COLLECTED PAPERS

ON

CIRCULATION AND RESPIRATION.

FIRST SERIES,

CHIEFLY CONTAINING

LABORATORY RESEARCHES.

BY

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Author's Dedication.

TO

DAVID FERRIER, M.A., M.D., LL.D., F.R.S.,

MY CHUM FOR THREE YEARS,
AND MY FRIEND FOR MORE THAN THIRTY

I DEDICATE THIS BOOK,

NOT ONLY AS A MARK OF LONG AND UNBROKEN FRIENDSHIP,
BUT ALSO IN RECOGNITION
OF THE MARVELLOUS ABILITY
WHICH HAS ENABLED HIM TO DO FOR THE BRAIN
WHAT HARVEY DID FOR THE CIRCULATION
AND BRING ORDER OUT OF CHAOS.

PREFACE.

SEVERAL of my friends have complained to me that my writings are so scattered that they have been unable to refer to them when they wished to do so. I have therefore collected and reprinted them. At first, I intended to publish them in two volumes, but I found that they naturally fell into two series, the first containing chiefly the results of experimental research in the laboratory, and the second those of clinical work. It is unsatisfactory to possess only one volume of a work, but one reader may be more interested in experimental, and another in clinical work, and so each might wish to possess the series dealing with the subject he desires. In some instances, the same paper appears in two languages, for I found on one occasion, at least, that the work described in an English paper had been ignored on the pretext that the writer had not access to the German original. One of the first things to strike a reader will be the number of papers with a joint authorship. One reason of this is that I like working with others who are interested in the same subject as myself, and thus have written conjointly with Dr. A. B. Meyer (now Director of the Royal Zoological Museum at Dresden), Sir Joseph Fayrer, Mr. Henry Power, and Mr. D'Arcy Power.

Two or three years after beginning to lecture on Materia Medica and Therapeutics at St. Bartholomew's Hospital, I tried to institute a pharmacological laboratory there. The place which I got for this purpose was about 12 feet by 6, and formerly had been used only for washing dishes and jars in the museum, but a table on one side served to hold the apparatus, and I got some students to work there with me. One research was that of Mr. Walter Pye, on Casca, and the other that of Mr. Tait, on Nitro-glycerine. The pulling down of this laboratory on account of the rebuilding of the Medical School prevented me from pursuing my plan of getting a number

of students to work, and before the new buildings were finished the claims of practice began to interfere with my experimental work. I soon found that when a great part of three days is taken up with hospital work, a very few consultations outside will interfere seriously with laboratory work, for just when one has everything prepared for an experiment, one may have to fix a consultation, and all the preparations, which required many hours to make, are rendered useless for the time, and have to be done over again. In consequence of this difficulty I soon determined to follow the plan of working at practice so as to obtain the money which would allow me to pay such a salary to a younger man as would enable him to devote his whole time to laboratory work. I planned the research and experiments, provided the apparatus and material, defrayed all laboratory expenses, and paid my assistant the salary which I was able to earn by my practice, and which at that period of his career he could not earn for himself. We then published the research under our joint names. This arrangement I considered a fair one for us both, as each gave what the other had not got, and we were then able to do the work which neither alone could have done. I have been exceedingly fortunate in getting such able assistants as the late Mr. Pye, Professor Weymouth Reid, now of Dundee, Professor Cash, of Aberdeen, Dr. Allen Macfadyen, of the Jenner Institute, Mr. T. J. Bokenham, Dr. Rayner Batten, and Professor Tunnicliffe, now of King's College.

I began to reprint these papers ten years ago, Messrs. Harrison having sent me the first proofs in 1896. The work has been interrupted by other occupations, and also by a serious illness lasting from the summer of 1902 to the autumn of 1903. In consequence of these interruptions and the irregular way in which the work proceeded, various errata have occurred, perhaps the most notable of which is the absence of the fifth lecture, "On the Experimental Investigation of the Action of Medicines," from its proper place, page 322, and its relegation to the Appendix. With this exception, and that of the Harveian Oration, most of the papers are printed in the chronological order of the experiments they record, though not

always of their actual appearance in print. The Harveian Oration has been placed first because the short history which it gives of the physiology and pharmacology of the circulation serves to some extent as an introduction to the other papers.

The period over which the researches described in these papers extends (1865 to 1883) is an important one in the history of the pharmacology of the circulation, for its beginning coincides with the first employment in this country of registering apparatus for the investigation of the action of drugs on the circulation, and before its end this method was in regular use. After Blake's experiments with a simple mercurial column in 1844, little or no work was done on the action of drugs until Traube, in 1851,* investigated the action of digitalis with one of Ludwig's kymographs, and in 1865 to 1866, Von Bezold did his classical researches on the action of atropine and veratrine.†

When I began my experiments on digitalis in 1865, I believe there was no recording physiological instrument of any kind in use in this country, with the exception of one or two of Marey's sphygmographs, one of which was kindly lent to me by Dr. Arthur Gamgee, and one kymograph which Burdon Sanderson completed in May, 1865, but which was not described until 1867.‡ Under the guidance of Dr. Gamgee I made experiments on the blood pressure in animals under the influence of digitalis with a simple mercurial column, and on myself with the sphygmograph. The facility which I thus acquired in using the instrument enabled me while acting as house physician to utilize it in ascertaining the rise in blood pressure which occurred in angina pectoris in a hospital patient, and by correlating the pathological data thus acquired with the knowledge of the pharmacological action of nitrite of amyl which Gamgee had obtained, I succeeded in discovering a remedy for angina pectoris.

