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1909-10

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PROF. T. G. BRODIE
PROF. G. CARL HUBER
PROF. LUDVIG HEKTOEN
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PREFACE

An introduction is no longer needed for the Harvey Lectures. They appeal annually to an increasing audience by the spoken word and in the printed book. As it would be difficult to raise the standard of the lectures, improvement will be looked for chiefly in an earlier publication of the annual volume.

The courtesy we have received at the hands of the Editors of the *Archives of Internal Medicine* in permitting our publication of the lectures by Prof. Pearce and Prof. Opie, and from the Editor of the *American Journal of the Medical Sciences*, for permission to publish Prof. Magnus-Levy's lecture, places us under an obligation which we here acknowledge.

Through the courtesy of the Wistar Institute of Anatomy we have been able to use some of their plates prepared for illustrations of previous publications of Prof. Huber's work. The lectures by Prof. Cohnheim, Prof. Brodie, Prof. Huber, Prof. Hektoen, and Prof. Meyer have not been published elsewhere.

December 12, 1910.

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THE PROBLEMS OF EXPERIMENTAL NEPHRITIS*

PROF. RICHARD M. PEARCE

University and Bellevue Hospital Medical College, New York

OUR present knowledge of nephritis is the result of the methods of clinical observation, pathological anatomy, and experimental pathology, successively applied. By means of the first of these, Richard Bright, in 1827, demonstrated that albuminuria and dropsy had an intimate relation to certain pathological changes in the kidney. Studies in pathological anatomy during the following years led to the differentiation of several types of nephritis, and, finally, to a classification based on morphological alterations. I do not think it an exaggeration to say that clinical observation has added little of essential importance to Bright's original conception of eighty years ago, or that pathological anatomy has added little to Weigert's classification, which has been generally accepted for thirty years. Bright's views, it is true, have been amplified, certain phases of the relation of renal disease to cardiovascular disturbances have been more clearly understood, and much negative evidence concerning uræmia and œdema has accumulated; but little has been added by clinical methods to our knowledge of the interrelation between a kidney lesion and its manifestations. The methods of pathological anatomy have given a classification, based on careful study of the gross and minute lesions of nephritis, and with these have been correlated in a more or less satisfactory way clinical manifestations and changes in the urine. This most important period of anatomical study began in 1851, with Frerichs, who considered all forms of nephritis as stages of a single process, beginning as an acute

* Harvey Lecture, Delivered Oct. 30, 1909.

nephritis and ending as the small granular kidney; the period terminated with Weigert, who, in 1879, demonstrated conclusively that Frerichs' stages do not represent the successive changes of a single lesion, but are distinct types of nephritis, caused by various injurious substances acting during varying periods of time, and representing the varied reactions of kidney tissue thus influenced. Weigert's view is the one held to-day. More recent studies by improved histological methods have added to our knowledge concerning certain details, especially in regard to the glomerular changes, the sequence of lesions, and certain unusual types of nephritis, but the methods of pathological anatomy offer no promise of an interpretation of the important problems of this many-sided disease.

The application of the experimental method to the study of renal disease is not a recent development. For many years experimental lesions of the kidney have been utilized, and with gratifying results, in the study of the sequence of the histological changes occurring in nephritis. With such studies, essentially anatomical in nature, have been combined, in recent years, investigation by methods which allow an interpretation of changes in function, upon which morphological studies throw no light. Such investigations necessarily demand the methods of chemistry and physiology; and we have witnessed in the past few years the curious spectacle of pathologists turning from the methods in which they were trained to those of the physiologist and chemist in which presumably they had, originally, little or no training. Investigation by such methods is termed "experimental pathology" merely because the pathologist, despairing of the anatomical method, has seen fit to adopt them in the study of altered function. It is to such methods that we must look for an advance in our knowledge beyond that which has been possible by the methods of clinical medicine and pathological anatomy; and if the pathologist is criticized, as frequently happens, for appropriating the methods of other sciences and for applying to the field of endeavor thus created the term "experimental pathology," it is sufficient to point out that the physiologist and the chemist, as well as the pharmacologist

who shares the same methods, have with few exceptions limited themselves to the field of normal function.

That nephritis has been one of the principal objects of attack by these methods is in part due to the importance of the disease, and in part also to the fact that the kidney lends itself very readily to experimental study. And, moreover, although the results of experimental study may not always be applied to explain disease in man, it must be evident that, owing to the peculiarities of the structure and function of the kidney, results of experimentation with this organ have a very definite application. Thus, some aspects of etiology, the almost specific action of certain substances in picking out certain kidney structures, the character of acute lesions and the relation of these to chronic lesions, questions of repair and regeneration, the matter of cast formation and the source of albumin, are problems which, when elucidated by animal experiments, can readily be transcribed to explain similar problems in human nephritis. But aside from these, the experimental method offers hope, in part already realized, of a solution of the more prominent problems of renal œdema, of anuria, the question of the relation of renal disturbances to hypertension and heart hypertrophy, and the most important, though at present the most hopeless, problem of uræmia.

Here I may at once call your attention to the fundamental problem of experimental nephritis, that is, the influence of the glomerulus as contrasted with the influence of the tubule. This enters into all phases of renal pathology, in some partially elucidated, but in most still a matter of doubt and speculation. The dual structure of the kidney is responsible for the difficulty which we have of interpreting the physiology as well as the pathology of this organ. We are familiar with glands in which different types of cell are concerned in the elaboration of different chemical substances, and with those in which cells are modified to produce an internal, as contrasted with an external secretion, but the kidney stands alone as an organ with two widely different structures, having for a common object the elimination of a single fluid representing the products of

metabolism. This is not the place to discuss the significance of this structural peculiarity and its bearing on the function of the kidney, though it must be considered in what follows. It may be permitted, however, to point out here that the glomerulus, as has been emphasized by Beddard, is a structure without analogy elsewhere in the body except, perhaps, in the choroid plexus of the brain; and that the urinary tubule differs from all other gland tubules in its length and complexity. On these peculiarities of structure, coupled with the peculiarities of the renal circulation, depends the power which the kidney has to remove from the blood-stream the fluid and solids which constitute the urine. If we disregard the one synthetic process of which we have positive knowledge, the formation of hippuric acid from benzoic acid and glycin, the essential function of the kidney is one of elimination, with the important feature that the resulting fluid contains all of the soluble components of the blood except its protein constituents and dextrose—in a different percentage, it is true, but still the same substances.

If we accept departures from normal elimination as evidence of disturbance of kidney function, the problem of experimental nephritis is to determine the part played in this disturbance by glomerulus and tubule, respectively. This may be done by the use of physiological methods which graphically demonstrate alterations in vascular reactions and by comparing such results with those obtained by chemical study and eventually correlating both with the anatomical changes. By such studies of simple phases of the problem of nephritis, enough has been accomplished to warrant their continuance with the prospect of adding essentially to our knowledge of renal pathology.

The study of experimental nephritis may be expected, however, to do more than explain the sequence and significance of pathological changes. By producing lesions which affect only certain structures as the glomeruli or the tubules, or but certain portions of the tubules, we may expect not only to solve some doubtful points in the physiology of this organ, but also to obtain data of considerable importance to the pharmacologist and therapeutist, thus bringing the work home to the clinician.

As a single example may be given the study of the effect of diuretics on the diseased kidney as compared with their effect on the normal. Our knowledge of the latter action is fairly complete, but we have very little knowledge of the former. The study of vascular dilatation and contraction in the kidney, the elimination of water, the general composition of the urine, the chloride-regulating mechanism and many other points, in distinctly tubular and distinctly glomerular forms of nephritis, which we are now able to produce, should yield practical information of great value. Some information in regard to these matters we now possess, but before it can serve as working knowledge, extensive chemical and physiological studies of various forms of nephritis must be made from the pharmacological point of view.

I have gone somewhat into detail in this introduction, not only for the purpose of demonstrating the value of the study of experimental nephritis, but also for the purpose of showing that the results of such study are of interest to every one concerned with the problems of normal and abnormal physiology—to the physiologist, the chemist, the pathologist, the pharmacologist, and the clinician. And, in order to maintain interest, if it has been aroused, I shall deal briefly with the methods of inducing nephritis, the character of the acute lesions, and the relation of these to chronic lesions, attempting to set forth clearly the types of experimental lesions known as tubular and glomerular. Time thus saved will be devoted to the more interesting questions of altered function.

ETIOLOGY AND CHARACTER OF THE EXPERIMENTAL LESIONS

In speaking of the etiology of nephritis in man, excluding, of course, lesions due to the localization of bacteria, we use, owing to our inexact knowledge, the phrase "soluble toxic substances reaching the kidney through the circulation." So, in experimental nephritis a direct nephritic poison must be capable of absorption, of solution in the body fluids and of causing injury to the renal cells when given in doses so small as not to cause death through its other actions. An indirect poison acts

through products formed by blood or tissue destruction, as with the hæmolytic poisons; here the action on the kidney is secondary. If we exclude Siegel's experiments on the production of nephritis by the application of cold, all forms of experimental nephritis are caused by substances falling in the above classification.

According to Sollmann, all metals, so far as they have been studied, cause nephritis, though some act only in corrosive doses or when given intravenously. Other nephrotoxic substances are aloin, coal-tar products, alcohol, anæsthetics, oxalates, cantharidin, essential oils, snake venom, ricin, abrin, bacterial toxins, hæmolytic poisons, and nephrotoxic immune serum.

Of these some act diffusely, while others affect the tubules or the glomeruli separately. Only such as have a more or less definitely circumscribed action are of value in producing experimental nephritis. Thus in the group affecting tubular epithelium with little or no primary glomerular injury, we may place, as most important, uranium nitrate, the chromates of potassium and of ammonium, and corrosive sublimate. Of those affecting glomeruli especially, the more important are arsenic, cantharidin and snake venom. All of these latter have some slight effect on tubular epithelium, probably secondary to circulatory disturbances dependent on the glomerular injury, but the latter lesion is so marked and so evidently primary that they are usually referred to as glomerular poisons. Another agent of value in experimental work is diphtheria toxin which combines glomerular and tubular injury.

All of these cause the appearance of albumin and casts in the urine; only uranium nitrate produces œdema.

Although I have, thus far, used the terms "tubular" and "glomerular" in reference to these poisons, they may more definitely be denominated, respectively, "epithelial" and "vascular" poisons. Until recently this division was made on anatomical grounds, that is, on histological evidence of degeneration, necrosis, exudation or cell proliferation, but the study of nephritis by physiological methods has brought out evidence of the existence of functional glomerular injury of extreme grade

accompanied by little if any anatomical evidence of vascular lesion. These methods have also shown that nephritides due to agents formerly supposed to act only as tubular poisons, present, in the late stages of intoxication, definite evidence of vascular incompetency.

It is necessary therefore to describe briefly the lesions produced by the more important nephritic poisons. This description will be limited to those poisons especially discussed in this address. It, however, by no means exhausts the list of substances which may be used.

The anatomical changes due to uranium and to the chromates are, in the early stages, confined essentially to the tubules, especially the convoluted tubules, and consist of granular or fatty degeneration and definite necrosis often affecting large groups of tubules. Corrosive sublimate causes similar lesions involving especially the ascending loops of Henle and characterized also by the deposition of lime salts. In these typical forms of tubular nephritis no anatomical lesions of the glomeruli are evident in the early stage, but in the late stages an ill-defined thickening [1] of the capillary walls may sometimes be seen and evidence of vascular disturbance is shown by physiological methods.

The glomerular form of nephritis varies. Arsenic, which acts through paralysis of the capillaries, causes little or no anatomical change in the glomeruli. The capillary loops may show slight thickening, the vessels may be overfilled, and the nuclei may stain peculiarly. Exudate into the glomerular space is usually absent, though a slight amount of coagulated serum may be present. By physiological methods, however, it is shown that despite the absence of anatomical lesions, serious vascular injury is present. Tubular involvement is slight and usually difficult to demonstrate.

Cantharidin causes a glomerular nephritis involving both the tuft and the capsular space. The lesions of the capsule have been variously described as desquamative, as consisting of

[1] In the uranium lesion, Christian has described hyaline droplets in the capillary loops.

a leucocytic exudate, and as due to the presence of epithelial cells pushed up into the capsule from the convoluted tubule. Lyon has recently emphasized this latter view and also describes degenerative changes in the convoluted tubules and ascending loops of Henle with necrosis of the latter. Functional tests demonstrate serious vascular injury.

The venom of the rattlesnake, as I have recently determined, causes a very remarkable glomerulonephritis of the exudative type. Single large doses or repeated small doses cause an exudation of serum and fibrin in both the capsular space and the glomerular tuft. This exudate is usually but not always hemorrhagic. Leucocytes are not prominent, but occasionally are present. The tubular changes are slight or entirely absent.

Diphtheria toxin is the best example of those poisons which combine both epithelial and vascular injury. Hyaline thrombi are found in the glomerular capillaries and small arterioles of the cortex in acute and intense intoxication. The vessel walls show hyaline changes and, in the later stages, cyst-like hemorrhages in the tuft (Lyon). Leucocytes are abundant in the tuft and slight necrosis may occasionally be seen (Flexner). With these changes are found extensive degenerative and necrotic lesions of the convoluted tubules and the ascending loop of Henle.

Undoubtedly, the lesion in both tubular and glomerular nephritis occurs in that portion of the kidney through which the poison is eliminated, though this has not been definitely demonstrated except in the case of uranium.[2]

From this, and our knowledge of the elimination of iron through the convoluted tubules, it seems probable that nephritis, due to the salts of various metals, is an indication of injury at the point of elimination. The peculiar involvement of the loops of Henle in the corrosive sublimate lesions supports this

[2] Schneider working with *Petromyzon fluviatilis* injected uranium solution in the muscle of the back, and also subcutaneously, and found that by the use of a fixing fluid containing potassium ferrocyanide, picric acid, and hydrochloric acid, the uranium was precipitated as a brownish-yellow deposit in the epithelium of the tubules.

view. It is not too much to hope that by careful study of such localized lesions experimental nephritis may eventually contribute to our knowledge, not only of altered function, but also of the normal physiology of the kidney.

The glomerular lesions likewise must be considered as a special manifestation of a general injury to capillary structures; the intensification of that action in the glomerulus being due to concentration of the poison at the point of elimination.

At present, then, we are familiar with several poisons which affect either tubule or glomerulus, respectively, the injury being recognized sometimes by anatomical changes, sometimes by functional disturbances, and sometimes by both.

The futility of judging of altered glomerular function by anatomical changes alone is best illustrated by Takayasu's histological study of the kidneys utilized by Schlayer and Hedinger in their investigations of disturbances of function in various forms of nephritis. This work will be discussed in detail later. Here it is sufficient to state that in arsenic and cantharidin nephritis characterized by constant and severe disturbance of vascular reactions, the glomeruli presented exudative lesions in only 2 per cent. of the kidneys examined, and this anatomical condition reached a degree comparable to the functional disturbance only in those kidneys showing total insufficiency. Proliferative lesions of tuft or capsule were not demonstrable. The only frequent lesion was increase in size of the glomerular nuclei and an indistinct outlining of the capillary walls, due, apparently, to an ill-defined thickening. The nuclear changes, moreover, occurred in tubular as well as in glomerular nephritis. Such results would appear conclusively to establish the possibility of serious functional disturbance with little or no evidence of structural lesion. To this problem I shall return in the discussion of altered function.

This brief description summarizes the more important types of acute injury caused by irritants acting directly on the kidney. It remains to discuss the relation of these to the production of lesions which may be termed chronic nephritis, or are accompanied by manifestations characteristic of the chronic

disease in man. The production of such a condition has been the object of nearly all work on experimental nephritis, and until recently with no success. Lyon, who worked with cantharidin, diphtheria toxin, and corrosive sublimate, with the object of following acute lesions to their termination in chronic, found that acute lesions rapidly disappear and that the kidney returns to normal. Such has been the experience of many other investigators, and it has incidentally served to strengthen the clinical observation that an acute nephritis, if the causative agent be no longer active, may go on to cure without the development of subacute or chronic lesions. This, however, is a phase of experimental nephritis which, in view of the very recent statement of Müller based on clinical observation and supported by the pathological studies of Löhlein, should again be investigated, and especially with regard to the matter of glomerular lesions. Müller expresses the opinion that a chronic nephritis may be the result of an acute lesion with a progressive course marked by acute exacerbations, or, on the other hand, there may be complete cessation of symptoms for many years with eventually a contracted or indurated kidney due to healing by scar formation.

Löhlein, as the result of a very careful study of selected material, has shown that many individuals dying of chronic nephritis present a definite history of an acute nephritis, followed by a quiescent period of several years, before the appearance of the chronic lesion responsible for death. His conclusions are based more especially on the kidneys of scarlet fever and acute coccus infections, in which he found inflammatory glomerular changes which seemed to be the starting-point of the fibrotic tufts and thickened glomerular capsules characteristic of the later developing chronic nephritis. Such observations are not new. Others have reported isolated instances of a chronic nephritis following the acute lesion of scarlet fever. Thus Handford describes such a condition after scarlatinal nephritis in a child 12 years old, in whom the chronic condition developed three years after the acute; and Councilman describes a chronic interstitial nephritis with heart hypertrophy following scarlet

fever, in a child of 2 years. Similar findings have been reported by Leyden, Mann, and others. Löhlein's extensive and thorough study, however, brings the problem once more prominently before us, and, coupled with the observation of Müller, makes it one of much importance. It would seem possible that by the use of a substance like venom, which acts as a definite glomerular poison and causes exudation and very striking endothelial destruction, experimental evidence of chronic nephritis following a single injury could be added to the clinical and pathological evidence now at hand.

Despite this possibility, it must be admitted that the experimental study of nephritis supports the more common conception of the etiology of chronic nephritis in man, that is, that it is a gradually developing lesion due to the long-continued insidious action of some ill-defined toxic substance. With the possible exception of the recent experiments of Dickson, the results obtained have been neither constant nor of such nature as to justify the term of chronic nephritis. Certainly if we take as a criterion a persisting lesion of the kidney characterized during life by elimination of albumin and casts, and histologically by changes involving glomeruli, tubules, and connective tissue, nearly all experimental efforts can be excluded. If we include œdema as a necessary corollary, chronic nephritis has not been produced experimentally. Some of the methods which have resulted in lesions approaching chronic nephritis are, however, worthy of mention. Ophüls, who investigated this subject, came to the conclusion that the best results could be obtained with lead, and, by the prolonged administration of a lead salt, he produced in guinea-pigs and dogs a definite sclerosis. The urine, however, did not contain albumin and casts. The same objection holds for experiments with many of the other metals (Petroff).

The experiments of Ehrlich and of Levaditi with vinylamin show that the primary necrosis of the papilla of the kidney caused by this substance may be followed by cortical injury with increase of connective tissue and considerable contraction. In a few of these experiments, in which mice were used, œdema,

hypertrophy of the left ventricle, and albuminuric retinitis were observed, with characteristic changes in the urine. Such changes, however, were not constant. The value of these experiments, moreover, is slight, for the diffuse nephritis followed destructive lesions of the papilla leading to mechanical obstruction, and were not due to a primary injury of cortical structures caused by a circulating poison, though it must be admitted that Lindemann has described the production of such injuries by the use of this substance.

Occasional positive results have been obtained with a variety of substances, as cantharidin (Aufrecht), oxalic acid and oxamide (Ebstein and Nicolaier), potassium chromate (Ophüls), and uranium nitrate (Siegel). I have myself found, in the course of a study which had for its object the production of œdema in the dog, a typical contracted granular kidney as the result of continued injections of potassium chromate and nephrotoxic immune serum. Chronic lesions, however, cannot be produced constantly by such methods and occasional positive findings, in view of the frequency of spontaneous lesions, must be regarded with suspicion. Or, to look at it in another way, these occasional positive results may have been due to the accidental presence of some secondary factor, as some metabolic or circulatory disturbance, necessary to the production of chronic nephritis. It was with this possibility in mind that Dr. Haven Emerson investigated experimentally the relation of circulatory disturbances to chronic nephritis. He recognized that, while a variety of causes are known to be responsible for, or contribute to, chronic interstitial changes in various tissues, there is almost constantly associated with them a circulatory disturbance, usually a venous congestion. It might be objected that such a disturbance is the result and not the cause of productive lesions in man, but Emerson's experiments are nevertheless of value, in that this hypothesis was, for the first time, investigated. The influence of vasodilators and vasoconstrictors was tested by inhalation and by subcutaneous and intravenous injection. Inhalation experiments during a period of half a year caused the appearance of degenerative parenchymatous lesions with

slight connective tissue changes. Though these experiments were few in number, the results, due apparently to disturbances of circulation and nutrition, suggest that with this background, the long-continued administration of a renal irritant in small doses might result in the fairly constant production of chronic nephritis. In this connection Caro's observation that nephritis occurs in cats five to eight days after extirpation of the thyroid is suggestive.

In other words, the evidence at hand supports the theory that chronic nephritis should readily be produced as the result of an irritant action associated with, or causing, circulatory and nutritional disturbances. This is in accordance with our clinical and pathological knowledge of chronic nephritis in man.

In accord with this view, also, is Bradford's suggestion that the many failures to produce chronic nephritis are probably due to the fact that we have no irritant capable of causing in animals a condition analogous to acute nephritis with œdema as seen in man. This statement was made in 1904. Such a substance we now possess in uranium nitrate, which, as Richter showed in 1905, causes a very definite acute tubular nephritis with the occurrence, when an excess of water is administered, of œdema of the subcutaneous tissues and accumulations of fluid in the serous cavities of the body. Uranium nitrate has come into general use as one of the most satisfactory of nephritic poisons, and Dickson, during the past year, has shown that its prolonged administration causes chronic nephritis in a large percentage of the animals treated. Unfortunately, his choice of experimental animals did not allow a study of œdema. If rabbits, in which œdema is readily produced, had been used instead of guinea-pigs, and the animals placed under conditions favorable to the production of œdema, it is possible that his results would have been the most satisfactory yet reported. As it is, he has shown (1) that prolonged administration of uranium nitrate causes a progressive "subchronic" nephritis; (2) that a series of six or seven acute attacks results in extensive fibrotic changes, with, in some instances, granular atrophy and associated polyuria; (3) that single injections not infre-

quently cause more or less severe fibrosis with occasionally granular atrophy; and (4) fluid, in small amounts, was found in the serous cavities of a few animals.

These experiments are of great importance in connection with what has been said about the influence of circulatory disturbances in the production of chronic nephritis. Uranium nitrate, in addition to its very decided action on renal epithelium, also causes very definite vascular disturbances. Several investigators have been forced to this conclusion, as Heineke and Meyerstein and Dickson. Recently, I have called attention to the necessity of assuming such an action in order to explain certain phases of the œdema caused by this substance. Final proof of this vascular injury is furnished by Schlayer and his associates, who have shown, by physiological methods, that although uranium primarily affects the tubules, there occurs a stage of glomerular injury characterized by dilatation of the vessels and decreased permeability. This will be discussed later in connection with œdema, but these observations serve here to indicate the value of uranium in combining the toxic effects apparently necessary to the production of chronic nephritis by causing not only structural changes, but circulatory disturbances also.

Thus may be summarized briefly the methods which have been employed in producing nephritis experimentally, the character of the acute lesions, and the relation of these to chronic conditions. Such a statement is necessary as a preliminary to the discussion of functional disturbances.

FUNCTIONAL DISTURBANCE

The study of anatomical changes in experimental lesions adds little to our knowledge obtained by the investigation of human material. By applying physiological methods on the other hand, we may correlate disturbance of function with any state of anatomical change and thus obtain information which clinical and pathological studies fail to give.

The kidney lends itself, perhaps more than any other organ, to investigation by physiological methods. The very abundant

blood-supply with its intimate relation to the function of the kidney, the close relation of function to general blood-pressure, and the influence of the circulation on diuresis are conditions which readily allow the application of methods, the results of which may be graphically registered. Changes in kidney volume dependent on general blood-pressure or on the influence of its own independent vasomotor system may be measured by the oncometer, and the results for the normal compared with those in animals with experimental nephritis. Likewise a simultaneous study of diuresis allows of the determination of the changes in the elimination of fluid. The injection of various substances influencing blood-pressure or diuresis yields information concerning the reaction of the kidney to these stimuli, and by their use it is possible to differentiate between the disturbances due to a glomerular and to a tubular nephritis. Further information concerning disturbances of function due to tubular or to glomerular lesions, respectively, may be gained by the use of phloridzin, and by correlated studies of the protein and salt elimination. Some information, as the result of such investigations, especially in regard to diuresis, is offered by pharmacological studies, but the most comprehensive study of this kind has been made by clinicians, by Schlayer and his associates, and deals particularly with the vascular reactions in the two types of nephritis.

Their work is based on the assumption that the vascular reactions of glomerular nephritis should differ from those of tubular nephritis and that this difference should be readily determined by the action of certain stimuli, the effect of which would be to cause either contraction or dilatation of the vessels. These changes, through decrease or increase of the kidney volume, would be readily recognized with the aid of the oncometer. It was necessary to choose stimuli the effect of which would be but transient and which would cause no injurious after-results, thus allowing a series of observations on the same animal within a comparatively short space of time. Furthermore, as the conditions of experiment were such that observation on the same animal before and after the development of nephritis could be made only in short-period experiments, it was necessary to demonstrate that these stimuli exerted a constant effect on normal animals.

To test the capacity of the vessels to contract they used sensory stimulation (tobacco smoke in the nose or transient suffocation) as an example of effect through the vasomotor centre, and adrenalin as an example of the effect of peripheral contraction. Each of these methods produced a transient diminution of kidney-volume with an increase at the same time in general blood-pressure. Caffeine and strong salt solution were used for the purpose of producing dilatation of the renal vessels. In connection with all these conditions the relation of diuresis to vascular changes and the power of phloridzin to cause glycosuria were also studied.

In brief, the study was one of the reaction of the renal vessels to various stimuli and the relation on the one hand to general blood-pressure and on the other to diuresis.

Necessarily, much depended on the uniformity of the control experiments, and for this reason rabbits of the same breed and similar weight were chosen, and with the exception of adrenalin, all substances were injected in definite ratio to body weight, and all but phloridzin, intravenously. Sensory stimulus and adrenalin (1 drop of 1 per cent. solution in 0.5 c.c. normal salt solution) increase blood-pressure with a corresponding fall in kidney-volume. In each instance this effect is transient, the normal condition being resumed in a very short space of time. On the other hand, 5 per cent. salt solution (5 c.c. per kilo) and 5 per cent. caffeine solution (2 c.c. per 1.5 kilo) cause a marked dilatation of the renal vessels with strong pulsation and immediate diuresis, the general blood-pressure remaining unchanged. At the end of the experiment, phloridzin was given subcutaneously; this caused a moderate diuresis with glycosuria but without increase in kidney volume or in general blood pressure.

These results were always obtained with normal animals, and the degree of reaction with each stimulus was practically the same. With such observations as controls, a study was undertaken of animals with various forms and differing stages of toxic nephritis. Potassium chromate and corrosive sublimate were used for the production of tubular nephritis, and arsenic, cantharidin, and diphtheria toxin for vascular nephritis.

Schlayer's opinion concerning tubular nephritis is based on 21 experiments with chromate and 15 with corrosive sublimate animals. The reactions to the various stimuli in the early stages of nephritis so produced do not differ markedly from the normal. It was found that the animals eliminated a larger amount of urine than do normal animals, which is in accord

with Weber's observations, and also that diuretics led to a still greater flow, as had also previously been demonstrated by Hellin and Spiro. The vascular reactions differed from the normal only in degree; the power of the vessels to contract after sensory stimulus and adrenalin was slightly increased and the power to dilate was greater also, to about the same extent. Phloridzin acted as normally, that is, caused polyuria and glycosuria.

The results with corrosive sublimate were similar except that the polyuria before the administration of diuretics was not so marked. In both forms, epithelial lesions were very prominent, but no anatomical changes were evident in the glomeruli. In short, the early stages of a tubular nephritis with albuminuria and cast secretion and severe anatomical changes in the tubular epithelium offer no physiological or anatomical evidence of vascular injury.

Before taking up the late stages of tubular nephritis, the reactions of vascular nephritis, for the sake of sharp contrast, may be described. Cantharidin and arsenic nephritis offer the best examples of this type. Severe vascular disturbances come on very quickly. In cantharidin nephritis, the early polyuria characteristic of the chromate lesion is absent. Within four to eight hours the effect of sensory stimulus and adrenalin is much less than in the normal, and after the administration of diuretics the power of the vessels to dilate decreases and with it diuresis. As the nephritis proceeds to severer degree, or if larger doses of the irritant be given, the power to contract after sensory stimulus and adrenalin becomes minimal and dilatation and diuresis become slight or cease entirely. Under such circumstances phloridzin produces no diuresis and no glycosuria.

The lesions due to arsenic are similar to those of cantharidin except that the general blood-pressure falls more quickly and remains at a lower level. This is to be explained by a greater peripheral capillary injury or perhaps by more intense action on the vasomotor centre.

This comparison is very instructive. A tubular nephritis

with extensive epithelial destruction and a urine rich in albumin and casts give no physiological evidence of vascular disturbance except a slight polyuria and a slightly heightened response to vascular stimuli. On the other hand, in a glomerular nephritis with little or no evidence of anatomical injury to either tubules or glomeruli, and with comparatively slight albuminuria and cast excretion, we find that the capacity of the vessels to contract and dilate is greatly altered, and with this a corresponding inhibition of diuresis, which may go on to total insufficiency.

These observations demonstrate for the first time the possibility of primary injury to glomeruli and tubules, respectively, and offer a sound experimental basis for the conception of a vascular as contrasted with a tubular nephritis.

But how, ask those who object to the direct application of experimental evidence to the problem of human pathology, is this to help us in explaining the majority of renal lesions in man? We admit its value from a pharmacological point of view. We admit also the possibility of primary glomerular injury and primary epithelial injury, and also that occasionally the glomerular lesion, as in scarlatinal nephritis, may remain the predominating lesion, and, on the other hand, that the acute renal lesions of certain intoxications, as cholera, eclampsia, and to a certain extent of diphtheria, may be purely epithelial lesions; but what is the bearing of this experimental evidence on those forms of nephritis in which both glomeruli and tubules are involved, and, most frequently, it would seem, the tubules first and more seriously? This question is a proper one, and while it cannot be fully met as yet, it is, I believe, answered in part by the studies which Schlayer and his associates have made of the later stages of tubular nephritis. They find that the late stages occupy a middle position between early tubular and typical vascular nephritis, and in severe forms may simulate the latter. The reaction to sensory stimulus and adrenalin remains practically normal, but the power of dilatation and diuresis, after the administration of diuretics, decreases gradually, and in severe late stages, that is, after two to four days,

dilatation is very slight or absent and diuresis does not occur. Phloridzin no longer causes glycosuria. These changes may be accompanied by slight histological alterations in the glomeruli, but the condition is, essentially, a functional glomerular disturbance following tubular injury. That this secondary glomerular involvement is a true vascular disturbance and not the result of compression of the glomeruli, due to the retention of urine in tubules blocked by casts, Schlayer and Hedinger have shown by experiments in which the ureters were ligated. Under such conditions no vascular disturbance resulted. Thus, these investigators have demonstrated not only tubular and vascular nephritis as experimental conditions, but have shown that the former may develop into the latter. The relation, however, of the late glomerular changes to the early epithelial changes cannot be explained without more complete experimental evidence. That the late vascular injury is due to the original poison is doubtful, but the possibility must be considered, in view of the fact that in Schlayer's experiments with diphtheria toxin, a gradually developing nephritis of the tubular type passed, after only twenty hours, into the typical vascular type. Again, it is possible that the tubular nephritis may cause the development of secondary poisons, consequent on metabolic disturbances in other organs, and capable of affecting the glomeruli. In this connection must also be considered the matter of the "give and take" of renal function recently emphasized by McCrae. This theory assumes the possibility of the glomeruli taking over in part at least the function of the tubules. It is possible that substances normally passing through the tubular epithelium are, when the latter is destroyed, eliminated by the glomeruli, the endothelial cells of which may be more susceptible to injury by such substances than is the tubular epithelium.

These are some of the problems suggested by Schlayer's work, which await the verdict of further experimentation by physiological methods. During the past year I have been interested in certain phases of these problems, and have repeated Schlayer's experiments, using the dog rather than the rabbit,

because of the more stable circulatory mechanism of the former.[3] The vascular reactions of the two types of nephritis, observed in the rabbit, I have found to occur also in the dog. The tubular form likewise develops into the atypical vascular form.

Additional evidence of the distinction between tubular and vascular nephritis is offered by chemical studies which, with the assistance of Dr. Miner C. Hill, were carried out in connection with the experiments just mentioned.[3] These depend on our knowledge that most, if not all, of the urinary nitrogen is eliminated through the tubules, and on the assumption that in tubular nephritis this elimination would be diminished. Daily estimations of the total nitrogen elimination in animals with tubular and glomerular nephritis, due to uranium nitrate and arsenic, respectively, were made. It was found that in the tubular nephritis a decrease of nitrogen equal to 9 to 14 per cent. of the normal elimination occurs, while in the glomerular form this decrease does not occur. Indeed, the arsenic animals showed an increased elimination varying from 7 to 16 per cent., demonstrating that the tubules not only were not injured, but also that they were able to care for the augmented output of nitrogen consequent on the increased metabolism due to arsenic.

These observations are of twofold interest. In the first place, the work with arsenic offers additional evidence of the possibility of producing a glomerular disturbance without affecting the function of the tubules, and, on the other hand, the diminished excretion of nitrogen in tubular nephritis[4] indicates the possibility of a retention leading to a disturbance, not only of the glomerulus in the "give and take" of kidney function, but responsible perhaps for some of the more general manifestations of nephritis.

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[3] Pearce, R. M., Hill, M. C., and Eisenbrey, A. B.: Experimental Acute Nephritis; The Vascular Reactions and the Elimination of Nitrogen, Jour. Exper. Med., 1910, xii, No. 2.

[4] Siegel also describes this decreased elimination of nitrogen in uranium nephritis, and Green, in a recent study of chromate nephritis, found a decrease of 20 per cent.

Here may be introduced also other evidence, of an entirely novel nature, which is of value in the differentiation of tubular and glomerular nephritis, and which would appear to be of definite physiological importance in the matter of normal tubule function. I refer to my recent investigations of the depressor substance of dog's urine, and I do this with some hesitation, as the application of the observation to the nephritis of man is not at all clear.

Elsewhere, in a discussion of the influence of kidney extracts on the blood-pressure, I have described the very striking depressor influence of dog's urine, when injected intravenously into other dogs. At that time this observation was of interest only in that it appeared to indicate that the similar depressor influence exerted by extracts of the dog's kidney was due to the content of urine which could not be removed.

My interest in this peculiar manifestation was again aroused by a chance observation made during the course of a recent study of diuresis in the pathological kidney. Dog's urine, on account of its very decided depressor influence, from which the animal quickly recovers, was used in this work as a means of rapidly lowering the blood-pressure.

It served most satisfactorily for this purpose and never failed with a large series of normal urines. Early in the investigation, however, it was observed that the urine from an animal in the third day of a chromate nephritis failed to cause the usual depressor effect. This chance observation led to the routine investigation of the urine of animals with various forms of experimental nephritis. As a result it was found that the depressor substance disappeared about the third to the fifth day from the urine of those animals suffering from renal lesions characterized by extensive tubular injury and persisted after the administration of substances causing glomerular injury with little or no tubular change.[5]

[5] Pearce, R. M.: Concerning the Depressor Substance of Dog's Urine and its Disappearance in Certain Forms of Experimental Acute Nephritis. Jour. Exper. Med., 1910, xii, No. 2.

This difference suggests that in the tubular lesion of chromate and uranium nephritis, which is characterized by extensive epithelial destruction, some substance normally eliminated is retained, while in the glomerular nephritis, caused by arsenic and cantharidin, this retention does not occur. The elimination of the depressor substance would appear, therefore, to be a function of the tubular epithelium. This view is supported by a study of the effect produced by normal urine as compared with that passed at the height of diuresis. Thus, in one animal, the urine obtained from the bladder at the time of inserting the cannula caused a drop of pressure of 64 mm. Hg., whereas at the height of caffeine diuresis the drop was but 30 mm. In another animal the figures were 60, 32, and 16 for (1) the normal urine, (2) the beginning, and (3) the height of diuresis, respectively. This indicates that the increased glomerular filtrate either dilutes the depressor substance eliminated by the tubule, or it passes through the tubules so rapidly that this substance is not added in the usual amount.

In animals with experimental nephritis of the tubular type the disappearance of the depressor substance [6] from the urine is frequently associated with a lowering of the blood-pressure, which would appear to indicate that the retained depressor substance may have a definite effect on the general blood-pressure. This observation is not, however, based on blood-pressure determinations on the same animal, before and after the development of nephritis, but by contrasting the pressure in animals with tubular nephritis with that in normal animals. It may, as is

[6] Concerning the exact nature of this depressor substance I have no knowledge. It dialyzes slowly, is not destroyed by boiling for a few minutes, but does disappear after prolonged heating. It can, however, be completely precipitated from the urine in impure form by large amounts of alcohol. The precipitate thus obtained, when dried and brought back to original volume with distilled water, has a depressor effect equal to that of the untreated urine, while the filtrate evaporated at room temperature to original volume has no effect whatever. The precipitate is not a single substance, but contains phosphates, chlorides, and sulphates and has a very small nitrogen content.

true in glomerular nephritis, be due to some other factor affecting the vascular system generally.

Investigations now in progress will, I hope, throw more light on the nature of this depressor substance, and, I trust, on the significance of its disappearance from the urine. At present the latter is of importance, as a manifestation of tubular nephritis, as contrasted with glomerular nephritis; as an indication of possible normal tubule function; and possibly, also, as an explanation of certain conditions of low arterial tension in man. Concerning the latter we have little information, for clinical studies have been confined largely to the condition of hypertension. It is of interest, however, that in the disturbances following too great experimental reduction of the dog's kidney, a condition of acute renal insufficiency, Janeway has demonstrated a definite fall in general pressure. If it could be shown also that the depressor substance disappears from the urine of these animals we would have a very substantial basis for a theory of acute renal insufficiency of tubular origin leading to hypotension.

It is perhaps needless to say that such observations have apparently no bearing on the hypertension of scarlatinal nephritis or that of the interstitial type of chronic nephritis. Also, one cannot assume that the experimental conditions here described hold for human nephritis. At present they must be considered merely as interesting experimental observations concerning the influence of the kidney on blood-pressure, and although it brings to this subject some confusion and uncertainty, future investigations may add unexpected knowledge, perhaps, in the direction of a better understanding of tubule functions.

ŒDEMA

As œdema is, in many ways, the most striking manifestation of certain forms of nephritis in man, it is natural that it should be considered in a discussion of experimental nephritis. I will not attempt, however, in this connection to present the conflicting views concerning the physiology of lymph formation

or the general pathology of œdema, which are admirably set forth in Meltzer's lectures on this subject, but will limit myself to the recent studies due to the stimulus of Richter's demonstration that acute uranium nephritis in animals is accompanied by œdema. The older literature contains much experimental evidence concerning the importance of hydræmic plethora or of vascular injury (Cohnheim and Lichtheim, Magnus, Albu) in the production of renal œdema, but as this is for the most part based on transfusion experiments in which large amounts of fluid were used, or experiments on dead or nephrectomized animals, it is not entirely satisfactory, as the conditions are too artificial. The results of such experiments are based on the absence of kidney function rather than on the influence of the altered function of the diseased kidney. Only uranium nephritis, of the various forms of experimental renal disease, is accompanied by a spontaneous œdema, and thus offers experimental conditions analogous to nephritis in man.

The more important theories of renal œdema may be briefly stated. On the one hand are those who support the importance of hydræmic plethora as enunciated by Grainger Stewart and Bartels, but more or less modified by later investigations, as those of Roth-Schultz and others. On the other hand are those who consider hydræmic plethora of secondary importance, and, following Cohnheim, ascribe to the injury of peripheral capillary blood-vessels the important rôle. With this theory is closely associated that of Senator, who presupposes injury of the renal vessels as well as of the peripheral vessels.

There is a tendency to bring these explanations together, giving each its share in a theory which ascribes the cause of œdema to the combined influence of renal vessel injury and peripheral (cutaneous) vessel injury, the former leading to retention of water or salts, or both, and the latter responsible for the increased permeability of the capillaries at the site of the local accumulation of fluid. In brief, the problem has become essentially that of the relative importance of vascular injury, hydræmia, and salt retention. Since the demonstration

of the value of uranium nitrate[7] for the production of a nephritis with œdema, the influence of these factors has been extensively reinvestigated.

Richter found that rabbits receiving subcutaneously small doses of uranium nitrate and at the same time 100 c.c. of water daily by stomach-tube, developed a well-marked œdema of the subcutaneous tissue with the accumulation of considerable amounts of fluid in the serous cavities. This œdema, it is true, differs in two respects from that of nephritis in man:

1. There is a greater tendency for the fluid to accumulate in the serous cavities and subcutaneous tissues than in the skin proper. This is probably due to histological differences between the skin of man and the rabbit, but is not of great importance, for the widespread œdema involving the subcutaneous tissues of the abdomen and thorax and frequently extending to the neck, head, and extremities, is sufficient evidence of general œdema.

2. The fluid is richer in albumin and tends to clot more readily than is the case in man. There is, however, no evidence that this fluid is of inflammatory origin; the high albumin content is probably to be explained by the acute character of the lesion, and in this regard approaches the character of the fluid in the œdema of scarlatinal nephritis.

Despite these slight differences the picture is sufficiently

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[7] It is a matter of local interest that, although macroscopic evidence of renal injury due to uranium was observed by Leconte in 1854, the first carefully recorded observations on uranium nephritis were from Professor Chittenden's laboratory at New Haven, and in 1889, in a communication from this laboratory, Professor Chittenden and Dr. Alexander Lambert of this city first described ascites in connection with uranium poisoning. Woroschilsky in the following year, in a communication from the pharmacological institute at Dorpat, described, accurately, diffuse œdema of the skin and subcutaneous tissues and the accumulation of fluid in the serous cavities of the body. These observations were, however, either overlooked, or their importance not appreciated, for it was not until 1905, when Richter's communication appeared, that the importance of this experimental lesion was generally recognized.

similar to the œdema of man to be considered a true experimental nephritic œdema, and is so regarded by the large number of investigators who have confirmed Richter's observation.

The studies of uranium œdema fall into two groups: those bearing on the question of water and salt retention, and those dealing with vascular injury. The first group includes experiments in which artificial plethoric hydræmia is produced and those in which the salt content of the body fluids is increased by administration of sodium chloride. The second group includes physiological studies of the renal vessels in uranium nephritis and also the study of the influence of vascular poisons in those forms of experimental nephritis not ordinarily accompanied by œdema.

The literature of water and salt retention in nephritis, which is voluminous and most confusing and contradictory, need not be summarized. The matters of greatest strife are (1) whether salt retention or water retention is primary; (2) if the salt retention is primary, whether it is a true tissue retention or secondary to vascular lesions which render the glomeruli less permeable to the salt. In either case the water retention is considered to occur as a result of the salt retention. The third possibility is that both water and salt are retained simultaneously as the result of glomerular injury.

The experimental evidence, based on altered kidney function in animals, which was at hand previous to the study of uranium œdema, may be illustrated by two types of experiment. Beck and Glucinski, as well as Lepine, had demonstrated that temporary ligation of the ureter of one kidney was followed by a lessened elimination of chlorides as compared with the opposite sound kidney, thus favoring apparently the theory of decreased renal permeability. On the other hand, Castaigne showed that, although there is a diminished chloride excretion in dogs with experimental nephritis, as compared with normal dogs, this difference was not observed if the respective animals received salt solution in the renal artery. In other words, if the salt was brought to the kidney, the kidney could excrete it. In other experiments normal and nephritic animals were bled and the blood replaced by saline solution. Shortly afterward 200 c.c. of blood taken from the renal artery of each showed the salt content to be less

in the animal with nephritis. These experiments are usually quoted as evidence of primary retention of chlorides in the tissues. It must be borne in mind, however, that in these experiments the renal lesion was not one accompanied by a spontaneous œdema.

In the early work on uranium œdema it was found that the administration of water in excess was essential for the development of a frank œdema, though occasionally, as in Georgopulos's series, a slight or moderate grade of œdema occurs in unwatered animals.

Richter took up the question of the relation of hydræmia to salt retention. He has found that if both salt and water are administered to animals a greater œdema is produced than with water alone. On the other hand, salt without water has no power to increase the hydrops, and if salt is given with half the amount of water usually administered, the œdema is not appreciably greater than in those receiving water only. On these observations and the demonstration that chloride retention occurs in other forms of experimental nephritis without the occurrence of œdema, Richter concludes that water retention is more important than salt retention.

Georgopulos has utilized uranium nephritis to determine the matter of chloride retention by direct quantitative analysis of the body fluids and tissues. His conclusions are very definitely stated as follows:

> In uranium, as well as in cantharidin nephritis, no constant relation exists between the water and salt excretion; more water than salt is retained, thus leading to a decrease in the chloride content of the blood. This indicates that water retention is dependent on a primary disturbance of the water-eliminating power of the kidney and is not secondary to chloride retention. Moreover, an increase of chlorides in the tissues with a reduction of chloride concentration of the blood could not be demonstrated in animals, with or without œdema.

Schirokauer, in a similar investigation, found that in œdema, although the tissues had a salt content greater than normal, it was no greater than the salt increase in the blood and in the

hydropic fluid of the body cavities. The increased salt content of the tissue does not therefore support the theory of primary salt retention, but indicates rather that in the process of transudation the salts and water leave the vessel in the same percentage relation, one to the other, as they occur in the blood. Other important studies are those of Bence concerning the altered distribution of water in the body and of Heineke and Meyerstein dealing with salt and water relations. The results of the latter, in that they indicate that salt retention may precede water retention, are not in accord with the other investigations quoted, but I have, I believe, sufficiently illustrated the value of uranium nephritis in the study of this phase of experimental œdema and also shown that the bulk of evidence does not support the theory of primary salt retention.

Of even greater interest are the recent experimental observations concerning the importance of vascular injury. It was early recognized that, although the administration of water in excess was necessary for the development of uranium œdema, this was not the essential factor, for the administration of water with or without salt to animals with chromium, aloin, cantharidin and other forms of nephritis did not cause œdema, despite the fact that in some of these forms, as chromium nephritis, the histological changes are practically the same as those of the uranium disease. Such observations naturally recalled the early experiments of Cohnheim and Lichtheim concerning the importance of vascular injury, due to various forms of irritation of the skin, and those of Magnus, in which vascular poisons, as arsenic, chloroform, and ether were used, and suggested the possibility of an action of uranium, or of substances formed during the course of nephritis, on the blood vessels, both renal and peripheral. Several investigators (Blanck, Heineke and Meyerstein, Georgopulos and Pearce) have expressed opinions to this effect. It remained, however, for Schlayer and his associates, Hedinger and Takayasu, to demonstrate by physiological methods a functional disturbance of the renal vessels in uranium nephritis, which disturbance, apparently, is an important factor in the production of œdema. Ura-

nium nephritis, it may be again emphasized, is anatomically of the type of tubular nephritis and characterized by extensive destruction, even to necrosis of complete tubules, and by abundant elimination of albumin and casts. Anatomical changes in the glomeruli, aside from slight thickening of the capillaries, the outlines of which are more or less indistinct, are not evident. Schlayer attacked uranium nephritis by the same methods which had served to differentiate tubular and vascular nephritis. It was found that in the early stages as well as in the late stages, uranium gives the reactions of a true tubular nephritis, of the type of the chromate or the corrosive sublimate disease. It has, however, an intermediate stage which differs strikingly from both the pure tubular and the pure vascular forms and which Schlayer has observed in no other form of nephritis except once in that form due to diphtheria. I may repeat, in order to present this peculiar reaction more clearly, that the characteristic feature of vascular nephritis is the failure of dilatation of the vessels with little or no diuresis after the administration of diuretics. These manifestations also occur in the late stages of tubular nephritis. They occur also at the end in uranium nephritis, but preceding it is an intermediate stage, during which the administration of 5 per cent. sodium chloride causes extreme dilatation with strong pulsation but no corresponding diuresis. This stage develops thirty-six to forty-eight hours after the onset of the experimental disease at a time when no œdema is evident, but when the urine is decreased in amount as compared with the preliminary polyuria. The vessels react to contraction stimuli strongly, the blood-pressure shows no change, the power of dilatation of the vessels is maintained but is unaccompanied by flow of urine. This occurrence, which was observed in fourteen animals, would appear to be definite evidence of decreased permeability of the glomerular vessels, marking a pre-œdemic stage, during which a retention of water and salt occurs. Later, when the renal dilatation fails, the capillaries of the general circulation presumably become permeable and œdema develops.

This phenomenon has one peculiar phase. Some minutes after the inhibition of diuresis caused by the salt injection a few drops of urine are excreted, but no further improvement in the flow of urine occurs. If, after a lapse of twenty minutes or so, caffeine is injected, the kidney volume, which has fallen, increases to the maximum attained after the previous salt injection, and a slight or moderate diuresis occurs. This diuresis is not so great as normal caffeine diuresis but is more prolonged, and the kidney-volume does not return to its normal level. That the production of diuresis under these circumstances is peculiar to caffeine was shown by the fact that if the injections were reversed, caffeine given first and followed by salt, each produced the same effect as before. Also it was impossible to cause diuresis by the administration of other diuretic substances, as urea, dextrose, and sodium sulphate, though all cause dilatation of the blood-vessels.

That caffeine alone produces diuresis in this stage is of interest pharmacologically, as Schlayer has pointed out, in that it supports those observations which ascribe its activity to a purely secretory process. Also from a therapeutic point of view it is well known that the action of caffeine in nephritis in man may differ from that of the saline diuretics.

Several objections might be raised to the view that the essential lesion in œdema is a diminished glomerular permeability. All of these, however, are met by Schlayer's carefully controlled experiments. It might be objected that the strong sodium chloride solution itself produces the glomerular injury. That salt is harmful to the normal kidney has been frequently demonstrated, and Castaigne and Rathery have shown that the injection of normal salt solution into rabbits with injured kidneys causes an increase in albumin elimination. Against this objection we have the observation of Schlayer that urea and dextrose, certainly non-toxic in the doses used, had the same effect as strong salt solution. Other objections, as that based on the theory of primary salt retention and the assumption that the body had almost reached its limit of salt fixation at the beginning of the experiment, and that the half-gramme of salt injected was sufficient to bind the water so that no diuresis could occur, are met by experiments in which three-hundredths of a gramme of salt produced about the same decrease in

diuresis as did the half-gramme, which should not be the case if these objections were valid. The objection that a salt retention associated with an early increased permeability of the peripheral vessels might account for the œdema is met by experiments which show that no œdema could be produced, during this intermediate stage, by transfusing the tissues with salt solution, whereas it could readily be produced in the final stage. In brief, the control experiments indicate that the increased permeability of the peripheral vessels follows, and is presumably the result of the glomerular impermeability.

One must admit the importance of Schlayer's observation concerning this peculiar condition of the renal vascular system in the intermediate stage of uranium nephritis; a functional disturbance which occurs only in that form of experimental nephritis which leads to œdema. It is the strong point of a theory of œdema which reconciles many of the conflicting views on this subject. Decreased glomerular permeability, occurring primarily and causing a retention of water and salts with secondarily an increased permeability of the peripheral blood-vessels is a convincing theory, and perhaps more than a theory, when the experimental work on which it is based is considered. Certainly the experimental evidence which Schlayer offers shows that, if either of these factors is absent, no œdema occurs.

Concerning the importance of these factors, I have reached similar conclusions as the result of a study somewhat different in nature. Accepting Schlayer's opinion that a vascular lesion is essential to the production of œdema I have attempted to produce œdema in true tubular nephritis by the administration of vascular poisons. The relative importance of hydræmia and vascular and renal injury was also studied. Potassium chromate was used to produce a type of experimental nephritis almost exclusively tubular and not accompanied by œdema. For the production of vascular injury, rattlesnake venom, ricin, and arsenic, all well-known vascular poisons, were utilized. Water administered by stomach-tube, in amounts of 100 c.c. daily, brought about a condition of plethoric hydræmia. A large number of rabbits were used; some received all three of these

substances, some only one, and others various combinations of two; thus all possibilities were controlled.

It was found that œdema resulted only when the three factors of renal injury, vascular injury, and hydræmia were present. No one of these factors acting alone and no combination of two was sufficient to cause œdema. The experiments in which venom was used were particularly valuable in that evidence of injury of the renal vessels as well as of the peripheral vessels was offered by easily demonstrable hemorrhagic lesions of these structures.

From this summary it is readily seen that the study of experimental nephritis has added much to our knowledge of the relative importance of glomerular injury, hydræmia, salt retention, and peripheral vessel injury in the production of œdema. This knowledge has been obtained in the only way possible, that is, by the study of a form of experimental nephritis accompanied by spontaneous œdema.

TOXIC SUBSTANCES IN ŒDEMA

In connection with the phases of experimental nephritis just discussed, the next problem is the determination, if possible, of the character or nature of the substance or substances concerned in the production of the vascular lesions, both renal and peripheral, but especially the latter, in nephritic œdema. Clinical and pathological studies offer no assistance. The early appearance of the prominent glomerular lesion of scarlet fever naturally suggests that the products of the etiological agent of scarlet fever are responsible for this lesion and possibly also, as Senator has suggested, for the vascular lesions of the associated œdema of the skin; but in the absence of definite knowledge of the etiology of scarlet fever or of its toxic products, no conclusions can be drawn. Likewise in certain infections, as with the pneumococcus and streptococcus (Councilman), in which capsular and intracapillary glomerular lesions are sometimes seen, the toxic products of the infecting organism may be considered responsible for the renal lesion. On the other hand, in those forms of chronic nephritis in which œdema most fre-

quently occurs, the etiology is obscure, the relation of parenchymatous to vascular lesions uncertain, and therefore conclusions are impossible. Even though it be granted that the general vascular lesions of the acute forms of glomerular nephritis are due to the poisons of the primary disease, our lack of knowledge of the toxic factors in chronic nephritis leaves no explanation for peripheral vascular lesions. The study of experimental lesions of the kidney has thrown little light on this problem, but certain observations with the serum of animals with experimental nephritis are very suggestive of the mode of development of peripheral vessel injury. Thus Heineke found that rabbits with chromate nephritis, which is not characterized by œdema, developed œdema when injected with the serum of animals with uranium nephritis. This phenomenon, since confirmed by Blanck, who, however, finds that it is not a constant occurrence, suggests that in the serum of animals with nephritis substances occur which operate to produce œdema. Two explanations seem possible: either the retention, as the result of kidney insufficiency, of substances which act as lymphagogues of the second order; or the injurious action on the endothelium, of some substance or substances causing an alteration in its permeability to fluids. The latter of these explanations is naturally more in accord with the experiments of Schlayer and his associates and with those which I have described. In a later series of experiments with Meyerstein, Heineke supports the theory of injurious action on blood-vessels. In this study is reported the production of œdema in 64 per cent. of chromate animals receiving uranium serum intravenously; but œdema was also found in an equal number receiving normal rabbit serum. As chromate nephritis, in the absence of serum injection, does not cause œdema, it is suggested that the serum in both instances had some injurious effect on the blood-vessels. Of similar import are the results obtained by Georgopulos, who produced a moderate œdema by injecting nephrectomized rabbits with the serum of animals suffering with uranium nephritis. In some of my own experiments with chromate nephritis I have found it possible to produce in the rabbit

moderate grades of œdema by injecting an alien serum (dog), and an œdema equal to that of uranium nephritis, by using nephrotoxic immune serum (dog).

Despite the difficulty of explaining Heineke's results with normal serum, the various observations presented suggest very strongly the presence in the serum of nephritis, of elements acting on vascular endothelium. Whether such substances are the retained products of metabolism or whether they are substances formed anew, in the course of nephritis, or are possibly due to disturbances in those organs characterized by internal secretion, it is impossible to say.

