diseases as smallpox or scarlet fever that we are loath to admit that cholera or typhoid fever patients emit anything which can be called an active contagium. I believe, also, that not a little of the difficulty of this admission comes from the popular notion that a source of active contagion must necessarily infect the surrounding atmosphere, as is the case with a smallpox patient.

It is, however, possible to reconcile the fact that the discharges of cholera and of typhoid fever patients contain a contagium, and that, too, in an active form, with the infrequency with which these diseases are communicated in a manner which is ordinarily understood as contagious.

Let us take for example cholera, and consider in the light of recently ascertained facts what conditions must be fulfilled in order that the disease may be contracted directly from a patient. It is to be borne in mind that the

cholera germ is discharged from the body only in the faeces, and very exceptionally in the vomitus. It is not present in the urine, nor in the breath, nor in the sputum, nor is it thrown off from the surface of the body. These are well established facts, so that we can conclude that the only danger of direct infection from a cholera patient is by means of the stools. It is necessary, however, to come into actual contact with the stools in order to become thus infected. It has been proven by exact and very interesting experiments of Naegeli and Buchner that bacteria are never lifted by currents of air from the surface of fluids or from moist surfaces in general. One could remain in a room containing any quantity of cholera stools swarming with cholera spirilla and there would be no danger of infection with cholera through the air. Bacteria are conveyed into the air only when they are in a dry condition, and the cholera organism is quickly destroyed by drying. So far as cholera is concerned, there is therefore no basis for the prevalent belief that the atmosphere becomes infected for a certain distance around substances containing an active contagium, although this belief is justified as regards certain other species of contagia.

But it does not suffice for infection merely to have come into contact with cholera stools; portions of the stools must actually be swallowed. There is every reason to believe that infection with cholera takes place only through the reception of the virus directly into the alimentary canal, and not through subcutaneous inoculation or through the respiratory organs.

If this last condition be fulfilled and portions of cholera stools be actually swallowed, even then in any given case the chances are probably at least three to one that no infection would follow; for cholera spirilla are destroyed by the acid of the gastric juice, and it is a matter of experience that only a minority of those exposed to the specific cause actually contract the disease. These considerations show how worthless are the isolated experiments of those foolhardy individuals who have voluntarily swallowed cholera dejecta and cultures of the cholera spirilla. Whatever had been the outcome of these few experiments, no positive conclusions could be drawn from them. A negative result, for reasons already given, was to be expected; a positive result would prove nothing, for the experiments were all made in districts already infected with cholera, and it would have been impossible to decide whether the infection had taken place in a natural way or as the result of the experiment. The conditions were of course entirely different in the instance of the doctor in Koch's laboratory who contracted cholera as a result of careless handling of cultures of cholera spirilla, for there was at the time no cholera in Germany and no other possible source of infection than the cultures.

Enough has been said to show what difficulties attend the direct communication of the disease by a cholera patient. It is perfectly explicable why direct contagion is so infrequent notwithstanding the fact that cholera stools contain the contagion in an active form, indeed sometimes almost as a pure culture. There is no necessity to resort to any such artificial, complicated and unsupported hypothesis as the miasmatic contagious doctrine in the sense at present under consideration.

But any satisfactory explanation the specific cause of cholera must account for occasional instances of transmission of the disease by contagion. I do not propose to discuss here in detail that most vexed question, Is cholera contagious? but I believe that he who denies absolutely the contagiousness of the disease must shut his eye to plain facts. There are instances, and of course they are to be sought not in regions where cholera is epidemic but where sporadic cases occur, where the only natural interpretation is in favor of direct contagion.

Now the miasmatic contagious hypothesis has no room for these contagious cases, whereas there is no difficulty in accounting for occasional instances of contagion according to the view, which I believe to be an established fact, that the cholera stools contain the active cholera virus. Indeed, such instances of contagion are to be expected, although least frequently of course among doctors and nurses, whose comparative immunity is usually cited to prove the non existence of any active contagium eliminated by a cholera patient. Doctors and nurses are the most likely to see that the cholera stools are properly disinfected, and also to disinfect their hands or other parts of their persons which may have become soiled by the dejecta. On the other hand, among ignorant persons living in cramped and unclean quarters the chances of direct contagion are much more favorable. It is probable that the statements in books relating to the frequency of cases of cholera caused by contagion are misleading, for such cases are least likely to come under the observation of those who contribute most largely to medical literature, namely, physicians with practice in hospitals and among the well-to-do classes living under good hygienic surroundings.

There is a general agreement upon the point that the epidemic spread of cholera cannot be accounted for by direct contagion. It is generally admitted that the specific agent of infection, derived from the dejecta of a cholera patient, may under favorable conditions multiply outside of the body, in the ground, upon vegetables and elsewhere. We are to seek the chief sources of infection in cholera epidemics in the drinking water, the food, the ground, in actual contact with substances containing the specific germs. A discussion of these various external sources of infection, notwithstanding the great interest and importance of the subject, is not pertinent to my present

argument, which is to show not only that it is not necessary to deny the existence of an active contagium in the fresh cholera stools, but that there is every reason to believe that such contagium is actually present.

I have selected cholera for the purpose of showing the falseness of the miasmatic contagious theory as expounded by Liebermeister and others, partly because our knowledge concerning its etiology has become much more exact since Koch's discovery of its specific germ, and partly because this disease has been generally regarded as the main support of this theory. Indeed, the hypothesis of the transformation or ripening of germs after they leave the body was constructed especially to account for the phenomena of Asiatic cholera. The arguments which I have presented apply equally to typhoid fever, another important member of the miasmatic contagious group of diseases. Here, too, the specific virus is eliminated from the body, as a rule, only in the faeces. There exist the same reasons in the one as in the other disease why infection is likely to take place only exceptionally in the form of direct contagion. It is not necessary to go over the same ground with typhoid fever which we have already traversed with cholera, for as regards the point now under consideration the evidence is of the same character for both diseases.

Our information is at present wholly insufficient to enable us to form any positive opinion as to the mode of elimination of the specific virus of yellow fever.

I have attempted, gentlemen, to make it probable that a patient with cholera or with typhoid fever emits a contagium in just as active a state as a patient with smallpox or with scarlet fever. We cannot explain the difference in frequency with which the two sets of diseases are propagated by direct contagion by assuming that only in the latter diseases is the virus eliminated in a condition capable of producing infection. The relative frequency with which infectious diseases are communicated by direct contagion depends, I believe, first of all, upon the channels through which the virus is eliminated from the body.

It may be stated as a broad proposition that every infectious disease can by artificial means be transmitted from an individual affected with the disease to another individual susceptible of the disease. This is only the natural inference from the fact that each infectious disease has its specific virus in the shape of a microorganism which is present and multiplies in the bodies of those affected with the disease. Although there is no evidence that under natural conditions malaria is ever transmitted from one person to another, still it is possible to accomplish this artificially, as has been proven by the experiments of such trustworthy observers as Gerhardt and Marchiafava and Celli, who inoculated successfully, with blood from malarious patients, persons who were entirely free from malaria.

Strictly speaking, therefore, in every infectious disease there is a contagium, but we should fall into grave errors if we drew our conclusions as to the natural modes of infection from the results of artificial inoculations, as is illustrated by the example of malaria.

To explain why, under natural conditions, some diseases, such as the exanthematous fevers, are usually transmitted by contagion; other diseases, such as typhoid fever and cholera, only infrequently, and other diseases, such as malaria, never by contagion, it is necessary, I repeat, to consider the channels by which the virus is eliminated, if at all, from the body.

If, as in the case of malaria, the virus is not discharged at all from the body, then of course there is no possibility, under the conditions of nature, of the communication of the disease from one person to another. If, as in the case of cholera and of typhoid fever, the virus is discharged only by way of the faeces, then contagion is possible, but it is not likely to occur with ordinary care and with ordinary cleanliness. If, as in the case of scarlet fever, measles and smallpox, the virus is eliminated from the skin and adheres to thin scales of epidermis which can be readily transported through the air, then contagion is likely to be a common occurrence.

I do not wish to be understood as implying that the mode of elimination of a virus is the sole factor in determining the degree of contagion of a disease. There are, of course, other important factors, such as the degree of resistance offered by the virus to drying, the chances of its being conveyed into the air, its quantity, etc., as well as the degree of susceptibility which exists on the part of those exposed and the portal through which the virus must enter in order to cause infection.

I trust, gentlemen, that this will be found a more rational, fruitful and satisfactory way of regarding the infectious diseases than to wander among the mazes of miasmatic, contagious, and miasmatic contagious diseases, and to imagine that in some diseases the virus is eliminated in a potent state, and in other diseases in a state requiring some subsequent transformation to make it potent.

It is unfortunate that our positive knowledge concerning the mode of elimination from the body of the specific poisons of the various infectious diseases is still very incomplete. Only for those diseases whose special agents of infection have been discovered is our information exact upon this point. For some other diseases we have good grounds for forming an opinion, while in the case of several infectious diseases, such as relapsing fever, we are quite in the dark on the subject.

It may not be out of place to call your attention to certain points which bear upon this question. The experiments of Wyssokowitsch, made in the Hygienic Laboratory of Göttingen, and published not quite a year ago, have shown that nonpathogenic bacteria injected into the blood of animals in a

few hours disappear from the blood and are deposited in certain organs, especially the liver, the spleen, and the marrow of the bones, whence they also disappear, as a rule, in a short time. They are not eliminated by the urine or by any other excretion. He found that microorganisms in general are discharged by the urine only when they form some local lesion in the kidney or some part of the urinary tract. He found, likewise, that organisms injected into the blood are not discharged by the intestine unless they first cause some lesion of the alimentary canal. Similar facts were determined regarding secretions from other mucous membranes. The experiments of Wyssokowitsch warrant the following statements:

The specific germs of infectious diseases can be and, in cases of recovery, doubtless often are, destroyed within the body.

Contrary to what many have believed, the kidneys and the intestines cannot be regarded as important means of freeing the body from microorganisms which have gained access to the blood.

When the specific microorganisms of an infectious disease are found in the urine or in the faeces, it may be inferred that the genito-urinary apparatus and the alimentary tract respectively are the seat of some lesion produced by these organisms.

These experiments justify also the inference, in itself probable enough, that the specific viruses of infectious diseases are discharged from those free surfaces which are themselves the seats of the characteristic lesions of the disease, as for instance from the respiratory tract in pulmonary tuberculosis, lobar pneumonia, whooping cough, diphtheria; from the skin, in scarlet fever, measles, smallpox, typhus fever, erysipelas; from the intestines, in typhoid fever, cholera; from the urethra or vagina in gonorrhoea, syphilis. For several diseases, however, we have no satisfactory data for determining in what manner the special poison is eliminated. This is true, for instance, of cerebrospinal fever and relapsing fever.

We are ignorant as to whether microorganisms may be eliminated by the breath, although it is a common notion that this occurs. In view of the experiments already cited, which show the difficulty with which microorganisms are detached from moist surfaces by currents of air, it seems improbable that organisms can be conveyed from the body by the breath. Of course, if the organisms were momentarily set free by acts of coughing, then they might be carried on by the respiratory current, but it is at least very questionable whether in ordinary breathing particulate substances can be thus transmitted.

We have up to this point, gentlemen, considered only the diseased body and its fresh excreta as the source of infection, and we have reached the conclusion that in every infectious disease there is a contagium, but that whether or not the disease is likely to be propagated as a contagious one

depends upon various circumstances, among which the mode of elimination of the contagium from the body is of the utmost importance.

A question of great interest, as well as of practical importance, is whether or not any given infectious agent finds conditions outside of the body favorable for its prolonged existence. This question is not identical with that of the reproduction of the special virus outside of the body. The importance of the latter point has been somewhat exaggerated in discussions relating to the etiology of infectious diseases. Special agents of infection may be widely distributed without their finding conditions favorable to reproduction outside of the animal body. Thus the bacillus of tuberculosis appears to be almost as widely spread throughout nature as the organisms which cause suppuration, and yet the tubercle bacillus can find only exceptionally the conditions of temperature and of nutriment which permit its multiplication outside of the body, whereas the pus organisms doubtless find abundant opportunities for their development on various substances outside of the body.

The mere facts of the wide distribution of certain infectious microorganisms and of frequent infection from external sources do not justify us in drawing conclusions as to the capability of growth of the organisms as saprophytes. This is a point which can be positively decided only by a knowledge of the life history and properties of the different infectious organisms.

So far as our present knowledge reaches, it is only such infectious microorganisms as form spores which are capable, under natural conditions, of prolonged existence outside of the body without reproduction. These spores can resist high temperatures, drying, and various other agencies which are destructive to the ordinary vegetative cells. Thus we can explain why, for instance, infection with the tubercle bacillus can take place from external sources, while infection with gonorrhoea always requires contact with fresh gonorrhoeal secretion, although in neither instance does the special virus reproduce itself outside of the animal body, except under such artificial conditions as we can produce in our laboratories.

The question as to the reproduction of infectious microorganisms outside of the body, although it has not all of the significance sometimes attached to it, is nevertheless one of much interest. It is from this point of view that infectious microorganisms are often classified by bacteriologists. Thus there are microorganisms which find only within the animal body the conditions suitable for their growth and development. Such organisms are called obligatory parasites. Examples are the parasitic organisms of syphilis, gonorrhoea, tuberculosis, and doubtless of smallpox, measles, scarlet fever, etc. Other infectious microorganisms are capable of growing under natural

conditions both within the body and outside of the body, as in the soil. Such infectious agents are called by bacteriologists potential parasites. In the case of some of the potential parasites their natural home seems to be the animal body, as appears to be true, at least in most localities, of cholera spirilla and typhoid fever bacilli; while in other cases the natural habitat of the organism is the soil, whence it makes occasional excursions into the animal body. The malarial parasite conforms to the latter type. The growth of microorganisms outside of the body is spoken of as saprophytic.

In the case of typhoid fever there is no *a priori* objection to supposing that its parasite may grow in situations where it has not been introduced by any human being. The weight of evidence seems certainly opposed to such a supposition; still Murchison and other authorities have contended for the so-called spontaneous origin of typhoid fever in some cases, and the question can be settled only by a careful analysis of epidemiological facts, in the interpretation of which there inhere, as is well known, important sources of error.

Of the utmost importance in the elucidation of the spread of many of the infectious diseases, particularly of cholera and of typhoid fever, is the investigation of the conditions favorable to the existence and growth of parasitic microorganisms in the soil, the drinking water, upon vegetables and other substances outside of the body, as well as of the means by which infection occurs from these external sources. These subjects, which pertain to public hygiene, can be touched upon only very briefly upon this occasion.

More attention has been paid to the influence of the soil and of the drinking water in the propagation of epidemic diseases than to any other of the factors named. Under the brilliant leadership of Pettenkofer a school of hygienists has developed who lay emphasis almost exclusively upon the soil in this matter, and are unwilling to admit that epidemic infection takes place through the drinking water.

We owe to this school valuable researches as to the physical conditions of the soil which favor the development into an epidemic of such diseases as cholera and typhoid fever, as well as to conditions hostile to such development. Among the conditions favorable to an epidemic may be mentioned a certain degree of porosity of the soil, a certain amount of moisture, and some impregnation with decomposing animal and vegetable material. But notwithstanding these painstaking investigations, which are much more extensive than this brief notice would indicate, it must be admitted that they have left us considerably in the dark as to how we are to regard the soil as concerned in the propagation of infectious diseases. There has been no actual demonstration of the infectious microorganisms of cholera and of typhoid fever in the soil, or of their multiplication there, and, above all,

no satisfactory explanation as to the means by which infectious agents are transported from the soil to the animal body.

To the medical profession in this country and in England it is not comprehensible how there can still be distinguished authorities who deny that epidemics of typhoid fever or of cholera are ever attributable to drinking water. Yet in Germany there are hygienists who are not only quite positively, but even somewhat violently opposed to what they call the drinking water hypothesis. It is doubtless true that we are often too ready to accuse the drinking water in an outbreak of typhoid fever; but if medical evidence is worth anything, there can be no reasonable doubt that many epidemics of typhoid fever have been due to contamination of the drinking water with the typhoid virus.

The experiments of Meade Bolton have revealed the important fact that most pathogenic microorganisms do not multiply in water sufficiently pure ever to be used for drinking purposes. Not only do the pathogenic bacteria not multiply in drinking water, but, if they do not contain spores, most of them are destroyed in drinking water in a short time, varying from a few hours to several days, according to the species and the quantity of bacteria. These experiments have been hailed by the Munich school of hygienists as opposed to the view that epidemic infection can take place through the drinking water, but they need not be so interpreted, nor are they so interpreted by Bolton.

These experiments make it necessary to suppose that a single infection of the drinking water with infectious organisms would not suffice for an epidemic lasting more than a few days. To keep up a long continued epidemic by means of contaminated drinking water, there must be some communication between the water and some focus in which the disease producing organisms are present in large number or are multiplying. This is in harmony with the fact that repeatedly in epidemics traceable to the water, communications have been proven to exist between the water and cess pools, drains, privies, or other possible foci of infection. In considering water as a source of infection, one must remember that this can occur not only by drinking, but also by the use of the water in cooking, and in washing dishes subsequently used to contain food.

As is well known, there have been several epidemics of typhoid fever in which the source of infection has been traced to the milk. Although in these instances it was believed that the milk was itself infected by the addition of contaminated water, nevertheless it is well to note that in one important particular milk differs from water in its behavior toward pathogenic microorganisms. Milk is an excellent nutritive medium for nearly all of these organisms. The typhoid and the cholera spirilla grow in milk rapidly

and abundantly, without producing any alteration in the external appearance of the milk. Inasmuch as certainty of infection depends, in the case of many diseases, upon the number of organisms which enter the body, it is apparent that this property imparts a particularly dangerous character to infected milk.

As regards the means of transportation by which the agents of infection are conveyed from external objects to the body, the most important is believed to be the air by those who lay the most stress upon the influence of the soil in the spread of epidemic diseases. It seems probable, however, that too big a rôle has hitherto been assigned to the air as a carrier of contagion. The fact has already been mentioned that currents of air are incapable of lifting bacteria from moist surfaces; and Naegeli has shown, also, that if bacteria be dried with their natural gelatinous envelopes or from albuminous substances, they are in much the same physical condition as insects attached to a surface by mucilage, and cannot be carried away by the air unless they are first converted into a dust-like powder. If it be furthermore considered that some bacteria are destroyed by complete desiccation, it is evident that these facts compel us to restrict within much narrower limits than most writers have done, the importance of the air in the transportation of agents of infection. Still there remains evidence enough that the virus of some diseases, notable of malaria, and probably of yellow fever, may be, and often is, conveyed through the atmosphere. As infection through the air is something which we have no means of combating, it is encouraging to learn that this resistless fate has a narrower sway than we had been led to believe.

There are many grounds for supposing that the chief means of infection are by actual contact, in one way or another, with the agents of infection. The conviction of the truth of this statement is borne in almost irresistibly upon one who has engaged extensively in the cultivation of microorganisms. I have kept for weeks at a time, side by side in a sterilized dish to which filtered air had free access, two watch glasses, one containing a culture of the typhoid bacilli in beef tea, the other containing simply sterilized beef tea. During this time, notwithstanding its close proximity to the typhoid culture, the beef tea in the second glass remained perfectly pure, without a trace of contamination from its neighbor. Many illustrations of the same principle might be drawn from the work of a bacteriological laboratory. We study the exposed cultures of such pathogenic organisms as anthrax bacilli, cholera spirilla, glanders bacilli, and run no risk of infection from these so long as we do not come into contact with the cultures.

There is one observation which we sometimes make in our laboratories in summer—to our discomfiture—which, although it may seem trivial, is not without its practical bearings. This is the readiness with which micro-

organisms may be disseminated by flies and other insects. Upon the so-called plate cultures we can sometimes trace the devious wanderings of an insect by the colonies of microorganisms which it has planted in its course. The application of this experience to a possible means of transportation of the special organisms of infectious disease is too apparent to need further elucidation.

I shall not weary you by attempting to elaborate in all of its details the doctrine that one of the chief means of infection is by contact. There are thousands of ways in which we can inadvertently come into contact with sources of infection. This teaches us that it is an error to construct exclusive theories of infection, such as are expressed by the terms "soil hypothesis," "drinking water hypothesis," etc.

There is one lesson, however, which has come from the epidemiological study of the relations of the soil and of the drinking water to infectious diseases, and that is the immense importance of the proper disposal of the refuse matter around human habitations and the supply of pure drinking water. The efficacy of a good system of drainage or of sewerage in preventing the development of many epidemic diseases is probably to be sought, not in the purifying of the ground so that pathogenic organisms cannot grow there, but in affording means by which these organisms, contained in human excreta and other substances, are readily carried away. The discussion of these points relates to sanitary science, and does not belong to my theme, but I cannot refrain from a brief allusion to the subject on account of its great practical importance.

What can be more instructive, as well as more encouraging, than to witness the manner in which Asiatic cholera, during its present journey, has failed to secure any foothold in those European cities which are characterized by cleanliness and proper sanitary arrangements, although it has been repeatedly introduced into such cities? These cities have secured their immunity, not by spasmodic precautionary efforts after the entrance of the disease, but at the price of systematic, vigilant and intelligent exertions during what may be termed the time of peace. Without wishing to pose as an alarmist, I believe that with the announcement of the appearance of Asiatic cholera upon this continent, the time has come to emphasize the fact that the only enlightened and civilized public policy is to be prepared at all times and in all places to meet the enemy.

Of the various factors entering into the causation of infectious diseases none is more obscure than that designated predisposition, and yet this is a factor with which we must undoubtedly reckon. This mysterious predisposition to certain infectious diseases plays, perhaps, even a greater rôle with us, at the present time, than it did with our forefathers in medicine, who wrote so much concerning *constitutio epidemica*.

It cannot be said that the increase in our knowledge concerning the specific causes of infectious diseases has illuminated to any great extent what is meant by predisposition, and still a few glimmers of light have been sent into this dark corner by recent bacteriological investigations.

Mention has already been made of the fact that the cholera spirilla are destroyed by the acid gastric juice, so that we are warranted in regarding all conditions which neutralize the acidity of the gastric juice as affording predisposition to this disease.

Perhaps the most positive addition to our knowledge in this direction has been the demonstration of the importance of preexisting diseases or lesions of structure in affording ready means of ingress and suitable conditions for the lodgment and growth of pathogenic microorganisms within the body. In this connection attention may be called to the experiments of Wyssokowitsch and of Prudden, which show the necessity of previous alterations of structure in the cardiac valves before they are adapted for the lodgment and development of the microorganisms which cause ulcerative endocarditis. Grawitz has shown that the bacteria of suppuration may be injected in large quantity into the healthy peritoneal cavity without doing any damage, but that they set up suppurative peritonitis if they meet there wounded tissues, stagnating fluids, or so-called dead spaces from which they are not readily absorbed.

Especially instructive in this light is the study of the manifold complications which attend scarlet fever, typhoid fever, and other diseases which are accompanied by necroses and ulcerations of the mucous membranes of the throat, intestine, and other parts with which microorganisms are normally in contact. While it has been shown that most of these microorganisms are harmless, there are not infrequently among them some which are pathogenic, such as the cosmopolitan bacteria of suppuration. The superficial necroses and ulcerations of the mucous membranes in scarlet fever and typhoid fever afford means of ingress for these bacteria, which often find within the body foci of least resistance resulting from the existing diseases. We are therefore not surprised to learn that many of the complications of these diseases are produced by the staphylococci and streptococci of suppuration, or that there are frequently found in these diseases in the tissues and fluids bacteria, particularly micrococci, which have nothing to do with the specific cause of the primary disease, although often enough mistaken for it by hasty observers.

Time will not permit me to elaborate the ideas here touched upon. Enough has been said to show that we need not despair of gaining some definite conception as to the nature of predisposition and immunity to disease, but we must not forget that our positive knowledge at present touches

only the outlying boundaries of the subject. We do not even know why different species of animals behave differently toward infectious agents—why, for instance, house mice resist the deadly glanders bacilli, while the more hardy field mice readily succumb—still less can we account for differences in susceptibilty of individuals of the same species.

It is easy enough to construct plausible theories of predisposition and of immunity, and such theories have their scientific uses; but we must remember that we have gained no explanation of the facts when we base our theories upon such popular phrases as struggle for existence between cells and bacteria, or fitness of the soil for the growth of bacteria, etc. Even the more tangible phagocytic doctrine of Metschnikoff cannot be said to have materially advanced our knowledge as yet, or to have met with much support in facts.

Before leaving this subject it may be well to say that possibly we are at present in the habit of assigning too great importance to predisposition as a factor in the causation of infectious diseases. It is such a convenient refuge that we are tempted to bury in its obscurity many etiological facts which we cannot readily explain. While I would not by any means ignore the importance of hereditary predisposition to tuberculosis, Is it not probable that cases are often included in this category which do not belong there? When we think of the especial dangers of infection to which the offspring of tuberculous parents are exposed from their youth upward, of the likelihood that a child will follow an occupation which has favored the development of phthisis in a parent, and of the frequency with which the concurrence of the disease in ancestor and descendant is mere coincidence, it is apparent that we are in danger of assigning to heredity a larger part in the causation of tuberculosis than it deserves.

It must be admitted that the instances in which we have been able by experiments upon animals of the same species to demonstrate different degrees of predisposition toward infectious agents are not very striking or very numerous.

And now, gentlemen, I bring to conclusion this imperfect survey of some points relating to the etiology of infectious diseases. We are only upon the threshold of a deeper insight into the nature of a class of diseases which have been more devastating to the human race than any upheavals of nature or any wars. They have left their imprint upon political, the social and the intellectual history of the world. One need not be of a very sanguine temperament to hope that our steadily increasing knowledge will bear fruit, not only, as in the past, in the prevention of these diseases, but also in a rational system of casual therapeutics.

CONSIDERATIONS CONCERNING SOME EXTERNAL SOURCES OF INFECTION IN THEIR BEARING ON PREVENTIVE MEDICINE[1]

No department of medicine has been cultivated in recent years with such zeal and with snch frnitfnl resnlts as that relating to the causes of infectious diseases. The most important of these results for preventive medicine and for the welfare of mankind is the knowledge that a large proportion of the causes of sickness and death are removable.

It is evident that efforts to preserve health will be most intelligently and effectually applied when they are based upon an accurate and full knowledge of the agencies which cause disease. Public and private hygiene, however, cannot and fortunately has not waited for the full light of that day, whose dawn has only begun to appear, when we shall have a clear insight into the causation of preventable diseases. Cleanliness and comfort demand that means shall be taken to render pure the ground on which we live, the air which we breathe, and the water and food with which we are supplied, and we must meet these needs without waiting to learn just what relation infectious agents bear to the earth, air, water and food.

It is a fortunate circumstance that modern sanitation has been controlled so largely by the belief in the dependence of endemic and epidemic diseases upon organic impnrities in the soil and in the water. Incomplete and even erroneous in many respects as are the views which have prevailed concerning the origin and spread of epidemic diseases by the decomposition of organic snbstances, the sanitary measnres which have been directed toward the removal of filth have achieved great conquests in limiting the development and extension of many infectious diseases. The benefits which one commonwealth of this country has derived from the intelligent employment of public sanitary measures were clearly and forcibly presented before this Association last year by Dr. Walcott in his admirable address in State Medicine.

While nothing should be said or need be said to lessen the importance of cleanliness for public health, it is important to bear in mind that hygienic cleanliness and aesthetic cleanliness are not identical. In water, which meets the most severe chemical tests of purity, typhoid bacilli have been found. On the other hand, the air in the Berlin sewers, which certainly

[1] An address in State Medicine delivered before the American Medical Association, Newport, R. I., June 28, 1889.

Maryland M. J., Balt., 1889, XXI, 201-208; 226-234.

does not meet the most modest demands of aesthetic cleanliness, has been found to be nearly or quite free from bacteria.

It needs only to be stated to be generally admitted that the scientific basis of preventive medicine must be the accurate knowledge of the causative agents of preventable diseases, a knowledge which can be derived only from a careful study of all the properties of these agents, the modes of their reception and of their elimination by the body, the circumstances which favor and those which retard or prevent their development and spread, their behavior in the various substances which surround us or which we take into our bodies, and the sources of infection, not only those which laboratory experiments show to be possible, but those which are actually operative.

So long as we were unacquainted with the living organisms causing infection, the means at our disposal for studying the etiology of infectious diseases were limited to the observation of all of the circumstances which we could determine regarding the origin and spread of these diseases. We could only infer what might be the properties of the infectious agents from the study of phenomena often obscure and difficult of interpretation. Chiefly by this method of investigation the science of epidemiology has been built up. It has established facts and laws no less of practical than of scientific importance. But it has left unsolved many problems, and has filled gaps with speculations. Admitted epidemiological facts are often open to various interpretations.

We are evidently at a great advantage when we can study the epidemiological facts with a knowledge of the substances which actually cause infection, and this we are now enabled to do for a limited number of the infectious diseases. This new method of research, which thus far has been mainly bacteriological, has aided us not so much by simplifying the problems of etiology, which still remain complicated enough, as by affording greater accuracy to the results.

It is my aim in this address to consider some results of the modern studies of pathogenic microorganisms in their bearing upon preventive medicine, more particularly upon the sources of infection. It is, of course, impossible within the limits of the address to attempt a complete survey of this important field. Time will permit the presentation of only some of the salient points.

Infectious diseases are those which are caused by the multiplication within the body of pathogenic microorganisms.

It has always been recognized that some infectious diseases, such as the exanthematous fevers, are conveyed directly from the sick to the healthy. It is not disputed that in these evidently contagious diseases the infectious germ is discharged from the body in a state capable at once of giving rise to infection.

In a second group of infectious diseases, of which malaria is the type, the infected individual neither transmits the disease to another person nor, so far as we know, is capable of infecting a locality. Here there is reason to believe that the infectious germ is not thrown off in a living state from the body, but is destroyed within the body. In this group the origin of infection under natural conditions is always outside of the body.

In a third group there is still dispute whether the disease can be transmitted directly from person to person, but all are agreed that the infected individual can infect a locality. It is especially fortunate that the bacteria which cause cholera and typhoid fever, the two most important representatives of this group of so-called miasmatic-contagious diseases, have been discovered and isolated in pure culture. These are the diseases about whose origin and epidemic extension there has been the greatest controversy. They, above all other diseases, have given the impulse to public sanitation during the last half century. The degree of success with which their extension in a community is prevented is an important gauge of the excellence of the local sanitary arrangements. A clear comprehension of the origin and spread of these diseases signifies the solution of many of the most vexed and important problems of epidemiology and of state hygiene.