This discovery may, I think, be fairly regarded as the first

* Traube, *Charité Annalen 2ter Jahrg. und Gesammte Beiträge*, vol. i, pp. 190 and 274.

† Von Bezold, *Würzburger physiol. Untersuchungen*, I and II.

‡ Burdon Sanderson, *Phil. Trans.*, 1867, p. 576.

complete example of rational therapeutics based on experimental pathological and pharmacological data. Magendie's application of strychnine in paralysis and Fraser and Argyll-Robertson's use of Calabar bean for ophthalmological purposes preceded it, but, in both instances, whilst the action of the drug employed was ascertained by experiment it was used to combat a symptom and not a definite pathological condition which had also been ascertained by experiment.

After a year in hospital I went to Vienna and worked for some months in Professor Brücke's laboratory on the action of digitalis upon muscle and nerve, but the experiments I made were never published. I then went to Berlin for a short time and took the opportunity of working with what I believe to have been the identical instrument employed by Traube in his researches. In my work on digitalis I felt deeply the want of a registering hæmodynamometer (*vide* p. 52), but in spite of the want I obtained proofs that digitalis both increases the force of the heart (p. 52) and causes contraction of the capillaries (pp. 55 and 56). Traube* ascribed the rise in blood pressure produced by digitalis entirely to changes in the action of the heart, and he left alterations in peripheral resistance altogether out of account, while they appeared to me to be a most important factor. I was very anxious to obtain confirmatory evidence of my view that digitalis contracts the peripheral vessels, and by means of the kymographion I succeeded, in conjunction with A. B. Meyer, in obtaining this evidence and thus establishing the view of the action of digitalis (p. 145) which is now almost universally accepted.

From Berlin I went for a tour to Egypt, Syria, and the South of Europe, and the next winter (1868 to 1869) I spent in Amsterdam, studying physiological chemistry with Professor Kühne, a man of marvellous ability and far in advance of his time. The knowledge which I gained from him enabled me to write the section on Digestion and Secretion for Burdon Sanderson's Handbook for the Physiological Laboratory.

I then went to Leipzig, and was fortunate enough to be admitted by my beloved and venerated Master, Carl Ludwig, as

* Traube, *op. cit.*

one of the first students in his new Institute, in which he delivered his first lecture shortly after I went. At that time he was busy furnishing his new laboratories and devising new instruments for artificial respiration, for measuring blood pressure and the speed of circulation, for artificial circulation in excised organs and for interchange of gases. He started me on a research, having for its subject the independent contraction of arterioles and capillaries when separated from nerve centres. He liked to be present himself, and indeed to perform most of the experiments on this subject, but in the intervals when he was otherwise engaged I made some experiments on the effect of nitrite of amyl and nitrite of soda. These were only intended as by-play, but the research on contractility took so long that Ludwig thought it better to publish a paper on nitrite of amyl with only a general mention of the work on contractility in order to secure priority. I intended to continue it after leaving his laboratory, but when I came to London my time was so much taken up with other things that it became impossible.

In 1871 I began to write the Experimental Investigation of Medicines, with the intention of expanding it into a complete text-book on "Experimental Pharmacology." Before the part dealing with the circulation, however, had been finished, I accepted the late Sir John Burdon Sanderson's invitation to join him in writing a Handbook for the Physiological Laboratory to which I was to contribute the section on Digestion and Secretion. As I performed every experiment mentioned in it and repeated several of them many times, the writing of this short section involved incessant work in the laboratory for more than two years. As an example of this I may mention that the statement at page 84 of the text-book "that pepsine, if absolutely pure, gives no xanthoprotein re-action," cost me many weeks' work. In 1873 and 1874 I was engaged with Sir Joseph (then Dr.) Fayrer in examining the action of snake venom and with Dr. Pye Smith on a report to the British Association on Intestinal Secretion. The re-building of the school at St. Bartholomew's Hospital caused an interruption in my laboratory work of nearly four years,

from 1876 to 1880, when I again resumed it with the aid of assistance from Dr. Cash and others in the manner I have already mentioned. From this time onward the pressure of other engagements has only permitted me to do most of my laboratory work by means of assistants in the manner I have mentioned at the beginning of the preface.

I am aware that for the majority of readers this preface is too long and too personal, but they can easily pass it over, and some of those friends (whose desire to read some of my old papers has led me to republish them) may be interested to know why my experimental work on the circulation has apparently been so fitful and so intermittent.

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THE HARVEIAN ORATION, 1894.

(Delivered before the Royal College of Physicians on October 18, 1894.)

MR. PRESIDENT, FELLOWS, AND GENTLEMEN,

THIS annual meeting in memory of Harvey is usually associated with feelings of pleasure and happiness, for it was intended by its immortal founder to commemorate the benefactors of the College and to encourage good fellowship amongst us.