Such observations must fall in the same category as those of Lindemann, Bierry, Sawyer, and myself, concerning the power which the serum of various forms of nephritis (chromate, uranium, spontaneous, and that due to nephrotoxic immune serum) has when injected intravenously, of causing albuminuria and cast excretion in normal animals. The effect of the serum in each group of observations suggests the influence of the common factor, the renal disturbance, but unfortunately, while suggestive, the observations are as yet of so indefinite a character that they cannot be applied to human renal pathology. They would appear, however, to form a promising basis for future experimental investigation.

THE STUDY OF CHRONIC RENAL INSUFFICIENCY

In this presentation I have thus far limited my discussion to those problems to which have been applied methods which offer a functional conception of the acute disturbances in nephritis. For this reason I have considered only those lesions to which may be applied the term "nephritis" without fear of contradiction. Such lesions are, for the most part, those of acute nephritis, and thus the problems of chronic nephritis, as uræmia, hypertension, and heart hypertrophy, have necessarily been excluded. The experimental investigation of these latter phases of nephritis, because of the inability to produce constantly chronic lesions, has been attempted by means of the so-called reduction experiments in which, by operation, the

kidney substance has been reduced to a minimum compatible with life. Such experiments have yielded information of much interest, and although, strictly speaking, they represent the effect of insufficient function, rather than the effect of a true nephritis, they may, I think, be discussed here in connection with the general problems of renal pathology.

DISTURBANCES OF METABOLISM AND URÆMIA

By the study of the metabolism in animals with experimental nephritis one might expect to obtain information concerning disturbances of elimination, or of the influence of the kidney lesion on general metabolism, and thus throw some light on the conditions determining the development of uræmia. Such studies do offer some information of early or mild disturbances manifested by diminished nitrogen elimination (Siegel, Green), but in the severer lesions, the early occurrence of vomiting and diarrhœa with inability to ingest, retain, or utilize properly the food administered, all symptoms evidently of renal insufficiency, so disturbs the nitrogen equilibrium that metabolism studies are impossible. This is true, not only of experimental nephritis, but also of those procedures by which the renal substance is greatly reduced by successive extirpations. Such experiments have therefore added but little to our knowledge of disturbances of metabolism as obtained by clinical studies. The reduction experiments bear particularly on the influence of the kidney on general metabolism. In the first important investigation of this subject, that of Bradford, the conclusion was reached that slight reduction was followed by an increase in the elimination of water, but no change in the solids; on the other hand, an increase in total solids was found to occur after the removal of three-fourths of the total kidney substance; an absolute increase when food was taken and a relative increase when the gastro-intestinal disturbances were present. As the blood and tissues under the latter circumstances showed an increase in nitrogenous extractives, Bradford concluded that these disturbances were due, not to retention of

products of normal metabolism, but to an increased tissue catabolism, affecting especially the muscles.

Recently Bainbridge and Beddard have repeated these experiments. They find that the increase of nitrogen elimination is not constant and occurs only during the last few days of life when the animals show a loss of 22 per cent. of body weight, the result of gastro-intestinal disturbances and loss of appetite. They conclude, therefore, that the kidney has no influence on nitrogenous metabolism, and that the disturbance of nitrogen elimination is to be ascribed to inanition, and is similar to that occurring in fasting animals. My own experiments on this subject led to conclusions in entire accord with those of Bainbridge and Beddard. It would therefore appear very probable that mere reduction of kidney substance, even to a minimum compatible with life, does not lead to disturbances of metabolic function capable of being utilized in the explanation of uræmia. Likewise these experiments indicate the improbability of the presence of an internal secretion of the kidney capable of influencing general metabolism.

It is evident, however, that although under such circumstances there is no disturbance of general metabolism which may be recognized by chemical examination of the urine, the very striking gastro-intestinal disturbances must be explained through some fault of kidney function. As these disturbances occur also in experimental nephritis of the tubular type (uranium, chromium, and corrosive sublimate) and not at all or to but a slight extent in the vascular form (arsenic), they would appear to be due to a fault of tubule function, and the natural inference is that these disturbances are to be explained by a vicarious elimination into the gastro-intestinal canal of toxic products normally eliminated by the kidneys, and presumably are the manifestations of experimental uræmia.

Some support of such a theory is offered by clinical studies of uræmia by von Noorden and his associates, who have found such a vicarious elimination, with an increase of ammonia nitrogen, to occur especially in the so-called uræmic diarrhœa.

In one of my early investigations I tested this theory as far

as fecal nitrogen is concerned in animals with kidney reduction, but with negative results. More recently, with the assistance of Dr. Hill, I have estimated the total nitrogen elimination in urine and fæces in a group of animals with various forms of experimental nephritis. A constant decrease in urinary nitrogen varying from 9 to 14 per cent. was noted in the tubular form of nephritis, during the few days preceding the development of gastro-intestinal disturbance, but at no time was the fecal nitrogen appreciably altered. Siegel in similar experiments has also found the same drop in urinary nitrogen without an increase in fecal nitrogen.

Metabolism studies, therefore, indicate that the alimentary disturbances are not due to vicarious elimination of nitrogenous substances into the intestine, or, on the other hand, to diminished absorption of such bodies therefrom. It may be possible, as I have suggested elsewhere, that toxic substances, non-nitrogenous in nature, which cause irritation by elimination into the intestines, are responsible for this disturbance; or that, accumulating in the blood, they act either through the central nervous system, or locally on the tissues with which they come in contact.

This problem I consider one of the most important offered for solution by experimental nephritis. The gastro-intestinal disturbances with the associated respiratory and circulatory disturbances, and, not infrequently, a period of unconsciousness, essentially coma, for several hours before death, constitute a syndrome characteristic of renal insufficiency, and, presumably, of experimental uræmia. It is not too much to assume that the determination of the factors responsible for this experimental condition may explain some phases of uræmia in man.

HYPERTENSION AND HEART HYPERTROPHY

The hypertension and left-sided heart hypertrophy so characteristic of the atrophic form of chronic nephritis have led to numerous investigations having for their object the experimental reproduction of these conditions. It is but natural, in view of the fact that the chief characteristic of the human lesion

is an atrophy of the kidney leading presumably to diminished function, that the experimental methods should at first be largely those causing a considerable diminution of the functional area of the kidney and at the same time allowing a survival of the animal for long periods of time. As the acute forms of toxic experimental nephritis cannot obviously be utilized for this purpose, and as atrophic forms of chronic nephritis cannot be reproduced with any constancy, the method employed has been that of gradual reduction of the kidney substance, by successive operations, to a minimum compatible with the life. Although conditions analogous to those accompanying the interstitial type of chronic nephritis in man have occasionally been observed as heart hypertrophy by Paoli, and an increased amount of dilute urine by Bradford, the exact study of this problem begins with the observations of Pässler and Heineke, who, in 1905, attempted for the first time to study the changes in blood-pressure by direct manometric observations. These investigators found that after the removal of a considerable portion of the kidney substance, approximately two-thirds to three-fourths, by successive operations, a rise of blood-pressure occurred which was permanent and associated with cardiac hypertrophy and the elimination of an increased amount of urine of lowered specific gravity. This result was not constant, but occurred in about 25 per cent. of the animals which survived, by at least four weeks, a considerable reduction of the kidney substance. In such it was observed also that arterial spasm with further rise of blood-pressure quickly followed stimuli which in normal animals would produce little effect. These observations suggest that the heart hypertrophy is due to increased work resulting from the circulatory disturbances caused by the tendency to arterial spasm, and that the vascular spasm is due in its turn to the effect of retained toxic substances.

The determination of the blood-pressure in these experiments was by direct measurement in the femoral artery; single readings were made before operation and one or more after operation. Although the differences noted, varying from 15 to

29 mm. Hg. with an average of 21.5, are quite definite, they are open to objection, as Theodore C. Janeway has pointed out, on account of the well-known normal variations in pressure which occur from time to time. To obtain more definite information of the changes from day to day, Janeway has utilized in such experiments the universally accepted clinical method of determining blood-pressure. He has modified the Riva-Rocci cuff so that it may be applied to the foreleg of the dog, and the pressure determined with a minimum of error, estimated at about 10 to 15 mm. This method of measurement he has used on animals in which the renal substance had been reduced by Carrel's method of ligating several of the branches of the renal artery. Observations on such animals, in some instances covering a period of fifteen months, show, as compared with the normal readings before operation, a decided increase in pressure; thus in one animal was observed an increase from the average normal pressure of 90 mm. to an average of 125 mm. after 100 days; in another an increase from 117 to 150 mm. The maximum and minimum pressures of the respective daily observations showed also the same relative increase.

From a consideration of the experiments of Pässler and Heineke and of Janeway, one cannot but conclude that a condition of experimental hypertension of renal origin is brought about as a result of the reduction of kidney substance. Such experiments, however, as yet offer no explanation of the mechanism by which the hypertension arises. It can hardly be due, in the extirpation experiments, to the influence on function of mere reduction of kidney tissue, for as I have shown, the "factor of safety" for the kidney is such that one-half of one kidney appears to be sufficient for the proper elimination of nitrogen and presumably also for other solids. Nor in the ligation experiments of Carrel and Janeway can it be due to the mechanical effects of the reduction of the kidney circulation, for, as Ludwig has shown, complete ligation of the renal arteries is not followed by permanent increase in the general blood-pressure. The single anatomical condition which is unavoidable and follows all forms of injury is a varying degree

of infarction-necrosis. This is slight in amount in the "polar" excisions of Sampson and myself, somewhat greater in the "wedge" excision of other investigators, and from the nature of the injury must reach its maximum in the ligation experiments of Carrel and Janeway. In itself this infarction cannot be responsible for hypertension, but the persistent albuminuria in Janeway's dogs indicates that it may be responsible for the development of a true nephritis which, of course, adds to the factor of diminution of functional area that of altered function. Similarly in the extirpation experiments, the irritation of sutures in the pelvis of the kidney, causes occasionally the localization of the colon bacillus with infection of the infarcted tissue and the development of a pyelonephritis (Sampson and Pearce), which must exert an injurious action on the remaining kidney substance, and as time goes on, lead through attempts at repair to a more or less chronic lesion.

I have gone into this matter somewhat critically because, although the results of reduction experiments are striking, the procedures by which they are obtained are not such as involve only a single factor, but bring several forms of kidney injury into play; that is, reduction of functional substance and productive, atrophic, and vascular changes accompanied by the elimination of albumin and casts. In other words, a chronic lesion of the kidney, characterized by hypertension, heart hypertrophy, and increased flow of dilute urine is produced, and this may be considered as an experimental disease analogous to certain phases of chronic renal disease in man, but it gives us no facts which explain the etiology of the vascular disturbances of the latter. The production, however, of hypertension experimentally is no small gain, and it is to be hoped that in future investigations the various factors involved in the experimental disease may be analyzed and controlled, and that the essential etiology of experimental renal hypertension may be established.

There is one aspect of these studies which is of considerable theoretical importance. Pässler and Heineke state that although an increased flow of urine of lowered specific gravity usually

accompanies the experimental heart hypertrophy, it may occur in the absence of hypertrophy and hypertension. This would indicate that polyuria is independent of increased blood-pressure, and is of interest in connection with Loeb's hypothesis of the influence of a glomerular reflex in the production of hypertension. This is based on the frequency with which hypertension in man is accompanied by glomerular lesions (Schmidt), and on the physiological law that the functional power of the kidney depends on the rate of blood-flow through the glomerulus. Loeb assumes that with greatly increased capillary resistance within the diseased glomerulus, the increase of flow due to local vasodilatation is insufficient for the needs of the kidney, and that the glomerulus sends a call beyond the local vasomotor system which, reaching the cerebrospinal centres, causes a reflex splanchnic vasoconstriction and thus increases the general blood-pressure so that a normal flow through the altered glomerulus results. This hypothesis might well be applied to explain the results of reduction experiments. The demands of water elimination on the greatly reduced number of glomeruli in the persisting kidney fragment might readily excite a reflex splanchnic constriction to aid in the proper elimination of water. Thus would be explained the increased blood-pressure, and by its continuance the eventual heart hypertrophy. This attractive hypothesis cannot at present receive support from reduction experiments if polyuria without increased blood-pressure, as observed by Pässler and Heineke, is found to be a frequent condition. Their experiments, however, were made on a comparatively small number of animals, and the investigation of this hypothesis should be an important phase of future studies of the reduction of kidney substance.

As all forms of experimental reduction of kidney substance are characterized by loss of glomeruli and by either increased blood-pressure or polyuria, or both, and frequently by heart hypertrophy; and, on the other hand, as hypertension does not occur in the presence of a normal splanchnic circulation, it would seem possible, by properly planned reduction experiments, either to disprove or to establish Loeb's hypothesis and

thus to clarify to some extent the at present confusing theories of hypertension in nephritis.

Several other aspects of this phase of renal disturbance might be discussed, as the influence of a possible internal secretion of the kidney on blood-pressure and the matter of the presence of blood-pressure-raising substances in the serum of nephritis; but to such problems the study of the acute forms of experimental nephritis has little application, and the results of the study of experimental chronic lesions, thus far obtained, are either contradictory or entirely negative.

In concluding this presentation, I admit that I have neglected several important phases of experimental renal pathology and have treated others in a more or less incomplete way. Such omissions have been intentional, as I have preferred to emphasize those problems to which have been applied methods which offer a functional conception of disturbance in nephritis, and which tend to distinguish between the results of tubular as contrasted with glomerular lesions and to show the relation of these to some of the more important manifestations of renal disease. To such a conception, supplementing the older anatomical knowledge, we must look for the ultimate solution of the problems of nephritis.

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THE INFLUENCE OF SENSORY IMPRESSIONS ON SCIENTIFIC DEDUCTIONS*

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PSYCHOLOGY and Philosophy teach that the only means of association between the mind and the world surrounding it lies in the sensory organs which carry sensations from the external world to the brain. We arrive at our knowledge, real or assumed, of the things around us through our sensations, and we can never be free of these, since they depend on actual definite structures, the sensory organs.

Optical and other sensory illusions may be easily produced; they have been carefully studied by physiologists and psychologists, and readily admit of laboratory demonstration. But, on the other hand, in the course of scientific investigation it may easily happen that in our deductions we may be deceived by illusions and be led by our sensations along a false path.

I will not discuss the philosophical questions connected with the property of sensation, but will give some of my own experiences, bringing out facts overlooked by earlier investigators who were led astray by sensations wrongly interpreted.

If the question is asked what foods are easily digested and what foods are not, the answer usually given is that carbohydrates, fine bread, sugar, and finely divided meat are easily digested, while fats, fat meat, and meat taken in large pieces are not. Why this answer? We all know that the chief seat of digestion, the most important organ of the alimentary canal, is the small intestine. Stimuli which come from the wall or the inner surface of the duodenum and the upper jejunum provoke or check the opening and closing of the pylorus and the movement and secretion of the stomach. They also provoke the secretion of bile and pancreatic juice.

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The greater bulk of the food taken is digested and absorbed in the small intestine. Hence it should follow that an easily digestible food is the one which is quickly digested in the small intestine, with the minimal amount of work. We usually find, however, that in recommending a food as easily digestible, the chief importance is laid on the quickness with which it leaves the stomach. That this is incorrect I have shown by the following experiment: A dog with a cannula in the upper duodenum was fed on meat in large pieces at one time and finely chopped at another. The finely chopped meat left the stomach in a much shorter time than the large pieces, which were held back by the pylorus. Thus the time required for the emptying of the stomach of 50 Gm. of meat was one hour and thirty-five minutes when taken finely chopped and two hours and thirty-one minutes when taken in large pieces. But a study of the composition of the chyme passing through the pylorus in each instance showed that the chopped meat had undergone much less solution and digestion in the stomach than the meat in large pieces. The latter was converted almost completely into peptone, and one-fifth had been absorbed before leaving the stomach. Of the chopped meat 40 per cent. had not been dissolved by the pepsin. In both meats there was 1.9 Gm. nitrogen. In the chopped meat 0.8 Gm. nitrogen needed further digestion, as opposed to 0.13 Gm. nitrogen in the meat in large pieces. This shows, then, that meat in large pieces requires more work on the part of the stomach than the chopped meat, but that the latter requires more work on the part of the intestine. So far as total work in these two instances is concerned, we are ignorant.

Bread is also classed as an easily digestible substance, but while it leaves the stomach quickly it demands much further work on the part of the intestine and digestive glands before it is prepared for absorption. According to common opinion, bread, just as finely chopped meat, is an easily digested substance because it leaves the stomach quickly. In support of this opinion there is only the absence of a sensation of fulness, a sensation which comes from the stomach, but not from the

intestine. It has been demonstrated lately by Meltzer that a nervous connection, by means of which impulses pass in a centripetal direction, that is, from the periphery to the central nervous system, exists between the intestine and the brain and spinal cord. But only severe pain can be conducted along these connections. As a rule, neither in health nor disease do we have sensations coming from the small intestine. We do, however, have a consciousness of sensations coming from the stomach or a slight feeling of pressure and fulness after eating. These sensations are not so distinct as those coming from the eye, the ear, or the skin. But the less distinct they are, the greater perhaps is their influence upon us, and they are undoubtedly responsible for the general belief that an easily digestible food is one which leaves the stomach quickly.

The real work of the digestive organs has not been considered, and the sensations, coming exclusively from the stomach, also afford the explanation of why diagnostic work in digestive disturbances is so apt to be confined to a consideration of the state of the stomach only, little or no attention being paid to the small intestine.

During the past three years I have carried out a series of experiments on dogs with the idea of inducing pathological conditions in the stomach. I have had the advantage of the collaboration of Prof. Krehl in this work, and we began with the purpose of studying the experimental pathology of the alimentary canal, a subject almost completely neglected heretofore. We used for our experiments dogs with cannulas in the stomach and in the duodenum. Such dogs live for many months or even for years in a healthy condition. The cannula in the duodenum is arranged so that if its mouth be closed food passes through the intestine in the usual way. If the mouth is open all food coming through the pylorus passes out through the cannula and can be collected, measured, and studied. Further, solutions can be injected through the cannula into the duodenum and upper intestine. In order to complete our experiments we have found it always necessary to reinject some of the fluid escaping through the duodenal cannula back into the duodenum. If this is not done, all stimuli, which bring on or

check movement and secretion in the stomach or secretion of the ferments in the intestine, are absent. These experiments are difficult for the investigator, but I believe that digestion goes on under normal conditions. It is possible by means of such duodenal fistulæ to obtain the whole or absolute quantity of the secreted gastric juice, and not only the concentration as in the Pawlow so-called "little stomach." And it is also possible to observe the time and manner of the emptying of the stomach as well as, and in some cases better than, in Cannon's excellent experiments with X-rays.

We studied first the normal digestion of a test breakfast and test dinner, such as are usually given to men for diagnostic purposes. We found that good results could be obtained after either of these; much better, in fact, than we had expected from a paper recently published by Greutzner and other authors, and I think it is even allowable to draw conclusions on the true condition in the stomach from the concentration of the contents when these are removed by means of the stomach tube. After the test breakfast the dog, and as far as we can judge this applies equally to men, secretes 150 c.c. of gastric juice and more than 250 c.c. of bile and pancreatic juice. The total acidity and free hydrochloric acid show the same values obtaining for man.

After the test dinner, meat, soup, and mashed potatoes, the stomach secreted 700–800 c.c. of gastric juice and there were obtained about 500 c.c. of bile and pancreatic juice. The concentration of stomach contents was 78–98 total acidity.

We next attempted to produce various pathological states by injuring the stomach, expecting to get such conditions as an acute catarrh. To our surprise, we were unable to do this, in spite of severe injury to the stomach. For example, we have filled the stomach with ice-cold ammonia solution of 10 per cent. strength, or with water heated to 55–60° C. (120–140° F.). These methods indeed induce marked disturbances in the animal's condition, such as loss of appetite, weakness, and vomiting, the vomitus containing blood; but these are of short duration. Recovery quickly takes place and the stomach digestion is then found to be normal, or almost so. Such experiments

have also been recorded by Pawlow and one of his pupils who, studying the "little stomach," found very little change in either the concentration or time of secretion.

With our method, which gives the absolute quantities as well as the concentration of the contents of the stomach at a given time, we could see no change not to be explained by experimental error. We were surprised by this great resistance of the stomach to injuries, and turned our attention to the small intestine. We injected strong salt solutions through the cannula into the intestine; the solutions of course did not enter the stomach. One solution contained 4 per cent. $MgSO_4$, the other 4 per cent. NaCl. Following the injection diarrhœa occurred as we had anticipated, but in addition to this the stomach, with which the solution did not come in contact, was also affected. During the diarrhœa and for some time after it the emptying of the stomach was stopped, or at least became much slower. Under normal conditions, after the test breakfast the stomach is emptied in one and one-half hours; after the test dinner in from three to three and one-half hours. In both instances the emptying begins within ten to twelve minutes after the meal is taken. When the intestine was injured by injection of the salt solution the emptying of the stomach began in from one to two hours after eating and was completed in two and one-half hours after the test breakfast and in from six to seven hours after the test dinner. Further, the gastric secretion, as well, was affected. After the injection of the $MgSO_4$ there occurred a strong hyperacidity; after the NaCl injection, a hypo-acidity.

In the first table below are seen the absolute values for the secretion in the stomach under normal conditions and after the salt injections. The dog was given one-half a test dinner and a test breakfast. The figures represent an average.

	Normal	$MgSO_4$	NaCl
Breakfast	158	290	60
Dinner ($\frac{1}{2}$).....	398	560	236

There is seen here an increased quantity after $MgSO_4$ and a decreased quantity after NaCl. In the second table is given

the concentration of the contents of the stomach, the total acidity, and the free hydrochloric acid after a test breakfast. The figures represent averages taken from nine experiments.

	Normal	$MgSO_4$	NaCl
Breakfast	T.A. 64	85	35
	HCl 26	51	8

This shows that we can induce a hyper- or hypo-acidity with a retardation of the emptying of the stomach by bringing about an abnormal condition in the intestine. We have proved this view by a series of experiments on a dog with both a gastric and a duodenal fistula. We have given a test breakfast and then injected hydrochloric acid into the duodenum either in the concentration and quantity present in the stomach contents under normal conditions or else in greater concentration or greater quantities than normal, and, further, we have injected instead of the hydrochloric acid more concentrated acetic acid, which is a weaker acid than hydrochloric acid. We found that both acid injections provoked a closure of the pylorus and a retardation of the emptying of the stomach, but, in addition to this, hydrochloric acid when given in greater concentration or in large quantities produces a hypo-acidity. Acetic acid, on the other hand, produces a hyperacidity. In cases of hyperacidity in the stomach a large quantity of hydrochloric acid enters the intestine and the hypo-acidity resulting indirectly from this may be considered in the nature of a compensation. Acetic acid occurs from bacterial growth in the intestine, and if the amount of bacteria increases markedly, as in some pathological conditions, acetic acid must increase also and this will result in an increased amount of hydrochloric acid found in the stomach.

We draw the conclusions from these experiments that gastric disturbances, such as difficulty in emptying the stomach, retardation of digestion, and the secretion of either too much or too little acid, can be produced, and probably are produced, indirectly from the intestine and that they cannot be produced in the stomach itself by changes confined to the stomach alone.

And if we study the anatomical and physiological arrangement of the alimentary canal we may expect that the actual seat of most of its disturbances will be in the intestine. I think that it is the capability of experiencing sensations coming from the stomach and the absence of such feelings coming from the intestine that explains why most work on the alimentary canal, not only in diagnosis, but along lines of investigation, has been so largely limited to the stomach. Our sensations have deceived us and have led us to believe that the seat of disease is in the stomach, whereas in all probability it is in the intestine.

Such vague but yet disturbing sensations coming from the alimentary canal are, I think, chiefly responsible for the spread of vegetarianism and other crusades against the use of meat.

For many years Americans have pointed with pride to the character and quality of the food used by their working classes, and to its richness in proteid. And now a new school has arisen here which insists that the whole idea of the nutrition of man must be changed. I know that this movement has been a popular one and that it has many enthusiastic followers not only in this country but in Europe as well. And I believe that physiological phenomena as well as sensations lie at the bottom of it. A man doing hard muscular work needs enough food to furnish 4000 calories. Such muscular work has been performed in past times by men occupied in agricultural pursuits or in other manual labor. With the development of civilization, and the improvements in manufacturing processes, machinery has replaced the human muscle to a large extent, and the workman of to-day makes much less demand on his own muscles than was the case with his ancestors. This means, of course, that the fuel value requirements of his food have been lessened correspondingly. The food of former times, both in this country and in Europe, consisted mainly of bread, potatoes, corn, and other vegetables. Such a diet was used by peasants for centuries. The proteid content is small in this vegetable diet, but the content of carbohydrate is large and the fuel value high. It is too high, in fact, for present-day needs, unless hard muscular work is done. The vegetable food has been cut

down therefore to a small amount and instead of bread, corn, and potatoes, the chief articles of diet are derived from the animal kingdom and consist largely of meat and dairy products. I give here two tables which demonstrate the differences.

100 Gm. Bread	320 calories
100 Gm. Corn	316 calories
100 Gm. Rice	336 calories
100 Gm. Meat	118 calories
100 Gm. Milk	65 calories

In the second table are given the fuel values for 100 Gm. proteid:

Bread	4700 calories
Potato	5000 calories
Corn	4100 calories
Rice	5600 calories
Meat	500 calories
Milk	2070 calories

We see that there has occurred a natural evolution in diet, that bread and vegetables have been supplanted by meat. This evolution has been most rapid and noticeable in those individuals who do the least muscular work, that is, professional people and merchants.

But this evolution may be a dangerous one. Bread, corn, and rice yield cellulose, meat and dairy products do not. These latter are dissolved to a large extent in the stomach, and reach the intestine as liquids. Bread and corn, on the other hand, pass into the intestine as a thick pulp, or paste, which contains a considerable amount of unchanged food. Bayliss and Starling, Cannon and Magnus have shown that liquids pass along the intestine by rhythmic intestinal segmentations and do not set up peristaltic waves. Solid matter only acts as a stimulus for peristaltic reflexes, and hence in the absence of solids no peristalsis occurs. The application of this is that on an animal diet, rich in meat and dairy products, poor in vege-

tables and therefore poor in cellulose, but little intestinal peristalsis is brought about. It is on this account that a diet containing much proteid and small amounts of vegetables leads to constipation, the harmful influence of which on health and disposition is so well recognized. It is not of course the meat itself which causes the constipation. The underlying cause is the same which is responsible for the occurrence of meat in the diet. Vegetarians and advocates of a meat-free diet fail to appreciate the true connection between constipation and diet, but they experience and see that others experience digestive disturbances if but little muscular work is done and the present-day diet employed. And they are aware that in former times, when hard work and a vegetable diet were the rule, such digestive disturbances were absent. Instead of realizing that it is the lack of muscular work which is responsible they ascribe the trouble to meat, and accordingly recommend its withdrawal from the diet.

Those who do little muscular work and eat little meat cannot live exclusively on bread, corn, or potatoes, because to obtain the required amount of proteid the number of calories in the food is far too great. Twenty-two hundred calories, suitable for a man not doing muscular work, can be obtained from a diet of bread, potatoes, and rice which contains only 43 Gm. of proteid. Such a daily proteid standard is even lower than that advocated by the most enthusiastic followers of vegetarianism. So, to obtain the necessary quantity of proteid, vegetarians must eat food-stuffs which are poorer in available carbohydrates, such as fruits, spinach, etc. These food-stuffs are rich in cellulose and contain therefore the remedy against digestive disturbances. It is not necessary to do without meat, since the same results may be obtained by combining it with fruits, etc. As a proof of the correctness of their idea, vegetarians and advocates of a lower proteid diet point to those athletes, students training for foot-ball or rowing, who perform hard muscular work on a diet containing no meat without losing in any way their strength or endurance. This is a mistake; for a person doing severe muscular work requires 4000–

5000 calories or more, and hence he can do without meat and yet obtain the required amount of proteids. But it is quite different in the case of those who lead a sedentary life and have neither time nor inclination for athletics. Such persons experience digestive disturbances with their ordinary diet and these unpleasant sensations form the root of the ideas of vegetarianism and a low proteid diet.

In the case of meat we have a further example of the connection between our unconscious feeling and scientific ideals and scientific error. Most individuals like the taste of meat and prefer it on that account to bread and vegetables. The taste of meat is due to the extractive substances, the meat extract. These substances provoke through their taste a psychic secretion of gastric juice, and Pawlow has shown that even without the taste the meat extract stimulates gastric secretion through a hormone formed in the mucous membrane of the pyloric end of the stomach. Meat extract then produces gastric secretion in both of these ways and hence facilitates digestion even in those without appetite.

We know to-day that the reaction of tissue, blood, and lymph is almost strictly neutral and that the human body is provided with a number of means to maintain this neutral reaction which seems to be necessary for the normal function of most enzymes. During metabolism acids are formed in considerable amount; bases to a small extent. In muscular work which passes beyond physiological limits and demands greater supply of oxygen than is furnished, there is formed lactic acid and it seems, according to Zuntz, that the resulting fatigue is due to the formation of organic acids. Fatigue upsets the equilibrium of the reaction of the blood and tissues toward the acid side and every process, therefore, which tends to lessen acidity must be helpful in removing fatigue. In the stomach hydrochloric acid is formed from the neutral blood from which it withdraws acid ions, and this process tends to move the equilibrium toward the alkaline side. For this reason gastric secretion may be preventative of fatigue or the feeling of fatigue. Those substances which incite gastric secretion must also lessen or remove

fatigue, and I believe that this assumption is what led Liebig to the idea that meat extract gives more strength and vigor to the body. Now we know that the fuel value of meat extract is very small, but yet we recommend it because it improves digestion, even though the appetite is lacking, and lessens the feeling of fatigue.

Another instance in which our sensations have probably given rise to scientific error and in which I have had some experience is the increase in the number of red blood-corpuscles at high altitudes. It was first pointed out by French physiologists in 1883 and later thoroughly investigated by Miescher that at an altitude of 6000 feet the number of red blood-cells per cm. is 8,000,000, as compared with 5,000,000 at sea level. Such an increase suggests at once, as a probable explanation, an increase in the concentration of the blood, and this increased concentration does occur at an altitude of 5000 feet or more. Abderhalden, studying rabbits and rats, has observed that the concentration of the blood is greater at St. Moritz, 6000 feet in altitude, than in Basel, 700 feet, but that the absolute number of red blood-corpuscles and amount of hæmoglobin are not at all changed.

As a result of work which I did last summer in the Monte Rosa laboratory I am able to give some explanation for this increased concentration and for the marked differences in the results obtained by different investigators. In high altitudes the air is dry and cold and the output of water through the surface of the lungs, which is a merely physical process, must be a great one. In addition, the water will be vaporized more easily and more quickly because the barometric pressure is lower than at sea level.

The loss of water by respiration at high altitudes is much greater than at sea level. We observed last summer at Heidelberg, which is practically at sea level, that a man loses 200–300 c.c. of water during a night's sleep, provided no loss occurs by perspiration through the skin. At 10,000 feet altitude he loses from 500 to 700 c.c. during the night; at 15,000 feet perhaps more, but other factors enter here. This loss of water

increases the concentration of the blood and the number of red blood-cells rises. But this holds true only for small animals, such as the rabbit, guinea-pig, and hen. In these animals, according to mathematical calculation, the body surface compared to body weight is relatively great, greater than is the case in animals of large size, such as man or the horse. If the body produces heat by food combustion and muscular work the smaller animal can easily rid itself of this heat by means of its large surface; the large animal finds difficulty in giving off the excess of heat and it has therefore special arrangements for bringing about heat output. It vaporizes water and becomes cold through the coldness of vaporization. Dogs perspire by means of the lungs and the surface of the mouth and tongue; men and horses through the skin. The human body is adapted therefore for the loss of water. If the body, and that means the blood surrounding the sweat-glands, loses water, this water is replaced by that coming from water-reservoirs in the muscle, probably in the connective tissue of the muscle. In the rat and rabbit such water-reservoirs are absent or not developed, and so the loss of water produces concentration of the blood. In man, most of the loss of water is compensated and the concentration of the blood either does not rise, or it rises in small amount or the concentration may vary at short intervals.

I ask now why these processes relatively so simple lay for such a long time in darkness. I think the reason is that most investigators have studied only the relations of gaseous exchange in the lungs and in the body, and the oxygen supply, and have tried to show that the oxygen was deficient in both air and body. They did so because they knew that in high altitudes the respiration was difficult, that dyspnœa occurred, but most of this dyspnœa was produced by fatigue, by the hard work of climbing, unusual for physiologists coming directly from the laboratory. In an altitude of 15,000 feet it seems that the oxygen supply is not efficient, or at least not for all men, and the study of oxygen consumption is justified, but at 6000 feet and even at 10,000 feet no evidence is brought forward of the lack of oxygen, or the lack of carbonic acid, assumed by

Mosso, and it is at these heights that the increase in red blood-corpuscles has been most studied and is most evident. That most physiologists have tried to find a greater metabolism at these altitudes and have tried to connect it with the increase in blood-corpuscles and with the concentration of blood, can be explained easily by the sensation of difficult respiration. Their sensations have led them along a false way and have prevented them from pointing out the true reasons of the concentration.

I think that we can find many more cases of the association between our sensations, especially if vague, unusual sensations and scientific deductions, but I will cite only two examples, the one having to do with the spinal cord and the central nervous system, namely, the association between reflexes and voluntary movements. In the lower animals von Uexküll has established the fundamental law that a stimulus, if it finds open anatomical paths, always goes to the stretched and relaxed muscles and cannot reach the shortened muscles. This law applies to animals of all classes, but it can be demonstrated best in the arms of the starfish. The starfish has five arms around its central body. The arms are composed of many segments, held together by joints and muscles. If I cut four arms and fix the central body and then stimulate the central body at different places, the arm always moves toward the stimulus. But I can change the position of the arm so that the muscles of the arm are shortened on the one side and stretched on the other side. Then I may stimulate here or there and the arm moves always toward this direction, upward. If I change again the position of the arm, the muscles are stretched here and shortened on the other side, and now the arm moves again in the upward direction for the opposite side of the muscles is now shortened.

According to von Uexküll the rhythmical movements of many or most of the lower animals are governed by this law. Then you see that by this law the movement in one direction is a reason itself for the movement toward the opposite direction, etc. The starfish moves by the swinging movements of its arms.

The law holds good also for the rhythmical movements of the heart. In the systole the muscles of the heart or the nervous system governing the muscles of the heart cannot be reached by any stimulus; this is called the refractory phase. Then the unstimulated heart relaxes, the muscles are no longer contracted, the heart is in diastole and now its nervous system is open to stimuli and a new cycle of the heart-beat can begin. By von Uexküll's law the continuous stimulus is changed into a rhythmical movement.

The law holds good also for the centre of respiration where the continuous stimulus of venous blood is changed into the rhythmical movements of the respiratory muscles. In the moment of inspiration only the expiratory muscles are susceptible to stimulation and in the moment of expiration only the inspiratory muscles can be affected by the stimulus coming from the main centre in the medulla.

A very important question to be decided concerning our knowledge of the spinal cord in its association with muscles was whether von Uexküll's law applies also to the innervation of the voluntary muscles of the body, of the head, arm, and leg. The answer to this question, involving the whole innervation of voluntary muscles, was in doubt for a long time, for the reason that all men, including physiologists, were led by the feeling that we can voluntarily completely innervate our muscles. As a student at Leipzig, I heard Ludwig deliver his lectures on Physiology. He taught that we must distinguish sharply between the muscles which produce respiratory movements or swallowing and those which move our arms, legs, or tongue. The first he held was a reflex, the second a voluntary movement, in which we can innervate any muscle according to our will. There can be no doubt of the correctness of the first point. If the sensory area in the root of the tongue is touched, the swallowing reflex begins, and we can neither stop it nor voluntarily induce any movement in the muscles of the pharynx or the striped muscles of the œsophagus. The second point that we can at will innervate any muscle whatsoever is in accordance with the general opinion, because it is based on the feeling that

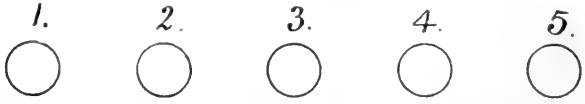
we have complete control of our arms and legs. This feeling is, at the bottom, the consciousness of ourselves. But is it warranted, or are we again deceived by our sensations?

The seat of consciousness, and therefore the seat of innervation, which provokes voluntary movements, is the brain. The movements of higher animals, especially the dog and cat, in which the brain has been removed, or the spinal cord cut, have been studied recently by Sherrington. He found that dogs whose brains had been removed still move the muscles of the legs in the same manner as those which can send impressions from the brain to the spinal cord. If a motor nerve be stimulated the muscle responds with a contraction which varies according to the strength and duration of the stimulation. But if a sensory nerve, or a sensory nerve end, for instance a sensory organ in the skin, be stimulated, there does not occur a simple contraction of a single muscle, but a reflex complex movement which includes a lessened tension of some muscles and an increased tension of others and a shortening or true contraction of others.

By varying the stimuli and by changing the place or strength of stimulation, other different reflexes can be produced, different in the involvement of associated muscles, in the strength and duration of movement. But first we do not find a close relationship between stimuli and effects, and secondly we do not obtain an indefinite number of movements, but only a limited number of co-ordinated reflexes. If, for instance, the skin on one side of the abdomen of a dog is touched, the leg moves in such a manner that all three joints are flexed, and a series of short rhythmic movements begins (the scratch reflex). If we touch the skin of a foot, either the whole leg will be extended in all its joints, or the hip is flexed and the knee and ankle are extended (stepping or jumping reflex). Thus the stimulation of a single sensory nerve provokes excitation in a great number of muscles, and touching the skin of the foot can bring about a complete step involving work of all the muscles of both legs. I will give you a scheme of the innervation of the reflexes in the spinal cord. The motor nerves arise

from the gray columns, and every muscle can be either shortened or stretched or relaxed. I represent here the centres of five muscles in the gray column of the cord. There are many possible combinations of movements of these muscles; 1 and 2 are shortened, 3 relaxed, and 4 and 5 stretched; or 1 and 5 are shortened, 2 and 3 relaxed, 4 stretched. So we may have many more such combinations and stimulation of each sensory nerve or end organ may produce one of them.

These combinations occur in the brainless dog. But Sherrington has found that the same combinations which are

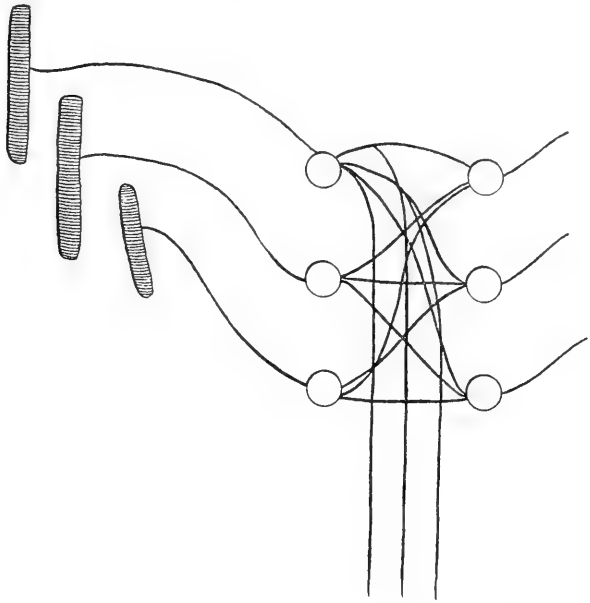


brought about in the spinal-cord dog by stimulation of sensory nerves, occur on stimulating the motor areas of the cortex of an intact animal, and that these combinations are exactly those made by voluntary movements of the dog. It is not possible, by brain stimulation or volition, to bring about a simple contraction of a muscle, there is always set up a reflex, in which some muscles are contracted, while others, antagonistic ones, are relaxed.

If we represent schematically the processes in the spinal cord and their connections with the brain we see that every movement controlled by the spinal cord is a reflex, comparable to the involuntary reflexes and that the impulses coming from the brain determine only what kind of a reflex is set up. Thus by means of the brain there occurs association throughout the whole body, and the stepping reflex described can arise or be checked through the eye or the ear, and so forth.

The brain acts as an engineer controlling his machine, the machine follows its laws of construction in its power and its structure, and the engineer can merely run it or stop it. The brain, however, has no selective power with regard to the reflexes; it follows von Uexküll's law, which governs also movements supposedly voluntary. It can be seen in some of the

Sherrington experiments that the stimulus passes to the stretched muscles, and further conclusive evidence of this is brought forward in Magnus's recent publications. If the flexor muscles of a leg are shortened, and the extensor muscles relaxed, then a stimulus wherever applied affects the extensor muscle and relaxes the flexor muscle. In such manner are the impulses



coming from the brain converted into the rhythmic stepping movements of the leg.

We must draw the conclusion from Sherrington's observations that we have been deceived by the illusion of the free voluntary movement and the innervation of our muscles. This illusion has been, I think, a fatal one for the physiology of nerve and muscle. Muscle, motor nerve, and the governing centre in the spinal cord form a functional unity. So long as they are united, so long can the muscle be either shortened or relaxed or stretched, and it follows from von Uexküll's law that

not only is the muscle governed by the nerve, but the nerve centre by the muscle, since the stretching of a muscle opens a path for stimuli to its centre and the shortening of a muscle closes the path for the same stimuli. If we separate the muscle from its centre we mutilate the muscle. In the last half century much work has been devoted to investigations of the frog's muscle, connected with its nerve, but separated from the spinal cord. Such muscles are in a condition never occurring in life. The close connection between muscle and centre has been neglected for the reason that the muscle is controlled directly by the brain and that the innervation is in the motor nerve carrying impulses only in one direction, toward the muscle. If a stimulus coming from the brain produces a simple contraction, then the natural impulse could be replaced by an electrical stimulus. This is not true. We realize to-day that all this work has been performed on abnormal muscles.

I feel, gentlemen, that many of the instances cited to you have been of a hypothetical character. It is certain, however, that we have illusions, and it is certain that physiologists travel often along false ways. That the illusions have been the reason for errors and misstatement may not have been proven. But if we realize the power of vague sensations we must believe that the cited association is a probable one. The physiology of the central nervous system and of the organs of sense is filled with examples of the close connection between the management of our sensations and our scientific deductions. And especially is this true of the physiology of the brain. It is the merit of Kant, a merit we must be grateful to for all time, to have pointed out how we are bound by the limitations of our sensations. In studying the physiology of the brain we must investigate the only tools with which we can make our investigations. I have attempted to explain to you by examples from different chapters in physiology that we may be independent of our sensations in any field of physiology. We must have sensations and we must follow them, but we must also be very cautious that they do not lead us in our scientific deductions along a false path.

RENAL ACTIVITY *

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IF asked to define the function of the kidney, I think the most usual answer given would be that the kidney eliminates from the body the excess of water and water-soluble waste products. I would, however, ask you to regard the renal function from a rather different stand-point, and to consider the kidney as that organ whose duty it is to maintain the constitution of the blood at a definite normal standard so far as its soluble constituents of small molecular size are concerned. Thus, in mammals it is the duty of the kidney to remove as far as possible all sulphates, urea, purin bodies, etc., from the blood. On the other hand, when dealing with such bodies as the chlorides the kidney must only remove them when an excess is present, and must thus maintain the chlorine content of the blood at a definite standard level. The kidney, then, deals with a water-soluble substance in the blood in one of three ways: either (a) it does not remove it at all,—*e.g.*, proteins and possibly dextrose,—or (b) it eliminates it completely (urea, sulphates, etc.), or (c) it eliminates it down to a fixed point only (chlorides, etc.). It is most interesting to note that in some animals even urea falls within the third category, for in the shark the blood normally contains as much as 2 per cent. of urea and only when it exceeds that limit is urea excreted. Further, we must not forget, in this connection, to pay attention to the basic constituents of the blood,—Na, K, Ca, and Mg. They too fall within this third category.

The more we regard the renal activity from this aspect the more are we impressed with the wonderful mechanism we are

* Delivered Dec. 11, 1909.

studying. With its accuracy, for over conditions which vary very widely the kidney maintains the blood constitution within quite narrow limits; or with its sensitiveness, as illustrated in the excretion of water. If water is being absorbed from the intestine, the kidney at once begins to secrete vigorously, although by chemical analysis we may not be able to detect any excess of water in the blood. Or, again, this sensitiveness to minute differences in the constitution of the blood stands out in a yet more wonderful manner if we watch the varying sodium and potassium excretions.

Anatomically, we may group the successive portions of the renal tubule in four divisions: (1) a capsule enclosing a glomerulus; (2) a pair of convoluted tubules, proximal and distal; (3) a loop of Henle, with its descending and ascending limbs interposed between the two convoluted tubules; and (4) various collecting tubules. We may group the parts in this way because of the distinctive structural peculiarities each presents. Thus, the convoluted tubules are lined by an epithelium strongly resembling in structure the secretory epithelium of many glands. The glomerulus within its capsule and the loop of Henle are structures the like of which are not paralleled in any other part of the body.

As soon as the main structural features of the kidney were discovered, speculations as to their mode of action were advanced. We may certainly conclude that we are here dealing with three different types of activity, the first performed in the glomerulus, the second in the convoluted tubules, and the third in the loop of Henle. Our problem then is, what are these three different activities? You are all thoroughly familiar with the two great theories of renal activity propounded in 1843–4 as the immediate result of a definite knowledge of the chief details of the renal structure,—viz., the Bowman-Heidenhain theory and the Ludwig theory. These are still the two theories universally discussed in considering the renal function, though in a form modified from that in which they were originally set forth.

The Bowman-Heidenhain theory considers the whole tubule

as secretory in function, assigning to the glomerulus the secretion of water and possibly of some salt, and to the tubule the secretion of urea, salts, and other solids found in the urine. The Ludwig theory has for its central idea the suggestion that the glomerulus is a filter through which water and solids are removed from the blood, the filtrate containing these substances in the same concentration as that in which they are present in the blood. As this concentration is very different from that of the fluid, the urine, ultimately discharged from the kidney, this theory necessitates yet another supposition,—viz., that the tubule as a whole or some portion of it reabsorbs. Such reabsorption is chiefly of the water, but is also of the salts as the need arises. Lastly, it may be that a combination of these two theories may give the correct solution to our problem. Thus, the glomerulus may be a filter, the convoluted tubules secretory structures, and the loop of Henle a tube for absorption. This view has one great advantage,—it assigns reasonable functions to the three distinctive structures found in the kidney.

In these theories there is one conjecture which stands apart from all the rest, because it claims to explain the action of one structure of the tubule from known mechanico-physical data. I mean, of course, the view that the glomerulus is a filter. If this were established beyond all cavil, we should have gained one big step forward in the elucidation of renal activity. During recent years a very great deal of evidence has been gradually collected tending to throw the gravest doubt upon this view, and to-night I wish to discuss all the evidence for and against this theory of the way in which the glomerulus works, for the theory has dominated all discussions upon the activity of the kidney as a whole. I propose, then, in the first place, to bring before you the evidence in favor of the view that the glomerulus is a filter; secondly, to criticise that evidence and bring forward further observations to prove the theory incorrect. In the last place, I will lay before you a new view explaining the peculiar structure of the glomerulus, for the glomerulus is in very many ways admirably constructed to act as a filter, and unless we have an explanation capable

of supplanting that idea we may be sure men's minds will tend to fall back upon that theory as offering a very plausible explanation of this curious structure.

THE GLOMERULUS AS A FILTER

The chief evidence employed in supporting the filtration theory may be considered under the following headings:

1. Evidence derived from the structure of the glomerulus. The points we may especially emphasize in this connection are, first, the very thin walls of the glomerular tufts, consisting only of a thin endothelial cell forming the capillary wall and an equally thin epithelial cell covering the loop. The thinner the membrane the more readily can filtration be effected through it. Secondly, the glomerulus is made up of a number of loops, thus greatly increasing the surface, and, of course, rate of filtration through a surface varies directly with the extent of that surface. In the third place, the blood-pressure within the glomerular loops must be high in comparison with the blood-pressure usually found in capillaries. This follows from a consideration of the short length of the arterioles leading to the glomeruli and their relatively large diameter; also, from the fact that when the kidney is actively secreting the blood-flow through it is often found extremely high. Thus, Barcroft and Brodie [1] recorded rates as high as 2.0 to 2.7 c.c. of blood per gramme of kidney substance per min. Burton-Opitz and Lucas [2] record rates of 1.5 c.c. per gramme per min. In some experiments as yet unpublished, I have on a few occasions found a flow as great as 6 c.c. per gramme per min. This high rate of flow is further evidenced by the fact, first pointed out by Claude Bernard, that the blood in the renal vein is often arterial in color, a condition which is always to be observed when the kidney is thrown into activity, in spite of the fact that the kidney is then absorbing a very large volume of oxygen, as Barcroft and I have shown. Yet another anatomical arrangement leading to a high intraglomerular blood-pressure is that the efferent glomerular vessel is of smaller diameter than the afferent, and when we consider all these points we may

well conclude that the glomerulus might form a most efficient filter.

2. Let us next consider the hæmodynamics of the glomerulus. Let us call the intraglomerular blood-pressure Pg, and the pressure of the fluid within the capsule, *i.e.*, the capsular pressure, Pc. Then, if the glomerulus is a filter, rate of filtration will vary with—

(a) The magnitude of the pressure difference, Pg — Pc.

(b) The viscosity of the fluid to be filtered.

(c) The rate of renewal of the fluid at the membrane.

(d) The physical constitution of the membrane. Let us consider each of these points one by one.

Taking first the variations in the pressure difference Pg — Pc,—*i.e.*, in the available filtration pressure head,—filtration should increase with a rise in the pressure Pg or a fall in the pressure Pc, and conversely. We ought then to obtain corresponding changes in the urine flow when we vary either of these two pressures. Taking first the variations in Pg, we have two cases to consider. In the first we may study the effects of changes set up in the aortic blood-pressure without active changes in the renal vessels, and in the second instance we may study the results brought about by constriction or dilatation of the afferent glomerular arteries. In connection with the first-mentioned changes, it has been shown that if the aortic pressure falls below 35–45 mm. Hg the flow of urine ceases completely and that above this value the flow of urine varies directly, broadly speaking, with the height of the aortic pressure. Thus, Goll [3] proved that when the aortic pressure fell in consequence of cardiac inhibition induced by stimulating the peripheral end of the divided vagus, the urine flow ceased, and that if the aortic pressure was made to rise by ligature of a number of large arteries, the urine flow increased. Further, Goll proved that the fall of pressure caused by bleeding led to a decrease in urine flow, which returned, however, when the blood was reinjected into the animal. Again, Eckhard,[4] Ustimowitsch,[5] and Grützner [6] confirmed and extended Bernard's observation that the fall of blood-pressure caused by

division of the spinal cord in the cervical region was followed by a cessation of the flow of urine. All these results are in the direction required by the filtration theory.

Let us next turn our attention to changes in the glomerular pressure, Pg, caused by changes taking place in the renal vessels themselves. Max Herrmann [7] proved that if the renal artery was clamped sufficiently to diminish the outflow of blood from the vein, a diminution in the flow of urine at once occurred. In the second place, it is proved that division of the renal nerves leads to a vasodilatation of the renal vessels and therefore to a rise of the intraglomerular pressure. With it there is, as a rule, a rise in the rate of urine flow. Excitation of these nerves or of the splanchnics causes constriction of the vessels and with it a decrease or cessation of urine flow.[8] Excitation of the spinal cord or of the medulla produces the same result, and here too the renal vasoconstriction is more than sufficient to counterbalance the big rise in aortic pressure caused by the excitation.[9] If the renal nerves be divided on the one side previously to the excitation, thus preventing the constriction of the kidney vessels on that side, the rise in blood-pressure can now act upon that kidney and there is a marked increase in urine flow, while that on the other side ceases as before.

But the most extensive study of the vascular changes taking place during activity of the kidney has been carried out by the application of the oncometric method,—*i.e.*, by following the volume changes in the organ. The deduction is that an increase in the volume of the organ means an increase in the blood-flow through it, a dilatation of the glomerular vessels, and therefore a rise in the glomerular pressure Pg. Without entering into these experiments in any detail, it has been shown that there is a general correspondence of increased kidney volume accompanying increased secretory activity. This result, stated on broad lines, has been further confirmed by accurate measurements of the actual blood-flow through the organ effected by one or other of the several methods we now possess for that purpose.

There remains yet one other factor which may result in an increase of capillary pressure and which has been suggested as a cause favoring filtration,—viz., plethora.[10] Experiments have been performed in which this condition was set up by the injection of blood, of serum, or of saline solutions. They do not, however, give any certain support to the theory, and we need not discuss them further here.

Let us next turn attention to the second factor we have to take into account when considering the possible pressure head which may exist for effecting filtration through the glomerulus. This is the intracapsular pressure, Pc. The chief test of the filtration theory that has been attempted by taking this into account consists of experiments in which the ureter pressure was artificially raised. By such experiments it was first proved that the kidney cells do not possess the power of setting up a secretory pressure head analogous to that observed in the case of the salivary gland. It was shown that the maximum height to which the kidney could force the urine during secretion was one equivalent to a pressure about 40 mm. Hg less than the blood-pressure. Also, that if the ureter pressure be raised in the first instance to such a height, the flow of urine ceases completely.[11] Here again, then, the general result is in the direction required by the filtration theory. Starling suggested that this minimum pressure difference between the aortic and ureter pressures was exactly the difference required by the osmotic theory of solutions to effect the separation of the proteins from the remaining constituents of the blood plasma.

The next character we have to mention is the vicosity of the fluid to be filtered, since the less viscous a fluid is the more readily will it filter. It is known that the injection of a salt solution, for instance, results in a very definite dilution of the blood,—*i.e.*, the blood becomes hydræmic, and concomitantly there is a free flow of urine. Hence the suggestion has been made that the hydræmia was one of the causes in operation producing the diuresis.

In the next place, it is obvious that the rate of renewal of

the blood at the filtering membrane will also have a direct influence upon the rate of filtration, and, as we have seen, a diuresis is usually accompanied by an increased flow of blood. In this connection the experiments in which the renal vein is partially or completely occluded are of direct bearing. The result is a diminution of urine flow more or less in proportion to the blocking of the venous outflow.[12] Ludwig explained this as meaning that the venous obstruction mechanically compressed the tubules and therefore restricted the outflow and impeded filtration. Heidenhain, however, referred it to the restricted flow through the glomerular and other capillaries which led to a proportional decrease in urine secretion.

CRITICISM OF THE FILTRATION THEORY

From the above considerations we see there undoubtedly exists a general relationship between urine flow and the various factors which would favor filtration at the glomerular surface. But before we can accept the theory we must subject it to a far stricter examination than that we have just applied. It is essential to show that urine flow strictly follows changes in the different factors which would favor or disfavor filtration. As soon as we put the view thus strictly to the test, it fails us in all directions.

Let us take the several points seriatim and first consider variations in the glomerular blood-pressure. According to the theory, with every rise in this pressure there should result an increased flow of urine, but it has been abundantly proved that this is not the case. I have frequently observed a high blood-pressure with a free flow of blood through the kidney, thus showing that the renal vessels were not constricted, and yet there was no flow of urine. In some of these experiments I have further found a free flow of urine to follow the injection of a diuretic without any further rise in blood-pressure and without any increase in the blood-flow. Filtration cannot possibly explain such results as these. Further evidence is also available from oncometric experiments. While there is a general correlation of increase in kidney volume and increase in

urine flow, there is no strict parallelism. The height of diuresis practically never coincides with the maximum dilatation of the kidney.[13] This result I can abundantly confirm from my own experiments. I must point out too that the oncometric method is not a thoroughly safe one for deciding upon vascular changes within the kidney. Thus, I have upon five occasions observed the following effects to follow the injection of a diuretic,—viz., a free flow of urine, an increase in the volume of the kidney, but a decrease in the blood-flow through the kidney. An increase in volume of the kidney must not be taken necessarily to indicate a dilatation of the renal vessels and an increased blood-supply. For it may also mean an accumulation of urine within the tubules, a fact abundantly proved by microscopic examination of kidneys excised at the height of a diuresis. Hence the value of a plethysmogram of the kidney as an indicator of the vascular changes is seriously discounted, especially so since many experimenters remove the capsule of the kidney before placing it in the plethysmograph, a procedure which only complicates matters and makes such experiments of a purely abnormal type. Unfortunately, experimenters do not, as a rule, state whether or no it is their usual practice to remove the capsule. In any case oncometric experiments distinctly disfavor the filtration theory, and the same result is arrived at when we turn to experiments in which the actual blood-flow through the organ is measured. It is true that the majority of such experiments show that diuresis is usually accompanied by an increased blood-flow.[14] But there is no strict parallelism. The blood-flow has usually fallen long before the diuresis ceases, and also the maximum blood-flow always occurs before the maximum diuresis. Moreover, I have frequently seen a marked diuresis start without any change whatever in the blood-flow and on some occasions even with a decrease in the blood-flow.