It is difficult to understand how those who accept the discovery that the bacteria causing typhoid fever and cholera have been found and cultivated from the stools of patients affected with these diseases, can doubt that these patients are possible sources of contagion or can entertain the view once so widely prevalent that the infectious germs of these diseases are discharged from the body in a condition incapable of producing immediate infection. In an address delivered on another occasion I have endeavored to present the considerations which reconcile the comparative infrequency of direct contagion for these diseases with the belief in the elimination of the causative germs in an active state from the body, and have there pointed out several well known factors which determine the frequency of conveyance of an infectious disease by contagion. There are reasons, some of them very obvious, why diseases in which the infectious substances are operative only when received into the digestive tract, and are discharged usually only with the feces, are less likely to be transmitted by immediate contagion than those diseases in which the virus is thrown off from the skin on epidermal scales.

But the field of operation of direct contagion for these so-called miasmatic-contagious diseases is at most a restricted one and the chief sources of infection are outside of the body from which primarily the infectious germs may have been derived. It is to these external sources of infection, which are of such importance in public hygiene, that I wish especially to direct attention.

A full comprehension of the sources of infection is, to be obtained only by a detailed study of the etiology of the individual infectious diseases, but this is, of course, impossible within the limits of an address. It may, however, be useful to present some of the facts which have a general bearing upon the subject. Let us consider, then, from the point of view of modern bacteriological studies, what rôle, in harboring or transporting infectious agents, may be played by those substances or media with which we necessarily come into intimate contact, such as the air, the ground, the water and our food.

It is universally admitted that many infectious agents may be transported by the air, but the extent of danger from this source has often been exaggerated. It is a popular error to suppose that most of the minute particles of dust in the air either are or contain living organisms. The methods for determining the number and kind of bacteria and fungi in the air are now fairly satisfactory, although by no means perfect. These have shown that while the number of living bacteria and fungi in the atmosphere in and around human habitations cannot be considered small, still it is greatly inferior to that in the ground or in most waters. Unlike fungus spores, bacteria do not seem to occur to any extent in the air as single detached particles, which would then necessarily be extremely minute, but rather in clumps or attached to particles of dust of relatively large size. As a result in a perfectly quiet atmosphere these comparatively heavy particles which contain bacteria rapidly settle to the ground or upon underlying objects and are easily filtered out by passing the air through porous substances such as cotton wool or sand. Rain washes down a large number of bacteria from the air. That the air bacteria are derived from the ground or objects upon it is shown by their total absence, as a rule, from sea air at a distance from land, this distance naturally varying with the direction and strength of the wind.

A fact of capital importance in understanding the relations of bacteria to the air, and one of great significance for preventive medicine, is the impossibility of currents of air detaching bacteria from moist surfaces. Substances containing pathogenic bacteria, as, for instance, sputum containing tubercle bacilli or excreta holding typhoid bacilli, cannot, therefore, infect the air unless these substances first become dry and converted into a fine powder. We are able to understand why the expired breath is free from bacteria and cannot convey infection, except as little particles may be mechanically detached by acts of coughing, sneezing or hawking. Those bacteria, the vitality of which is rapidly destroyed by complete desiccation, such as those of Asiatic cholera, evidently are not likely to be transported as infectious agents by the air, if we except such occasional occurrences as their conveyance for a short distance in spray.

The only pathogenic bacteria which hitherto have been found in the air are the pus organisms, including the streptococcus found by Prudden in a series of cases of diphtheria, and tubercle bacilli, but no far reaching conclusions can be drawn from the failure to find other infectious organisms when we consider the imperfection of our methods and the small number of observations directed to this point. The evidence in other ways is conclusive that many infectious agents—and here the malarial germ should be prominently mentioned—can be and often are conveyed by the air. While we are inclined to restrict within narrower limits than has been customary the danger of infection through the air, we must recognize that this still remains an important source of infection for many diseases. All those, however, who have worked practically with the cultivation of microorganisms have come to regard contact with infected substances as more dangerous than exposure to the air, and the same lesson may be learned from the methods which modern surgeons have found best adapted to prevent the infection of wounds with the cosmopolitan bacteria which cause suppuration.

We are not, of course, to suppose that infectious germs floating in the form of dust in the atmosphere are dangerous, only from the possibility of our drawing them in with the breath. Such germs may be deposited on substances with which we readily come into contact, or they may fall on articles of food where they may find conditions suitable for their reproduction, which cannot occur when they are suspended in the air in consequence of the lack of moisture.

From the facts which have been mentioned concerning the relations of bacteria to the air, what points of view present themselves to guide us in preventing infection through this channel? Surely something more than that this purpose is accomplished simply by abolishing foul odors.

Certain indications are so plain as to need only to be mentioned in this connection, such as the disinfection and removal, as far as possible, of all infected substances, an indication which applies equally to all channels of infection and which it is much easier to mention than it is to describe how it shall be realized. But there are two indications which apply especially to the prevention of the transportation of disease germs by the air. One is the necessity of guarding, so far as practicable, against the dessication, when exposed to the air, of substances which contain infectious germs not destroyed by drying, and another is free ventilation.

For no disease is the importance of the first of these indications so evident and so well established as for tuberculosis, the most devastating of all infectious diseases. Against this disease, formidable as it may seem to cope with it, the courageous crusade of preventive medicine has begun and is destined to continue.

It is now generally recognized that the principal, although not the sole, sources of tuberculous infection are the sputum of individuals affected with pulmonary tuberculosis and the milk of tuberculous cows. Cornet, who has made a laborious and most instructive experimental study of the modes and dangers of infection from tuberculous sputum, has also elaborated the practical measures which should be adopted to diminish or annihilate these dangers. These measures have been so recently and so widely published in medical journals, and so clearly presented before a section of this association, that I mention them only to call the attention of practitioners of medicine to their importance and to emphasize the fact that they are based chiefly upon the principle that infectious substances of such nature as tuberculous sputum should not be allowed to become dry and converted into dust when exposed to the air.

By means of free ventilation, disease-producing microorganisms which may be present in the air of rooms are carried away and distributed so far apart that the chance of infection from this source is removed or reduced to a minimum. It is a well established clinical observation that the distance through which the specific microbes of such diseases as smallpox or scarlatina are likely to be carried from the patient by the air, in such concentration as to cause infection, is small, usually not more than a few feet, but increases by crowding of patients and absence of free ventilation. The well known experiences in the prophylaxis and treatment of typhus fever are a forcible illustration of the value of free ventilation.

It is, of course, not to be understood that by ventilation we accomplish the disinfection of a house or apartment. Ventilation is only an adjunct of such disinfection which, as already mentioned, is of first importance. Time will not permit, nor is it in the plan of this address, to discuss the details of such questions as house disinfection, but I may be permitted to say that the methods for disinfecting apartments have been worked out on a satisfactory experimental basis and should be known, at least by all public health officers. Whether it be pertinent to this occasion or not, I cannot forbear to add my protest to that of others against placing reliance upon any method hitherto employed of disinfecting houses or apartments by fumigation. And I would, furthermore, call attention to the lack in most cities of this country of public disinfecting establishments such as are in use, with excellent results, in many cities of Europe, and which are indispensable for the thorough and convenient disinfection of clothing, bedding, carpets, curtains, etc.

After this short digression let us pass from the consideration of the air as a carrier of infection to another important external source of infection, namely, the ground. That the prevalence of many infectious diseases de-

pends upon conditions pertaining to the soil cannot be questioned, but the nature and the extent of this influence have been and are the subjects of lively discussion. The epidemiological school, led by Pettenkofer, assigns, as is well known, to the ground the chief and even a specific and indispensable influence in the spread of many epidemic diseases, particularly cholera and typhoid fever. The statistics, studies and speculations of epidemiologists which have related to this subject probably surpass in number and extent those concerning any other epidemiological factor. The exclusive ground hypothesis has become an ingenious and carefully elaborated doctrine with those who believe that such diseases as cholera and typhoid fever can never be transmitted by contagion. These authorities cling to this doctrine with a tenacity which indicates that on it depends the survival of the exclusively localistic dogma of these diseases.

To all who have not held aloof from modern bacteriological investigations it must be clear that views which have widely prevailed concerning the relations of many infectious germs to the soil require revision. The question is still a difficult and perplexing one, but on some hitherto obscure or misunderstood points these investigations have shed light, and from the same source we may expect further important contributions to a comprehension of the relations of the ground to the development of infectious diseases.

The ground, unlike the air, is the resting or the breeding place of a vast number of species of microorganisms, including some which are pathogenic. Instead of a few bacteria or fungi in a liter, as with the air, we find in most specimens of earth thousands and often hundreds of thousands of microorganisms in a cubic centimeter. Fraenkel found the virgin soil almost as rich in bacteria and fungi as that around human habitations.

This vast richness in microorganisms belongs, however, only to the superficial layers of the earth. Where the ground has not been greatly disturbed by human hands there is, as a rule, about three to five feet below the surface an abrupt diminution in the number of living organisms, and at the depth where the sub-soil water usually lies, bacteria and fungi have nearly or entirely disappeared. Fraenkel, who first observed this sudden diminution in the number of microorganisms at a certain level beneath the surface, explains this singular fact by the formation at this level of that sticky accumulation of fine particles consisting largely of bacteria, which forms the efficient layer in large sand filters for water. Of course the number of bacteria and the depth to which they penetrate will vary somewhat with the character, especially the porosity, of the soil and its treatment, but the important fact that all, or nearly all, of the bacteria and fungi are retained in the ground above the level of the sub-soil water will doubtless hold true for most situations.

The conditions are not favorable for the multiplication of bacteria in the depth of the ground, as is shown by the fact that in specimens of earth brought to the surface from a depth of a few feet, the bacteria which are at first present rapidly multiply. What all of the conditions are which prevent the reproduction of bacteria in the deep soil has not been ascertained, but the fact necessitates similar precautions in the bacteriological examination of the soil as in that of water.

We have but meagre information as to the kinds of bacteria present in the ground in comparison with their vast number. Many of those which have been isolated and studied in pure culture possess but little interest for us so far as we know. To some of the microorganisms in the soil appears to be assigned the rôle of reducing or of oxidizing highly organized substances to the simple forms required for the nutrition of plants. We are in the habit of considering so much the injurious bacteria that it is pleasant to contemplate this beneficent function so essential to the preservation of life on this globe.

Among the pathogenic bacteria which have their natural home in the soil the most widely distributed are the bacilli of malignant oedema and those of tetanus. I have found some garden earth in Baltimore extremely rich in tetanus bacilli, so that the inoculation of animals in the laboratory with small bits of this earth rarely fails to produce tetanus. In infected localities the anthrax bacillus and, in two instances, the typhoid bacillus, so far as it was possible to identify it, have been discovered in the earth. There is reason to believe that other germs infectious to human beings may have their abiding place in the ground; certainly no one doubts that the malarial germ lives there. As the malarial germ has been shown to be an organism entirely different from the bacteria and the fungi, we cannot apply directly to its behavior in the soil and its transportation by the air, facts which have been ascertained only for the latter species of microorganisms, and the same precautions must be observed for other diseases with whose agents of infection we are not acquainted, as, for instance, yellow fever.

In view of the facility with which infectious germs derived from human beings or animals may gain access to the soil, it becomes a matter of great importance to determine how far such germs find in the soil conditions favorable for their preservation or their growth. We have, as is well known, a number of epidemiological observations bearing upon this subject, but with few exceptions these can be variously interpreted and it is not my purpose to discuss them. The more exact bacteriological methods can, of course, be applied only to the comparatively small number of infectious diseases, the causative germs of which have been isolated and cultivated, and those methods hitherto have been applied to this question only imperfectly.

We cannot regard the soil as a definite and unvarying substance in its chemical, physical and biological properties. What has been found true of one kind of soil may not be so of another. Moreover, we cannot in our experiments bring together all of the conditions in nature which may have a bearing on the behavior of specific microorganisms in the soil. We must, therefore, be cautious in coming to positive conclusions on this point on the basis of experiments, especially those with negative result. With these cautions kept constantly in mind the question, however, is one eminently open to experimental study.

The experiments which have thus far been made to determine the behavior of infectious microorganisms in the ground have related especially to the bacilli of anthrax, of typhoid fever and of cholera, and fortunately these are the diseases about whose relations to the ground there has been the most discussion and concerning which we are most eager to acquire definite information.

As regards anthrax bacilli, it has been determined that in ordinary garden or field earth they do not multiply, but in earth contaminated by blood, urine or feces their reproduction can occur. They can grow on various vegetable substrata. There is no reason to doubt, therefore, that the anthrax bacilli can find in or on the ground suitable conditions for their multiplication, although such conditions are not everywhere present. For durable infection of the soil with anthrax bacilli, it is, however, more important that these bacilli should find there suitable conditions for the formation of spores, than that they should be able simply to multiply. The vegetative forms of anthrax bacilli would not, as a rule, be able to survive for a great length of time the hostile influences which they are likely to encounter in the ground, such as insufficient or exhausted moisture and the attacks of saprophytic organisms. On the other hand, against these injurious influences the anthrax spores have great resistance. In the superficial layers of the ground the anthrax bacilli may often find those conditions of moisture, of temperature, of oxygen supply and of insufficient food, which we know are most favorable for the development of their spores; indeed Soyka has shown that the ground presents often these conditions better than our culture media. A circumstance discovered by Feltz, which, however, needs confirmation, is, if true, of not little significance. He finds that anthrax bacilli may undergo a progressive diminution in virulence in the soil. If this should be true likewise of other infectious microorganisms, we should be able to account in some instances for the variable degree of virulence which clinical observation indicates that certain agents of infection acquire.

So far as anthrax bacilli are concerned, we may conclude, therefore, that the ground occasionally offers suitable conditions for their reproduction,

but what is of greater importance, it offers especially favorable conditions for their long continued preservation in the form of spores. I must forego here the further consideration of the special circumstances inherent in the soil which control the origin and spread of epidemics of anthrax in cattle, although many interesting investigations have been directed to this subject.

Of greater interest to physicians is the behavior of typhoid and of cholera bacteria in the ground. As has already been intimated the ground is regarded by Pettenkofer and his school as the principal breeding place of these microorganisms outside the body. This view, however, is not supported by bacteriological investigations. Inasmuch as the cholera and typhoid bacilli may multiply on various vegetable substrata and substances derived from animals at temperatures often present in the ground, it is evident that here and there conditions may be present for their growth in the ground, but this growth is likely to be soon interrupted by the invasion of ordinary saprophytic organisms and other harmful influences. The typhoid bacilli are more hardy in resisting these invaders than are the cholera bacteria, which easily succumb, but even for the former, so far as our present knowledge extends, the ground can rarely serve as a favorable breeding place.

It is not, however, necessary that these organisms should multiply in order to infect for a considerable time the ground; it is sufficient if their vitality is preserved. As to this latter point, the reports of different investigators are not altogether concordant. Such excellent observers as Koch, Kitasato and Uffelmann found that the cholera bacteria, when added to feces or a mixture of feces and urine, rapidly diminished in number and at the end of three or four days at the most, had wholly disappeared. In a mixture of the intestinal contents from a cholera corpse with earth and water Koch found many cholera bacteria at the end of three days, but none at the end of five days. On the other hand, Gruber reports the detection of cholera bacteria in dejecta fifteen days old. The weight of bacteriological evidence, therefore, is opposed to the supposition that the bacteria of Asiatic cholera preserve their vitality for any considerable time in the ground or in the excreta.

With respect to the bacilli which cause typhoid fever, it has been shown by Uffelmann that these may live in feces, mixture of feces and urine, and mixture of garden earth, feces and urine for at least four or five months, and doubtless longer, although they may die at the end of a shorter period. He also finds that under these apparently unfavorable conditions some multiplication of the bacilli may occur, although not to any considerable extent. Grancher and Deschamps found that typhoid bacilli may live in the soil for at least five months and a half. Unlike the cholera bacteria, therefore, the typhoid bacilli may exist for months at least in the ground and in fecal matter, holding their own against the growth of multitudes of

saprophytes. This difference in the behavior of cholera and of typhoid germs is in harmony with clinical experience.

As regards other infectious bacteria than those which have been considered I shall only mention that tubercle bacilli, although incapable of multiplication under the ordinary conditions of nature outside of the body, may preserve their vitality for a long period in the ground, on account of their resistant character, and, furthermore, that the pyogenic cocci, on account of their considerably resistant nature and their modest demands in the way of nutriment, can be preserved and sometimes probably grow in the ground. Indeed *Staphylococcus pyogenes aureus* has been found in the earth by Lübbert.

The conclusion which we may draw from the observations mentioned is that, in general, the soil is not a good breeding place for most of the infectious bacteria with which we are acquainted, but that it can retain for a long time with unimpaired vitality those which produce spores or which offer considerable resistance to injurious agencies, such as anthrax bacilli, typhoid bacilli, tubercle bacilli and the pyogenic cocci.

In order to become infected with bacteria in or on the ground, these bacteria must in some way be introduced into the body and we must, therefore, now attempt to determine how bacteria may be transported to us from the ground. So various and intricate are the possibilities for this transportation that it is hopeless to attempt to specify them all.

There occurs to us first the possibility of the conveyance of infectious microorganisms from the soil by means of currents of air, a mode of carrying infection which has already been considered. Here I shall only repeat that the wind can remove bacteria from the ground only when the surface is dry and presents particles of dust, and that the sole, and perhaps the chief, danger is not that we may inhale the infected dust.

Manifold are the ways in which we may be brought into contact with infectious bacteria in the ground, either directly or by means of vegetables to which particles of earth are attached, by the intervention of domestic animals, by the medium of flies or other insects, and in a variety of other ways, more or less apparent.

An important, doubtless for some diseases the most important, medium of transportation of bacteria from an infected soil is the water which we drink or use for domestic purposes. From what has been said it is evidently not the sub-soil water which is dangerous, for infections like other bacteria cannot generally reach this in a living state, but the danger is from the surface water and from that which trickles through the upper layers of the ground, as well as from that which escapes from defective drains, gutters, cess-pools, privy vaults and wrongly constructed sewers or improper dis-

posal of sewerage. I shall have something to say presently of water as a source of infection, and shall not further elaborate here the dangers of infection of drinking water through contaminated soil, dangers which, especially as regards typhoid fever, are widely appreciated in this country, even if often imperfectly counteracted.

A point which has been much discussed and one of interest is, whether bacteria which are in the depth of the ground can come to the surface. Two agencies especially have been considered by some as capable of transporting bacteria from the depth to the surface. One is ascending currents of air in the ground and the other is the capillarity of fluids in the minute pores of the ground. The first of these suspected agencies must be unquestionably rejected in view of the fact that even a few inches of sand is sufficient to filter all of the bacteria out of the air, even when it is in much more rapid motion than can occur within the ground. Moreover, that degree of dryness which is essential for the detachment of bacteria by air-currents is not likely to be present much below the surface of the ground. The experiments which have been made to determine to what extent bacteria may be carried upward by the capillarity of fluids in the ground have not yielded harmonious results, but the weight of evidence is opposed to the belief that this is a factor of any considerable importance for this purpose.

From what has been said concerning the growth of pathogenic bacteria in the soil we shall not be inclined to attribute to the multiplication and the motility of these organisms much influence in changing their places in the ground.

The somewhat sensational rôle assigned by Pasteur to earthworms of bringing bacteria to the surface cannot be wholly ignored and has received support from observations of Bollinger regarding anthrax, but it is questionable whether much importance is to be attached to this agency.

Regarding the depth to which typhoid bacilli may penetrate in the soil, the experiments of Grancher and Deschamps shows that at the end of five weeks they may reach a depth of 16 to 20 inches below the surface. As Hoffmann has demonstrated the extraordinary slowness with which fluids and fine particles penetrate the soil, it is probable that in the course of time a greater depth than this may be reached. Indeed, Macé claims to have found in the neighborhood of a well suspected of infection, typhoid bacilli, together with ordinary intestinal bacteria, at a depth of at least 6½ feet below the surface. There are a number of instances recorded in which there is good reason to believe that turning up the soil and cleaning out privies or dung-heaps in which typhoid stools have been thrown, have given rise to typhoid fever, even after the infectious excreta have remained there a year or more.

It cannot be said that bacteriological investigations have as yet shed much light upon a factor which plays a great rôle in epidemiology, namely, predisposition to infection from the ground, according to locality and time, and this deficiency receives constant and vehement emphasis from the localistic school of epidemiologists. We can, however, readily understand that varying conditions, such as temperature, moisture, porosity, quality of soil, may exert a controlling influence in determining the behavior of infectious germs in the soil and the facility of their transportation to human beings or animals. As regards that much-discussed question, the significance of variations in the height of the sub-soil water, in relation to the prevalence of certain epidemic diseases, particularly cholera and typhoid fever, we now know that this cannot depend upon the presence of bacteria in the sub-soil water itself or in the capillary layers immediately above it. It has been plausibly suggested that with the sinking of the sub-soil water fluids from infected cess-pools, privy vaults, and other localities may more readily be drawn into wells or other sources of water supply, and that by the same cause the surface of the ground becomes dry so that dust particles may be lifted by the wind. Other more or less plausible explanations have also been offered, but it must be confessed that our positive information on the point is meagre. There can, however, be little doubt that this significance of the variations in sub-soil water is apparent only for certain localities and has been considerably exaggerated and often misunderstood. It is not, however, pertinent to my theme to discuss this or other purely epidemiological observations concerning the relations of the ground to the spread of epidemic diseases, interesting and important as are many of these observations.

Before leaving the subject of the ground as a source of infection, permit me to indicate briefly some conclusions which may be drawn from what has been said as to the principles which should guide us in preventing infection directly or indirectly from the ground.

First in importance is to keep infectious substances so far as possible from the ground. This implies the early disinfection or destruction of such substances as typhoid and cholera excreta and tuberculous sputum.

Second. The ground should be rendered so far as practicable unsuitable for the continued existence of infected germs. This, at least for some diseases, is accomplished by a proper system of drainage, which, moreover, for other reasons possesses hygienic importance.

Third. Means should be provided to prevent waste products from getting into the ground around human habitations or from gaining access to water used for drinking or domestic purposes. In cities this can be accomplished only by a properly constructed system of sewers. The system of storing waste products in cess-pools whence they are to be occasionally removed

cannot be approved on hygienic grounds. There are conditions in which the disposal of waste products in deep wells only used for this purpose and whence these products can filter into the deep layers of the ground may be permissible, but this can never be considered an ideal method of getting rid of excrementitious substances, and is wholly wrong in regions where wells are used for drinking water. But I am trespassing with these remarks upon a province which does not belong to me, but rather to practical sanitarians and engineers. I shall only add that the advantage gained by preventing organic waste from soaking into the ground is not so much that the ground is thereby rendered better adapted for the existence of infectious microorganisms, but is due rather to the fact that this waste is likely to contain infectious germs.

Finally, in cities, good pavements, absence of unnecessary disturbance of the soil, cleanliness of the streets, and laying of dust by sprinkling are not only conducive to comfort, but are sometimes hygienically important in preventing infection from the ground and dust.

In passing from the consideration of the ground to that of water, one feels that he now has to do with a possible source of infection against which in this country and in England he is at liberty to make any accusation he chooses without fear of contradiction. There is reason to believe that such accusation has been repeatedly made without any proof of misdemeanor on the part of the water. It is not, therefore, with any desire to awaken further the medical or the public conscience that I wish to say a few words concerning the behavior of bacteria in water and the dangers of infection from this source. That such dangers are very real must be apparent when we consider the universal employment of water and its exposure to contamination from all kinds of sources.

Ordinary water, as is well known, contains bacteria in large number. Not a few species of bacteria can multiply rapidly and to a large amount even in distilled water. These are the so-called water-bacteria, and like most of the microorganisms found in ordinary drinking water are perfectly harmless saprophytes. What we wish to know is, how pathogenic microorganisms conduct themselves in water. Can they grow or be preserved for any length of time in a living condition in water? As regards the multiplication of pathogenic bacteria in water the results of different experimenters do not altogether agree. Whereas Bolton failed to find any growth, but rather a progressive diminution in the number of pathogenic bacteria planted in sterilized water. Wolffhügel and Riedel observed a limited reproduction of such bacteria, including those of typhoid fever and cholera. This difference is due, probably, to the methods of experimentation employed. According to Kraus, these latter bacteria diminish rapidly in number in unsterilized

spring or well water kept at a low temperature. These experiments indicate that water, even when contaminated with more organic impurities than are likely ever to be present in drinking water, is not a favorable breeding place for pathogenic bacteria. Still it is to be remembered that these laboratory experiments do not reproduce exactly all of the conditions in nature, and it may happen that in some nook or cranny or vegetable deposit at the side of a well or stream some pathogenic bacteria may find suitable conditions for their multiplication.

But as has been repeatedly emphasized in this address it is not necessary that pathogenic bacteria should actually multiply in a medium in order to render it infectious. It is sufficient if their life and virulence are not destroyed in a very short time. As to this important point Bolton found that in sterilized water typhoid bacilli may preserve their vitality for over three months and cholera bacteria for 8 to 14 days, while Wolffhügel and Riedel preserved the latter in water for about 80 days. Under natural conditions, however, these organisms are exposed to the over growth of the water bacteria so that Kraus found in unsterilized water kept at a temperature of 10.5° C. (50.9°F.) the typhoid bacilli no longer demonstrable after 7 days, and the cholera bacteria after 2 days. The conditions in Kraus's experiments were as unfavorable as possible for the continued existence of these pathogenic bacteria, more unfavorable than those often present at the season of prevalence of cholera and typhoid fever, nevertheless I do not see that they justify the conclusions of Kraus as to the slight probability of drinking water ever conveying infection with the germs of typhoid fever and cholera. To render such a conclusion probable it would be necessary to demonstrate a much shorter preservation than even Kraus himself found. In judging this question it should not be overlooked that infection of drinking water with the typhoid or the cholera germs is not so often the result of throwing typhoid or cholera stools directly into the source of water supply as it is the consequence of leaky drains, cess-pools, privy-vaults or infected soil, so that there may be continued or repeated accessions of infected material to the water.

In view of the facts presented, there is no sufficient reason, therefore, from a bacteriological point of view, of rejecting the transmissibility of typhoid fever and cholera by the medium of the drinking water. This conclusion seems irresistible when we call to mind that Koch once found the cholera bacteria in large number in the water of a tank in India, and that the typhoid bacilli have been repeatedly found in drinking water of localities where typhoid fever existed. Nor do I see how it is possible to interpret certain epidemiological facts in any other way than by assuming that these diseases can be contracted from infected drinking water, although I know that there

are still high authorities who obstinately refuse to accept this interpretation of the facts.

In this connection it may be mentioned that pathogenic bacteria may preserve their vitality longer in ice than in unsterilized drinking water. Thus Prudden found typhoid bacilli still alive which had been contained in ice for 103 days.

When we come to consider the ways in which water may become infected with pathogenic microorganisms we recognize at once a distinction in this respect between surface water and sub-soil water. Whereas the sub-soil water may be regarded under ordinary circumstances and in most places as germ-free, the surface water, such as that in rivers, and streams, is exposed to all manner of infection from the ground, the air, and the admission of waste substances. Unfortunately in the ordinary way of obtaining sub-soil water for drinking purposes by means of dug wells this distinction is obliterated, for the water which enters these wells free from bacteria is converted into a surface water often exposed, by the situation of the well, to more dangerous contamination than other surface waters used for drinking purposes.

Now let us turn our attention as we have done with other sources of infection to a brief outline of certain general principles which may help us in avoiding infection from the water.

We shall in the first place avoid so far as possible the water suspected of infection, especially with the germs of such disease as typhoid fever and cholera. When it is necessary to use this suspected water it should be boiled.

As regards the vital question of water supply, it may be stated as a general principle that no hygienic guarantee can be given for the purity of surface water which has not been subjected to a proper system of filtration, or for the purity of spring or well water fed from the sub-soil unless such water is protected from the possibility of infection through the upper layers of the soil or from the air. This is not saying that water which meets certain chemical and biological tests and which is so situated that the opportunities for its contamination appear to be absent or reduced to a minimum is not admissible for the supply of drinking water, but the possibility of infection can be removed only by the fulfillment of the condition named, and upon these conditions the hygienic purist will always insist.

Unfortunately we have at present no domestic filters which are satisfactory and most of these in common use are worse than none, as they soon furnish a filtrate richer in bacteria than the original water. The only effective method of water-filtration for the general supply is by means of large sand filters such as are in use with excellent results in Berlin and some other cities. These require skilled attention. I cannot on this occasion discuss

the construction or working of these filters but would refer those who are interested to the full and careful investigations of the Berlin filters by Wolffhügel and by Plagge and Proskauer.

What is accomplished by these artificial sand filters is accomplished under natural conditions, also by the ground, which furnishes a sub-soil water free from microorganisms, and to obtain pure water we have only to devise means by which this sub-soil water may be secured without the chance of contamination. Just as the water, which has passed through the sand filters, is collected in suitable reservoirs and is distributed in pipes, which do not admit contamination from without, so by means of properly constructed artesian or driven wells we may secure the naturally filtered sub-soil water with the same freedom from the chances of infection.

It is well to bear in mind that no biological or chemical tests of water can replace those measures which have been mentioned as necessary to secure purity of water supply. These tests are of value only when applied with proper precautions and with due consideration of the special circumstances of each case for which they are employed. There has been much profitless discussion as to whether greater significance is to be attached to the chemical or to the bacteriological examination of water. Each has its own special field of application and in this the one cannot replace the other method. The bacteriological examination has for hygienic purposes the specific agents of infection in the form of microorganisms, as has already been done for cholera bacteria and typhoid bacilli, but this is a comparatively rare result and does not at present afford a wide field of application for this method. The significance of the bacteriological test is to be based more frequently upon the fact that it concerns itself with the same class of microorganisms to which some of the recognized and doubtless many of the undiscovered infectious agents belong and from the behavior of which in some respects conclusions can be drawn as to the behavior of the pathogenic organisms. Thus the bacteriological test is the only one which enables us to judge correctly of the efficacy of those methods of filtration of surface water and of construction of wells which insure purity of water supply. The points of view from which we can estimate correctly according to our present knowledge the relative merits and fields of application of the chemical and of the bacteriological methods of water examination have been clearly indicated by Plagge and Proskauer and by Wolffhügel. The theme is one beyond the limits or the scope of this discourse and I have referred to its chiefly to emphasize the fact that we cannot rely upon chemical or bacteriological tests of water to the exclusion of those protective measures which have been mentioned, although I do not intend to imply that each of these tests when properly employed does not afford important information and is not of great value in many cases.