Such commemoration of those who have benefited the College in the past, although it necessarily recalls many who have passed away, is, notwithstanding, on ordinary occasions pleasant instead of painful, because the feeling of loss through their death is completely overpowered by the recollection of the good they have done in their lifetime. To-day the case is very different, for the first thought that must needs occur to every one present here is that on this occasion last year our late President showed for the first time what seemed to be imperfect fulfilment of his duty to the College by being late in his attendance at the meeting. Perhaps nothing else could have shown more clearly his deep concern for the welfare of the College, and his thorough devotion of every faculty of mind and body to its interests, than the fact that no duty, no pleasure, and no press of occupation could tempt him to leave one iota of his work in the College undone. The only thing that did keep him back was the hand of Death, which, although at the last meeting he and we knew it not, was already laid upon him. Though his death was less happy than that of the great Harvey, inasmuch as he lingered on for days instead of hours after he was first struck down, yet their deaths were alike in this respect that, up to the time of the fatal attack, each was in the full possession of his faculties, each was in the enjoyment of his life. Like Radcliffe and Mead, like Halford and Baillie, and like many other dis-

tinguished Fellows of this College, the greatness of Clark is to be estimated not by the published works which he has left behind, but by the influence he exerted on his contemporaries. For the very estimation in which his professional skill was held led to his whole time being taken up in giving advice, and prevented him from having the leisure to work out or record the results of the pathological and clinical observations which both his useful publications and his later career showed him to be specially fitted to make. I might say very much more about him, but it has already been said much better than I could possibly do it by yourself, Mr. President, in your annual address, and in the eloquent and heart-stirring words which you addressed to the College on the occasion of your taking the presidential chair rendered vacant by the death of Sir Andrew Clark.

But while we are saddened by the death of our late President, we hope to be gladdened by the presence amongst us again of one whom we all reverence not only as a former President of this College, but as one of the greatest leaders of clinical medicine in this century, Sir William Jenner. Like Harvey, Sir William Jenner is honoured by his College, by his country, by his Sovereign, and by the world at large. In time of trial and danger the lives of the Royal children were committed to the keeping of Harvey by his King; and to-day the care not only of her own life, but of that of her nearest and dearest, is committed to Sir William Jenner by his Sovereign, in the full and well-grounded assurance that in no other hands could they be more safe. The great clinician, Graves, wished to have as his epitaph, "He fed fevers"; but Jenner has advanced much beyond Graves, and, by showing us how to feed the different kinds of fevers, has saved thousands of valuable lives. To-day this College is acknowledging his right to rank with Sydenham, Heberden, Bright and Garrod, by bestowing upon him the Moxon medal for clinical research. In numbering Sir William amongst its medallists, the College honours itself as well as him, and in acknowledging the great services he has rendered, it is, on this occasion, acting as the mouthpiece of the medical profession, not only in this country but in the world at large.

It was with the wish to keep green the memory of the benefactors of the College that this oration was instituted by Harvey, and not at all with the intention that it should be devoted to his own praise. But Harvey stands out so high above all others, that it is only natural that in the numerous orations which have been yearly given before the College of Physicians, the subject-matter should have been to a great extent confined to a consideration of Harvey and his works. On looking over many of these orations, I find that everything that I could say about Harvey, his person, his circumstances, his character, and his works, has already been said so fully and eloquently that I could not add to it any further, nor could I hope to express it even so well. I purpose, therefore, to consider to-day some of the modern developments of Harvey's work, more especially in relation to the treatment of diseases of the heart and circulation. There is, I think, a certain advantage in this also, inasmuch as one is apt, by considering Harvey's work only as he left it, to overlook the enormous extent to which it now influences our thoughts and actions and thus to comprehend its value very imperfectly.

As he himself says, "From a small seed springs a mighty tree; from the minute gemmule or apex of the acorn, how wide does the gnarled oak at length extend his arms, how loftily does he lift his branches to the sky, how deeply do his roots strike down into the ground!"*

How very minute is the gemmule from which has sprung everything that is definite in medical science, for this gemmule is no other than the idea which Harvey records in these simple words: "I began to think whether there might not be A MOTION AS IT WERE IN A CIRCLE."†

Out of this idea has grown all our knowledge of the processes of human life in health and disease, of the signs and symptoms which indicate disease, of the mode of action of the drugs and appliances which we use, and the proper means of employing them in the cure of disease. In the works that have come down to us we find that Harvey developed his idea physiologically in several directions. He discussed its application to the absorp-

* *The Works of William Harvey*, Sydenham Society's edition, p. 320.
† *Ibid.*, p. 46.

tion and distribution of nourishment through the body, the mixing of blood from various parts, the maintenance and distribution of animal heat, and excretion through the kidneys. How far he developed it in the direction of pathology and therapeutics we do not know, as the results of his labours on these subjects have, unfortunately, been lost to us by the destruction of his manuscripts during the Civil War.