Let us return now to those experiments in which the response of the kidney to an increased ureter pressure was studied. These have been chiefly used in testing the other assumption which necessarily follows from accepting the filtration theory,—viz.,

the presence of a very active absorbing surface at some part of the tubule. This reabsorption should be markedly favored by a high ureter pressure, and, as pointed out by Heidenhain, the maximum ureter pressure according to this theory simply indicates that pressure at which reabsorption is taking place as rapidly as filtration. Now, it is true that a high ureter pressure does restrict the flow of urine;[15] but this is not the whole statement of the facts, for several observers have seen an increased flow of urine resulting from a partial obstruction to the outflow along one ureter. The discrepancy has been definitely settled by Miss Cullis and myself,[16] for we were able to show that if the experiment were performed upon a pithed animal, so that the kidneys were in no way damaged by an anæsthetic, then the kidney which was made to work against a small ureter pressure invariably secreted more than the control kidney. In every instance it secreted at some stage or other more of the diuretic injected and in most instances it also excreted a greater volume of urine. If the pressure was raised considerably higher, then that kidney excreted less of both water and diuretic substance. The essential point then is that with a moderate pressure stimulus the kidney can be excited to work more actively, a result which can in no way be explained upon the filtration-reabsorption theory. It has been objected that the small rise in ureter pressure might reflexly lead to an increased vasodilatation, a conjecture which had no great likelihood and which I have been able to show is incorrect.

If, in the next place, we examine the experiments in which the hydræmia caused by the injection of the diuretic is followed closely, again we find there is no true parallelism. Once more it is found that the hydræmia disappears before the diuresis ceases, and that the maximum hydræmia is not coincident with the maximum diuresis.[17] Moreover, diuresis may still persist even though, as a result of the diuresis, the blood has become more concentrated than at the commencement of the experiment.

Let us, in the last instance, turn our attention to the last point we have to consider in dealing with this suggested mode

of action of the glomerulus,—viz., the nature of the glomerular membrane. Certainly so far as mere histological appearance goes we see, at first sight, an ideal filtering membrane, for it is excessively thin. If now this membrane does act as a filter, either it must be sufficiently rigid to withstand a pressure of some 90 mm. Hg from its inner side, or it must be constantly pressed against the wall of the capsule, thus gaining support sufficient to prevent its rupture while not being brought so closely into contact with the surface of the capsule as to prevent filtration. But the glomerulus appears to be an elastic structure. Its size varies considerably. At times it is found filling the capsule of Bowman completely, but often it is found partially collapsed and with a considerable collection of fluid lying between it and the capsule wall. This last-mentioned condition is not produced by overdistention of the capsule, the glomerulus remaining rigidly fixed in its first position, but careful examination shows that it is mainly, if not entirely, the glomerulus itself that varies in size. Hence to explain the appearance we should have to imagine that after filtering for a time the glomerulus was made to cease acting by vasoconstriction of the afferent vessel, so allowing the intraglomerular pressure to fall, and then fluid was driven back from the tubule into the capsule and caused the glomerulus to collapse. But we may ask, where is the pressure that could set up this back flow? for the essence of the filtration theory is that the intracapsular pressure should always be low or absent.

Yet greater difficulties confront us when we consider the physical characters that the membrane must possess. Under normal conditions no protein is ever found in the fluid within the capsule. Hence we must conclude that the membrane is one whose pores are so small that the protein molecules of the plasma cannot pass through them. Hence of the total intraglomerular pressure a part must be used up in separating the proteins from the remainder of the plasma, and only the residual part is available for filtration purposes. We can find how great a pressure is needed to separate the proteins from the plasma by determining the osmotic pressure of the proteins.

This has been estimated at about 40 mm. Hg,[18] but it is probably much lower than this. It will be remembered that the suggestion was made (Starling) that the maximum ureter pressure and the pressure required to separate the proteins from the plasma together balanced the intraglomerular pressure. The figures taken were from 80 to 90 mm. Hg for the maximum ureter pressure, 35 to 40 for the osmotic pressure of the proteins, and about 120 for the intraglomerular pressure. But, in the first instance, this fails to take into account Heidenhain's contention,—viz., that according to the theory the maximum ureter pressure is that at which reabsorption balances filtration; secondly, it estimates the osmotic pressure of the proteins too highly; and, thirdly, it makes no allowance for a fall of pressure head of the blood from the aorta to the glomerulus. Although undoubtedly not so great as in the case of other capillaries, still there is evidence, as I shall show, that it amounts to as much as 40 mm. Hg.

While it is certain that the proteins do not pass through the glomerular wall, it is also certain that any filtrate which could be produced there by the blood-pressure alone must contain all the constituents of the plasma of small molecular size in practically the same concentration as in the plasma, for to effect any concentration or dilution of these salts, etc., would, as measurements of their osmotic pressures teach us, require very high pressures, pressures out of all proportion to the available blood-pressure head in the glomerulus. It is not possible to obtain a sample of the fluid leaving the glomerulus, but we can obtain a fluid which resembles it very closely. It is certain that practically the whole of the water secreted by the kidney comes from the glomerulus. Hence, if we collect the urine in cases in which excessive diuresis is established, we have a very close approximation to the glomerular fluid, for a minimum amount of time has now been allowed for secretion or absorption of solids by the tubule cells. If we examine the urine in such cases, we find that often it may be almost pure water.[19] Such a fluid could not possibly have been filtered from the blood at the glomerulus, and the supposi-

tion that reabsorption has effected this great dilution is excessively improbable. The time allowed for reabsorption is far too short.

Let us take one more type of observations bearing upon this point. During diuresis brought on by injecting such substances as sodium sulphate, the urine has frequently been observed to be very poor in chlorides. On many occasions I have collected urines in such experiments entirely free from chlorides. To effect this separation of the chlorides is quite impossible by filtration at the glomerulus; so again those accepting the theory are compelled to assume an extremely rapid reabsorption of water sufficient to give the necessary concentration of the diuretic and of sodium chloride up to the last particle. Again the magnitude of the absorptions here needed to explain the result is excessive in the extreme. Such considerations as these then provide very cogent arguments against the filtration theory.

Let us take one further set of observations and we may then leave this question of filtration. The kidney in amphibians is supplied with two sets of blood-vessels,—one set, the arteries, carrying blood at high pressure directly from the aorta, the other carrying venous blood from the legs, a blood supply at a low pressure. Now, it has been proved (Nussbaum and others) that the glomeruli all receive blood at high pressure from the arteries, and further that none of them ever receive a blood supply from the renal portal vein,—*i.e.*, are never placed on the low-pressure circulation through the kidney. Utilizing these facts, Miss Cullis [20] studied the results following perfusion of the frog's kidney with saline solution, driving the solution either through the arteries alone, through the portal vein alone, or through both simultaneously. Of the results I only wish to refer to one in this connection. It was first shown that here once more the water of the urine comes from the glomerulus practically entirely. It was found that by sending saline through the glomeruli a good flow of fluid was obtained along the ureters, and chemical evidence was found to prove that this was a true secretion, not a mere

leakage of fluid or effusion from the blood-vessels through damaged epithelial cells. In one group of these experiments, after the establishment of a flow of urine the perfusing saline was changed to one very poor in oxygen. Gradually the urine flow ceased. If the flow were merely a filtrate we should never expect such a result as this; rather, on the other hand, should we expect to find that a membrane damaged by asphyxiation would allow fluid to pass through it more readily. The cessation of urine flow was not due to vasoconstriction, since the rate of flow of the saline was just as rapid with the oxygen-free saline as with the original. Further positive evidence was also gained by watching what happened when the perfusing fluid was changed back again to the well-oxygenated saline. There was a long latent period, often amounting to many minutes, and then the urine flow began to return and returned gradually, exactly the result we should expect from a secreting surface recovering from asphyxiation, but certainly not one to be expected from a passive filtering membrane.

I have not attempted to deal with all these points in any detail this evening; but, taking all these pieces of evidence collectively, I think you will agree with me when I say that I have no hesitation whatever in stating that the filtration theory of urine secretion must be entirely abandoned.

THE GLOMERULUS IS A "PROPULSOR"

I now wish to bring before you the view I offer in explanation of the highly characteristic structure which the glomerulus presents to us. Ever and always men's minds tended to veer round again to the idea that a body exhibiting the structure of the glomerulus must be a filter. This idea has up to the present dominated all discussions upon renal activity. The glomerulus cannot be merely a water-secreting surface, for that would offer no explanation of its curious structure. Thus, I set myself the problem: If the glomerulus is not a filter, what is it? Why has it its peculiar form? The explanation I finally hit upon is that the glomerulus is

a mechanism for driving the secreted water down the tubule. I term it a "propulsor."

I consider the glomerulus a true secreting surface, a surface secreting the main bulk of the water of the urine and possibly also some of the saline constituents, the amount of the latter depending upon their excess in the blood. As a secreting surface it is large in extent. Are the capillaries arranged in loops simply to give that large surface or is this arrangement to serve yet another end? My view is that this arrangement of the loops is to utilize the blood-pressure within the loops as a means of setting up a sufficient pressure head to discharge the water secreted at the surface down the tubule. Thus the glomerulus performs two works,—it secretes and it propels. The glomerular epithelium performs work in secreting, deriving the necessary energy from the foodstuffs it takes in, just as is the case with ordinary secretory epithelium. Secondly, the glomerulus as a whole propels, the energy required being derived in this instance from the blood-pressure. In our preliminary discussion we may for simplicity consider these two activities to take place consecutively, though of course they may and probably do occur concurrently. This, however, makes no difference from the theoretical point of view.

Let us imagine, then, that the glomerular epithelium has secreted water into the interior of the capsule. In so doing its surface has been moved back away from the capsule wall. The walls of the glomerular loops are, even when the glomerulus fills up the whole capsule, exerting but a slight if any retracting force. Consequently, in a partly retracted state the blood-pressure within the glomerular loops is communicated directly to the fluid within the capsule in practically undiminished amount. That is, there is set up a pressure head in the fluid within the capsule which pressure head is required to drive the fluid down the tubule.

Let us consider the various data we possess in illustration and confirmation of this view. First, we know that the glomerulus is variable in volume. Thus, Nussbaum, in his observa-

tions upon the living newt's kidney with the circulation intact, states that the glomerulus can be seen to expand and contract and that it pulsates with each heart-beat. He also states that on some occasions it leaves the capsule wall and becomes retracted towards the point of entrance of the vessels. We also get abundant confirmation of this variability in size of the glomerulus from the histological examination of kidneys removed in different conditions of activity. As previously mentioned, it is usual during diuresis to find a considerable accumulation of fluid between the glomerulus and the capsule wall.

Perhaps the most striking evidence of the truth of my view comes from the following consideration. It is proved from many directions that the water of the urine comes mainly from the glomerulus. This fluid then has to be expelled down the whole length of the tubule, and to do this there must be a supply of energy in the form of a pressure head. If we measure the length of the tubule, its average lumen, and the volume of fluid driven along it in a given time, we have the necessary data to determine, by Poiseuille's law, the pressure head which must exist in order that the fluid may be discharged at the rate observed. I therefore performed the following experiment upon a dog. A diuresis was produced by an injection of sodium sulphate. The blood-pressure was 130 mm. Hg. The rate of flow of urine per minute was then determined and the animal at once killed and its kidney fixed. Sections of the kidney were next made and the glomeruli counted. Lastly the lumina of the tubules were measured. Without entering into details, I may state that on making the calculation I found that a pressure head of 83 mm. Hg was required to drive the fluid down the tubules, on the supposition that all the tubules were actively and equally secreting. This of course was in a case in which a free flow of urine was induced. The result accords very well with the forces which are available within the glomerulus, for, allowing a fall in blood-pressure head of some 35 to 40 mm. Hg for driving the blood from the aorta to the glomerular capillaries, there re-

mains a head of 95 to 90 mm. Hg in those capillaries. This pressure head is but little in excess of what is needed according to my approximate calculation.

I would point out in passing that this consideration completely disposes of any possibility of filtration as an effective force in urine secretion. As practically the whole blood-pressure head is required to drive the urine along the tubule, no pressure is left to effect filtration. But the filtration theory requires much more than this. It has to assume that the volume of fluid filtered at the glomerulus is as much as 35 times greater than the volume of urine issuing from the ureter. True, it does not require that this fluid should be driven the whole length of the tubule, but, even making full allowance for this, the pressure head at the capsule would have to be many times higher than the blood-pressure to produce the flow assumed.

The propulsor view of the glomerulus explains a number of facts observed in connection with the kidney. First, it explains the appearance of the tubule after a copious diuresis. Here the tubules are found widely dilated, especially the first convoluted tubules. This dilatation is due to the high pressure of the urine within the tubules in these conditions.

Secondly, it gives a reasonable explanation of the phenomena of maximum ureter pressure. The pressure in the ureter can, of course, only rise as high as the glomerular capillary pressure, since there is no secretory pressure. This is, of course, on the supposition that there is no extensive reabsorption, or that if any reabsorption does take place it is much less in extent than the secretion from the glomerulus. The determinations of the maximum ureter pressure give us, then, a means of estimating the glomerular blood-pressure.

Thirdly, this view explains why the kidney is placed within a capsule, and that the kidney suffers if the capsule be removed. The capsule is to prevent a dangerous over-expansion of the glomeruli and capsules, and it is an every-day experience when working oncometrically with the kidney that the organ can only expand to a very limited degree. When

thrown into activity the organ soon becomes very tense. I have made attempts to measure the pressure within the kidney substance during a diuresis, but hitherto without much success.

In the fourth place, the theory explains the meaning of the experiment to which I referred earlier in my lecture, in which I found an expansion of the kidney accompanying diuresis but with a diminution in the rate of blood-flow. Obviously here the kidney expanded until it filled up the capsule, much of the expansion being due to the urine within the tubules. The pressure of this transmitted through the whole kidney substance acted to some extent upon the capillaries and veins and thus to some degree impeded the circulation.

In conclusion, I would refer to a difficulty which many have expressed when discussing my theory. This is, how are we to picture to ourselves the mechanism of the secretory process at the glomerular surface? These cells cannot set up any appreciable secretory pressure. How, then, are they to discharge fluid into a capsule already containing fluid at, say, 90 mm. Hg pressure? But it must be remembered that the glomerular wall is freely movable and that these cells are pressed upon on either side by the same pressure. There is no difficulty in picturing how these cells could continue their work even though subjected to a pressure from all sides even higher than this. For instance, we know that when a man or animal is inclosed within a caisson and the pressure then raised far above this small pressure of 90 mm. Hg, still the secretory epithelium of the kidney or any other gland can continue to work in a perfectly normal manner. The cells are not in any way damaged, for the pressure is uniformly applied on all sides. This, then, is the case for the glomerular epithelium when exposed to the very moderate pressure of 90 mm. Hg acting upon both surfaces. When those cells secrete a drop of fluid, what happens is that there is a similar diminution in the volume of the blood within the glomerular capillaries—the glomerular epithelium, as it were, moves back towards the blood. There must theoretically be a momentary pressure difference set up between the intracapsular pressure

and the intraglomerular pressure, but it is probably infinitesimal in amount, nor is it necessary to assume that it has any measurable amount. The necessary energy for this purpose is part of the energy expended by the cell in secreting, and in amount is altogether out of comparison with the large expenditure of energy required, for instance, to separate water from blood plasma.

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THE MORPHOLOGY AND STRUCTURE OF THE MAMMALIAN RENAL TUBULE*

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IT is with some diffidence that I address you this evening, in response to a request to speak to you concerning the structure of the kidney, since I am aware that the organizers of this Society were actuated by a feeling "that lectures dealing with what is generally considered the purely experimental side of medicine, given by those who devote their time to experimental work, would not be unwelcomed by the medical profession," words found in the preface to the first volume of "Harvey Lectures." It has seemed to me, however, that we have here, not an expression of a want of appreciation of the value of contributions dealing with results gained by other than the experimental method, namely, morphologic and anatomic studies, but rather an endeavor to give emphasis to the experimental method as an efficient means of analysis of the results obtained through investigations of the morphologist, a method of checking his results and a means of stimulating him to further investigations, since it will ever be his effort to ascertain a structural basis for all functional activities elucidated or merely postulated. It is not necessary here to affirm that the morphologist appreciates fully the experimental method, which has found wide application, especially in the field of embryology. Our knowledge of the structure and the function of a cell, tissue or organ are interdependent, the one elucidates and supplements the other. In conjunction, therefore, with the consideration of certain phases of renal activity, as has been done in two previous lectures of this course, it seemed well to present also a summary of our knowledge of the structure of the kidney. "Mehr als in der Niere hat man wohl bisher in

* Delivered Dec. 18, 1909.

keiner anderen Drüse bestimmte Beziehungen zwischen Bau und Function auffinden zu können geglaubt, and nichts ist natürlicher, als dass wir diese Beziehungen von Neuem prüfen müssen, nachdem unsere Ansichten über den Bau nicht unwesentliche Veränderungen erfahren haben."[1] Our knowledge concerning the structure of the majority of epithelial glands with persistent ducts and producing external secretion is fairly complete. The shape of their secreting compartments has been ascertained by methods of reconstruction and corrosion, and we know much concerning the structure of their secreting cells in the different phases of secretory activity. Their blood and nerve supply is relatively simple, following more or less closely certain definite laws. Their development is also relatively simple, consisting in the main of an epithelial anlage, which in further growth divides repeatedly to form ultimately a duct system with peripherally placed secretory compartments. The kidney forms a distinct exception to the above made general statement. The length and complexity of form and the varied structure of the different parts of the renal tubules have rendered their study a problem presenting many difficulties. The developmental history of the permanent kidney, the metanephros, is unique and its blood supply differs from that of any other gland. The numerous diagrams, giving form and structure of the renal tubules of mammalia current in recent literature evidence the difficulties met in ascertaining its form and, while the majority of the diagrams are based on that given by Schweigger-Seidel in his classic contribution to which reference has been made, a study of Fig. 1 will show that each of the diagrams selected presents characteristics which make it differ from the others given. To emphasize a discordance of views as to the shape of the tubule under consideration, shape alone is here considered and no reference is here made to the position of the different parts of the renal tubule in the kidney substance, even though this be considered in the original diagram. This want of unanimity of views as to the shape and structure of the renal tubule and the feeling that a definite understanding as to their shape and structure was necessary before their func-

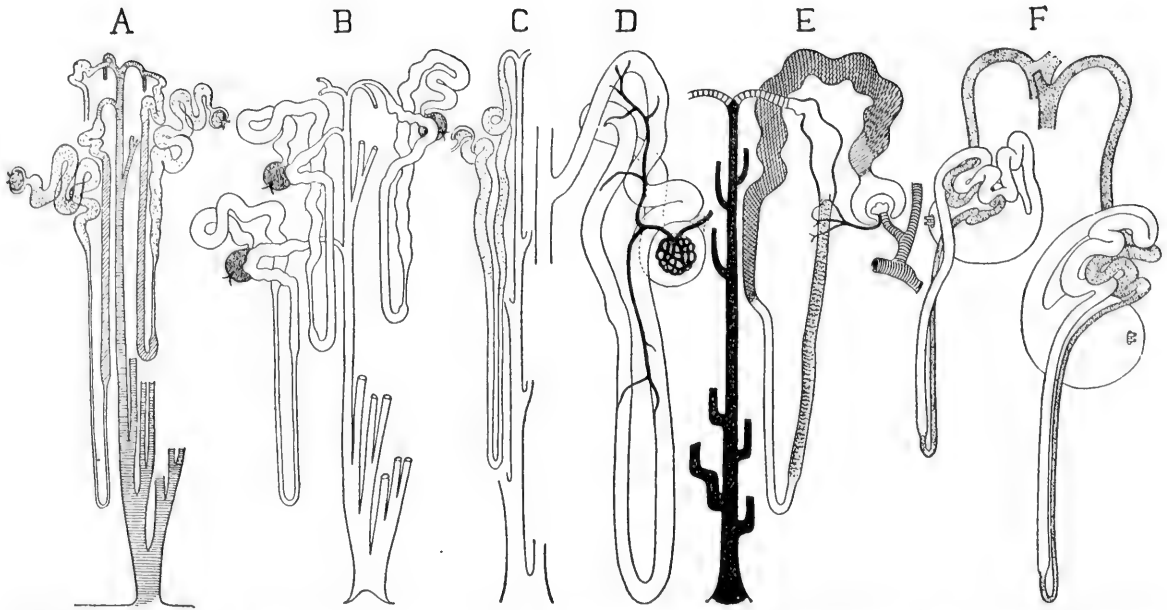

FIG. 1.—Diagrams showing different conceptions held of the form of the renal tubule. *A*, Schweigger-Seidel; *B*, Von Ebner; *C*, Haycraft; *D* Golgi; *E*, Disse; *F*, Stoerk.

tion could be fully ascertained, actuated the writer some years ago to a renewed study of this problem. The work was undertaken with the hope that by the use of newer methods and especially the Born reconstruction method, new light might be thrown on a problem which has not been fully illumined. This method, which in the hands of many had given such trustworthy results and in my own laboratory had proven the means of giving us a better knowledge of form and relation of certain minute structures too small to dissect satisfactorily, too complex to follow clearly in sections and not always successfully isolated by methods of maceration, seemed especially adapted to the problem projected. It was soon learned, however, that the reconstruction of a renal tubule in an adult kidney presented many difficulties, some of which might no doubt be now met, but at that time appeared as real obstacles. Recourse was taken, therefore, to the embryological method in the hope that, could the morphogenesis of the renal tubule be portrayed in a series of reconstructions, a fundamental type-form of the renal tubule might be ascertained. For it should be emphasized that too much stress should not be laid on the form portrayed by a reconstruction of any minute anatomic unit or part. The form presented is accurate in so far as pertains to the particular part or unit reproduced. It must be conceded, however, that not all other like parts or units are of identical form. A certain type-form may usually be ascertained. A successful reconstruction is to be regarded in the light of an accurate diagram. That through the morphogenesis of the renal tubule one may obtain the clue to its adult structure will become evident, I trust, in what is to follow.

Numerous investigations dealing with the development of the urogenital system of vertebrates are at hand and of these a goodly number deal with the development of the metanephros of amniotes. Here it is necessary to distinguish between the development of what are termed the straight collecting tubules on the one hand and the convoluted or glandular tubules on the other hand. That the former are developed by a process of budding as in the majority of other glands was recognized

from the beginning and is now universally conceded. Concerning the development of the latter, however, the views until recently have been at variance. One school, following Remak and later Von Kölliker, taught that the convoluted portions of the renal tubules were developed as outgrowths from the developing collecting tubules, both straight and coiled tubules developing by direct budding from the epithelial renal anlage derived from the mesonephric duct; another school following Kuppfer described a discontinuous origin for the convoluted or glandular portion of the renal tubule, and perhaps a third group who assume an intermediate position and who, while accepting a discontinuous anlage of the convoluted portion, assume a histogenetic relationship between the cells from which the convoluted tubules are developed and the epithelium of the straight collecting tubules. And while until quite recent times supremacy has been sought and contended for by the upholders of one or the other view as here briefly summarized, one must concur with Felix in the statement that Kuppfer's view of the discontinuous origin of the convoluted glandular portion of the renal tubule is now receiving almost universal acceptance, several of the more recent and comprehensive investigations, namely those of Schreiner,[2] Huber,[3] and Felix[4] aiding largely in its substantiation. A discordant view has recently been expressed by Janosik,[5] not as concerns the discontinuous anlage of this portion of the renal tubule, but as to its early stages of development, concerning which the other writers cited are also more or less in accord.

Schreiner's contribution, in which the results of observations on the anlage and early developmental stages of the tubules of the mesonephros and metanephros of representatives from different classes of amniota are discussed, has deservedly received much consideration and may, I believe, be accepted as bringing non-controvertible evidence of the discontinuous development of the convoluted portion of the renal tubule. It may be briefly stated that the glandular tubules of the mesonephros and metanephros are developed from a cell mass known as the nephrogenic tissue, derived from the intermediate cell

mass, extending on each side as an unsegmented cord along the mesial and dorsomesial side of the mesonephric duct. The evaginations arising from the mesonephric duct, just before this terminates in the cloaca, known as the renal buds and from which are developed the ureters, the pelvis of the kidneys, and the straight collecting tubules, soon after their anlage come in contact with the caudal end of the nephrogenic tissue, this tissue enveloping the distal ampullar expansions of the renal buds, forming the metanephrogenic tissue, with an inner zone composed of densely arranged epithelioid cells and an outer zone having the appearance of a dense mesenchymal tissue. With the differentiation of the renal buds into primary ureters and primary pelvis and the development by process of budding of the primary collecting ducts, the metanephrogenic tissue, and especially its inner zone, becomes separated into masses, each surrounding the ampullar expansion of a primary collecting duct, and this relation is maintained through the entire period of kidney development in which the collecting tubules increase in number by division and budding; and with each such division, the metanephrogenic tissue capping the bulbous end of a collecting tubule prior to its division also divides as this division takes place, the bulbous end of each new collecting duct being thus capped with metanephrogenic tissue. In Fig. 2 is shown a portion of a sagittal section of a metanephros of a human embryo of 18 mm. crown-breech length, in which the distal end of a primary collecting duct of the third order with ampullar expansion is shown. The groups of cells *b* and *b'* represent the inner zone of the metanephrogenic tissue; *c*, the outer zone, and *d*, the primary capsule. If the inner zone of the metanephrogenic tissue is carefully studied in serial sections, it will be found that its border is not an even one, but that it presents a bud-like extension along the side of the collecting duct, in which the cells often show definite arrangement in two layers continuous at the end of the prolongation. Such bud-like prolongations of the inner zone early acquire a narrow lumen, around which the cells assume a radial position, certain of the cells of the bud in the region of its junction with the

main mass of the metanephrogenic tissue turning with their ends toward the lumen. In the further differentiation of such a cell-mass, the lumen increases in size, the cells assume a columnar shape and there is formed a small vesicle, distinctly separated from the collecting duct, although in immediate contact with it. Such vesicles may be termed renal vesicles. They constitute the anlagen of the convoluted or glandular portions of the renal tubules. The beginning and end of the formation of a renal vesicle is shown at *b'* and *c* in Fig. 2. Beginning with a relatively early stage in the development of the kidney, through nearly its entire period of development, there may be

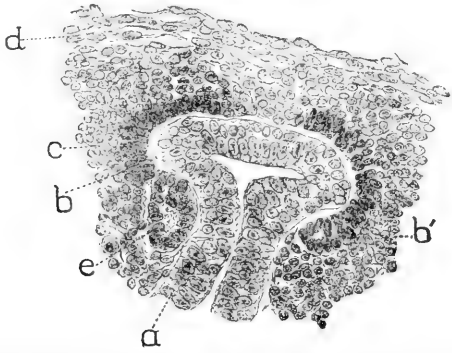

FIG. 2.—From sagittal section of kidney of human embryo 18 mm. crown-breech length. × 233. *A*, primary collecting tubule with ampulla; *b*, *b'*, inner zone of metanephrogenic tissue; *c*, outer zone of metanephrogenic tissue; *d*, anlage of capsule; *e*, renal vesicle.

observed a peripheral zone containing the end-branches of the collecting ducts with ampullar enlargements surrounded by an inner zone of metanephrogenic tissue, with forming and formed renal vesicles. This peripheral zone is known as the neogenic zone (Hamburger and Stoerk). Beneath this zone are found many generations of renal tubules, developed from renal vesicles, and in various stages of development, those first formed showing the greatest advance in development and differentiation and situated in the depth of the developing cortex. Before considering the further development of the renal vesicles, I desire to call attention to two points in their mode of origin.

In the first place and by way of emphasis, it may again be stated that the convoluted or glandular portion of the renal tubule is not developed by process of budding, as is the case with the majority of glands with persistent ducts having external secretion, but, as has been shown, from a tissue distinct and separate from the duct system. In the second place it may be stated that the tissue from which the renal vesicles are differentiated is of mesodermal origin and from the mesoderm there is also differentiated the mesothelium lining the large serous cavities, the endothelium of blood- and lymph-vessels and spaces and the mesenchymal epithelium of certain lymphatic and perilymphatic spaces. It is true that one is not permitted to draw deductions as to the functional activities of tissues arising from the same germ layers, basing such deductions on the similarity of germ-layer origin, since it is well known that the cytogenetic glands,—the ovaries, the testes and the blood-forming glands,—as also the cortex of the adrenals are also of mesodermal origin, yet a similarity in the structure of the epithelium of the glomerular capsule (Bowman's capsule) and perhaps also the epithelium of the proximal limb of the medullary loop (Henle's loop) to mesothelium is at least suggestive of a certain similarity in functional activity.

We may now consider the further development of the renal vesicle. In doing this, I shall discuss briefly a series of models, made by the Born method of reconstruction, showing successive stages in the metamorphosis of the renal tubule. These were made from a series of sections of the kidney of a 7-month human embryo. This series of models reproduced in Fig. 3 is accompanied by a series of figures, in each of which is reproduced the most comprehensive section of the series of sections used in making each model (Fig. 4). The renal vesicle, soon after its separation from the metanephrogenic tissue, elongates and comes in close contact with the ampullar enlargement of the collecting duct. Its outer wall thickens, so that the lumen of the vesicle assumes a hook shape or now and again the form of an inverted T. There may now be observed a slight depression on the outer wall of the vesicle, beneath which a cleft

makes its appearance, which cleft begins to separate the thickened wall into two parts. This is better seen in suitable sections than in reconstructions, since the slight depression and cleft do not extend across the entire outer wall of the vesicle. In further development, this cleft deepens and extends laterally so as to involve more than the outer wall of the vesicle, its lower and outer portion becoming thus separated in the form of a crescent-shaped lip. At about the same time there is observed a slight depression on the uppermost part of the inner wall of the vesicle, causing it to assume a characteristic S-shape, perhaps also more clearly seen in suitable sections than in reconstructions (*B* and *C* of Figs. 3 and 4). Usually when this stage is reached, the tubular anlage becomes connected with the ampullar enlargement of the collecting duct, the lumen of the two becoming continuous, this being accomplished according to Jägerroos,[6] by the upper end of the tubular anlage becoming inserted into the collecting duct. This S-shaped stage in the development of the renal tubule has long been recognized. As it represents an important stage, it may be characterized somewhat more fully. For purposes of description, we may speak of an upper S-curve, with concavity toward the collecting tubule, a middle S-segment, having primarily a horizontal position, but as development proceeds and the S-shape becomes more pronounced, inclining upward toward the collecting tubule, and a lower S-curve with convexity toward the collecting tubule. From reconstructions, we may learn that the upper S-curve is formed by a tubule having narrow lumen and extending without definite boundary into the S-middle segment, also of tubular form. The lower S-curve is not of cylindrical shape but from the time of its formation is flattened from above downward and presents the form of a double-walled saucer or shallow bowl with concavity directed upward, the cavity or lumen which extends into this portion having a similar shape. Both sections and reconstructions show that the lower end of the upper S-curve at its junction with the S-middle segment rests in the concavity of the saucer-shaped lower S-curve, so that only a narrow space separates these parts. In suitable

sections this space appears as a curved cleft and contains soon after its formation a delicate strand of mesenchymal tissue. In *D* of Fig. 3 is shown a tubular anlage, which in Section *D* of Fig. 4 shows a very typical S-stage, with lumen cut through its entire extent. The reconstruction shows that what appears in sections as the lower S-curve is in reality a shallow bowl, the edges of the saucer-shaped structure recognized for earlier stages having grown upward, thus deepening the concavity, which is now occupied by a vascularized mesenchyme. This vascularized mesenchyme has long been recognized as the anlage of the glomerulus, this forming with the lower S-curve the anlage of the renal corpuscle. Further development affects simultaneously the different parts of the S-shaped tubular anlage. The anlage of the renal corpuscle early differentiates to a structure having the form of a fully developed renal corpuscle. This morphogenesis is accomplished by a growing upward and a turning inward of the double-walled epithelial structure forming the glomerular capsule and by a growing outward of a fold which arises from the inner wall of the glomerular capsule in the region of its attachment to the tubular portion. This turning in of the glomerular capsule and the further development of the fold just mentioned gradually narrows the opening which leads into the glomerular capsule. This opening serves to give entrance and exit to the afferent and efferent vessels of the glomerulus which with its capillary loop has in the meantime differentiated from the vascularized mesenchyme found in the concavity of the shallow bowl-shaped structure from which the glomerular capsule develops. The place of entrance and exit of the glomerular vessels marks the vascular pole of the renal corpuscle. The formation of the fold above referred to marks clearly the attachment of the renal tubule to the renal corpuscle, the place of attachment being designated its urinary pole. It is often stated that the double-walled glomerular capsule is formed by invagination. That this is not the case is, I trust, apparent. The renal corpuscle marks the beginning of the glandular portion of the renal tubule and attains a relatively advanced state of develop-

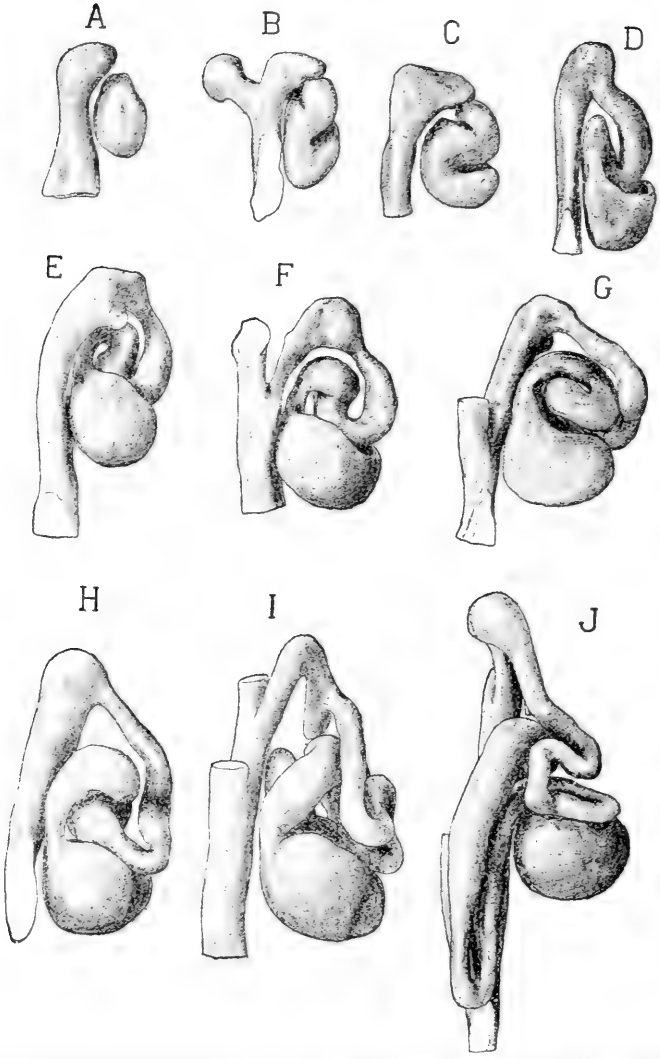

FIG. 3.—A series of models, *A* to *J*, showing successive stages in the development of tubular anlagen and early stages of renal tubules, with a portion of the collecting tubule to which each is attached; from a human embryo of the seventh month. × 160.

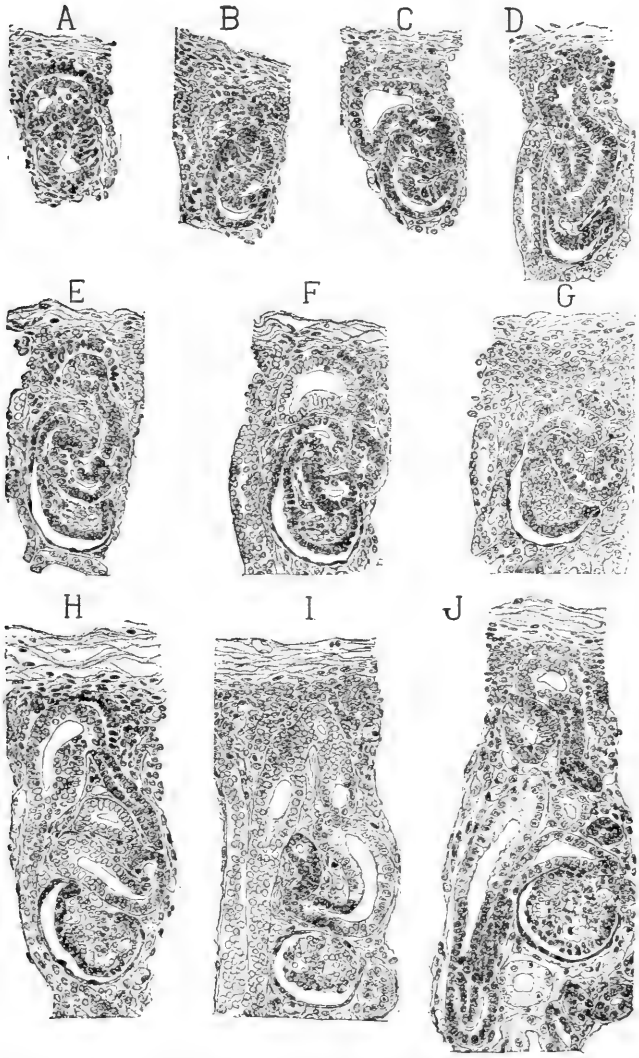

FIG. 4.—A series of figures, *A* to *J*, of sagittal sections of tubular anlagen and of renal tubules in early stages of development. In each figure of the series, there is reproduced the most typical of the series of sagittal sections used in making the reconstructions shown in Fig. 3.

ment before the other parts of the tubule show a corresponding degree of development. Furthermore, it is the part to be first clearly made out in the differentiation of the renal vesicle. The glandular portion of the renal tubule may, therefore, be said to begin its development at its distal end quite contrary to the majority of epithelial glands with persistent ducts, which develop and differentiate from their anlage toward the periphery. In considering the further development of the tubular portion of the S-stage of the tubular anlage, it should be borne in mind that this is relatively fixed at its two ends, being attached above to the collecting tubule and below to the renal corpuscle, so that in its elongation it is forced to acquire secondary curvatures. One of these is fairly constant both as to time and location appearing soon after the S-stage is reached and involving about the middle of the upper S-curve, the convexity of this curvature often being directed toward the collecting tubule. Soon after the anlage of this curvature or coincident with it, the region of the junction of the S-middle segment and the lower S-curve develops into an arched tubule with convexity upward. The region of the junction of the S-middle segment and the upper S-curve now develops into a distinct loop, the crest of which holds a position just above the developing renal corpuscle or a little to one side of it. Models and figures *E* to *G* of Figs. 3 and 4 may serve to elucidate these statements. In a tubular anlage developed to the extent here described there may be recognized, I believe, the essential parts of a renal tubule of full development. Briefly stated, the morphogenesis of the different parts of a renal tubule is as follows: Concerning the formation of the renal corpuscle with its double-walled glomerular capsule and glomerulus, I have spoken. The region of the junction of the lower S-curve and the S-middle segment differentiates into an arched tubular segment which represents the anlage of the proximal convoluted portion of the renal tubule; the region of the junction of the S-middle segment with the lower end of the upper S-curve, often forming a distinct loop, marks the anlage of the medullary loop of the renal tubule

(loop of Henle); the secondary curvature of the upper S-curve, which appears relatively early, marks the distal convoluted portion of the renal tubule. A careful study of several series of models will, I believe, lend evidence substantiating these statements, if it is recognized that no two models, representing essentially the same stage of development of the renal tubule, are exactly alike; they all vary more or less in details. It is, however, possible to recognize a type-form for a given stage, to which the models of said stage may be referred for interpretation. In further development, the loop which forms the anlage of the medullary loop elongates toward the pelvis of the kidney, growing in front of the renal corpuscle or in front of the tubular segment attached to it. The anlagen of the proximal and distal portions of the renal tubule elongate, acquiring secondary loops, especially the former (see models and figures *H* to *J*, Figs. 3 and 4). The account here given of the morphogenesis of the renal tubule differs slightly from that given by Stoerk [7] and accepted by Felix.[4] Stoerk describes a primary and secondary S-stage, the secondary S involving that portion of the tubular anlage not engaged in the formation of the renal corpuscle. This secondary S is said to develop five loops, the further development of which he traces. I have elsewhere discussed his results and to this discussion the interested reader is referred. Janosik, who has recently published concerning the early developmental stages of the mammalian renal tubule, describes a secondary separation of the anlage of the renal tubule from the collecting tubule after this has reached about the S-stage, also budding of tubules and fusion of the tubular portions and of renal corpuscles of neighboring tubular anlagen. The figures he gives, largely of graphic reconstructions, are so at variance with those given by other authors that I am forced to assume that his observations are based on poorly fixed material and relatively thick sections and that he has joined parts of several tubular anlagen so as to form a single tubule in regions where there may be contiguity but not continuity of tubule segments. His results will need full confirmation before they can be accepted. My own observations and the

conclusions reached concerning the anlage and early developmental stages of the renal tubules, as also the genesis of the different parts of these tubules, I have summarized in a series of diagrams given in Fig. 5.

At about the time when the renal corpuscle has attained a

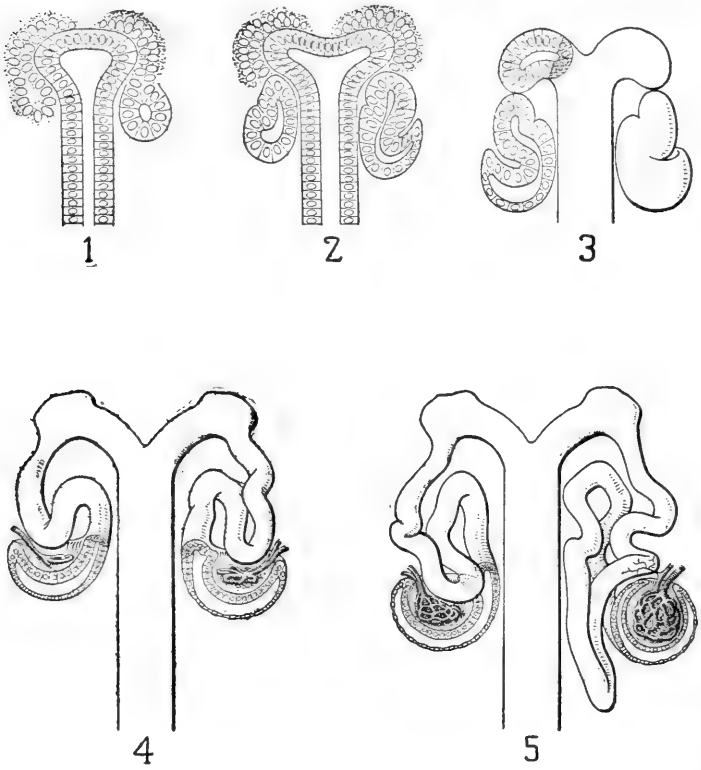

FIG. 5.—Semidiagrammatic figures of the anlage and differentiation of renal vesicles and early developmental stages of renal tubules of mammals. 1 and 2, anlage and successive stages in the differentiation of renal vesicles, as seen in sagittal sections; 3, section and outer form of tubular anlage before union with the collecting tubule showing beginning of S-stage; 4 and 5, successive stages in the development of the renal tubule, glomerular capsule, and glomerulus, beginning with a well-developed S-stage.

nearly spherical form, there may be observed a cellular differentiation in that portion of the developing tubule recognized as the anlage of the proximal convoluted portion. The cells of this segment of the tubule increase in length and their pro-

toplasm shows an affinity for acid stains, notably eosin and erythrosin; their nuclei assume a position in the basal portions of the cells and stain less deeply. This portion of the tubule increases in length relatively rapidly, acquiring secondary and tertiary curvatures. The tubule further elongates through increase in length of the medullary loop. This, while thus elongating, presents a characteristic cellular differentiation evident in its proximal arm, the epithelium of this portion differentiating into one of a flattened, pavement type with flattened nuclei. The tubule obtains in this portion a smaller diameter than in other parts. In the developing medullary loop, the flattened epithelium extends in the proximal arm from the region where the epithelium of the proximal convoluted portion ceases to near the crest of the loop. A little later, the epithelium of the distal arm of the loop, as also the distal convoluted portion, acquires a slightly granular protoplasm, often showing a faint striation, which is also acidophile, though not as distinctly so as the epithelium of the proximal convoluted portion. The structural differences between proximal and distal arms of the medullary loop as here given can readily be made out, by the aid of reconstruction, in renal tubules of sufficient advance in development to present a cellular differentiation of the different parts of the tubules. That the proximal arm of the medullary loop contains the segment which is of smaller diameter and is lined by a flattened epithelium has been the generally accepted view since the time of Schweigger-Seidel's comprehensive contribution. Stoerk regarded it as a distinct achievement to be able to show that this generally accepted view was incorrect, since his reconstructions revealed clearly that the descending or proximal arm of the medullary loop is to be regarded as representing genetically and morphologically the end segment of the tubulus contortus of the first order, the proximal or descending arm of the loop being lined by an epithelium which is like that which lines the proximal convoluted portion, these two parts of the tubule presenting a like diameter, while the distal or ascending arm of the medullary loop is of smaller diameter and is lined

by cells having a "darker" protoplasm. I have elsewhere shown that Stoerk was led into this grave error by drawing conclusions from observations made on reconstructions of early developmental stages, stages in which epithelial differentiation had not taken place. It is to be regretted, therefore, that these views of Stoerk should be given any credence by Felix in his comprehensive chapter on the development of the kidney in the Hertwig Handbook, a regret which Peter [8] has also expressed. Janosik has recently stated that it is not possible to identify the medullary loop—loop of Henle—in as early stages in the development of the renal tubule as is contended by a number of observers, citing more particularly Stoerk. He further states, if I read him correctly, that there is no definite relation between topography of loop segments and characteristic epithelial structure. I can only disagree with him in both of these contentions.

The anlage and morphogenesis of the renal tubule take place in essentially the same manner in all mammals studied by myself and others. Differences in the distribution of the neogenic zone as between mammals having simple kidneys with single renal pyramid and those having lobulated kidneys with several renal pyramids are recognized in early stages of development. From the primary renal pelvis of the developing human kidney, there are usually developed four collecting ducts of the first order; the branches resulting through the further development of each of these become grouped in four primary renal pyramids, the base of each of which is surrounded by a neogenic zone which extends to the developing pelvis, marking off four primary lobes, the neogenic zones of two contiguous primary lobes forming the primary renal columns (Bertini). During further development, the four primary renal lobes and pyramids are subdivided by the formation of new renal columns, this process going on until the final number of renal pyramids is reached, the base of each of which is surrounded by developing renal tubules surrounded peripherally by a neogenic zone. Attention has already been called to the fact that renal vesicles first to differentiate develop into renal

tubules which lie nearest the developing pelvis, generations of renal vesicles and renal tubules developing external to them. The most fully developed tubules are, therefore, those found deepest in the developing cortex and they attain a marked degree of development and differentiation at a time when new renal vesicles are still developing from the neogenic zone of the periphery, a point to which I shall have occasion to refer again. I may also refer briefly to the fact that it is generally believed that certain of the first-formed renal tubules degenerate after they have attained a certain degree of development. As above stated, there are usually developed in the human kidney four primary collecting ducts of the first order, while in the adult kidney somewhat over one hundred large collecting ducts terminate in the pelvis. It has been learned, more particularly through the careful investigations of Hauch,[9] that the increase in the number of collecting ducts which terminate in the pelvis is attained, as development proceeds, through a proximal expansion of the terminal end of a collecting duct of a certain order, this expanded end being then taken up into the wall of the developing pelvis, the branches of the said duct then opening separately into the pelvis. It is estimated that the collecting ducts to about the fifth division are thus taken up into the pelvis. Accompanying the reduction of the collecting ducts, there is stated to take place a reduction or degeneration of certain of the first-formed renal tubules which for instance in the human kidney toward the end of the second month are relatively large, with well-developed renal corpuscles and tubules (Felix). The question is of especial interest to me since these degenerating tubules may furnish an explanation for the existence of certain irregular vascular branches to which reference will be made in discussing the vascular supply of the kidney.

It has been stated that the anlage of the different parts of the renal tubule may be recognized at a relatively early stage of development and that these parts may be definitely determined as soon as epithelial differentiation is observed. It has seemed to me that not only could the different parts of the

renal tubule be thus early recognized, but that the relative position of the different parts was also determined at a relatively early stage. The parts of the S-shaped tubule from which the proximal and distal convoluted portions are developed lie above the lower S-curve from which is developed the capsule of the renal corpuscle. It forms for each tubule, as development proceeds, a coil-complex situated above the respective renal corpuscle. The loop which forms the anlage of the medullary loop rests, as will be remembered, in the concavity of the lower S-curve. As the loop elongates, it passes down over the developing renal corpuscle or the tubule connected thereto, and grows toward the pelvis. The upper end of the proximal and distal arms of the medullary loop are thus from the beginning in close relation with the renal corpuscle of the respective tubule, especially the upper end of the distal arm which lies from the very beginning nearer the developing vascular pole of the renal corpuscle, a relation which is permanently maintained and attributed by Hamburger and Peter to the fact that the upper end of the distal arm of the medullary loop is fixed in this position by means of branches from the efferent glomerular branch, a point which is not always confirmed in reconstructions and may be more apparent than real in maceration preparations. The upper end of the proximal limb of the medullary loop in the region where it leaves the coil-complex is generally in close relation with the upper end of the distal limb, sometimes lying to the inner side of it—toward the collecting duct—sometimes over it and not often to the outside of it, as would be seen from reconstructions; therefore also near the renal corpuscle of the respective tubule, retaining thus in later stages of development the relations borne in earlier stages. In all stages of development it may be seen that the two limbs of the medullary loop are quite parallel and take quite a direct course toward the renal pelvis or the apex of the renal pyramid. Development also shows that the medullary loops of the tubules first formed extend, from a time soon after their formation, to the neighborhood of the renal pelvis or to the apex of the renal pyramid, as soon as this develops.

The medullary loops of the several generations of tubules which develop later terminate at various levels in the medulla and in general terms it may be stated higher up in the medulla for each successive generation of tubules.

In tracing the development of the renal tubule by means of reconstructions, it becomes evident, if one notes the anlage of the different parts, that the proximal limb of the medullary loop lies nearer the collecting tubule than does the thicker, the distal, limb. This appeared to me to be the more typical relation and was so interpreted in reconstructing the diagrams of the renal tubules shown in Fig. 6. Peter,[8] in a recent and most painstaking and important contribution, which I shall consider more fully and freely draw upon in succeeding pages, has taken exception to this statement, he finding that the distal or thicker arm is nearer the collecting duct, although he states in discussing this point with reference to the human kidney (see page 211), "Doch wird diese Lagerung nicht stets beibehalten; da die Schleifen nicht selten längsgedreht sind, so kann sich das Verhältnis umkehren, auch können beide Schenkel nicht radiär, sondern tangential in der Säule des Markstrahles zum zentral befindlichen Sammelrohr liegen. Für die Rindenschleifen gar lässt sich überhaupt kein Gesetz herauslesen; sie sind bisweilen derartig ineinander verschränkt, dass sich kein Schenkel als innerer oder aüsserer bezeichnen lässt." Peter courteously excuses this error in interpretation on my part on the ground that my observations were based on renal tubules from kidneys of embryos and the new-born, and that I did not examine the renal tubules of kidneys of full grown animals. One may question, however, the validity of such an argument, for the reason that in the kidneys of embryos in later stages of development and in the new-born, from which certain of my reconstructions were made, the first formed renal tubules, those situated in the deeper part of the renal cortex, have attained a degree of development and are surrounded by a connective tissue of such a state of organization that it does not seem reasonable to suppose that the relations of their parts are materially altered in further development and growth. In

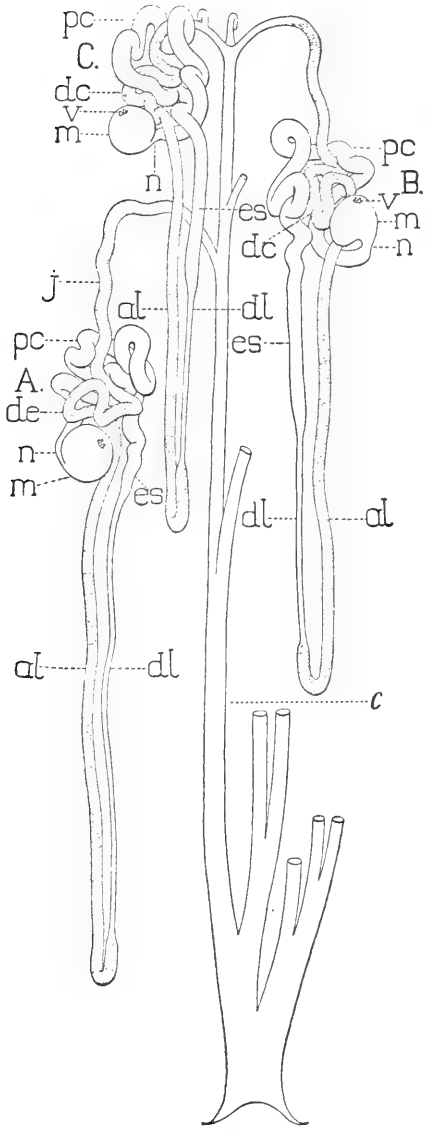

FIG. 6.—Diagram of three renal tubules and their relation to a collecting tubule. *A*, of a tubule, the renal corpuscle of which is situated in the lowermost portion of the cortex; *B*, about the middle of the cortex; *C*, in the outer portion of the cortex. *m*, renal (Malpighian) corpuscle; *v*, vessel porta; *n*, neck; *pc*, proximal convoluted portion; *es*, medullary segment; *dl*, descending limb; *al*, ascending limb of medullary loop (loop of Henle); *dc*, distal convoluted portion; *j*, junctional tubule; *c*, collecting tubule.