I have already taxed so largely your time and patience that I must pass over with brief mention the food as a source of infection. Unlike those external sources of infection which we have hitherto considered, many articles of food afford an excellent nutritive medium for the growth of a number of species of pathogenic microorganisms, and in many instances this growth may be abundant without appreciable change in the appearance or taste of the food.

When we consider in how large degree the certainty and the severity of infection with many kinds of pathogenic microorganisms depend upon the number of such organisms received into the body, we can appreciate that the danger of infection from food which contains a mass of growing pathogenic bacteria may be much greater than that resulting from the reception of infected water or air, media in which infected organisms are rarely present in other than a very dilute condition. The entrance into the body of a single infectious bacterium with the inspired air is, at least in the case of many, many diseases, not likely to cause infection, but let this bacterium fall upon some article of food, as for instance milk, where it can multiply in a short time at a favorable temperature many thousand fold, and evidently the chances of infection become vastly increased.

Among the various agencies by which infectious organisms may gain access to the food may be mentioned the deposition of dust conveyed by the air, earth adhering to vegetables, water used in mixing with or in the preparation of food, in cleaning dishes, clothes, etc., and contact in manifold other ways with infected substances.

Fortunately a very large part of our food is sterilized in the process of cooking shortly before it is partaken, so that the danger of infection from this source is greatly diminished and comes into consideration only for uncooked or partly cooked food and for food, which, although it may have been thoroughly sterilized, is allowed to stand considerable time before it is used. Milk, in consequence of its extensive use in an unsterilized state and of the excellent nutritive conditions which it presents to many pathogenic bacteria, should be emphasized as especially liable to convey certain kinds of infection, a fact supported not less by bacteriological than by clinical observations. Hesse found that also a large number of ordinary articles of food prepared in the kitchen in the usual way for the table and then sterilized afford a good medium for the growth and preservation of typhoid and cholera bacteria, frequently without appreciable change in the appearance of the food.

Upon solid articles of food bacteria may multiply in separate colonies, so that it may readily happen that only one or two of those who partake of the food eat the infected part, whereas with infected liquids, such as milk, the

infection is more likely to be transmitted to a larger number of those who are exposed.

In another important particular the food differs from the other sources of infection which we have considered. Not only the growth of infectious bacteria, but also that of bacteria incapable of multiplication within the body, may give rise in milk and other kinds of food to various ptomaines, products of fermentation and other injurious substances which when ingested are likely to cause more or less severe intoxication or to render the alimentary tract more susceptible to the invasion and multiplication of genuinely infectious organisms.

It is plain that the liability to infection from food will vary according to locality and season. In some places and among some races the proportion of uncooked food used is much greater than in other places and among other races. In general, in summer and in autumn, the quantity of fruit and food ingested in the raw state is greater than at other seasons, and during the summer and autumn there is also greater danger from the transportation of disease germs from the ground in the form of dust and the amount of liquids imbibed is greater. The elements of predisposition, according to place and time upon which epidemiologists are so fond of laying stress, are not, therefore, absent from the source of infection now under consideration.

I have thus far spoken only of the secondary infection of food by pathogenic microorganisms, but, as is well known, the substances used for food may be primarily infected. Chief in importance in the latter category are the various entozoa and other parasites which infest animals slaughtered for food. The dangers to mankind resulting from the diseases of animals form a separate theme, which would require more time and space than this address affords for their proper consideration. I shall content myself on this occasion with only a brief reference to infection from the milk and flesh of tuberculous cattle.

It has been abundantly demonstrated by numerous experiments that the milk from tuberculous cows is capable when ingested of causing tuberculosis. How serious is the danger may be seen from the statistics of Bollinger who found with cows affected with extensive tuberculosis the milk infectious in 80 per cent of the cases, in cows with moderate tuberculosis the milk infectious in 66 per cent of the cases and in cows with slight tuberculosis the milk infectious in 33 per cent of the cases. Dilution of the infected milk with other milk or with water, diminished or in sufficient degree it removed the danger of infection. From statistics furnished me by Mr. A. W. Clement, V. S., it appears that the number of tuberculous cows in Baltimore which are slaughtered is not less than 3 to 4 per cent. Among some breeds of cattle tuberculosis is known to be much more prevalent than this.

There is no evidence that the meat of tuberculous cattle contains tubercle bacilli in sufficient number to convey infection, unless it be very exceptionally. Nevertheless one will not willingly consume meat from an animal known to be tuberculous. This instructive repugnance, as well as the possibility of postmortem infection of the meat with tubercle bacilli in dressing the animal seem good grounds for discarding such meat. The question, however as to the rejection of meat of tuberculous animals has important economic bearings and has not been entirely settled. As to the rejection of the milk from such animals, however, there can be no difference of opinion, although this is a point not easily controlled.

The practical measure to adopt in order to avoid infection from the food are for the most part sufficiently obvious. Still it is not to be expected that every possibility of infection from this source will be avoided. It is difficult to discuss the matters considered in this address without seeming to pose as an alarmist. But it is the superficial and the half knowledge of these subjects which is most likely to exaggerate the dangers. While one will not under ordinary circumstances refrain from eating raw fruit or food which has not been thoroughly sterilized or from using unboiled or natural waters in the fear that he may swallow typhoid or cholera bacteria, still in a locality infected with cholera typhoid fever he will, if wise, not allow himself the same freedom in these respects. Cow's milk, unless its source can be carefully controlled, should when used as an habitual article of diet as with infants, be boiled or the mixed milk of a number of cows should be selected, but this latter measure offers less protection than the former.

In most places in this country we are sadly lacking in good sanitary inspection of the food, especially of the animal food, offered for sale. One cannot visit the slaughter house in Berlin or in Munich, and doubtless similar ones are to be found elsewhere, and watch the intelligent and skilled inspection of the slaughtered animals without being impressed with our deficiency in this respect. In large cities an essential condition for the efficient sanitary inspection of animal food is that there should be only a few places, and preferably only one place, where animals are permitted to be slaughtered. Skilled veterinarians should be selected for much of the work of inspection.

It may reasonably be asked that the national government which has already spent so much money for the extermination of such diseases as pleuropneumonia and hog cholera, which are not known to endanger the health of mankind, should turn its attention also to means for eradicating tuberculosis from cattle, which is scourge not only to the economic interests of farmers and dairymen, but also to the health of human beings.

Without any pretension to having done more in this address than to sketch here and there a few principles derived from bacteriological researches concerning only some of the most widely distributed external sources of infection, I trust that enough has been said to show the folly of any exclusive dogma as to modes of infection. The ways of infection, even in one and the same disease, are manifold and various, and can never be resolved into exclusive hypothesis, such as the drinking water hypothesis, the ground hypothesis, etc.

It follows, therefore, that it is not by sanitary improvements in one direction only that we can control the spread of preventable epidemic diseases. In one situation improvements in the supply of drinking water check the prevalence of typhoid fever, in another place similar measures show no such influence; or, again, in one city the introduction of a good system of sewerage diminishes epidemic diseases, and in another no similar result follows. We should, therefore, aim to secure so far as possible good sanitary arrangements in all directions and in all respects.

It has also been rendered evident in what has been said that infectious agents differ markedly from each other in their behavior, so that while public sanitation aims at those measures which are found to be most widely beneficial, it should not forget that each infectious disease is as much a separate problem in its prophylaxis as in its symptomatology, etiology and treatment. It will not aim to combat cholera with the means found best adapted to scarlet fever, but it will adapt preventive measures as directly to the specific end in view as possible.

In presenting to you the results of researches, chiefly bacteriological, concerning the scientific basis of preventive medicine, I hope to escape the accusation of one-sidedness and narrowness by the statement that I do not for a moment intend to imply that the bacteriological method is our only source of accurate knowledge on the subjects which have been considered. My aim is accomplished if I have succeeded in making clear that this method has established facts which aid in a clearer conception of the causes of some important infectious diseases, in a better understanding of the sources and dangers of infection, and in a more efficient selection and application of sanitary measures.

If this science of only a few years' growth has furnished already acquisitions to knowledge so important, so far reaching, may we not look forward with assurance to the solution of many dark problems in the domain of infectious diseases, problems the solution of which may yield to preventive medicine a future of usefulness and success which we cannot now foresee.

SANITATION IN RELATION TO THE POOR[1]

The sanitary condition of the poor is a matter which concerns not the poor alone, but the whole community. There is abundant evidence to show that the health of a city is influenced in a large measure by the condition of the abodes, the habits and the surroundings of the poor. The removal, so far as practicable, of unsanitary conditions attendant upon poverty is not a philanthropic undertaking only, but it is a duty which states and cities owe to all of the citizens.

There are several reasons why it seems proper and desirable to bring before this Charity Organization Society a question which is so largely one of the state and municipal policy.

The charity organizations of this country have become one of the powerful agencies for influencing and directing public sentiment, and consequently civic action, in such matters as public sanitation.

These organizations, moreover, are interested, not only in the immediate alleviation of distress due to poverty, but also in searching after the underlying conditions and in basing remedial measures so far as possible upon these conditions. There can be no complete study, no adequate solution, of the social question without a knowledge of the influence of unhygienic conditions upon the physical, mental and moral state of the poor, as well as of the effect of poverty in producing these conditions.

A third reason why it is desirable to introduce this subject here, is that it is in the power of individuals doing the work of this organization to diffuse some sanitary knowledge among the poor. The results of such individual effort may not be great as compared with what may and should be done by public agencies, but they will do some good, especially in the direction of domestic hygiene, a subject of which women can be excellent teachers.

Sanitation among the poor in this threefold relation to public hygiene, to the social problem and to the individual work of this organization is of course a theme far beyond the limits assigned to me upon this occasion. I shall be able to touch upon only a few of the salient points.

The two circumstances which have had the most potent influence in the development of modern sanitary science have been the occurrence of great epidemics of disease, especially of cholera, and also in this country of yellow

[1] An address delivered before the Charity Organization Society of Baltimore, November 14, 1892.
Balt., 1892, 14 p., 8°.

fever, and the belief in the dependence of those diseases usually called zymotic or infectious upon filth.

If the public cannot be awakened in any other way to the correction of glaring sanitary defects than by an outbreak of cholera, then such a visitation is not an unmixed evil, for in a few years more lives will probably be saved by the removal of well known causes of preventable disease than are destroyed by the cholera, and the chances of a renewal of the epidemic will be lessened, if not wholly abolished.

Hamburg has been warned time and again by sanitarians of the danger of using unfiltered Elbe water for drinking purposes, but it has required the sacrifice within the space of a few weeks of eight thousand lives and untold misery for this warning to be heeded.

It is fortunate that public sanitary measures have been controlled so largely by the belief that most infectious diseases depend upon filth. In this belief the main purpose of public sanitary efforts has been to render pure the water we drink, the air we breath, the food we eat and the soil upon which we live.

Within the last dozen years we have acquired definite knowledge of the causes of some of the most important infectious diseases and we now know that these diseases are not generated by filth in so direct a manner as was once supposed. We may drink contaminated water, breath impure air and live on a polluted soil without getting typhoid or typhus fever, or diphtheria or scarlet fever or other infectious disease. These influences may be and doubtless are deleterious to health, but unless the specific germs of disease have been introduced, they do not produce well defined diseases.

Many of these disease germs, however, are widely distributed and there is good reason to believe that such unhygienic conditions as those mentioned afford to many the best opportunities for multiplication and for conveyance to the human body.

If we render difficult or impossible the contamination of our water, air, food and soil, with ordinary impurities which may not in themselves be demonstrably harmful, we make difficult or impossible their contamination with the germs of many diseases.

We are thus enabled to understand how there may be serious sanitary defects in a place without such an injurious influence upon health as to attract much attention. Nevertheless, these defects are a constant menace to the health of the inhabitants. The demonstration of sewage contamination in the sources of supply of drinking water is significant, not because the admixture with sewage is in itself dangerous, but because it indicates that the gates are open for the entrance into the water of the germs of typhoid fever or of cholera, if these germs are present in the sewage. It is true that cholera,

for instance, might be introduced into such a place and by a fortunate chance the germs of the disease not gain entrance to the soil or to the water so as to produce an epidemic, but is it not foolish and short sighted to leave the lives and happiness of thousands dependent upon such a chance when we know what measures are necessary in order to reduce the chance to a minimum, if not to eliminate it altogether? The most ordinary prudence demands that the open gates be closed. One of the most instructive lessons of the visitations of Asiatic cholera in Europe since 1884 has been the failure of this disease to gain a foot-hold when introduced into cities with irreproachable water supply and sewage disposal.

That there are serious sanitary defects in Baltimore, is well known. Attention has been called repeatedly to most of them by the health officers of the city and by others. The annual reports of the health department have for many years recommended the abolition of the present primitive methods of disposal of excreta and house-wastes. Dr. Rohe in his report for 1890 says: "It is impossible to find language capable of expressing in its entirety the filthiness and dangers to life and health by which we are surrounded so long as the present privy system is maintained," and Dr. McShane, the present Commissioner of Health endorses these views and says: "Nothing of greater importance can be suggested than the adoption of some means for the proper removal and disposal of household and other sewage."

The present health commissioner and others have recently called public attention to serious sewage contamination of the sources of water supply of Lake Roland, which affords drinking water to a large part of the city.

Notwithstanding these notorious violations of sanitary principles, this city appears to be reasonably healthy. Indeed during the latter half of the decade 1880-90 the death rate of Baltimore as officially given out, reached a point which has been regarded as the ideal of perfection for modern cities, so that the mayor in his message in 1887 claimed for Baltimore "a lower rate of mortality than prevails in any city in Europe or America." I deem it, however, proper to say, that during this decade the official death rate was computed upon the basis of a gross exaggeration of the population, and was therefore smaller than the true death rate. At the beginning of the decade, in the Report of the Health Department for 1880, the estimated population was 61,483 in excess of the U. S. Census for the census year 1879-80, and at the end of the decade in 1888 and 1889 the estimated population was 65,904 in excess of the U. S. Census for 1890 and 44,916 in excess of the police census for 1890. In accounting for the apparently great increase in the death rate in 1890 as compared with 1889—an increase from 17.4 per 1000 in 1889 to 22.41 in 1890—the commissioner of health in his report for 1890 says, "Inasmuch as the estimated population on which the calculation of the

mortality rate was based was nearly 50,000 too high, the increase in the death rate is only partly an actual increase."

In calling attention to the serious errors in the official death rates of this city during the period mentioned, I would not be understood as basing the plea for sanitary reforms upon an alarming mortality in this city. While there is nothing alarming in the death rate of this as compared with other cities, I believe that we have now sufficient experience as to the beneficial effects of sanitary reforms to justify the prediction that, as regards infant mortality and certain infectious diseases, the mortality in this city could be materially reduced by the introduction of such improvements in public sanitation as belong to a well managed modern city. The teaching of experience is direct and uniform in this regard.

I have already endeavored to point out that serious sanitary defects, although for a time they may not appear to injure the health of those exposed to them, become a standing menace to health upon the approach of certain epidemic diseases.

But I do not consider it necessary to base the argument for sanitary improvements exclusively upon their demonstrable influence on public health, manifest as their influence often is. Such things as pure drinking water, well paved and clean streets, and well drained soil are conducive to comfort and happiness and to the commercial welfare of a city. They exert in this way a direct influence upon prosperity and an indirect influence upon health, not appreciable by any mortality statistics, but clear enough to the experience of individuals and of the community.

This matter of public sanitation is one purely of municipal administration. I suppose that those who have the power to initiate and carry out measures necessary to secure to us a water supply free from danger of contamination, a civilized system of disposal of sewage, well paved and clean streets, good drainage, freedom from pollution of our water courses and harbor, removal of dwellings which cannot be made fit for human habitation, conceive that their personal and political interests lie in quite different directions, and for this indifference the apathy of the general public is largely responsible.

Recommendations of health officials, reports of special commissions, addresses to tax payers' associations, are unheeded.

Great as are the cost and the practical difficulties in executing municipal engineering works, they have been successfully surmounted by cities less favorably placed as to natural advantages and pecuniary resources than is this city.

Mr. Andrew D. White makes a strong statement when he says that, "Without the slightest exaggeration we may assert that, with a few exceptions, the

city governments in the United States are the worst in Christendom, the most expensive, the most inefficient and the most corrupt," but so high an authority in sanitary matters as Dr. John S. Billings says that this statement "is true so far as municipal engineering work is concerned with regard to several of the largest cities in this country." I cannot forbear from quoting in this connection a passage from Mr. Joseph Chamberlain's article in the last number of the "Forum" on "Municipal Institutions in America and England." After showing that the expenditures for local purposes in the city of Boston are largely in excess of those in the City of Birmingham, England, he says: "The leading idea of the English system may be said to be that of a joint stock or cooperative enterprise in which every citizen is a shareholder and of which the dividends are receivable in the improved health and the increase in the comfort and happiness of the community. The members of the council are the directors in this great business, and their fees consist in the confidence and the gratitude of those among whom they live. In no other undertaking whether philanthropic or commercial, are the returns more speedy, more manifest or more beneficial. To give a single illustration the reforms in Birmingham carried out in a few years reduced the death rate from 26.8 per 1000 in 1874 to 19 in 1888. In other words the initiation of the unpaid members of the council and their supervision of the loyal and assiduous labors of the paid officials have been the means of saving the lives of more than 3000 persons in a single year; and inasmuch as for a single death many cases of illness not actually fatal may be reckoned, it is easy to see what a mass of human suffering has been lightened and how much misery has been prevented."

In view of Mr. Chamberlain's description of municipal administration in Birmingham it is interesting to note that the Special Commission appointed in 1889 by Mayor Davidson to examine all the departments of the city government of Baltimore and to make such recommendations as they deem appropriate, recommended the appointment of unpaid commissions of citizens to be at the head of several departments of the city government, such as the Board of Health, the Board of Public Works and the Board of City Charities.

It has seemed to me necessary to say at least these few words regarding the relation of public health to municipal government, in order that we may be under no illusion as to what can be accomplished for sanitary reform in the condition of the poor outside of public agencies. I realize fully that what is needed in this matter is active work. Interested observers and critics we have in abundance, but the active workers for reform are few. Our dissatisfaction with the intruments at our disposal should of course make us try to get better ones, but in the meantime we can accomplish much with those which we already have, and it is the part of practical wisdom to take

hold of these instruments and apply them to the best use possible under the circumstances. Our health officials are often well aware of the vices of the system under which they are obliged to work and I believe that they will welcome any cooperation and assistance which public spirited citizens and organizations are able to render them. Under our existing political conditions, experience seems to show that more can be accomplished by the quiet, intelligent and well directed efforts of individuals and of such organizations as societies for city improvement, which do not directly antagonize those who wield political power, and which receive the approval of the general public, than by spasmodic political movements for reform.

Of the problems more directly relating to sanitation among the poor in its bearing upon public health, the medical relief of the poor is the most amply, even if not the most judiciously, provided for. The medical treatment of the poor is to a very large extent gratuitously assumed by the medical profession. In this respect physicians perform an amount of unpaid labor without any parallel in other professions or business. So great are the abuses of medical charities that these have been described as the greatest pauperizing agency now in existence. This subject has been so often discussed and has been so frequently presented before Charity Organization Societies, that I shall not dwell upon it. Great benefit has been derived from the cooperation in some cities of Charity Organization Societies in investigating the circumstance of patients applying for gratuitous medical relief in hospitals and dispensaries, and a more extended and perfect system of such cooperation might be usefully inaugurated in this city.

There is one need which is so urgent in this city that public attention should be forcibly directed to it and that is a hospital for infectious diseases. Dr. Rohe, when he was commissioner of health, in 1890 urgently recommended the construction of such a hospital, and his successor has emphatically endorsed this recommendation. At present no hospital in the city will undertake to receive cases of scarlet fever, diphtheria or smallpox. When one considers the necessity of prompt isolation of these cases in order to prevent their epidemic distribution and of our helplessness in this regard in the emergency of a visitation of cholera or yellow fever, it is clear that this is a matter which should receive immediate attention.

A public establishment for disinfecting by steam is scarcely less important and is now provided in most large cities which can lay any claim to decent sanitation. Among the most important results of the discovery and study of the specific germs which cause infectious diseases, has been the development of the methods necessary to destroy these germs outside of the body when their presence is suspected in such substances as clothing, bed linen, household furniture, etc. Some methods of disinfection which were formerly and are still sometimes relied upon, are now known to be inefficacious.

There is now universal agreement of opinion that heat is the most powerful and useful disinfectant agent. Every large city should be supplied with a public establishment for disinfecting by steam, with which it would be well to combine a crematory for burning articles which cannot be disinfected or are not worth disinfecting. The disinfection of rooms, furniture, bedding, etc., should be intrusted to a corps of men who are trained for the purpose.

The housing of the poor is a sanitary problem which offers the greatest difficulties, but there are few sanitary questions which have received more intelligent discussion and treatment from philanthropic and practical men and women.

In all efforts to benefit the poor, but especially here, we have to distinguish two classes of the poor, between which the lines cannot be sharply drawn. In one class are those who earn small wages, to whom the struggle for existence is hard, who manage to preserve decency and self-respect, and in the other class are the failures of life, the criminal, the drunkard, the tramp and the loafer and also a few who have been temporarily forced by adverse circumstances to this low level, but who are capable of rising.

For the first class, it seems to have been demonstrated that healthful dwellings can be furnished at a price within their ability to pay, and that these yield a fair return on the investment. Over the construction of these dwellings and tenement houses, the health officials should exercise a rigid sanitary supervision to insure their proper supply with water, air and light and to control the arrangements for drainage and disposal of excreta.

Of the second class of the very poor, Mr. Theodore Thomson in his paper on "The Housing of the Poorer Classes," read before the Seventh International Congress of Hygiene and Demography in London says: "Something else will have to be done with the lowest class of all. Of these it may be said that were they to-morrow housed in a palace, they would in ten days make it a pig sty. For them remedies are required other than those needful for the class immediately above them. No doubt they will, despite themselves, to some extent be benefited by sanitary arrangements in their dwellings, by demolition of unhealthy areas, by improved lodging houses under existing laws. But so long as there is an insanitary building left, they will go to it, for they do not admire sanitation. They will avoid all model dwellings for they do not wish to be cleanly and orderly as there prescribed by rule, and they will destroy and fill with filth any interior that becomes theirs. It is to be hoped that the benefits of education will effect some improvement in the members of this class, but it must be a long time before these benefits create any appreciable effect. Private effort, such as the noble work of Miss Octavia Hill and others, is one of the means to which one may look with hope. Possibly registration of the worst class of houses with frequent and stringent supervision of the habits of the inmates, may be useful. Such supervision

would not be pleasant to the inmates, but it is perhaps desirable that life should not be made too pleasant for this class of society, most of whom deserve no sympathy other than that which one bestows on the victims of heredity."

Mr. Alfred White, who is to speak to us this evening, in his paper on this subject at the Conference of Charities and Corrections in 1885, believes that the class of people who prefer squalor and darkness to decency and light, who need moral reformation before they can be properly moved into better surroundings, is a small minority of the laboring class here as compared with London.

Something must be done for this apparently hopeless class; if not for their own sake, at least for the sake of the rest of the community. If their existence among us is inevitable, they at any rate should not be permitted to occupy abodes unfit for human habitation, which endanger the health of their neighbors and of the whole community and which may become the breeding places of pestilence. I believe that such houses if they cannot be made decently healthful, and some cannot, should be demolished. What is to become of the inmates? I reply that some will move elsewhere, and that is well, some will be forced to lead more decent lives, and that is also well, and some will go to the almshouse. It is better and in the long run cheaper for the city to take care of this remnant in the almshouse than to permit them to live as they now do.

Between 1879 and 1890 in the city of Dublin 2556 unsanitary houses have been cleared of tenants and closed. More than one-half have been completely removed and the other half have been extensively repaired and rendered habitable. This is one of the great sanitary reforms which have been carried out in that city by Sir Charles Cameron during the past twelve years, and which have led to the almost complete extinction of typhus fever and to other most gratifying results in the improvement of public health.

The impression is a general one that the working classes are better housed in Baltimore than in most large eastern cities, and I think that this is correct. According to the 10th census (the returns of 11th census on this point are not yet available) the average number of persons to a dwelling was in Baltimore 6.54, in Philadelphia 5.79, in Boston 8.26, in Cincinnati 9.11, and in New York 16.37. This means that with us the great majority of the families of the working classes have each a separate house. There are, however, in this city instances in which several families are crowded into houses intended originally for a single family, and this condition is of course worse than that of a well constructed tenement house intended for many families. How common these instances are is not known, and it is much to be desired that trustworthy data should be collected concerning the housing of the poor in this city. An important and useful work might be done if this

Charity Organization Society, or some other public agency, or even some individual, had the inclination and the means to put to work a body of volunteer sanitary inspectors who should do for this city what a corps of similar inspectors under Mr. Dwight Porter has done in the investigation of tenement house districts in Boston. Mr. Porter was assisted by certain students from the Institute of Technology. They received the hearty co-operation of the official board of health.

The most important means at the disposal of departments of public health for the prevention, detection and removal of unsanitary conditions, is a body of efficient sanitary inspectors acting under suitable sanitary laws. In some cities such inspection is carried out with admirable system. It requires intelligence, tact and special training on the part of the inspectors. We are sadly deficient as regards the inspection of slaughter houses, animal food, milk and dairies. The services of one or more skilled veterinarians are needful for much of this work and they cannot act efficiently without better laws regulating these matters than we now have. The number of sanitary inspectors now employed by our board of health seems to me too small to perform efficiently the work which should be done.

We have thus far considered the sanitary state of the poor more especially in its relation to the rest of the community. I hope that it is apparent that merely from a mercenary and commercial point of view it is for the interest of the community to take care of the health of the poor. Philanthropy assumes a totally different aspect in the eyes of the world when it is able to demonstrate that it pays to keep the people healthy. "The health of the people is the wealth of the state." This may be a sordid and mercenary way of looking at the question, but it is the way which has enabled reformers to convince mankind of the necessity of public sanitary measures. It is estimated, and of course such an estimate can be only a rough one, that nearly 100,000 deaths occur annually in this country from preventable causes. For each death there are of course several cases of illness not fatal, due to preventable causes. One can form from such a statement some idea of the enormous loss in money and productive labor which we suffer from preventable causes of illness and death.

The influence of unsanitary conditions upon the health, the character and the morals of the poor is manifestly an important question in sociology. A good deal has been written upon it, but mostly in a vague and indefinite way. The subject has not received the scientific investigation which it deserves and many of the existing data are untrustworthy.

The death rate is stated to be from two to three times greater among the very poor than among those better situated. But it is not only as to the influence of unsanitary conditions upon the health, but upon the whole

physical, mental and moral constitution of those subjected to them, that we wish information.

It is of course self-evident that insufficient and wretched food, filthy surroundings, close and impure air and overcrowding must effect not only the health but also the habits and morals of those subjected to such an environment. Is any moral regeneration possible under such circumstances? Is not the first step a regeneration of the physical environment?

The picture has been drawn of the man of the alley who comes home from his work. After stumbling over the filthy refuse heap in front of the house, he enters a dingy and repulsive abode in which the air is close and depressing. The small room is crowded and it is pervaded with offensive odors. The food is scanty and ill cooked. Near by is a capacious room, relatively clean, where conversation and excitement may be found, where to him everything is bright and alluring and where for a few coppers he can get something which for a time stimulates him and makes him forget his misery. The wonder is not so much that one man reels home drunk and a brute, but that for every such one there are not a dozen. It is not difficult to comprehend the reply which was made by such a man to the clergyman who remonstrated with him. "If you were to come and live and sleep here, you, sir, would drink whiskey too."

The immorality which must necessarily ensue from bestial over-crowding has been depicted often enough.

But it is not so much these gross and flagrant vices which spring from unwholesome living that I wish to emphasize at present. These are the themes of sermons and tracts and are well known. These vices belong in a large part to a class of the poor which many believe to be irreclaimable.

The class best worth helping are the industrious, hard-working wage earners, struggling to make a decent living, who possess a fair degree of intelligence and preserve their self-respect.

Whether many of these shall keep their heads above the water or shall sink to the submerged class, depends I believe in larger measure upon their sanitary surroundings than is generally supposed. Many of these worthy people live under very unfavorable hygienic conditions which can be remedied. Many are ignorant of the simplest rules of health. They suffer often a gradual physical deterioration not amounting to actual illness. Their minds and characters suffer with the body. Many of these poor people become intemperate, not usually, as many temperance reformers seem to think, because they deliberately choose to be drunkards, but as a natural result of the circumstances under which they are forced to live. It is useless to appeal to the self-control of these individuals and to leave them breathing a polluted atmosphere in unwholesome houses with scanty and bad food.

It has become more and more evident that the great work of charity in the future is to consist, not so much in almsgiving, as in efforts to educate

the poor, to strengthen their characters, to lift them up physically, mentally and morally. A fundamental part of this uplifting must be an improvement in the sanitary conditions in the abodes of the poor and instruction in domestic hygiene. I have little confidence in the remedial efficacy of measures which do not include this fundamental work.

I believe that the workers in this and similar organizations who visit the houses of the poor, can do much good in carrying to them the simpler lessons in domestic hygiene as to such matters as ventilation, cooking, household cleanliness, etc. They can also make clear the necessity of certain simple precautions, such as boiling the water and the milk, to be exercised at the approach of certain epidemic diseases, such as cholera and typhoid fever.

This implies that these workers themselves possess the requisite information. Sanitary science is less of an intuitive nature than many seem to suppose. Knowledge of it is to be gained by reading good books on the subject, by demonstrations and by lectures, and I venture to suggest that it might be well for this organization to make some provision for its workers in the way of instruction in sanitation. Although my theme has been sanitation among the poor, it is not to be understood that the rich do not also suffer their full share from sins of ignorance and neglect in matters of health.