We are proud to reckon Harvey as an Englishman by birth, but he is far too great to belong exclusively to any country; men of various nations, and scattered all over the face of the earth, acknowledge him as their teacher, and have played, or are playing, a part in developing his discovery in its various branches of physiology, pathology, pharmacology, semeiology, and therapeutics. Americans, Austrians, Danes, Dutchmen, French, Germans, Italians, Norwegians, Russians and Swedes have all shared in the work, and so numerous are they that it would be impossible for me to name them all. Stephen Hales, however, deserves special mention, for he was the first to measure the pressure of blood in the arteries, and the resistance offered to the circulation of the blood by the capillaries was investigated by Thomas Young, a Fellow of this College, who ranks with Harvey, Newton, and Darwin as one of the greatest scientific men that England has ever produced, and whose undulatory theory has been as fertile of results in physics as Harvey's idea of circulation has been in physiology and medicine.

Harvey's desire that those who had done good work should not be forgotten was founded upon his knowledge of mankind, and of the tendency there is to forget what has already been done by those who have gone before us. The opposite condition often prevails, and the past is glorified at the expense of the present. But sometimes the present is wrongly glorified at the expense of the past, and past work or past benefits are forgotten.

Good examples of this are afforded by physiological views regarding the action of the vena cava and pulmonary veins and the causation of the cardiac sounds. Harvey appears to have thought that the vena cava and pulmonary veins were simply dilated passively by the passage of blood into them: but the

fact that they possess a power of independent pulsation was known to Haller,* and was brought prominently forward by Senac,† who regards the vena cava as the starting point of the whole circulation. He says: "The vena cava is therefore the first motor cause which dilates the cavities of the heart; it fills the auricles, and extends their walls in every direction."

These observations appear to have been almost forgotten until they were again made independently a few years ago,‡ and in one of the latest and most accurate physiological treatises which now exist, the description of the cardiac cycle is nearly the same as that given by Senac. "A complete beat of the whole heart, or cardiac cycle, may be observed to take place as follows:—

"The great veins, inferior and superior venæ cavæ and pulmonary veins are seen, while full of blood, to contract in the neighbourhood of the heart; the contraction runs in a peristaltic wave towards the auricles, increasing in intensity as it goes."§

The pulsation of these veins, however, cannot be a constant phenomenon, or it would have been noticed by such a keen observer as Harvey.

The sounds of the heart were discovered by Harvey, or at least were known to him, for he speaks of the sound caused in the œsophagus of the horse by drinking, and says: "In the same way it is with each motion of the heart, when there is a delivery of blood from the veins of the arteries that a pulse takes place, and can be heard within the chest."‖

This observation remained, as far as we know, without any further development until the time of Laennec, who introduced the practice of auscultation; but it was a Fellow of this College, Dr. Wollaston,¶ who first discovered that muscles during contraction give out a sound. Although many observations were made regarding cardiac murmurs by Corrigan, Bouillaud and

* Haller, *Elementa Physiologiæ*, 1757, tome 1, pp. 410 and 399.
† Senac, *De la Structure du Cœur*, livre iv, ch. iii, p. 24.
‡ *Proc. Roy. Soc.*, 1876, No. 172.
§ M. Foster, *Text-book of Physiology*, 6th edition, part i, ch. iv, p. 231.
‖ *The Works of William Harvey*, Sydenham Society's edition, p. 32.
¶ Wollaston, *Phil. Trans.*, 1810, p. 2.

Piorry, it was chiefly by Fellows of this College, Dr. Clendinning, Dr. C. J. B. Williams, and Dr. Todd, that the question was finally settled, and the conclusions at which they arrived are those now accepted as correct, viz., that "the first or systolic sound is essentially caused by the sudden and forcible tightening of the muscular fibres of the ventricle when they contract; and that the second sound which accompanies the diastole of the ventricle depends solely on the reaction of the arterial columns of blood in the semilunar valves at the arterial orifices."*

Yet in recent discussions regarding the origin of cardiac sounds, little mention has been made of the work of this committee; and, indeed, I first learned of its value from a German source, viz.: Wagner's *Handwörterbuch der Physiologie.*

The importance of these observations in the diagnosis of heart disease it would be hard to over-estimate. But diagnosis alone is not the aim of the physician, whose object must be to prevent, to cure, or to control disease. A knowledge of physiology may greatly help us to prevent disease, not only of the heart and vessels, but of every member of the body. The control and cure of disease may also be effected by diet and regimen, but it is undoubtedly in many cases greatly assisted by the use of drugs, and is sometimes impossible without them. Harvey knew that drugs applied externally are absorbed and act on the body,† so that colocynth thus applied will purge, and cantharides will excite the urine; but the action of drugs when injected into the blood appears to have been tried first by Christopher Wren, better known as the architect of St. Paul's than as a pharmacologist. According to Bishop Spratt, "he was the first author of the noble experiment of injecting liquors into the veins of animals, an experiment now vulgarly known, but long since exhibited to the meetings at Oxford, and thence carried by some Germans, and published abroad. By this operation divers creatures were immediately purged, vomited, intoxicated, killed, or revived, according to the quality of the liquor injected. Hence arose many new

* Report of Committee consisting of C. J. B. Williams, R. B. Todd, and John Clendinning, *Brit. Assoc. Rep. for* 1836, p. 155.