Peter's text-figure LVIII, page 340, reproduced in Fig. 7, giving a scheme of the form of a mammalian renal tubule. in the long tubule to the left of the figure, the relations of the upper ends of the proximal and distal arms of the medullary loops are, it seems to me, correctly given, or, as one may interpret such a relation through development,—namely, the proximal arm nearer the collecting tube. In this same tubule, just below the renal corpuscle, the two arms of the loop are rotated so that the distal, the thicker arm, lies nearer the collecting tubule. I would not imply that Peter would have it understood that such a rotation takes place in the medullary loop of every renal tubule, nor that it would take place very late in development, perhaps after birth, as may be implied in the criticism of observations based on embryological material. It should be understood that only in a general way can the course, structure, and relation of the different parts of a mammalian renal tubule be represented by way of scheme or diagram. For, as concerns form and relations of the proximal and distal convoluted portions and their relation to the renal corpuscle and its relation to the upper ends of the proximal and distal arms of the medullary loop and the relations of all these parts to the collecting tubule, each renal tubule presents slight differences and variations. And it has seemed to me that a fundamental type-form of a mammalian renal tubule, the sequence of its parts and their relation is more readily and more accurately ascertained through development than by a study of segments of renal tubules obtained by maceration and subsequent isolation, even though such maceration and isolation is carried out as successfully as was done by Peter, judging from his results as shown in his excellent figures. In very early stages of development of the renal tubule, at a time when the medullary loop is in anlage, the proximal arm lies nearer the collecting tube. The same is true in certain reconstructions of slightly older stages, made by myself and Stoerk. But even in such stages, one may find renal tubules in which the two arms of the medullary loop are not in radial position with reference to the collecting tubule, but in a tangential position, in which the distal, the thicker,

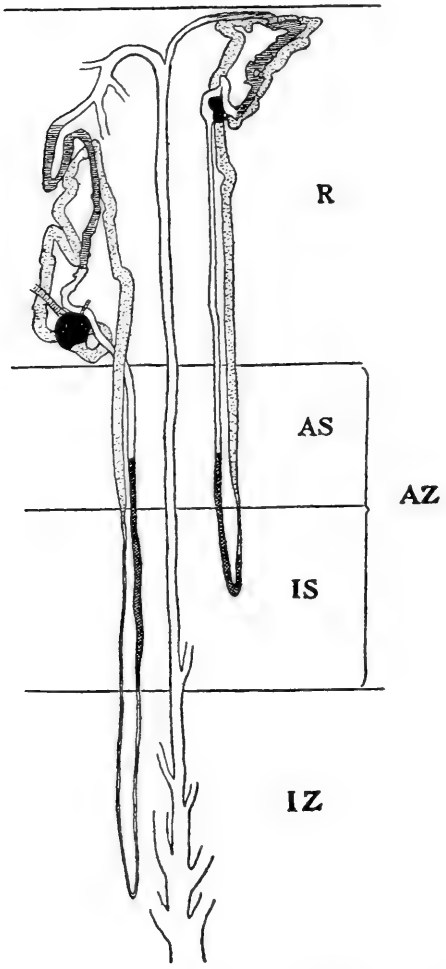

FIG. 7.—Scheme of course of renal tubule of mammalia, *AS*, outer stripe; *IS*, inner stripe; *AZ*, outer zone; *IZ*, inner zone; *R*, cortex; black, renal corpuscle; stippled, proximal convoluted portion with medullary segment (Hauptstück); cross-lined, intermediate segment (eigentliches Schaltstück), distal convoluted portion; cross-hatching, thicker, darker part of Henle's loop; clear, lighter, thinner part of Henle's loop, part of distal convoluted portion (Zwischenstück) and collecting tubule. After Peter.

arm of the medullary loop may be regarded as nearer the collecting tubule. It seems to me that Peter has selected, as concerns this point, tubules showing one extreme, in his reconstruction of a scheme showing a mammalian renal tubule, while the writer has selected the other extreme, basing his diagram of a mammalian renal tubule on what appeared to him as the type-relation as ascertained through development. Both statements, it would seem, should be interpreted in this light, with the added statement that there are undoubtedly numerous renal tubules in which the two arms of the medullary loop hold a tangential position with reference to the collecting tubule, with respect to which one or the other arm may be slightly nearer, or neither of which may be regarded as nearer.

We may discuss somewhat more fully the different parts of what may be regarded as a fully developed mammalian renal tubule and the relations which these parts bear to each other, to the collecting tubule, and also their position in the kidney substance. In naming the different parts of the renal tubule, it has been the custom to begin with the renal corpuscle, naming the parts in sequence to the end of the collecting ducts. This is contrary to the established custom of naming the tubular parts and secretory compartments of other glands with persistent ducts, in which the designation and description begins with the large ducts and proceeds toward the periphery, following the course of their development. A number of observers, among whom may be mentioned Stöhr, as quoted by permission by Peter, have suggested that the parts of the renal tubule be named beginning with the large collecting duct and passing to the renal corpuscle. Bailey and Miller ("Text-book of Embryology") have reversed the generally accepted meaning of proximal and distal, since "in development it is more convenient to speak of the terminal part of a tubule as its distal part." Attention has already been drawn to the fact that the secretory part of the renal tubule, which has its anlage in the renal vesicle, begins its development with the differentiation of the renal corpuscle and that its epithelial differentiation proceeds from the renal corpuscle to the collecting tubule. For this reason,

therefore, and for the added reason that the fluid that enters the renal tubules through the renal corpuscles is subjected to alteration by way of addition thereto and resorption therefrom in its course through the renal tubule to the collecting tubule, is it more consistent to name the parts of the renal tubule in the order of their sequence from the renal corpuscle, proximal and distal having reference to this sequence. The renal tubule begins, therefore, with the renal corpuscle (Malpighian corpuscle), which is of spherical or of round-oval form in the human kidney and presents a urinary and vascular pole, which lie about opposite, and consists of a double-walled capsule, the glomerular capsule (Bowman's capsule), usually spoken of as the invaginated end of the renal tubule, though it is not developed by invagination, and of the glomerulus. The glomerular capsule is easily traced through its development. The outer lamella, the capsule proper, consists from the time when the tubular anlage has reached the S-stage of a single layer of pavement epithelium. The inner lamella consists at this stage of a layer of cuboidal or short columnar cells, sharply contoured with large nuclei. These cells, as development proceeds and the glomerulus differentiates and the whole renal corpuscle attains its spherical form, assume the character of pavement epithelial cells which in the fully developed renal corpuscle are often difficult to make out clearly, since the very thin and transparent cells which surround the glomerulus are indistinctly bounded and have nuclei which in sections often resemble the nuclei of endothelial cells. The epithelial layers of the two lamellæ are continuous at the vascular pole, a fact easily ascertained through development. From Johnston's [12] reconstructions of the glomerulus of a human kidney (a child of three months) we learn "that the afferent vessel of the glomerulus, after entering the capsule of Bowman, immediately divides into five diverging branches, which with their subdivisions and with the efferent vessel form an almost spherical tuft of blood-vessels." The tubule is attached to the renal corpuscle by a short though often not distinct neck continuous with the outer lamella of the glomerular capsule, the epithelium

of the tubule which becomes shorter in the neck extending for a variable though relatively short distance into the outer lamella. The first portion of the tubule, which I shall designate as the proximal convoluted portion with the medullary segment, is for the greater part markedly convoluted. This portion, often known as the tubulus contortus of the first order, Peter describes as the convolute, forming with the medullary segment,—a segment which in part forms the end segment of Argutinski or the spiral tubule of Schachowa,—the main segment (Hauptstück), terms which do not seem to me to characterize this portion of the renal tubule as definitely as the term proximal convoluted portion with medullary segment. This portion of the tubule, as will be remembered, develops from an arched tubular segment, recognized soon after the S-stage and, although it increases greatly in length and becomes markedly convoluted, one may recognize in this convolute, both in reconstructions of tubules representing various stages of development, as also in Peter's excellent figures of maceration preparations, the primary arch, often with two or three secondary curvatures, each of which presents a variable number of minor curvatures. It may be emphasized that while it is possible to ascertain a certain type-form for this tubular segment, especially if traced through development, each tubule presents individual variations. The main or primary arch may be low with prominent secondary curvatures or may extend for a relatively long distance toward the periphery to return again toward the renal corpuscle, a fact which was not clearly recognized by me at the time I was making reconstructions of renal tubules and was revealed rather by accident in preparations of human and other mammalian kidneys injected with celluloid with a view of obtaining corrosion preparations of the blood-vessels. Now and again, and especially in material not perfectly fresh, the corrosion mass broke through the glomerular vessels and entering the renal tubule extended in this for a variable distance. After macerating and washing away the kidney substance, there would be found numerous casts of the lumen of renal tubules, each attached to a glomerulus, the form and course of

each tubule, as far as injected, being preserved. Such tubular casts are easily studied under the stereoscopic binocular and the course of the tubules traced, since representing the casts of only the lumen of the tubules, the convolutes are not compact.

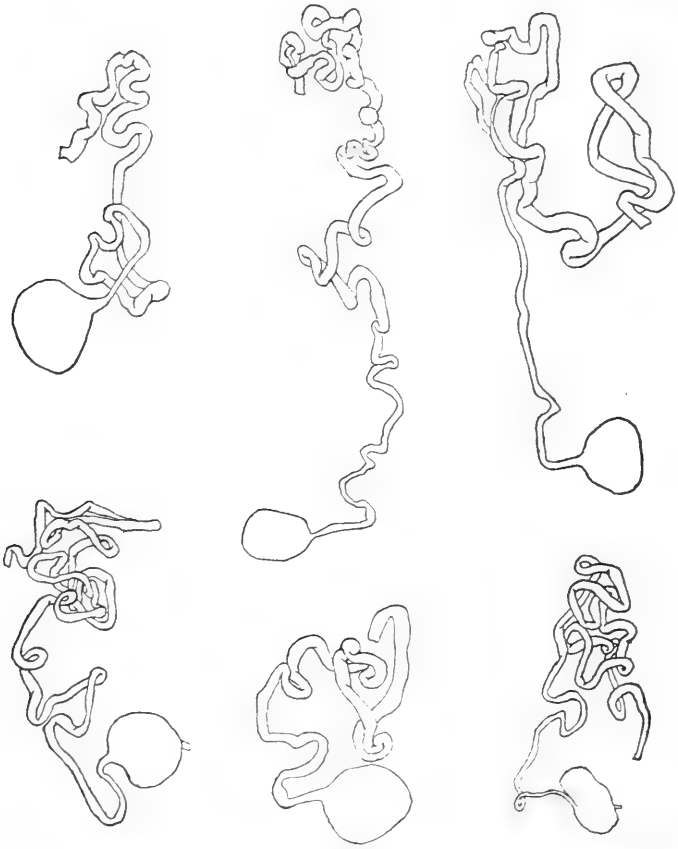

FIG. 8.—Outlines of celluloid casts of glomerular capsule and parts of proximal convoluted portion of the renal tubules of the human kidney.

In Fig. 8 are given a number of corrosion preparations obtained in this way, from an adult human kidney. The outline of the renal corpuscle with vascular and renal pole, the former shown in only a few of the tubules, the course of the tubule as it leaves

the renal corpuscle and its further course can here be ascertained. Probably not the entire proximal convoluted portion was injected, certainly not the medullary segment; the general arched form, with one or several secondary curvatures and numerous minor curvatures, however, are shown. The main mass of the convolute, formed by the proximal convoluted portion of each tubule, lies peripheral to its renal corpuscle, that is, toward the peripheral part of the cortex. Now and then one or several small loops may lie central to it. The proximal convoluted portion of each tubule forms a fairly compact coil. The medullary segment varies in length. It is longer for tubules situated in the peripheral parts of the cortex and extends for a short distance into the medulla as will be stated more definitely in giving the relative position of the different parts of the renal tubule. The characteristics of the epithelium lining the proximal convoluted portion and medullary segment, essentially the same throughout, are so well understood that they may be dealt with very briefly. The relative scarcity of the nuclei, the indistinct cell boundaries, the rodded protoplasm of the basal portion of the cells, the striated free border of the cells and the fact that the protoplasm stains more readily in eosin, erythrosin or Congo red than do other tubular segments found in the cortex are all distinguishing features of the epithelium of this tubular segment. The medullary segment of the proximal convoluted portion is followed by that portion of the tubule which extends for a variable distance into the medulla to return again to the region of the renal corpuscle of the respective renal tubule, thus forming a long loop, generally known as the loop of Henle, for which, however, I would suggest the term medullary loop, even though I am aware of the fact that not in all cases, though this is the exception, does it extend into the medulla. This tubular segment was named by Von Kölliker as Henle's loop after its discoverer, who, however, had an erroneous conception of its course and its relations to other parts of the renal tubule. For this reason and for the sake of consistency, since the B. N. A. has dropped all personal names, though long used to designate certain

tubular portions or parts of kidney substance, the term medullary loop is suggested. To characterize the parts of the loop more fully one may speak of its proximal (descending) arm or limb, its distal (ascending) arm or limb, and the crest of the loop. The qualifying adjectives, proximal and distal, as here used by me, have been adopted by Peter. It is the proximal arm of the medullary loop which contains the narrow segment with flattened epithelium as first described by Schweigger-Seidel and accepted by the majority of writers and again established by myself, in reconstructions and by Peter in maceration preparations, after Stoerk had stated the contrary, basing his conclusions also on reconstructions. The transition from the medullary segment of the proximal convoluted portion to the thin segment with flattened epithelium is rather gradual in the human kidney (Peter) and takes place in the peripheral part of the medulla. This segment of the tubule has a relatively small diameter, about 20 μ as compared to about 60 μ for the proximal convoluted portion, though a relatively large lumen. The epithelium is of a thin pavement type, with relatively large oval nuclei, which reach from top to bottom of the cell and may cause the cell to bulge into the lumen. Two or three nuclei may be met with in one cross-section of this segment of the tubule, often assisting in distinguishing it from capillaries, which have fewer nuclei, a point which Peter also recognized. The length of the thin and transparent segment of the proximal arm of the medullary loop varies with the length of the loop. In the reconstructions at my disposal, including tubules from new-born mammals, the thin segment ceased before the crest of the loop was reached, this being formed by a thicker tubule with darker epithelium, such as is characteristic of the distal arm. In the diagrams of the tubules given in Fig. 6 it was so represented. Peter states, however, and I think correctly, that the crest of the loop is not always formed by the thicker, the distal, arm of the loop. It is necessary, as he has shown, to distinguish between long and short loops, this depending on the extent to which the loop enters the medulla. The crest of the loop in the long medullary

loop is in the thin transparent segment, which extends for a distance on to the distal arm, while for the short loop, those ending in the peripheral part of the medulla, the crest of the loop (in the human kidney) always falls to the thicker and darker, the distal, arm of the loop, the thin segment of the proximal arm being in a short loop relatively short and may be lacking entirely in a very short loop. I am glad to correct the diagrams of tubules given in Fig. 6 to this extent; the source of error is, I think, readily seen. In even the late stages reconstructed there was evidently not complete epithelial differentiation; the epithelium forming the crest of the loops reconstructed, and which had the appearance of the epithelium of the distal arm, is rather to be regarded as an embryonic epithelium, the region representing a growth zone. It has seemed to me that the same explanation and interpretation might be given to the mixture of the two types of epithelia,—thin and transparent and thicker and darker,—observed by Peter near the end of the medullary loops in the kidneys of children, but never observed by him in the adult. The distal arm of the medullary loop extends from the crest of the loop to the renal corpuscle of the respective tubule, its upper end often arching over the renal corpuscle in the region of its vascular pole. This tubular segment is lined from the region where the thin transparent epithelium of the medullary loop ceases to the region of the renal corpuscle by an epithelium which I have characterized as presenting essentially the same structure throughout. The diameter of this tubular segment is about 30 μ (Peter). It is lined by a short columnar epithelium in which cell boundaries are indistinct, possessing slightly granular protoplasm with indistinct striation in the basal portions and staining somewhat less deeply in eosin or erythrosin than does the epithelium of the proximal convoluted portion. There is no striated free border. The nuclei are relatively large and stain readily. Peter has called attention to the fact that the distal end of the distal arm, the portion near the renal corpuscle, presents an appearance and structure which differs somewhat from that of the lower or proximal portion of this

arm. In the rabbit, the distal portion of the distal arm has a smaller diameter and much lower epithelium. In the human renal tubule, the distal portion of the distal arm of the medullary loop presents in macerated preparations a diameter which is slightly larger than the proximal portion of this arm, while the lumen of the distal portion is distinctly larger, this at the cost of the height of the epithelium. Peter recognizes in this distal segment of the distal arm of the medullary loop a distinct tubular segment, and it is represented as a distinct tubular segment in all of the schemes of renal tubules given by him. Whether this is justified seems to me to be questionable, especially as concerns the human renal tubule. He himself states as concerns this point with reference to the human renal tubule: "Der Zellbelag hat sich ganz erheblich verdünnt, und ohne dass sein Charakter auffallend wechselt, wird dadurch doch das Aussehen des distalen Schenkels nicht unbeträchtlich verändert: Das ganze Kanälchen wird einmal heller; ferner bedingt die Dünne der Wand, dass das Röhrchen von anderen benachbarten Gängen eingeengt wird und sich der Gestalt seines Querschnittes nach diesen richten muss" (see page 166).[8] The tubular segment following the distal arm of the medullary loop, which ends, as has been stated, near the vascular pole of the renal corpuscle, assumes a very irregular course and may be spoken of as the distal convoluted portion, although this portion is much shorter and not so distinctly convoluted as the proximal convoluted portion. Peter uses the term "Schaltstück"—intercalated portion or tubule, to designate this tubular segment, which he further divides into a relatively short segment, known as the "Zwischenstück"—intermediate portion, which differs structurally not at all or only slightly from the distal end of the distal arm of the medullary loop and the intercalated portion proper—"eigentliches Schaltstück," the beginning of which is determined in preparations macerated in hydrochloric acid, by the presence of minute dust-like crystals, which give this portion a characteristic dark appearance in isolated preparations when viewed by transmitted light. The term "Schaltstück"—intercalated portion—does not seem to me to be well

chosen, since it has been customary to designate a narrow tubular segment following the secretory alveoli or tubules of many glands by this term, which has thus acquired a somewhat distinctive meaning. For this reason, the term distal convoluted portion, which is consistent with the other terms used, would seem to me more desirable. As has been stated, the distal convoluted portion, which I would have extend from the place where the renal tubule breaks contact with the renal corpuscle near its vascular pole to its junction with the initial collecting tubule, is not nearly as long as the proximal convoluted portion—only about one-fourth to one-third the length of the latter. The convolute formed by the distal convoluted portion is not nearly so complex as that formed by the proximal portion, consisting frequently of one or two main loops with secondary curvatures, often having the form of a zigzag (Peter). In this segment the tubule shows irregularities of contour, enlargements and constrictions, and irregular bulgings and bud-like appendages, the latter not so apparent in reconstructions (see figures of reconstructions by Huber and also Figs. 37*a* and 38*a*, Pl. V of Peter[8]) as in maceration preparations and it is a question whether or not a certain amount of the irregularity in contour in this tubular segment as seen in preparations macerated in hydrochloric acid is not due to compression caused by a contraction of the surrounding proximal convoluted tubules which have a firmer consistency. This variation in the contour of the distal convoluted portion is quite apparent in sections. The lumen is prominent and often of irregular form. The nuclei of the lining cells are relatively large and stain readily while their protoplasm does not stain as readily in eosin or erythrosin as in the cells of the proximal convoluted portion. Peter states that the faint basal striation evident in the cells of the distal arm of the medullary loop is not evident in the cells of the intercalated segment proper, "eigentliches Schaltstück." The peculiar dust-like crystals, seen in preparations of this segment after maceration in hydrochloric acid, are not observed in sections. The loop or zigzag formed by the distal convoluted segment usually lies to the outside of the convolute

formed by the proximal convoluted portion and, as stated by Peter, usually on the side turned toward the collecting tubule. The main loops of the distal convoluted portion are often found near and a little above the renal corpuscle of the respective tubule. Now and again a loop of the proximal convoluted portion covers a loop of the distal convoluted portion and a loop may penetrate the coil complex formed by the proximal convoluted portion, as is shown in the left upper tubule of Fig. 6, which is drawn after a reconstruction. Peter feels that such an arrangement is impossible, stating "Auch ist eine derartige Durchflechtung von Hauptstück und Schaltstück, wie sie das obere linke Konvolut zeigt, in welchem das letztere durch eine Schlinge des Hauptstückes hindurchschlüpft, undenkbar" (see page 343).[8] It requires only a slight rotation outward of the proximal arm of the medullary loop of the tubule under discussion to expose the distal convoluted portion, not more rotation than is permitted in the long loop to the left in Peter's text figure LVIII. The distal convoluted portion is continued as the initial collecting tubule which ends in the collecting tubule of the medullary ray and forms the end of the secretory portion of the renal tubule. There is a gradual transition of the epithelium of the distal convoluted portion to the initial collecting tubule and it is somewhat difficult to state where the one ends and the other begins. It is also impossible to state with any degree of certainty whether the initial collecting tubule develops as an outgrowth from the collecting tubule or is differentiated with the other parts of the renal tubule from the renal vesicle, since soon after the fusion of the S-shaped renal tubule with the ampulla of the collecting tubule, all trace of place of fusion is lost. The epithelium lining the thicker portion of the medullary loop, the distal convoluted portion, and the first portion of the initial collecting tubule presents many points of similarity. Throughout these parts, the cells are of a low columnar type with indistinct cell boundaries. It is true that the vertical diameter of the cells varies somewhat, the cells being somewhat shorter in the distal part of the distal arm and the cells of the distal

convoluted portion present a somewhat more irregular inner border and stain less deeply in eosin. The differences in shape and structure are, however, so slight that it has not seemed to me necessary to recognize distinctive types with perhaps distinctive functions. We are, it seems to me, justified in recognizing four distinct types of epithelium in a renal tubule, if we include the glomerular capsule as a part of the renal tubule. First, the flattened epithelium of the glomerular capsule; second, the epithelium of the proximal convoluted portion with the medullary segment; third, the pavement epithelium of the medullary loop; fourth, the epithelium of the distal arm of the loop, or from the region where the pavement epithelium ceases, the distal convoluted portion to the first part of the initial collecting tubule. Concerning the first three types, there can be no question. Slight variations in shape of cells and in their structure are met with in the different portions of the tubular segments, the epithelium of which is grouped under type four, variations which are more marked in certain forms than in others. In the rabbit, for instance, the distal segment of the medullary loop presents a relatively small diameter and the epithelium of the distal convoluted portion possesses an epithelium which resembles that of the proximal convoluted portion (Peter). It would seem to me, however, that the differences in the structure of the epithelium of the tubular segments grouped as having the epithelium of type four are not sufficiently marked to warrant the recognition of further types. It is also of some importance to note that these four types of epithelia of a renal tubule are met with not only in a mammalian renal tubule, but also in the renal tubules of certain of the other classes of vertebrates. I cannot at present speak of the renal tubules of the bird's kidney; a reconstruction of this type is under contemplation. In the renal tubule of the reptilian kidney, four parts with characteristic epithelia are recognized. In Fig. 9 is shown a reconstruction of the renal tubule of the kidney of a turtle (Chrysemys marginata) in which the renal corpuscle, which is relatively small, with its renal capsule with distinctive epithelium is joined to an arched tubule which

corresponds to the proximal convoluted portion with its characteristic epithelium. This is followed by a short narrow segment, not in the form of a loop, but slightly convoluted, with a low epithelium which corresponds to the epithelium of the thin arm of the medullary loop of the mammalian renal tubule. The remainder of the tubule corresponds in epithelial lining to the distal arm of the medullary loop and distal convoluted portion of the mammalian renal tubule. In Fig. 10 is shown a

FIG. 9.—Reconstruction of renal tubule of the kidney of a turtle.

reconstruction of the renal tubule of a kidney of a frog, therefore a mesonephric tubule in which the four distinctive regions possessing characteristic epithelium may also be observed. It would seem evident, therefore, that it is necessary, in considering the function of a renal tubule, to take cognizance of the fact that the renal secretion from the time when its presence in the glomerular capsule is noted to the time when it reaches the collecting tubule meets with at least four types of epithe-

lium, each of which presumably has a specific function to perform. Starling states, "In all organs of the body whose functions have been investigated by physiologists, it has been found that a difference of function is invariably associated with a difference of structure, so that interdependence of function and

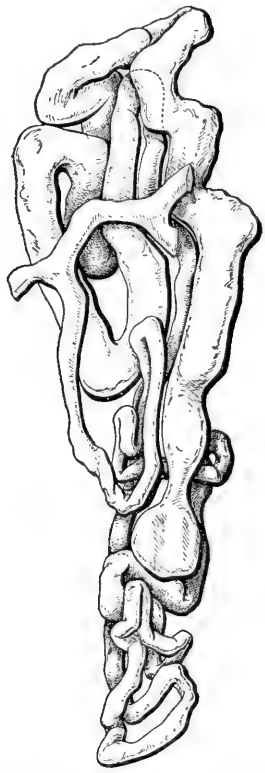

FIG. 10.—Reconstruction of the renal tubule of a frog's kidney.

structure has become an axiom. We are therefore justified in founding theories concerning the physiologic function of an organ on a purely anatomical study of its structure, although the complete establishment of such theories must ultimately be afforded by physiological investigations." Before leaving the

consideration of the form and structure of the mammalian renal tubule, a word may be said concerning the collecting tubules. Their function is very probably merely that of conveying the fluid received from the renal tubules to the pelvis of the kidney. As was stated, the collecting tubules are developed through budding and dichotomous division of the primary collecting tubules, which bud from the primary renal pelvis. The central division of the collecting ducts, or, to state it in other form, the central union of the collecting ducts, takes place in about the inner half of the medulla. In the outer part of the medulla, the collecting ducts show no or very little division. In the cortex, the collecting tubules receive the initial collecting tubules, through which the renal tubules are united to the definite collecting tubules, the details of which vary in different forms and need not be discussed here, but are discussed very fully in Peter's excellent account. The collecting tubules throughout are lined by a short columnar, sharply contoured epithelium not to be confused with the epithelium of any portion of the renal tubule.

A knowledge of the relative position of the different parts of the renal tubule in the kidney substance is essential to a correct interpretation of sections of this organ and Peter's recent contribution has very materially increased our knowledge in this regard, especially as concerns the relations of the different parts of the medullary loop. In the following presentation, I have made free use of the data which he gives. It is a well-known fact that the renal corpuscles, the proximal convoluted portions, the distal convoluted portions, the upper ends of the medullary loop, especially the distal arm and the initial collecting tubule, are found in the cortex and between the medullary rays, constituting what is often known as the labyrinth of the cortex. In the medullary rays are found the medullary segments of the proximal convoluted portion which pass from the region of the renal corpuscle of a respective tubule to the medullary ray, further the distal end of the distal arm of the medullary loop and the cortical collecting tubules. The medulla of the kidney, whether of a simple or lobulated kidney,

may be divided with reference to the position of the different parts of the medullary loop into distinct zones which have a definite and constant relation to the parts of the medullary loop, showing distinctive structure, as has been shown by Peter, who must be recognized as advancing very materially our knowledge of the structure of the kidney in this regard. He has shown that one may recognize in the medulla an inner and outer zone and that the latter may be further divided into an inner and outer band or stripe. He has characterized these zones and bands somewhat more fully for the kidney of a rabbit. In a sagittal section of a fresh rabbit's kidney, the cortex presents a brown color, while the greater part of the medulla, beginning with the apex of the renal pyramid, presents a grayish-white color and a somewhat transparent appearance. This zone is relatively broad, measuring 9.5 mm. in a kidney measuring 15 mm. from periphery of cortex to apex of renal pyramid. This constitutes the inner zone of the medulla. Peripheral to this zone there may be recognized a zone of a yellowish to a reddish color about 2.5 mm. broad and bounded externally by the cortex, forming the outer zone of the medulla. In this outer zone there may be recognized two bands or stripes of about equal width, the inner having a more yellow color, the outer a redder color, and known respectively as the inner and outer band or stripe of the outer zone. In the human kidney about the inner one-half of the medullary substance of a renal pyramid presents a grayish-white color and constitutes the inner zone, which is not sharply bounded toward the outer zone. The inner and outer bands of the outer zone are not as distinct in the human as in the rabbit's kidney, except in the kidneys of children and young individuals. The outer band has a width of about one-fourth of the width of the outer zone. These zones may also be recognized in tissue fixed in Zenker's, Müller's, and Van Gehuchten's fluids and are especially clear in tissues macerated in hydrochloric acid. Peter has further shown that the boundary line between the inner and outer zones represents the region of transition of the narrow segment of the medullary loop with pavement epithelium to the

thicker segment with darker and thicker epithelium in the long medullary loop, those extending to the deeper parts of the medulla; this transition occurs, it will be remembered, in the distal arm of the medullary loop. In the inner zone of the medulla there are found, therefore, only collecting tubules and medullary loop segments with flattened epithelium. The boundary line between the inner and outer band of the outer zones of the medulla is found in the region of transition of the epithelium of the medullary segment of the proximal convoluted portion to the thin flattened epithelium of the proximal arm of the medullary loop. This transition for long and for short medullary loops takes place at about the same level and marks the inner boundary of the outer band of the outer zone of the medulla. The crests of the short medullary loops are found in the outer zone and for the rabbit in the inner band of the outer zone. In the human kidney, the inner band of the outer zone contains thin proximal arms of the medullary loop, the distal, thicker arms of the medullary loops, the crests of the short medullary loops, and collecting tubules, while the outer band of the outer zone contains the medullary segments of the proximal convoluted portions, the thicker distal arms of the medullary loops and now and again a crest of a short medullary loop (Peter). The relations as here stated as existing between the different portions of the medullary loop and the medullary zones and bands pertain not only to the medullary substance of the kidneys of rabbit and man, but also to other mammals. For comparative investigations it is, however, necessary to remember the following facts which I have taken from a summary given by Peter[8] (see page 285). Carnivora (cat and dog) possess only the long medullary loop, those extending into the deeper parts of the medullary substance; in the rabbit, the proportion between long and short loops is as 3 to 2; in the sheep, the proportion is 1 long loop to 2.3 short loops; in man, 1 long loop to about 7 short loops; in the pig, the short loops greatly predominate. The general relations of the renal tubule and the relative positions of the different parts of the medullary loop to the medullary zones and bands are shown in Fig. 7,

giving a diagram of the course and relations of a renal tubule of a mammal (Peter's text-figure No. LVIII).

Having thus considered the course and structure of the renal tubules of mammalia, we may now consider their relation to the renal vessels and in doing this, cognizance shall be taken more particularly of the terminal vascular branches and their relation to the different parts of the renal tubules. That the vascular supply of the kidney differs in many respects from the vascular supply of other glands with persistent ducts and external secretion is well understood. In the majority of glands of this type, the arterial branches follow in the main the duct system, to terminate in capillary networks which surround the secretory compartments, the vascular branches developing in relation with the duct system and in the majority of such glands one may recognize more or less clearly defined vascular units. No such fundamental relations pertain with reference to the blood-vessels of the kidney. The course and relations of the main branches of the renal artery are well understood, thanks to the very successful corrosion preparations of Broedel and others. It is not my purpose to consider these further than to state that the renal artery, on entering the pelvis of the kidney, courses, after further division, in the peripheral part of the medulla. These main branches, having a course which in the main is parallel to the surface of the kidney or the renal lobule, therefore describe arcs with convexity outward. They are known as the arcuate arteries. From the convex side of such an arcuate artery there arise at relatively short intervals branches which form acute angles with the parent stem and pass with slight inclination toward the cortex. The length of these branches varies and from their cortical sides are given off at short intervals branches which pass more directly toward the cortex, subdividing further and giving origin to numerous branches which radiate toward the periphery of the cortex and may be known as the radial branches (interlobular arteries). The arcuate arteries ultimately terminate in smaller branches which also end in radiate arteries. Small arterial twigs, which shall be designated as the afferent glomerular branches, arise

from all the branches of the renal artery, beginning with the arcuate branches; from the latter and from the main stems relatively few, from the radiate arteries, however, and from the branches from which they arise, there are given off numerous afferent glomerular branches. As is well known, the afferent glomerular branches divide to form the capillary plexuses of the glomeruli, these in turn uniting to form the efferent glomerular branches, which in turn again break up into capillary networks. There has been much discussion as to whether all the terminal branches of the renal artery constitute afferent glomerular branches and whether certain terminal branches may not end in capillaries without being connected with glomeruli, and the chief controversial question concerns the vasa recta of Henle and Donders or the arteriolæ rectæ of other authors. Several views are current in the literature pertaining to the origin of these arteriolæ rectæ. According to one view, they arise from the efferent glomerular branches of the renal corpuscles lying nearest the medulla, a view early expressed by Bowman, also by Gerlach, Von Kölliker, and Ludwig. According to another view, recognition and prominence is given to arterial branches which arise directly from renal vessels, these dividing to form arteriolæ rectæ without the interposition of glomeruli, and known as arteriolæ rectæ veræ in contradistinction to such as are formed by a division of efferent glomerular branches and are known as arteriolæ rectæ spuriæ. According to still another view, the arteriolæ rectæ are said to arise from the capillary networks surrounding the renal tubules of the cortex. Virchow and perhaps the majority of the writers have tried to harmonize these conflicting views by recognizing both arteriolæ rectæ veræ and spuriæ, their relative proportion being variously given by different writers. Since the question under discussion is one of some importance to the physiologist, it seemed to me worthy of renewed investigation and with methods other than those formerly used. In such an investigation (Huber[10]) it was found that a celluloid injection mass stained with alkanin could be so injected as to cause it to pass through the successive divisions of the renal artery to and

beyond the glomeruli. After injection, time was allowed for the mass to set. The kidney as a whole or in pieces was then placed in 75 per cent. hydrochloric acid for a time sufficient to thoroughly macerate the connective tissue and glandular elements, which were then washed away by carefully playing water against them, usually by means of a dropper with rubber bulb. Smaller or larger pieces of such corrosions were then cut out under the stereoscopic binocular, thoroughly washed, dehydrated, and mounted in balsam. Preparations from 2 to 5 mm. thick, or even thicker, thus prepared, can be

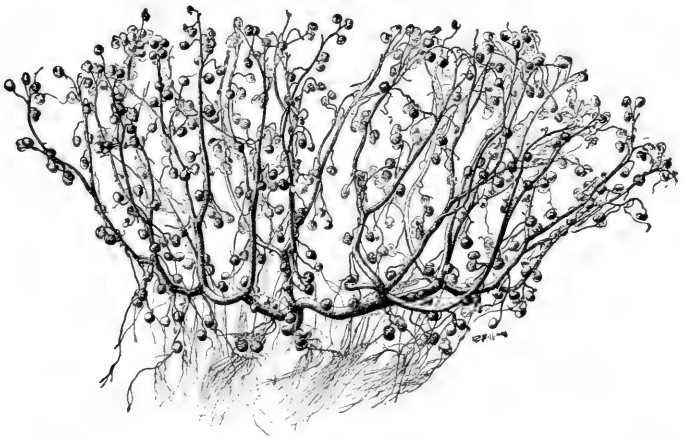

FIG. 11.—Corrosion preparation of terminal arterial branches from kidney of cat.

studied under the stereoscopic binocular and the entire vascular tree with the relations of the branches ascertained. This method has proven very satisfactory in the study of the renal vessels, as it has often been possible to obtain corrosions in which the course of the vessels could be followed through their several divisions until the capillaries are reached (see Fig. 11). The renal vessels of the dog, cat, rabbit, rat, and guinea-pig were thus studied. The human material at my disposal was not sufficiently fresh to give really successful corrosions. In corrosions of very fully injected material there are

often observed very small branches arising generally from the concave side of the more distal parts of the arcuate vessels, which can be traced as afferent glomerular branches to glomeruli. These small branches are not numerous and may attain a length of about 1 mm. They may end in one glomerulus or, after branching, in several. On the branches which arise from the convex borders of the arcuate vessels, the afferent glomerular branches become more numerous, the number increasing with each successive division of these arterial branches. Such afferent glomerular branches vary in length. Branches ending in one glomerulus are met with; clusters of one, two, three, four or even more afferent branches, each ending in a glomerulus, are also seen. Numerous afferent glomerular branches arise from the arterial branches which divide to form the radiate arteries. Here also they may arise singly or in small groups or a small arterial twig may divide into four, six, or eight branches, each ending in a glomerulus. From the radiate arteries (interlobular arteries), as is generally stated, there arise at all levels in the cortex and from all sides numerous afferent glomerular branches, not regularly, as usually figured, but more often in clusters of several branches, each ending in a glomerulus. The radiate arteries, as they reach the periphery of the cortex, divide into afferent glomerular branches. As is well known, each glomerulus constitutes a rete mirabile, its capillary branches uniting to form a single efferent glomerular vessel which is regarded as an arterial and not a venous branch. The efferent glomerular vessels, soon after leaving the glomerulus, divide to form capillaries, the disposition of which differs in different portions of the kidney. The efferent glomerular branches of the glomeruli, the afferent branches of which arise from the arcuate arteries and from the successive branches of these until the radiate arteries are reached and of a varying number of glomeruli, the afferent branches of which spring from the lowermost portions of the radiate arteries, divide into bundles of long slender branches and capillaries which pass into the medulla and constitute the arteriolæ rectæ spuriæ of writers. The efferent glomerular

branches of the remaining glomeruli form capillary plexuses which surround the renal tubules of the cortex. The majority of recent writers recognize terminal arterial branches which end directly in capillaries in the kidney substance without the interposition of glomeruli. Such branches are described as formed in the boundary zone between cortex and medulla,—arteriolæ rectæ veræ,—and in the periphery of the cortex as terminal branches of the radiate arteries. Only very few branches of this type are recognized in my corrosion preparations. If present, they should be injected more readily than the branches with glomeruli, since in the latter it is necessary for the injection mass to pass through the capillaries of the glomerulus, before reaching the more peripheral capillary plexus. A few such branches are recognized in corrosions as the nutrient arteries of the renal pelvis. Their arrangement is such that they are not to be confused with the arteriolæ rectæ. One may now and then find small arterial twigs which terminate directly in arteriolæ rectæ,—arteriolæ rectæ veræ. They constitute, however, a very small percentage, the great majority resulting through a division of efferent glomerular branches. In the dog there are observed a small number of very small glomeruli which appear fully injected. These may represent the small rete mirabile described by Golubew [11] in the dog and cat and designated by him as "retia mirabilia renum nova," as situated in the deeper portion of the cortical substance and periphery of the medulla. The very small glomeruli observed by me always end in vessels which divide to form arteriolæ rectæ. And from this fact, I have been led to conclude that they represent the remains of normal glomeruli associated in their development with renal tubules, which tubules, in later stages of development, have undergone regressive changes and degeneration, a portion of the glomerular plexus with afferent and efferent vessels remaining intact, the regressive changes varying with different glomeruli and in some instances going on to complete obliteration of the glomerular plexus, the afferent and efferent branches alone remaining as a continuous structure. The arteriolæ rectæ veræ, which are

relatively rare, I would regard, therefore, as the remains of glomeruli, present in early stages of development, the renal tubule and a portion, perhaps all, of the glomerulus of the respective tubule degenerating as development proceeds. The very few arteriolæ rectæ veræ noted form therefore only apparent exceptions to the general statement that all arteriolæ rectæ are formed by a division of efferent glomerular branches. So far as may be determined in corrosion preparations in which the peripheral portions of the radial arteries are completely injected, these end in afferent glomerular branches and do not present terminal branches which end directly in capillaries in the peripheral portion of the renal cortex. Now and again radial arteries pass to the periphery and pass to the capsule, anastomosing with capsular branches. From observations made the conclusion seems warranted that practically all of the blood found in capillaries surrounding the different parts of the renal tubule is blood that has first passed through the glomerular vessels, a fact clearly recognized by Bowman many years ago, as I have stated elsewhere. Such a statement as made by Metzner ("Nagel's Handbuch der Physiologie des Menschen," page 227, vol. ii, part i), "Demnach ist das die Marksubstanz versorgende Blut gemischt aus arteriellem und aus Glomerulusblut der Rinde," is therefore untenable. Numerous venæ rectæ return the blood from the medulla to larger arcuate veins and radial venous branches collect the blood from the cortex, these also ending in the arcuate veins. It should be stated, however, that while the arterial supply is fundamentally the same in the kidneys of various mammals, so far as I have been able to determine, the arrangement of the veins, especially the larger venous branches, varies very materially in different forms. In the rat, guinea-pig, and rabbit, the veins begin in the cortex in radial venous branches, which are similar in arrangement and course to the arterial radial branches. They end in arcuate veins, which also receive the venulæ rectæ. In the cat there is found a system of relatively large veins situated immediately under the capsule, which converge toward the hilum of the kidney and receive all along their

course radicals which drain about the outer half of the cortex, and arcuate veins situated in the periphery of the medulla, which receive short radial veins, which drain the lower portion of the cortex and receive also the venulæ rectæ. The arcuate and subcapsular veins unite at the hilum. In the dog there are found immediately under the capsule relatively large veins receiving venous radicals which drain about the outer half of the cortex and unite to form numerous relatively large veins which pass vertically through the cortex to end in arcuate veins, these receiving also short venous branches from the cortex and numerous branches formed by union of the venulæ rectæ. The venous system of the human kidney is in its general arrangement very probably much like that of the dog, although the preparations at my disposal do not enable me to speak positively on this point.

It is not my purpose to speak extendedly concerning renal secretion. It may be permitted, however, to call especial attention to certain points in the structure of the renal tubule and their relation to the terminal branches of the renal artery. The regular sequence and distribution of the four types of epithelium to which I have called attention is to be noted and further the fact that all parts of the renal tubules are bathed in blood which has first passed through the glomeruli of the renal corpuscles; the small percentage of arterial blood which may pass directly to the tubules, it seems to me, may be disregarded. There are, as is well known, two leading theories on the nature of urinary secretion, tersely stated by Hans Meyer as follows in a recent summary of observations on renal function: "According to one of these theories, which was developed most fully by Heidenhain, we have to do with a true secretory process by which water and perhaps the salts pass through the glomerulus, whereas the specific constituents of the urine are liberated from the tubules, so that the sum of both secretions is represented by the outflowing urine. According to the other hypothesis, which was first proposed by Ludwig and subsequently modified by his successors (in a biological sense), there goes on in the kidney, side by side with the glomerular

activity, dependent essentially on the mechanical conditions of the circulation, and independently also of the secretion of certain urinary constituents, a process of resorption in the urinary tubules. Through this resorption, the slightly concentrated secretion of the glomerulus, corresponding to the water of the blood, undergoes concentration to a point characteristic of the urine.'' The weight of evidence appears to substantiate the statement that blood-plasma minus the albuminates, but with certain salts present in the blood, is secreted or passes out by filtration or transudation by the glomerular epithelium. What significance should be ascribed in the process of secretion or filtration to the fact that the endothelium of the glomerular capillaries, which are relatively large, is of the nature of a syncytium and presents minute pores (Drasch, V. v. Ebner), I am not prepared to say. It seems to me, however, of importance to note that it has been estimated that about one-twelfth to one-fourteenth of the volume of blood entering through the glomerular vessels is abstracted during the course of the blood through the glomerular vessels, and since about 345 to 430 litres of blood pass through the human kidney in the course of 24 hours, 30 litres of fluid would thus be abstracted from the blood and pass into the glomerular capsule of the renal corpuscle (Tigerstedt), the blood leaving the glomeruli being thus proportionately concentrated. To this latter fact attention may be especially drawn, since, as has been shown, practically all the blood found in the capillaries surrounding the various parts of the renal tubules is blood which has passed through the glomeruli and is presumably thus concentrated. The proximal convoluted portions of the renal tubule have very generally been regarded as the tubular segments in which a secretion, perhaps a secretion of specific constituents takes place. Distinct secretory granules such as described for mucous and serous glands have not been discovered in any tubular segment of the renal tubule, although there are many data at hand which are suggestive and point toward a specific secretion by the epithelium of the proximal convoluted portion. We may mention, for instance, the sodium sulph-

indigotate experiments of Heidenhain and Ribbert, the detection of uric acid granules in this epithelium and the presence of what has been regarded as secretory granules, also the presence of fat granules more particularly in certain animals. Uric acid and phosphoric acid appear to be specifically secreted, since Hans Meyer states that their quantity in the urine cannot be increased by any of the known diuretics. And it may be suggested that the presence of concentrated blood in the capillaries surrounding the proximal convoluted portion of the renal tubules may favor the specific secretion. Experimental evidence seems to favor the view that there is a compensatory resorption of water, perhaps also certain salts, during the passage of the renal secretion through the tubules. The suggestion is made that this resorption takes place in that portion of the medullary loop lined by the flattened epithelium. The arteriolæ rectæ of the medulla, which result, almost without exception, through a division of efferent glomerular branches, thus carrying what, for want of a better term, is here spoken of as concentrated blood, are in close relation with the medullary loop, thus also that portion lined by the pavement epithelium. The venulæ rectæ are especially numerous. This view is also held by Peter. The experiments of Ribbert and Hausman and Hans Meyer, who obtained an increased flow of urine of less concentration after removing one kidney and the medullary portion of the other kidney, are cited as favoring the view that resorption takes place in the medullary loop and presumably in that part lined by pavement epithelium, since the segments thus lined would be removed more fully than other parts in removing the medulla. Since, however, in such experiments and for the tubules injured, the urine could not pass from the proximal to the distal parts of the injured tubules, such experiments can only be suggestive, though not conclusive, since for instance it would be impossible to show that the distal convoluted portions do not participate in this absorption. More conclusive seem to me the arguments used by Peter, who shows that in animals with renal tubules having long medullary loops and long segments lined by the flattened pavement epithelium,

in which there would thus be given greater opportunity for resorption, the urine is more concentrated, for instance, in the dog and cat with renal tubules having only long loops and the rabbit in which these predominate; the urine of these animals has a higher concentration than the urine of man and the pig, in which the short medullary loop, with short segments lined by the pavement epithelium are present in greater number than the long loops. What function may be ascribed to the distal, the thicker, arm of the medullary loop and the distal convoluted portion, which again has a special epithelium, is difficult to say. Metzner believes that certain portions of the distal segment of the medullary loop have a secretory function, while Ribbert states distinctly that "a secretion of specific substances takes place only in the convoluted tubes of the first order, while in the loops of Henle the distal convoluted portions and the collecting tubules there takes place exclusively or for the greater part a resorption of water." The staining observed in these tubular segments after the injection of sodium sulphindigotate may be explained by an absorption of the stain after its secretion in the proximal convoluted portion and after a concentration due to absorption of water in the tubular segments lined by flattened epithelium, preceding the distal arm and distal convoluted portion. Toxic agents secreted from the kidney are said to affect first the renal corpuscle and secondly the distal convoluted portion, explained perhaps also by the fact that the urine secreted in the renal corpuscles is concentrated in its passage through the renal tubules and it is owing to this concentration that the distal convoluted portions are primarily affected. On the other hand Peter states with reference to the function of the distal arm and distal convoluted portion, and I use his own words: "Ich glaube nicht dass man diesen verschiedenen Bezirken völlig die gleiche Aufgabe zuerteilen kann, wie dem hellen dünnen Schleifenteil,—dazu sind die Epithelien gar zu verschieden." Peter, as will be remembered, recognizes several types of epithelium in these tubular segments, which appeared to me not sufficiently characterized to warrant such subdivision. May I in closing express the hope that in future

experimental work on the mammalian kidney, due recognition be given to the structural and morphological characteristics of the mammalian renal tubule, to the relative position of its different segments and to the very characteristic relations of these to the terminal branches of the renal vessels.

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ON THE FORMATION AND FATE OF ANTIBODIES*

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IT is not any part of my purpose at this time to dwell especially on the importance of antibodies in immunity, recovery, and treatment in infectious diseases. Nor will any attempt be made to discuss the nature or the diverse modes and range of action of this remarkable group of substances or the theories in regard to them. I wish to confine myself to the discussion of some of the aspects of the formation and fate of antibodies under various conditions.

Any substance capable of inciting the formation of antibodies, when introduced into suitable animals, is an antigen. Of late it has been customary to designate as vaccines bacteria used as antigens after having been altered in various ways and especially after having been killed by heating. Microbes and various microbic derivatives, toxins of various kinds, red corpuscles, and other cells as well as serum constitute or contain the most important antigens, which appear to be protein colloids, and the antibodies which will concern us most at present are antitoxins, lysins, agglutinins, and opsonins.

THE SIMPLE ANTIBODY CURVE

By accurate measurements at frequent intervals of the content of the blood in newly-formed antibodies, after the introduction of antigen, interesting facts have been learned in regard to the manner of antibody formation. The most noteworthy generalization so far attained in this respect is represented by the antibody curve or curve of immunization. In this curve the ordinates represent the time after the introduction of antigen and the abscissæ the amounts of antibody pre-

* Delivered Jan. 15, 1910.

sent in the serum of the animal as determined with respect to some accepted standard.*

The simplest antibody curve, that obtained by measurement of the antibodies that develop on a single injection of a suitable quantity of antigen in a wholly normal animal, may be described, briefly and in general terms, as follows: During the first two or three days there is, as a rule, either no change in the previous condition, or there may be a fall in specific antibody if such is present as often is the case; this period of latency or incubation, also referred to sometimes as the negative phase, the duration and intensity of which are largely dependent on the dose of antigen, is succeeded by a rather sudden appearance of newly formed antibody or antibodies, which increase at first rather rapidly until about the sixth or seventh day and then somewhat slower until the maximum is reached, which in most cases seems to take place about the ninth day; soon after this culmination a general fall in the amount of antibody begins and continues until the normal standard is reached. This is the third phase of the antibody curve and it may last in some instances only a few days, in other cases it may extend over several weeks, and even longer.

ILLUSTRATIONS OF THE ANTIBODY CURVE

In order to substantiate the statement that the course outlined is fairly representative of antibodies in general under the conditions mentioned and represents a law of fundamental importance in the physiology of immunization, it may be well to refer to specific instances.

Ehrlich who first recognized the double relation between

* In order to determine the content of the blood in antibodies over a longer period it is necessary to make tests at frequent intervals so as to obtain sufficient data for the construction of comprehensive curves. For this purpose the different samples of sera for the same curve should be tested at the same time and so far as possible with the same test-objects. As the samples of sera are secured at successive bleedings they should be stored away from the light at or below 0°C.

antigen and antibody was also the first to observe that the development of immunity as measured by the formation of antibodies takes a wave-like course, and Brieger and Ehrlich [1] constructed the first antibody curve by measuring tetanus antitoxin in the milk of goats immunized with tetanus toxin. The experiment was made on previously immunized animals evidently in the period of decline of antitoxin production, and the immediate consequence of the reinjection was a fall in the antitoxin followed by a rise on the third or fourth day, the acme being reached on the fifteenth day whereupon a gradual decline set in. Salomonsen and Madsen [2] determined that in horses antitoxin after the subcutaneous injection of diphtheria toxin develops according to the same general plan, and their observations were confirmed by Dean [3] and others.

In these instances the curves represent the course of antibodies in the blood after the injection of a single dose of antigen in animals in the declining phase of antibody formation. Much the same sort of curve results when antigen is injected in suitable normal animals that have not been immunized before. In guinea-pigs Pfeiffer and Marx [4] found a single intraperitoneal injection of cholera vibrios succeeded by the appearance of antibodies in the blood on the third day after which followed a rapid rise until the eighth day when a gradual fall set in. The investigations of Morgenroth [5] showed that antirennin appears in a wave-like manner in the blood of goats injected with rennin, only that here the acme was reached quite early.

According to Von Dungern [6] the precipitins that form in rabbits after the injection of the plasma of certain sea animals also describe a more or less typical curve, the latent period after the primary injection of the quantities he used lasting about five days. Forssman and Lundström [7] obtained a typical curve for botulismus antitoxin after a single injection of toxin, as did Madsen and Walbum [8] for antiricin and Famulener [9] for the antitoxin against the bacterial hæmolysins in beef-broth cultures of vibrio naskin (vibriolysin) and *Staphylococcus aureus* (staphylolysin). In rabbits injected with ox blood,

Bulloch [10] traced a typical curve for the specific hæmolysin and numerous instances, many from personal observation, might be given of the wave-like rise and fall described by the antibodies for red corpuscles that develop in response to the injection of alien blood.

Numerous researches have established definitely that the antibodies, especially the agglutinins, for typhoid bacilli, colon bacilli, cholera germs, and dysentery bacilli after a single injection in the normal animal of the respective antigen in various modifications all give typical curves.[11] This also holds true for the pyocyaneus bacillus,[12] the glanders bacillus,[13] and paratyphoid bacillus B.[14]

This enumeration, which makes no claim to completeness, must include, however, a general statement in regard to the opsonins. One outcome of the recent investigations of this antibody by Wright [15] and others is the demonstration that the course of newly-produced opsonins in the blood does not differ essentially from that of other newly-formed antibodies.

THE EFFECT OF QUANTITY AND MODE OF INTRODUCTION OF ANTIGEN ON PRODUCTION OF ANTIBODIES

The height and duration of the simple curve naturally vary much, depending on the kind and amount of antigen introduced, the place of introduction, and in large measure also on the individual animal. General statements only can be made in regard to the relation between the quantity of antigen introduced at one time and the range of the resulting curve. In the case of many antigens it seems that up to a certain point the larger the amount of antigen the animal tolerates without serious disturbances the greater the production of antibodies and the longer the time before the normal level is reached again, but in the case of many antigens the optimum dose, as measured by the resulting amount of free antibody, may be far below the maximum quantity the animal can stand. Certainly the yield of antibodies does not appear to increase with the same ratio as the quantity of antigen is increased. As I shall

point out, the power of the cells to take up and dispose of antigen soon reaches its limit. Now the optimum dose of antigen as measured in free antibody probably should not exceed this limit because the antigen in excess of this limit to an extent may remain in the body fluids and by uniting with the antibody as it is produced prolong the period of latency and reduce the amount of free antibody.

Relatively small quantities of certain bacteria and of alien corpuscles cause a greater output of specific antibody on intravenous than on subcutaneous injection. Friedberger and Dörner [16] found that 300,000 to 900,000 goat corpuscles injected intravenously in rabbits would raise the specific hæmolytic power of rabbit serum 5 to 20 times above normal, which was considerably more than the rise obtained on subcutaneous injection. Mertens secured 20 to 150 times as much antibody on intravenous as on subcutaneous injection of the same quantity of cholera germs killed by heat. In other cases the intravenous injection does not seem to be so productive of antibodies as the subcutaneous. This is true of diphtheria toxin and Simonds had greater response as measured by the opsonic index on subcutaneous than on intravenous introduction of killed streptococci in rabbits. Probably the intravenous injection of relatively small quantities of antigen is the preferable method in many cases when it is attempted to study experimentally under comparable conditions the effect of various factors on antibody formation.

In animals previously subjected to the action of a certain antigen the mechanism of antibody production may be especially sensitive to that antigen and respond to proper doses more promptly and freely than is the case in the fresh animal. This may be the reason of the quick rise in opsonin noted by Wright and others to occur sometimes on injection of specific vaccine in chronic infections.

When a series of successive injections of antigen are given at varying intervals in suitable animals more or less complex antibody curves are obtained which differ much from the simple curve. It is out of question to consider in detail the many

schemes that have been and are used to secure a maximum concentration of antibodies in immunization. Speaking generally, it is the rule in immunization with toxins and bacteria to begin with relatively small and harmless quantities and to reinject with increasing quantities, carefully graded in order to avoid severe reactions and prolonged depressions of antibody production, at intervals of a few days, three or four or more, over a considerable period or until the desired antibody concentration is reached in the blood.* In the case of horses immunized with diphtheria antitoxin great variation exists in the power to produce antitoxin and sooner or later the power is lost to be recovered, if at all, only after intervals of complete rest. Rarely an animal is discovered in which a sort of high antitoxic equilibrium is established that continues for months without much change either on bleeding or injection of toxin.[17] Experience has shown that usually it is most advantageous to bleed animals in the course of forced immunization eight or ten days after the last injection as the antibody concentration is likely to be high at that time.

What may take place when the antigen is injected in increasing quantities every three or four days is indicated by the agglutinin curves obtained by Jörgensen[18] in animals immunized in that way with typhoid bacilli. This curve appears to consist of a number of superimposed simple curves of gradually increasing height up to a maximum; the decline which eventually sets in and continues in spite of the continuation of the injections is marked by elevations of regularly decreasing height. Deutsch found that weekly intravenous injections of swine erysipelas in gradually increasing quantities gave a series of curves each with the apex approximately 8 to 10 days after the corresponding injection, the maximum being reached in the fourth month.[19] And Famulener[20] by repeated injections of increasing doses of vibriolysin and

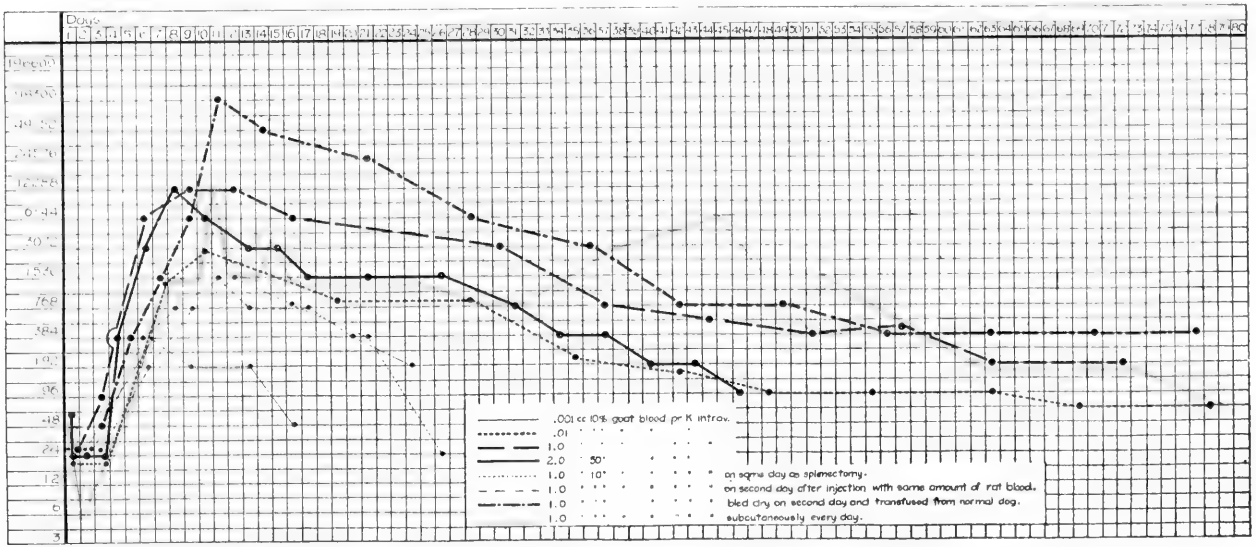
* The possibility of producing a prolonged or "cumulative" negative phase in case of established infection by too large and too frequent doses of vaccine, and its dangers to the patient, are emphasized by Wright.

staphylolysin every second, third or fourth day for about six injections produced gradually increasing but zigzag curves in which the maximum was attained about ten days after the last injection. On the other hand, the curves obtained by Klien [21] in rabbits injected at intervals of about five days with progressively increasing quantities of typhoid bacilli and by Meakins [22] in rabbits injected with increasing quantities of dysentery bacilli, staphylococci and streptococci at more irregular intervals show a steady increase of the antibodies up to a certain point when some antibody or other would fall behind while others would continue to increase, their ultimate fate not having been traced. Whether the differences between these curves and those of Jörgensen and others are dependent on differences in technic must be left unsettled.