In conclusion I would say that in emphasizing the importance of sanitary reform, I do not for a moment suppose that this is the only agency to be used in elevating the condition of the poor. There are other motives to work and other agencies to be employed which occupy a much loftier plane than those which I have treated.

Still less do I suppose that even perfect sanitation would be a panacea for the evils attendant upon poverty. The roots of these evils lie far beneath the surface. It may be that they are inseparable from existing conditions of society and from the present industrial system and that nothing short of a social revolution can wholly remove them.

But we need not wait for a reconstruction of society and the introduction of some scheme which we would now call Utopian in order to bring relief. How many generations will pass before this radical relief will come, if it come at all, no one can tell. Our present duty is to make use of the best instrumentalities available and among those which promise the surest and quickest and happiest results is sanitary improvement. I would therefore earnestly commend to the attention of those engaged in the great and rapidly developing work of our modern organized and associated charities the importance of including in this work efforts to improve the sanitary surroundings of the poor and to educate the poor in matters pertaining to health.

ASIATIC CHOLERA IN ITS RELATIONS TO SANITARY REFORMS[1]

Since the appearance of Asiatic cholera in Europe last summer, and especially since its arrival in the harbor of New York last autumn, and its persistence in Europe during the winter, an unusual degree of public interest in sanitary matters has been awakened throughout this country. This is due mainly to the popular apprehension lest this most dreaded of epidemic diseases should gain a foot-hold in this country during the coming summer and autumn.

Unwonted attention is given to public health administration. The national government provides additional legislation regarding quarantine. There is a general cry for cleaner streets, removal of public nuisances, and more efficient sanitary inspection. The character of the water supply is scrutinized. Measures, often more vigorous than wise, are taken to remedy sanitary defects of long growth. Hospitals for infectious diseases and modern disinfecting plants are demanded. Committees and conferences of citizens and of various civic organizations are formed. Magazines and newspapers are lending their aid, often most efficiently, toward education of the public and measures for improved sanitation. The public is readier to listen than at ordinary times.

A similar awakening of public interest in sanitation has attended the approach of cholera in the past. However near or remote one may consider a visitation of cholera, whether or not one may approve of much which is written on this subject at present, and of some of the measures urged for the prevention of this disease, anyone interested in sanitary improvements must welcome the increased attention given to this subject and the larger opportunity to secure some permanent additions to our sanitary resources. This feeling may be tempered by the fear that now as in the past excitement and sudden emergencies may lead to hasty and inconsiderate measures and foolish and wasteful expenditure of money, but this makes it all the more desirable to take advantage of the opportunity and to try to direct thought and action into the right channels.

In this way surely some good can be done. Knowledge of the simpler principles of hygiene can be more widely diffused among the people. The sanitary sense, even of the more enlightened, can be further cultivated. The

[1] Pop. Health Mag., Wash., 1893-94, I.

inhabitants of cities may be led to take some active personal interest in the sanitary condition of their towns. Sanitary defects can be brought into clearer light and to some extent remedied. Public health administration can be aided and improved. Possibly a hospital for infectious diseases, a public disinfecting establishment, even some important work in municipal engineering, improved methods of registration of vital statistics or better sanitary legislation can be secured.

Some knowledge of the nature and mode of distribution of infectious diseases must be useful to those interested in questions of public health, and, although each infectious disease presents its own peculiar problems there is none which can teach more important and helpful lessons in sanitation than cholera, and there is none which has had so profound an influence upon the development of modern hygiene.

Cholera is to us of the nineteenth century the chief reminder of the great pestilences of former centuries which have disappeared from civilized lands. These great pestilences were attributed for the most part to causes beyond human control, such as the anger of an offended Deity or some mysterious epidemic constitution of the atmosphere. The careful study of the mode of spread of epidemic cholera has given the early impulse and chief support to the doctrine, which is the mainspring of modern sanitation, that the causes of many infectious diseases are preventable. There is no disease about which so much has been written as concerning Asiatic cholera, the mere list of titles of books and articles on this subject occupying one hundred and forty-eight pages in the great Index Catalogue of the library of the surgeon-general's office.

Although cholera has existed in parts of India probably from time immemorial, it was not until the year 1817 that it spread over India, and in the following six years over a large part of Asia. The second cholera pandemic began in 1826, but not until 1831 did it reach for the first time western Europe, and in 1832, Canada and the United States. Each pandemic of cholera has lasted for several years, during which the disease has travelled over most of the inhabited regions of the globe, only a few remote countries, such as the islands of the Pacific ocean and Australia, having thus far escaped. According to the usual reckoning the present is the sixth of the great pandemics of cholera.

The sixty-two years which have passed since the first appearance of Asiatic cholera in western Europe have witnessed the most important developments of modern hygiene. It is interesting to note to what extent sanitary science and sanitary works have been influenced by the occurrence and the study of this disease.

It was under the direct impressions of the first terrible visitation of cholera that in England the office of Registrar General was established and William Farr was appointed to fill it. We owe to this office and to the work of this man the application of statistics to public health. As has been said by Dr. Parkes, an English hygienist, "It is impossible for any nation, or for any government, to remain indifferent when in figures which admit of no denial, the national amount of health and happiness, or disease and suffering, is determined. The establishment of the Registrar General's office in 1838, and the commencement of the system of accurately recording births and deaths, will hereafter be found to be, as far as the happiness of the people is concerned, one of the most important events of our time. We owe a nation's gratitude especially to him to whose sagacity the chief fruits of the inquiry are due, William Farr."

The English have taken the foremost place in the art of formulating laws for the protection of health and in the organization of the machinery for public health administration, which is entirely of modern growth as a separate department of government. In 1832 the dread of cholera led to an act of Parliament, empowering the privy council to take certain preventive measures against the spread of the disease, and every extensive visitation of cholera has been followed by activity in the passing of fresh sanitary acts. During the discussion in Parliament in 1875 on the Public Health Act, the most complete code of sanitary law in existence, Disraeli said: "The public health is the foundation on which repose the happiness of the people and the power of a country. The care of the public health is the first duty of a statesman."

A decisive part in the development of the doctrine that certain infectious diseases are propagated chiefly through impure drinking water and contaminated soil is traceable to the investigations concerning the mode of spread of cholera. The celebrated instance of the Broad street pump in London, in 1854, furnished conclusive evidence that the cholera poison may be conveyed by the drinking water. A distinguished modern hygienist has said, "The Broad street pump has played not only a decisive rôle in the cholera question, but it has furnished also the most important impulse for the development of a new era in the department of public hygiene."

That pioneer and master of modern hygiene, Max von Pettenkofer, bases to a large extent his views as to the agency of contaminated soil in the spread of certain infectious diseases, upon forty years' study of the relations of the soil to the distribution of cholera.

These views widely held as to the propagation of some infectious diseases by the drinking water and by the soil, and based so largely upon the study of cholera, have been not of theoretical interest only, but they have influenced

profoundly the practical measures which have been undertaken to preserve and promote the health of the people.

Cholera has destroyed millions of human lives, but it has been the means of saving millions more. It has been one of the levers of progress in modern sanitation. The same measures which are needed to protect a city against occasional epidemics of cholera are needed at all times to protect it against other infectious diseases, such as typhoid fever, which are spread in a similar manner, and which, although they do not come with the terrible impetuosity of cholera, steadily do their deadly work, and in the course of time destroy among us far more lives than cholera. These measures for the sanitary welfare of the people should be provided independently of the danger of cholera, but it has often happened that governments and citizens are not aroused by the common, but preventable, causes of death to undertake sanitary works, the necessity for which is evident enough to sanitarians. Unfortunately, they have required sometimes the violent impressions of an outburst of cholera to stir them to undertake these long-needed sanitary improvements. Witness at this moment Naples, Marseilles, and Hamburg, which are spending millions of dollars for destruction of insanitary quarters, for better sewage disposal, for improved water supply. But think of the thousands of lives destroyed, the panic, the commercial depression, the untold misery through which these cities have passed before the warning was heeded.

When we consider the properties of the infectious agent of cholera and the facts established concerning the mode of spread of the disease, it is not difficulty to understand why cholera should have had so large an influence upon the historical development of modern sanitary science and art, and why measures which are useful in preventing the invasion and propagation of this disease are applicable also to typhoid fever and some other infectious diseases. There have been and still are conflicting views as to some points in the causation of cholera, but as to many points there is substantial unanimity of opinion.

Asiatic cholera is an infectious disease. By an infectious disease is meant one which is produced by a specific microorganism in the body. Whether or not an infectious disease is contagious, that is, communicable from person to person, depends upon the properties of the causative microorganism, and especially upon the manner in which this organism is usually eliminated from the body and must be received in order to cause infection. When, as is the case with cholera, the infectious germs are discharged, solely or chiefly, by the intestine, and must be taken in by the mouth in order to cause the disease, it is evident that the disease is not likely to be conveyed directly from the sick to the healthy.

The species of bacterium which is always associated with Asiatic cholera, and which there is the best reason for believing to be the cause of the disease, is usually called the comma bacillus of Koch, from its shape and the name of its discoverer.

The recognition of this bacillus is the only absolutely positive means of diagnosis of Asiatic cholera. After the establishment of an epidemic mistakes in diagnosis are not likely to occur, and if they do, they are of little consequence, but it is important that a bacteriological examination should be made in the earliest suspected cases, in order that suitable preventive measures may be taken.

One of the most important properties of the cholera germ is that it is killed in a short time by complete drying. Bacteria float in the air with particles of dust only when they have been desiccated. Currents of air are incapable, under ordinary circumstances, of lifting bacteria from moist surfaces. The inference is therefore justifiable that the germs of cholera are not disseminated through the atmosphere, and that we cannot contract the disease by taking the germs in with the air which we breathe. This inference, which is a most comforting one, is supported by observations of the mode of distribution of the disease and is manifestly of great practical importance as regards the care and prevention of cases of cholera. The cholera patient is not a source of danger to those in proximity in the same way that a smallpox or scarlet fever patient is. Neither the patient nor his discharges infect the surrounding air. The inhumanity with which those seized with cholera are sometimes treated by the public is based upon groundless ideas as to the real sources of danger.

The cholera germs must be taken in by the mouth and swallowed in order to produce the disease in human beings. In other words, the principal sources of infection are the drink and food, sometimes the hands or other objects contaminated with cholera spirilla and brought into contact with the mouth.

But even if the cholera germs in this way gain entrance to the stomach, there are many chances that they will not produce the disease. They are weakened or killed by acids, and the acidity of the normal juices of the stomach is an obstacle to their passage in a living and virulent condition into the intestine, which is the only part of the body where they can multiply and flourish. This teaches the importance of a healthy stomach in cholera times, and the danger of indiscretions in diet or in other ways, which impair the functions of this organ. We can understand why during epidemics of cholera there is often a marked increase in the number of cases a day or two after the carousing of a popular holiday or a Continental Sunday.

Aside from the condition of the stomach there appears to be a marked difference in individual susceptibility to cholera. A large number of persons do not contract the disease even when exposed to its causes. Some develop only a slight or moderate diarrhoea, which would not ordinarily attract attention, although cholera spirilla may be present abundantly in the intestinal discharges. Others are carried off in a few hours by the most malignant type of the disease. To what extent these differences depend upon variations in susceptibility, or to variations in the virulence of the cholera germs, or to other causes, is not definitely known, but we know enough to indicate that among our prophylactic measures should be included such as tend to produce and to preserve individual resistance to the disease so far as this is within our control.

It is well known that the largest proportion of the victims of epidemic cholera is among the crowded poor living under insanitary conditions. Hence it is plain that improvements in the abodes and the conditions of living of this class will do much to lessen the chances of an epidemic of cholera. Every large city has its dangerous spots, which may become breeding places of infectious diseases, and the thorough overhauling and cleaning up, often indeed the destruction, of these places are an important part of municipal sanitation.

It has already been mentioned that the cholera germs multiply only or chiefly in the intestinal tract and that they are discharged with the intestinal contents, sometimes with the vomit. They are never eliminated with the breath or from the surface of the body. The real danger from a cholera patient to other persons is in his discharges and in objects soiled with these discharges. With ordinary care and in decent conditions of living the chances of any part of these discharges being received directly into the alimentary tract of those in the immediate neighborhood of the patient are so slight that cholera is not ordinarily regarded as contagious. In properly conducted cholera hospitals instances of such contagion are very infrequent, but in the crowded homes of the poor such instances are not so uncommon, so that in every large epidemic of cholera a certain number of cases, particularly in the so-called house epidemics, are attributable to contagion in the sense in which this term is ordinarily used.

The thorough disinfection of the discharges of cholera patients and of objects soiled by them is obviously of the first importance. The cheapest and most generally applicable and efficient of the disinfectants for the discharges are milk of lime and chloride of lime of good quality. One of the great obstacles to checking the spread of the disease in this way is the occurrence of mild cases, which are not recognized as cholera, but which are capable of distributing the germs.

Outside of the endemic home of cholera, in southern Bengal, Asiatic cholera is always to be referred to the importation of the cholera germs, although often the exact time and mode of entrance cannot be traced. Human beings and their effects are the chief carriers of these germs. Restraint of human intercourse with infected localities has naturally been regarded as a chief measure of protection. The achievements of quarantine in keeping out cholera have been relatively to its vexations, hardships, cruelties, and interference with commerce so small that many distinguished sanitarians would discard it altogether. As we are situated in this country it would doubtless be unwise to relinquish quarantine, but all the good which can be accomplished by quarantine can be attained by scientific and humane methods, which should be uniform and under unrestricted national control.

The public should realize that quarantine is at best an uncertain and often inefficient protection against cholera, and that far greater safety is to be sought in measures which render the city or locality unsuitable for the multiplication and distribution of the germs of the disease. All great epidemics of cholera are referable to infection of the locality. One of the fundamental facts in the epidemiology of cholera is that the disease has been introduced time and again into certain places without spreading, whereas at other times or in other places the introduction of a single case has been the starting point of a terrible epidemic. There are cities which are naturally immune against the epidemic spread of cholera; there are other cities which have made themselves virtually cholera-proof. It is this predisposition in time and in place which has been and is still the subject of much of the controversial literature regarding cholera.

We do not know the nature of all of the local and seasonal factors concerned in the causation of epidemics of cholera, but concerning some we have sufficient information to indicate the line of action to be pursued in endeavoring to make a place unsuitable for the spread of the disease. From what has already been said in this article it is clear that the susceptibility of a place to cholera must depend in very large measure upon the facility with which the discharges of cholera from a patient can get into the soil and into the sources of supply of the drinking water. In other words, the characters of the drainage, of the disposal of sewage and of the water supply will often decide the fate of a city when cholera has been introduced. The evidence that some of the great epidemics of cholera and especially of the explosive outbursts of the disease are due to infection of the water supply seems conclusive. The recent epidemic in Hamburg will be cited hereafter as a classical example of a drinking water epidemic.

The lesson to be learned from experience seems clear enough. A city can make itself nearly if not wholly immune against cholera. This requires

much time, money, and intelligence. It demands the aid of skilled sanitary knowledge. The problems of municipal sanitation must be appreciated by intelligent public opinion, but they can be solved only by those who have special knowledge and who are trained for the purpose. The necessity of calling in the assistance of skillful sanitary experts for the work of municipal sanitation is one of the most important objects of education of the public in sanitary matters. As soon as there is a demand for those possessed of the requisite training, there will be no lack of the supply.

The problems of protection of a city against cholera are essentially the problems of municipal sanitation in general. They relate to such matters as the protection of the water supply against contamination; to the proper disposal of sewage; to good drainage; to cleanliness of streets; to improvement or removal of insanitary quarters; to thorough sanitary inspection; to the provision of public disinfecting establishments, public bathing places, and hospitals for infectious diseases; to education of the public in hygiene; to the employment of sanitary experts. If the apprehension of an invasion of Asiatic cholera and the consequent interest in sanitary matters should prove the incentive to sanitary reforms, there will result permanent increase in happiness and health and the prevention of other infectious diseases, which, although less dreaded because they are more familiar, are in reality more serious and constant objects of concern than cholera.

THE RELATION OF SEWAGE DISPOSAL TO PUBLIC HEALTH[1]

I am somewhat perplexed how to treat the subject assigned to me, for, although it is a very broad one, its various parts have been so parcelled out that those who are to follow will take up most of the points which would naturally fall within my theme.

The basis of modern sanitation is the recognition of the fact that certain diseases, particularly those called infectious, are preventable. So familiar is this conception, that it is difficult to realize that it is essentially of modern origin. While it is true that in all ages there have been enlightened physicians to whom this conception of the preventability of disease was not entirely foreign, nevertheless the prevailing opinion in ancient and medieval times referred the origin of epidemic diseases to such supposed causes as the anger of an offended Deity, the influence of the planets and comets, poisoning of wells by the Jews, some mysterious epidemic constitution of the atmosphere, etc. Under the control of such ideas, it is clear that public and private sanitation could not develop. Certain great public works of antiquity to which we must attach hygienic value, such as the monumental aqueducts and drains of ancient Rome, were undertaken for public convenience and not with any clear appreciation of their relations to public health.

The doctrine of the preventability of infectious diseases was first established upon a firm basis by the collection and analysis of vital statistics. This great contribution to preventive medicine we owe to the establishment of the Registrar General's Office in England, in 1838, concerning which an English hygienist has justly said: "It is impossible for any nation or for any government to remain indifferent when in figures which admit of no denial the national amount of health and happiness, or disease and suffering, is determined. The establishment of the Registrar General's Office in 1838, and the commencement of the system of accurately recording births and deaths, will hereafter be found to be, as far as the happiness of the people is concerned, one of the most important events of our time."

The impetus which led to this systematic collection and study of vital statistics, as well as to other great sanitary reforms, was the invasion of

[1] Remarks made before the Joint Meeting of the Medical and Chirurgical Faculty of Maryland and the Maryland Public Health Association, to discuss the Sewage Disposal of Baltimore, Baltimore, November 19, 1897.

Maryland M. J., Balt., 1897-98, XXXVIII, 199-204.

Asiatic cholera for the first time into Western Europe in 1831. The careful study of the mode of spread of this pestilence led to the clear recognition of the fact that it is a preventable disease, and it was soon discovered that the same conception is applicable to typhus fever, typhoid fever and many other infectious diseases. Cholera has destroyed millions of human lives, but it has been the indirect means of saving millions more.

The visitation of great epidemic diseases, such as cholera and yellow fever, has been one of the levers of progress in modern sanitation. Although we have constantly with us diseases, notably typhoid fever, which teach the same lessons and are as preventable as cholera, it has often required the violent impressions of the outburst of some rapidly spreading and strange pestilence to stir a community to undertake sanitary improvements, whose necessity has been long pointed out by sanitarians. We in Baltimore can, if we choose, wait to receive such a violent lesson, but it is the part of wisdom and prudence to profit by the same lesson which existing circumstances teach no less distinctly, even if with less impetuosity.

It is fortunate that those who instituted the first public sanitary measures did not wait to find a thoroughly scientific basis for them. Even in this day with our greatly extended knowledge of the causation and mode of spread of infectious diseases, there are many proved measures for preventing the development and spread of disease, for which we cannot give an entirely satisfactory scientific explanation. We must utilize the results both of practical experience and of scientific investigation in determining the character and the efficacy of sanitary procedures.

The early English sanitarians based their practical sanitary measures upon a belief in the efficacy of cleanliness in preventing the development and extension of infectious diseases, and they directed their efforts especially to securing pure soil to live upon, pure air to breathe, pure water to drink, and pure food to eat. While modern bacteriology has taught us the particular impurities in our environment most to be dreaded and consequently better means to guard against them, this programme of the early sanitarians remains to this day the broadest and most satisfactory basis of preventive medicine.

While the great media of our environment, soil, water, air, and food, are so intimately associated in their sanitary relations, that impurities of one are likely to affect others, my theme on this occasion relates especially to the dangers of pollution of the soil.

The soil is the place to which sooner or later all organic matter returns. From it comes all life and to it all life returns. "Dust thou art, and unto dust shalt thou return," embodies a profound scientific truth. The soil is the greatest laboratory in the world. It is there through the agency of

microscopic organisms that organic matter derived from plants and animals is decomposed and converted finally into the simple inorganic substances which make the food of plants. The plants again build up these simple mineral constituents into the complex organic materials of their bodies, which make the food of animals. In this continual circulation of matter, agencies at work in the soil play an indispensable part, a part so essential that if this link in the chain should drop out all life upon this globe would cease in a comparatively short time.

It is through these agencies, which are chiefly living microorganisms present everywhere in the superficial soil, that the soil is able to dispose of organic matter which it receives and thus continually to purify itself. Upon this principle is based the method of disposal of sewage by irrigation and filtration through the soil. But there is a limit to the capacity of soil to convert organic material into a harmless state and if this limit is exceeded we have a polluted soil. There are likewise various circumstances, which cannot be considered here, which influence the rapidity and extent of this process of self-purification. For example, when the organic material is not received upon the superficial layers of the soil, but leaks out, as through cesspools, into the deeper layers, the process of purification is much slower and less efficacious. In this way the soil may become contaminated to great depths and may bring serious injury to people living upon it. There are various artificial conditions, such as pavements, which render much of the ground in cities incapable of doing the work of virgin soil in transforming organic waste.

What are the dangers of such contamination of the soil? Some of these dangers we can point out with reasonable certainty; others, which we have reason to believe exist in view of certain benefits which regularly follow purification of the soil, we understand at present either very imperfectly or not at all.

Pettenkofer has called especial attention to the fact that the air in the lower parts of our houses is derived in no small part from air drawn from the ground, unless the special construction of the cellars prevents this. If this ground air comes from a polluted soil, it contains foul gases, the precise influence of which upon the health of the inhabitants it has not yet been found possible to determine, but there is reason to believe that it may be injurious, and certainly it must be regarded as offensive. That such air under certain circumstances may contain disease-producing microorganisms is highly probable. When the soil has become saturated with illuminating gas derived from leaky or broken gas pipes, the air of houses in the neighborhood may become so contaminated with gas drawn in from the soil, that serious poisoning of the inhabitants may result, as has repeatedly been observed.

The view is widely held that serious contamination of the soil is injurious to the health of those living upon it, independently of the actual presence in such soil of the specific germs of disease. Exposure to such influences is thought to be capable of impairing mental and physical vigor and in general of lowering resistance to disease. Among the various factors which determine the higher death rate in many crowded and insanitary localities, pollution of the ground is doubtless one of importance.

It is, however, more especially in the presence of the specific microorganisms which cause infectious diseases, that we have to seek the chief dangers from contamination of the soil with human and animal excreta and household waste. Without proper methods of disposal of sewage abundant opportunities are afforded for the escape of such pathogenic microorganisms into the soil.

The fate of such organisms after they have reached the soil is various. It has been demonstrated that the bacilli of tuberculosis and of typhoid fever may survive months, perhaps even years, and that those of cholera may persist for weeks in the soil. Whereas in virgin soil they do not find requisite food for their multiplication, the bacilli of typhoid fever may actually multiply in soil contaminated with organic material.

Having once reached the soil, these disease-producing germs may be conveyed to us in manifold ways. An important medium of transportation of bacteria from an infected soil is the water which we drink or use for domestic purposes. Our chief interest here in Baltimore in the contamination of drinking water from the soil relates not to our own soil, save in the occasional use of wells, especially in the recently annexed districts, but relates to that bordering on the streams and reservoirs from which we receive our naturally excellent drinking water. It is, therefore, not necessary to dwell upon this point on this occasion.

Among the various other ways by which harmful bacteria may reach us from contaminated ground it will suffice to specify their conveyance attached to particles of dust in the air, their transportation by flies and other insects, and by domestic animals, their presence upon vegetables, especially those eaten uncooked, and our own direct contact with the soil. It is evident that the possibilities of infection from soil contaminated with disease germs are numerous and often intricate.

The list of diseases whose causation has been shown to stand under certain conditions in more or less direct relation to contamination of the ground with their specific germs is a long one. Among the more important may be mentioned malaria, typhoid fever, cholera, yellow fever, dysentery, tuberculosis and the summer diarrhoeas of infants. Experience teaches, unmistakably, that contamination of the soil with organic refuse favors the develop-

ment and spread of such diseases as these, and that drainage and purification of the soil by proper systems of sewerage are among the most effective measures for their prevention.

No more instructive illustration of the value of modern methods of public sanitation can be found than the inability of Asiatic cholera to secure a foothold during the last two European epidemics in clean cities with proper sewerage and water supply and its ravages in notoriously filthy or insanitary cities, such as Toulon, Marseilles, Naples and formerly Hamburg. The public should realize that quarantine is an extremely vexatious, expensive, uncertain, means of protection, and that far greater safety can be secured by measures which render a city unsuitable for the multiplication and distribution of the germs of epidemic diseases. A city can make itself cholera-proof by well understood sanitary measures.

Insanitary conditions, to adopt a metaphor employed by Pettenkofer, represent the powder and the germs of cholera or typhoid fever sparks. It is wiser to keep no powder of this sort than to engage in frenzied and often futile efforts to drive away the sparks which, if they reach the powder, will cause a destructive explosion.

Although the nature of the relationship between the conditions of the ground and the prevalence of tuberculosis is not well understood, practical experience has shown that many localities have secured, by good drainage of the soil, great reduction in the mortality from this most deadly scourge of the human race, a reduction amounting in some places to nearly fifty per cent of the former death rate. Similar measures in Berlin and elsewhere have notably lowered the mortality among infants, particularly from summer diarrhoea.

I call your attention to these various charts hung upon the wall which illustrate some of the beneficial results which have been secured by purification of the soil through proper systems of sewerage. The charts speak for themselves.

Upon this one the black column represents the average number of deaths from typhoid fever in 313 cities without sewers and the next column, less than one-quarter of the first in height, shows the deaths in 39 cities with efficient sewers.

This second chart shows on the left side the deaths from typhoid fever to each 10,000 inhabitants in each of a series of cities with good sewers and a general water supply, and upon the right side the deaths from the same cause in cities without sewers or very imperfectly sewered. You will observe that the average in the first series is 2.4 and in the second is 10, with many cities lower than the average in the first series, notably Munich, Dantzic,

Vienna and Frankfort, and many higher than the average in the second series, notably several Italian cities.

Especially instructive is the next chart, which shows the experience of Munich during the gradual improvement of an originally highly contaminated soil. During the first period represented, when the inhabitants drank water from wells and the excreta were stored in ordinary privy vaults, the death rate from typhoid fever was 24.2 per 10,000 inhabitants. When the city required the cementing of the vaults, the death rate fell to 16.6. The remaining three lines show the successive reductions in the death rates with the gradual extension of the sewerage system, until in 1884 the deaths from this fever were reduced to 1.4 per 10,000, and in 1888 to 1 per 10,000 inhabitants. By systematic and intelligently directed sanitary improvements the cities of Munich and Vienna have been converted from hot-beds of typhoid fever to places from which this disease has been practically eradicated. All of the money which they have expended in carrying out these great sanitary reforms has been repaid a hundredfold in the increased health, happiness and productive capacity of the inhabitants and in the increased value of property.

The same results can be secured by Baltimore and other cities, as is demonstrated by this chart, which shows for Dantzic, Breslau, Frankfort, Berlin, Vienna, Brussels, London, New York, Boston, Brooklyn, and other cities the deaths from typhoid fever to each 10,000 inhabitants before, during and since the introduction of sewerage and general water supply. You will observe that the experience has been everywhere the same, lowering of the death rate to a quarter, a sixth, an eighth, a twelfth, even a twentieth, of the former rate.

This red line represents the mortality from typhoid fever in Baltimore. It is the official mortality from this disease. The actual mortality is considerably higher, for, as Dr. Osler has pointed out, doubtless most of the deaths in this city returned to the Health Department as from malarial fever and from typho-malarial fever are in reality due to typhoid fever. The death rate from typhoid fever in this city, as he has shown, is that which belongs to an unsewered city with general water supply, and it can be confidently predicted that the introduction of efficient sewerage and the protection of the sources of our water supply will reduce this mortality to the low rate of well sewered and well watered cities.

The reduction in typhoid fever shown by the charts cannot be attributed wholly to the introduction of good sewers. In many instances it has been due mainly to the introduction of a general supply of pure drinking water. Authorities have differed as to the relative value of sewerage and of water supply in influencing the prevalence of typhoid fever. We need not pause

here to discuss this matter. Both factors are important, the drinking water usually the more important. But it is sufficient for our purpose to show that purification of the ground by proper disposal of sewage is one of the factors in determining a reduction in the occurrence of typhoid fever and other diseases.

It is by no means an easy matter in all cases to assign to each one of the various recognized elements which go to make up an entire system of satisfactory municipal sanitation its due share in the beneficial result, for it rarely happens that one is introduced by itself alone, and the harmonious working of the whole system is often necessary to secure the best results from the individual factors, such as pure water supply, efficient sewerage, good drainage, cleanliness of streets, improvement or removal of insanitary quarters, thorough sanitary inspection of dairies and food-stuffs, public disinfecting establishments, hospitals for infectious diseases, municipal laboratories, etc. In some instances, however, the conditions have been such as to furnish conclusive demonstration of the separate influence of the introduction of effective sewerage upon the death rate from typhoid fever. This is notably true of Dantzic and Stockholm, as is illustrated by these charts. In the former city a high death rate from typhoid fever persisted after a good general water supply, but after the introduction of the system of sewerage it fell from nearly 10 per 10,000 to 1.5. You will observe in this striking chart how in the city of Stockholm the mortality from typhoid fever fell, *pari passu,* with the gradual extension of the sewerage system, reaching in 1887 the low figure of 1.7 per 10,000.

Much more evidence might be adduced, if it were necessary, to show the beneficial influence of good sewerage upon the health of a community, but enough has already been said to demonstrate the hygienic importance of proper disposal of sewage. Indeed it might seem unnecessary to dwell upon these matters upon which sanitarians are agreed, were it not that public indifference to this subject indicates lamentable ignorance, although for two generations the gospel of public sanitation has been preached to this city by its health officers and others. Trite and wearisome as the tale may be, it is one which must be told and retold and we cannot choose but hear until the end desired is attained.