† *The Works of William Harvey*, Sydenham Society's edition, p. 72.

experiments, and chiefly that of transfusing blood, which the Society has presented in sundry instances, that will probably end in extraordinary success."*

The method originated by Wren, of injecting drugs into the circulation, was skilfully utilised by Magendie for the purpose of localising the particular part of the body upon which the drugs exerted their action, and he thus conclusively proved that the symptoms produced by strychnine were due to its effect on the spinal cord. His experiments showed that the rate of absorption from various parts of the body varied enormously, and, through the teaching of Christison, led to the introduction into practice by Dr. Alexander Wood of that most useful aid to modern therapeutics, the hypodermic syringe.

The first quantitative experiments on the effect of drugs upon the circulation were made, to the best of my knowledge, by James Blake in 1844, in the laboratory of University College, at the suggestion of the late Professor Sharpey, with the hæmadynamometer of Poiseuille, which had then been recently introduced.

In speaking about the work of Blake and Sharpey, who are both dead, one requires to use the greatest care not to unduly detract from the merit of one by ascribing more to the other; but those who knew Prof. Sharpey's enormous range of knowledge, his readiness to put it all at the disposal of others, and the influence he exerted over all who came in contact with him, as well as his unselfishness in making no claim whatever to what was justly his due, will at once recognise how greatly Blake was indebted to Sharpey. More especially is this the case when we consider that, although the credit for the observations themselves belongs to Blake, yet after the impetus which Sharpey gave him had passed away, he did very little more during the course of a long life. It seems all the more necessary to commemorate Sharpey on this occasion, because he has left comparatively few writings behind him, and anyone who should judge by them alone of his influence upon physiological progress in this country would grievously under-estimate it.

* *The History of the Royal Society of London for the Improving of Natural Knowledge*, by T. Spratt, late Lord Bishop of Rochester.

For Sharpey was above all a teacher, and his work was written not with pen and ink on paper or parchment, but was engraved upon the hearts and minds of his pupils and his friends. Upon two of these, especially, has Sharpey's mantle fallen, and to Burdon Sanderson and Michael Foster we owe a revival of experimental physiology in this country, a revival of the method which Harvey not only used in making his great discovery, but also employed to demonstrate the truth of it to the rulers of this land. By their writings, by their lectures, by their original experiments, by their demonstrations, and by the pupils they have trained, Burdon Sanderson and Michael Foster, under the auspices of Acland and Humphry, have diffused amongst the medical men of this country a knowledge of physiology so extensive and exact as could only be found, before their time, amongst those who had made a special study of the subject. Yet more than to them, more than to anyone else since the time of Harvey, do we owe our present knowledge of the circulation to Carl Ludwig. He it is who first enabled the pressure of blood in the arteries to record its own variations automatically, so that alterations could be noticed and measured which were too rapid or too slight to be detected by the eye. To him, also, we owe the plan of artificial circulation by which the changes in the functions of the organs and in the vessels which supply them can be observed, quite apart from the heart, lungs, or from the nervous system.

Like Sharpey, Ludwig is a great teacher, and, like the great architects of the Middle Ages, who built the wonderful cathedrals which all admire, but whose builder's name no man knows, Ludwig has been content to sink his own name in his anxiety for the progress of his work, and in his desire to aid his pupils. The researches which have appeared under these pupils' names have been in many instances, perhaps in most, not only suggested by Ludwig, but carried out experimentally with his own hands, and the paper which recorded the results finally written by himself. In the papers which have appeared under his pupils' names we find their obligation to the master recorded in such terms as "unter Mitwirkung."

But no one, except those who have worked with him, can understand what such "co-operation" meant.

The graphic method introduced by Ludwig for the purpose of measuring the blood pressure, was adapted by Volkman to the registration of the pulse in man, and the same method has been modified and rendered more easily applicable at the bedside by Marey and Chauveau, to whom we chiefly owe our knowledge of the modifications in the form of the apex-beat and of the pulse curve. It is to Ludwig and his scholars, however, that we owe the greater part of our knowledge of the mechanism of the circulation and of the varying distribution of the blood in various parts of the body.

The effect of emotion upon the heart was carefully noted by Harvey, who says: "For every affection of mind which is attended with pain or pleasure, hope or fear is the cause of an agitation whose influence extends to the heart.*

Not only was Harvey well acquainted with the fact that the beats of the heart vary very much in strength and rate, but he also knew that the circulation in various parts of the body may be very different at one and the same time. He says: "It is manifest that the blood in its course does not everywhere pass with the same celerity, neither with the same force in all places, and at all times, but that it varies greatly according to age, sex, temperament, habit of body, and other contingent circumstances, external as well as internal, natural, or non-natural. For it does not course through intricate and obstructed passages with the same readiness that it does through straight, unimpeded, and pervious channels. Neither does it run through close, hard and crowded parts with the same velocity as through spongy, soft and permeable tissues. Neither does it flow with such swiftness when the impulse (of the heart) is slow and weak, as when this is forcible and frequent, in which case the blood is driven onwards with vigour, and in large quantity."