On daily injections subcutaneously in goats of typhoid bacilli and cholera germs in constant doses Jörgensen obtained agglutinin curves with a somewhat prolonged latent period, the maximum being reached a few days later than after a single injection; the curve now maintained a high level for a number of days and then gradually declined in spite of the continuation of the injections. Von Dungern was not able to materially modify the course of the precipitins in the blood of rabbits injected with crab plasma by repeated injections during the latent period.

I have made observations on dogs injected subcutaneously every day for several months with the same quantity of goat blood. In one set the quantity was 1 c.c. of a 10 per cent. suspension of goat blood per kilo of dog, in another one thousandth that amount, and in a third one two-thousandth. In all the content of the blood in antibodies reached a fairly high level on about the tenth day, which represents some prolongation of the first and second phases of the simple curves obtained from a single injection of any of the doses given. And in the case of the smaller quantities the concentration reached was much greater than obtainable with a single dose, at the same time as it was maintained at a fairly constant high level for months. With the larger doses, however, the concentration at

CHART I.



Antibody production under different conditions as illustrated by the formation of lysin for goat corpuscles in dogs injected with goat blood.

the acme was not any greater than usually obtained with a single injection of that dose; in the third phase of the curve definite rises occurred, but on the whole a steady decline seemed to be taking place.

There are then various procedures that may be used to secure an accumulative and continued production of antibodies. With small doses of antigen it may be accomplished by daily injections of constant quantities, at least in certain cases. With increasing doses the indications are that in many cases the best results are obtained when the injections are made toward the end of the second phase of the simple curve, the new curve starting, so to speak, from one of the levels of the previous curve. It appears, however, that animals under the continuous influence of antigens eventually lose the power to produce antibodies and that in cases where different antibodies are formed at the same time this loss of power may occur earlier for some antibodies than for others.

McClintock and King [23] were able to produce a considerable degree of immunity in animals by the oral administration of toxins at the same time as digestion was inhibited by suitable means, but as yet the exact course of the antibodies in the blood under such conditions has not been traced.

THE SIGNIFICANCE OF THE ANTIBODY CURVE

From the foregoing statements we are warranted in concluding that the antibodies which form in response to antigens in animals of different species appear to pass in and out of the blood in a similar and typical manner, at least when the conditions are relatively simple and uncomplicated. The close similarity in formation of various antibodies in different species indicates that the mechanisms of immunization are governed by the same law and constitute physiological entities. Taking the curve as a whole it represents the rise and fall of free antibodies in the blood after immunization. To explain the rise and fall of diphtheria antitoxin Salomonsen and Madsen assumed that production and destruction of antitoxic substance take place at the same time. Assuming this to be true of anti-

bodies in general, then we may regard the antibody curve in any part of its course as representing the balance between production and loss of antibody. On the basis of this view it is evident that during the second part of the curve the amount of antibody that is being produced exceeds increasingly the amount that is being lost and consequently antibody accumulates in the blood and other fluids. When the acme is reached production and loss are equal, but the production soon falls so that it no longer makes up for the loss and the curve gradually sinks until a permanent level is reached. The primary fall, so often noted in the curve, was first observed (Ehrlich) in animals that were reinjected during the declining phase. It also occurs, though apparently not always, when the blood normally contains antibodies for the antigen injected. By Ehrlich the fall was regarded as the result of neutralization by the antigen of antibodies in the blood, but in many instances the amount of antigen introduced hardly seems enough to account in this way for the fall observed. And there is room also for the conception that the antigen, at least in part, promptly is bound by cells whose power to produce antibodies for a period may be hindered soon to be resumed at increased rate. In the meantime the temporary depression of function in conjunction with possible neutralization by antigen of antibodies in the blood registers itself in the primary fall.

THE RELATION OF NEWLY-FORMED TO NORMAL ANTIBODIES AND THE EFFECT OF THE PRESENCE OF PREFORMED ANTIBODIES ON THE ACTIVE RESPONSE TO ANTIGEN

The blood of various animals, including man, normally contains small amounts of a large number of antibodies. As in the case of many animals, the blood of normal human beings contains lysins, agglutinins, and opsonins for many different bacteria and red corpuscles. Other antibodies are also present, such as antitoxins. Small amounts of diphtheric antitoxin are present in the blood of new-born infants. These so-called normal antibodies which appear to arise in the course of normal

metabolism usually maintain a fairly constant balance between production and loss in health. In many instances they have been found to possess specific affinities for antigenic substances and there are grounds for the view that they are not essentially different either in structure or otherwise from the corresponding bodies that are produced on immunization. One important reason in favor of this view, it seems to me, is the fact that the primary fall below normal may occur when an antigen is introduced in a normal animal is specific, that is, affects only the preformed or normal antibodies for the particular bacterium or corpuscle injected. Against the view that in immunization there is produced an increased quantity of some preexisting antibody or antibodies may be urged the fact that instances occur in which the antibody produced by immunization appears to lack the normal analogue. Thus normal goat blood is said not to contain antivibriolysin which is produced when goats are injected with vibriolysin, and Von Dungern failed to find any precipitin in normal rabbits for the plasma of certain sea animals. It is possible that in cases of this kind minimal amounts only of the antibody occur normally.

That diphtheria toxin in certain animals fails to give rise to antitoxin on intravenous injection has been ascribed (Dzierzgowski) to neutralization of the toxin at once on its injection by antitoxin normally in the blood. (That subcutaneous injection of toxin does evoke the formation of antitoxin has been accounted for by local production.) Leaving aside the question whether the explanation is correct or not, the facts with reference to the effect of preformed antibodies on the response to other antigens are quite different from those assumed to be true with respect to diphtheria toxin in this explanation. The facts are that normally the blood may contain vastly more antibody than sufficient to completely neutralize the amount of antigen which when introduced in the blood nevertheless gives rise to the formation of antibody. Thus botulismus antitoxin is formed on intravenous injection of toxin, notwithstanding the fact that the blood of the animal normally in a few cubic centimetres contains antitoxin enough to wholly neutralize

in vitro the toxin injected. In view of these facts we may assume that the cells which produce antibodies in many if not most instances have a strong affinity for antigenic substances. In actively immunized animals we know that even when newly-formed antibodies are present in the blood and other fluids in relatively large amounts reintroduction of antigen may increase anew the output of antibodies. In this case there is no indication that neutralization of antigen takes place to the extent that seems possible. It does look, however, as if the affinity for antigen on the part of the cells charged with forming antibodies becomes augmented in the course of the active perform-

CHART II.

Passive immunization by transfusion and subsequent injection of antigen.

ance of their function. It has been found further that the introduction of antibody at the same time as antigen, separately or mixed with it, may give rise to antibody production. Special methods of immunization based on this principle have been devised by Calmette and by Besredka. The injection of rabbits with mixtures of typhoid bacilli and agglutinating rabbit serum was found by Nicolle to incite the formation of agglutinins. Recently Theobald Smith [24] has demonstrated that well-marked active immunity may be induced in guinea-pigs by mixtures of diphtheria toxin and antitoxin that produce no local lesions and no constitutional disturbances. In addition to the more

obvious explanation of such phenomena we have the one urged by Forssman in his attack on Ehrlich's theory, namely, that the antigen proper and the substance that unites with the antibody are different substances. But this view, although it might appear to simplify matters, does not seem to me to harmonize well with some of the results obtained on active immunization of passively immunized animals. In animals injected with typhoid or cholera antiserum, Jörgensen and Madsen [25] failed to obtain any evidence of active production of antibodies on subcutaneous injection of the respective bacteria in quantities that in fresh animals result in typical curves. In this case the antigen appears to become neutralized. Tallquist [26] obtained analogous results on combined passive and active immunization against vibriolysin. He found, however, that if the toxin is injected intravenously in the passively immunized animals an antibody curve of small range may be obtained; furthermore, that an active curve results if the antigen is introduced intraperitoneally or subcutaneously immediately after the antiserum is injected into the circulation; but if the preformed antibodies have circulated in the blood for two hours or more no active curve results if antigen is injected extravascularly. It is noteworthy that in these experiments Tallquist used an alien antiserum for the passive immunization.

We may conclude that under certain conditions of passive immunity the circulating antibodies do hinder union of antigen with antibody-producing cells. This fact would speak against the view advanced by Forssman. That antibodies are formed in passively immunized animals when antigen is introduced directly into the blood indicates again a special affinity for antigen. When the antigen is injected subcutaneously the process of absorption may give the antibodies a better opportunity to bind it firmly.

THE FORMATION OF DIFFERENT OR SISTER ANTIBODIES FOR THE SAME CELL

In many investigations on antibody formation after the injection of substances, some of which contain distinct antigens, attention was first centred on the study of some single

antibody, *e.g.*, of agglutinin on the injection of typhoid bacilli or of lysin on the injection of alien red corpuscles. In such cases several kinds of antibodies are developed; typhoid bacilli and alien corpuscles in suitable animals give rise to specific lysins, specific agglutinins and specific opsonins, and probably also other specific bodies. In some cases different antibodies appear to be increased in the same proportions and to describe parallel curves. This is true of the lysin, agglutinin, and opsonin for goat corpuscles in the blood of dogs injected with goat blood. But the serum and the other fluids of dogs injected once with rat corpuscles may give marked rise in the agglutinin and opsonin for these corpuscles but not in the lysin. After a single injection of dead typhoid bacilli in man the agglutinin does not fall at the same time as the lysin and the opsonin.

Lack of parallelism has been noted also in the course of immunization by repeated injections at intervals of increasing doses of antigen. At first the antibodies may all increase at the same rate, the agglutinins later falling behind, as in Klien's experiment with typhoid bacilli,[27] or the lysins and opsonins may decrease while the agglutinins are still increasing, as in Meakins' experiments with dysentery bacilli.[28] In rabbits progressively immunized against staphylococcus and streptococcus Meakins observed a steady rise in opsonin, but only an insignificant increase in agglutinin and lysin.

This asymmetry in the curves of the antibodies educed in the same animal suggests that we are dealing with distinct substances, the production of which is dependent on similar yet not identical mechanisms.

MULTIPLE IMMUNIZATION

The influence of the simultaneous or successive introduction of distinct antigens on the production of the corresponding specific antibodies is of interest because of its bearing on certain aspects of mixed infections. Several writers [29] conclude that in multiple infections and immunization the production at the same time of different agglutinins takes place without any change in the onset, intensity, and duration of the production

of any single agglutinin which is claimed to proceed as in infection or immunization with the single bacterium.

On the other hand, Iversen [30] and Kraus found that secondary infections, especially pneumonia, in the course of typhoid fever depress the agglutinin curve. In rabbits infected with typhoid bacilli or with rabbit septicæmia, Friedberger [31] found a considerable diminution of the production of amboceptors for cholera germs. I have repeatedly observed that in dogs in the course of immunization against alien blood, the development of pneumonic infection may suspend almost completely the production of antibodies for the alien corpuscles (see Table I).

TABLE I. THE INHIBITIVE EFFECT OF INTERCURRENT PNEUMONIA ON THE FORMATION OF SPECIFIC LYSIN IN DOGS INJECTED WITH GOAT BLOOD.

Days	0.1 c.c. 10 per cent. goat blood per K. subcutaneously daily		1.0 c.c. 10 per cent. goat blood per K. subcutaneously daily	
	Healthy dog	Pneumonic dog	Healthy dog	Pneumonic dog
1	24	24	24	24
2	24	24	6	6
3	48	24	12	12
4	96	24	..	..
5	..	..	96	24
6	3072	192	..	..
7	6144	96	768	48
8	..	..	1536	96

The figures give the dilution of the heated serum at which lysis of goat corpuscles ceases, guinea-pig serum being used as complement.

Working with dead typhoid and colon bacilli Jörgensen [32] found that injections in the second phase of the curve—3rd to 9th day—of either the antigen already introduced or of some different antigen produces a relatively small development of antibodies. Analogous facts are recorded by Von Dungern in regard to precipitins. I find that the simultaneous introduction in dogs either subcutaneously or intravenously of two or three different kinds of alien corpuscles in moderate doses may result in the production of less antibody for any one corpuscle than when the same amount of that kind only is injected. Further, that in dogs injected with alien corpuscles the injection of a different corpuscle a few days later may give less antibodies for

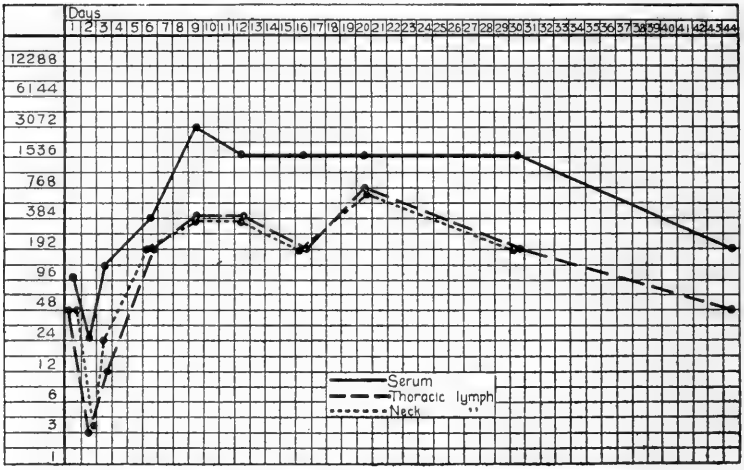
either corpuscle than are usually obtained when but one injection is made. This apparent inability of the dog when influenced by more than one antigen to produce any of the respective specific antibodies to the same extent as any single antibody is produced under the influence of the corresponding antigen only, might be taken to indicate that largely the same mechanisms or groups of cells produce all antibodies. It would be different if distinct groups of cells were charged with the exclusive production of definite antibodies. Crippling of the mechanisms of antibody formation by the simultaneous or successive introduction of different antigens might be urged in explanation of the gravity of many mixed and secondary infections. The lessened resistance to streptococcus and other infections of the acute infectious diseases, notably smallpox and scarlet fever, and of tuberculosis may depend in large measure on the inability of the cells charged with the production of antibodies to respond freely to the stimulus of more than one antigen at a time. And the aggravation of the primary disease, *e.g.*, tuberculosis, on the occurrence of a secondary infection may depend on depression in the manufacture of tuberculous antibodies by the antigen of the new infection. This possibility is illustrated by the suspension in a tuberculous person of the tuberculin reaction by an attack of measles. Here we can assume with Von Pirquet [33] that the measles antigen suspends the production of the antibodies on which the tuberculin reaction depends. In connection with this may be cited the observation by Ransom that in a calf the loss of tetanus antitoxin, introduced in kindred serum, was quite gradual until the 45th day when tuberculous toxins were injected. This was followed by fever and rapid fall in the tetanus toxin—a possible hint to the effect that the loss of antibodies may be hastened under such conditions.

ON THE DISTRIBUTION OF ANTIBODIES IN BLOOD AND OTHER FLUIDS

In his classical experiments on immunity through inheritance and nursing, Ehrlich [34] demonstrated that in active immu-

nization certain antitoxins appear in the milk in considerable quantities, and Brieger and Ehrlich [35] constructed our first antibody curve by means of data obtained by measurement of the tetanus antitoxin in the milk of immunized goats. Since then other antibodies have been found in milk and the occurrence established of antibodies in transudates and other fluids besides the blood, as, for instance, of destructive substances for typhoid bacilli in the thoracic lymph by Meltzer and Norris [36]; but systematic study on the distribution seems not to have been made until recently.[37] In a number of instances it is found that

CHART III.



Specific agglutinin in blood and lymph of dogs injected with rat blood.

normal antibodies are most concentrated in the blood, less in the thoracic lymph, and still less in the neck lymph, while traces only occur in the cerebrospinal and pericardial fluids and aqueous humor; and at the height of the immunity curve this relative concentration remains practically the same, at least so far as blood and lymph are concerned.

For the purpose of closer study of the distribution of antibodies in the course of immunization Dr. Carlson and myself selected dogs which we injected intravenously with the blood of

white rats and of goats. Only one injection was made, the amount being 1 c.c. of a 10 per cent. suspension per kilo of the weight of the dog. The animals so injected were killed at different intervals after the injection and the amount of antibodies in the blood, lymph, etc., carefully determined. In this manner estimations were secured of the antibody content of the fluids examined at various stages of immunization.

The results show clearly that so far as the blood, the lymph from the thoracic duct, and that from the neck are concerned the changes in the concentration of the antibodies during the course of active immunization run practically parallel. This applies to the lysin, agglutinin and opsonin for goat corpuscles, and to the agglutinin and opsonin for rat corpuscles, no increase demonstrable taking place in the lysin for rat corpuscles. The concentration in the two lymphs is about the same and always somewhat lower than in the blood-serum, but in the case of lymph as well as blood, composite curves,—in which the abscissæ mark the day after injection on which the dog was killed and the fluids collected,—correspond quite accurately with the simple curve obtained by determinations at short intervals of the content in antibody of the blood of the same animal. We may say then that in dogs injected with goat and rat blood the newly formed antibodies in the lymph appear and disappear at the same time and describe the same wave-like curve as that in the blood.

As regards the cerebrospinal fluid and aqueous humor of dogs injected with goat blood, there was a complete absence in these fluids, at any stage of the reaction, of agglutinin. Lysin and opsonin, however, were present in both the fluids during the period of high antibody content in the blood and lymph, but only in traces. It is noteworthy that in dogs injected with rat blood, opsonin only was demonstrable in the cerebrospinal fluid in which it gave a typical antibody curve suggesting that an easy passage exists for this antibody. (The aqueous humor was not studied in the rat dogs.)

In dogs transfused with the blood of actively immunized dogs, the antibodies may be detected in the thoracic and neck

lymph in from one-half to three hours and very soon the same relative concentration of antibodies in lymph and blood is established as in normal and in actively immunized animals. Hence it seems probable that in active immunization the distribution depends on the relative antibody content in blood and lymph rather than on place of formation of antibodies and that the rate of passage into the lymph probably is in part dependent on the concentration in the blood.

ANTIBODY FORMATION IN ACUTE INFECTIOUS DISEASES

Specific antibodies are produced in microbic diseases in response to the action of the infecting agents which contain antigenic substances. Naturally the degree and manner of formation of antibodies in infectious diseases are subject to variation depending on the nature of the infection and other factors. While there is still room for much systematic study in this part of the physiology of infectious diseases the facts at hand appear to warrant certain statements of a more or less general character.

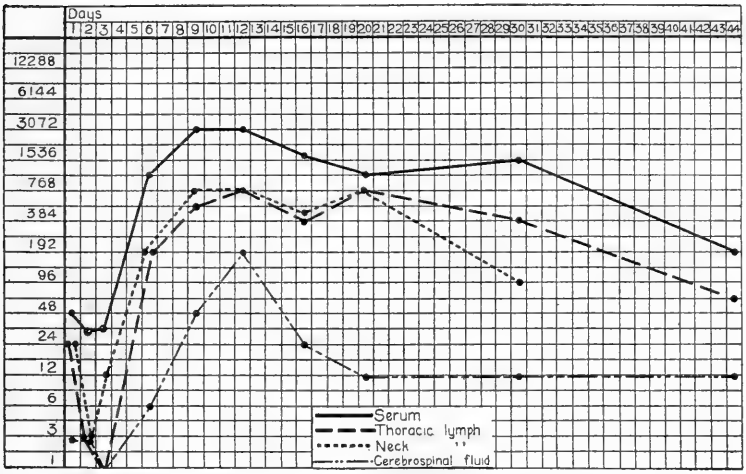
In several acute bacterial diseases the course of specific antibodies for the infecting agent in the typical attack terminating promptly in recovery without complications resembles altogether that of the antibody curve obtained after a single injection of antigen in a normal animal. This has been found to hold good for the pneumococco-opsonin in pneumonia,[38] for the streptococco-opsonin in erysipelas,[39] for the diphtherio-opsonin in diphtheria,[40] and also for the diplococcus of Laveran in mumps.[41] It is of interest to note that a rise in diphtheria antitoxin occurs in spontaneous recovery from diphtheria.[42]

The streptococcus opsonin presents characteristic variations in scarlet fever and we have in this fact an additional direct indication that streptococcus from the beginning plays an important rôle in scarlet fever whether it be regarded as the primary cause or not. I say from the beginning because the curve presents a degree of parallelism with the phenomena of the acute stage of the attack,—showing an early fall and rising

as the symptoms abate,—so that streptococcus infection must be the cause of at least some of these phenomena.[43]

In acute articular rheumatism the opsonic index for *Micrococcus rheumaticus* and *Streptococcus pyogenes* follows the same course.[44] As new joints are involved and fever develops the index falls below normal, and on improvement of joint and symptoms the index rises above normal. In certain forms of acute otitis in which pseudodiphtheria bacilli are dominant the

CHART IV.



Specific opsonin in blood, lymph and cerebrospinal fluid of dogs injected with rat blood

opsonic index for these bacilli may cover a wide range, the changes often corresponding to changes in the clinical symptoms.[45]

In the diseases mentioned the specific opsonin practically is the only antibody for the bacteria in question that under present circumstances permits of measurement. The curves obtained all show certain definite relations to the clinical phenomena: During the early stages when the symptoms are pronounced there is a more or less distinct fall in the amount of specific opsonin in the blood. As the symptoms begin to subside the curve rises, suggesting that more antibody is being

set free than necessary to neutralize the pathogenic substance. The curve usually reaches the highest point one or two days or more after the symptoms have passed their acme and then in many cases it falls rather abruptly as if the production of opsonin falls suddenly while a relatively rapid loss continues. The course of the curve is readily affected by complications, at the onset of which it commonly undergoes a distinct depression. In rapidly fatal cases, for instance of pneumonia, the curve may not return from the primary fall but sink lower and lower.

Most of the measurements, on the basis of which the foregoing statements are ventured, have been made by means of Wright's opsonic index. In reply to objections as to the reliability of this method, I would point out that the results obtained in the different diseases and in different cases of the same disease appear consistent; that in scarlet fever, diphtheria, and pneumonia independent observers have reported similar results; and finally that the dilution method whenever used has given results that compare closely with those given by determinations of the opsonic index.[46] For these reasons I have no doubt but that the opsonin curves in question closely represent the actual facts. At the same time I am not blind to the chances for error and the inherent shortcomings of the method for determination of the opsonic index. I would emphasize especially the fact that inasmuch as different bacterial and leucocytic suspensions are used in the different determinations the results cannot be as strictly comparable as they would be if all determinations could be made with the same suspensions and at the same time. And it is also evident that in the comparison as now made between the opsonic power of the fresh serum of the patient and the fresh serum used as the normal standard, no account can be taken of the effect on the opsonic power of each serum the differences in the proportion between the specific heat-stable opsonic element and the heat-sensitive element or opsonic complement of the two sera must have. Assuming on the basis of the duplex constitution of opsonins that, in the case of this antibody as in the case of the similarly constituted lysins, it is the heat-stable element that is increased

in immunization, there can be no question but that a more reliable method of determination of the opsonic antibody in infections will be found in measurement of the heat-stable element by itself. But discussion of the means by which this may be accomplished need not detain us now.

The conditions are more complicated in cholera, dysentery, and typhoid fever in which it is possible to follow the course of at least three antibodies at the same time. In cholera Amako[47] found the opsonin, agglutinin, and lysin curves to run practically parallel in the mild cases and the cases of medium severity. The curves obtained resemble the simple antibody curve, the negative phase being more pronounced, the acme higher and the fall less rapid, in the severe than in the mild case. In extremely severe and foudroyant cases there was no evidence of antibody formation; in the so-called cholera-typhoid cases the negative phase was prolonged and the lysin curve rose earlier than the opsonin and agglutinin curves, this curve being the only one that he obtained in some cases.

A somewhat different type of curve is presented by typhoid fever, especially with respect to the agglutinins. According to the careful observations of Jörgensen,[48] the agglutinin formation in typhoid fever in most cases begins in the first or the early part of the second week of the disease. The maximum is usually reached in the third week—according to Iversen as a rule about the 20th day. In some instances the period of latency may last much longer than indicated, but it must be remembered that it is often difficult to determine the exact period at which an attack of typhoid fever begins. In the prolonged latency and the length of time intervening between the onset of the infection and the acme of the agglutinin curve of typhoid fever, this curve resembles more the curve given by animals which have received daily injections of typhoid bacilli for some time than the curve given by animals which have received but a single injection of antigen. In some cases of typhoid fever the agglutinin curve begins to fall while the infection is still more or less active and herein we see still further resemblance to the curve of daily injections of antigen

in which the fall may begin and persist while the injections are continued. This is all in accord with the character of the typhoid infection which we know continues more or less unaltered for a considerable though variable number of days and subsides more or less gradually so that the agglutigens and other antigens are not received in one concentrated dose as it were, but continuously so long as the infection lasts.[49]

Whether the curves are parallel in the latter part of their course has not been determined. Scattered observations show that typhoid agglutinins and opsonins may remain above normal for several months and even years after convalescence. It may be that in such cases the bacilli persist in some part of the body and there maintain a more or less plentiful supply of antigen.

The course of the lysin and opsonin in typhoid fever has not been followed so closely as that of the agglutinins. The results obtained by Richardson,[50] by Stern and Körte,[51] and others from study of the lysin, and by Aaser,[52] Clarke and Simonds,[53] and Böhme [54] from estimations of the opsonin indicate that the course of these three bodies is essentially the same at any rate so far as concerns the first and second phases of the curve. Gaethgens [55] and Hamilton [56] find that while the opsonin returns to normal in three or four weeks after complete recovery from typhoid fever, in chronic carriers it may be increased so much as to be of diagnostic value. A systematic study of the antibodies in typhoid and paratyphoid fever by means of careful, simultaneous measurements in each case of the series would surely develop facts of great interest.*

* According to Bert and Lamb [57] in sharp attacks of Malta fever lasting a short time only, agglutinins appear in large quantities early in the disease and remain nearly constant until convalescence is established. In cases that set in acutely, but become subacute or chronic, agglutinin is present in large quantity early but in lower and variable amounts in later stages. In severe cases ending fatally in a short time agglutinins develop in small amount only and in severe cases running a prolonged course with one or two relapses agglutinins may be present in large quantities early in the disease but disappear almost wholly before death.

WHERE ARE ANTIBODIES PRODUCED?

The formation of antibodies furnishes many difficult problems, one of which concerns their place of origin. So far the principal experimental investigations attacking this problem directly have dealt largely with antibodies for bacteria. Pfeiffer and Marx,[58] Deutsch,[59] Wassermann, and others obtained results that point to the blood-making organs as the seat of formation of the antibodies for cholera and typhoid germs. Pfeiffer and Marx brought to light the fact that after a single injection in guinea-pigs and rabbits of cholera bacteria, killed by heat, the spleen, the bone-marrow, and the lymph-nodes show a definite increase of specific antibodies before any increase can be detected in the blood. A little later these tissues become less active while the blood steadily gains. From this result it was inferred that the antibodies either are formed in the blood-making organs and given off to the blood or that they are formed elsewhere and stored temporarily in the organs in question. However, as no storage in the spleen could be demonstrated in passive immunization and as the leucocytes in actively immunized animals at no time were found to contain as much antibody as the serum or plasma it was concluded that the seat of production is in the spleen and other lymphoid structures. Certain results of splenectomy favor this view. In guinea-pigs Deutsch found that splenectomy soon after the injection of typhoid bacilli reduced the production of antibodies and that if spleens so removed were placed in the abdomen of normal animals antibodies soon appeared in their blood.[60] On the other hand, splenectomy some days before the injection seemed to be without any effect, and Pfeiffer and Marx failed to find that splenectomy exercised any effect on the production of cholera antibodies in guinea-pigs. In my own experiments on dogs injected with alien blood, splenectomy just before and just after the injection has been followed by a much lower but otherwise typical antibody curve than is usually the case in dogs under otherwise comparable conditions. If antibodies are produced in the blood-making organs a certain amount should be produced in splenectomized animals by the bone-marrow and

lymph-nodes in which we would expect even a higher degree of activity than usual in order to make up for the loss of the spleen.

Acute loss of blood, as I shall point out shortly, has been found to increase the formation of antibodies in immunized animals; this points to the blood-making organs as a principal factor in their formation. The same inference may be seen in the fact that under certain circumstances the exposure of immunized animals to X-rays prevents the appearance of antibodies in the blood (see p. 30).

Certain facts are interpreted as showing that antibodies may be produced at the place where the antigen is introduced. The most important observations on this point are those of Römer [61] and of Von Dungern [62] to the effect that on immunization by way of the conjunctiva or the anterior chamber specific antibodies may be demonstrable in the aqueous humor before they can be detected in the blood.[63] Naturally the question arises as to the possibility in these instances of importation of antibodies produced elsewhere, and Metchnikoff ascribes their source to accumulating leucocytes.

Forssman [64] obtained botulismus antitoxin on single intravenous as well as subcutaneous injections of toxin. The two curves differ considerably, the subcutaneous curve reaching its highest point on the 15th day and the intravenous on the 10th, the latter being the lower of the two. He interprets this difference between the curves as evidence that different cell-groups with different secretory power are thrown into activity. On the basis of this view there might be obtained, as Forssman points out, as many curves as there are distinct antibody producing tissues; thus there might be a renal curve, a cerebral curve, etc. In all these instances the blood curve would have to be reckoned with because of the absorption of antigen into the blood, and it may well be that the difference in Forssman's curves is the result of the difference in the mode in which the antigen enters the circulation on intravenous and subcutaneous injection, in the former case rapidly, in the latter gradually and much more slowly. For the same reason the greater yield of

antitoxin in horses injected subcutaneously with diphtheria toxin as compared with that in horses injected intravascularly does not necessarily prove a local production of antitoxin at the site of inoculation.

The suggestion is often made that antibodies are formed in the blood itself by the leucocytes. There is, however, no conclusive evidence that this actually is the case. Recently Dreyer and Walker [65] report that in the early stages of agglutinin formation the serum contains more agglutinin than the plasma and they regard this excess in the serum as coming from disintegration, during clotting, of the leucocytes, which they hold either produce or carry agglutinins. But Pettersson [66] and others, notably Schneider,[67] did not succeed in extracting from leucocytes of immunized animals any substance that may be classed with lytic amboceptors or agglutinins.

Now if antibodies are formed by the blood of immunized animals it would be reasonable to look for their production in dogs transfused with the blood of dogs injected with goat blood —1 c.c. 10 per cent. suspension per K, which is an optimum quantity with respect to antibody formation,—a short time previously. But in experiments of this nature by Dr. Carlson and myself we found that no production took place. In the recipients of blood from dogs in the second phase of antibody formation,—*e.g.*, 4th or 6th day,—the antibody course is typical of passive immunization as established by Madsen and others, the decrease taking place rapidly at first and then more slowly. Neither in this nor the other case was there any evidence of formation of antibodies in the transfused animal. Our results warrant the inference that in some animals certain amounts of antigen are quickly removed from the blood or in some way so changed that the antigenic property is lost. In full accord with this result as to the recipient is the fact that the new formation of antibodies proceeds in a perfectly typical manner in donors that are transfused immediately from healthy dogs, the curve in some cases reaching a very high mark, possibly on account of the stimulus of the loss of blood on the blood-forming organs.

It is reasonable to assume that the power of the antibody-forming cells to take up antigenic substances sooner or later reaches its limit. If that be the case the quantity of antigen in excess of this limit might remain in the circulating blood for some time after its introduction. After the injection of rabbits with 30–35 c.c. of ox blood freed from serum, Sachs [68] found by means of a specific lysin, which did not lake rabbit corpuscles, that ox blood remained free in the rabbit blood for two to three days and even longer, disappearing in a more or less critical fashion as the lytic amboceptor was produced in response to the immunization. Free excess of antigen may be detected also by the method of transfusion as shown by the following experiment: The donor was injected with 1 c.c. of goat blood per kilo of weight 14 hours previously; just before the transfusion 500 c.c. of blood were removed from the recipient; the transfusion was continued until the pressure reached normal; the 500 c.c. of blood removed from the recipient were defibrinated and infused into the donor. The following figures give the highest lytically active dilution of the serum of the recipient in the presence of 0.2 c.c. of a 5 per cent. suspension of goat corpuscles and 0.012 c.c. of fresh guinea-pig serum:

DAYS AFTER TRANSFUSION	HIGHEST ACTIVE DILUTION OF SERUM	DAYS AFTER TRANSFUSION	HIGHEST ACTIVE DILUTION OF SERUM
1	24	10	1536
2	24	12	768
3	48	14	384
4	48	17	384
6	768	19	192
8	1536	21	192

So far as the amount of lysin in the blood of the recipient indicates a small quantity only of antigen was introduced in the transfused blood. Evidently the larger part of the goat blood had been removed from the blood of the donor, and that the antibody-forming cells took part in this removal is indicated by the fact that antibody formation proceeded without disturbance, the serum on the sixth day causing lysis in a dilu-

tion of 1 to 36864. These results also support the view that antibodies are produced outside the circulating blood which they enter at the end of the latent period.

THE EFFECT OF ACUTE ANÆMIA ON ANTIBODY FORMATION

In view of the strong indications that the blood-forming organs are the principal seat of the production of antibodies it is of interest to inquire what effect, if any, acute loss of blood, which we know profoundly influences these organs, may have on antibody formation. The earliest observations on this point are those of Roux and Vaillard [69] who found that in horses actively immunized against tetanus toxin, bleeding caused a drop in the antitoxin content in the blood, succeeded by a sharp rise in a short time. They suggested that the immunization had so changed certain cells that they could replace antitoxin just as other products of cellular activity are replaced. Salomonsen and Madsen [70] applied the same explanation to the increase of diphtheria antitoxin in the blood after bleeding. By repeated bleedings during the third stage Schroeder [71] found that the agglutinin curve in the blood of animals injected with typhoid bacilli could be kept up for a considerable time after it usually reaches low level and in some instances even increased above the former maximum. In immunized rabbits as well as in typhoid patients each bleeding was succeeded by a fall and then by a more or less well-marked rise. Madsen and Tallquist [72] show that certain poisons that destroy red corpuscles increase the production of some antibodies by virtue, so they believe, of the same mechanism as that whereby hemorrhage exercises its stimulative effect. These observations were made during the period of decline in antibody production and the question might be raised as to whether the rise of antibody in the blood after bleeding might not be caused by absorption from the lymph. It has been shown further that loss of blood in the earliest stages of immunization appears to increase production of antibodies. In rabbits injected intravenously with small quantities of goat blood Friedberger and Dörner [73] found that moderate loss of blood would increase the amount of hæmolysin

considerably above that in the controls and especially if the loss were sustained on the first day after the injection of the antigen. Friedberger made analogous observations with respect to cholera lysins. Certain hæmotoxic antigens give higher antibody curves on intravenous than on subcutaneous injection, and it has been suggested that this may be the result of the greater destruction of red corpuscles by the antigen when introduced intravenously and the consequent greater regenerative activity in the blood tissues. In my own experiments on dogs under strictly comparable conditions the largest output of antibodies thus far has been obtained in two animals that on the second day were bled quite dry and then transfused with the blood of normal dogs.

The effect of acute loss of blood on antibody production under certain conditions consequently is to increase the production. This fact lends strong support to the view that antibodies are products of the blood-forming organs. At the same time perhaps it also furnishes something of a rational though belated basis for venesection which our forefathers regarded as a most important therapeutic measure in infections.

THE EFFECTS OF ALCOHOL, CHANGES IN TEMPERATURE, AND OTHER FACTORS ON ANTIBODY FORMATION

A number of investigations have been carried out to determine the effect of various factors on antibody formation. Unfortunately the methods used in many of the investigations are not satisfactory because of the attempt to settle the outcome of the experiment by a single determination only of the antibody content in the blood, the day selected usually being that on which the simple antibody curve in the particular case was most likely to be at its height. There is individual variation in this respect and for this and other reasons the results in some cases have been variable and often suggestive rather than decisive.

According to Trommsdorff [74] severe physical exhaustion, prolonged hunger and great chilling of the body, as well as certain other factors that are known to lower resistance, all lessen the production of antibodies in immunized animals.

With respect to the effects of alcohol in rabbits the results of Friedberger,[75] Wirgin,[76] and others [77] indicate that the giving of alcohol in mildly intoxicating quantities for several days after the injection of the antigen restrains the formation of antibodies. Wirgin found that the longer after the injection before he gave the alcohol the less its depressive effect. Friedberger and Trommsdorff's results point to a favorable influence on antibody formation by alcohol in a single mildly toxic dose at or near the time the antigen is introduced, but Wirgin's experiments go rather to the contrary effect.

Benjamin and Sluka [78] and Läwen [79] find that the production of antibodies may be unfavorably affected by X-rays. In rabbits previously treated with X-rays and injected with beef serum two to four days later there was produced little or no precipitin and the antigen disappeared slowly from the blood; but the rays had no effect if applied four days after the injection or on animals whose serum was rich in precipitin (Benjamin and Sluka).

Febrile processes are associated intimately with the production of antibodies and it lies near at hand to wonder whether this production proceeds in the same way at heightened and normal temperature. The influence of experimental hyperthermia on the formation of antibodies has been studied by Rolly and Meltzer,[80] Lüdke,[81] and others. Rolly and Meltzer find that typhoid agglutinins and bacteriolysins are produced more rapidly and abundantly in rabbits that are kept overheated than in those which are kept cool. Lüdke reports similar results; he finds stimulation of the heat centre by puncture to cause not merely an increase in the output of agglutinin but also to so modify the agglutinin that an unusually firm sort of agglutination results. Torri, [82] on the other hand, who also studied the effect of puncture of the thermic centre on the development of typhoid antibodies in rabbits, was unable to determine whether the hyperthermia had any effect one way or the other.

Graziani [83] found that of rabbits injected in the same way with filtrates of typhoid cultures but kept at different temperatures, viz., + 32°, + 38°, and + 2–4° C., those kept at the low

temperature developed the most agglutinin. In another experiment he kept all the animals at +32° C., bathing one-half of them in water at +20° for 30 minutes morning and evening, and in this case the bathed animals produced more agglutinin.

These experiments as well as those of Agazzi,[84] who attempts to show that arsenical substances promote the formation of typhoid agglutinins in properly immunized animals, might have given more convincing results if the agglutinin content had been measured at more frequent intervals.

The experiments I have mentioned deal mostly with the earlier phases of antibody production. The course may be influenced in the later stages also. Lüdke, being immunized with typhoid and with dysentery bacilli, found that hot baths during the stage of decline were followed by a distinct rise in the agglutinins. And in rabbits in the declining phase after being injected with typhoid bacilli, Fukuhara[85] found various influences to cause a temporary rise in the agglutinin and lysin, such as chilling and warming the surface of the body, the giving of a single dose of alcohol, and the introduction of certain organ extracts. And reference has been made to the observation by Madsen and Tallquist that pyrodin and pyrogallol,—poisons which destroy red corpuscles,—cause a distinct rise in certain antibodies if given in the third phase of the immunity curve.

ANTIBODIES IN PASSIVE IMMUNIZATION

Loos in 1896[86] was the first to demonstrate that antitoxin enters the blood of children injected with antidiphtheric serum. E. Mueller[87] and others found that the antitoxin disappears from the blood quite early, none being demonstrable after three weeks. Since then the time of appearance, the concentration and the fate of the antibodies in the blood in passive immunization have been subjected to special study.

The results as to the influence of the place of introduction on the time when the maximum concentration of antibodies in the blood in passive immunization is reached may be summarized to this effect: On intravenous injection the maximum

concentration is reached at once while on subcutaneous, intramuscular, and intraperitoneal injection it is reached only after an interval variously stated at 24 to 48 or 72 hours.[88] In man, J. Henderson Smith [89] found absorption of diphtheria antitoxin from the subcutaneous tissue complete only after 2 to 3 days. In the case of certain agglutinins and of diphtheria antitoxin Levin [90] determined that the maximum concentration in the blood in animals is reached in about three days after subcutaneous and intramuscular injections, but during the first 24 hours the absorption is greater from the muscles than from the subcutaneous tissues—at the end of 10 hours, 14 times greater.

Levin also found that the introduction in animals of immune serum, no matter whether from the same or different species and whether by intravenous, intramuscular, or subcutaneous injection, appears to be followed by an immediate and marked loss in antibodies for which he could offer no explanation. That is to say, the demonstrable content of antibody in the serum of the animal in all cases falls far short of the amount calculated on the basis that the antibodies are simply diluted in the blood. This deficit was greatest when the antiserum was introduced subcutaneously, less when introduced intramuscularly and least when introduced intravenously, but even here it amounted to 40 to 60 per cent. and in some cases more. Marked individual differences occurred. It was less in the case of kindred than of alien antiserum; and especially marked when several different antibodies were introduced at the same time. On subcutaneous injection of antivibriolytic serum Tallquist noted that only about one-half as much antilysin appears to reach the blood as when it is injected into the blood. Dr. Carlson and I find that in dogs first thoroughly exsanguinated and then transfused with blood from dogs injected with goat blood antibodies almost immediately begin to pass into the thoracic and neck lymph, and that they soon reach the same proportion in these fluids relative to that in the blood as in normal and in actively immunized animals; hence it seems to me that the amount of antibody passing into the lymph, notably after intra-

venous injection, may go a long way towards making up the deficiency between the amount injected and the amount found in the blood.

Ehrlich observed that after passive immunization antiricin and antiabrin may remain in the blood for 30 to 60 days, depending for one thing on the quantity introduced. In an ass injected subcutaneously with antidiphtheric horse serum Bulloch [91] was able to demonstrate minute quantities of antitoxin even at the end of 100 days. That definite traces of antibodies could be detected so long after their introduction was received with considerable astonishment. It has since been learned that introduced into the blood antibodies at first are lost rapidly and then more and more slowly. Madsen [92] has shown that, at least in certain cases, the loss of antibody is expressible by the same formula in both active and passive immunization, kindred serum being used in the latter case. When it was found [93] that in horses injected with antitetanic serum the tetanus antitoxin is lost at about the same rate as in active immunization, Von Behring concluded that there is no essential difference in the immunity of the blood after active and passive immunization.

Famulener [94] and Levin determined that after successive intravenous injections of antibodies (antivibriolysin, typhoid and colon agglutinins) at intervals of seven days or so, there was no difference in the rapidity of the loss—the antibodies disappeared at the same rate after each injection. This proved to be the case also when a mixture of antibodies was injected at the same time. In rabbits injected by Levin with serum of goat immunized with colon bacilli all agglutinin disappeared at the end of the same time,—4 to 6 days,—even if the serum (of the same antibody strength) was injected in quantities ranging from 10 to 40 c.c. Consequently, it may be advisable, if we wish to maintain the concentration of alien antibodies in the blood at a certain level for a longer period to give a series of relatively small doses rather than a single large dose.

At this point brief reference may be made to the fact that in passive immunization antibodies are retained longer if the

animal is injected with antiserum obtained from its own species than if serum from alien species is used. Tizzoni and Catani, who were the first to ascribe to the origin of the serum injected importance with respect to the rate of disappearance of antibodies, found that rabbits injected with antidiphtheric serum from different species retained the antitoxin longest when it was introduced in rabbit serum. Knorr and Ransom observed that tetanus antitoxin is retained longer in passive immunization if the serum used is derived from the same species as the passively immunized animal. At the same time as kindred antitoxin is retained the longest Ransom found that not all alien antitoxins are lost with the same rapidity. Consequently it is not possible to lay down a general law in regard to the fate of the antibodies of one species in the fluids of another.[95] Alien agglutinins and alien bacteriolysins also disappear more rapidly than the kindred,[96] in some cases three times as rapidly.

To account for the disappearance of antibodies from the blood of healthy animals at least three possible mechanisms have been considered, namely, elimination in the urine and other excretions, deposition in the organs, and chemical transformation. The failure to find antibodies except in exceedingly minute quantities in the urine, saliva, and other secretions (Bomstein,[97] Bulloch,[98] Staubli [99]) and in the organs of immunized animals (Bomstein) lends favor to the view that chemical transformation plays an essential rôle in the gradual disappearance of antibodies from the blood. Certain antibodies, *e.g.,* tetanus antitoxin, pass into the milk in passively immunized animals. The suggestion has been made that antitoxin and other antibodies may induce the formation of antibodies and thus lead to the eventual defeat of the purpose of passive immunization. The possibility of formation of anti-antibodies cannot be discussed now, but it may be noted that Kraus and his co-workers [100] failed to obtain any antibodies for diphtheria antitoxin and typhoid agglutinins, and quite recently this is confirmed so far as antitoxin and typhoid agglutinins are concerned.[101]

The fact that intravenous injection immediately gives a far

greater concentration of antibody in the blood, and hence in the lymph also, than is ever attained by the gradual absorption from the subcutaneous tissue is a strong point in favor of the direct injection into the blood of diphtheric antitoxin in severe cases as urged by Behring, Madsen, and others. The principle is, of course, equally applicable to other conditions, notably tetanus. According to Berghaus,[102] the curative value of antidiphtheric serum for guinea-pigs on direct injection into the blood is 500 times greater than on subcutaneous injection and 80 to 90 times greater than on intraperitoneal injection. The one objection of consequence that might be urged against the intravenous method is the possible greater danger of anaphylactic shock in susceptible persons.

NOTE.—Schreiber[103] has injected antidiphtheric serum intravenously in 20 cases. He states that general improvement follows sooner than on subcutaneous injection while the local process in the throat follows about the same course in both cases. In his series no dangerous symptoms developed. In case of difficulty in entering the vein he advises that the injections be made into the buttock, which, so far as concerns the rapidity and degree of absorption of antitoxin into the blood, is a more favorable place for injection than the subcutaneous tissue. According to W. H. Park (Jour. Am. Med. Assoc., 1910, liv, p. 258) large doses of antitetanic serum injected intravenously within a few hours after the onset of the symptoms of tetanus have given good results.

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INFLAMMATION *

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THE obvious causal relationship of bacterial infection to inflammation has tended to obscure the broader significance of the inflammatory reaction. An immense number of sterile substances, both fluid and solid, soluble and insoluble, organic and inorganic, incite a reaction which differs in no essential respect from that which follows the invasion of microorganisms. Even so-called physiological salt solution introduced into the body may cause acute inflammation; absorption of a protein such as egg albumen or of a fatty substance such as sterile olive-oil is in part dependent on the same process. Views concerning the nature of inflammation are widely diverse, but all are agreed that inflammation accomplishes the destruction and solution of a variety of substances, and notably of those proteins which form the bodies of parasitic invaders.

Although absorption from the tissue, so-called parenteral resorption, is made possible by processes which resemble those occurring within the digestive tract, recent compendiums of biochemistry are almost silent concerning the nature of such processes and limit their discussion to a consideration of the part of filtration, osmosis, and the secreting activity of lining membranes. The pathological problems are unfamiliar to the physiological chemist, and the pathologist is poorly prepared to solve them.

It is well known that there is no agreement on what shall be regarded as inflammation, and some have wished to discard the word. I shall cite historical data with the sole purpose of showing that its historical associations offer little aid in deter-

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mining its application; that accepted usage furnishes no more definite criterion.

The cardinal symptoms of inflammation—heat, pain, redness, and swelling—described by the classical writers, have reference to inflammatory conditions affecting the surfaces of the body; perhaps well illustrated by erysipelas or by a boil. By a series of analogies the term has been applied to changes in the internal organs which exhibit, in some instances, none of these symptoms. Virchow, in the "Cellular Pathology," shows that each one of the cardinal symptoms at some period has been used as a test of the true nature of inflammation. The name, which implies taking fire, shows that the early writers attached greatest significance to the increased heat of the inflamed part. At a later period, the condition of the blood-vessels indicated by congestion and redness, attracted more attention, and Boerhaave taught that inflammation was the result of stasis caused by obstruction of blood-vessels. This view prevailed during the period when, in France, pathological anatomy was studied with greatest industry. Ponfick cites the aphorism of Cruveilhier: "Phlebitis dominates pathology." Yet Cruveilhier defines inflammation as a blood-stasis in the capillaries which is associated with exudation at times of coagulable lymph, at times of pus, perhaps finally of caseous or tuberculous substance. As a criterion of inflammation, accumulation of exudate received increased attention, and the swelling or tumor of inflammation held a predominant place in the views of Rokitansky.

The experimental studies of Cohnheim inaugurate modern views on the nature of inflammation. Inflammation is the reaction which follows an injury affecting the wall of blood-vessels; increased permeability facilitates the escape of plasma and corpuscles into the surrounding tissue. Attempts to study the effect of various injurious substances upon a tissue devoid of blood-vessels, such as the cornea, have shown that well-known inflammatory changes occur in the adjacent vascular tissues and hence flood the injured part with exuded fluid and corpuscles.

Most of the substances which act as inflammatory irritants cause obvious injury to tissues with which they come into contact. At first sight it may appear unimportant to decide whether injury to tissue, including its blood-vessel, is the stimulus which puts in motion the numerous processes grouped as inflammation; or if the irritant itself acts directly on the structures with which it is in contact, and attracts to itself elements of the blood or of the tissues capable of neutralizing or destroying its toxicity. The decision will modify any interpretation of the phenomena of inflammation. One group of writers who have regarded injury to tissues as the inciting cause of inflammation, have included within its domain all those phenomena which tend to restore to normal the injured part; formation of fibrous tissue replacing elements which have been destroyed becomes a part of the inflammatory reaction. Inflammation is regarded as a process adapted to diminish the harmful consequences of an injury. This is the view expressed by the well-known definition of Burdon Sanderson; it represents the opinion maintained by Cohnheim, Weigert, Ziegler, Neumann, Letulle, Adami. Another group of writers, including Leber, Metchnikoff, Marchand, Ribbert, Councilman, Klemensiewicz, regard inflammation as a reaction excited by the presence of something injurious to the tissues; inflammation is adapted to counteract and destroy the injurious substance. Study of the phenomena by which bacteria are destroyed and dissolved has given this view a predominant place.

All inflammatory irritants produce some form of injury, and moreover, tissue which has been destroyed may act as an inflammatory irritant; nevertheless, there is a fundamental distinction between a reaction which repairs an injury, and reaction which renders harmless an injurious substance. Certain invertebrates with simple structure (hydra, planaria) repair an injury by rapid regeneration of a part removed; phenomena suggesting an inflammatory reaction are wholly lacking. Those who believe that inflammation is adapted to neutralize and destroy the injurious body usually exclude those regenerative changes which replace with fibrous tissue structures which have

been destroyed, for all writers agree in excluding the regeneration which affects the surviving parenchyma when part of an organ has been removed or destroyed.

To determine if inflammation is dependent on changes in the blood-vessels attempts were long made to study the process in tissues such as the cornea or cartilage, which contain no vessels. The nearest vascular tissue became inflamed and the attempt failed. Directing his attention from the vertebrates which had heretofore served as objects of experiment to the lowest invertebrates, Metchnikoff has found the long-sought opportunity to study inflammation in tissues containing no blood-vessels. His well-known treatise on the comparative pathology of inflammation defines the relatively simple reaction which follows application of injurious agents to such animals.

Throughout the animal kingdom methods used to obtain food are often employed to destroy enemies. The amœba survives because it can destroy and digest the bacteria which it takes into its substance. In certain sponges, phagocytic cells, which digest the food of the animal, accumulate about a foreign body thrust into its substance. The lower orders of invertebrates, such as the medusa, the starfish, and certain worms possess no vascular system; situated between the outer covering and the digestive cavity are mesodermic cells which, having no part in the digestion of food, approach, engulf and often digest foreign particles, bacteria, and other organisms which have found their way into the tissues of the animal. By means of amœboid movement they accumulate about any substance capable of exciting their activity. Shall this reactive accumulation of phagocytic cells be designated "inflammation"? Those who believe that inflammation is a response of blood-vessels to injurious agencies are unwilling to include it. With a broader view, those processes by which protective elements are drawn from adjacent tissues cannot be separated from those changes by which similar cells are drawn from adjacent blood-vessels. Nomenclature of the process is relatively unimportant. Yet study of what is universally designated "inflammation" in animals with fully developed blood-vessels shows that phago-

cytic cells which react in response to the inflammatory irritant are not necessarily derived from the blood-vessels.

To illustrate the chaotic state of prevailing views concerning inflammation, the status of tuberculosis may be cited. Cohnheim, who attached prime importance to vascular changes, excluded the infectious granulomata; yet many of those who believe that inflammation occurs only in vascular tissue regard tuberculosis as inflammation. Marchand, on the contrary, separates such processes from inflammation, because he believes that they are characterized by multiplication of fixed cells of the tissue.

Inconsistencies of accepted nomenclature are readily found. The term parenchymatous nephritis, a survival of Virchow's conception of inflammation now long abandoned, is applied to a lesion which exhibits none of the vascular and cellular changes which are associated with inflammation of other organs. Injury to the spinal cord is designated as inflammation when it is called traumatic myelitis; yet the secondary occurrence of inflammatory changes common to all forms of injury merely serves to emphasize the confusion of two distinguishable conditions (Marchand[1]). The name "acute hemorrhagic pancreatitis" has been applied to a lesion which is essentially necrosis, and not inflammation of the pancreas, and its use has hindered a rational classification of pancreatic disease.

Should we assume that inflammation occurs in order that injurious substances may be destroyed or removed, the nature and action of the fluid and cells which accumulate acquire predominant importance. The swelling of inflammation is in great part referable to accumulation of fluid derived from the plasma of the blood; yet the wall of the vessel controls this transit, for the protein content of the fluid which passes through the wall of the blood-vessel into the tissue is constantly less than that of the blood-plasma. The proteins of the plasma do not enter the spinal fluid nor the aqueous humor, yet with inflammation they are found in both fluids.

Studies of Klemensiewicz[2] have shown the effect of increased pressure exerted by exudate within the tissue on local

vascular tension. By an ingenious device he has been able to measure directly under the microscope the pressure capable of producing stasis within the capillaries. When an inflammatory irritant is applied to the tissue under examination, accumulation of exudate increases extravascular tension, and a smaller pressure is now capable of causing capillary stasis. This observation may help to explain the obvious truth that accumulation of fluid in the subcutaneous tissue in response to an irritant, is quickly self-limited; whereas the same irritant causes an immense serous exudate when introduced into a serous cavity. Later it will be shown that this difference has an important influence on the outcome of the inflammatory reaction and may determine whether suppuration or resolution occurs.