But it is not necessary or even desirable to rest the argument for an efficient sewerage system exclusively upon its effects on public health, important as these are. Quite apart from the large saving of human life, the proper disposal of excreta, household waste, water and garbage contributes so much to the comforts, conveniences and even decencies of living and so essential a part of such disposal in large cities is a good system of drains and sewers, that it is positively uncivilized for a modern city to be deprived of the

advantages of such a system. The conditions in this respect here in Baltimore with its leaky and overflowing surface drains, with its utterly insufficient storm water drains, with one-twentieth of its area, exclusive of streets and parks, occupied by privy pits and cesspools, permitting often overflow and leakage into the ground and cellars, with arrangements by which sewage and garbage are allowed to befoul the streams and the harbor basin, are obnoxious in the extreme. That greater damage to health and property has not been the result of these primitive conditions is due in large part to the natural salubrity of the city and the configuration and character of the ground.

Mr. Mendes Cohen, in a published address delivered before the Taxpayers' Association of Baltimore about six years ago, pointed out very clearly and forcibly the injury to property caused by the defective drainage of this city and he showed how the rental value of property would be so much enhanced by the introduction of good drainage that a large share of the necessary cost of the improvements would be thereby covered. Dr. Fulton will tell you this evening something about the loss in money due to sickness and death entailed by the present conditions and the estimated pecuniary gain which can reasonably be expected to follow the establishment of a good system of sewers. But who can estimate the suspense, the suffering, the grief, the despair caused by the unnecessary sickness and sacrifice of life through neglect of the plainest laws of sanitation?

The immediate occasion of our assembling this evening upon the call of the physicians and sanitarians of this state is the consideration of the recently published Report of the Sewerage Commission of the City of Baltimore, of which an abstract has been presented to you by Dr. McShane. Those who are to follow me will discuss the details of this Report. It seems to me to be an admirable document, supplying as it does the necessary data, based upon a careful and scientific investigation of the problems involved, to enable the reader to form an intelligent judgment upon the subject. It would be a great misfortune if the city of Baltimore should not take advantage of this opportunity to come to some definite solution of this problem which must be solved sooner or later and which becomes more complicated the longer it is deferred. It behooves our citizens and above all our legislators to give earnest heed to this matter and to see to it that this Report does not remain as fruitless in practical results as did its predecessors.

RELATIONS OF LABORATORIES TO PUBLIC HEALTH[1]

Mr. President and Members of the American Public Health Association: I am very glad of the opportunity of appearing before you, and desire to say a few words with reference to the general subject of the relations of laboratories to public health. A laboratory is a workshop where those, who are suitably trained, have charge of the work which is done, where they have the proper supply of material and adequate means for carrying out the study of such material. Such laboratories may be used for different purposes. Some of them we may regard as private laboratories; some as purely investigating laboratories; others are intended for purposes of instruction, and still others are mainly to make available to the general public the results of scientific work by the conduct of certain technical procedures. Laboratories in one form or another have existed from the earliest times. We must suppose that Aristotle had something in the nature of a laboratory, and although we know very little definitely about the remarkable Alexandrian period in medicine and science, it is clear that laboratories must have existed then. But public laboratories, which were freely opened for purposes of instruction and investigation, are modern. With the exception of the anatomical laboratory, which has existed in some form since the fifteenth century, laboratories, as now understood, are the creation of the present century.

It is usually stated that the first laboratory in a modern sense was the chemical laboratory founded by von Liebig in 1825. This is not strictly correct as a physiological laboratory was established by Purkinje in Breslau in 1824. It nevertheless remains true that Liebig's laboratory had the greatest influence upon the subsequent development of laboratories throughout the world, and to this day our chemical laboratories are the best supported and best equipped laboratories which we possess. I shall not attempt to trace the evolution of laboratories up to the present time. But it is of interest to note the very recent development of laboratories devoted to the study of hygiene.

The first laboratory of hygiene was started by von Pettenkofer in Munich and opened for students and investigators in 1878. It is rather surprising that the existence of public hygienic laboratories goes back only to that

[1] Report of an address delivered before American Public Health Association, Minneapolis, Minn., October 31, 1899.

Am. Pub. Health Ass. Rep., 1899, Columbus, 1900, XXV, 460-465.

quite recent period, and those of you, who are familiar with the outcome of the foundation of that remarkable laboratory in Munich, know that it was one which included all departments of hygiene in the broadest sense—the physical side, the chemical side, the bacteriological side of hygiene, all represented there by separate departments with the respective directors of these departments. What inestimable benefits it has brought to the city of Munich! In this laboratory were investigated the great problems relating to the disposal of sewage, the public water supply, the factors concerned in the prevalence of epidemic diseases, and more especially of cholera and typhoid fever. The well-known doctrine as to the relation of typhoid fever to ground-water was promulgated and thoroughly discussed. The result has been of inestimable value to the inhabitants of that city—a city which was once the very hotbed of typhoid fever, and which, at the present day, is practically free from it, so that I have heard von Ziemssen say that he has found it extremely difficult to give practical demonstrations to medical students of the lesions of this disease. The great work of von Pettenkofer and his coadjutors cannot be expressed in dollars and cents.

A great impulse to the foundation of hygienic laboratories came about this period from the epochal discoveries in bacteriology. It was then that Koch introduced his remarkably simple methods for the isolation and study of bacteria of certain infectious diseases. The stimulus from these great discoveries led to the very rapid foundation of hygienic laboratories in connection with universities, so that within a few years nearly all of the great universities in Germany were provided with such laboratories. Another factor which has exerted a great influence in the development of hygiene has been the occurrence of epidemic diseases, more particularly such diseases as cholera, and in this country also yellow fever, and possibly it may turn out in the East that the plague may have a similar influence upon public sanitation there. Devastating as these diseases have been, it is a question whether the final outcome has not been on the whole to the advantage of the human race, because it does often seem as if it required the violent impressions of such pestilences to stir the people up to an appreciation of the needs of sanitation which are realized by sanitarians themselves, but who find it very hard to bring these matters to the attention of the public in a forcible way. As the result then of the very natural development of laboratories in general, of the developments in bacteriology and of the lessons of epidemic diseases, we have witnessed during the last twenty years the rapid foundation of hygienic laboratories connected particularly with universities, and with boards of health, both municipal and state. It is more particularly with reference to the latter laboratories, connected with municipal and state boards of health, that we are especially interested.

It will be appropriate to say a few words with reference to the development and organization of such laboratories, the important results which have been achieved and the prospects which we can reasonably expect from their work. These laboratories, as you already know, have been founded in large number in this country, and, in fact, the development of laboratories connected with boards of health is one which is peculiarly American. The appreciation of the need of such laboratories, of what can be accomplished by them and of the benefits which the general public derive from them, has been greater in this country than elsewhere. We have led in this particular direction. The work of these municipal and state laboratories should in the first place, be put in charge of those who are especially trained in modern methods in bacteriology, in chemistry, in hygiene and in pathology. These are very often the younger men who have had opportunities for these special lines of study. Such laboratories are, in a few instances, well supported, better supported than the laboratories in connection with universities. The kinds of work undertaken in these laboratories relate more particularly to practical problems concerned in the diagnosis, prevention and cure of disease; whereas the broader biological aspects are more properly considered in laboratories which belong to colleges and universities. But it has been difficult indeed for medical colleges and universities to supply suitable laboratories. They are expensive, and comparatively few of the educational institutions of this country are supplied with anything which is worthy of the name of a hygienic laboratory. I think one could count upon the fingers of one hand the laboratories connected with medical colleges or universities in this country which are appropriately called hygienic laboratories, not that hygiene is not represented in a larger proportion than that, but suitably equipped hygienic laboratories exist in small number in this country. This, of course, is to be very much regretted, and it is to be hoped that the influence of this Association may be such as to lead to a greater appreciation of the need of such laboratories in connection with our teaching bodies, because I think that such hygienic laboratories in connection with universities should work out problems that are different from those which interest municipal and state boards of health.

Let us consider for a moment some of the results obtained from such laboratories. As you all know, one of their main purposes is to assist physicians in making exact diagnoses of certain diseases. Their greatest triumphs are in relation to diphtheria, in the recognition of the cases of genuine diphtheria, on the one hand, and in seeing to it that specific treatment by antitoxin is properly carried out. But their field of usefulness is by no means limited to diphtheria, but extends to the diagnosis of other diseases, such as

tuberculosis, typhoid fever and malaria. While often tuberculosis is readily recognized by the physician, once in a while cases occur in which the physician must be in doubt as to the diagnosis, and he should be able to call to his aid those who are working in these laboratories for the purpose of enabling him to make a correct diagnosis. The diagnosis of fevers, such as typhoid and malarial fever, offers an important field of usefulness for these laboratories, particularly in the south. In the recent war we are told that the diagnosis of typhoid fever was made with great reluctance, and that physicians often made a diagnosis of malarial fever in many cases of genuine typhoid fever. We have means at our disposal for the accurate diagnosis of these two diseases. The diagnosis of typhoid fever can frequently be made with the Widal reaction, and it looks now as if there were to be other methods added which will enable us to make a diagnosis at an earlier stage of the disease than where the Widal reaction is applicable or in cases where this reaction fails. Especially to be desired is the establishment of laboratories available for the diagnosis of malaria in the regions where malaria prevails, particularly the severe forms of the affection. Nothing should be called malaria unless the malarial parasite is present, and an exact diagnosis of the disease can be made by samples of blood properly collected. With a little instruction the physician should be able to send these specimens in such a way that a report could be returned within a short time as to the existence of malaria. When we consider the practical importance of these two diseases in this country, and the fact that typhoid fever is preventable and that the recent discoveries regarding the relation of the mosquito to the spread of malaria offer prospects of eradicating malaria, the importance of extending in the direction indicated the work of municipal and state laboratories is apparent.

Then, there is the chance of one of the greater devastating epidemics making its appearance. The municipal and state boards of health can make early diagnoses. Thus if Asiatic cholera should make its appearance, effective measures of prevention can now be taken at the onset, for it is important to recognize the first case of the disease before it can gain a foothold. The experience during the last cholera epidemic in Germany was that when the first cases were recognized and immediate measures were taken to check the spread of the disease, those measures were very effective. But where the disease was allowed to gain a foothold, it was difficult to put an end to the epidemic. Suppose the plague should make its appearance in this country; if the city or state is provided with a suitable laboratory, with well trained physicians, the first case or two should be recognized and effective measures of prevention should be taken, so that these laboratories should stand as an effective defence between us and the outbreak of this great pestilence. It is

not clear that these laboratories can be so useful with reference to the diagnosis of yellow fever, because we have not exact methods, still they can be helpful in many directions with reference to this disease.

These laboratories can carry on original investigations and important practical work with reference to water supplies, to the disposal of sewage, to examinations of food, of milk, etc. All of these are subjects which properly pertain to some aspects of the work of laboratories, but I shall not attempt to consider them now. The foundation of such laboratories has had a very important stimulating influence upon boards of health, both local and state. It has introduced a scientific spirit into the work; it has brought into connection with executive officers the younger men who are full of enthusiasm with reference to studies along these lines, and I think that we may say that the general tone of boards of health has been elevated and stimulated by the foundation of laboratories of this character.

It is to be deplored that our National Government has had so little share in this important movement in public hygiene. This Association has advocated a plan by which the various states may secure aid from the National Government for the support of public laboratories of hygiene analogous to that in operation in the case of Agricultural Experiment Stations, and it seems to me very desirable that this or some similar plan should be adopted. Then we are all agreed that our government should have a central sanitary organization in connection with which a laboratory of public hygiene should be established. We can now appeal as never before to the furtherance thereby of commercial interests, a motive which seems to be more efficacious with our legislators than the lives and health of human beings, possibly even more than the welfare of cattle.

Many of you know that the workers in these laboratories have come together on this occasion in unusual numbers, largely through the very excellent work of our public-spirited member, Dr. Wyatt Johnston. These workers have been brought together here with a view to organizing a Laboratory Committee or Section of this Association. A few years ago a somewhat similar meeting of bacteriologists was held under the auspices of the Water Committee of this Association in New York, and we all felt at that time that it would be fortunate if we could have a permanent organization composed of such men as were there assembled. In fact, the idea of organizing the working bacteriologists and allied chemists into a biochemical section has been in the air for some time, and the outcome seems to be the best form of organization, viz.: one which will bring these experts into this Association. What we propose to do is to bring them as a group here and have them become members of the Association. There are many questions which are

very technical, relating to methods of procedure, etc., which it would not be at all appropriate to bring before the general body of the Association, such as chemical examinations of water, classification of water bacteria, etc., etc. It is proposed, therefore, that this relatively small group of members of this Association shall constitute a sub-group—call it what you like. I do not think Laboratory Committee is a designative term, in that it does not express exactly the scope of the work. However, matters of detail can be readily settled by a conference committee. The idea is that we should be called a section of this Association, which shall assemble here at the same time that the general Association comes together, but that the meetings of the smaller body or section shall take place on the day preceding the meeting of the general Association, and, if possible, their special work should be completed then. If any work remains over, provision should be made for finishing it without conflicting with the sessions of the general body. Subjects of special interest only to the practical worker should be discussed before the meeting of the section, and members of this section having papers of general interest should present them before the Association. The details of organizing such a section can be worked out later. It is clear to us, however, that none should be eligible to membership in the section who do not become likewise members of the American Public Health Association. That is our understanding, and we ask no special autonomy other than that we shall come together in connection with your meeting by such an arrangement as will be mutually advantageous, increasing your membership in quantity and quality, bringing certain kinds of members whom, I am sure, you will all be glad to welcome here to add to the usefulness of the Association. It will be of advantage to bacteriologists to come into close contact with the practical work of this Association, and to this Association to receive these workers.

DUTIES OF A HOSPITAL TO THE PUBLIC HEALTH[1]

It is a well known fact that there are no social, no industrial, no economic problems which are not related to problems of health. The better conditions of living, housing, working conditions in factories, pure food, a better supply of drinking water, all these great questions, social, industrial and economic, are bound up with the problems of public health. The humanitarian movement has been one of the great agencies in promoting the better health movement. There have been two great means by which interest in public health and the movement for the promotion of the health of the community have been advanced. One has been the new humanity, the other has been the advance in knowledge. I regret to say that I believe the impulse has been stronger, on the whole, from those interested in the humanitarian movement than it has been from my own profession. Anyone who is informed as to the influences which are operative in the last century, from 1830 to 1850, which initiated the modern public health movement and culminated in the passage of the public health act in 1848 in England, knows that it was less a movement on the part of the medical profession than it was on the part of philanthropists. Those interested in the conditions of the laboring classes and informed as to the steps taken for the prevention of disease, know that it was the human impulse more than any other which started the modern public health movement—at least, the governmental activities, and the recognition that the care of the health of the people is an important function of government.

But, after all, that impulse alone would not have been sufficient. It is of vital importance that health activities should be based upon accurate knowledge of the cause and of the spread of disease. At the period (1848) of which I am speaking, they knew little about how such diseases as typhoid fever and cholera were spread. Public hygiene was a blundering affair then. Efforts costing vast sums of money were misdirected and wasted. However, one idea dominated at that time, which was in many ways a fortunate one at that stage; this idea was the relation of disease to conditions of filth. It was known that one disease, typhus fever, especially bore a relation to filth, and through the application of this knowledge typhus fever was checked.

[1] Report of an address delivered before the National Conference of Charities and Correction, Baltimore, May 14, 1915.

Proc. Nat. Confer. Char., Balt., 1915, 209-218.

Until its recent appearance in eastern Europe typhus fever was practically exterminated from civilized countries. But the new knowledge came with the discovery of the causation of the class of disease of the greatest significance to mankind, the infectious diseases.

We could have no more striking example of the health-saving, the life-saving knowledge which comes from penetration into the cause of disease, deeper insight into the manner in which disease is spread, than the vast benefits which have come from the discoveries of Pasteur and Koch and the work carried on by them and those following them. These discoveries initiated a movement in medicine which gave a new face to things, so that we think of modern medicine as something quite different from the medicine of the past. We think of it often as being more different than we are justified in doing. The truth is that there has been no change in the real aims of medicine from the beginning. From the days of antiquity, the aim of the physician has always been to cure and to prevent disease. It is precisely that consistency of purpose which gives such interest to the future of medicine, no matter how futile the efforts of the past may have been nor how long men wandered in ignorance and darkness.

But there came to us a new light, and with it a new power. The physician acquired a control over the spread of many of the infectious diseases and in the case of some a new power in the treatment of disease which rendered his mission a far more significant one for the world than it had ever been before. It is now possible to control great pestilences. We believe even in the possibility of the complete eradication of such pestilences. Only the other day I attended a conference in New York where the possibility of taking up the complete extermination of yellow fever was considered. It is possible that will be initiated. Anyway, the problem seems a soluble one, and the work undertaken in that direction full of promise. This advance in medicine was not merely in relation to this class of diseases but it affected all branches of medicine. It stimulated investigation, so that the physician can do far more in all classes of diseases than was possible in the past. Therefore medicine makes an appeal to the community, it makes an appeal to the government, for support, it makes an appeal to public spirited philanthropists, which it never could have done in the past. Far-sighted, public spirited philanthropists who appreciate the possibilities of further exploration in this field have enabled medicine to undertake investigations, and it is above all important that we should acquire further knowledge as to the causation of disease.

I have no doubt that we are today directing our efforts in the wrong way, as I have said they were doing sixty and seventy years ago. I have no doubt we are spending millions of money fruitlessly, wastefully, as compared with

what the possibilities might be if we had a more exact knowledge of the causation and propagation of disease. Consider for a moment the vast sums formerly wasted in efforts to control yellow fever by quarantine, and how simple the problem became when we learned that yellow fever can be spread only in one way, by the bite of a particular species of mosquito.

There are a great variety of agencies concerned in the promotion of public health, prevention of disease, and the treatment of disease. While the theme assigned to me relates to one particular agency in this warfare upon disease—the hospital—I must say at least a word about two others of most importance, namely, the governmental agencies, public health boards, commissioners and officials, simply to emphasize the importance of better organization and better support of our public health officials and boards. Among our chief needs I would mention, in the first place, larger appropriations; in the second place, better trained experts; and, in the third place, taking the work out of politics. I am not going to elaborate on these, but I hardly like to speak before an audience of this kind without at least referring to the importance of better support and organization of our boards of health, and the great need of opportunities for the better training of experts in that field. The selection of a commissioner of health is of course, a matter in which the whole community is interested. The entire country should be looked over in order to find the best man for the position—not simply the one who can easily be found in the community.

One other agency I should at least like to refer to, and that is the public health nurse. One of the contributions of the hospital to public health work has been the trained nurse. We are familiar with the incalculable advantages which come from the introduction of the system of visiting nurses. They should be extended into larger use and there should be a more specialized training for the public health nurse. It is of the greatest importance that her activities should extend to the rural districts. One of the striking circumstances of the modern public health movement is the limited advantage which rural communities have derived from this new knowledge.

As regards the relation of the hospital to health, there is no activity of the hospital that is not related to health directly or indirectly. I shall speak somewhat disconnectedly on certain points, I think, because it is quite impracticable in the time available to present the subject in a comprehensive and systematic manner. First, as regards certain types of hospitals. We have the general hospital and various kinds of special hospitals. There is one of these special hospitals, the tuberculosis hospital, which has had such influence and which brings so important lessons that I would like to refer to it. I do not propose to discuss the importance of the hospital in the tuberculosis crusade, as that would lead too far. Suffice it to say that it has the

very first place. The tuberculosis hospital has two functions which it is important to bear in mind. One is the educational function. The benefit of residence in a tuberculosis hospital to a consumptive is not measured solely by improvement in his health. So far as the community is concerned, it is measured also by the education of the patient in methods of right living. There has probably been no influence which has had larger effect in stirring up the public mind as regards many of the problems of the public health than the tuberculosis crusade. It has taught people the value of fresh air; it has emphasized the importance of proper conditions in the household and in the factory, because tuberculosis is a disease which is spread by the immediate environment—in houses, workshops or factories. The lessons which have reached the public, largely through the work of our tuberculosis hospitals and sanatoria, have been of inestimable value in their effects upon public health.

I would like to point out in this connection, familiar as it is, that just as in the case of tuberculosis, so in nearly all the efforts to control infectious diseases there are incidental benefits which are often not foreseen but which in many instances equal, if not exceed, the actual effect upon the control of the particular disease in question. Take, for instance, the control of typhoid fever, with the consequent insistence upon a pure water supply, pure food, and certain conditions relating to the spread of disease from person to person, using the military to clean up unsanitary morasses and swamps around human habitations and rendering large areas fertile and suitable for cultivation. One might go on and point out benefits often far in excess of the actual results which are immediately in view when the attack is first made.

The tuberculosis dispensary is something very different from the ordinary dispensary. It is perfectly obvious that it would be absurd to conduct a tuberculosis dispensary as most dispensaries were conducted before the great movement initiated by our chairman, Dr. Cabot, came into use, by having the patient simply come to the dispensary, receive a dose of medicine, and then go away. The idea of following the patient to the home, of instruction in the home, not only of the patient but of all in proximity to him—all that conception, which, thanks to Dr. Cabot, is now so familiar in the work of a dispensary, although so imperfectly attained in many cases—is exemplified in a striking way by the tuberculosis dispensary.

There are many other special hospitals for the eye, ear, throat, and children's diseases. I have only one remark to make in regard to these. It is a pity that these hospitals have developed to such a large extent as independent, detached hospitals, often unsuitably located, and out of touch with the general hospital movement. I cannot pause to consider why this has been.

It is mainly because the movement started about a century ago and became active about sixty or seventy years ago, and those who were interested in these branches were not welcome in general hospitals and were more or less compelled to go to one side to establish these special institutions. It is unfortunate, and it is very important that in future we should do all we can to remedy this condition, and when a new hospital of this kind is founded it is probable that it should be in connection with a general hospital. Referring to the three special hospitals we have been so fortunate as to secure in connection with the Johns Hopkins Hospital, they are far more useful institutions and do a far larger service to the community by virtue of the fact that they are on the grounds of the hospital and in intimate association with the Johns Hopkins Hospital—in fact, administered by that hospital.

I cannot pause to discuss the development of the modern hospital, but it is something very different from the hospital of the old days. One of the most significant developments in medicine, and therefore in public health, has been the development of the modern general hospital. This has come about largely through increased knowledge of the methods of study and diagnosis and treatment of disease. It has come about also to some extent through a more correct view as to the function of the hospital in education and in the treatment of patients. These new conceptions are responsible for a situation where the patient profits by the resources of modern medicine and of education in sanitary ways of living to an extent quite impossible in private practice. The best that can be done with existing knowledge for the treatment and relief of disease is to be found now in the well equipped and well organized general hospital.

For whom are these benefits available? In all the American hospitals where the rich and the poor are both admitted they are available for the very rich and the very poor. On the whole I think the poor derive the greatest advantage. The rich formerly did so, and still, I think, to a considerable extent, share the opportunities of medical discoveries in the treatment of their diseases. But there is a large middle class which at present is not adequately provided for. I see that that is a subject for a paper in the program of the Conference. I was not fortunate enough to hear the paper, but the very title shows an appreciation of the situation. One of the urgent needs is to supply adequate accommodations in the best of our general hospitals for all classes of the community. Whether they shall be provided for in inexpensive private rooms or whether by more attractive arrangement in public wards, so as to make the accommodation more acceptable, I am not prepared to say. Although I am talking on these subjects, I am not a hospital physician and am not in practice and have not that intimate personal contact with the subject that would make my opinion as to the best solution of a problem of this character of particular value.

Why is it that hospitals offer these superior advantages in the treatment and care of disease? It is because they are well equipped and organized and because there is a whole staff of assistants. The study of modern disease requires all sorts of examinations by new methods that are in many cases intricate. Sometimes it is doubtful whether the knowledge so derived is applicable to the case in hand, but whatever sheds light upon the extent and character of disease must eventually be found of advantage to the patient. In many cases the private physician is enabled to bring to bear upon his patient all of these resources essential to the accurate diagnosis and treatment of disease. The hospital reaches only a relatively small fraction of the entire community—I do not know how many. It has been said that not more than one-tenth of the sick are cared for in hospitals. The opportunities are inadequate at present for meeting this great need. It is possible that the private physicians may be enabled in some way or other to have at their disposal such advantages as exist at present almost solely in hospitals.

Some think that the solution is going to be the eventual disappearance of the private practitioner as we know him today. Some think the profession is to be socialized. Steps in that direction have already been taken in Denmark and other Scandinavian countries where the doctors are paid by the state, and it is interesting to learn the results of those experiences. But I think it would be a pity to have the whole practice of medicine institutionalized. There was something so fine about the best type of family doctor in the old days. My father was a country doctor and I know something of the life and what it meant to patients so that I cannot help feeling that every effort ought to be made to rescue this situation. A recognition of it is, of course, the first step. How it is to be met I do not know. I have read that in Fall River the physicians have arranged for coordinated effort in their laboratories which results in conditions similar to those which exist in hospitals. I desire to call your attention to the situation without attempting myself to suggest a solution; but there is this contrast today as between the organized, well equipped hospital and the opportunities there afforded for the treatment of disease, and the situation in private practice. As regards the services rendered by the hospital, the side of it with which I am most familiar is the educational one. The primary purpose—and it must remain the primary purpose, is the care of the patient. Nothing can be done in a hospital which in any way can be of possible injury to the patient. The argument is so familiar that perhaps it hardly needs presentation, that the use of the hospital for educational purposes really is for the benefit of the patient. If this can be demonstrated, then we shall be convinced that a hospital which serves not merely a humanitarian purpose, but educational and scientific purposes as well, is doing a far more important and larger work than the

hospital which has nothing more to do than to care for the patient. We must bring this to the attention of the public at every suitable opportunity.

The medical school and hospital in the past have developed abroad separately, and the real problems of medical education in this country are the result of that divergent development. We know now that it is important to bring them together. They never should have developed apart. But the difficulties are greater than one might imagine. The medical school must have satisfactory relations to a hospital. It is fortunate if the university or medical school has its hospital, as we have at the Johns Hopkins. But as the future of medical education really depends upon its connection with a hospital, I should consider the future of medical education dark indeed, in this country, if we were to build hospitals without the university assuming the administration of them. The important thing is for the trustees of privately endowed institutions to feel that they are doing the best for the hospital in making it freely available for medical teaching. This superior kind of hospital is to a large extent at present in this country the well endowed private hospital, but our municipal and state-supported hospitals are beginning to awake. It is important, and it is a requirement of modern sanitation, that these facilities should be supplied. When I speak of the educational side of the hospital, I have in mind not merely opportunities for training doctors and nurses, but for the training of patients as well. Take, for example, the movement for the early recognition of cancer—the importance of the public being instructed that sores that do not heal up should have the physician's attention, that early operation for cancer is usually successful and the results of delay lamentable—the result of which has been an organized effort to bring this knowledge home. Do we make use of our knowledge as we should with patients coming to the dispensary? There are the same opportunities for bringing lessons home as to right conditions of living, health, and prevention of disease as are exemplified in the case of tuberculosis.

There is the scientific work of a hospital. Definite knowledge, of course, is the most obvious result of the work of those engaged in hospital activities, but the spirit of investigation has a value so great for the workers that I do not believe it can be overestimated. It is incumbent upon municipal and state-supported hospitals to make provision whereby the staff, especially the young men, may be stimulated by laboratory opportunities. The equipment can be relatively modest, but there should be opportunities which make them see that medicine is something more than a trade. I would emphasize that the value of the investigating spirit is not to be measured by making discoveries in science. The spirit of investigation is a stimulus to a real pleasure in work, to better work and better care of patients, and unless the workers have it, their task becomes merely routine.

I want to say a word about autopsies. *Postmortem* examination is not my theme, but it is through the knowledge derived from them that many of the great advances in medicine have come. There is every reason why they should be characterized as a matter of routine. Dr. Brookings, who has done so much at the Washington University Medical School has said: "I would not care to put myself in the hands of a physician who, if I should die, did not want an autopsy and did not want to face the results." The matter is of sufficient importance, I think, to bring to the attention of an audience of this character.

I have only touched here and there upon my subject. In conclusion, I would like to add just one thought. It is of the utmost importance that hospitals should be more linked together with all the agencies which are concerned with public health work. Dr. Cabot has done immense service in waking us up on the question of dispensaries. It is a wonder we could have slept so long. The new era that has been ushered in by social service work is certain to see the dispensary brought into closer relations with other agencies concerned in all its fields of activity. I think there is room for a better organization, a better coordination, a more effective cooperation of the hospital with the boards of health. I happen to be a member of a state board of health, and know that we see ways in which the hospitals could be more cooperative than they are at present with all kinds of charity and relief organizations. The hospitals that take this form are to be, not the only ageney, but I think a primary one in the promotion of public health.

OPENING REMARKS BY THE PRESIDENT OF THE SECTION ON PATHOLOGY AND BACTERIOLOGY OF TUBERCULOSIS[1]

I esteem it a high honor and privilege in behalf of my American colleagues to extend a most cordial welcome to all in attendance upon this first section of the Sixth International Congress on Tuberculosis, and especially to those who have come from foreign countries to participate in our proceedings. We are indeed fortunate in the presence of so many distinguished investigators whose papers and discussions enrich our program and give assurance that this Congress will not pass without substantial contributions to our knowledge of tuberculosis.

It will not be deemed invidious if I express the special gratification which we all feel in having with us, as an active participant in the work of this Section, his Excellency, Professor Koch, the illustrious discoverer of the tubercle bacillus, who must rejoice to witness, in such a gathering as this, the evidences of the far-reaching and inestimable benefits to mankind which have come from this discovery, and the promise of greater benefits in store. We appreciate most highly the participation of so many eminent colleagues from France, who have cooperated so generously and so effectively in our efforts toward the success of this Congress. We welcome warmly our kindred in speech and in blood from Great Britain and her possessions and with equal cordiality our fellow-workers from Germany and Austria-Hungary, from Holland and the Scandinavian countries, from Spain, Russia and other European countries, from Japan and the Orient, and from our sister republics of Central and South America.

Every effort has been made to assure the truly international character of this Congress, and a glance at our program will indicate that this result has been secured. Over seventy per cent of the papers on the program of Section I are contributed by participants from foreign countries—a gratifying result made possible by a certain measure of self-restraint on the part of American workers, who are prepared to furnish papers, if the time permitted.

A word concerning the construction of the program of this Section may be of interest. After consultation with other officers of the Section I determined that, instead of selecting themes for discussion and inviting referees and

[1] Remarks made before the First Section of the Sixth International Congress of Tuberculosis, Washington, D. C., September 28, 1908.