"And what, indeed, is more deserving of attention than the fact that in almost every affection, appetite, hope, or fear, our

* *The Works of William Harvey*, Sydenham Society's edition, p. 70.

body suffers, the countenance changes, and the blood appears to course hither and thither. In anger the eyes are fiery and the pupils contracted; in modesty the cheeks are suffused with blushes; in fear, and under a sense of infamy and of shame, the face is pale, but the ears burn as if for the evil they heard or were to hear; in lust, how quickly is the member distended with blood and erected."*

Harvey's great contemporary, Milton, though so violently opposed to him in politics, would certainly not remain in ignorance of Harvey's work, and he has noted the changes in the colour of the face produced by emotions. In describing the behaviour of Satan on his journey from Hell to Paradise, he says:—

> "Thus while he spake, each passion dimm'd his face,
> Thrice changed with pale, ire, envy, and despair;
> Which marr'd his borrow'd visage." †

But although these facts were known to Harvey so long ago, it is only in comparatively recent years that the mechanism by which they are brought about has been investigated, and it is only within the last decade that physiologists have begun regularly to believe that the cardiac muscle has a power of rhythmic pulsation independent of its nerves, although Harvey had noted that when the heart was cut into small pieces the fragments would still continue to pulsate.‡ We may fairly, indeed, compare the movements of the heart, as regarded by physiologists of the present day, to those of a horse which is capable of going independently, although its pace may be slowed or accelerated by the reins or spur of the rider. The power of the vagus to act as a rein to the heart, and slow its movements or stop them altogether, was first noted by Edward and Ernest Heinrich Weber, while the effect that it sometimes has of accelerating instead of slowing, like the effect of shaking the reins of the horse, was observed by Schiff, Moleschott and Lister, and the transmission of excitation from one chamber to another was experimented on by Paget.

* *The Works of William Harvey*, Sydenham Society's edition, pp. 128—129.

† *Paradise Lost*, by John Milton, book iv.

‡ *The Works of William Harvey*, Sydenham Society's edition, p. 28.

The accelerating nerves of the heart, and the position of the nerve-centre from which they spring, were more thoroughly investigated by von Bezold,* while the power of the vagus to weaken as well as slow the heart was observed by Gaskell. The position of the cardiac centre, which, like the rider, regulates the movements of the heart, was located in the medulla oblongata chiefly by Ludwig and his scholars. Like the heart, the vessels are regulated in diameter by the nervous system in accordance with the wants of the body generally; and the effect upon the vaso-motor nerves which, when cut, allow them to dilate, and, when stimulated, cause them to contract, was discovered by Bernard, Brown-Séquard and by our countryman, Waller; while the power of other nerves to cause immediate dilatation was discovered by Bernard, Eckhardt, and Ludwig in the submaxillary glands, penis and peripheral vessels respectively.†

The heart, when cut out of the body, still continues to beat, although removed completely from the influence of the central nervous system, and the vessels have a somewhat similar power of independent contractility. The alterations produced in the circulation, generally and locally, by the contractile power of the vessels, and the changes caused in the vessels by the central nervous system, by peripheral stimulation of the nerves, or by variations in the quality of the blood, have formed the subject of a series of researches extending over many years; and though originated, and in many cases entirely conducted by Ludwig, have appeared to a great extent under the names of his pupils. The starting-point of these investigations was an examination of the changes in blood as it flowed through isolated organs, with the view of ascertaining in what manner the combustion by which the animal heat is maintained, is effected in the body. While keeping up the circulation of blood through the vessels of muscles severed from the body, Ludwig and Sczelkow‡ observed variations in the flow which appeared to

* Von Bezold, *Untersuchungen über die Innervation des Herzens*, 1863. Leipzig: Engelmann.

† Ludwig and Brunton, *Ludwig's Arbeiten*. Vierter Jahrgang, 1869, p. 106.

‡ Ludwig and Sczelkow, *Henle and Pfeuffers Zeitschrift*, 1863, vol. 17, p. 106, and *vide* p. 122.

indicate contractile power in the vessels themselves. This research was carried on under Ludwig's direction by various of his scholars in succession, Alexander Schmidt, Dogiel, Sadler, myself, Hafiz, Lépine, A. Mosso, von Frey, and Gaskell. Their observations, as well as those of Cohnheim and Gunning, have shown that the muscular fibres of the arterioles, not only in the muscles but throughout the body generally, have a power of independent, and sometimes rhythmical, contraction and relaxation. Their contractility is, however, controlled by the central nervous system in accordance with the wants of the body generally. For the amount of blood contained in the body is insufficient to fill the whole of the vascular system at once; and when the vessels are fully dilated, as they are after death, we find that nearly the whole of the blood of the body may be contained in the veins alone. It is, therefore, necessary that when one part of the body is receiving a larger supply of blood, another should be receiving a smaller supply; and the functions of the vaso-motor centres have been well compared by Ludwig to the turncocks in a great city, who cut off the water supply from one district at the same time they turn it on to another. Thus it is that when the brain is active the feet may get cold, and Mosso has shown this in an exceedingly neat manner by placing a man on a large board delicately balanced at its centre, and demonstrating that whenever the man begins to think, the increased supply of blood to his brain causes the head to go down and the heels to rise up. A similar condition was indicated by Mayow, who gave a different explanation. He said that the "vital spirits" were not able to be in more than one place at once, and therefore it happens that if a man eats a heavy meal he is apt to become drowsy, because the "vital spirits" descend from the brain to the stomach in order to carry on digestion; and, on the other hand, if a man thinks vigorously after dinner, the "vital spirits" have to leave the stomach to go to the brain, and consequently digestion is imperfectly performed. If we substitute the word blood for "vital spirits," we have an exact expression of present physiological ideas.