During the last ten years an immense amount of laborious study has been devoted to the character and origin of the various cells which accumulate at the site of inflammation. The studies of Cohnheim and of Von Recklinghausen have afforded convincing evidence that the common pus corpuscle is the polynuclear leucocyte of the blood which, under the stimulus of the inflammatory irritant, passes through the walls of blood-vessels. Some of the earlier observers have believed that such polynuclear leucocytes may become cells of the fixed tissue, colonize the part, as it were, but there is now universal agreement in the view that they may degenerate but undergo no progressive transformation after they have left the blood-stream. The origin and fate of the numerous mononuclear cells which accumulate in the inflamed tissue, on the contrary, is doubtful. The subject, repeatedly investigated by histological methods, often uninteresting because they are inconclusive, has great biological importance, for it deals with the significance of lymphatic tissue and the normal and pathological relationship between lymphatic and other tissues of the body. It seeks to determine if a cell formed in one part of the body may establish itself in a distant part and there form an integral constituent of the tissue.

Insight into the changes associated with inflammation assumes an accurate knowledge concerning the tissue in which

the inflammatory reaction occurs. All of these changes have their origin within the connective tissues of the body whence inflammatory exudates may find their way into other situations. There are yet many defects in knowledge of the connective tissues of the body. In early stages of embryonic life this tissue is represented by a network of cells with branching processes which are continuous with one another. Within the substance of this protoplasmic syncytium, and hence within the cells, according to observations of Fleming, and in recent years of Mall,[3] the white fibres are laid down. At first all the cells which compose this tissue are fixed, but later cells make their appearance within the meshes of the network. Since these unattached cells exhibit irregular projections which suggest that they are capable of amœboid movement, and since they resemble amœboid cells of the circulating blood, they are regarded as wandering cells. Part of them have all the characters of lymphocytes and in many situations form small collections about the blood-vessels. Part of them are larger than lymphocytes and resemble the large mononuclear cells of the blood; they are frequently collected about blood-vessels.

Von Recklinghausen has maintained the opinion that the spaces which, filled with fluid, exist in the meshes of the network formed by the fixed elements of the tissue, are in direct communication with lymphatic capillaries and constitute the origin of the lymphatics within the tissue. Nearly half a century ago (according to Sabin) Langer showed that these lymphatics grow as blind sprouts of endothelial cells. Ranvier has confirmed this almost forgotten observation in recent years, and Sabin [4] and others have shown that the entire lymphatic system sprouts from the endothelial lining of veins and gradually pushes its way into various tissues and organs to form a closed system everywhere lined by endothelial cells. Endothelium separates the lymph within the lymphatic capillaries from fixed cells of a part. This well-known relationship, usually little considered, has much pathological significance; indeed early observers (Hering, Heller, Thoma [5]) of the movements of amœboid cells within the tissues, have noted the important

truth that leucocytes which have wandered from the wall of the blood-vessels and have passed through the spaces within the fixed tissue, may penetrate the endothelial wall of a lymphatic vessel.

Embryological study of the lymphatic nodes has explained the relationship of lymphatic tissue to lymphatic vessels. Gulland,[6] Sabin,[7] and others have shown that lymphoid tissue makes its appearance in the walls of lymphatic channels which have already been formed; and consequently a layer of endo-

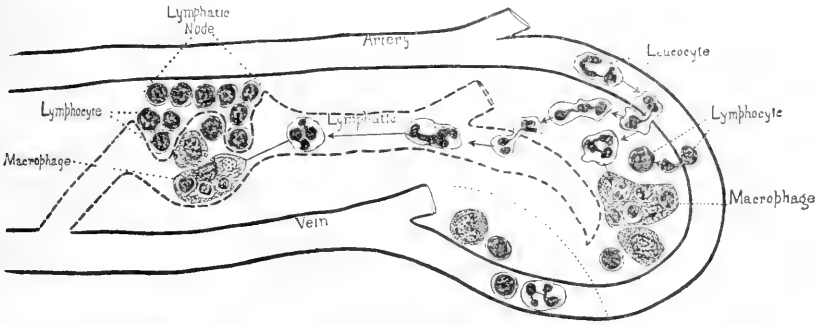

FIG. 1.—Diagram showing the relation of the site of inflammation to the regional lymphatic node. An artery is shown dividing to form a capillary which in turn enters a vein; within the capillary loop is a lymphatic vessel which becomes the sinus of the adjacent node and finally discharges its contents into the venous system. Within the capillary loop to the left of the dotted line is shown the normal position of wandering cells. To the right of the dotted line are shown cells having part in the inflammatory reaction. Polynuclear leucocytes which migrate from the blood-vessels may be ingested by macrophages or may enter the lymphatic, pass to the adjacent lymphatic node and perhaps undergo ingestion by a macrophage within the sinus of the node. The data on which the diagram is based are described in the text.

thelial cells separates the lymphatic tissue from the lumen of the lymphatic vessel, and later from the tortuous sinus to which the primitive channel gives place. The lymphocytes of the lymph-node appear within the meshes of a fibrillated network and in their relation to lymphatics are analogous to the lymphocytes in the meshes of connective tissue elsewhere.

The local changes which with inflammation occur in the lymphatic vessels of the affected part and in the tributary lymphatic nodes (see Fig. 1) are not separable from the changes which have their seat in the blood-vessels and in the interstitial

tissue. Muscatello [8] has shown that finely granular material, such as carmine powder, introduced into the peritoneal cavity of a dog, appears within ten minutes in the retrosternal lymphatic nodes; the two retrosternal lymphatic channels which follow the internal mammary arteries are quickly rendered conspicuous by the injected material. Within these lymphatic vessels some of the granules are free in the lymph, whereas others are contained in wandering phagocytic cells which, as MacCallum [9] has shown, penetrate the endothelial lining of the diaphragm. Within three-quarters of an hour after injection of *Staphylococcus aureus* into the subcutaneous tissue of the leg of a guinea-pig, Bezançon and Labbé [10] found that the afferent lymphatic vessels of the adjacent lymphatic node were dilated and contained many polynuclear leucocytes which were entering the sinuses of the node. The subsequent changes within the node are well known.

The well-known studies of Maximow [11] have defined the changes which occur in and about a sterile foreign body, introduced into the subcutaneous tissue of various species of animals. In later experiments he has impregnated the body with an inflammatory irritant such as turpentine, or has infected it with pyogenic bacteria, namely, with *Staphylococcus aureus* and with streptococcus. He has pictured with great clearness the changes observable at intervals varying from a few minutes to many days after onset on the inflammatory reaction. The reaction caused by a sterile body differs from that produced by bacteria in its intensity and in the rapidity with which corresponding phenomena occur, but the character and sequence of events are identical.

Serous fluid quickly accumulates about the infected body and the surrounding tissues become œdematous. Within the first four hours polynuclear leucocytes emigrate from the blood-vessels in large numbers, and properly prepared tissue exhibits many leucocytes making their way through the endothelial lining of vessels. Early emigration of lymphocytes as well has so frequently been observed that its occurrence has been placed beyond doubt. The small round cells which migrate from the

blood-vessels quickly give place to larger cells with paler, larger nucleus and fairly abundant cell substance. Those cells which have a predominant part in the late stages of inflammation are known by no familiar name, and it is difficult to designate them conveniently. The term "macrophage," used by Metchnikoff, is applicable, for these cells exhibit phagocytic activity, but the name has a wide significance and may be applied to all large cells capable of ingesting solid particles. The attack on living virulent micrococci is apparently conducted wholly by polynuclear leucocytes. With the disappearance of micrococci, mononuclear cells increase in number and in size and begin to exhibit ability to ingest cells and cellular débris. Such phagocytic cells or macrophages may contain six, a dozen or more leucocytes in various stages of disintegration, together with a variety of inclusions whose origin is no longer recognizable. On the activity of these cells is in large part dependent the solution and removal of the leucocytes which have previously attacked the invading bacteria.

The serous cavities, particularly the peritoneal and pleural cavities, offer a convenient opportunity for study of the cellular phenomena of inflammation. The early changes, whether produced by various bacteria or by sterile irritants, do not differ materially. A noteworthy peculiarity of inflammation within serous cavities is the unobstructed and rapid accumulation of serum; the cells which accumulate are in part suspended in this fluid but a greater part adhere to the membranes, such as the omentum or mediastinum which are contiguous with the cavity. Numerous observations have shown that the changes which occur in the serous cavity during the first few hours after inoculation are identical with those which are demonstrable under similar conditions in the subcutaneous tissue.

The importance of vascular changes in inflammation has long been recognized; less has been written concerning the significance of the lymphatic system. The studies which have been cited show that the lymphocytes which are in great part at least derived from the lymphatic glands migrate from the blood-vessels and are perhaps transformed into macrophages.

At the same time lymphocytes and similar larger cells which are scattered in the normal tissue outside of the blood-vessels and often according to Ribbert form rudimentary lymphatic nodes mingle with the cells of the exudate and perhaps take part in the formation of macrophages. The intimate relationship of the local focus of inflammation to the adjacent lymphatic glands is well illustrated by the experimental pleurisy produced by injection of a sterile irritant such as the vegetable protein, aleuronat, into the pleural cavity. The lymphatic glands which are situated in the anterior mediastinum become greatly swollen and microscopic examination shows that changes which occur in the sinuses of these glands are identical with those in progress within the pleural cavity itself. At the end of four or five days the serous cavity contains abundant fluid in which polynuclear leucocytes are abundant; at this time mononuclear phagocytic cells are large and numerous and are engaged in ingesting and dissolving polynuclear leucocytes. The sinuses to the adjacent mediastinal lymphatic glands are much distended and closely packed with the same large phagocytic cells whose protoplasm often contains many polynuclear leucocytes in various stages of disintegration. In some instances almost the entire lymphatic gland is replaced by these cells. Ingestion of polynuclear leucocytes and other cells, essential to complete resolution of the exudate, is begun in the serous cavity and is completed in the regional lymphatic node. By the method previously described cells make their way along lymphatic channels from the primary site of inflammation to the adjacent node.

Studies of the fate of bacteria injected into the body have demonstrated the rapidity with which micro-organisms enter the regional lymphatic nodes, and the partial efficiency of these nodes as filters. Buxton and Torrey [12] have injected typhoid bacilli in considerable quantity into the peritoneal cavity of small animals and have estimated by the enumeration of colonies in agar plates the relative abundance of bacteria in the substernal lymphatic nodes, in the blood and in various organs such as the liver, spleen, lungs, bone-marrow, and kidney.

Within ten minutes after inoculation, they found an enormous number of bacteria in plates prepared from the regional lymphatic node, and in sections prepared for microscopic examination bacilli are found in the afferent sinus, in part free, in part within phagocytic cells. Notwithstanding this regional fixation of those bacteria which had escaped from the site of inoculation, a not inconsiderable number had entered the blood and were scattered throughout the body. Within the interval from five to thirty minutes after inoculation, from twenty to thirty thousand bacteria per cubic centimetre were recovered from the blood. Nevertheless at the end of an hour, the number had fallen to several hundred. Likewise within the first half hour after inoculation the number of bacteria in the liver, spleen, lungs, and kidney was very great; but it fell suddenly and soon became relatively small. This initial rush of bacteria from the peritoneal cavity to the blood has been found to occur with equal readiness in normal and in immunized animals.

Experiments of Muscatello have shown that inanimate particles such as powdered carmine pass through the diaphragm into the lymphatic vessels of the mediastinum and reach the circulating blood only through the lymphatic system. Wells and Johnstone[13] have successfully attempted to show that bacteria do not pass into the blood-vessels of the peritoneum but reach the blood wholly by way of the lymphatic vessels. They have prevented the initial rush of bacteria from the peritoneal cavity into the blood by ligation of the thoracic duct. By estimation of the number of bacteria in the lymph they have shown that the thoracic duct, during the first hour after inoculation of the peritoneal cavity with *Bacillus coli* discharges an immense number of bacteria into the blood.

The foregoing observations show that the lymphatic nodes, during the first hour after inoculation, are not efficient filters for bacteria. Although two lining membranes are interposed between the peritoneal cavity and the interior of lymphatic vessels, solid particles pass with the utmost rapidity from one to the other; the greater part of these particles are not contained within phagocytic cells. The membranes separating the

cavity and the lumen of the vessel are uninterrupted but solid particles pass as if there were direct communication. Furthermore, both bacteria and inanimate particles at first pass the lymphatic nodes, but later at the end of the first half hour or hour after inoculation, although the peritoneal cavity and the regional lymphatic nodes contain an immense number of bacteria, their escape is obstructed and they have almost completely ceased to enter the circulating blood. At this time an inflammatory reaction has begun both at the site of infection and within the lymphatic node. There is little doubt that the quiescent lymphatic node is an inefficient filter whereas the inflamed node, containing even at this early period many phagocytic cells, is effective in restraining the dissemination of bacteria.

Noetzel [14] injected *Bacillus pyocyaneus* into the knee-joint of rabbits, and from five to ten minutes later found the organism both in the inguinal, lumbar, and crural lymphatic nodes and in the circulating blood. Pawlowsky [15] has demonstrated the presence of staphylococci in the blood and organs of guinea-pigs from twenty-four to forty-eight hours after inoculation of the knee-joint, but has been able to show that this dissemination is inhibited or wholly prevented if before inoculation acute inflammation of the joint has been produced by the injection of some sterile irritant such as turpentine, alcohol or solution of quinine. His observation recalls the studies of Issayeff, who showed that the peritonitis induced by a variety of sterile irritants such as foreign blood-serum, bouillon or normal salt solution, temporarily increases resistance to subsequent intraperitoneal inoculation of bacteria. Such observations help to explain the well-known resistance to infection exhibited by a granulating wound.

A great variety of substances which are either non-dialyzable or insoluble in water are dissolved and removed when introduced into the tissues of an animal. It is difficult, perhaps impossible, to cite any substance which introduced from outside of the body into the tissues of an animal fails to excite an inflammatory reaction; physiological salt solution introduced

into the peritoneal cavity produces active emigration of leucocytes. Comparatively little systematic observation has been made on the pharmacology of inflammation and we are as yet ignorant of the factors on which depend peculiarities in the intensity of the reaction and in the character of the exudate which is produced. The reaction is in all instances characterized (*a*) by a stage of leucocytic emigration followed when resorption begins, (*b*) by accumulation of macrophages. It is noteworthy that tubercle bacilli and typhoid bacilli, whose presence in man is usually associated with peculiar lesions exhibiting little resemblance to acute inflammation, produce the same changes during the first twenty-four hours after introduction as *Staphylococcus aureus* (Helly) and other pyogenic cocci.

Nevertheless one large group of substances, unlike bacteria, excite the large mononuclear phagocytes with much greater activity than polynuclear leucocytes. The cells of one animal introduced into the body of another of the same or of a different species are attacked by large mononuclear cells and are gradually dissolved within their substance. This experiment has been repeated under a great variety of conditions by Metchnikoff and his pupils. The same process occurs under physiological conditions, for in the spleen red blood-corpuscles, perhaps those which have undergone some degenerative change and are no longer useful to the body, are ingested and destroyed by large mononuclear phagocytes. When hemorrhage occurs into the tissues, phagocytic cells of similar character, by taking red corpuscles into their substance, aid in the process of absorption. Necrotic tissue in the liver or in other organs is absorbed by aid of the same cells. A similar process occurs when degenerative changes affect the central nervous system. Absorption of tissues no longer useful to the body, and perhaps already the seat of degenerative change, is accomplished by the aid of mononuclear phagocytes and has many analogies throughout the animal kingdom. Metchnikoff, studying the progress of the metamorphosis of insects, has lately found evidence that the organs and tissues first undergo degenerative changes, and

later become the prey of phagocytes. Furthermore, one large group of parasitic invaders, including protozoan micro-organisms such as malarial parasites and trypanosomes, excite almost exclusively the activity of the mononuclear phagocytes.

The observations which have been cited show what cells accumulate about a foreign substance introduced into the body. The more important of these cells are capable of engulfing solid protein particles, and of dissolving them. By what means is this absorption accomplished?

The occurrence of products of protein digestion in inflammatory exudates was recognized almost fifty years ago; Eichwald in 1864 found in pus what was then called peptone; and later, Maixner found peptone in the urine in association with a considerable variety of suppurative conditions such as empyema, peritonitis, cerebrospinal meningitis, pyelitis, etc. An observation of Friedrich Müller has explained the constant presence of so-called peptone in purulent phthisical sputum; a glycerin extract of such sputum is capable of digesting fibrin or coagulated albumin in a weakly alkaline medium. Other purulent sputum has the same property: the sputum of a patient with pneumonia does not exhibit this digestive action before crisis has occurred, but later when it has assumed a white pus-like appearance, the enzyme may be demonstrated. The pus of an abscess contains the same enzyme, but the pus-like fluid from a tuberculous lesion, a so-called cold abscess, fails to contain it. Various observers have shown that enzyme of pus is capable of digesting a considerable variety of protein substances, such as gelatin, fibrin, coagulated egg albumen, and casein. The well-known studies of Salkowski first showed that animal tissues preserved under conditions which prevent the growth of bacteria undergo changes similar to those which occur during the digestion of protein. Friedrich Müller showed that the pneumonic lung consolidated by the presence of inflammatory exudate within the alveoli is especially susceptible to such autolysis. By the self-digestion of this inflamed pulmonary tissue at body temperature are formed albumose, leucin, tyrosin, and other products of protein disintegration; nuclei

of the autolyzed tissue quickly disappear as a result of decomposition of nucleins. These observations have been used to explain the solution of fibrin and the disappearance of leucocytes and other cellular elements which occurs with resolution of the exudate.

Biondi,[16] Hedin and Rowland,[17] and others have found that various normal organs of the body autolyze with greater activity in weakly acid than in alkaline solutions, and in this respect resemble pepsin rather than trypsin.

Studying the cells of an inflammatory exudate obtained by injection of aleuronat or other sterile irritant, I have repeatedly confirmed the observation that they digest coagulated protein with greatest activity when they are suspended in an alkaline medium. Digestion may be accurately measured by allowing the cells to act at body temperature on blood-serum coagulated by heat; the amount of protein which goes into solution may be accurately determined. Testing the liver, kidney, spleen, lymphatic node, and bone marrow, it is noteworthy [18] that the bone-marrow alone resembles the cells of an acute inflammatory exudate, and digests with greater activity in alkali than in acid.

The cell which is predominant in the inflammatory exudate produced by the injection of aleuronat is the polynuclear leucocyte, and histologists are agreed that this cell has its origin in the bone-marrow. In other words, polynuclear leucocytes which, constituting the greater part of the white corpuscles of the blood, migrate during the early stage of the inflammatory reaction, and approach and digest solid particles, contain an enzyme which resembles trypsin of the pancreas. They carry this enzyme from the bone-marrow to the site of inflammation. Dochez has shown that this enzyme, unlike trypsin, exists within the cells in an active state, and will, without further change, act on protein in the presence of alkali. Trypsin, on the contrary, exists in the pancreatic cells as zymogen, and requires activation by enterokinase or by acid before it is able to attack protein.

The enzyme of the polynuclear leucocytes, which may be

conveniently designated "leucoprotease," may be purified by precipitation with alcohol, and after drying may be preserved almost indefinitely.[19] In the moist state, the enzyme thus prepared is destroyed by heating at a temperature between 70° and 75° C. Temperatures between 50° and 65° C. acting on the enzyme during half an hour increase its activity. It acts in an alkaline or in a neutral medium, but is inhibited by acid. Sodium carbonate in concentration of 0.2 to 0.5 per cent. favors its action; greater concentration is destructive. The enzyme is much less active than trypsin, but it is not improbable that its activity, tested outside the body, is less than its activity under the favorable conditions which doubtless exist within the leucocyte.

Examination of the properties of the enzyme which has been described, demonstrates that it is not identical, as several writers have claimed, with the alexin or complement of the blood-serum, for the latter, it is well known, is destroyed by heating to a temperature of 56° C. Jochmann[20] has shown that it has no bactericidal power and asserts that it digests bacteria which have been killed by chloroform or by heat, whereas it fails to dissolve living bacteria.

It is not difficult to bring proof[20] that the cells which accumulate in response to the presence of an inflammatory irritant contain a second enzyme capable of digesting albuminous substances; its properties are different from those peculiar to the enzyme of the polynuclear leucocytes. The enzyme which is obtained by treating the cells with alcohol, it has been mentioned, acts in both neutral and alkaline solutions, but is inactive in acid; the fresh cells, however, digest in acid as well as in alkali. This observation suggests that alcohol destroys a second enzyme, present in the fresh cells. Further study has shown that this second enzyme is more labile than leucoprotease; for whereas temporary heating to temperatures between 50° and 65° C. increases the activity of leucoprotease, it greatly diminishes the activity of the enzyme which digests in the presence of acid.

I have previously cited many observations which show that two types of cells are abundant in all inflammatory exudates

which exhibit a tendency to resolve. When aleuronat is injected into the pleural cavity of a dog the proportion of large mononuclear cells, which act as phagocytes, gradually increases and with this increase there is increasing power to digest in the presence of acid. I have already pointed out that the phagocytosis of micro-organisms, foreign particles, polynuclear leucocytes, red blood corpuscles, and cellular débris begun in the pleural cavity is completed in the regional lymphatic nodes. At the end of four or five days after the onset of inflammation incited by aleuronat the retrosternal lymphatic nodes are enormously enlarged beyond their normal size and their sinuses are distended with large cells identical with those in the pleural cavity and actively engaged in the phagocytosis of polynuclear leucocytes and other cellular elements. An emulsion prepared from such a lymphatic node in which mononuclear phagocytes are predominant, fails to digest protein in an alkaline or neutral medium but exhibits active proteolysis in the presence of acid. Moreover, this form of enzymotic activity increases with the duration of the changes in the node. The regional lymphatic node contains in almost pure form that enzyme which in the exudate increases with the increased number of macrophages. I have suggested for this enzyme the name "lymphoprotease."

This enzyme, like pepsin, acts in an acid medium and is inhibited by alkali; but it is not identical with pepsin, for it acts with greatest activity in a very weak concentration of hydrochloric acid and is destroyed by that strength (0.2 per cent.) which is favorable to the action of pepsin. It is more closely related to the autolytic enzyme of various tissues. The factor of essential importance is the increase of this enzyme which is associated with an increase of large mononuclear phagocytes in the exudate or with an increase of similar cells in the lymphatic nodes tributary to the inflamed area.

The enzymes which have been found in the cells of the serous inflammatory exudate just described are present as well in fibrinous exudates.[21] When a small quantity of turpentine is injected into the pleural cavity, coagulable fluid accumulates and reaches a maximum at the end of two or three days. The

exuded fibrin, which contains polynuclear leucocytes during the first three or four days of inflammation, undergoes solution when suspended in an alkaline medium, whereas at a later period when polynuclear leucocytes have disappeared, this property is lost. On the second or third day after onset of the inflammatory reaction, products of proteolytic digestion appear in the serum; reactions indicating the presence of albumose are readily obtained. Such decomposition products are doubtless absorbed with great rapidity, for large quantities artificially introduced disappear from the exudate within twenty-four hours.

Although leucocytes contain active enzymes, serous inflammatory exudates containing cells in abundance fail to undergo autolysis. Experiments which I made several years ago have explained the absence of such autolysis and have disclosed a mechanism by which the activity of the enzyme is limited to the locality in which it is needed. The cells of the exudate separated from the serum undergo autolysis and are capable of digesting foreign protein; but if to the cells the exuded serum is added, digestion is wholly inhibited.

The serum contains some substance capable of restraining the action of the enzyme; it is convenient to designate this substance "antienzyme," without implying thereby that it is a specific antibody adapted to combine with enzyme in accordance with laws of chemical union. The antienzymotic action of the exuded serum is exhibited by the serum of the blood as well; it passes with the serum into the inflammatory exudate. The observation of E. Müller [22] that the antienzyme fails to enter the normal cerebrospinal fluid has a considerable interest.

The antienzyme is destroyed by heating to 75° C. It is apparently attached to the albumin fraction of the serum for the globulin exhibits no antienzymotic action, whereas the albumin fraction is active. The antiaction occurs in an alkaline or neutral medium, but is destroyed by acid. The phenomenon can be accurately studied by adding to weighed quantities of leucoprotease different volumes of serum. Such experiments do not afford evidence that enzyme and antienzyme com-

bine in definite quantities. Nevertheless, if to a fixed quantity of serum, increasing quantities of enzyme are added, a point is reached at which the serum fails to restrain completely the activity of the enzyme. In the study of suppuration this observation has considerable importance.

Antienzymes in the blood serum similar to that which restrains the action of leucoprotease have long been known. Hahn in 1897 showed that the blood-serum inhibits the action of trypsin. It is not improbable that the inhibitory effects on trypsin and on leucoprotease are dependent upon some peculiarity of the same substance, for Jochmann and Kantorowicz [23] have found that blood-serum which has abnormally high antitryptic action exhibits an increased ability to restrain the action of leucoprotease. Furthermore, there is no specific relationship between the enzyme of one species and the antienzyme of the same species; the serum of the rabbit has greater antienzymotic action on dogs' enzyme than dogs' own serum.[24] Birds' serum, unlike mammalian serum, fails to inhibit leucoprotease, which is peculiar to mammals.

The relationship between leucoprotease and its antienzyme in the serum furnishes a mechanism by which the action of the enzyme is limited to the locality in which it accomplishes its function. The polynuclear leucocyte is suspended in a fluid which neutralizes the effect of its enzyme, should this enzyme be set free by disintegration of the cell or by other means. When the polynuclear leucocyte ingests a solid particle of protein matter, for example, a bacterium, it removes it from contact with the serum and brings it into contact with its enzyme.

The mononuclear phagocytes are subject to a similar influence, for numerous experiments have shown that the enzyme which they contain is restrained by the serum of the blood, and similarly by the serum of an inflammatory exudate. In what degree this antienzymotic action depends on the apparent alkalinity of the serum, and in what degree on a thermolabile antibody, has not been established.

The relation between leucoprotease of the polynuclear leu-

cocytes and the antienzyme of the serum has served to explain the essential nature of abscess formation. Ribbert[25] defines suppuration as follows: "It is an intense inflammation with which polynuclear leucocytes wander from the blood-vessels in unusually great quantity; the tissue is softened and the serum between the collected pus cells does not coagulate." It may be added that solution of tissue in some instances has a beneficial result, for softening of the least resistant tissues may result in superficial rupture with healing; without escape of pus, it is well known there is little tendency to heal.

The peculiar appearance of pus is in part dependent on the presence of a great quantity of pus cells suspended in a relatively small proportion of fluid. A serous or serofibrinous exudate, on the contrary, contains abundant fluid and a relatively small proportion of cellular elements. Whereas the serum of the serous or serofibrinous exudate inhibits the digestive action of leucoprotease, the serum obtained from pus not only fails to inhibit leucoprotease, but itself contains unrestrained enzyme.[26] By disintegration of leucocytes, doubtless referable to the inflammatory irritant, increasing quantities of leucoprotease have been set free, so that the antienzymotic activity of the exuded serum is finally overcome. The proteolytic enzyme may now come into contact with tissue and with fibrin, and softening is the result.

The following experiment serves to explain why the same irritant in the same quantity may cause two different types of inflammation. If a small quantity of turpentine is injected into the subcutaneous tissue of a dog, a large fluctuating abscess filled with creamy pus is formed within four days; there is wide-spread undermining of the skin. The same quantity of turpentine injected into the pleural cavity causes a serofibrinous inflammation which undergoes resolution so that the pleural cavity is restored to its normal condition after about ten days; there is no destruction of tissue and a scar is not formed. In the subcutaneous tissue only a small amount of œdematous exudate can accumulate; the undiluted irritant causes active migration of leucocytes so that the antibody of the exuded

serum is soon overbalanced by the enzyme set free by disintegrated pus cells. In the pleural cavity, on the contrary, a large quantity of serum quickly accumulates and the exudate is serofibrinous instead of purulent; the antienzyme it contains is capable of holding in check the leucoprotease of the accumulated leucocytes. If a bit of the fibrinous exudate is suspended in the exuded serum, it is preserved intact. Nevertheless, by repeated injection of turpentine at short intervals into the pleural cavity, accumulation of leucocytes may be prolonged so that finally a condition is produced in which antienzyme can no longer restrain the enzyme. The softened fibrin of such an exudate quickly disintegrates in the serum of the exudate.

The foregoing observation introduces a new factor into the discussion concerning the pyogenic activity of many bacteria. It helps to explain how the typhoid bacillus produces abscesses in certain situations such as the kidney and bone; how the pneumococcus, which rarely causes abscess of the lung, in which conditions are somewhat similar to those within the pleural cavity, may cause suppuration in other localities, such as the middle ear, or in the subdural space; how the tubercle bacillus may, under peculiar conditions, cause true suppuration.

It is noteworthy that the normal spinal fluid, unlike other body fluids, contains neither enzyme nor antienzyme, and for this reason, Dochez [27] has made a special study of the changes which occur in association with inflammation. With epidemic meningitis, antienzyme may enter the spinal fluid and quickly leaves it. With more virulent infection caused by pneumococcus or streptococcus, enzyme derived from disintegrated polynuclear leucocytes gives to the fluid well marked power to digest protein. Such active enzyme itself doubtless acts as an irritant and increases the severity of the disease.

A few writers, notably Marchand, exclude the infectious granulomata from the domain of inflammation; they are those who, on the one hand, accept the opinion of Baumgarten that the tubercle is formed from elements of the fixed tissue, and on the other hand, do not apply the term "inflammation" to regenerative changes in the fixed tissue. Nevertheless, the

greater number of pathologists give weight to the truth that the tubercle is formed by a reaction in response to the presence of an invading parasite, and this reaction, in its early stage, is identical in character with that which follows the entrance of other bacteria into the tissues. Tuberculous tissue, moreover, is composed in large part of so-called epithelioid cells; these cells have the anatomical structure and phagocytic activity of the large mononuclear cells which predominate in the later stages of an acute inflammatory reaction. With present knowledge, it is impossible to define clearly the relationship of the tubercle to the later stage of inflammation, for the available evidence has permitted no agreement concerning the origin of the epithelioid cells. Study of acute inflammations produced by a sterile foreign body or by bacteria demonstrates with considerable certainty that lymphoid cells leave the blood-vessels and, it is probable, assume the characters of macrophages. In the immense accumulation of cells which follows, the identity of various elements is lost and only the uncertain means of tracing transitions from one form to another is available for determining origin of various types. Large mononuclear cells are accumulating in the tuberculous and in the non-tuberculous inflammation after the first twenty-four hours. There is no doubt that small round cells with the character of lymphocytes accumulate in the neighboring blood-vessels and migrate from them during the formation of the tuberculous lesion. Though transitions from this lymphoid cell to epithelioid cells are not wanting, there is no convincing evidence that one is derived from the other.

Polynuclear leucocytes occur in scant number in tubercles found at autopsy; yet in man (Benda), as in other animals, they are the first cells to accumulate about tubercle bacilli which are free in the tissues. Within an hour after injection of tubercle bacilli into the blood or into a serous cavity, they are surrounded or ingested by polynuclear leucocytes; mononuclear cells subsequently appear. In some animals, polynuclear leucocytes are very numerous in tuberculous tissue. In the dog, during the first few weeks after inoculation of the pleural

cavity, polynuclear leucocytes occur in immense number in the tuberculous tissue which is formed in and on the mediastinum. The relative abundance of these cells is dependent on the character of the bacillus, and in some degree is an index of the activity of resistance upon the part of the host. Virulent tubercle bacilli excite a more active emigration of polynuclear leucocytes than non-virulent organisms.

If the lesions which are classed as infectious granulomata are passed in review, various conditions intermediate between the tubercle and a simple abscess are found. The actinomycotic nodule has many of the characters of the tubercle, yet polynuclear leucocytes are so abundant that a small abscess is formed in the immediate neighborhood of the micro-organism. Glanders, in man and in lower animals, is usually characterized by abundant accumulation of polynuclear leucocytes with necrosis and suppuration. Duval and White [28] have shown that the character of the lesion produced in animals varies with the virulence of the micro-organism. Very virulent strains of the bacillus of glanders rapidly cause necrosis of tissue and formation of small abscesses in the liver, lungs and other organs, whereas less virulent organisms produce nodules which are composed of epithelioid and giant cells and have all the characters of tubercles.

The specificity of the tubercle is impaired by the observation that various sterile foreign bodies produce somewhat similar nodular lesions. When, for example, finely powdered meal (Kopec [29]) in suspension is introduced into the peritoneal cavity, the particles are collected together in clumps and tubercle-like nodules are formed about the clumps scattered upon the peritoneal surface. In other respects these foreign body tubercles do not accurately reproduce the histological peculiarities of the true tubercle. Similar foreign body tubercles have been found scattered throughout the peritoneal cavity when, under conditions which cannot be accurately defined, food particles have entered the cavity through a perforation in the wall of the gastro-intestinal tract.

It is well known that the tubercle bacillus contains an insol-

uble wax-like substance on which, in part at least, depends its ability to resist solution in the tissues; it is not improbable that its peculiar staining properties are dependent on the same substance. Such wax may be obtained by extraction from tubercle bacilli and introduced in suspension into the body of an animal first attracts polynuclear leucocytes; later mononuclear phagocytes accumulate, and among them occur giant cells. At the periphery a fibrous capsule is formed; the wax remains undissolved (Tschistowitsch [30]).

One form of pseudo-tubercle accurately reproduces the histological characters of the true tubercle. About the eggs of the blood-fluke *Schistosoma japonicum* deposited in the liver and in the intestinal wall nodules with all the characters of true tubercles are formed. Through the kindness of Dr. Henry J. Nichols,[31] I have lately had opportunity to examine tissues from a case of schistosomiasis occurring in the Philippine Islands. The nodules are composed of epithelioid cells containing giant cells; at the periphery of the nodule lymphoid cells are abundant. Coagulation necrosis with the histological characters of caseation occurs in the centre of the nodules in contact with the egg, and the epithelioid cells at the margin of the necrotic area assume the arrangement frequently seen in true tubercles, namely, with long diameter at right angles to the margin of necrosis.

The observations just described suggest that the tubercle has a close relationship, on the one hand, to the late stage of acute inflammation at a time when absorption is in progress and, on the other hand, to the changes which occur about an insoluble substance. The histological data which are available, fail to furnish conclusive evidence concerning the origin of the macrophage, which has an important part in acute inflammation, nor of the epithelioid cell of the tubercle. Both cells are capable of ingesting and dissolving protein bodies, and both contain enzymes with similar properties.

The dog offers a favorable opportunity for study of the enzymes of tuberculous tissue and for comparison of these enzymes with those present in the sterile inflammatory exudates

which are readily obtainable from the same animal.[32] When tubercle bacilli are injected into the pleural cavity, an immense mass of tuberculous tissue is formed in the mediastinum and the adjacent lymphatic glands undergo enormous hypertrophy. The power of this tissue to digest protein material exhibits certain noteworthy peculiarities. During the first two or three weeks after its formation polynuclear leucocytes are abundant and it exhibits the ability inherent in the leucoprotease of these cells to digest in the presence of an alkaline medium. At a later period with the disappearance of polynuclear leucocytes, this property diminishes and is finally lost. In the early period of its formation the tuberculous tissue digests in weak acid as well and at a later period when leucoprotease is no longer demonstrable the power of energetic digestion in acid persists. The enzyme which has this property may be extracted from the cells with water and preserved during a limited period of time. There is little doubt that it is contained in the epithelioid cells which digest within their substance tubercle bacilli, polynuclear leucocytes, red blood-corpuscles and other cellular elements; for such cells constitute almost the entire bulk of the newly formed tuberculous tissue. Moreover, when the tuberculous tissue undergoes caseation and the epithelioid cells undergo necrosis so that a fibrous capsule alone persists, protein-digesting activity disappears from the tissue.

Autolysis in the presence of acid is exhibited by the liver, spleen, and kidney, and these organs exert a limited power to digest foreign protein. There are at present no available means of determining if the enzyme of tuberculous tissue is a peculiar enzyme or is identical with the autolytic enzyme of certain other tissues. Of especial interest is the observation that the enzyme of phagocytic cells which are capable of intracellular digestion is more active than the autolytic enzymes. Opportunity for an accurate comparison is afforded by the liver studded with innumerable miliary tubercles. Such tissue contains much more enzyme than normal liver.

A peculiarity of the serous effusion which accumulates in the infected pleural cavity in contact with the tuberculous tissue

previously described emphasizes what has been said concerning the character of the enzymes contained in this tissue. Such serous effusion, like other serous effusions, inhibits the enzyme of the polynuclear leucocytes but unlike the serum of all other inflammatory exudates which have been tested, fails to restrain the enzyme which is abundant in the tuberculous tissue.

To complete the study of enzymes produced during the course of an inflammatory reaction, it is necessary to examine the adjacent lymphatic nodes. Such tuberculous nodes show enzymotic action which differs in no respect from that of the tuberculous mediastinum. The sinuses of the node are filled with large mononuclear phagocytes, many of which contain tubercle bacilli. Before caseation has begun, the histological appearance resembles that of the same node during the late stages of pleurisy produced by a sterile irritant such as aleuronat; and in both instances there is active enzymotic power of the same character.

Evidence of the existence of lipolytic enzyme in the cells of tuberculous exudates and in similar mononuclear cells from other sources has been obtained first by Bergel.[33] On plates of wax small excavations are produced after a period of incubation by exudates containing lymphocytes and especially by the exudate obtained from so-called tuberculous abscesses; ordinary pus produces no superficial solution of the wax plate. Tuberculous pus-like exudates, moreover, are capable of splitting neutral fat obtained from butter. Lymphatic gland and spleen pulp have similar lipolytic action, but bone-marrow, according to Fiessinger and Marie,[34] who have confirmed the observations just cited, fails to exhibit it. These authors have injected wax and various fats into the subcutaneous tissues and peritoneal cavity of animals and have found that polynuclear leucocytes first accumulate; an intense mononuclear reaction follows and effects the absorption of the fat. They think that the wax-like substance of the tubercle bacillus is dissolved by the lipolytic enzyme of the mononuclear cells.

The conditions under which in the body the intracellular enzymes act and the factors which bring them into action are

not clearly understood. Intracellular digestion by amœbas and other protozoa occurs in the presence of an acid medium and granules of litmus, and other indicators ingested by amœbas undergo the usual color changes indicative of an acid reaction. When phagocytic cells of vertebrates are allowed to ingest such indicators in granular form, no such change of color occurs. Whatever change of reaction occurs is not indicated by this gross method.

The enzyme of the polynuclear leucocytes is active in a neutral or alkaline medium and its behavior *in vitro* indicates that the reaction of the normal body fluids is favorable to it. The acids, such as acetic acid, which have usually been employed to demonstrate the activity of the enzyme of the mononuclear phagocytes are not present in the cells or in the serum. Nevertheless, other acidifying substances such as carbon dioxide, or lactic acid, are capable of bringing the enzyme into action. It is not improbable that conditions which diminish the oxidation of pathological tissue or inhibit its gaseous interchange increase its acid content and produce conditions favorable to the action of the enzyme.

Solution of bacteria, such as pyogenic cocci, is doubtless effected by the proteolytic enzymes contained within the polynuclear leucocytes. Metchnikoff has brought abundant proof that living bacteria are ingested by the leucocytes, but it is uncertain what part enzymes have in destroying bacteria. The proteolytic enzyme of the leucocytes and the bactericidal complement of the serum are not identical. Abundant histological evidence previously cited has shown that the mononuclear cells which accumulate at the primary site of inflammation dissolve within their substance polynuclear leucocytes, many of which have probably undergone degenerative changes before they have been ingested; this process is continued and completed in the adjacent lymphatic nodes. Indeed, it is not improbable that polynuclear leucocytes, together with other products of tissue degeneration, serve as the principal stimulus to the activity of the mononuclear cells. Such intracellular digestion of polynuclear leucocytes is the first step in the resolution of an

inflammatory exudate. There is scant evidence that polynuclear leucocytes disappear by autolysis unless suppuration occurs.

Absorption of fluid constitutes a second factor in the resolution of an exudate. When, with diminishing activity of the inflammatory irritant, exudation from the blood-vessels ceases, the physiological factors which favor absorption of tissue juices rapidly diminish the accumulated fluid unless the inflammatory irritant or inflammation itself has produced changes which alter the adjacent vascular and lymphatic structures; necrosis, suppuration, which is always accompanied by necrosis, and new formation of fibrous tissue, three conditions which are usually associated, produce such structural changes.

The large mononuclear cells which act as phagocytes are at first only slightly larger than the cells which they ingest, but those which are engaged in digesting many cells attain great size. The fate of these large cells after they have accomplished their function is probably not always the same. Some may enter lymphatics and reach adjacent lymphatic nodes. According to Maximow, some undergo degenerative changes, whereas others remain in the tissue. It is not improbable that disappearance of exuded fluid produces conditions unfavorable to their prolonged existence and many probably undergo autolysis. Diminished blood-supply and other factors which might impair oxygenation doubtless increase the acidity of their protoplasm and favor self-digestion.

Human pathology affords numerous instances in which inflammation pursues its course without noteworthy destruction of tissue and, followed by complete restoration to normal, is unaccompanied by any fibrous induration of the part. Lobar pneumonia, acute serofibrinous pleurisy and erysipelas may be cited. Such inflammatory reactions are well represented by the serofibrinous inflammation which follows the introduction of turpentine into the pleural cavity of an animal. The fibrin of such an exudate undergoes autolysis *in vitro* under conditions which indicate the presence of leucoprotease only during the first three days after onset of the reaction. During this early

stage autolysis occurs when the fibrin is suspended in weak acid and this ability to undergo self-digestion in acid persists at a later stage when fluid has completely disappeared from the chest. Fibrin obtained by whipping freshly drawn blood exhibits the same property. Since the blood-serum contains an enzyme exhibiting similar proteolytic activity it is probable that fibrin carries with it some of this enzyme when it is precipitated during coagulation. Autolysis referable to the presence of this enzyme may explain the disappearance of fibrin which persists after the fluid of an exudate has been absorbed. In some instances under conditions which are not understood, fibrin fails to undergo absorption and organization with new formation of fibrous tissue follows; fibrin is then slowly absorbed and replaced.

Further evidence that formation of scar tissue is not a necessary result of inflammation even when the reaction is inaugurated by extensive destruction is afforded by recent experiments of Whipple and Sperry [35] on the necrosis of the liver after poisoning by chloroform. The hepatic cells constituting a large part of the liver lobule undergo coagulation necrosis; a considerable number of large mononuclear phagocytes collect at the site of injury and accomplish the absorption of the dead liver cells. By active multiplication of adjacent liver cells, the parenchyma which has been destroyed is replaced and no new formation of fibrous tissue follows. The liver is restored to normal and there is complete absence of cirrhosis, though a bit of tissue removed three weeks before has demonstrated necrosis of three-fifths of each hepatic lobule.

Human pathology affords little evidence that tuberculous exudates may undergo resolution with restoration to normal; yet such resolution is doubtless possible and is probably accomplished by the same enzymotic action, which brings about the disappearance of an acutely formed exudate. Experiments of J. L. Nichols [36] have shown that the exudate of tuberculous pneumonia in immune rabbits undergoes complete resolution.

After suppuration has occurred, restoration to normal by the processes which have been described is no longer possible.

The inflammatory reaction pursues the course which brings it to an end only when enzymes set free by disintegration of polynuclear leucocytes are fully held in check by the serum which accumulates. When intensity of the irritant calls forth increasing numbers of leucocytes, and the density of the tissue affords restricted opportunity for accumulation of fluid, free enzyme overbalances antienzyme and fibrin, necrotic tissues, and perhaps to a limited extent adjacent living tissues undergo solution; in the wall of the abscess fibrous tissue is formed; what is the immediate stimulus to the new formation of fibrous tissue has not been determined.

Since long-continued inflammation is associated with new formation of fibrous tissue, such sclerosis has been commonly used as an index of chronic inflammation. Increase of interstitial tissue may furnish evidence of pre-existing inflammation even though the regenerative changes in the connective tissue are not included in the conception of inflammation. Nevertheless, the resulting confusion has introduced many inconsistencies into the nomenclature of disease.

In many instances of hepatic cirrhosis, the increased interstitial tissue is sclerotic and scar-like and all evidence of inflammation is wanting; the lesion, indeed, has all the characters of a scar and chronic hepatitis is not more applicable than is chronic inflammation to the scar from a burn of the skin (Marchand). The same remark is applicable to certain instances of granular atrophy of the kidney and to chronic lesions of other organs. Such diseases are a combination of degenerative change, notably necrosis, inflammatory reaction, regeneration of parenchymatous elements, and regenerative changes affecting the interstitial tissue. The relationship of these processes has not been sufficiently analyzed.

In most instances of so-called chronic endocarditis the existing lesion, perhaps preceded by inflammatory changes, is sclerosis of the valvular segments, and functional derangement of the valve is referable to peculiarities of scar tissue found in any part of the body. The same objection is applicable to fibrous myocarditis, applied to the lesion which occurs in asso-

ciation with arterial disease, impairing the vascular supply of the cardiac muscle. The common designation of chronic arterial disease does not have the affix "itis" indicating its inflammatory origin, but arteriosclerosis is used almost synonymously with endarteritis and mesarteritis, lesions in which degenerative and regenerative changes are conspicuous, whereas true inflammatory reaction is in most instances wholly absent. Thoma has pointed to the truth that the present use of the term "chronic inflammation," applied to the liver, kidney, heart, blood-vessels, and other organs, means nothing more than chronic disease. Study of pathological structure, eagerly pursued during the last two centuries, is not infrequently regarded as an unprofitable field for investigation and perhaps this view is correct should its scope be limited to the observation and description of pathological lesions; but examination of present knowledge concerning the nature and classification of various forms of inflammation shows how meagre is our knowledge concerning the significance of altered structure.

If it were possible to define the origin of the mononuclear cells concerned in the inflammatory reaction of all vertebrate animals as well as it is possible to define the character and source of the common polynuclear leucocytes concerned in the same phenomenon, it might be possible to describe with an accurate generalization the essential nature of the cellular accumulation which follows the action of substances foreign to a tissue. The possibility that the various mononuclear cells which accumulate are derived from the lymphocytes of the blood, offers attractive solution of the matter; but proof is wanting. A definition of inflammation, as Metchnikoff has pointed out, must be applicable to the entire animal kingdom unless it can be shown that the changes which follow the same stimulus in one group of animals are different from those which occur in another group. Metchnikoff has shown very clearly that the possession of a well-formed vascular system does not furnish this distinction.

In order that the cells which accumulate at the site of inflammation may preserve their vitality, a proper medium is

essential; exudation of serous fluid serves to dilute the inflammatory irritant and doubtless to furnish to migratory cells a suitable habitat.

To survive, an organism must prevent, or at least set a limit on, the entrance of foreign substance. Identical phenomena follow the entrance both of an insoluble foreign body and of a living invader capable of multiplication. The exclusion of inanimate material is relatively simple, but the struggle of one group of living beings to exclude other groups has been the source of almost infinitely complex relationships. The difficulty of distinguishing what is physiological and what pathological is here obvious. Since partial exclusion of bacteria is an essential condition of life, it is not inconceivable that special powers which accomplish no other physiological function may have developed. Phagocytosis of inanimate particles, such as carmine and charcoal, occurs equally well in serum and in normal salt solution, but most bacteria must be altered by the serum (acted on by opsonin) in order that phagocytosis attain its maximum activity. It is probable that agglutination and precipitation have a part in the phenomena which, during the course of an inflammatory reaction, fix and finally destroy certain inflammatory irritants. The bactericidal substances of the serum, both those which are normally present and those which are formed during the progress of immunization, are brought by exuded serum to the site of inflammation. Serum and cells co-operate.

From another point of view, cellular migration from the vessels and within the tissues may be regarded as a process by which certain enzymes are quickly concentrated at a point where they are needed. Study of the protein-digesting enzymes of inflammatory exudates has shown that cells and serum must maintain certain quantitative relations in order that the inflammatory reaction may accomplish its purpose and permit restoration to normal without excessive destruction and regeneration of tissue. Disturbance of this balance is followed by grave consequences which give to suppuration much of its ominous character.

Throughout the animal kingdom, the inflammatory reaction affords means by which various substances, notably enzymes, are delivered in unusual quantity in response to unusual local need. Inflammation may be defined as the process by means of which cells and serum accumulate about an injurious substance and tend to remove or destroy it. In lower animals with no vascular system this process with little or no accumulation of fluid occurs in the supporting tissues. In higher animals, it begins in the supporting tissues, proceeds with the co-operation of the blood-vessels and is completed in the adjacent part of the lymphatic system.

SUMMARY

Inflammation is a process which tends to render harmless an injurious substance; it has its site in the interstitial tissue of the body. This tissue consists of fixed cells and fibrillated substances and is penetrated by closed lymphatic vessels. With inflammation certain cells migrate through the wall of the blood-vessels of the part and enter the spaces within the interstitial tissue. Some of these cells are destroyed; others penetrate the endothelial membrane which forms the lymphatic capillaries and hence are carried by way of lymphatic vessels to the regional lymphatic nodes.

Bacteria and many other injurious substances are attacked and ingested by the polynuclear leucocytes which migrate from the blood-vessels. These leucocytes, often injured by the inflammatory irritant, are in turn ingested by large mononuclear cells (macrophages) which quickly appear at the site of inflammation. The origin of these mononuclear cells is still undetermined. Ingestion of polynuclear leucocytes and other cellular material is begun at the site of inflammation and completed in the regional lymphatic nodes.

The ability of phagocytic cells to remove injurious material is dependent on the possession of proteolytic enzymes. Peculiar to the polynuclear leucocytes is an enzyme which, like trypsin, exerts its digestive action in an alkaline medium. The serum of the blood contains an antienzyme which restrains the

action of this enzyme should it be set free by disintegration of the leucocytes; the action of the enzyme is thus limited to the locality in which it accomplishes its proper function, namely, within the cell. When enzyme is set free in such quantity that it overbalances the antienzyme of the exuded serum, suppuration occurs, for the purulent exudate has in virtue of its unrestrained enzyme acquired the power to soften and erode the adjacent tissues.

The mononuclear phagocytes which appear in the late stages of acute inflammation, the similar cells which appear in the regional lymph-nodes, and the cells of similar structure which constitute the greater part of tuberculous tissue contain an enzyme which, like pepsin, digests in the presence of acid. Such phagocytes are active at the site of inflammation, but their work is completed in the regional lymphatic nodes.

Inflammation is the process by means of which cells and serum accumulate about an injurious substance and tend to remove or destroy it. This process does not include the regenerative changes which replace injured tissue by newly formed parenchymatous elements or by new interstitial tissue. Present nomenclature of chronic disease contains many terms which are inconsistent with knowledge of the underlying disease. Terms such as "parenchymatous nephritis," "traumatic myelitis," acute "hemorrhagic pancreatitis" are applied to conditions which have not primarily the characters of inflammation; the term "chronic inflammation" is applied to complex morbid changes (*e.g.*, cirrhosis, chronic nephritis, myocarditis, arteriosclerosis, etc.) in which inflammatory processes have an insignificant part.

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THE PRESENT STATUS OF APHASIA AND APRAXIA*

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IF I understand my duty rightly, a Harvey lecturer from the field of psychopathology has to present a line of investigation giving a clear picture of the problems and methods of some special domain of his science. He must also show the broader ramifications and, if possible, the common interests between the physician and the research man, and the lines of live activity and co-operation.

It was my aim to give you a picture of the present problems of aphasia and apraxia and their correlation with the *simpler* neurological integrations of the hemispheres on the one hand, and the ramifications into *psycho*pathology on the other hand culminating in the efforts of the Wernicke school to make the theory of speech-disorders the foundation of the theory of mental disorders. The material grew to such proportions that it would have made unreasonable demands on my audience. I have, therefore, decided to limit myself in to-night's presentation to a discussion of aphasia and apraxia.

I shall cover the following ground:

1. A brief sketch of the classical theory of aphasia.

2. The observations that roused mistrust in the fond delusions of perfection, and a survey of our experience supplemented by some cases from the literature.

3. The principal anatomical and functional facts, and gaps of knowledge, concerning the organ involved, the cerebral hemisphere, including the special advances in the domain of apraxia, and

4. A summary of the questions worth the physician's attention.

Passing the history of the problem with the mere mention

* Delivered March 5, 1910.

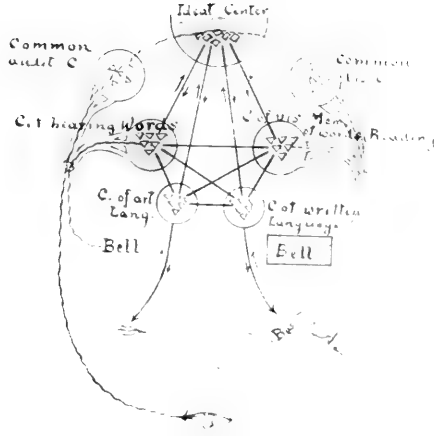


FIG. 1.—Mechanism for the representation of a bell in hearing (centre for hearing words, distinct from the common auditory centre for hearing sounds) and in reading (centre of visual memories of words independent of the common visual centre), the relation to the ideational centre and the avenues to the centre of articulated language and written language.

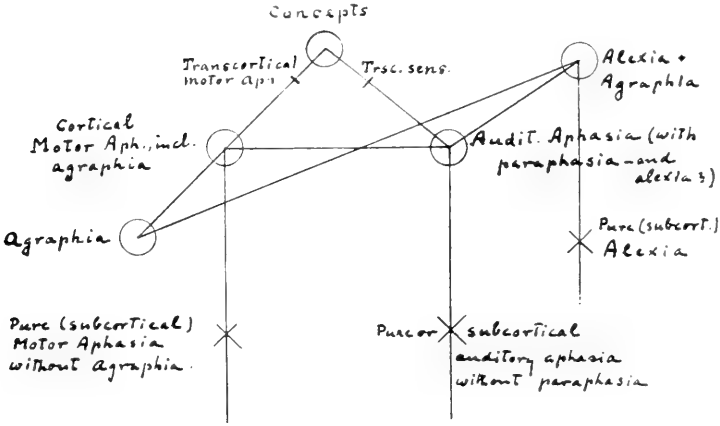


FIG. 2.

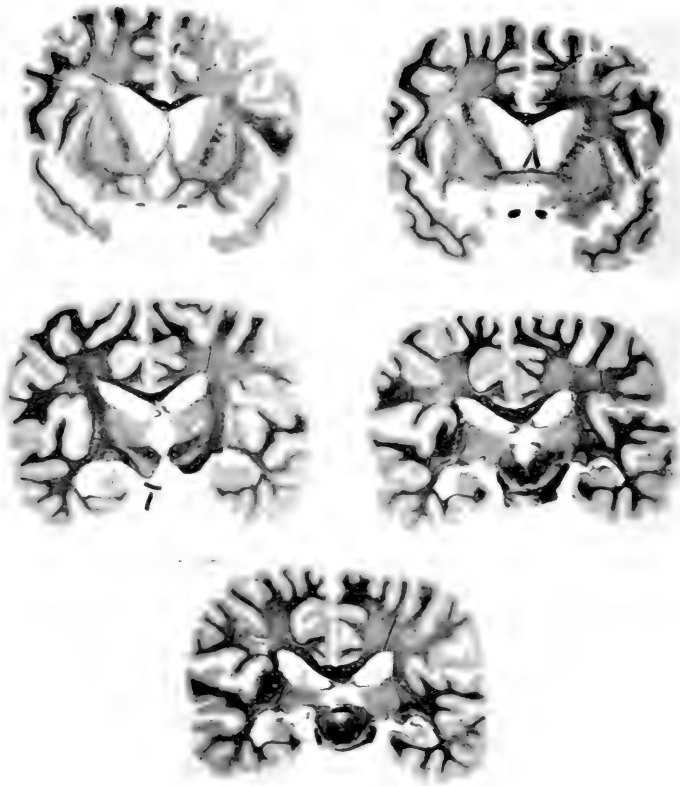


FIG. 6.—Subcortical cavity underneath the left third frontal gyrus visible in the first two sections (beyond the level of the anterior commissure) and extending as a focus of degeneration through the posterior sections, similar to the case of Fig. 5.

of a few names, we find Gall, Bouilland, and Dax, in the stage of premonitions, then Broca claiming a localization of speech, vigorously opposed by Trousseau; then a clearing of the issues by the master-mind of Wernicke, and a practical and didactic adjustment by Lichtheim, Charcot's pupils, Bastian, and Dejerine's school and others, with a revival of interest in the later nineties, and a recent renewal of the discussions following the publications of Pierre Marie.