Tr. VI Internat. Cong. Tuberc., Phila., 1908, I, Sect. I, 2-4.

co-referees in accordance with the usual custom, I would accept papers voluntarily submitted and then arrange them in groups with the expectation that the result would be much the same, and that the more important and larger themes would thus be presented by those actually engaged in their study and whose interest was for the time concentrated upon the subjects presented by them. By thus grouping the titles of papers voluntarily submitted, the larger topics, such as the biology and chemistry of the tubercle bacillus, the channels and sources of infection, the specific tuberculin reactions, immunity, the relations of human and bovine tuberculosis, will be presented in a satisfactory and authoritative manner.

In view of the crowded condition of our program I must remind the readers and discussers of the necessity of strict enforcement of the rules, that the time allotted for referees and co-referees is not to exceed fifteen minutes, for readers of papers ten minutes, and for participants in the discussions five minutes; and especially I would urge the importance of handing to the Secretary of the Section the written remarks in discussion before the close of each meeting in order to secure their appearance in the "Transactions."

The main significance of the International Congresses of Tuberculosis has been in the past, and will continue to be, on the side of prevention of the disease. As has been said, tuberculosis is indeed the disease of the people, in a truer and larger sense than can be affirmed of any other malady. From the discovery of the tubercle bacillus, and the study of its properties, and of the sources and modes of infection, there has come a new message of hope to suffering humanity, so full of untold blessing that the peoples of the earth have been aroused to its significance, and in all civilized countries there has been inaugurated what is appropriately called the crusade against tuberculosis. Already in certain places the application of intelligent measures of prevention, based upon a new knowledge, has achieved results so full of promise that the hopes of even the most enthusiastic no longer seem so extravagant as they may once have appeared. Nowhere has the existing knowledge been applied to the prevention of tuberculosis save in part and inadequately, but the achievements of even this imperfect application are sufficient to inspire the world to the search for fuller knowledge, and to better directed and more efficient efforts toward prevention. The crusade against tuberculosis is truly a battle of the people, by the people, and for the people. It is not a doctors' fight merely, but all the forces of society—economic, social, moral, legislative, administrative, philanthropic—must be enlisted in this contest.

The benefits to the community which result from success in the prevention of disease extend, as a rule, far beyond the mere control of the particular

disease in question, incalculable as this benefit may be. As regards tuberculosis, it has become increasingly apparent that successful prevention will be attended by improved conditions of living, of work, and of play; in a word, by a general social betterment of the people. It is this aspect of the crusade which has very properly stimulated the interest of philanthropists, social workers, and statesmen.

When we contemplate the popular interest and enthusiasm which have already been aroused in the campaign against tuberculosis, the readiness to institute preventive measures, the large pecuniary resources which are available, and the great expenditure of money and of energy already made or in the process of making, we must be impressed with the importance of making sure that our measures of prevention are really based upon accurate and full knowledge of the mode of spread of the disease, and are so applied as to yield the best results, in the most economical way, most surely and most quickly. The campaign must rest upon a sound scientific basis, and must be conducted along correct scientific lines. This scientific foundation is supplied mainly by the knowledge furnished by investigation of the subjects represented in this first section of the Congress, namely, the pathology and bacteriology of tuberculosis. Other sections of the Congress may seem to be concerned more directly with the marshalling of the forces, with the conduct of the assault, with the stirring of the martial spirit, and the appeal to arms, but ours is the division which must supply the ammunition and the weapons and the strategy of the campaign.

While our existing knowledge of tuberculosis already furnishes the basis for vigorous and intelligent measures of prevention against tuberculosis, it must be conceded that there are many important open problems awaiting further investigation, and that there is still much diversity of opinion regarding the points essential to the proper conduct of the campaign. We may confidently anticipate that the proceedings of this section will contribute something of value towards the elucidation of some of these problems and toward a closer agreement of authoritative opinion. They will be, I trust, a source of pleasure and of profit to all in attendance.

WHAT MAY BE EXPECTED FROM MORE EFFECTIVE APPLICATION OF PREVENTIVE MEASURES AGAINST TUBERCULOSIS[1]

Mr. Chairman, Ladies and Gentlemen: To those who have so long pleaded the cause of public health in this country, often, it seemed to deaf ears, this occasion must be a source of great encouragement and inspiration. The interest manifested by this large audience, the presence as presiding officer of one of our most distinguished citizens, the stirring addresses of the Governor and other speakers, and the participation of so many eminent in public life, in philanthropic effort, and in medicine and sanitation, are indications of a great awakening in behalf of the health of the people of this state.

This awakening has come mainly through interest in that disease which may truly be called "the disease of the people." No other disease merits this designation in equal measure with tuberculosis, which carries off one-third of those who die at a time of life which should be that of the greatest productive energy. The people have recognized their true foe in tuberculosis, and are stirring to the combat throughout the civilized world.

It may be asked why it is necessary to arouse the public regarding the prevention of tuberculosis more than concerning other preventable diseases. Many triumphs of preventive medicine have been achieved without the great upheaval of popular interest. The necessity of enlisting the active interest and support of the public in the campaign against tuberculosis is due not solely to the extent of the ravages of this disease, enormous as these are, but to the fact that the prevention of tuberculosis is a social and economical problem as well as a medical one, and that therefore not only medical and sanitary measures but also other forces of the community—legislative, administrative, philanthropic, educational—must cooperate in the struggle. An important aspect of the crusade against this disease is that success in the struggle signifies also social betterment, enlightenment in ways of healthy living and working and intelligent interest and education in individual and public hygiene in general.

[1] Report of an address delivered before a Public Meeting under the auspices of the State Charities Aid Association in cooperation with the State Department of Health, in behalf of a State Campaign for the Prevention of Tuberculosis, Albany, N. Y., January 27, 1908.

Albany M. Ann., 1908, XXIX, 256-262.

The thought which comes first to my mind, as I have witnessed the enthusiasm and interest manifested by this large meeting, is how such energies and forces as have been aroused and are ready to be moved can be so directed and applied as to secure in the most effective manner the best results. It is of fundamental importance to secure the cooperation and coordination of all the necessary agencies and to proceed along well defined, systematic lines.

Since the discovery of the tubercle bacillus by Koch in 1882 it has been known that tuberculosis is a preventable disease, and experience has demonstrated that in the initial stage it is curable in the majority of cases. Without the aid of experimentation upon animals this greatest discovery in the domain of bacteriology could not have been made.

It is in my judgment a conservative statement that at least one-half of the existing sickness and mortality from tuberculosis could be prevented within the next two decades by the application of rational and entirely practicable measures, and I believe that we can look forward to a much larger success. You can be assured that the expenditure of money and of well directed energy in this cause will lead to a very considerable saving of human life, and that in no other direction will money expended for sanitary reform yield equally important results to the community.

The essential elements in the solution of the problem of prevention of tuberculosis are clear understanding of the modes of conveyance of the disease, well considered, practicable measures of prevention based upon this knowledge, the application of these preventive measures under the direction of skilled sanitary officers, and adequate resources for their application.

The justification for the statement that the death rate from tuberculosis may be cut in two is based upon the fact that the saving knowledge which we possess regarding this disease is at present only most inadequately and imperfectly applied in prevention, and that even this inadequate application has brought about a notable decline in the mortality from tuberculosis in many communities, and it would appear, precisely in those places where preventive measures have been most effectively employed.

In Prussia the death rate from tuberculosis has diminished about forty per cent in the last twenty years. In Sweden there has been a similar reduction. Particularly significant is a like diminution in New York City, which offers unusually difficult problems in consequence of the tenement house conditions and the resulting density of the population and of certain other unfavorable factors. The Health Department of New York City, largely through the admirable work of Dr. Biggs, has achieved a triumph in this regard which has attracted the attention of sanitarians throughout the world.

In England the decline in the death rate from tuberculosis began long before the discovery of the tubercle bacillus and has continued to the present time, but in this country there have been throughout this period special hospitals for consumptives and intelligent public sanitation.

Permit me to indicate very briefly what I conceive to be the more important agencies necessary for the control of tuberculosis.

1. A leading rôle in the campaign against any infectious disease is the notification of the disease to the health authorities, and in my judgment this should be recognized as an essential feature in the administrative control of tuberculosis. New York City deserves the credit of having demonstrated the feasibility and the practical benefits of the notification and registration of tuberculosis. In the light of this actual experience of the workings of the system little weight can be given to most of the arguments which have been and are still urged against its adoption, and I am pleased to hear from Dr. Porter that an effort is to be made to secure a state law along similar lines.

2. Mr. Choate, in his opening remarks, touched upon the importance of early diagnosis of tuberculosis. An important aid to this end, which is indeed of the utmost significance, is the establishment of laboratories maintained by municipal and state boards of health and freely at the service of physicians.

There are at least three classes of institutions which are of primary importance.

3. First in importance for the treatment of tuberculosis are sanatoria. This country owes a great debt to Dr. Trudeau, the pioneer in the establishment of sanatoria for tuberculosis in America and the leader in the crusade against this disease. While I consider that hospitals for advanced cases of tuberculosis are more important than sanatoria in the prevention of the spread of tuberculosis, still the latter institutions are also valuable for this purpose in accomplishing the arrest of the disease in those who would otherwise become possible sources of infection and especially in their educational influence extending far beyond the actual inmates. Here the great lesson is most effectively taught that by proper disposal of his expectoration and certain simple precautions the consumptive may render himself entirely harmless as a source of infection to others.

In Germany today some twenty-five thousand patients in the early stages of tuberculosis are treated in sanatoria, a number equal to about one-fourth of the total deaths from this disease. Sanatoria on such a scale and frequented by patients to such an extent must rank among important preventive agencies.

4. Hospitals for the isolation of advanced cases of tuberculosis are given by Koch the first position among the agencies for checking the spread of the disease, and their importance is especially emphasized also by Dr. Biggs. These hospitals unlike the sanatoria, receive the patients who are most dangerous to others and are responsible largely for the spread of the disease. Every populous community should be provided with one or more hospitals for patients in the advanced stages of tuberculosis, and every effort should be made to secure the transfer to the hospital of such patients, when they cannot be suitably cared for in their homes. Much more should be done than is now customary to make these hospitals attractive to these patients and their friends. One of the greatest difficulties in the crusade against tuberculosis at the present time, especially in this country, is the utterly inadequate provision for these hospitals. There is also difficulty, even where the hospitals exist, in inducing patients to enter them in sufficient numbers.

Under present conditions only a relatively small number, in this country not more than 4 per cent at best, of tuberculosis patients are cared for either in sanatoria or in hospitals. It is evident that through some other agency the largest number of consumptives must be reached. This is now being accomplished more and more effectively and in constantly increasing measure by the special tuberculosis dispensary. This is or should be an institution in many respects different from what is ordinarily understood by a dispensary. The German conception of this institution is expressed by the designation "information and aid station." The French idea is also that of an antituberculosis bureau, forming a centre for the enlightenment of the public, for hygienic education, for the discovery of centres of tuberculous infection in households and workshops, for the instruction of patients in the precautions necessary to prevent spread of the disease, for the improvement of living and working conditions, for medical care and kindred purposes. Visiting nurses and health inspectors constitute an essential part of the machinery of these tuberculosis dispensaries, which we must rank among the most important and effective agencies in the campaign.

Time forbids more than the mere mention of such recognized preventive measures as the disinfection of rooms vacated by consumptives through death or removal, enforcement of laws and regulations against expectoration in public places, protection of food, especially the milk supply, by suitable laws and their enforcement, sanitary inspection of factories, workshops, lodging houses, etc., destruction of tuberculous sputum and the education of consumptives, of the public and of school children in the elementary facts regarding the origin and spread of tuberculosis, and in ways of healthful living.

Scarcely less important than measures, like the foregoing, specifically directed against tuberculosis, are all conditions which make for the improvement of the dwellings and working places of the poorer classes. Air, light, and food are as important for the prevention as for the cure of tuberculosis. Parks, playgrounds, in a word all measures to improve the health of the people, operate in a very direct way in increasing resistance to tuberculosis and in lessening chances of infection. There is reason to believe that no small part in the diminution of the amount of tuberculosis has been due to improvement in the general conditions of living.

The specific measures against tuberculosis must be carried out by the health officials and especial emphasis must be placed upon the need of a larger number of well trained sanitary experts in the work of our state and municipal boards of health and of larger resources at their disposal. Upon them must fall the main part of the work in the campaign against tuberculosis. With some notable exceptions our city and state boards of health are far behind in efficiency similar boards in England and Germany. The need of special training for the successful conduct of public health work is most inadequately appreciated by the general public and, it is to be feared, even by the medical professions in this country.

Progress in the struggle against tuberculosis is largely a question of ways and means. I have enumerated some of the more important agencies needed for the control of this disease not with the intention of outlining a programme, but to indicate how inadequately at present preventive measures are in operation and thereby to substantiate the opinion that wider and more effective application of these measures would yield correspondingly better results. Much larger funds are needed than are now available, but it can be confidently predicted that the returns in the saving of human life and in increase of happiness and of productiveness will be out of all proportion to the pecuniary outlay.

What New York accomplishes in this world-wide movement against tuberculosis and the way she accomplishes it have a significance not limited by the boundaries of this Empire State. An especial incentive to prompt action is the opportunity which will be presented next September of demonstrating to the world at the International Congress of Tuberculosis what this state has done and is doing in the most stupendous struggle against disease ever undertaken by man.

CONSIDERATIONS RELATING TO THE CONTROL OF TUBERCULOSIS[1]

The people have been aroused as never before in this combat against the most devastating disease of mankind. They have recognized that it is a disease of the whole people, and as in no other battle the question arises, How can the forces which have been aroused be directed into those channels which will yield the best results in the shortest time and the most economic way? In other words, what course of action should be taken in order to secure domination of this terrible disease? All these various agencies, of which the campaign is composed, must, of course, be brought into action, but the foundation of our work rests upon our exact knowledge of the nature of the disease. Our exact knowledge of the mode of origin and spread of the disease is only about twenty-five or twenty-seven years old. It was not until the fact was thoroughly established that the disease was due to a micro-organism that we could undertake intelligent measures of prevention. We had to learn much more as to the nature of the germ, the conditions under which the disease was acquired and how it spread. It may now be stated that while all of these problems have not yet been solved, we have an amount of information which enables us to state positively that if practical measures based upon this exact scientific knowledge are properly applied, the amount of tuberculosis can be reduced to a relatively small figure. It would be most hazardous to prophesy how soon that will be, but it is safe to say that in less than one generation the mortality from tuberculosis will be cut in two if we apply the knowledge we already possess.

I cannot, of course, at this time attempt to state in any detail what should be the program of prevention, but it may not be out of place to run over a few of the leading measures in this program. As a consideration of first importance, I would place the registration of all cases of tuberculosis, at least in the larger cities. I know objections have been raised to this, and these have come not a little from the members of our profession; but in reply to those objections we can say that these laws have already been applied and successfully carried out in certain cities. That, I think, is a sufficient answer to those objections. It is fundamental, in this campaign, that there should

[1] Report of an address delivered before the National Association for the Study and Prevention of Tuberculosis, Washington, D. C., May 14, 1909.
Nat. Ass. Study & Prev. Tuberc., Tr., Phila., 1909, V, 34-36.

be notification and registration. We should know of the existence of the disease; where it is and how much there is of it. There should be everywhere also means at the disposal of the physician for the prompt and accurate diagnosis of the disease, because the sooner it is recognized, the better the results, in both prevention and treatment. We now come to institutional treatment, of which there should be a number of types, and each of these has its part to play in this preventive campaign. The first of these in importance is the sanatorium for the treatment of the early cases. One of the greatest blessings to mankind has been the establishment of these sanatoria, where patients with tuberculosis in its earlier stages can be cured. There is no agency which makes so strong an humanitarian appeal as the sanatorium, and it takes the very first place in the preventive campaign against tuberculosis.

Another kind of institution is the hospital for advanced cases, and this leads me to the central point of what I have to say. In Scotland and Ireland, as well as in England and Wales, and especially in Germany, there has been a notable reduction in the death rate from tuberculosis. Now, of course, it must be evident to you that if we can put our finger upon precisely the factor or factors which are responsible for this reduction in the mortality of tuberculosis, we have there the agency or agencies which we should bring into operation immediately. It is not so easy to say exactly what has been responsible for this progressive diminution in the amount of tuberculosis, and it would lead altogether too far if I should attempt to bring before you the various opinions on this subject, but I would like to state what is the conclusion of the highest authorities on this subject, men who have studied this matter very fully, such as Koch in Germany, and Arthur Newsholme, the best vital statistician in English-speaking countries. Both of these authorities are of the opinion that the factor that has done the most is what is called institutional segregation. That means the isolation of patients with tuberculosis so far as is possible, in institutions. That should be emphasized today as the central feature of the campaign against tuberculosis, and the great need in this country is a supply of suitable hospitals for these cases of advanced tuberculosis. That does not make the same appeal as does the establishment of sanatoria. You have two patients, one hopelessly ill, the other a young man in the early stages of the disease. It is the latter that makes the strongest humanitarian appeal. Hence, we can leave to a much larger extent the establishment of these sanatoria to private philanthropy, while it is to the legislature and public health boards that we must look for the segregation of the more advanced cases. By that we will doubtless gain more than by any other single factor. Further than this, I believe the time has come when we should emphasize the importance of institutional segregation as the most important factor in reducing the incidence of the disease:

and in dealing with patients who are a serious menace to the community and who cannot or will not be taught to take proper safeguards against the infection of their fellow-men, I think that the health authorities should be empowered to place them in proper institutions.

Another agency that should be considered in this connection is the dispensary for tuberculosis. It is there that many of these patients first apply for treatment, and it is there that the plans of this campaign are more or less centralized. However, I cannot elaborate further on these points. These institutions, their establishment and maintenance, cost money, but the amount of money which is expended, in proportion to the return, is most trifling. The returns to the community are out of all proportion to the sum required. It has been estimated that it would increase by only about 50 per cent the cost of the dependent poor already provided for by the state. Fewer would have to be provided for than are provided for now in the insane hospitals. When you estimate how prevalent tuberculosis is today, and how great a loss it entails upon the community, who could hesitate to go before our legislatures, with this great force of public sentiment behind us, and demand that they shall carry out a program which rests upon exact knowledge, and which will yield returns beyond all conception as to their final value to mankind.

The proper housing of the poor and the establishment of playgrounds are incidental to the problem under discussion, but do not represent the central idea. The prophylaxis of tuberculosis makes such a strong appeal to the community because everything connected with it leads to better conditions; but all diseases are similar in that respect. The same holds true in regard to the prevention of typhoid fever and malaria. All these factors are of importance, and we can use everyone to the greatest advantage, but nevertheless we should make it clear to the public that there are a few definite agencies which should first be emphasized as the central ideas of our program, and which give the greatest promise of return.

THE SIGNIFICANCE OF THE GREAT FREQUENCY OF TUBERCULOUS INFECTION IN EARLY LIFE FOR PREVENTION OF THE DISEASE[1]

Permit me, in behalf of the members of the Association, to extend a welcome to all our guests; also to express our gratification at this opportunity of meeting in the city of Denver. The custom of the Association as a national organization has been to meet in the city of Washington. There has been only one exception to this rule in the past, namely the meeting held in 1908 in the city of Chicago, for which there were special reasons. This meeting, therefore, marks a departure from our precedents, but one, which, I think is to be welcomed. I believe the influence of the Association will be extended by meeting occasionally, say once in three or four years, outside of the city of Washington. While it is important to preserve the national character of the Association, it is likewise important to extend the influence of the Association and its benefits by occasional meetings in different parts of the country.

With peculiar satisfaction I express our pleasure in meeting in this city, which has been so actively identified with the anti-tuberculosis movement. We shall certainly feel well repaid if this meeting is a help in any way to the great cause in which we are engaged, and I am confident that the Association itself will derive great advantage from meeting in this place. We have experienced already enough of hospitality and of the excellent arrangements for our meeting to justify me in expressing even now our thanks to the committee of arrangements and to all who have cooperated with them.

Since our last meeting, my predecessor in this office, Dr. Edward G. Janeway, has passed away, and it is fitting that we should pay our tribute to the memory of this great physician, who enjoyed to an unusual degree the confidence and esteem of all his colleagues, and was one of the most influential and useful men who have adorned the profession of medicine in America. His remarkable powers as a diagnostician, which to some seemed almost intuitive, rested upon long years of training, the first fifteen years of his professional life being devoted largely to that combination of work in the

[1] President's address delivered before the Seventh Annual Meeting of the National Association for the Study and Prevention of Tuberculosis, Denver, Col., June 20, 1911.

Nat. Ass. Study & Prev. Tuberc., Tr., Phila., 1911, VII, 17-28.

deadhouse with close observation in the hospital wards which has been the basis of the diagnostic skill of so many famous physicians.

Dr. Janeway was interested greatly in the subject of tuberculosis and in the movement to which we are committed. Dr. Knopf has kindly furnished me with data which I hope he will embody in an article pointing out many of the specific contributions of Dr. Janeway to the subject of tuberculosis. He and Dr. Austin Flint, the elder, were among the first in this country to recognize the significance of Koch's discovery in 1882 of the tubercle bacillus. Even shortly before that he published a paper on the contagiousness of pulmonary tuberculosis. It is rather difficult to trace all the contributions of Dr. Janeway through his published writings. For this purpose it is necessary to go through the reports of societies, and especially the discussions in societies. He made a large number of reports to the New York Pathological Society. Without exhaustive search I have counted not less than seventy published contributions of Dr. Janeway, a record which, while not prolific, is certainly not sterile, when one considers the value of his papers.

The great work of the New York City Board of Health in initiating the municipal control of tuberculosis, with which a former president of the Association, Dr. Hermann Biggs, has been so actively identified, received from the beginning the active and influential support and advice of Dr. Janeway. He was prominent in the work of the Committee on Prevention of Tuberculosis of the Charity Organization Society of the City of New York, and of that of the New York State Charities Aid Association. He was much sought for as a member of committees, for the voice of no medical man carried greater weight with the public.

I shall ask the audience to rise in respect to the memory of Dr. Janeway.

Shortly after our meeting last year, early in May, there died Robert Koch, to whose great discoveries is due the movement against tuberculosis which was the occasion for the organization of this Association and to which our presence here today is due.

The name of Robert Koch is immortal in the history of medicine. He was endowed with the divine genius for scientific discovery, and was undoubtedly one of the greatest benefactors of his kind who has ever lived. We have only begun to reap the benefits to be derived from his discoveries. Generation after generation will continue to glean the harvest.

The real significance of Koch's work is that he gave us the key which enables us to unlock the secrets of that class of diseases, the infections, which are of the greatest racial and social significance to mankind, whereby medicine, and especially preventive medicine has been revolutionized. Medicine has come into relation with the problems of society in a way never before

approached, and has a part to play of the highest significance for human welfare.

The greatest of Koch's discoveries is that of the tubercle bacillus, announced in 1882, not quite three decades ago. Not even Koch himself, far less others, could foresee all the beneficial results which would flow from this discovery, nor can we realize it all today.

Koch's interest in the subject of tuberculosis was paramount. He not only introduced the methods which enable us to learn the mode of origin and spread of this disease, but he continued, for over thirty years, a leader in investigation in this field. It is rare that man opens the path and at the same time enters in and reaps such a rich harvest as Koch did.

Koch's discovery and study of tuberculin, while at first arousing hopes destined to disappointment, have proved to be of vast significance, not merely in their practical bearings, but in elucidating many problems connected with tuberculosis and other infections. I need in this connection only to remind you of the interest which now attaches to the subject of hypersusceptibility or anaphylaxis of which the tuberculin reaction is an example.

Koch's pronouncement on the question of the relation of human to bovine tuberculosis, bitterly contested as it has been, has been of great service in advancing our knowledge of a subject of great practical as well as scientific importance. It may be doubted whether a voice less powerful than his could have arrested the attention of investigators and have led to such numerous and valuable investigations as those which are now bringing the opinions of scientific students into fair agreement as to the extent and character of the dangers to human beings from bovine tuberculosis.

We recall with especial gratification Professor Koch's visit to this country and his participation in the International Congress on Tuberculosis in Washington in 1908, to which he gave such luster.

I would like to add a word about another important contributor to our knowledge of tuberculosis who has passed away more recently, namely, Professor Arloing, of Lyons, France. I speak of him particularly on account of the charming impression which he made upon all who met and heard him at the International Congress on Tuberculosis in Washington. He was one of that agreeable and important group of French colleagues who honored us by their presence, and I feel that you would wish me to pay at least this tribute of a few words to the memory of one for whom we came to have great admiration, almost, I may say, affection, on account of his delightful personality. He is a real loss to the cause of tuberculosis, and especially to that in France. It is significant that in the city of Lyons, where he worked, in contrast with so many of the French cities, there has been a decided decline in the incidence and mortality from tuberculosis.

The Association has reason to feel much gratification at the work which it has done in the six years since it was started. While the general aims of the Association have been clear from the first, there has been no attempt to formulate a definite program. The effort has been to further the propaganda against tuberculosis in a national way, and to direct our energies in channels, which, for the time being, seemed most promising, so far as the resources of the Association permitted. The effort has been to stir up general interest in the subject, and especially to aid and encourage local organized movements. When we consider the large number of associations against tuberculosis which have started during these years, numbering now, I believe, nearly five hundred, many in affiliation with our national body, and initiated through its efforts; when we regard the good that has been done by our traveling exhibits, going from place to place, accompanied with lecturers, and usually associated with public meetings stimulating the interest of physicians and the general public wherever they go; when we note the specific contributions in the Transactions of the Association, and the stimulating influences of our meetings, it is evident that the relatively small amount of money which we have had at our disposal has accomplished an immense amount of good. We have received generous contributions from individuals, and we have reason to be especially grateful to the Russell Sage Foundation, without whose generous aid our work would have been seriously curtailed.

We can look forward most hopefully to the continued and enlarged activities of this Association. You will all wish me, I am sure, in this connection to express our appreciation and thanks to our very energetic and able executive secretary, Dr. Farrand, who is really the one so largely responsible for it all, working with singular unselfishness, devotion, intelligence, and sympathy in this great cause.

There are so many topics which I should like to bring before the Association that I am somewhat embarrassed at attempting a selection. I should like to say a word, at least, with reference to the scientific basis of the campaign against tuberculosis. It is, of course, self-evident that rational and effective measures of prevention against any infectious disease must be based upon as exact knowledge as possible concerning the modes of origin and of propagation of that disease, and it is because we have at least a measure and a saving measure of such knowledge relating to tuberculosis that we are engaged in the campaign, which is so full of hope, but no one would pretend that there are not before us many unsolved problems. No one would claim that our preventive measures could not be more effective, more economically concentrated, more intelligently directed if a good many of these problems were solved. Did we know more precisely, for instance, the paths of infec-

tion; did we know the full significance of the almost universal infection with tubercle bacilli, at least in certain strata of the community, in the early years of life did we know, in a word, a great deal more concerning the origin and spread and nature of the disease, we would certainly be better armed to fight this enemy. We should, therefore, always in this Association keep in mind the importance of having the scientific side represented, as is now done in our pathological and clinical sections, and our sociological brethren, whom we are glad to have with us, must bear with us at times in the presentation of subjects of somewhat special and technical interest, which they may not feel bear directly and immediately upon the campaign. On the other hand, the scientific members must welcome all the aid which those engaged in great social reforms can render. It is here in this Association, as it is in the whole movement, that all the forces of society must be coordinated, and the Association is fortunate in having secured the cohesion of all who are interinterested in the subject of tuberculosis, whatever may be the special line of interest and activity.

The important subject of the portals of entry and paths of infection for the tubercle bacillus is to be treated by Dr. Ophüls, the chairman of the Pathological Section.

I have referred to the work which has been done to determine the share of tubercle bacilli of bovine origin in causing human tuberculosis. There is now general agreement of opinion that bovine bacilli are negligible as a cause of pulmonary consumption, the only question left open being the possibility of the transformation of the bovine into the human type by prolonged survival in the human host, a view for which, at present, there is very little satisfactory evidence. When one considers that most of the cases of open tuberculosis, which are the chief source of danger in spreading the disease, are pulmonary infections, it is apparent that a good share of Koch's contention upon this subject has been substantiated.

There is no doubt, however, that Koch gave a somewhat misleading impression, and underestimated the risks of infection from bovine sources. Such infection plays a rôle by no means negligible in the tuberculosis of infancy and childhood, particularly in the scrofulous infections of lymphatic glands and of other parts, which are so common at that period of life. Our prophylactic measures, therefore, should not neglect the dangers of tuberculosis infection from milk, although these dangers are far exceeded by the risks from human sources.

The most important contributions which have been made in recent years to the genesis and pathology of tuberculosis are those concerned with the study of tuberculosis infection in infancy and childhood, and the interpretation of

the bearings of such infection upon the manifestations of the disease, particularly upon pulmonary consumption, in later life. I wish more particularly to call your attention to some of the results of these investigations.

The first thorough investigation of the frequency of tuberculosis infection in human beings was made by Nägeli and published in 1900. He found that 97 per cent of adults examined at autopsy in Zürich showed either active latent, or healed tuberculosis; in other words, that infection with the tubercle bacillus is practically universal by the time adult life is reached. That is, of course, not equivalent to saying that every one has or has had the disease, tuberculosis. It signifies merely that in the class examined practically every one had received into the body tubercle bacilli, and that these had left their record behind. Nägeli's observations startling as they seem, have been confirmed by similar methods elsewhere, notably by Burckhardt in Dresden.

Further studies have shown that in the great majority of cases this almost universal infection with tubercle bacilli in the classes examined dates from before the fourteenth year of age. This conclusion is based partly upon autopsies, especially of those tested during life with tuberculin, and partly upon the results of the testing of large numbers of infants and children for the tuberculin reaction by the harmless cutaneous and puncture methods. There is every reason to believe that a positive result of these delicate tests is certain evidence of an existing or healed tuberculous infection.

By means of data of this character it has been demonstrated by Hamburger and Monti that about 95 per cent of all the children in the Vienna hospitals are already tuberculous by the time they reach the twelfth to the thirteenth year of life. Similar results have been obtained in Prague, and it is probable that they hold true for children of the poorer classes in other large cities. While the percentage is doubtless considerably smaller for children of the well-to-do and in smaller towns and country places, the significance of the figures cited is scarcely diminished thereby, for it is especially to the poorer classes that our measures of prevention in the control of tuberculosis as a racial problem must be directed.