Ubi stimulus ibi affluxus is an old doctrine and expresses a great truth. Wherever the need for increased nourishment or increased supply of oxygen exists in the healthy body, thither does the blood flow in larger quantities than usual. If the glands are active, their blood supply is greatly increased, as was shown by Bernard, and a similar occurrence takes place in the contracting muscle, as has been shown by Ludwig and his scholars. The vessels of the intestines and skin, as well as their numerous glands, have their calibre regulated by the vaso-motor nerves which proceed from the centre in the medulla oblongata. This centre acts most readily upon the vessels of the intestine, and rather less readily on those of the skin. In consequence of this, when the centre is irritated, the vessels of the intestine contract and drive the blood through the skin, so that it is warmer than before, and it is only when the stimulation is very great that the vessels of both contract, so that the skin receives less blood than normal, and becomes colder than before. But if the vessels of the skin and intestine are both contracted, where does the blood go? This question was put by Ludwig, and answered by the experiments which he made with Hafiz. It is evident that if the heart be stopped while the blood pressure is being measured in the artery of an animal, the pressure will fall regularly and steadily, because the blood is flowing out all the time through the arterioles and capillaries into the veins. One would naturally expect that if the arterioles were contracted by irritation of the vaso-motor centre in the medulla, the fall of blood pressure would either not take place at all, or would be very much slower than before; but on trying the experiment, Ludwig and Hafiz found, to their surprise, that the blood pressure fell almost as quickly as when the vaso-motor centre was left alone, and the vessels of the skin and intestine therefore remained uncontracted. In other words, the vessels which supply the muscles of the body and limbs are capable of such extension that when fully dilated they will allow the arterial blood to pour through them alone nearly as quickly as it usually does through the vessels of the skin, intestine and muscles together. This observation, it seems to me,

is one of the greatest importance, and one that has hardly received, as yet, the attention which it merits. One consequence of it is obvious—viz., that contraction of the cutaneous vessels, such as occurs upon exposure to cold, will drive more blood through the muscles, and as oxidation goes on more rapidly in them the result will be increased production of heat.

The experiments I have just mentioned show that the vessels of the muscles are not controlled by the vaso-motor centre in the medulla oblongata in the same way as those of the intestine and skin. How far their vascular centres may be associated with those for voluntary movements, which have been so admirably localised by Ferrier in the cerebral cortex, still remains to be made out. The circulation through the muscles is indeed a complex phenomenon, and it was shown by Ludwig and Sadler to depend upon at least two factors having an antagonistic action. When a muscle is thrown into action, it mechanically compresses the blood vessels within it, and thus tends to lessen the circulation through it, but at the same time the stimulus which is sent down through the motor nerve and calls it into action, brings about a dilatation of the vascular walls, and thus increases the circulation through the muscle.

When the amount of blood is measured before, during and after stimulation of the motor nerve, it is sometimes found that the flow is diminished, at others that it is increased. This difference depends upon the comparative effect of the mechanical compression of the vessels of the muscles just mentioned, and upon the increase of their lumen by the dilatation of their walls. It invariably happens, however, that after the muscle has ceased to act, the flow of blood through the muscle is increased. This increase is quite independent of any alteration in the general pressure of blood in the arteries, and it occurs when an artificial stream of blood, under constant pressure, is sent through the muscle. The dilatation in the muscular vessels, as indicated by the increased flow of blood, and consequent change of colour in the frog's tongue, was observed by Lépine after stimulation of the peripheral ends of the hypoglossal and glossopharyngeal nerves,* and the actual changes

* Lépine, *Ludwig's Arbeiten*, 5ter Jahrg., 1870, p. 114.

in the vessels themselves were observed microscopically by von Frey and Gaskell.*

The dilatation of muscular vessels on irritation of peripheral nerves was thus brought into a line with the dilatation noticed in the vessels of the submaxillary gland by Bernard, and in the corpora cavernosa by Eckhardt. It is evident that alteration in the size of such a huge vascular tract as the muscular arteries must influence, to a great extent, the blood pressure in the arteries generally. It is equally evident that the changes induced in the condition of the blood pressure by muscular action may be of two kinds, either a rise or a fall. If the arterioles are compressed by the muscles so that the flow through them is impeded, the general blood pressure will rise. When this effect is more than counteracted by the dilatation of the arterioles themselves under nervous influence, the general blood pressure will fall, for the blood will find an easy passage from the arteries into the veins through the muscles. We can thus see how readily a rise or fall in the general blood pressure may be induced by exercise of the muscles. If they contract suddenly or violently they will tend to compress the arterioles, and raise the blood pressure, whilst if they contract gently their contraction will have little effect in compressing the arterioles, and these, becoming dilated, will allow the blood pressure to fall.