A mere glance at Charcot's and Lichtheim's schemes (Figs. 1 and 2) will recall to your mind the graphic summary of the various teachings current when most of us first began to be interested in the aphasia question.

We were taught localization of the 'word-memories' in the leading hemisphere: two kinds of memories, the motor in the Broca convolution, and the sensory in the first or second temporal, considered to be distinct from the general articulation or hearing centres, independent centres specialized for language, or possibly even special languages, and music (these independent centres are still maintained by Starr, Fig. 3); further special memories for reading in the angular gyrus and writing in the second frontal gyrus; further connections beyond the word-sound memory and utterance centres, constituting the word-notion or internal language, not definitely localized.

With these centres a number of classical forms of aphasia were stipulated (Fig. 2):

1. Subcortical or pure aphasias, abolishing either hearing or reading, utterance or writing of words, without interfering with the internal language—the lesions subcortical.

2. The cortical aphasias, involving internal language or the use of language in thought: the *sensory* with signs of paraphasia and difficulty of finding words and especially names of objects; and the *motor,* involving the planning of words or at least of word combinations in speech and in writing and even affecting the reading; and cortical alexia involving also the writing.

3. The transcortical aphasias, leaving the automatic speech-mechanisms at work but without understanding or without initiative.

The occasional discrepancies of theory and experience were largely met either by Charcot's theory of individual differences into auditory, visual or motor individuals, or by Bastian and Freud's claim of difference in the extent or kind of isolation of the centres and character of the lesion; and the bilaterality of the structures helped in the rest.

My work in hospitals confronted me with the practical issues of aphasia ever since 1895. From the start, in the observations at the Worcester Insane Hospital and later, I was struck with the excessive dogmatism and the easy-going disregard for many contradictions in the classical teachings.

My first case (Fig. 4) with classical complete destruction of the Broca convolution was able to repeat words after me and thus approached the type of transcortical motor aphasia (*C.*). The classical postulate would have been: lesion of the Broca centre, abolition of practically all utterance, of ability to repeat or write (or even read); instead of that the patient showed recovery of the ability to repeat words.

Another case (*R.*, Fig. 5) of rather complicated but complete motor aphasia, with reduction to but one recurrent sound (hi hi hi) and *inability* to *write*, had merely an extensive subcortical lesion of the centrum ovale from beneath $l\,F_3$ to beneath the angular gyrus. Thus we had a subcortical lesion for what was clinically a typical 'cortical aphasia,' and in turn a review of the so-called *subcortical* motor aphasias of the literature proved that the majority of the cases of so-called subcortical aphasias had really cortical lesions.

Another case (*T.*, Fig. 6) merely with partial difficulty of word-finding and limitation of vocabulary proved to have a lesion of the subcortex of $l\,F_3$, extending backward as in the last case, only with very much less destruction. Still another case (*Fro.*, Fig. 7), who, it is true, lived only six weeks, but with complete motor aphasia with some difficulty of understanding, had a typical hemorrhage into the lenticular nucleus cutting also through the posterior limb of the internal capsule and no cortical lesion. Several cases with lesions in the region of the left first temporal gyrus were much more clearly related

FIG. 7.—(Viewed from below). Encapsuled hemorrhagic clot destroying the left external capsule and putamen and cutting through the posterior limb of the internal capsule and even the dorsal part of the optic radiations.

Fig. 8.—Motor aphasia with a lesion only of the anterior central gyrus and brachio-fascial monoplegia.

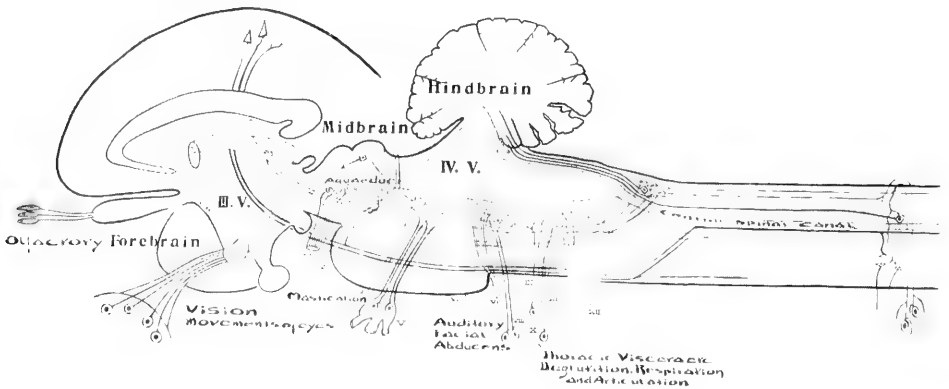


FIG. 9. (From Journ. of Compar. Neurol., 1898.) General plan of the nervous system, the cranial and spinal segments olfactory visual, masticatory, auditory facial, abducens, visceral and spinal segments and the cerebellar and cerebral supra-segmental mechanisms superimposed upon the segmental apparatus.

FIG. 10. —The quadrilateral between the two lines. I=isthmus. (From Pierre Marie.

to the classical paraphasic speech disorder. But chance would have it that (Fig. 8) the first autopsy on a senile case with motor aphasia of four months' duration, at Ward's Island, in 1902, proved to present a lesion of *Ca* in the face and lower arm region, but no lesion of $l\,F_3$, the Broca convolution; and thus the confidence with which diagnoses of lesions used to be made in aphasia dwindled perceptibly.

In the meantime two divergent developments influenced my attitude concerning localization: on the one hand, under the influence of the teachings of Hughlings Jackson, and of comparative anatomy of the nervous system and the experience with certain selective effects of poisons and diseases on special parts of the nervous system, the plan (Fig. 9) of division of the body and the nervous system into a series of relatively independent segments, and a division of the nervous system into segmental and cerebellar and cerebral *supra*segmental mechanisms had impressed itself upon me, and with it the realization that we knew something of centres for excitation and disturbance of mechanisms, but less of their actual functional and anatomical integration. On the other hand, the interests in localization were fostered by the remarkable development of the mapping out of definite cortex areas by the embryological method and especially also in the adult brain. Altogether, these interests and the rebuffs of the classical doctrines by nature's experiments suggested the advisability of collecting seriously all the facts within reach, and what I shall have to show is largely chosen from the fruit of the highly appreciated collaboration with my former associates in the New York State Hospitals, and supplemented by some specially important observations from the literature.

In 1906 and 1907, Pierre Marie precipitated a remarkable conflict of opinions. Briefly put, he accepts but one kind of aphasia or intrinsic speech disorder and that connected with a large temporoparietal zone, which he calls the Wernicke area, and considers only as part of the sphere of intelligence; the pure or simple aphasias he calls extrinsic disorders. He declines the existence of a pure auditory form, but accepts the existence

of pure alexia as an encroachment of the lesion of the visual zone upon the block of tissue representing speech-intelligence. The disorders of utterance he throws all together under the term anarthria, as the effect of lesions in a lenticular zone or 'quadrilateral,' in front of the isthmus and beneath and behind the third frontal gyrus (Fig. 10). For lesions in front of the isthmus he denies the existence of the so-called cortical motor aphasia implicating writing, and especially when complicated by difficulties of reading or understanding or intellectual encroachment, he claims them to be invariably combinations with a lesion in the Wernicke region.

I refer to this phase in the discussion of aphasia because no doubt many of you have your attention focussed on this issue. As far as possible I shall present my facts without polemic interests, mainly as a picture of the material available to-day and a consideration of our present means of arriving at constructive perspectives in this great domain of unfinished work.

I shall now pass the material for our inquiry before you, in almost barbarous brevity, but so as to pick out the essential points.

1. The first case (*Sh.*, from the Rochester State Hospital) has a remarkably well circumscribed destruction of the lower two-thirds of the central gyri, and the greater part of F_3 (Fig. 11), but perfect integrity of the lenticular and caudate nuclei and most of the island (Figs. 12 and 13). She presented,—

Right hemiplegia without noticeable sensory disorder.

Gestures free; understanding good.

Use of fingers for numerals. Reading silent and summary, not analyzed for words or letters.

Absolutely *no utterances and no writing obtainable.*

Condition unchanged two years and five months.

To sum up: Lesion of left hemisphere; corpus striatum free. Writing not obtainable—hence not pure loss of speech utterance, and anatomically and functionally adverse to several claims of Pierre Marie. It might indeed be used for the support of the classical conceptions.

2. A case (*N.Q.*, from the Manhattan State Hospital) with

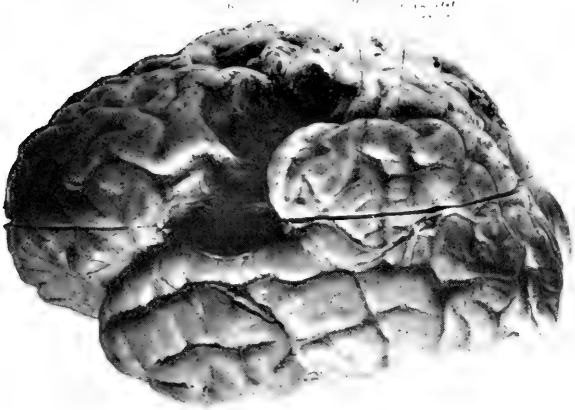


Fig. 11.

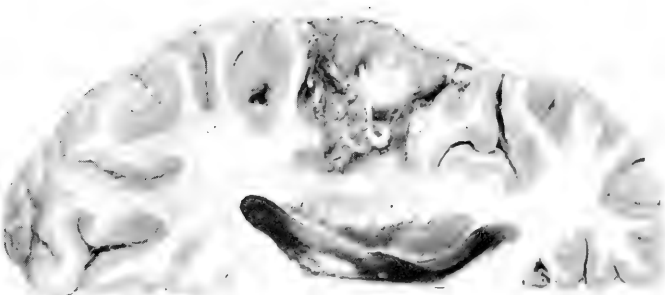


Fig. 12.

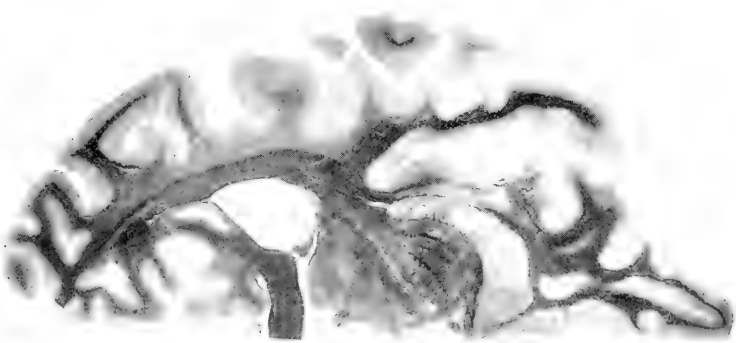


Fig. 13.—Motor aphasia without involvement of corpus striatum.

FIG. 14.—Transcortical motor aphasia; extent of precentral lesion marked by dotted line.

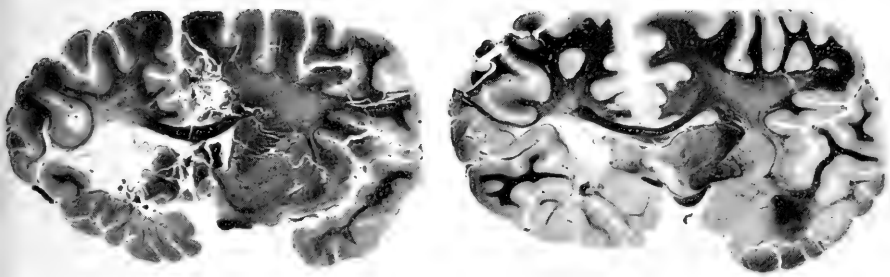
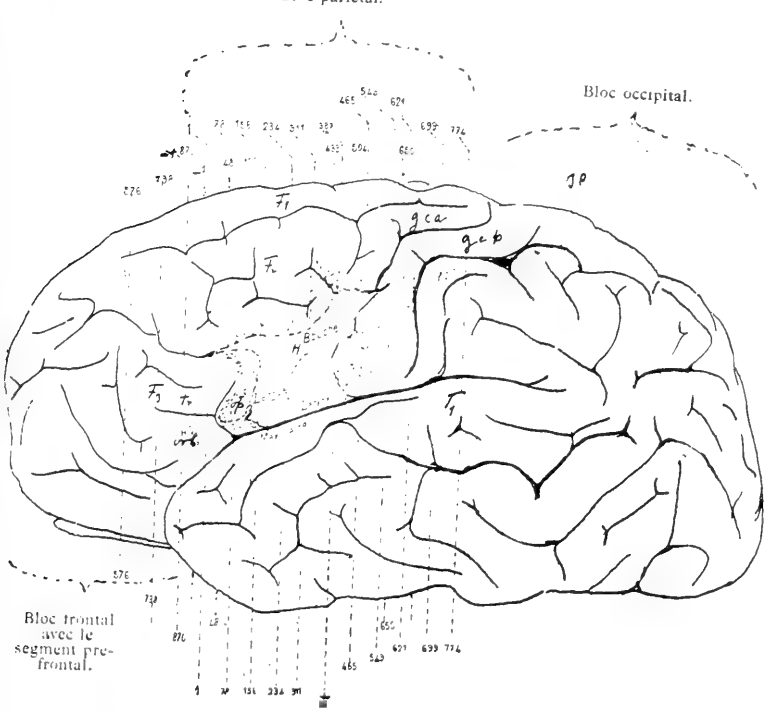


FIG. 15.—Dr. Fraenkel and Dr. Onuf's case of subcortical pure motor aphasia. Destruction of and subcortex of corpus striatum.



Reproduction au dioptographe (diminution d'un dixième environ) de la surface externe de l'hémisphère gauche.

FIG. 16.—Case Ladame von Monakow. Pure motor aphasia with cortical lesion.

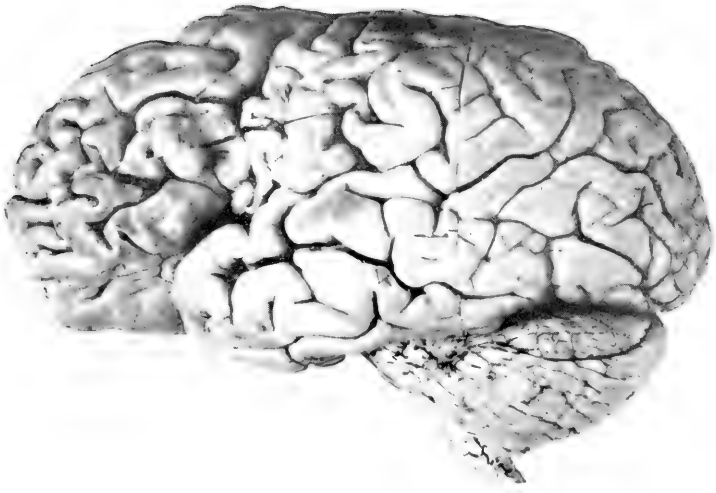


Fig. 17.—Transitory motor aphasia with extensive softening of Broca convolution.

a small focus at the transition of *Ca* to F_2 and F_3 partly covered up in the photo (Fig. 14), and another atrophy in the supramarginal gyrus, had first complete motor aphasia; after one year she began to use the recurrent utterance 'visiting to himself' without any other spontaneous speech, but perfect ability to repeat sentences even in, to her, unknown languages, and ability to name objects; inability to write. Hence: after a transitory complete motor aphasia, a typical 'transcortical motor aphasia,' or loss of initiative of utterance; with recurrent utterance and ability to repeat sentences and name objects—remaining practically without change the last three years of her life.

3. The next case (*W.*, Fig. 15, from Dr. Fraenkel and Dr. Onuf) was one with typical inability to speak, but *preservation of writing* lasting several years and with a typical *subcortical* and really 'lenticular' lesion, and undermining of the whole lower motor and Broca region; hence, truly a pure motor or 'subcortical motor aphasia.'

4. With this we must, however, contrast a case of the same clinical condition of so-called pure or 'subcortical' motor aphasia, also with *preservation of writing* and without disorder of the internal language, of eleven years' duration, published by von Monakow and Ladame (Fig. 16), with a lesion not unlike that of our first case who, as you remember, had however also lost her writing—strong evidence of the impropriety of distinguishing these disorders as 'cortical' and 'subcortical' aphasia.

Another case (*S.T.*, Fig. 17, from the St. Lawrence State Hospital) had a right motor and sensory hemiplegia with complete motor aphasia, but gradual return of speech within a few months, with a lesion of the third frontal and undermining of the central gyri.

To this I add again the monoplegic (*R.*, Fig. 8, from Manhattan State Hospital), who did not regain her speech except once for the one utterance 'police' in a state of emotion, but presented only a cortical lesion of the face and hand area; further (*E.*, Fig. 18, from the St. Lawrence State Hospital), a

patient who had a transitory motor aphasia recovered from in about six weeks, with a slit of softening within the marrow of the arm and face area of *Ca*, and complete integrity of F_3 and of the lenticular block in the narrower sense.

The next case (*F.*, Fig. 19, from the Kings Park State Hospital) is most interesting on account of a right-sided lesion of $R\,F_2$, and the lower $R\,Ca$ and $R\,F_3$ in a *left*-handed person, with slight convulsion, inability to utter more than a few sounds, and left hemiparesis; within a week 'she wrote distinctly of her own accord and from dictation, could read and repeat words, understood what was said to her, and named objects or tried to.' Later her articulation remained somewhat indistinct and she had some difficulty in answering questions. She was originally left-handed but wrote equally well with either hand—a case which suggests the partial solidarity of the two corresponding areas of the two hemispheres, and shows moreover (Fig. 20) the possibility of very superficial essentially cortical affections.

To these cases we should have to add negative evidence, such as one case (*M.*, Fig. 21, from St. Lawrence State Hospital), of which I would only say that the *record* gives no evidence of motor aphasia in the face of a typical lesion of $l\,F_2$ and $l\,F_3$; further, the well observed *case B.* (Fig. 22) *of von Monakow*,—a druggist who had but a few episodes of aphasia lasting a few hours at a time, and complete recovery before death, but an encephalitic destruction of $l\,F_3$. To this I must add another negative case (*S.*, Fig. 23, from the St. Lawrence State Hospital) with lesion of the lenticular region near the knee of the internal capsule, without any record of aphasia.

The majority of these lesions show that affections of and around the articulation-centre of the motor area are apt to cause various affections of expressive language. The characteristic traits are (1) simple abolition of *utterance*, where other expressions such as by writing are preserved, *or* (2) abolition with involvement of word planning *and* writing, or (3) abolition of mere initiative (in all three forms the speech rests are apt to be recurrent utterances). The type of disorder in each

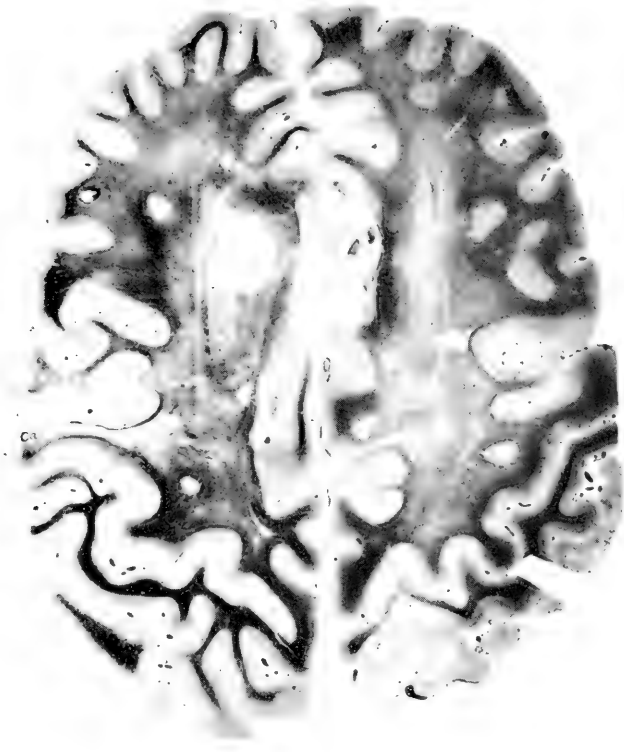


FIG. 18.—Transitory motor aphasia with a slit of degeneration in the subcortex of the left anterior central gyrus. Cortex, striatum and subcortex of Broca-region free.

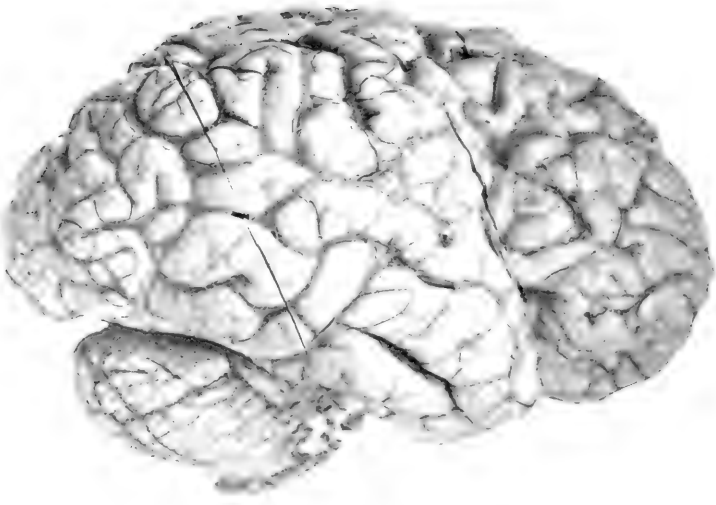


Fig. 19.

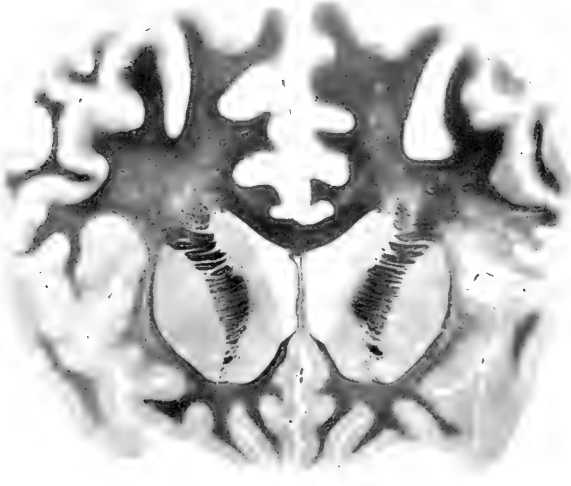


Fig. 20.—Chiefly cortical softening of right Broca-region and adjoining part of insula in a left-handed woman. Recovery from speech-disorder in one week.

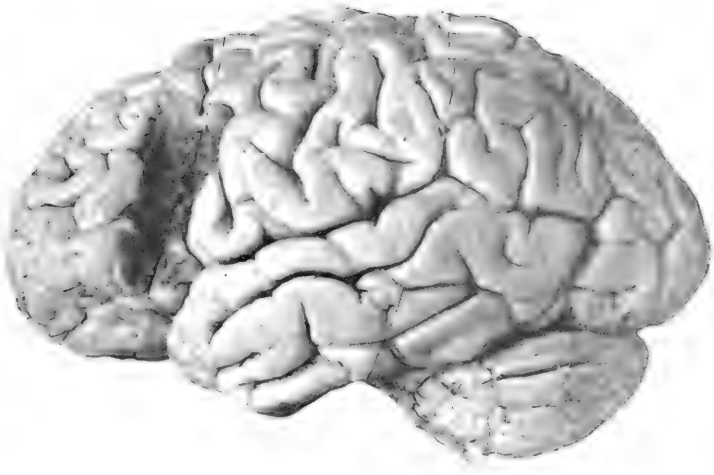


FIG. 21.—Negative case.

Fig. 81.

FIG. 22.—Essentially negative case of v. Monakow.

FIG. 23.—Negative case.

case is, however, not as clearly reducible to a simple localizatory principle as seems to be the case for the following types which go under the term *sensory aphasia.* I select but three representative cases from the series of eight already published in Forel's Festschrift (Journal f. Neurologie u. Psych.).

The first case (*B.,* Fig. 24, from the Hudson River State Hospital) with a temporoparietal softening, presented for over two years a typical jargon-aphasia, with complete inability to take in any word in hearing or reading whether for repetition, writing or execution of orders. This complete word-deafness goes with complete destruction of the left auditory receiving centre (as shown in a transverse section, Fig. 25, and in a reconstruction of the Sylvian surface of the temporal lobe, Fig. 26), and an extension of this lesion backward through the inferior parietal lobules.

The next case (*A.,* Fig. 27, from the Buffalo State Hospital) presented the typical *trans*cortical sensory aphasia; he understood words *heard* and *read* sufficiently to repeat and read them aloud, but he did not grasp the sense, and spoke in paraphasia. Here the lesion (Fig. 28) left intact the auditory entrance-zone, and with it the apparatus for mechanical verbal reaction, but affected the transition and extension into the actual personal co-ordination, into the domain of comprehension,—with an extensive temporoparietal lesion later complicated by a frontal lesion.

The third case (*H.,* Fig. 29, from the Kings Park State Hospital) had practically no difficulty of a sensory character, but difficulty of spontaneous elaboration of words in naming things and in showing occasional paraphasia; and this with a lesion sparing the entrance zone of the auditory area, but cutting into its lateral connections (Figs. 30 and 31).

These and the other cases made evident the rôle of the place of entrance of the auditory path into the auditory zone, for actual *word-deafness;* while lesions leaving it intact had mainly paraphasia and difficulty of naming,—elaboration disorders.

Besides these cases we should bear in mind the few cases of Freud, Liepmann, and Barrett, in which a purely or essen-

tially subcortical focal destruction of the auditory and callosal path abolished the *word-understanding* without any lasting paraphasia or other elaboration disorders. Further I should recall the cases of Pick and others in which diffuse lesions in both temporal lobes led to more disorder of understanding words than was warranted by the deafness.

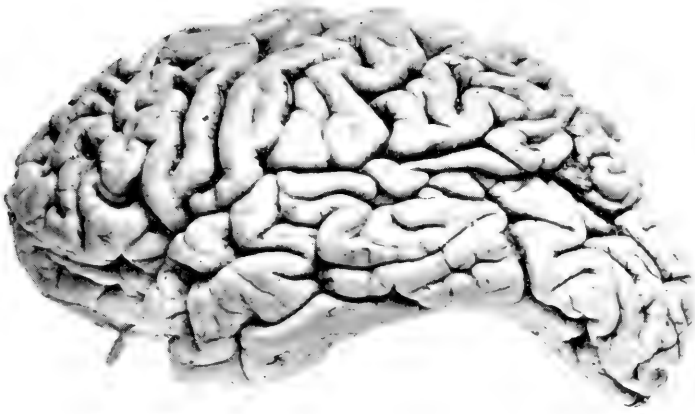
These cases show clearly a much greater rôle of the auditory receiving-station proper than is assumed in Charcot's diagram and many others, which call for a special word-hearing centre. There is a much greater regularity in the *lesions* in receptive aphasias, and in the corresponding affection of speech and internal language in the form of paraphasia and difficulty of word-finding; and the greater frequency with which these cases reach our hospitals for the insane shows how much more closely these disorders encroach on the more complex integrations or functions of the personality.

A further case (*E.*, Fig. 32, from the Buffalo State Hospital) deserves mention for our purpose, that of a woman who presented the very opposite of the transcortical aphasias, namely, relatively normal spontaneous speech, but total inability to repeat any word on request and refusal to write, with a lesion in the retrocentral operculum.

To complete the material for a really comprehensive review of the whole problem, I should have to refer to certain further cases reported in the literature, such as those of pure agraphia (Gordonier of Troy, a tumor, Fig. 33, encroaching upon the arm-centre from the frontal region), Dejerine's musician who first had simple alexia from occlusion of the posterior cerebral artery (calcarine region + splenium), and later alexia + agraphia from additional angular lesions (Fig. 34); and I should further mention some cases in which the reading and writing were *preserved independently* of word-deafness with its special marks of paraphasia and elaboration disorder or destroyed independently, and certain negative cases,—but I must hasten on to the discussion of the brain functions on which we shall have to interpret these facts.

I must here return to the interesting transition from the

FIG. 24.



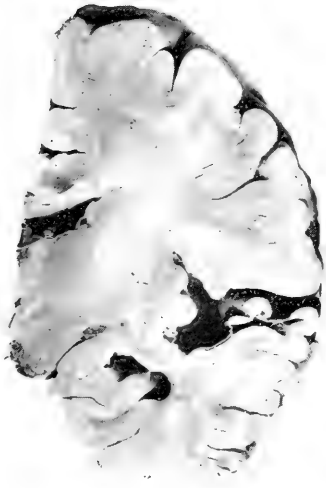


FIG. 25. FIG. 26.

Case of permanent word-deafness and paraphasia. Reconstruction of the Sylvian surface of the temporal lobe; the dotted region the undermined or destroyed transverse temporal gyrus or auditory entrance-zone.

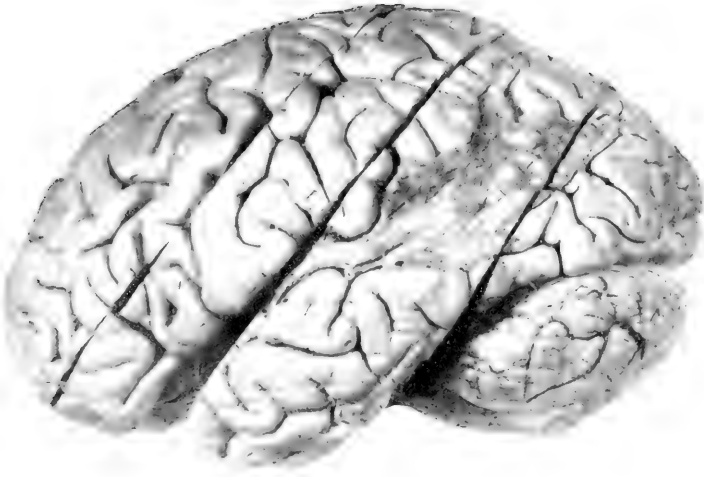


FIG. 27.

FIG. 28.—Transcortical sensory aphasia. Entrance of auditory zone intact. (Dotted area degenerated; area with small crosses normal auditory cortex.)

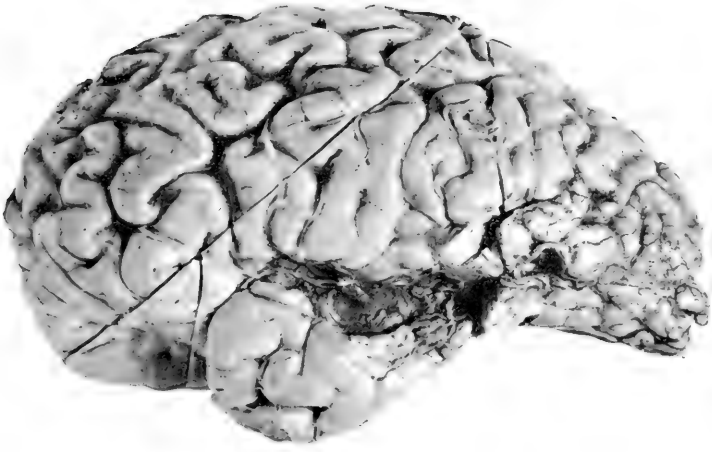


FIG. 29.

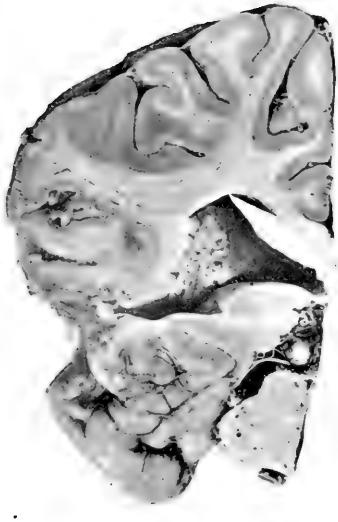


FIG. 30.

FIG. 31.

Case of anomia and paraphasia. Mesial part of transverse temporal gyrus (entrance of auditory path) intact.

FIG. 32.—Occlusion of retrocentral vessels and softening of P^2.

subdivision of the cortex according to experimental localizations to that of a real anatomical analysis. A wonderful amount of work lies between the classical map of ring-like centres by Ferrier (Fig. 35) and the myelogenetic maps of Flechsig and those who determined the subdivisions in the *adult* brains (Fig. 36), with a remarkable harmony in the results obtained by the different methods.

What is actually brought out in these plans or maps throws a clear light on the problem we have on hand. In the first place there is one zone in which functional excitability and structure coincide: the giant-cell area concerning which the experiments of Sherrington and Vogt on monkeys and the results of Cushing and others in man, are in substantial harmony. There are definite foci of excitability and vulnerability, definitely limited to the region of origin of the pyramidal tract, while the frontal zone for head and eye movements has not been reduced yet to a special cortex-type. In the lower motor area Vogt (Fig. 37) finds a representation of face, tongue, palate, jaw, larynx, and finally rhythmic movements of the mouth. Anything like speech-movements has never been produced in man, but Oppenheim could stop the speech in one of his cases by compression of the third frontal with the finger. Now, before we shall consider the aphasia material we certainly want to make sure of what localization means in the best studied motor centres.

We must admit that even here the common self-satisfaction of physicians is not altogether warranted. Over the exclusive faith in the pyramidal tract some important facts seem to have escaped. In the first place section of the pyramidal tract in the medulla in monkeys leaves the animal without paralysis. Hence the pyramids are but one component of the possible higher motor controls. In man, Horsley and others have excised the excitable cortex of the arm region with the result of only a transitory palsy, so that Horsley considers voluntary movement possible through the connection of mechanisms outside of the pyramid and the motor cortex proper. Maxwell found that injection of salts into the cortex produced but slow and limited results, while an injection into the immediately subjacent white

matter acted very suddenly, probably in part because it affected a much more extensive range of connecting fibres and mechanisms. Sherrington found that restitution does not take place through training of neighboring cortex, that the extirpation of the corresponding area of the opposite side does not abolish the regained function in the first affected limb. The only conclusion is that evidently the mechanisms of voluntary cerebral control are organized more broadly than our simple schemes assume. The rubrospinal tract, a path from the midbrain, is pointed to as the carrier of the returning extrapyramidal function. But how it is reached and governed is not clear. Nobody but the investigator in brain anatomy realizes the gaps of knowledge in this field so glibly disposed of by the average teacher. In the sections (Fig. 38) of the first case of complete motor aphasia we find that not even the knee of the internal capsule so readily claimed as the facial and articulatory part of the pyramid can be accepted as such any longer, that the articulation paths lie behind the knee and that our data conflict seriously with von Monakow's. But what now, after these admissions of unwarranted assurance on the part of the classical teachings? Shall we overthrow our anatomical or our functional conceptions? It is very probable that we stand on rather delicate ground on either side. Yet in the face of it all, the anatomical findings of the cortex-map call for specially renewed efforts of study. The excitable motor area (Fig. 39) borders on a strip of intermediate cortex beyond which the third frontal shows a remarkable spur extending not merely as Broca's area, but with even greater emphasis of medullation to the posterior margin of the orbital cortex. It so happens that the vascular lesions are coarse, like the effect of the bull in the china shop; it hardly ever destroys special cortex fields by themselves; our elaborate and expensive studies of serial sections furnish but slowly, fragment by fragment and often only by exclusion, some sort of a picture of the pertinent mechanisms, and in *this* region we are trying to localize.

The next best known mechanism is the visual cortex, the calcarine cortex proper, exceedingly well marked off; the peri-

Fig. 33.—Gordonier's case of agraphia, frontal lobe tumor in l. F_2.

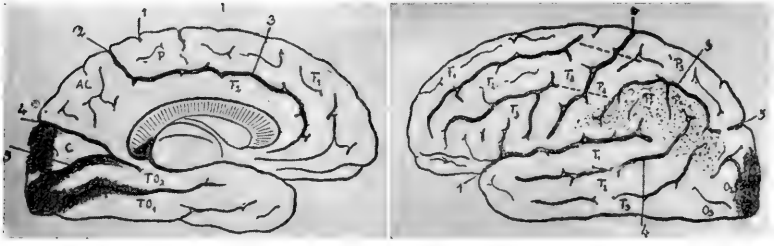


Fig. 34.—First focus deeply shaded; later lesion dotted

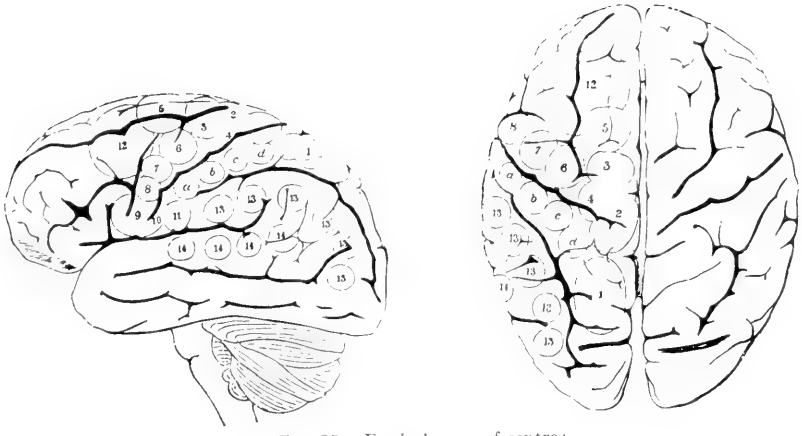


FIG. 35.—Ferrier's map of centres.

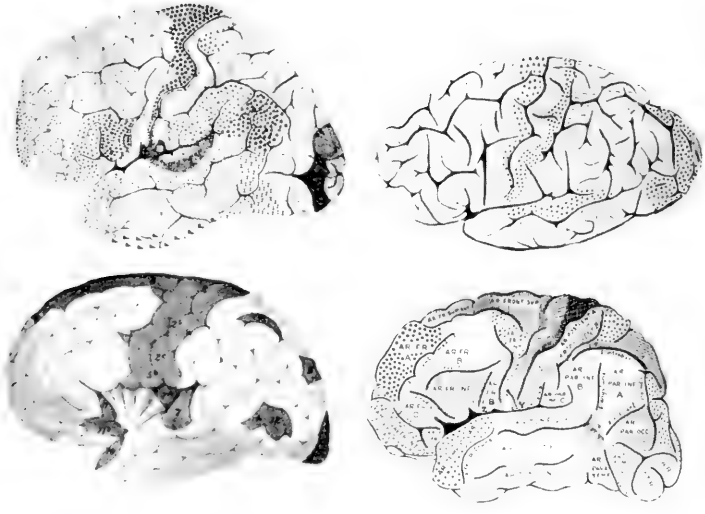


FIG. 36.—Maps of the cortex according to differentiation of structure by Brodmann, Campbell, Flechsig, and Elliot Smith.

Fig. 28b. Dgl. wie Fig. 28a.

Erklärung der Zeichen:

Gleichseitig konvexe Verbiegung der Columna vertebralis.
Cauda.
Anus.
Digiti pedis. Tarsus. Tibia. Femur.
Truncus. Truncus oralis. Truncus caudalis
Scapula. Scapula + Humerus. Humerus. Brachium ant. Carpus. Digiti
2—5 Digiti. Pollex
Orbicularis oculi. Auris. Nucha. + Facialis inferior. Lingua. Mandibula.
Velum palatinum. Larynx. Rhythmische Mundbewegungen.
Bulbi ×. —Bulbi × mit Mydriasis. Bulbi × mit Miosis. Bulbi × und oben. —Bulbi × und oben mit Mydriasis. Heben der oberen Augenlider. Bulbi × und unten. Nach oben gestellte Bulbi in die Mitte. Gesicht ×. Auris. Apertura oculorum. Hochziehen der Augenbrauen. Die übrigen gelben Zeichen sind aus den eben erklärten zusammengesetzt.

FIG. 37.—Vogt's record of electrical stimulation in monkeys.

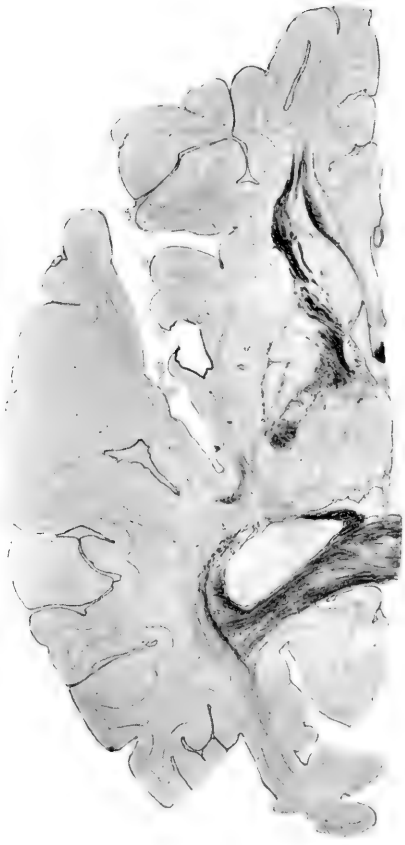


FIG. 38.—Integrity of the knee of the internal capsule in the brain (Fig. 11).

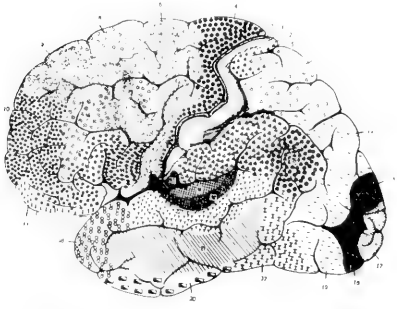


FIG. 39.—Brodmann's map of the lateral view of the hemisphere.

striate zone less so, the lateral field of the occipital lobe passing into the so-called posterior association field of Flechsig, which also has a few as yet unexplored islands of specialized appearance.

The typical integrative function of the hemisphere for vision (Fig. 40) is evidently half-vision, and its negative, hemianopsia. The structures with which we can reckon to-day are the striate cortex, probably the exclusive end-station of the geniculo-calcarine tract or optic radiation; the relation between cortex and the occipital efferent path is probably broader, but the functional rôle of this large efferent path is a secret. The association paths studied on a most interesting case, of limited bullet wound (Fig. 41) from the Willard State Hospital, were limited (Fig. 42) to a connection with the motor zone, and some fibres towards the auditory zone and others through the callosum, while in the deep or sagittal marrows the *external* fibres degenerated plainly backward, and the internal fibres forward. The functional integrations or losses of integration of this region point to a quadrantic representation, so that the upper lip of the calcarine cortex and the more dorsal radiations go with hemianopsia in the opposite *lower* quadrants of the visual field; and excitation of the upper lip with movements downward; if Wilbrand's third observation can be accepted, a horizontal strip of half-blindness may correspond to lesion of the valley of the cortex (Fig. 43). An efferent motor path attributed to the angular gyrus is not demonstrated. The visual integrations are thus singled out by:

1. Hemianopsia (in quadrants or complete, either only for colors or usually for forms and light as well), usually from lesion of the posterior cerebellar artery (Fig. 44).

2. Mind-blindness (difficulty of interpretation with sufficient vision—separation of the visual sphere from the posterior association field, Fig. 45).

3. Simple alexia (mind-blindness limited to words or letters), superseded by

4. Alexia with agraphia—a more intense disorder interfering with the planning of letter forms (Fig. 34).

5. Isolated disability to recognize distances and depth.

These varieties are more easily explained by lesions of the optic radiation and the striate cortex and by the lesion of the connections with or among the other leading parts of the hemispheres than by the assumption of special centres for each type.

With the auditory field (Fig. 46) we seem to approach ground much more definitely related to the speech-function evidently with some differentiation of the parts. Mott's case (Fig. 47) shows that the bilateral destruction of the transverse temporal gyri entails complete deafness, and to this we have to add the striking regularity with which circumscribed lesion of the auditory sphere in the leading hemisphere goes parallel with definite disorders of the speech integrations, a finding corroborated independently by Quensel. Spiller published a negative case, destruction of the whole area without any aphasia; but in a case in which also tabes was found only post mortem. The general uniformity is surprising in view of the fact that in the dog, tone-differentiation can be obtained even after ablation of both temporal lobes as shown by the noteworthy training experiments of Kalischer. Functionally we have the following steps of integration and disintegration in the material at hand:

1. Complete deafness from bilateral lesion of T tr. (Hemiacusia from unilateral lesion? Cerebral loss of special tones or islands of the scale unlikely.)

2. Loss of word-identification, without further disturbance (subcortical and partial bilateral lesions).

3. Preservation of mechanical repetition without understanding.

4. Loss of word-identification and disorders of elaboration (paraphasia, anomia, etc.), lesion of T tr. and of connections.

The greatest advance in the general co-ordination of data of the *tactile and motor integrations* comes from a brilliant pupil of Wernicke and his discovery of *unilateral apraxia.*

Liepmann examined a man committed to an asylum as a case of apoplectic dementia. The patient was aphasic and had

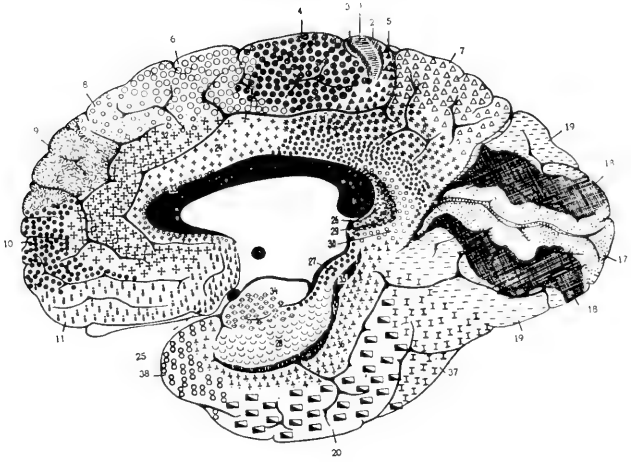


FIG. 40.—Brodmann's map of the mesial view of the hemisphere. The area striata or visual receiving station proper with fine dots, the area peristriata with dark cross-hatching.

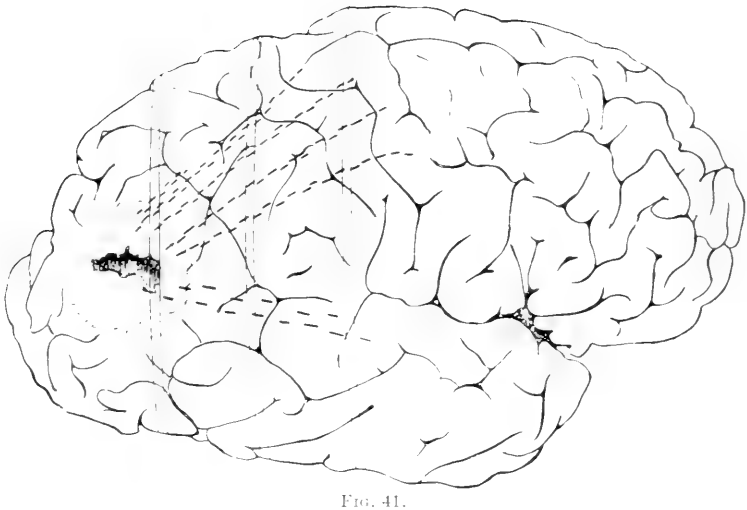


FIG. 41.

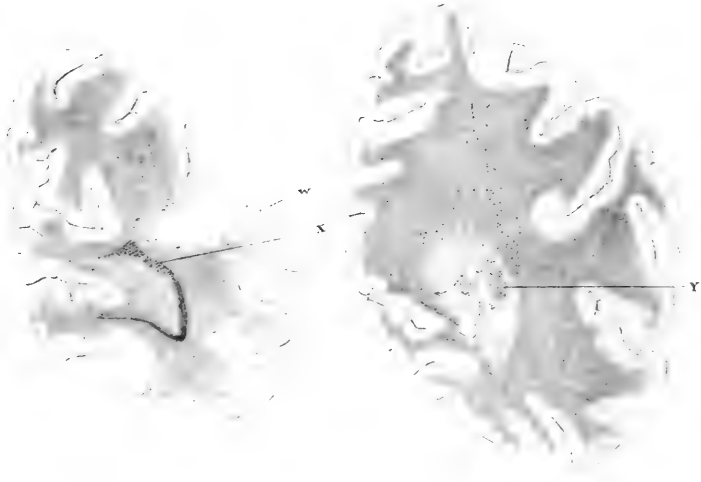


FIG. 42.—*W*, wound. *X*, degenerated fibres of the external sagittal marrow marked by dots (behind the lesion). The normal lower rest of the external sagittal marrow indicated by a compact dark streak. *Y* degenerated fibres of the internal sagittal marrow in front of the lesion.

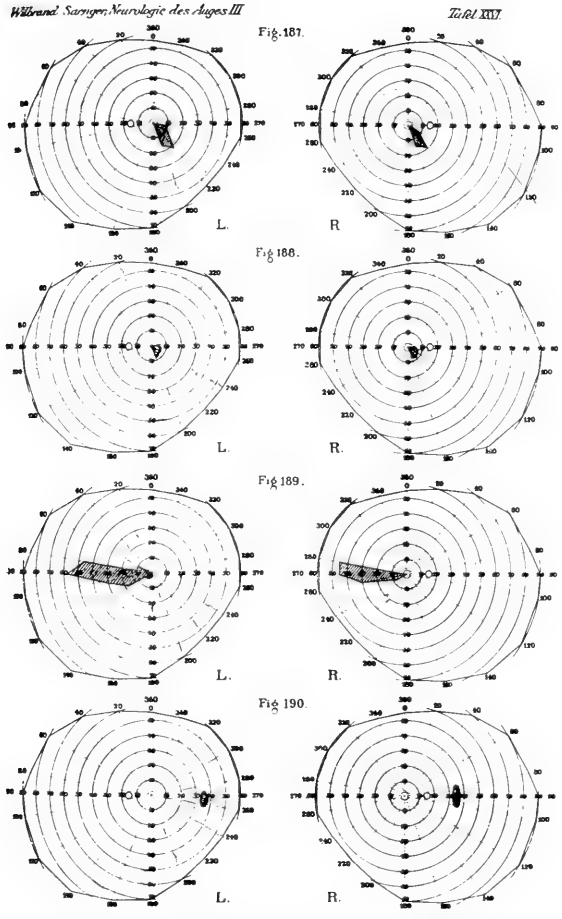


FIG. 43.—Smallest defects of visceral field of supposed origin in small lesions of the calcarine cortex (Wilbrand).

FIG. 44.—Typical occlusion of the posterior cerebral artery with right homonymous hemianopsia.

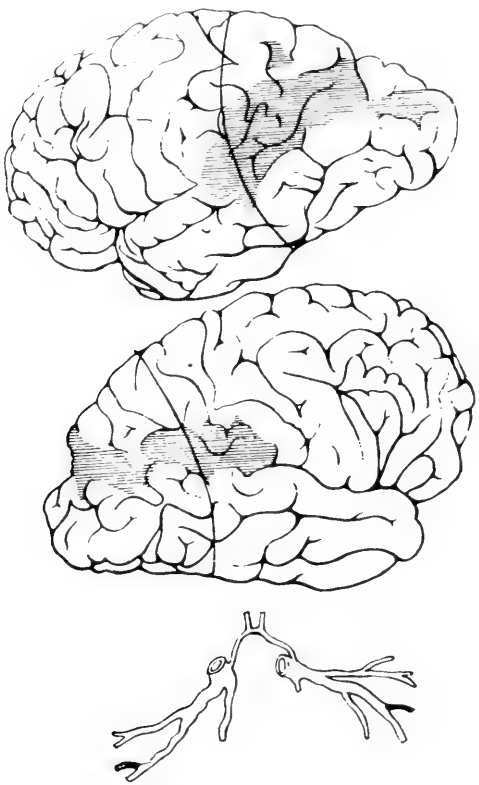


FIG. 45.—Mind-blindness in bilateral symmetrical occlusion of the postparietal artery.

but few words left. He had no hemiplegia, but a slight *disturbance of sensibility* on the right side, as was later seen, especially for position and motion. This patient seemed to be completely demented, and since he merely fumbled very queerly when asked to do things, he was under suspicion, at first, of being word-deaf, and even mind-blind. Liepmann then observed that the patient carried out any request for which the body as a whole was required; he would go to the door as told, sit down, get up, etc.; he further saw that the confusion invariably started with a strange fumbling of the right arm, and by it the whole course of action would be side-tracked. Liepmann found that when he *held* the patient's *right* arm and forced the *left* arm into initiative, the dementia disappeared: the right cards were picked out, even writing was possible, and the whole case was plainly one of pseudo-dementia and really a 'one-sided apraxia.' Instead of being looked upon as merely an ordinary demented individual, the patient was recognized as having mainly a partial disorder.

On examination of serial sections, the motor area and the pyramidal tracts were found intact. There was a subcortical softening underneath F_2 and F_3 and a cyst under the supramarginal and the inferior parietal gyri, and moreover degeneration of the corpus callosum with the exception of the splenium, and a shrinkage of the right angular gyrus. What simulated that which in neuropsychological slang is called a loss of memories of movements, proved to be the partial lack of support by the sensory part of the brain, and the inability to use the experience of the other side. A *deep* disorder of tactile responses, a *complete* hemianæsthesia, usually shows rather different results from what this patient showed. One of my cases with hemianæsthesia and atrophy of the parietal region could move his left hand with some ease and force as long as he looked at it; but the movements were ataxic and when he shut his eyes or kept his hands out of sight, and I asked him to close his hands rhythmically, he ceased doing it with the left and still thought he was keeping it up (*mind palsy*). He was wholly unable to recognize objects within the hand which had the

receptor difficulty. In Liepmann's case there was no ataxia, and the hemianæsthesia was *not* profound, nor was the astereognosis complete. Liepmann, therefore, concluded that at least part of the apraxia, of the faulty motor responses, was due to improper use of the motor cortex owing to isolation and not owing to destruction of any special part of its intrinsic motor mechanism; and he laid the emphasis to quite an extent on the lesion beneath the supramarginal gyrus.

Further studies led Liepmann to the observation that in some cases of right hemiplegia the left side had lost the capacity to indicate from memory very ordinary signs and movements (the patient would be unable to indicate with his non-paralyzed left arm the motions of beckoning, threatening, throwing a kiss, making a fist, saluting, ringing a bell, counting out coins, catching a fly, grinding an organ, playing the fiddle, snapping the finger, or the use of a comb or brush, or lighting a candle or putting on a stamp), while actual handling of objects, the actual use of a match, etc., was less frequently affected. A few of the cases examined anatomically so far corroborate the hypothesis that this loss is not merely one of intelligence in the broad sense of non-localizable general capacity, but due to the interruption of the callosal path and the elimination of the help of the leading hemisphere, a point which can indeed be used for the localization of lesions (Fig. 48, from Wilson).

These studies have given a remarkable impetus to the whole problem of synthesis of cerebral activity and to anatomoclinical correlation.

Hartmann, who participated in the studies of Anton on the frontal lobes, communicated two cases of lesion of the frontal lobe and one of the corpus callosum, which led him to the conclusion that the impetus to serial movements roused from the various sensory spheres of the cerebrum requires the co-operation of the frontal lobe for the imparting of their impulses to the motor zone. The elimination of the left frontal lobe leads to motor mind palsy or loss of initiative of the opposite extremity. The right frontal lobe requires the co-operation and guidance of the left or leading frontal lobe beside the connec-

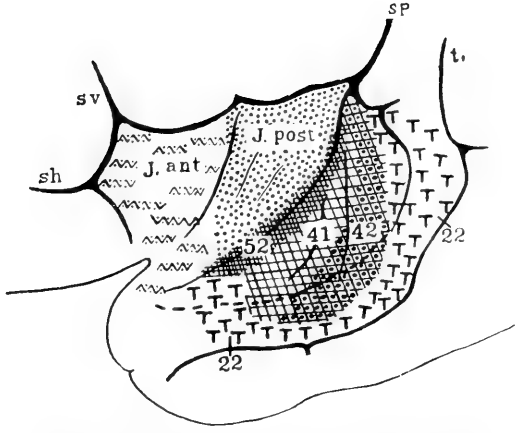


FIG. 46.—Bordmann's subdivision of the island and transverse temporal gyrus.