In considering this question of the frequency of tuberculosis we must, as already mentioned, keep clear in our minds the distinction between tuberculosis as a cause of death and tuberculosis as found, often only after long and patient search, as an accessory lesion in the inactive, latent, or healed forms. Regarded from this point of view, it is important to note that in the first weeks of life tuberculosis in any form and the positive tuberculin reaction are extremely uncommon. During the second half of the first year of life the number of cases increases, and in the second year they are no longer uncommon, and when the infection is found at this period, it is

usually as the cause of death, most frequently as a tuberculous meningitis or acute miliary tuberculosis. After this period, up to the age of puberty, while the percentage of cases increases year by year, reaching over 90 per cent by this time, the infection appears more and more frequently as an inactive or healed lesion, fatal tuberculosis being relatively uncommon.

As has long been known, pulmonary consumption is rare in the first decade and a half of life, the prevailing forms of tuberculosis in the earlier years being tuberculous meningitis and acute miliary tuberculosis, and after the third or fourth years chronic lymphatic disease and affections of the bones and joints. It is not, however, justifiable to infer from the prevalence of these types that the primary infection has been through the alimentary canal, as in the vast majority of cases of tuberculosis in infancy and childhood there exists tuberculosis of the bronchial lymphnodes, usually associated with a focus in the lungs.

In the light of these facts we must concede that von Behring was right in his statement that in the great majority of instances pulmonary consumption develops in an individual who has previously been infected with the tubercle bacillus, although he was in error in his view that the primary infection usually dates from the first year of life and is derived from the milk of tuberculous cows.

Much light has been thrown upon the significance of this startling frequency of primary tuberculous infection in early life, as regards its bearing upon the genesis of pulmonary phthisis, by the study of the influence of an existing tuberculosis upon renewed infection with the tubercle bacilli.

Koch, in his first study of tuberculin, observed that a tuberculous guinea pig behaves differently from a normal one when reinfected with tubercle bacilli. In the former the reaction is immediate and is followed by a local necrosis, ending in complete healing of the site of reinfection, unless the dose of bacilli be too large. This observation comparatively neglected by subsequent experimenters, has been made the starting point in the last few years of interesting experimental studies by Römer and Joseph, Hamburger, and others. That a measure of protection may be afforded by previous inoculations with tubercle bacilli was demonstrated experimentally by Trudeau in 1890.

On account of the high degree of susceptibility of guinea pigs it requires special methods of inoculation and small doses of tubercle bacilli to demonstrate readily the protective influence of an existing tuberculous infection of limited extent to reinfection, but such demonstration has been conclusively brought by Römer and by Hamburger. Particularly impressive and convincing are Römer's experiments with the tuberculous reinfection of sheep, which closely resemble man in their sensitiveness to tuberculin. These

animals may be rendered by a localized tuberculosis completely insusceptible to the subsequent intravenous injection of quantities of bacilli which kill the control animals in a few weeks with generalized tuberculosis.

The condition which is present in these animals as the result of a localized tuberculous infection is that designated by von Pirquet as allergy, and is characterized at once by immunity and by hypersusceptibility, the former being manifest upon the introduction of small or moderate doses of tubercle bacilli, which are readily disposed of, and the latter by the death of the animal or rapid development of the disease when the doses are excessive. In both instances the reaction follows speedily the reinfection.

There would appear to be also significant differences in the character of the tuberculous lesions according as these are the result of a primary infection or of a reinfection. It has long been known that ulcerative pulmonary tuberculosis is rarely produced experimentally in animals, and the usual assumption has been that they are but little susceptible to this form of tuberculosis, so common in human beings, but this cannot be the complete explanation. In 1894 Prudden demonstrated to the Association of American Physicians genuine pulmonary phthisis in tuberculous rabbits subjected to secondary intratracheal streptococcus inoculations. Concurrent or mixed infections, however, are not necessary, as it has been shown by von Behring and others that phthisis can be induced by renewed inoculations with tubercle bacilli in animals already tuberculous. Reinfections from without are not absolutely necessary, provided there exist the proper ratio between the degree of resistance of the animal and the number and virulence of the bacilli. Given this condition, a single inoculation, even in guinea pigs, has been known to produce a progressive chronic tuberculosis, resembling phthisis in man, but here it may well be that there are repeated autoinoculations, such as are assumed to occur in man in chronic progressive tuberculosis.

There is abundant evidence that human beings, as well as animals, are protected by slight or limited tuberculous infections, dating in the former, as has been stated, usually from childhood, against the effects of renewed inoculation with tubercle bacilli both from without the body and from within. It is by virtue of the alteration or allergy effected by the primary tuberculous infection that the subsequent entrance of tubercle bacilli from without or their distribution from the primary focus to other parts of the body leaves no record behind in the majority of cases, for it is impossible to suppose that the two or three old scars or foci of tuberculous infection usually found represent the only penetrations of bacilli into the body during the life time of the individual.

Gratifying as is the recognition of the protective value of an existing tuberculous focus of limited extent, we must keep in view that there is another

side to the shield, and that it is precisely upon the basis of the altered reaction resulting from a primary infection that pulmonary consumption develops. Here there are doubtless many factors concerned which require further clinical, anatomical, and experimental study before we shall reach a satisfactory understanding of the pathogenesis of pulmonary phthisis.

We are in the dark as to the relative frequency in the causation of pulmonary consumption of auto-inoculations from existing tuberculous foci or of reinfections from without, but in view of the difficulty of tracing sources of infection in individual cases it is important to learn that it is not necessary to have recourse to extraneous infections, and my own belief is that in many instances pulmonary consumption results from auto-inoculations from previously inactive or latent foci of tuberculosis in the lungs or bronchial glands, possibly in other parts of the body.

Furthermore, we lack precise information concerning the causes which determine the occurrence of pulmonary consumption as the result of reinfections. It is probable that in some instances the explanation is to be found in the massive doses of bacilli received into the lungs, or in their repeated introduction at shore intervals of time, but it seems difficult for many cases to dispense with the doctrine that the resistance of the individual is lowered as the result of unfavorable conditions of health and of living. There still remains room for appealing to the various factors which have so often been presented as influencing the disposition of the individual to tuberculosis.

Another question requiring investigation is, Whether immunity persists after complete disappearance of all tubercle bacilli from the body, and if so, how long? In view of the difficulty of making sure that there are no living bacilli in the body, the question is not easy to settle, but the evidence seems to be in favor of a return of susceptibility within a certain period after complete recovery.

Although analogies in medicine are dangerous, there is much which is suggestive in that which has often been drawn in recent years between tuberculosis and syphilis. In both diseases an existing infection affords protection from reinfections, and both are characterized by a remarkable "Umstimmung" of the system of allergy, whereby primary infections pursue a course different from the later manifestations of the disease, which in both affections are marked by extensive caseous masses, with a greater tendency to liquefy and form cavities in tuberculosis than in syphilis. According to this analogy, pulmonary consumption would correspond to the late or tertiary lesions of syphilis. I do not think, however, that we are justified in pressing this analogy too far.

It hardly needs to be emphasized that the facts which I have briefly sketched have important bearings upon methods of prevention of tubercu-

losis, and must be taken into consideration in formulating the plan of campaign.

Perhaps the most important lesson is the necessity of protecting infants and children from infection with tubercle bacilli, so far as possible. It may perhaps have occurred to you that if, in so many instances, the primary tuberculous infection dating from early life be, as it has been called, a "beneficent vaccination," we should not be overanxious to prevent it. In reply to this argument it may be stated, in the first place, that experience indicates that we hardly need concern ourselves with this matter of securing protection. We are not likely to escape, if we would, the minimal tuberculous infections. "Am Ende bekommt jeder ein bischen Tuberkulose," as the old German physician said many years ago. The preventive vaccinations will take care of themselves.

On the other hand, as I have mentioned, the forms of tuberculosis which appear in the first two or three years of life are predominantly fatal forms, and not innocuous vaccination and these surely we should do all in our power to prevent. Furthermore, there is much in support of the view that the ultimate fate of the individual as regards progressive tuberculosis, it may be later in life, depends largely upon the extent of the primary infection, which is itself related to the number and virulence of the bacilli received into the body.

In the light of our newer knowledge there is abundant reason for the ever-increasing emphasis placed upon the importance of attacking the problem of tuberculosis in the early years of life. The key note is the segregation of patients with open tuberculosis, that is, in the main, the consumptive, so that they will not be the means of spreading the infection to other members of the family, especially the children. In France much is done in the way of removal of children from homes where there is a consumptive member, but while this procedure is effective, and perhaps can be employed oftener in this country than is now customary, it is not likely to be widely applicable with us. The results of constructing tenements especially adapted for the home treatment of consumptives must await further trial before we are warranted in drawing conclusions as to the efficacy of this interesting experiment. Our main reliance, as has been so often urged before this Association, must be upon hospitals designed for the reception of advanced or open cases of tuberculosis, and it would appear that there is no other measure of equal importance in lessening the spread of the disease.

A further deduction from the newer views as to the pathogenesis of pulmonary consumption is the importance of preventing reinfections, whether extraneous or autogenous, and of maintaining and increasing the resistance to the effects of such reinfections. Here come into consideration not only

the hospitals for the care of tuberculous patients, but all those procedures for the after care of those who are able to resume work, but are so likely to relapse after return to previous conditions of living and work. Working farms and colonies for the tuberculous have an important place in the compaign against the disease.

I believe that no mistake is made in preaching the gospel of hygiene to increase resistance to tuberculosis. Even if it should appear that undue emphasis is laid upon measures of general hygiene as a special feature of the anti-tuberculosis crusade—and I do not believe that such is the case—the incidental benefits in furthering the cause of individual and public hygiene and the general improvement of the health of the people, derived from this part of the campaign, have been of incalculable value. It has been, above all, the movement against tuberculosis which has taught people the value to health of fresh air, of proper and sufficient food, of exercise and play, of well ventilated and sanitary homes and workshops, of shorter working hours, of a living wage, and other social reforms.

There has been in the last half century, and especially since the discovery of the tubercle bacillus, a notable, steadily increasing diminution in the amount of tuberculosis. The fact that this decline is not universal, and that where it has occurred it has been in varying degrees in different places, indicates conclusively that special causes have been operative in bringing it about. I believe that it can be shown that the reduction stands in relation to the character and efficiency of the activities directed against the disease, although there may be difficulty in assigning to each factor in these activities its precise share in the result. As is well known, Koch and Newsholme, after careful analyses of these factors, have reached the conclusion that the segregation of consumptives in hospitals far outweighs in preventive value all others.

The results which have already been obtained and the greater ones which we can reasonably expect to follow, both in the control of tuberculosis and in the improvement of the health and efficiency of the people, are full of encouragement to press forward with increasing zeal in the greatest task ever attempted in the domain of preventive medicine. As tuberculosis is a disease of society, it must be met by a combination of all the forces of society, and we may be assured that such combined efforts, intelligently directed and based upon accurate knowledge, will bring direct and indirect benefits to mankind far outweighing all the money and time and energy expended.

CONTROL OF BOVINE TUBERCULOSIS[1]

It is clear that there are certain matters which are established; there are others which are very much in dispute; and still others which we must regard as hardly approached as yet. It depends a good deal upon where we lay the emphasis. We may agree on some body of facts, and still lay emphasis more upon one than upon the other feature, and we may reach somewhat different conclusions without disagreeing as to the facts.

It is true that Koch in his address in London certainly left the impression by the conclusion drawn from his own words that there was practically no danger whatever of infection from bovine sources. It is true also, and the point has been emphasized in this country, that Koch did not add very material new facts. Dr. Theobald Smith, one of the most careful workers on the subject, had previously pointed out the rather subtle morphological and biological differences between the human voice and bovine types. He also noticed (it was known before) that it was difficult to inoculate successfully calves or cattle with tubercle bacilli from human sources. With characteristic caution, however, he did not venture to draw the conclusion that because calves are insusceptible, relatively to human tuberculosis, we should infer that human beings are insusceptible to bovine tubercle bacilli. That was the difference mainly between Theobald Smith's and Koch's presentation of the subject. Koch drew that inference without basis of facts. It is also true that Professor Koch at the Washington Congress somewhat shifted the position he had previously taken. He took the position that, in the campaign against tuberculosis, pulmonary consumption is the main factor to be considered. I think he stated that eleven-twelfths of the deaths from tuberculosis in human beings were traceable to pulmonary tuberculosis; that the other forms of tuberculosis—the glandular, the surgical forms of tuberculosis—were not open cases; that is, they did not figure as an important factor in the spread of disease; therefore, those who are interested in tuberculosis as a problem with reference to the extermination of the disease might almost neglect the dangers from bovine tuberculosis; that it was upon pulmonary

[1] Report of remarks on a paper of Mazÿck P. Ravenel made before the National Association for the Study and Prevention of Tuberculosis, Denver, Col., June 21, 1911.

Nat. Ass. Study & Prev. Tuberc., Tr., Phila., 1911, VII, 367-370; 374.

tuberculosis we should concentrate our attention, and that there was little or no evidence of infection from bovine tuberculosis, or that bovine infection played no particular rôle in it. Dr. Park, as you know, has come to the same conclusion at which Dr. Ravenel has arrived with reference to the rôle played by the bovine bacillus in the causation of phthisis. There have been a few cases in which it is claimed the bovine tubercle bacillus has been found in phthisis, chiefly in the sputum. I know that Professor Koch considered that the most important thing, at present, was further investigation on that subject. He called attention to certain important sources of error, in butter and milk, where the bovine tubercle bacillus was present. One might readily have in the sputum the presence of the bovine tubercle bacillus accidentally, and, at the same time, playing no part whatever in the disease process in the lung; therefore, it requires much more than mere demonstration of the tubercle bacillus of bovine type in the sputum of consumptives before one could draw the inference that it was really causing the disease in the lung.

I happen to have had the good fortune to spend an hour with Professor Koch, in the Institute for Infectious Diseases, a year before he died, after he had returned to Berlin from America and I found him engaged almost exclusively in the study of this subject. He must have collected a good deal of material and new facts. I have heard nothing about any prospect of these being published. He showed me figures and charts, all in confirmation of his previous position, that the bovine tubercle bacillus played no part in the production of pulmonary tuberculosis; that is on the assumption that there is no transformation of the bovine into the human type. Of course there is the point at issue. Koch believed there was no such transformation. That is the opinion very cautiously expressed by Dr. Theobald Smith, and I do feel that his position on anything relating to this question is almost the most authoritative one in the world; and he thinks that the evidence is, to say the least, very inconclusive; that here is a point for further work, and research along this line ought to be followed out. There have been a few scattered observations. An attempt has been made to determine whether or not the bovine tubercle bacillus is transformed into the human type in human beings, namely, by studying those light necrophilic warts so commonly seen on the hands of butchers, to try to find out whether they contained the bovine type of tubercle bacilli. There is nothing easier than to get such material on which to work. These warts remain on the hands of butchers for a considerable time, and if one could get the history of a number of years, and has a chance of using that material, the results of such investigations might be valuable. I think it ought to be had in great abundance in Chicago. We must have opportunities of studying these warts and seeing whether we get

a transformation of this type of bacillus. One investigator has come to the conclusion from considerable clinical examination that there was such a transformation of the tubercle bacillus, with apparent preservation of virulence, indicating that the bovine type was due to the fact that the animal had spontaneous infection from another source. That case has been analyzed and the proof found inconclusive. These are more or less, I think, facts on which there can be general agreement. I myself am disinclined to the view which Dr. Ravenel favors as to the transformation of type. One should be open-minded on the subject and consider it still *sub judice*. There are so many sources of error which we have to consider in connection with this work. If you have inoculated a cow with the human type of tubercle bacillus, what appears to be a transformation, as indicated by the production of a generalized tuberculosis in the calf, is really the result of your experimental inoculation, and not the result of spontaneous infection. That is a difficult matter to control. Mr. Stiles has stated most impressively his views on this subject, giving us a series of fatal cases, making a very notable percentage, to say the least, of fatal cases of tuberculosis in human beings, chiefly in children. If you let these cases run they will doubtless play an important rôle in the spread of the disease from person to person, and they are of significance from every point of view, particularly from a humanitarian standpoint.

Shall we do anything to check that large mortality? I think one can accept all the facts which Koch himself admitted at Washington, and still maintain that it is of importance to recognize that there is a serious danger from the infection of human beings from the milk of tuberculous cattle, and that while human sources are far more important in the spread of the disease, we should not by any means neglect the other. The character of evidence which Mr. Stiles has brought forward here is one deserving of every respect, and more especially by physicians, who do not have to discuss some of these more subtle laboratory points. Koch himself realized that in his London address he took the position that there was very little evidence of primary alimentary infection. There are extraordinary differences as to the incidence of tuberculosis according to locality. To bring that into exact relation with the milk supply has been difficult. While the experience of Edinburgh which Mr. Stiles has presented is very important and apparently conclusive on the points he has brought before us, still in Kiel and in Vienna they claim they have scarcely any primary intestinal tuberculosis, and, of course, we are informed by Kitasato that in Japan, where milk in not used, and where there is little or no tuberculosis among cattle, they have the same types of glandular and bone and joint tuberculosis, and we can exclude positively the milk. These statistics we find are interested somewhat differently. However, the

high percentage of deaths mentioned by Mr. Stiles teaches us the great importance of such clinical facts as he has brought before us, so that my opinion is that we are justified in insisting upon a better control of the purity of the milk in our cities. It is the great sanitary problem of today. It is a great white river, and it is just as much a river as the water flowing through our cities, but it is much more difficult to keep pure this great white river of milk. It is just as important, nevertheless, and the most urgent problem before our municipal health authorities today is the protection of the milk supply.

I will say that there is little or no value attached to the method of differential diagnosis which Detre advised.

CHILD WELFARE[1]

Mr. President, Ladies and Gentlemen.—I may perhaps be permitted, as a resident of this city, to reinforce the words of welcome which have already been expressed, and I know that I speak in behalf of my fellow citizens, who are also present, these words of welcome, to the members of this Association, to the guests and others who have been so good as to come here. We wish especially to express our gratitude to his Eminence, the Cardinal; to his Excellency, Ambassador Jusserand, who has brought us these kind messages from France; and to Professor Fisher, who has made himself an inspiring leader of the great movement for the improvement of public health in this country; and I would like especially to impress the note of welcome to my old master and teacher and friend of these many years, Professor Jacobi, of New York.

We are very glad, indeed, to have this first meeting of an Association, which I believe initiates one of the most important campaigns in preventive medicine in this country, in this city, partly, perhaps, because there is no city which needs the influence and benefits which will come from the work of this Association more than the City of Baltimore; partly, also, because we have a certain measure of loyal pride in the fact that that great tuberculosis association, The National Association for the Study and Prevention of Tuberculosis—which, I judge, the name of this Association has followed—had its first meeting in this city, and in connection with it was an exhibition which Dr. Fulton devised and which has turned out to be one of the most interesting and important factors in the whole crusade against tuberculosis. And I trust that there is a future of lasting usefulness and power before this Association equal to that which has been demonstrated to have been the outcome of the work accomplished already in these few years by the Tuberculosis Association.

There is, of course, no need of my saying anything more than has already been said as to the fundamental importance of the subject of infant mortality. Statistics are tiresome for most people, but, trite as it may be, it certainly is enough to arrest one's attention, no matter how busy he may be, to learn that in the state of Maryland over one-fifth of all the deaths of all ages occur under one year of age; that one-third of all the deaths occur

[1] Report of an address delivered before the American Association for the Study and Prevention of Infant Mortality, Baltimore, November 9, 1910.
Tr. Am. Ass. Study & Prev. Inf. Mortal., Balt., 1910, I, 51-56.

under five years of age. The rate is a little higher in this state in consequence of our negro population than in some other parts of our country. In the registration area of this country the deaths under one year of age are a little less than one-fifth of all deaths at all ages, and about one-third under five years of age. In the first three months of life, one-ninth of all the deaths occur. Such figures as these are enough, of course, to indicate the fundamental importance of this subject.

When one inquires into the leading causes of death during this period one finds that the greater number are operative in the first months of life. Some of these are sometimes spoken of as unavoidable, but, as Dr. Jacobi has said, most of them are not. We do not think, however, that the crusade in the prevention of infant mortality will yield the quickest results if directed against those causes which to some seem unavoidable—such causes as premature births, congenital defects, hereditary taints, accidents at birth, causes of that kind. It is more especially against another set of causes of infant mortality, namely, the so-called diarrhoeal and digestive disorders, the acute respiratory diseases, bronchitis and pneumonia and the infections that the campaign should be directed. Probably the infections play a very important part in the digestive disorders, and tuberculosis we know plays a by no means unimportant part in the deaths during the first year of life. During this period, especially in nurslings the infectious diseases which we associate with childhood are less common than after the first year of life. Whooping cough and measles occur, but scarlet fever is uncommon and this is especially true among those that are nursed at the breast. This is in itself suggestive; it shows that the infant receives from the mother a certain measure of protection against diseases toward which she is herself immune. There are many reasons why the cow's milk can never be an entirely satisfactory substitute for the mother's milk, and one reason is that the protective substances in the cow's milk—admirable as they may be for protecting the calf against the diseases of cattle—do not protect the infant against the diseases of the human being. We have the most satisfactory experimental evidences that the milk contains immune substances which have been generated in the body of the mother, and see how important it is that she should transmit these protective substances to the offspring at this period of life when the offspring is attempting to adjust itself to these new conditions and is exposed to all these changes. This kind of protection is needed particularly in the class of diseases which I have specified, the acute respiratory and diarrhoeal infections and the infections which are most preventable. Professor Fisher has made interesting investigations, which he himself would not consider to be anything anything more than approximate, but they are certainly suggestive as to what is the ratio of preventability of these various diseases of childhood and infancy. At least 60 per cent of this class

of diseases is preventable, and readily preventable, by the application of knowledge already in our possession. With further additions to knowledge, the ratio of preventability would be still further increased, but at present we probably are within entirely safe bounds to say that 60 per cent of the deaths of infants in the first year of life due to the causes which I have mentioned could be prevented.

It will be the purpose of this Association to point out in considerable detail what the causes of these preventable diseases are and the measures which are to be taken for prevention. One cannot have the most cursory reference to the subject of infant mortality without having at once brought to one's attention the fundamental importance of material nursing in preserving the life of the infant. That will be repeated over and over again. I think that those in the audience who are familiar with the subject only in the families of the well-to-do can hardly realize the risks in artificial feeding. It is not because artificial feeding is not possible. It is possible we all know, but it requires an amount of care and education on the part of those entrusted with it which is not to be expected in the families of the poor. It is not surprising to hear that the deaths are at least 15 to 1 among the artificially fed, as compared with those fed at the breast.

Our time for keeping you here has passed, but before closing I would like to point out what I conceive to be certain of the useful functions of this Association. Of course, one of the most important is the education of the public, the enlightenment of the public. The responsibility is with you; it is with me; it is with the public. When one is told that the application of knowledge which we now possess in an entirely practicable manner will lead to the saving of 125,000 lives yearly among these infants, is that not enough to stir one to activity? In this country at least—in any democratic country—the public must be enlightened, otherwise we cannot secure from our legislatures the necessary laws and the necessary funds, resources for carrying out these preventive measures. I regard, therefore, the stirring up of the public, the enlightenment of the public, as one of the most important functions of the Association. It should stimulate better sanitary organization and administration in the country all along the line. It should lend its whole force toward the organization of a National Health Department, which movement has been so forcibly presented to us by Professor Fisher tonight. We should all be familiar with the character of the opposition to the movement. I do not propose to discuss it, but it is based upon misconception and it is based upon ignorance, and sometimes, I think, it is based upon intentional misrepresentation, as has been pointed out, putting personal interests and commercial interests above the interests of health and life. This Association, therefore, should stand, for a strengthening of the activities of the Federal Government in public health work. That department will

surely have a Department of Child Hygiene. We have had demonstrated to us in New York City how much good can be accomplished by the creation in a Department of Health of a division of Child Hygiene. They have taken the lead there in this regard as so often and to such a great extent in public health work.

The question of registration of births is at the bottom of this whole movement. I hope those who are here will be able to be present when Dr. Wilbur reads his paper on this subject tomorrow night. Then you will learn that we are creeping in the dark until we have an accurate and tolerably full registration of births. There must be a pressure brought to bear upon the medical profession, who are woefully lacking in the performance of their duty in this matter, and I simply mention that it is a matter of very first importance to be considered in the activities of this Association to see that our country is no longer in the scandalous and disgraceful condition in which it is today as regards an accurate recording of births. It would be the topic of an entire lecture to make clear to you exactly why we should have an accurate registration of births. Until there is such a registration one cannot tell what the rate of infant mortality is, the ratio of deaths of infants under 1 year of age per thousand living. One can only guess at it. One cannot define the rate of infant mortality at all in this country today. One estimates it is something like one-seventh; in New York perhaps one-seventh of those born die in the first year of life.

Another very important activity will be the correlation of all the various agencies that are acting separately. The various public and private agencies should be all brought together in order to secure the best results, because they will often be working at cross purposes otherwise. This is specified as one of the very important activities of the Association, and it is indeed to be very much emphasized.

Then I hope the Association will stimulate investigation in this field. We have by no means the amount of knowledge which is to be desired. It is a big and significant fact that the campaign for the prevention of infant mortality has been long delayed in this direction. One reason is, I think, that we have not such tangible, accurate or precise knowledge of the many causes of infantile diseases that we have about some other diseases. Take, for instance, yellow fever, typhoid, malaria. How relatively definite our knowledge is of the etiology. There are a great many problems connected with this entire subject, which must be solved before we can go ahead with as full knowledge as is to be desired.

I think also one of the important purposes of the Association must be to formulate a definite program of preventive measures. When one goes over all the possible factors and influences concerned, one will find that one is brought to problems of poverty, of ignorance, of dirt, of insanitation, of in-

dustrial conditions, etc., and one is confused to know exactly where to take hold in order to secure in the shortest time the best results. I hope one of the purposes of this Association will be to formulate as definite a program as possible as to where and how efforts should be concentrated in order to secure the best results in the shortest time and in the most economical way.

These are what I conceive to be among the important functions of this Association. What one may expect from the direct benefit in the saving of human life would, of course, justify all efforts; but I am very fond of dwelling upon the indirect benefits which come from all these movements. "Infant mortality is the most sensitive index of social welfare"; it takes hold of the very foundations of society. Its prevention means improvement in the homes, improvement in the mothers, and improvement in the social conditions, the industrial conditions and the sanitary conditions in general. This, as Professor Fisher has pointed out, is sufficient answer to those near-sighted persons who think they are extremely philosophical in this matter when they argue that we are interfering with natural selection. Newsholme, who is the greatest student of this whole subject, at least from a statistical point of view, says the high rate of infant mortality brings about conditions which make for national degeneracy and infirmity, and I believe firmly that this is true. Those who plead that our preventive efforts are interfering with the natural selection of the individual are pleading virtually for the retention of what are the most unfortunate social conditions. They are pleading that the woman shall continue to work in factories to the end of her pregnancy. They are pleading for continuance of the intolerable social conditions. I think we can look forward, even if this Association meets only a part of its expectations of what it is going to accomplish in this country, to a great future of usefulness, both of direct and indirect benefit.

Let me urge upon you the importance of studying the exhibit. I have not myself had the opportunity to do so yet, but I know that that exhibit has been brought together with great sacrifice of time and thought and energy on the part especially of the Chairman of the Committee, Dr. Price, Secretary of the State Board of Health. We are particularly indebted to Dr. Schereschewsky of the Public Health and Marine Hospital Service, who has been of invaluable assistance in helping us to get together this exhibit. We are also indebted to Dr. Wilbur, head of the Vital Statistics Department, Bureau of the Census, and to many others, who have been so good as to send exhibits. No such exhibit has ever been brought together before. It will be, I think, the most distinctive and instructive feature of this meeting, and I believe it will be an example to those who are engaged in similar movements elsewhere and that they will recognize this feature as their strongest means of reaching efficiently the general public.

INSTITUTE OF HYGIENE[1]

At a conference[2] on training for public health service held at the offices of the General Education Board in New York on October 16, 1914, discussion seemed to develop substantial agreement on the following points: (1) That a fundamental need in the public health service in this country at the present time is of men adequately trained for the work; (2) that a distinct contribution toward meeting this need could be made by establishing at some convenient place a school of public health of high standard; (3) that such an institution, while maintaining its separate identity, should in the interest both of economy and of efficiency be closely affiliated with a university and its medical school; (4) that the nucleus of this school of public health should be an institute of hygiene.

Mr. Rose and Dr. Welch were asked to formulate a plan for such an institute of hygiene and in compliance with this request offer the following report, which is designed to set forth the scope and general character of the organization of the institute and the service which it should render in training in hygiene, preventive medicine and public health and in the advancement of these subjects. If desired, the report can be supplemented by a detailed statement of organization, plan of building, budget and courses of instruction.

I. Public Health and Hygiene in England and in Germany

The origins of the modern public health movement and of the cultivation of hygiene as an independent science may be found especially in the passage of the Public Health Act in England in 1848 and in the establishment of the first hygienic institute by von Pettenkofer in Munich in 1865. The greatest stimulus to further development came from the discoveries relating to the causation and the mode of spread of the infectious diseases and the conse-

[1] William H. Welch and Mr. Wickliffe Rose.

The following report, prepared by Dr. William H. Welch and Mr. Wickliffe Rose, was presented to the Trustees at their meeting, January 12, 1916. The Rockefeller Foundation Annual Report, (The Rockefeller Foundation, 61 Broadway, New York), 1916, p. 415-427.