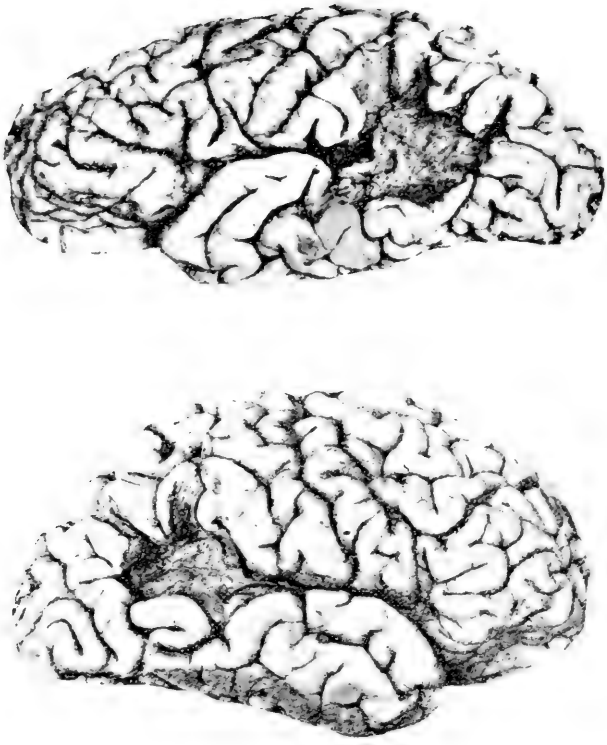


FIG. 47.—Mott's case of bilateral destruction of the transverse temporal and auditory zone. Complete deafness with preservation of reading.

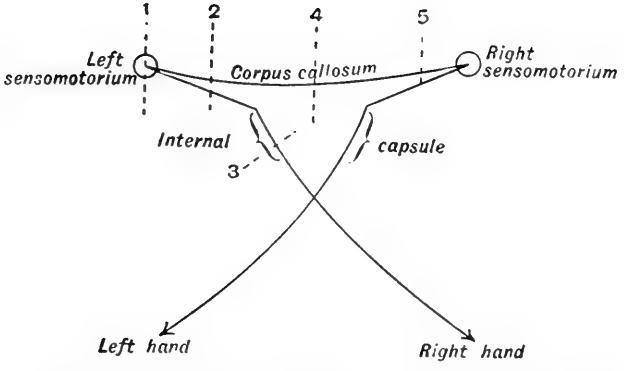


FIG. 48.—(From Wilson after Liepmann.) 1, cortical lesion; 2,subcortical lesion; 3, capsular lesion; 4, lesion of corpus callosum; 5, subcortical lesion.

tion with its own sensory spheres to have its serial movements properly guided. Thus we see again that separation of the left frontal lobe from the right abolishes *those* serial movements of the left side which depend on memory. We have here another but more definite formulation of the data of Liepmann, and a prospect to bring harmony into the impressions concerning the production of agraphia and aphasia through lesions approaching the motor zone from the frontal lobe, as was the case in Gordonier's case of isolated agraphia.

We seem to have gone far away from the consideration of the cortical areas of the frontal lobe furnished by the brain-maps. From what was said before, it is evident that a most painstaking inquiry into the details of anatomical relations must nevertheless pave the way before it pays to speculate about the mode of insertion of the cerebral motor apparatus upon the subcortical and segmental mechanisms or lower nuclei. But we certainly have gained some broad lines of hemisphere function worth summing up.

We can distinguish now:

Intellectual disorders pure and simple, not specially charged to any of the senses.

Focalized intellectual disorders appear either on the *receptive* or the *emissive* or in the *co-ordinative* or elaborative function. The *common link* is covered by the term *agnosia,* which covers knowledge of things sensed and remembered, as well as knowledge of how to do things.

Agnosia (see diagram) has its more essentially receptive aspect in general or ideatory *asymbolia* or disorientation, and its more essentially emissive aspect in general or ideatory *apraxia.*

Asymbolia, complicated by essential anæsthesia of general or special senses, or independent, can be partial; the disorder of primary identification may be kinæsthetic, as astereognosis, or visual, as mind-blindness, or auditory, as mind-deafness, or involve the taste and smell sphere. The agnosia may show especially in the effects on the wording (and then probably involves *all* the senses), so that probably there is no such thing

as isolated 'optic aphasia'; *or* agnosia affects more the direct motor reactions.

We may miss the proper kind of *plan* of action, as in *ideatory apraxia;* or the plan may be correct, but one whole side or only one limb or motor unit like the *arm* or the *tongue* is out of commission for the act, although not paralyzed as such; this covers the *limb-kinetic apraxia* in the frontal lesions; and as *dyspraxia,* I should group the losses from severing the corpus callosum. Beneath this we may further find the possibility of

Submental hemiplegic complexes		Essential anæsthesias
Dyspraxia		Disorders of primary identification
Limb-kinetic apraxia		Astereognosis
One-sided	Mind Palsy	Mind blindness
Motor apraxia	Cerebral Ataxia	Mind deafness ?
General / Ideatory apraxia	\ Ideatory	asymbolia ?

AGNOSIA

INTELLECTUAL DISORDERS

Emissive Disorders—Elaboration Disorders—Receptive Disorders

APHASIA

Gen. loss (motor aph.)	Paraphasia	Word deafness
Limb-kinetic loss (pure motor aphasia and pure agraphia)	Anomia	Word blindness
Disorders of initiative		

interference with mere submental co-ordination as in the *ataxia* dependent on anæsthesia, and corresponding reduction of the sensory support of the motor apparatus of the hemisphere leading to mind palsy.

As a counter part of the other tables of integrations we can therefore give the following summary for the tactile and motor sphere:

Tactile and muscular sense:

1. Hemianæsthesia with possibility of some circumscribed foci (more or less of the axial type in the limbs) and possibly a splitting off of the muscular sense by itself.

2. Astereognosis alone (elaboration disorder).

3. Astereognosis with hemianæsthesia. (Note the special loss of the muscular sense component.)

4. Hemianæsthesia with ataxia, hemianæsthesia of tactile sense component (tactile aphasia and dyschiria hysterical).

Then the motor integrations—motility:

1. Complete hemiplegia (or possibly monoplegia in lesions above and in the internal capsule): (*a*) either Wernicke's type by joints (purely cortical), or (*b*) the normal arm-flexion and leg-extension type, or flaccid, or with contractures.

Complete flaccidity and occasional atrophy depend on the thalamus involvement; athetosis and tremor as complications or alone belong especially to the rubral complex; while lesions of the pyramid in the medulla and decussation give no symptoms, at least in the monkey; lesions of the lateral columns of the cord again spastic hemiplegia; and uniform diffuse weakness of trunk and extremity is said to go with one-sided lesion of the pyramid in the pons.

2. Mere ataxia or inco-ordination of balance of movement through lack of sensory support (cerebral ataxia).

3. Lack of control of execution as in simple mind-palsy.

4. Motor apraxia (through relative isolation) in which the patient has the sensory and intellectual support needed for a movement, and the movements perfectly well planned, but inability to perform such movements as making a fist, showing the tongue, or speaking a word (which the patient can plan and perhaps can write), or at least a wholly senseless miscarriage or substitution, such as raising an ink-well instead of showing the tongue.

5. In ideatory apraxia, crude movement is preserved and also the sensory support; but the intellectual support is lacking in the form of lack of attention or of planning as shown in the failure of the use of a candle, a pistol, a shoe, etc. (*Psych. Bull.*, ii, 279.)

Aphasia in such a scheme becomes a part of the agnosia-asymbolia and apraxia problem.

A certain type of associative reactions involve linguistic signs. According to our survey we distinguish linguistic elaboration or co-ordination, that which has been called internal language, or which covers Marie's linguistic intelligence.

In contrast to Marie's views I am, however, inclined to recognize the close relation of the word-deafness to lesion of the auditory entrance zone and the relative independence of the word-blindness complex and its connection with the visual apparatus, without, however, being able to determine a cortical area or any definition of the connections, except the general rule that the more we encroach on the block under the so-called posterior association field, the more apt do we become to disturb even the mechanism of writing and to get complications of the paraphasia-paralexia type. Evidently few cases work with both hemispheres, to judge from the rarity of recovery by substitution.

On the motor side we evidently meet with more ambidextrous organizations, and an understanding of the mechanism in anatomical terms is as yet difficult. There is a broader zone of vulnerability, though not quite as large as the *quadrilatère* of Marie, and it seems to take a large area practically involving the motor operculum to abolish speech permanently. The Broca area is an empirical unit not to be ruled out completely. The duration and recoverability in motor aphasia depends on the size of the lesion and possibly the extent of ambidexterity. The broader interruption in the cases of Liepmann and Hartmann suggest the possibility of a definition of the frontal lobe functions as the co-ordinator of serial movement.

To put the present position briefly:

The available facts suggest a plan also chosen by Rieger in his very original studies on hemisphere-function, viz., that of following the impressions of the various senses to the responses along the line of speech and symbolic thought (der sprachlich-begriffliche Apparat) on the one hand, and along the line of direct activity (räumlich-sachlicher Apparat) on the

other. Within each field we may have our special and isolated disorders open to interpretation by localization or along the lines of the disorders of serial movement, the analysis and synthesis of reactions, as Rieger depicts the disorders, and the mere disorders of control.

The great risk of didactic schemes is excessive condensation and excessive desires for one-word designations for really compound disorders. Size up and detail the mechanisms which enter into the picture, call the spade a spade, the functional disorder a functional disorder, and the lesion a lesion, but do not try and mix it all into one confusing word. The only real and lasting solution comes from the utilization of adequately defined anatomical and functional mechanisms (which can more safely replace the rough schemes of Ferrier and the early localizers). We cannot afford to brush aside really commanding facts, and replace them by vague units such as the lenticular zone and an arbitrarily extended Wernicke zone, without slighting the natural lines of analysis and synthesis. Marie's strong appeal is a recall to general perspectives of great value, viz., (1) the close relation of the intellectual and linguistic differentiations; (2) their great dependence upon the posterior field; (3) the great variability of the lesions and results in connection with the motor utterances; but the simple data of large enough chains of consecutive observations bring out the *true* points of his claim quite naturally, without any need for arbitrary negations.

Von Monakow has introduced the term diaschisis to account for the fact of transitory interferences with function and relative localization. He wishes to distinguish clearly the mere vascular shock and pressure and distance effects and the functional disorders actually attributable to the effect of cutting fibres which would enter into the other mechanisms which thus become deprived of certain functional influences without being directly injured as such. He assumes that where we deal with transitory symptoms it is due to indirect and remote dynamic effects and that the effects from actual destruction alone would give the permanent symptoms. I cannot befriend myself with

the term; all lesion is diaschisis and the recoverability or permanence depends on the question whether balance of function can be maintained with what is left or not. A diaschisis according to von Monakow would then cover all the losses of function or balance which need not be permanent. Von Monakow assigns all apractic asymbolic and aphasic disorders to such diaschisis. After all we must admit that if you destroy enough, you will finally get permanent loss even with mechanisms which are very diffuse and not strictly localized. Bickel's experiments on the reappearance of cerebellar defect symptoms through new lesion of the cerebral motor area and many other data of motor regulation show a certain amount of surplus provision and factors of safety in our organization and many transitory disorders are merely a disturbance of adjustment, possibly in an otherwise weakened part. Diaschisis is therefore the thing to be explained and not an explanation; it is a matter to be sized up in every case and a query as to which part is thus weakened, if it is to be more than an emphasis of the obvious for those of us who have a broader view of localization. If we cut one leg off a tripod it falls, and yet you would not say that the tripod stood on that leg alone. If there are more than three legs the loss of one is less serious and as we see at times in dogs almost negligible. That many transitory disorders are such disorders of balance is a much safer assumption than that of a peculiar agency acting at a distance, as when von Monakow tries to explain the 11 years of pure motor aphasia in his case as a corticobulbar diaschisis.

When the physician meets a case of speech-disorder, he does well to pin his attention first on the existing motor and sensory disorders, and secondarily upon the capacity for *elaborations from* the various points of hearing, vision, tactility, etc., (1) into the various types of *direct action* and (2) into *speech- or thought-functions,* with attention to the possible independence of the hemispheres and of the individual mechanisms. The sum of free or blocked connections ultimately indicates best the probable extent of lesions. The next considerations are the nature and extent or number of lesions. Exten-

sive autopsy experience tempers one's diagnostic assurance. A symptom or complex may be due to a simple or unitary lesion, or to several foci, or a focal accentuation of a diffuse process, such as senile or paralytic atrophy, or merely the result of one of those as yet insufficiently explained causes of hemiplegia in uræmia or other asthenic states (hemiplegia without lesion). Their distinction is an issue of successive developments rather than of final combination of symptoms.

Before concluding I must turn briefly to a group of experiences more or less unanalyzed, but suggesting distinctly an attempt to explain the condition by some focal process. I remember a patient who suddenly developed a pseudo-Korsakow state, really a systematic disorientation lasting till death within several months—no autopsy. Another somewhat peculiar Korsakow syndrome was ultimately found to be dependent on traumatic lesions of the frontal and temporal base (State Hospital Bulletin, vol. i, 140, 1908); further I recall certain peculiar conditions in which a patient would speak of fictitious matters and then complained that she was a humbug, who said things she did not want to utter and that were not so; a form of paralogia rather than paraphasia (Kr. and Mi.), twice observed by me in connection with brain-tumor compressing the anterior part of the Sylvian fissure; further the peculiar states of *focal hallucinations* connected with hemianopsia, and finally the occasional conditions of *vitiation of character* and of a peculiar jocose attitude in tumor of the frontal lobe, or as Taylor in Boston observed it, a condition of psychasthenia; or we meet states simulating hysteria in brain-tumor—these are grounds which sometimes present great difficulty even if we have fairly definite principles with which to work out the less complex problems.

In all these doubtful states the only safe road is to analyze first the motor and sensory symptoms, and the symptoms of language in direct connection with them with attention to the several levels or units, viz., (1) word identification, word-finding, word-elaboration, paraphasia, and special attention also to music, for the auditory zone and the lower parts of the

lateral parieto-occipital region; (2) the reading or reading and writing disorders for the posterior and upper areas of the parieto-occipital zone, supplemented by the search for defects in the lower, visual quadrant, and evidences of disorientation, or (3) the sensory area with the conditions of astereognosis. In the domain of motor speech and writing, the appearance of the speech symptoms before any motor or sensory symptoms speaks strongly in favor of a disorder in front of the motor area; otherwise it may be mere guessing to decide in what direction from the actual tongue-larynx region the focus may be.

I must pass the problem of distribution of the mechanisms according to blood-vessels. While this offers excellent landmarks the problem will always be complicated by some individual variations, the possibility of multiple lesions, or of diffuse alteration beside the focal one, and the occasional existence of slowly progressing affections with sudden apoplectiform manifestations.

The slowness of progress in this complex problem is to a large measure due to the uncertainties as to whether autopsies can be obtained and as to whether the great amount of work required in the repeated examinations will be allowed to receive its final control. The other reason is the great amount of work and expense implied in the examination of the brains. In all these respects physicians should collaborate not only in the State hospitals (where the cases are often greatly complicated by mental disorders, but are studied with growing efficiency and admirable determination, so as to put the scientific and medical world under growing obligations), but especially also in general hospitals, in traumatic states or embolisms, not complicated by additional deterioration of the brain. Another very commendable way to help is encouraging fellowships of research. Perhaps when the North Pole and the South Pole shall at last be properly discovered, man will bestow more attention upon the most wonderful creation of nature, the organ of plasticity of behavior.

URIC ACID IN GOUT*

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INTRODUCTION

UP to the present time the only chemical problem considered in gout has been that of uric acid. As yet no other chemical stand-point has been found. Are we on the right track in doing this? Is the uric acid really the principal toxic agent in gout, or only one of several? From time to time, especially when there appeared to be no progress in the investigation of the subject, protests arose that research was on the wrong path.

The relations between uric acid and the occurrences in gout became evident in the acute periods. The attacks are certainly connected in some way (yet to be determined) with the accumulation of this substance in the body, and during the attacks the output of uric acid is greatly altered. Experiments made with uric acid injections prove their toxic character; the inflammation and the pains provoked by them resemble in many respects those occurring in attacks of gout.

Though conceding this, Von Noorden a number of years ago, following Ebstein's theory of the formation of uric acid in the bones, expressed the opinion that the deposits of uric acid were quite independent of the general metabolism of uric acid. Although local influences play an important part in gout, this view of Von Noorden is easily to be refuted. The microscope shows clearly that the crystals are first found near the free surface of the cartilage and that they advance slowly towards the deeper layers. Thus they must pass from the

* Delivered March 19, 1910.

cavity of the joints into the cartilage. Secondly, when a tophus on the finger reaches the size of a chestnut and even larger, it is impossible to imagine that the enormous masses of sodium urate stored up here could be formed in loco, even in the course of many years. The metabolism of connective tissue is much too torpid, and nuclear material, known to be the sole source of uric acid, is contained only in small amounts in the cuticle and neighboring tissues. Moreover, wherever you find deposits of sodium urate in the body, that is, wherever gout is apparent, there occurs at the same time an excess of this substance in the blood. Although this principle is not reversible, it proves certain connections between the local and the circulating uric acid.

PRELIMINARY NOTES

In reference to uric acid, gentlemen, please remember that in reality we have to deal only with monosodium urate in the fluids within the body. Some authors have pretended the existence of a quadriurate of sodium, or as we would call it now, of monosodium biurate or hemiurate; others have insisted that in a fluid containing a number of basic molecules like serum, the chemical union of an acid with one of the bases could not be recognized. Physically considered there exists no monosodium urate in the serum, no more than does monosodium carbonate. All these salts are dissociated into their ions, and we have to deal only with sodium, potassium, calcium ions and with uric, chloric, carbonic acid ions, existing side by side. But with the same right with which one speaks in the common language of chemistry of the existence of sodium chloride, of monosodium carbonate and monosodium phosphate in the serum, with just as much right you may also speak of a monosodium urate. Ninety per cent. of the kations in the serum belong to the sodium, only 10 per cent. to potassium, calcium, and so on. In a neutral solution which, in a physical sense, the serum is, the proportion between kations and anions, or between acids and bases, is such that we can only speak of monosodium carbonate and of monosodium urate. The existence of bisodium

urate is just as impossible here as the existence of a bisodium carbonate. It is to Gudzent that we owe this clear exposition.

FUNDAMENTAL PRINCIPLES

As compared with former times we now stand on a firm foundation in regard to our knowledge of the formation of uric acid. This substance is derived from the nuclear purins, adenin, guanin, hypoxanthin, and xanthin. Their transformation into uric acid is the work of hydrolytic, or desamidizing and oxydizing ferments. The ferment which katabolizes uric acid is called the uricolytic ferment. I need not detail these processes, but will refer you to Prof. Mendel's lecture delivered on this subject three years ago before this society.

This being established, two questions arise:

First, whether this intermediate way of metabolism is obligatory in the sense that every molecule of the purin bases must reach the stage of uric acid, or whether adenin or hypoxanthin, and so on, can be katabolized without first being converted into uric acid. Thus far the possibility of the latter proposition has never been demonstrated in the organism. Chemical considerations and biological analogies lead us to consider the transformation of purin bases into uric acid as the only process effective in mammals.

The second question, whether in mammals there are still other sources of uric acid, is doubtful. No proofs have yet been brought forward of formation of uric acid from urea and from acids with three-carbon atoms, a process which is of fundamental importance in birds. So we may neglect this kind of synthesis. On the other hand it is beyond question that purins are newly formed in suckling animals, whose food is practically purin-free. It seems improbable that the synthesis effected here starts from urea; we must rather look for a higher amino-acid compound, as a material which can yield purins. It would be very surprising if this synthesis were performed on a larger scale than was needed for the growth and for the renewal of the tissues, *i.e.*, for the synthesis of nucleoprotein.

I do not think that in this process an excessive formation of purins takes place, nor that superfluous material for the formation of uric acid is left over. We may, with our present knowledge, consider the purins as the only source of uric acid in human metabolism.

We distinguish the exogenous purins ingested with the food from the endogenous derived from the nucleins of the body. By dieting we can make ourselves independent of the great variations in the output of uric acid due to the different amounts of ingested purins. By giving a purin-free food, which need not be absolutely the same every day, the urine will contain endogenous uric acid only. The quantity eliminated, although varying in different men from three to six tenths of a gramme, is fairly constant in the same person under normal conditions, thus proving the existence of an equilibrium between formation and destruction of uric acid. The simplest conception of this is, not that formation and destruction vary always in the same sense and proportion, but that both formation and oxidation are constant.

The katabolism of uric acid leads to the formation of allantoin in dogs and rabbits. In men its fate is unknown. In contrast with the results in most animals human organs have failed to show a distinct uricolytic power. Hence Wiechowsky drew the conclusion that uric acid was indestructible in the human body. He based this opinion also on a second fact, namely, that uric acid injected into the muscles of men is found again almost quantitatively in urine. Schittenhelm, although confirming Wiechowsky's experiments with human *organs,* was able to show that uric acid undergoes destruction in *living* men. When a person, who was in a nearly perfect N equilibrium, was fed with 10 grammes of nucleic acid, the output of purin substances was only slightly increased, and instead, an increase of urea (or a substance behaving similarly) was found, and in amount corresponding nearly to that of the N of the ingested purin compounds. It would be of the greatest interest for physiological chemistry to determine what are the intermediate and end products of the uric acid break-down; but for the knowl-

edge of gout, this is of less importance. It suffices for the present to know, that this toxic substance disappears as such.

If Wiechowsky's opinion were right it would mean a simplification of experiments and of theory, for one unknown component in the complex equation of urate metabolism, the destruction of uric acid, would have been eliminated. Recapitulating, one may say that the present foundation for investigations of the metabolism in gout is as follows: We have to deal only with *one* source of uric acid, namely, the purins; and, after excluding the exogenous purins, we anticipate finding a uniform elimination at certain periods. This we accept as a firm basis for comparison, both as regards the metabolism of healthy men as also with regard to the variations which occur in different periods of gout.

THE FACTS IN GOUT

What are the facts in gout which are established with such accuracy that we can take them as a basis for our consideration? What results are sufficiently probable to be taken into serious discussion? The facts and the probable truths are as follows:

1. The presence of uric acid in the blood.

2. The presence of crystalline deposits.

3. The increased output of uric acid in the attacks of gout. The augmentation can reach from three to five tenths of a gramme daily and more, and may sometimes last for a week or even two.

4. A decline in the output often precedes the attack, but this diminution is not as marked as the subsequent increase, and its duration is only one or two days.

5. In the intervals between the attacks the elimination of endogenous uric acid is asserted to be lower than in normal health. There are doubts whether this statement has been proved beyond question.

6. The elimination of exogenous uric acid is often retarded.

To elucidate the connections between these data it would

be necessary to have a complete knowledge on the quantitative side of the following processes in both health and disease:

1. Of the formation of uric acid and
2. Of its destruction.
3. Of its elimination by the kidneys.

From a combination of these three processes arises a knowledge

4. Of the accumulation of urates in the body, especially in the blood.
5. Of the conditions of the sodium urate precipitation in the tissues, as well as the conditions of its removal. Herein is included a knowledge of the physical and chemical behavior of sodium urate.

FORMATION OF URIC ACID

Is the formation of uric acid increased or is it diminished in gout? In almost every case where we see an increased output of uric acid, for example in leukæmia and pneumonia, we find an enlarged destruction of nuclear material and vice versa. In gout, at least in the intervals, and when the patient receives a purin-free diet, neither one nor the other is to be remarked. The katabolism of nuclear material therefore is certainly not increased.

On the other hand, we have just as little reason to assume a diminished formation. Brugsch and Schittenhelm, it is true, have recently advanced the theory, that the total nuclear metabolism in gout is retarded. But even if this were true, I must insist that retardation of metabolism is not in every case identical with diminution. Perhaps in *advanced* stages of the disease, a decrease in the formation of nuclear compounds may take place, due to a kind of cachexia or premature aging. In the experiments made hitherto, I miss clearly defined statements as to the age and the general state of health. Most of the gouty patients treated in hospitals are in an advanced stage of their illness and evince signs of cachexia, even when showing a good volume of muscles and of subcutaneous fat. The healthy people, whose nuclein metabolism has been com-

pared with that of the gouty were generally younger. In order to obtain a more reliable material for the comparison between normal and gouty metabolism, stricter attention ought to be paid to this point regarding age. Bearing this criticism in mind the following exposition may be considered. In any case it seems to be certain, even though in opposition to former opinion, that the occurrences in gout cannot be explained by excessive formation of uric acid. In the older days whenever an increased output of uric acid was noticed, the cases were mostly those of wealthy people overfed with meat. Gouty patients are generally hearty eaters. The high amount of uric acid in these people is due to the ingested purins, not to the diathesis. Analogy with obesity produced by polyphagy is striking. The gouty process, though no doubt aggravated by an excess of exogenous purins, does not depend on an increased uric acid formation.

DESTRUCTION OF URIC ACID

In many experiments the twenty-four hour output of uric acid in the urine of gouty men is diminished. As far as this is not due to lessened formation, it proves an increase in the *absolute* quantity of uric acid destroyed. The accumulation in the body does not reach such an extent as to explain the difference of excretion between healthy and gouty men. This difference often reaches 100 mg. in 24 hours. Supposing this quantity were retained in the body day by day for one year only, the total sum would amount to 36 Gm. Deposits of such enormous size are extremely rare, at least in Germany. I doubt whether in the majority of cases 10 Gm. of sodium urate may be extracted from the gouty body. Since the lower quantity of uric acid in the urine is not explained by an accumulation, it must be ascribed to an increased destruction. As Brugsch and Schittenhelm rightly suggest, this does not mean absolutely that the oxydizing power of uricolytic ferments is greater than normally or that their quantity is increased. The reason may be, that each molecule of uric acid circulates a longer

time in the body, it is exposed more often to the influence of the oxydizing ferments, and thus there is more chance for its destruction. The investigation of the blood renders it probable that such prolonged circulation of urates really occurs in gout.

The conclusion that the *endogenous* uric acid is katabolized in greater amount is confirmed by the results of experiments in which the fate of *exogenous* purin was studied. In a great number of these observations the output of uric acid after feeding on sweetbread or other nuclein-containing material was less than in healthy persons. It also is to be remarked here that more time is needed for the elimination of exogenous purins than normally, in spite of the fact that smaller quantities are excreted. Different gouty patients do not behave alike. There are some in whom destruction and elimination are performed in the same length of time and to the same extent as in healthy persons. It would be premature to assume a retardation of the purin metabolism as being the constant rule. I refer again to the above mentioned objections concerning the influence of age and general state of health on the purin metabolism.

EXCRETION OF URIC ACID

The excretion of uric acid by the kidneys depends, like that of any other substance, on two factors. The elimination can be diminished when the secretory power of the kidney is lessened; and it can be prevented also, when the substance in question is united to another complex and thus bound.

In nephritis secretion of uric acid is strongly disturbed. Thus during favorable periods, even when no other substance is retained (in any amount worth mentioning), some milligrammes of uric acid are always present in the blood of the nephritic patient. It seems to me as though the special capacity for the excretion of urates is more limited and can more easily become deficient than any other function of this organ. I will try to explain this.

In administering an excess of any substance, the level of its end-products rises in the blood. That is due to the fact that

the output by the kidney does not keep pace with the influx into the blood. But though with every other substance the level rises only by a small amount, with *uric acid* it may rise to ten times its normal height. While scarcely one-half a milligramme is contained in one hundred c.c. of normal blood, Weintraud found 5 milligrammes after feeding with an excess of sweetbread.

We may now speak of the second factor, that is, of preventing the elimination of a substance by its chemical combination with another. Such a theory has been offered in order to explain the non-excretion of sugar in the healthy organism. Minkowsky tried to introduce this idea into the theory of gout. He assumed a chemical union of uric acid with a nucleic acid. But the search for such a compound in the blood has not been successful. Gudzent, on applying Michaelis' method of compensation to the dialysis of gouty blood, was able to show that the urates exist only in the free state. I might also mention Garrod's thread experiment as speaking against any organic union. Acetic acid, which sets free all uric acid in the serum or at least the greatest part, is an extremely weak acid, its strength being some hundred times less than that of hydrochloric acid. Under the conditions of the thread experiment it would not suffice to split any organic union.

The hypothesis of Minkowsky having been thus refuted, Gudzent showed another possibility. By physico-chemical methods he pointed out that the sodium urate exists in two modifications, which differ only in their solubility. He ascribes the existence of these two forms to a difference in the chemical structure, to a tautomerism. The lactam form, that is, the substance having the formula which is generally used for the structure of uric acid, is the more soluble one, but it tends to pass into the lactim form, which is less soluble. If the difference in solubility of the sodium urates is really due to a difference in the chemical structure, and not purely to physical reasons, one could imagine that the tautomeric forms would behave differently in regard to their excretion by the kidneys. Experiments in this direction have not been performed.

URIC ACID IN THE BLOOD, ETC.

Normal blood is practically free from uric acid. In gout it can contain 5–10 mg. per 100 c.c. after a mixed diet has been taken; after a purin-free diet the amount is lower, being from 2–4 mg., and in no case is uric acid absent. Its presence in gout cannot be explained by an excess in the production of uric acid as is the case in leukæmia and in pneumonia. This conclusion, though it is contrary to the opinions of a former time, is beyond doubt.

It can be attributed chiefly or partly to a passive retention in those cases where the kidneys are suffering from what has been called kidney gout (Nierengicht), whether this occurs at the beginning of gout or in its later stages. On this point no controversy exists between the different authors. But how is the presence of uric acid to be explained in those cases where the most accurate research does not reveal any sign of nephritis? The answer is only to be given conditionally.

If neither the formation of uric acid is increased, nor its destruction greatly diminished,—and these two conditions seem to be realized in gout,—if moreover the uric acid is not prevented by a chemical union or by an abnormal structure from passing into the urine, only one conclusion is possible. The retention is due to a deficient and restricted secretory power of the kidneys.

The existence of such a renal inadequacy does not mean a real nephritis. I think it possible that a single function of this organ can become almost entirely insufficient. Later on, real damage to the kidney and a nephritis frequently follow.

As stated already by Garrod, uric acid is present also in lead poisoning. Here, as in gout, it is present at a time when no sign of nephritis can be noticed. Concerning this phenomenon, resembling that in gout, one may assume the same explanation, namely, a deficiency in the secretory power of the kidneys, or a kind of incipient and latent nephritis.

If you are not willing to accept the above explanation for the very early stages of gout because of the absence of albu-

minuria, you must deny it also for the first periods of lead-poisoning. Whatever interpretation avails in gout must also be admitted for lead intoxication. *In any case the mechanism of the accumulation of urates in the gouty blood is not a specific phenomenon of gout.*

Brugsch opposes this explanation on account of an experiment in which uric acid injected into the muscles of a gouty patient was eliminated just as completely and quickly as in a healthy man. I do not consider this objection to be conclusive. The gouty kidney although not able to eliminate one gramme of urates quickly enough on the *normal* level of urates in blood, could accomplish this task very well at the *higher* level already existing before the injection of uric acid. That this conception is right, Widal has obviously proved by the example of the behavior of urea in nephritis.

Brugsch and Schittenhelm fall to a somewhat mystical explanation. They ascribe the accumulation of urates in the blood to a diminished destruction. But when a substance has once entered the blood, its elimination depends *only* on the relation between this fluid and the kidneys. I think the following argument will be convincing. On feeding with sweetbread, or during absorption of pneumonic exudates, the blood contains just as large a quantity of urates as does that of a gouty patient. Now, persons who do not suffer from gout will eliminate the excess of urates within a few days, and, even when adhering to a mixed diet, their blood will soon be free from urates. In gout, on the contrary, notwithstanding the ingestion of a purin-free diet under the influence of which the formation and the influx of uric acid into the blood is much lower, uric acid will by no means disappear from the blood. Brugsch and Schittenhelm ascribe this to a retarded decomposition, though conceding that the total amount of uric-acid break-down is above the normal. Something is lacking in their theory and they seem themselves to be aware of it. Although denying that the threshold (''Schwellenwert'') of the kidney for the output of urates is elevated in gout, they speak of a certain torpidity of this organ.

The deduction which ascribes the retention of uric acid to the kidneys as enunciated by Garrod and adopted since by several authors, is rather repugnant to me as well as to pathologists in general. The disturbance which affects the entire organism would, according to this opinion, depend principally on the *passive* retention of a single metabolic product. This conception is not very satisfactory. I would be very much pleased indeed if any other solution of the problem could be found. However, *rebus sic stantibus,* and without fixing my opinion for the future, I find no other solution for the problem than that given above.

Another interpretation might terminate the unpleasant dualism in the theory of gout. The distinction between a primary metabolic and a primary kidney gout, which has always found supporters from Garrod down to Brugsch and Schittenhelm, would become unnecessary.

Against the doctrine of gout being due to deficient kidney function, clinical doubts arise which we are unable entirely to remove. Why does not gout appear in each case of nephritis, why not in leukæmia where we always find an excess of uric acid in the blood? Many cases of interstitial nephritis progress so slowly that secondary changes, such as deposition of urates and other abnormal phenomena, might have time to develop. Is perhaps the retention of uric acid present only in the later stages of contracting kidneys? We know nothing certain about this, nor about the supposed deficiency of the kidneys in gout. Does the condition reach back to youth or even to childhood? The deficiency in that case would have lasted much longer than in any case of nephritis. At any rate we must emphasize the fact that in many autopsies of uræmics concretions are found in the joints, without any history that the patients had ever suffered from primary gout. There is no doubt that other organs besides the kidneys must play an important part in the pathogenesis of gout.

Of all the organs, only the *joints* and the part they play in the pathology of gout can be discussed in detail. Are the cartilages and the connective tissues implicated only in a passive

way in gout, or are they active? Further questions to be answered are the following: By what mechanism and at what period does the deposition occur? What symptoms are produced by the precipitation of crystals and what happens to the crystals during the paroxysm?

Contrary to the opinion of Ebstein we may at present take it for granted that deposition of urates does not occur in necrotic but only in living tissue (Minkowski, Freudweiler). And also in these deposition can only occur if the liquids which circulate in them are saturated with sodium urate. As to this point whether the amount of urate of soda in the blood corresponds to the saturation point, the opinions of most authors are or were erroneous. It was generally believed that the serum of the gouty patient was not saturated with urate of soda. This assumption has been put forward on account of the experiments of G. Klemperer. He observed that 100 c.c. of normal serum can dissolve 150–200 mg. of uric acid; that is ten times more than it ever contains during life. The serum of a gouty patient behaved in the same manner. This observation is correct, — of that there is no question. But Klemperer failed to observe the reaction to its end; if he had done so, he would have seen the abundant precipitation of urates after some time. Serum indeed has the power of dissolving a good deal of uric acid, by transforming it into urate of soda, but only a small amount of the soda salt is kept in solution. The problem has been attacked from a wrong direction. The biological question is not how much uric acid can be transformed by the alkalies of serum into urate of soda, but how much sodium urate the serum is able to take up without precipitation. Roberts in 1890 carried out experiments and, by the use of a correct method, found that serum holds only a few milligrammes of urate of soda in solution. The figures found by Gudzent twenty years later were almost identical with those of Roberts, and from them Gudzent has calculated that theoretically 100 grammes of serum are saturated when containing 8 mg. of urate of soda. If we apply these figures to the free acid instead of to urate of soda, and to blood instead of to

serum, we are surprised to see that 100 grammes of blood are saturated when they contain 4 milligrammes of uric acid. Such an amount has indeed been found in the blood of people suffering from severe gout when on a mixed diet.

At the point of saturation the conditions for precipitation are nearly always present. In the circulating blood, however, precipitation never takes place; it is prevented by its continuous movement and by the perpetual exchange of the urate molecules. While some of them pass to the urine others enter the blood from the organs.

PRECIPITATION OF URIC SODA

The conditions for precipitation are much more favorable within the lymphatics and within the synovia of the articular cavities than elsewhere, for here the flow of liquids is very slow. I myself found four and six milligrammes of uric acid in 100 c.c. of the fluids aspirated from inflamed knee-joints. But in spite of this saturated state one rarely finds crystals in suspension, and when such are encountered they may perhaps have originated from the impregnated cartilages which had undergone destruction, or from tophi which had forced a way into the articular cavity. As a rule, crystallization takes place only in the organized tissue.

By many it has been taken for granted that the cartilages possess a *specific* power to attract dissolved urate of soda and to bring it to crystallization. Moreover, the phenomenon can also be produced by excised cartilaginous tissue. This was shown by Roberts many years ago, and later on by Almagia and Brugsch. Tarsal bones of a pig were suspended in phials charged with a saturated solution of urates; after a few days they were incrusted with needles and presented an aspect which, in intensity and distribution of deposits, resembled that of a gouty joint. The process of precipitation is thus not a vital one, but is purely passive, brought on by certain chemical relations and properties still existing in the dead cartilaginous tissue. But possibly even this chemical reaction is not of a complicated order. Roberts in a purely experimental way

showed that the solubility of sodium urate decreases with increasing concentration of soda salts in the liquid. The theory of solution agreed fully with the actual experiment. An addition of 0.2 per cent. sodium chloride to a saturated solution of urate of soda brought about precipitation. Roberts and Gudzent suggested that cartilage, tendons, etc., are richer in sodium salts than the blood serum. Their sodium content reckoned as sodium chloride, rises to 0.9 per cent., while in serum it is only 0.7 per cent. When the lymph saturated with urate of soda penetrates into the cartilaginous tissue where the concentration of the sodium ions is higher, a state of supersaturation is brought about, and precipitation can take place. In this hypothesis, the supposition is made that the sodium exists in the state of ions in the cartilages. Whether this is true or not is unknown. If they do not, if they be united to an organic compound, the explanation of Roberts and Gudzent would not hold good.

In response to the question why precipitation does not occur in all joints,—their chemical composition being the same everywhere,—we must refer to mechanical and thermal injuries, the influence of which on the localization is clearly proved by daily experience, even though we do not find such explanation entirely satisfactory.

But the nephritic patient is exposed to the same influences. Why does not precipitation occur in every man suffering from contracting kidney? For the second time we are obliged to put this question. If the retention of uric acid in the blood is a passive process, if the deposition within the tissues is a purely physical process, by what properties is gout then to be characterized?

There must be an active element in its pathogenesis belonging exclusively to gouty diathesis. What then is this active principle? Science as yet gives no answer to this question, which touches the central point of the problem. Therefore I will not attempt to present any hypothesis. Surely a hereditary influence exists in gout, and a neuropathological influence is present as well as the chemical and the humoral-pathological.

The clinician must always be aware of this. But as long as we cannot determine the mechanism by which the nerves act on the metabolism in gout, no advantage results from emphasizing such an influence.

All organs yielding or destroying uric acid (and they are many) were at one time thought to be implicated in the phenomena of gout. Thus a predominant part was formerly attributed to the liver, to the bowels, or to the spleen, etc. But their influence, if indeed any exists, is not a controlling one over the uric acid metabolism. It is for the present worthless to search for increased formation or for decreased destruction in the single organs, since we know that *as a total* the uric acid metabolism always remains within the ordinary limits. If muscular work prevents paroxysms or lessens their violence, this need not be referred to an increased destruction of uric acid, but rather to an immediate action on the joints, changing the quantity of synovial liquid or its composition, or the rapidity of its circulation. The action of other organs too might be such an indirect one.

Thus the active principle, so much sought for, which causes gout remains a mystery, not to be unravelled by our present means. Leaving the solution of the problem to the future, we return to the fate of urate deposits. We can discuss the essentials of this question without regard to the problems of gouty diathesis and pathogenesis.

RELATION BETWEEN THE ATTACKS AND THE URATE DEPOSITS

At what time does precipitation take place? Is it a chronic process going on continuously, or does it depend upon attacks and in what manner is it connected with them? When considering those tophi whose fate we can trace with the eye, we know that they may appear, grow, and disappear without the bearer knowing anything about it. Especially the largest deposits, those upon the hands, grow with hardly any inflammatory reaction. But this fact does not absolutely exclude a relation between the precipitating process and the attack. The

same process which on slow development causes no strong reaction may induce the most violent symptoms if the onset is one of great intensity.

According to Garrod the attack is provoked by a sudden precipitation of crystals in the tissues. The attack consists merely of such deposition of urates and of the inflammation induced by their presence. The deposits, once formed, remain for a lengthened time, often throughout life. "When crystallization of the salt takes place in any tissue, inflammation is suddenly lit up by its presence and a paroxysm of gout ensues." Roberts is of the same opinion.

There is one objection, which renders it difficult to consent in this respect to the authority of the eminent English clinician. One of the chief rules of chemistry, *corpora non agunt nisi soluta,* is applicable also to the conditions in the organism. If the uric acid salt is precipitated, the chemical influence of the solid material upon the tissues stops instantly and does not reappear until it is dissolved again. In the meantime its action is purely physical. The mechanical irritation may perhaps be stronger at the moment of crystallization and during the growth of the crystals than in periods of absolute rest. But the pressure which the crystals exert upon the tissues is scarcely sufficient to bring about serious reaction. Garrod's opinion is just as improbable to me as the hypothesis which refers the symptoms of bronchial asthma to an irritation of the air-conduits by Charcot-Leyden crystals. In opposition to the English authors, I am rather inclined to ascribe the irritation to the dissolved urates. According to this conception a sudden increase of concentration will induce the inflammation.

This supposed rise of the amount of urates within the synovia could be brought about in a twofold manner. According to Garrod's opinion, it is only a part of the general urate accumulation in the whole body, induced by a deficient excretion. The urate molecules would pass from the serum to the synovia and hence to the cartilages. However a contrary conception could also be supported. A rapid solution of the deposits might lead to an increased concentration in the syno-

vial liquid, thus explaining the violence of reaction perhaps better than the hypothesis of Garrod. As to the question why a solution of deposits should occur so rapidly, I own I am not able to reply.

The above conception is an elaboration of Pfeiffer's ideas somewhat changed. In opposition to Garrod Pfeiffer considered the attack as consisting of a solution and removal of the deposits of urate. He based his opinion upon reasons which do not seem to me to be justifiable. Still his idea as a whole seems to me probable and for the following two reasons:

1. The inflammation spreads far beyond the places of the crystalline deposits. One may find an aspect of the skin fully resembling a phlegmon, and even a severe lymphangitis, which though aseptic has sometimes misled the surgeon. This proves that an irritating substance is carried away from the afflicted joints. If the sodium urate is really the inflammatory agent in the joints, it seems likely that the irritation of the more distant tissues is caused by the same substance, carried away through the lymphatics.

2. The second reason in favor of Pfeiffer's views is the excess of endogenous uric acid excreted during the attack. The excess is far greater than the diminution preceding the paroxysm. In one of my observations the surplus eliminated in eight days of a violent attack amounted to more than 3 grammes. Although the origin of these urates cannot be pointed out with accuracy, it may probably be attributed in whole or in part to a solution of the crystalline deposits.

I might also lay stress upon the fact that in aspirating the joint exudate as completely as possible, the last portions, originating from the interior parts of the cavity, are always found to be richer in leucocytes than the first portions. And it is well known that leucocytes are the instruments for attacking the urate crystals as well as the vehicles for their removal. Perhaps the theory of Garrod and that of Pfeiffer might be combined in such a way as to assume that a general retention of urates provokes the outbreak of an attack, and that the inflammation which follows leads to a removal of the deposits.

PECULIAR EXCITING CAUSES FOR THE ATTACK

The accumulation of uric acid in the fluids of the body supposed by Garrod to precede and to provoke the attack has not yet been demonstrated by analysis of the blood itself. If it were possible to determine the uric acid in the blood day by day before and during the paroxysm, we would be able to judge the part played by the accumulation of urates better than we can now. We are now obliged to rely upon analysis of the urine. The decrease of the uric acid output in the twenty-four hours prior to the attack, which amounts to from one hundred to two hundred milligrammes, may be interpreted as meaning an accumulation in the body; but sometimes this is altogether lacking. The best support of this part of Garrod's theory is to be found in the more recent observations, that consumption of sweetbread *sometimes* brings about the paroxysm. It may be asked whether this coincidence is not merely accidental. In spite of such doubts and gaps, this part of Garrod's doctrine is generally acknowledged and accepted.

However, this is not true as concerns the second part of his theory. Garrod assumed a decreased alkalinity of the blood to be the second cause exciting the gouty attack. *This part of his doctrine should be dropped entirely.* It is refuted by the actual examination of the gouty blood, as well as by the proofs in the test-tube, and it is contradicted also by the doctrine of physical chemistry. In measuring the alkalinity of the blood by means of titration in more than twelve patients before, during, and after the paroxysm and also during the intervals, I failed at any time to find any marked difference. Moreover, all chemical analogies teach us that an addition of hydrochloric acid to the solution of any salt may bring about precipitation of the *free* acid, but never that of the *salt*. If we had to deal with bisodium urate, the addition of an acid would produce its conversion into monosodium urate, and this, being less soluble than the original salt, would crystallize out. This would be the same process as the precipitation of monosodium sulphate produced by adding sulphuric acid to a solution of neutral

sodium sulphate. But please remember, gentlemen, that in the serum only *mono*sodium urate is present, which, according to the above exposition, is not precipitated by acids.

Roberts's test-tube experiments correspond fully with these theoretical deductions. Serum contains about 0.5 per cent. of sodium chloride and 0.2 per cent. of monosodium carbonate. The addition of hydrochloric or acetic acid to serum saturated with urate of soda brings about a precipitation of uric acid. If, on the other hand, sodium carbonate be removed from the serum by dialysis, not the slightest crystallization occurs, although the serum has lost its alkalinity. On the other hand, addition of monosodium carbonate to the serum causes precipitation, although this be contrary to Garrod's opinion, and in spite of the high increase of the so-called alkalinity. The solubility and the precipitation of urate of soda have nothing to do at all with the alkalinity, but depend merely on the concentration of sodium ions or salts in the solution. Indeed, addition of sodium chloride effects a precipitation just as well as does monosodium carbonate.

The question of diminishing alkalinity is of the utmost importance for the precipitation of uric *acid* in urine, it is predominant in the pathogenesis of *gravel,* but it must be excluded entirely from the theory of gout. It is replaced by the factor of salt concentration, and especially of the concentration in soda ions. Please remember, gentlemen, in connection with these explanations of the conception of Roberts, that it is the high amount of soda salts in the connective tissue which very likely determines the place of the crystallization of urates.

It will be hard for many to drop entirely the doctrine of the importance of a varying alkalinity of the blood in gout. You may feel inclined perhaps to found your conservatism on the valuable experiments of Loghem. This Dutch scientist had found that deposits of uric acid, produced by hypodermic injections in the rabbit, are soon converted into deposits of urate of soda, and that this transformation is followed by a serious inflammation. In dogs this transformation is not observed nor is there any inflammation. The metabolism of the

rabbit kept on green food is, roughly speaking, an alkaline one. In the same sense, we might apply the term of an acid metabolism to a dog fed on meat. According to this difference the fate of uric acid injected varies in the two species. But if the dog receives 20 grammes of sodium carbonate, his metabolism becomes more alkaline, and the conversion of the uric acid into urate of soda takes place exactly as in the rabbit. Vice versa, in the rabbit it is prevented by administering hydrochloric acid. The results of the older experiments of Pfeiffer and the later ones of Silbergleit coincide fully with those of Loghem.

In these experiments the influence of acids and alkalies upon the chemical occurrences in the body are evident. In many respects these experiments are of high value and they have justly attracted attention. However, the observations have nothing to do with the conditions in gout. In Loghem's experiments an entirely different problem was attacked, namely, the transformation of uric acid into urate of soda. It is obvious that the transformation is favored by an excess of alkalies in the body, as well as in the test-tube, and that it is retarded or prevented by an increase of acid substances alike in the body and in the chemist's phial. As to the solubility and precipitation of urate of soda, Loghem's experiments prove just as little as Klemperer's experiments on the degree of saturation of serum with urate of soda.

THERAPEUTICS

Gentlemen, if I now consider the therapeutics of gout, I must of course confine myself to the discussion of such points as bear relation to the metabolism of uric acid.

The two drugs which are the most efficacious in the paroxysm, colchicum and salicylate, behave entirely differently as regards the elimination of uric acid. Salicylates in sufficient doses increase the output of uric acid materially, by half a gramme and more daily. This effect, however, seems to disappear within a few days. Colchicum, which, no doubt, is the stronger remedy, produces no change, or if so, it diminishes the

quantity of uric acid elimination. I do not believe that these two drugs, the chemical effects of which are so different, owe their efficacy to the same pharmacological action. One should try to define the mechanism of their action. Setting aside their soothing capacity I shall discuss only their action upon the uric acid within the body.

If, according to Pfeiffer's opinion, the attack were a process of solution and removal of urates, one could conceive that salicylates favor the elimination, since increased uric acid output follows the administration of these substances. But we do not know whether this increased output originates from the deposits. Even healthy persons when taking salicylates show a slight increase of uric acid elimination. Comparative experiments with this remedy ought to be made on a large scale upon healthy and gouty people.

As to colchicum, one might think that it inhibits the process of solution, thus putting an end to the inflammation and to the paroxysm. Its effect is certainly more rapid and more intense than that of sodium salicylate. If this conception were right the colchicum would be only a palliative remedy for the attack, while the salicylates in spite of their slower action would be the preferable remedy. It is well known that colchicum is useless in chronic gout. If the attack be interpreted in the sense of Garrod, the efficacy of both drugs would have to be explained otherwise. A discussion of this subject bears as yet the character of mere conjecture. Therefore, I do not wish to enter into details. I have felt that the ideas were worth mentioning in order to encourage investigations on these points.

Alkalies and acids are not given during the attack, at least not in large quantities. However, considering the importance of these substances in chronic gout, their application should be tried and observed—also during the paroxysm. In recommending them I do not expect any therapeutic effect. Indeed in one of my patients the largest doses of hydrochloric acid did not influence either the pains or the inflammation, which is contrary to the results observed in the experiments of Loghem.

In administering alkaline carbonates during the attack, I do not expect a curative effect either. I think merely that the comparative investigation of the action of both acids and alkalies during the attack should throw some light upon their action in the chronic stages.

In the therapeutics of chronic gout, restriction of meat in the diet has been in use since olden times. The treatment is older than our recent knowledge of the uric acid metabolism. In lessening the formation of exogenous uric acid we only practise to-day what the old physicians practised with less precise ideas. However, the extremists of to-day do not even go so far as to forbid meat entirely. Empiricism shows that the disadvantages induced by an exclusive lacto-vegetarian diet prevail over the benefits which could be expected from a diminished formation of uric acid. Generally we prescribe a diet poor in purins. Investigations of the purin metabolism, during years of strict adherence to such a diet, will teach us to indicate its application with more accuracy. Repeated analyses of the purin compounds in the blood are needed just as well as balances of the purin intake and output, and also repeated investigations of the behavior of ingested nucleic acids. Hospital patients are not very well fitted for such researches, which have to be extended for years. It is fortunate that wealthy patients of to-day are inclined to enter the clinics and sanatoria and to undergo willingly longer observation. They have an understanding of the importance of such investigations. However, it will take a decade at least before sufficient data concerning the behavior of uric acid in urine, blood, etc., collected from a sufficient number of patients, will be at our disposal. We can look forward to this time with great hope.

Of all remedies, deemed useful in chronic gout, alkalies have for centuries been applied more than all others. Two theories as to their value have existed. Regarding the first it was believed that alkalies dissolved the concretions of urates within the body. I have already explained to you that this idea has been entirely refuted by modern research. The second quality ascribed to the alkalies was their power of facilitating

the output of uric acid. This surely should be of benefit. But experiments carried out in this direction do not speak at all in favor of the conception. In therapeutics, however, the first principle for the practitioner as well as for the scientific observer is to observe and to judge therapeutic effects with impartiality, leaving aside both prejudice and theory. If empiricism should speak in favor of the alkalies another theory is required, without need of change in therapeutic treatment.

Cool judgment, however, is more difficult in the therapeutics of gout than in any other disease. There is a lack of a pronounced criterion by which we may measure the effects of our prescriptions. In diabetes we measure the amount of sugar eliminated, in obesity the changes of weight. In nephritis, and in cirrhosis of the liver, and in diseases of the circulation, the increase or decrease of effusions and the height of the blood-pressure represent the criterion of therapeutics. Even in tuberculosis and in syphilis, the course of which is so difficult to judge, there are still better points of support for judgment than in chronic gout. As yet we are allowed to judge the results of therapeutic action only by the measure of diminished urate of soda excretion in the urine. Probably a diminished amount of urates in the blood represents a standard of improvement, but as yet this standard is not available for obvious reasons. Thus the measure by which we may now judge of lasting improvement consists merely in a postponement of the attacks, in a lessened intensity of the paroxysm, and in a diminution of chronic troubles. Regarding this point I can only repeat Roberts's words: "The incidence of diathesis even in fairly typical cases exhibits a waviness, an afflux and reflux, which is very puzzling. In the less typical cases the irregularity is such as to baffle all explanation. In most instances the manifestations become intensified with advancing years, but sometimes the converse is observed. All these perplexing vagaries are within the compass of the natural history of the disorder."

Even if a physician may dare ascribe the improvement of a gouty patient's health not to nature itself, but to his own prescriptions, to which of them is he allowed to attribute this success?

All procedures which we believe to be beneficial in gout, namely, the restriction of meat diet, the choice of green food, muscular exercise, the use of baths, all these prescriptions are generally given at the same time and accompanied by the administration of drugs; and even these the most conservative physician and patient will change time and again. Similar objections are to be borne in mind in judging the effect of alkalies. Roberts, in whom scientific criticism was united with the abilities of a born physician, asserts that in a long experience he had never seen any distinct improvement even after administering alkalies for many years.

What remedy can be substituted for alkalies? You all know, gentlemen, that a German practitioner, Falkenstein, has pleaded for the entire abolition of alkaline treatment and recommended instead the administration of hydrochloric acid. His ideas of gout and of its therapeutics stand on a very weak foundation. However, success is the decisive factor. Falkenstein reports that after years of severe trouble he finally got rid of his pains by the use of hydrochloric acid, without having changed his mode of living, his diet or his habits. Such a report deserves every attention, even though this new therapeutic method might not benefit every patient. Falkenstein asserts that he has obtained good results in many patients. Other physicians have been less successful. Thus we must leave time for further observations.

I wish to add a few more words regarding the use of mineral springs. Physicians are inclined at present to ascribe the undoubted efficiency of mineral waters not to the content of salts, but to the emanations of radio-active substances. Gudzent has observed that radio-emanation was able to destroy uric acid. It has been hoped that such influence was also active in the organism of gouty patients. Since the emanation leaves the body rapidly with the expired air, Löwenthal constructed a respiration chamber, in which the amount of emanation was kept at a high rate. Thus the quantity of radio-emanation from men rose to 150,000 units. Preliminary experiments were carried out last winter by Löwenthal and Gudzent in the clinic

of Prof. His. The results have not been published in detail, so judgment is somewhat difficult. In healthy persons the output of uric acid was materially increased, but gouty patients behaved differently. There was a marked improvement of health, but it was not possible to refer this to a distinct change in the uric acid metabolism. In experiments with animals, however, the influence of radio-emanation was more conspicuous. The symptoms of inflammation produced by hypodermic injections of uric acid in the rabbit were modified under the influence of the emanations; leucocytosis and phagocytosis were retarded for several days. By this observation the marked influence of radio-emanation on the occurrences within the organism is established beyond every doubt. It may be hoped that investigations of this kind will advance our knowledge of theory as well as of therapeutics. Thanks to Löwenthal's ingenious devices, it will soon be possible for any hospital to avail itself of these new resources.

Since the production and destruction of uric acid, like that of other chemical substances, are the work of protoplasm, it is for future research to study the lesions in the protoplasm itself, and to reveal the mechanism which leads to a derangement of the metabolism. At present we only recognize the results and the chemical products of this derangement. Also in gout the researches must rise from the present level to investigations of a higher order. But this is the same in every field of pathological metabolism. When, on looking back after a lapse of twenty future years, during which we shall have advanced into a more profound region of knowledge, we will not regard the older investigations on uric acid, of which I have endeavored to give you a short account, as having been made in vain.

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