[2] Dr. A. C. Abbott, Dr. Hermann M. Biggs, Dr. Simon Flexner, Mr. Jerome D. Greene, Dr. Victor G. Heiser, Dr. Edwin O. Jordan, Mr. Starr J. Murphy, Dr. Wm. H. Park, Mr. Wickliffe Rose, Dr. M. J. Rosenau, Dr. Theobald Smith, Dr. George C. Whipple, Dr. C. E. A. Winslow, Dr. Wm. H. Welch, Prof. D. D. Jackson, Dr. F. Cleveland, Dr. Wallace Buttrick, Dr. E. C. Sage and Dr. Abraham Flexner.

quent vastly increased power to control these diseases. It is instructive for the present purpose to note the different conceptions and directions of development in this field in the two countries. In Germany every university has its department or institute of hygiene, conducted by a professor and corps of assistants, where the subject is presented broadly in all its varied aspects, students are taught by lectures, laboratory courses and field work, and the science is advanced by research. In England, on the other hand, the important hygienic laboratories are few and mostly governmental or independent. For training the emphasis is laid upon public health administration, in which respect Great Britain leads the world. Those desiring to qualify as medical officers of health must possess the diploma in public health, obtained by passing an examination after at least nine months of special preparation, most frequently under a qualified medical officer of health and in a hospital for infectious diseases. It seems obvious that lessons are to be learned from both the German and the English systems, and that the ideal plan will give due weight to both the scientific and the practical aspects of hygiene and public health.

II. The Situation and Needs in America

In this country we are woefully lacking both in laboratories of hygiene and in opportunities for training in public health work. Three or four medical schools have hygienic laboratories, but none is complete, and adequately equipped and supported. Still other schools attempt something in the way of instruction in this subject, but it is all inadequate and unsatisfactory.

The need for supplying these deficiencies is at present the most urgent one in medical education and in public health work, and is recognized on all sides. The cry comes loudest from public health officials, social workers and others interested in public health administration, national, state, municipal and rural, who realize the lack of trained leaders and trained workers in all grades of the service. Here with the rapidly growing appreciation of efficient public health organization new and promising careers of useful service are opening for those who are qualified by ability, character and training. Scarcely less important is it for medical students and physicians who engage in practice to be well grounded in the principles of hygiene and of preventive medicine. Furthermore, the advancement of knowledge in this field, the cultivation of hygiene as a science, is one of the great needs of this country and should be a fundamental aim of an institute of hygiene.

III. Various Classes to be Trained

The first and in many respects the most important class of persons who will seek to be trained in a school of public health are those who expect to devote their lives to health work in some of its branches. These will aim to

become for the most part public health officials or to be engaged in some capacity in public health service, but some may become teachers or be connected with institutions or find other opportunities for a career in the ever widening field of sanitation. It is of the first importance to consider and to supply the needs for the education of the prospective public health officials.

Without attempting an exhaustive analysis, the following classification will suffice to indicate the various types of officers or experts required in public health administration:

1. Higher administrative officials, as commissioners of health and health officers in cities and districts, and division or bureau chiefs in the larger state and city departments of health.

2. Health officers in towns, villages and rural communities.

3. Higher technical officials or experts, as statisticians, sanitary engineers, chemists, bacteriologists, diagnosticians, epidemiologists, etc.

4. Inspectors of various kinds, as school, sanitary, food, factory, etc. inspectors.

5. Public health nurses.

With this class may be included those preparing to enter the Public Health Service of the federal government.

An institute or school of hygiene should furnish suitable training for all of these, and while courses adapted for special needs will be supplied, it does not seem desirable to conceive of such an institute as constituted primarily to provide training for higher or lower grades of service so much as to furnish opportunities for a good general education in all branches of hygiene.

While it is hardly possible to over estimate the importance of providing opportunities for the training of those who are to become public health officials, the need here is at present so acute that there is some danger of overlooking the conception of hygiene as a science and art which is much broader than its application to public health administration. Hygiene includes much more than state medicine. It is not necessary to consider here the distinction sometimes made, especially in this country, between hygiene and sanitation. In this report the term "hygiene" is used to include both, that is, the whole body of knowledge and its application relating to the preservation and improvement of health of individuals and of the community and to the prevention of disease.

With this broad conception it is obvious that the educational and scientific opportunities of an institute of hygiene should not be limited to the use of those who intend to become specialists in public health work and should cover a wider field than that of state medicine or sanitation.

It is of the utmost importance that education in the principles of hygiene should be available for students and graduates in medicine who are to engage

in the practice of their profession. With the present crowded medical curriculum obligatory courses in hygiene for undergraduate students of medicine must necessarily be restricted, but with the tendency toward greater freedom of election of medical studies there is the need and opportunity to provide more extensive optional courses in hygiene. There is a wide field for the establishment of graduate courses in hygiene for physicians. Even in Great Britain, where the character of training is designed almost wholly for public health officials, many who intend to become medical practitioners secure the diploma in public health. The mission of the practising physician is in many respects changing, and there can be no doubt that a year or more of graduate work in hygiene would be eagerly sought by many physicians and and would greatly increase their capacity of useful service to their patients and to the community, if the proper opportunity for such work were provided.

Sanitary engineering has become a specialized profession, and the institute of hygiene should combine with the engineering school in supplying the requisite training.

The public health nurse, both as a part of the public health service and independently of such connection, is destined to play a rôle of increasing importance in the improvement of conditions of health living and working and in the control of infectious and industrial diseases in this country. The institute of hygiene should cooperate with schools and organizations for training nurses in meeting the need for a supply of trained public health nurses.

When one considers the many points of contact between the modern social welfare movement and the public health movement, and to what an extent social and economic factors enter into questions of public health it is clear that an institute of hygiene must take full cognizance of such factors and that students of social science should profit by certain opportunities in the institute, as well as students of hygiene by training in social science and social work.

An important class to be provided for in an institute of hygiene will be those engaged in special advanced work in some branch of the subject and in original investigations of hygienic problems. A main function of the institute should be the development of the spirit of investigation and the advancement of knowledge, upon which intelligent public health administration and individual hygiene are absolutely dependent. It will be especially from this class of advanced workers and investigators and from the group of assistants in the institute that the teachers and the authorities and experts in hygiene will be recruited for service in different fields of activity and the standards of the profession of hygiene and of public health will be elevated.

IV. Field to be Covered

The field covered by the terms "hygiene," "sanitary science," "public health," "preventive medicine" is so broad and varied that it is hardly possible within a brief compass to indicate all of the subjects here included. Strictly speaking the territory embraces a group of sciences or the application of various underlying sciences. Unity is to be found rather in the end to be accomplished—the preservation and the improvement of health—than in the means essential to this end. It is the focussing upon this definite purpose which gives coherence to the organized body of knowledge embraced under the designations "hygiene" and "sanitation," and makes important its study and cultivation as a professional pursuit.

Although the practitioner should have knowledge of hygiene and of the means of preventing disease and has abundant opportunity in the practice of his calling to apply this knowledge, and the public health worker, if he is to prevent disease, must have a knowledge of the origin, mode of spread and diagnosis of disease, still it is becoming increasingly clear that public health work constitutes a distinct profession, and the wider recognition of this fact will be an important result of the creation of institutes or schools of hygiene.

The wide scope of the professional training required for the well equipped public health worker is sufficiently indicated by the mere enumeration of the more important subjects to which more or less attention must be given in an institute of hygiene, at least so far as their scientific groundwork in relation to sanitation is required. Such subjects are vital statistics; epidemiology or the causation, spread and prevention of transmissible diseases, including tuberculosis and the venereal diseases; diagnosis of infectious diseases; industrial hygiene; sanitary parasitology, including bacteriology and immunology; sanitary chemistry; sanitary engineering; hospital construction and administration; housing, ventilation, heating, lighting; disinfection; the hygiene of air, soil, water and climate; water supplies and sewage disposal; infant mortality and child hygiene; hygiene of schools; mental hygiene; heredity and eugenics; social hygiene; personal hygiene; diet and nutrition; rural, farm and dairy hygiene; milk supply; food and drug adulterations; nuisances; public health administration and organization, sanitary laws and codes; quarantine and immigration; tropical hygiene; relation of animal diseases to human diseases; public education in healthy living; social service work; sanitary surveys.

V. Agency Required to Perform this Function

The central, essential and main agency required to meet the needs which have been indicated is an institute of hygiene, housed in its own building, provided with the requisite laboratories and facilities and with its own staff

of teachers giving their entire time to the work of teaching and investigating. Given such a central institute it is easy to add to the curriculum, when found necessary, certain courses which are now given, or could readily be supplied by various existing departments of the medical school, the engineering school or other faculties of the university. The mere assembling of such courses does not constitute a school of hygiene. The great need of the country today in the promotion of public health is the establishment of well equipped and adequately supported institutes or laboratories of hygiene, where the science of hygiene in its various branches is fruitfully cultivated and advanced and opportunities are afforded for thorough training in both the science and the art. It would be a misfortune if this broader conception of the fundamental agency required for the advancement of hygienic knowledge and hygienic education should be obscured through efforts directed solely towards meeting in the readiest way existing emergencies in public health service.

1. *Relation to a Medical School.*—The profession of the sanitarian or public health worker not being identical with that of the practitioner of medicine, the institute of hygiene, as the essential part of a school of hygiene, should have an independent existence and should not be regarded merely as a department of a medical school. But the medical school offers much which the institute of hygiene will require either as preliminary training or in course and which it will not care to duplicate. In the interest of economy and efficiency, therefore, the school of hygiene should be closely related to a medical school of high standard in such way that the facilities of each should be open to the students of both.

It is likewise important for study and training in preventive medicine that the institute should have access to the facilities of a good general teaching hospital, as well as to various special hospitals. The need of opportunities for observation and study of patients in an infectious disease hospital is of course obvious.

2. *Connection with a University.*—To perform to best of advantage its function, the institute should be a part of a university. The medical school has found such connection to be a practical necessity. The institute of hygiene would draw even more heavily upon certain schools or departments of the university, as those of engineering and of sociology. In additon to having at its disposal the facilities of the university, the institute would find the stimulating and sustaining scientific spirit and ideals of the university an indispensable asset.

3. *Separate Identity.*—While intimately related to the university and its medical school, the institute of hygiene should be established on its own

fonndation, and should preserve and emphasize its own identity as a separate institution devoted exclusively to the science and the service of health; it should have its own building, and its own corps of instructors with adequate provision for teaching and research.

While it is not difficult to bring together on paper a group of courses selected from the several schools and departments of the university and by the addition of a few new courses make a presentable prospectus of a school of public health, this is not the conception of such a school or institnte as we believe will best fulfill the functions of developing the science and art of hygiene and of training for this new profession. If the institute is to make itself felt as a constructive force it must have in it a gronp of scientific investigators and teachers whose absorbing interest is in developing the science of hygiene and applying it to the conservation of health.

While the concentration of work here advocated involves some duplication of equipment, this is not as large as might be supposed and in view of the great advantages, does not constitute a serious objection. The institute must have its own chemical laboratory; it would be inconvenient and unsatisfactory in the extreme to attempt to use chemical laboratories devoted mainly to other purposes for the many important studies in sanitary chemistry. The principle microbiological laboratory of a medical school could without detriment be transferred to the institute of hygiene, although provision must exist for bacteriological work in the pathological laboratory, as well as in the hospital. Most of the other physical equipment of the institute would involve little duplication.

4. *Organization and Departments.*—At least in the beginning there should be a director of the institute, who will also be the head of one of the main divisions. Eventually the heads of these divisions may constitute a group or faculty with coordinate powers in directing the policy and affairs of the institute.

It is possible to indicate only in outline and in a general way the principal departments or divisions of an institute of hygiene, as details of organization and division of work should be left to the staff of teachers whose interests and qualifications will very with the individuals.

a. *Chemical Division.*—The applications of chemistry to sanitary science and art are extremely important and varied, and already highly developed.

b. *Biological Division.*—Here there would be a number of subdivisions, as bacteriology, protozoology, medical zoology.

c. *Engineering or Physical Division.*—A part of this can best be provided for in the engineering school, but the institute should provide opportunities for the study of certain hygienic problems reqniring the application of physical science.

d. *Statistical Division.*—While the various questions connected with the collection and study of vital statistics constitute the most important subject in this field, there are other important applications of statistical science to hygiene.

e. *Division of General Hygiene and Preventive Medicine.*—Under this broad head may be included epidemiology, industrial hygiene, the principles of public health administration and other subjects not embraced under the previous captions.

The foregoing classification is not designed to be either final or exhaustive and is manifestly reduced to its simplest terms.

If qualified men can be found there should be three or four teachers of the rank of full professors, but in their absence it would be better to select even for some of the important divisions younger men of great promise with the grade of assistant professors or of associates. In addition to these probably at least eight or ten assistants at moderate salaries would be required.

As already stated, the institute once established on its own foundation will draw upon the medical school, the engineering school and other departments of the university for courses of instruction which it will not care to provide on its own grounds, and it will itself cooperate in furnishing instruction to students in other departments.

5. *Field Work.*—Hygienic excursions to inspect water filtration plants, sewage disposal systems, methods of heating and ventilation and for kindred purposes constitute a valuable part of practical sanitary training. The most important training in the field, however, will be provided by establishing working relations with state and municipal departments of health and with the United States Public Health Service. This arrangement will provide for giving to the students practical experience in every department of public health work. The students may in this way become acquainted under favorable conditions with the methods of handling the health problems of the large city as well as those of the rural community. There will be opportunity for participating in the work of sanitary surveys. Cooperation with the Federal Public Health Service will give good opportunity for experience in quarantine work and in sanitary and epidemiological work on a large scale. Such relations will be mutually helpful. The states and cities will reap the benefit of intelligent and scientifically trained workers who will enter the service as real workers in all fields of its activities. The institute and its students in turn will have the benefit of this practical experience.

6. *Museum.*—An important feature of the institute will be a good hygienic museum, which will contain models, charts, preparations, and other material which can be gradually brought together. This will serve not only for demonstrative teaching, but also for the education of the public. The

influence and usefulness of the institute will be extended by popular lectures, conferences and extension courses.

7. *Special Courses.*—The institute should provide for the needs of those already engaged in health work, who desire to pursue short courses or to do advanced work in special branches.

8. *Requirements for Admission; Certificates and Degrees.*—The details regarding the conditions for admission to the institute may be left to future consideration, but it should be stated that while the majority of candidates for diplomas and degrees will doubtless be graduates in medicine, these distinctions should not be limited to physicians. The institute should be ready to receive and to reward with its diplomas and degrees all who come with a satisfactory preliminary education and pursue the required training, which need not be rigidly uniform for all matriculates. Even those who may not meet the requirements for matriculation and become candidates for the degree may find opportunity to pursue special courses of study. It has been abundantly demonstrated that the profession of public health work can be successfully followed by sanitarians whose principal training has been sanitary engineering, sanitary chemistry and sanitary biology.

9. *Influence of the Institute.*—The benefits to be expected from the establishment of such an institute as that proposed are not to be measured solely by the number of students trained within its walls. The institute can supply only a relatively small number of those who desire to enter upon public health service. The far-reaching influence of the institute should be felt in the advancement of the science and the improvement of the practice of public health, in establishing higher standards and better methods of professional education in this field, in stimulating the foundation of similar institutes in other parts of the country, in supplying teachers and in cooperating with schools of a simpler character designed for briefer technical training which should be established in each state in connection jointly with boards of health and medical schools.

THE SCHOOL OF HYGIENE AND PUBLIC HEALTH AT THE JOHNS HOPKINS UNIVERSITY[1]

Our president, with a self-denial which I might appreciate, has intrusted to me the agreeable function of announcing upon this occasion one of the most important and gratifying gifts ever bestowed upon this university, a benefaction likewise of national interest. This is the provision of funds by the Rockefeller Foundation for the purpose of establishing in connection with the Johns Hopkins University a school of hygiene and public health. This action of the Foundation was communicated to the trustees of the university only today shortly before these exercises. It is hardly necessary to add that the trustees have acted promptly in accepting this generous gift and have already taken the first steps toward organization of the new school in selecting Dr. Howell as the head of the physiological division of the Institute of Hygiene and to cooperate in the work of organization and development, and in appointing me as director.

It is expected that the school will be opened in October, 1917, as it is estimated that a year will be required for the planning, construction and equipment of the building and the gathering together of the staff of teachers. The necessary funds for construction, equipment, maintenance and expenses of the school will be provided by the Rockefeller Foundation.

When we consider the revolutionary discoveries of the last forty years in our knowledge of the causes and means of prevention of diseases, the great progress in the science and art of public health and the incalculable benefits to the community in the application of this knowledge, we can all realize the beneficent service rendered to this great cause by this latest gift of the Rockefeller Foundation, which has already contributed so largely to the advancement of medical science and education. Not only this university, but also this city and state and the whole country owe a great debt of gratitude to the Foundation for the provision thus made of improved opportunities for training in preventive medicine and public health work and for cultivation of the sciences which find application in public and personal hygiene.

It is naturally most gratifying to us that Baltimore and the Johns Hopkins University have been selected for the location of the new school of

[1] Report of remarks made at the Commencement Exercises of the Johns Hopkins University, June 13, 1916.

Johns Hopkins Univ. Circ., Balt., 1916, XXXV, No. 7, 9-13.

hygiene and public health. Our city, in its situation, its relations to the south and other parts of the country, its proximity to the national capital, and its opportunities for study and work in the field of preventable diseases, is favorably located for such a school. I think that I may say that determining considerations have been the advantages arising from close association of the school with the medical school, the hospital, the school of engineering and other departments of the Johns Hopkins University, and it is for these reasons especially that the decision reached by the Foundation after prolonged and careful study of the situation in different parts of the country is so gratifying to us. The wider extension of the influence and usefulness of the university, the possibilities of greater service to this city and state and to the country at large about to be opened by the new school, should materially strengthen the position of the Johns Hopkins University and aid in securing much-needed support in the development of other departments.

While the detailed plans of organization of the school of hygiene and public health will be worked out and announced later, a few points may here be touched upon.

Inasmuch as the profession of the sanitarian and worker in public health, although closely connected, is not identical with that of the practitioner of medicine; the school of hygiene and public health, while working in cooperation with the medical school, as well as with the school of engineering, will have an independent existence under the university coordinate with these schools. Opportunities in each will be available to students of the other schools.

The central and principal feature of the school will be an institute of hygiene housed in its own building, provided with the requisite laboratories and facilities and with its own staff of teachers giving their entire time to the work of teaching and investigating.

There will be here laboratories of sanitary chemistry of physiology as applied to hygiene—a most important although much neglected subject—of bacteriology and protozoology, and provision for epidemiology, industrial hygiene, vital statistics, a museum, library, etc. Additional facilities for instruction and research will be supplied by the medical and the engineering schools, the hospitals, especially the newly opened wards for infectious diseases of the Harriet Lane Home for Invalid Children, and other departments of the university, which will be aided in undertaking the new work.

It is anticipated that mutually helpful relations will be established with our municipal and state departments of health, assurance of which has been given by our public-spirited Mayor and other authorities, and with the Federal public health service, whereby opportunities will be afforded for field

work and other practical experience in various branches of public health work.

Especially advantageous will be the relations with the International Health Commission of the Rockefeller Foundation, which is engaged in the study and control not only of hook-worm, but also of malaria, yellow fever and other tropical diseases, which will receive due attention in the work of the Institute.

It is intended that the school shall furnish opportunities of a high order for the cultivation of the various sciences which find application in hygiene, sanitation and preventive medicine, and for the training of medical students, engineers, chemists, biologists and others properly prepared who wish to be grounded in the principles of these subjects, and above all for the training of those who desire to fit themselves for careers in public health work in its various branches—that most attractive profession for those qualified to practise it. The most urgent need at the present time is provision for the scientific training of prospective health officials and for supplementary and advanced courses for those already engaged in sanitary work. Suitable recognition of the satisfactory completion of work in the school will be given by the bestowal of certificates and degrees.

Directions in which it may be expected that the usefulness of the school of hygiene and public health will be extended are cooperative efforts with our training school for nurses and other agencies in the training of public health nurses, who have become such important agents in voluntary and public health work, and in the education of the public by exhibits, lectures and other means to a better application and understanding of the significance and needs of public and personal hygiene.

The dreams which many of us in the medical faculty have long cherished are now about to be realized. The opportunity which this great benefaction places in the hands of the Johns Hopkins University is most inspiring. It is comparable to that presented to the university at its beginning for the promotion of higher education, and later to the medical school and the hospital for advancement of the standards and methods of medical education. The responsibilities devolving upon the university in this new undertaking, entrusted to it with such high hopes, are commensurate with the splendid opportunities. May we not confidently anticipate that in this new field the results will be in keeping with the achievements of the university in the other fields it has cultivated so successfully?

REMARKS AT OPENING OF MEDICAL CONFERENCE OF RED CROSS SOCIETIES[1]

I esteem it a very great privilege to speak on behalf of my colleagues who are delegates to this Conference. I think it is not going too far to say that the entire medical profession of America and, indeed, all those who are interested in the prevention of disease and in the promotion of public health, would be glad to express their appreciation to the Committee of Red Cross Societies for having called together this Conference. Especially, I think all present will agree that we are indebted to Mr. Davison, who has again added to the very great service he has rendered in leading the American Red Cross during the war, by looking to the future, and for having conceived the idea that the great forces, resources, energies and thoughts which have been called into action by the Red Cross during the war, should continue to operate for the benefit of mankind.

How quickly we who have been interested in these questions have responded to this invitation! How warmly we have welcomed this great opportunity, carrying with it an equally great responsibility! I think that those of us who have often felt that we have been preaching to deaf ears the gospel of health have come here feeling actual joy that at last such great forces as are embodied in the Red Cross Associations are to be strengthened and expanded into a world-wide organization, for the promotion of health and the prevention of disease. We are confident that there are great possibilities of good in the application of this knowledge to the welfare of mankind.

It is a subject for congratulation that the minds of men have been awakened to the possibilities of improving the health and welfare of mankind through the control of disease, and it is a matter of the utmost gratification that these objects are to be attained through the Red Cross whose organizations are to be continued, strengthened and expanded for the good of mankind.

We who have been joined together in close association during this war in fighting the common enemy, an enemy of civilization, are to continue in

[1] Report of remarks as Presiding Officer at the Second General Session of the Medical Conference, held at the invitation of the Committee of Red Cross Societies, Cannes, France, April 1, 1919.

Proc. Med. Conf., Cannes, France, 1919, 24-25.

closer bonds of friendship, because we are joined together not to forge weapons of destruction, but united to consider what we can contribute for the healing of the nations. There are assembled in Paris delegates to consider the formation of a League of Nations. We are assembled here to confer upon the formation of a League of Health. And I venture to say that what we negotiate here will signify to mankind fully as much as the result of the deliberations in Paris.

I believe that we are contributing to the good and welfare of mankind by the creation of this League of Health under the Associated Red Cross Societies of the World, quite as much as will be contributed by the League of Nations under whose sanction, if not under whose direction, I trust we shall be permitted to act. We, therefore, pledge the loyalty of our delegates from America to this Committee of Red Cross Societies, and we wish at the same time to express our pleasure at being associated with our colleagues from France, England, Italy, and Japan, in this great movement.

SCOPE OF THE PROPOSED HEALTH ACTIVITIES OF THE LEAGUE OF RED CROSS SOCIETIES[1]

In our deliberations upon the general plan and purposes of a central health organization under the associated national Red Cross Societies, there are certain points which it seems to me important for us to bear in mind.

The first consideration is the importance of starting the new work along the right lines. A broad, comprehensive and detailed program will doubtless eventually be developed, but this must be a matter of growth, determined by the results of experience and by the available resources. We cannot precisely define or foresee these lines of future development, although I believe that we are all agreed that their possibilities are of incalculable importance for the welfare of mankind. Our more immediate task is to make recommendations concerning the initial steps which should be taken, trusting that time will indicate the paths which subsequently may be followed to greatest advantage. The future developments are obviously dependent in no small measure upon the successful initiation of the plan upon relatively simple lines.

In the second place, we should keep in mind that we have been called together to confer upon what an association or league of Red Cross Societies can wisely undertake in the promotion of health and the prevention of disease among the peoples of the world. While present conditions do not permit this league to assume a completely international character, it is permissible to look forward to the time when it will possess this character, but even under existing circumstances, we should not lose sight of the fact that our recommendations should concern themselves with the activities of an organization representative of many countries of the world.

Inasmuch as the central organization will operate mainly through the various constituent national societies, and upon their invitation, it is clear that a primary and main purpose of this organization will be to strengthen and develop existing Red Cross Societies, aiding them to enter upon these new and promising fields of work, and also to create such societies where they do not now exist.

[1] Report of remarks as Presiding Officer at the Fourth General Session of the Medical Conference, Cannes, France, April 3, 1919.

Proc. Med. Conf., Cannes, France, 1919, 50-51.

It should require little argument to show that the Red Cross in entering upon the field of preventing human misery caused by disease and suffering, is not diverting from its great work of relief, but is rather following a natural and logical path of development; for preventable disease is a continuing calamity, and its control is the best kind of relief, which will render unnecessary many of the large expenditures and appeals assumed by the Red Cross in the past.

Although public health administration is in the main a governmental function, we all know how helpful in manifold ways are voluntary organizations, such as those concerned with tuberculosis, with child hygiene, with mental hygiene, with venereal diseases, etc., in educating and organizing public opinion, in carrying on demonstrations, in influencing beneficially sanitary legislation and administration and in promoting in various other ways modern health movement. The Red Cross will not supplant any of these agencies, governmental or voluntary, but rather will aid them and help to coordinate their activities.

It cannot fail to be a source of the utmost gratification to all interested in the betterment of health and the prevention of disease that the Red Cross, with its unequaled influence and power, and its record of magnificent work in fields of activity of the greatest importance is to continue its labor in times of peace for the future welfare of the world. That these activities will be guided by the voice of science is indicated by the character of the Conference which we have been summoned to attend.

One of the important functions of the central health bureau of the associated Red Cross Societies will be to collect and distribute for the information and education of the public, the best available knowledge concerning hygiene and methods of preventing disease. A survey of the incidence and distribution of diesase, and the general health conditions in the different countries with the methods of control adopted would be an extremely helpful and much-needed contribution.

The modern health movement started in England less than a century ago with such a survey, which indicated clearly that there were controllable factors determining the prevalence of disease in certain localities, and under certain conditions of living and of working. As a result, there developed in England a practice of local public health administration in which this country still leads the world. Besides England, each of the countries represented in this conference has something of value to contribute. France, the country of Pasteur, so worthily represented at this Conference by his successor and our President, Dr. Roux, and his colleagues, has been a leader in scientific discovery, and has given us such men unmatched in the power of orderly thinking and clear expression. We owe to Italy studies of malaria

and methods for its control, of the greatest importance in sanitation, and it is gratifying to find in attendance on this Conference those who have made these great contributions. I had the opportunity four years ago of becoming personally acquainted with the fruitful activities of scientific investigation in Japan, in her admirable institutes. I think that America, largely through the efforts of Dr. Biggs, may claim to have had a leading share in the application of scientific discoveries in public health organization and administration, and especially in the organization and development of public health diagnostic laboratories, which we regard as a central feature of our sanitary methods. I cite these instances merely to illustrate the benefits which may be expected from a central health organization, such as that contemplated under the Red Cross, in which the sanitarians and methods of the leading civilized countries are represented.

ERRATA

L. F. T. means line from top; L. F B. means line from bottom

Page	Location of Error		Correction	
12	L. F. T. 3	"cachechtischen"	should read	cachectischen
12	L. F. B. 14	"haden"	should read	haben
14	L. F. T. 8	"Versuch"	should read	Versuche
24	L. F. B. 18	"23"	should read	20
28	L. F. B. 11	"os"	should read	so
34	L. F. B. 2	"eden"	should read	eben
54	L. F. T. 6	"then"	should read	than
54	L. F. T. 7	"massed"	should read	masses
61	L. F. T. 8	"elestic"	should read	elastic
61	L. F. T. 19	"lighted"	should read	lighter
64	L. F. B. 11	"conglutionation"	should read	conglutination
66	L. F. T. 18	"other"	should read	others
68	L. F. T. 17	"statments"	should read	statements
81	L. F. B. 25	"an"	should read	on
85	L. F. T. 3	"showing"	should read	slowing
118	L. F. T. 6	"from"	should read	form
145	L. F. T. 17	"envoloped"	should read	enveloped
154	L. F. B. 6	"enothelium"	should read	endothelium
203	L. F. B. 12	"ligual"	should read	lingual
220	L. F. B. 17	"occurence"	should read	occurrence
222	L. F. T. 17	"gapping"	should read	gaping
259	L. F. T. 22	"suject"	should read	subject
276	L. F. T. 4	"branchial"	should read	brachial
298	L. F. T. 17	"may"	should read	make
303	L. F. T. 18	"system"	should read	symptom
358	L. F. T. 3	"infectionus"	should read	infectious
403	L. F. T. 26	"hydroprobia"	should read	hydrophobia
417	L. F. T. 19	"mucous"	should read	mucus
418	L. F. B. 1	"lacohol"	should read	alcohol
420	L. F. T. 10	"oedema"	should read	oedema,
446	L. F. T. 7	"sebaseous"	should read	sebaceous
449	L. F. B. 8	"boogy"	should read	bogy
453	L. F. B. 16	"vulvulae"	should read	valvulae
486	L. F. T. 2	"febris *tertanae*"	should read	*febris tertianae*
506	L. F. B. 3	"*faliciparum*"	should read	*falciparum*
519	L. F. T. 5	"malanotic"	should read	melanotic
530	L. F. T. 10	"pyogenic"	should read	pyrogenic
536	L. F. B. 7	"*Cystirercus*"	should read	*Cysticercus*
537	L. F. T. 22	"*trico-cephalus*"	should read	*trichocephalus*
539	L. F. T. 11	"*Cysticeri*"	should read	*Cysticerci*
539	L. F. T. 18	"*of dochmius*"	should read	or *Dochmius*
539	L. F. B. 19	"Ascaris mystax"	should read	*Ascaris mystax*

Page	Location of Error		Correction	
540	L. F. T. 2	"*drassicollis*"	should read	*crassicollis*
543	L. F. T. 3	"creditate"	should read	crepitate
551	L. F. B. 17	"definitian"	should read	definition
575	L. F. T. 18 and other pages	"feces"	should read	faeces
576	L. F. B. 1	"fecal"	should read	faecal
577	L. F. B. 16	"remore"	should read	remove
586	L. F. B. 21	"cholera typhoid"	should read	cholera or typhoid
595	L. F. B. 13	"houses"	should read	housed
648	L. F. T. 18	"shore"	should read	short
653	L. F. B. 1	"interested"	should read	interpreted
658	L. F. B. 1	"insanitation"	should read	unsanitation
663	L. F. T. 19	"health"	should read	healthy
666	L. F. B. 9	"very"	should read	vary
670	L. F. B. 12	"chemistry"	should read	chemistry,