But there is still another factor which may tend to increase the blood pressure during severe muscular exertion, viz., a quickened pulse, for stimulation of the nerve fibres passing from the muscles to the central nervous system greatly accelerates the beats of the heart. In this respect stimulation of the muscular nerves differs from that of the cutaneous and visceral nerves, inasmuch as the latter tend rather to slow than to quicken the pulse. This peculiar effect of the muscular nerves upon the heart would, indeed, appear to be a provision of nature for the purpose of maintaining an exceedingly active circulation during the active calls upon nutrition which violent exertions entail. Muscular exercise, therefore, has a special tendency to raise the blood pressure in the arterial system, and conse-

* Von Frey, *Ludwig's Arbeiten*, 11ter Jahrg., 1876, p. 106; and Gaskell, *ibid.*, p. 79; and *Centralb. f. die Med. Wiss.*, 1876, p. 557.

quently to increase the resistance which the left ventricle has to overcome. Moreover, in the case of the intestinal vessels, there is a special provision made for preventing their contraction from causing too great a rise of arterial pressure. This consists in the depressor nerve, which passes from the heart and tends to produce dilatation of the abdominal vessels, and thus to prevent any undue pressure occurring within the heart from their excessive contraction. But in the case of the muscles, we have no such nerve. Its place seems to be taken by the dilating fibres which occur in the motor nerves. As I have already said, however, their power to dilate the muscular vessels may be at first more than counteracted by mechanical compression at the commencement of exertion. Thus the blood pressure in the arteries, and the resistance which it opposes to the contraction and emptying of the ventricle, may be unduly increased at first by any effort, especially if it be sudden or severe.

As a general rule, the distension of any hollow muscular organ is attended with great pain. How great is the suffering when obstruction of the bowel prevents evacuation of its contents; or when calculi, in their passage down the gall duct or ureters, forcibly distend their walls. One of the severest tortures of the middle ages was to distend the stomach with water, and the Emperor Tiberius could imagine no more awful punishment for those whom he hated than to make them drink wine, and, at the same time, by means of a ligature, to prevent the distended bladder from emptying itself. The heart is no exception to this rule, and distension of its cavities brings on most acute physical suffering. Its inability to empty itself is a question of relative, and not of absolute power; for a strong heart may be unable to work only against enormously increased resistance in the peripheral arterioles, while a heart, weakened by degeneration, may be unable to empty itself in face of pressure little, if at all, above the normal.

When the contractile power of the heart is not, as it is in health, considerably in excess of the resistance opposed to it in the vessels, but is only nearly equal to it, a slight increase in the resistance may greatly interfere with the power of the heart to empty itself, and bring on pain varying in amount from slight

uneasiness to the most intense agony in angina pectoris. This is, indeed, what we find, for a heart whose nutrition has been weakened by disease of its arteries, and consequent imperfect supply of blood to the cardiac muscle, is unable to meet any increased resistance if this should be offered to it, and pain is at once felt. In such cases, unless they be far advanced, we find, precisely as we might expect, that walking on the level usually causes no pain, but the attempt to ascend even a slight rise, by which the muscles are brought into more active exertion, brings on pain at once. Yet here again we find, as we should expect, that if the patient is able to continue walking, the pain passes off and does not return. These phenomena would be inexplicable were it not for Ludwig's observations on circulation through the muscles, but in the light of these observations everything is made perfectly intelligible. Walking on the flat, by causing no violent exertion of the muscles, produces no mechanical constriction of the vessels, and thus does not increase the blood pressure. The greater exertion of walking up a hill has this effect, but if the patient is able to continue his exertions, the increased dilatation of the vessels—a consequence of muscular activity—allows the pressure again to fall and relieves the pain.

As muscular exertion continues and the vessels of the muscles become dilated, the flow of blood from the arteries into the veins will tend to become much more rapid than usual. The pressure in the arterial system will consequently fall, but that in the veins will become increased, and unless a corresponding dilatation occurs in the pulmonary circulation, blood will tend to accumulate in the right side of the heart, the right ventricle will be unable to empty itself completely, shortness of breath will arise, and even death may occur. At first the right side of the heart is affected, and the apex beat disappears from its normal place and is felt in the epigastrium. But the left ventricle also becomes dilated, though whether this is simply through nervous influence tending to make it act concordantly with the right, or for some other reason, it is at present impossible to say. Severe exertions, even for a few minutes, may produce this condition in healthy persons,* and when the

* Schott, Verhandl. de ix. Congresses in *Med. zu Wien*, 1869.

exertion is over-continued it may lead to permanent mischief. More especially is this the case in young growing boys, and it is not merely foolish, it is wicked to insist upon boys engaging in games or contests which demand a long-continued over-exertion of the heart, such as enforced races and paper-chases extending over several miles. Intermittent exertion, either of a single muscle or of a group of muscles, or of the whole body, appears to lead to better nutrition and increased strength and hypertrophy, but over-exertion, especially if continuous, leads to impaired nutrition, weakness and atrophy. If we watch the movements of young animals, we find that they are often rapid, but fitful, irregular and varied in character, instead of being steady, regular and uniform. They are the movements of the butterfly, and not of the bee. The varied plays of childhood, the gambols of the lamb, and the frisking of the colt, are all well adapted to increase the strength of the body without doing it any injury; but if the colt, instead of being allowed to frisk at its own free will, is put in harness, or ridden in races, the energy which ought to have gone to growth is used up by the work, its nutrition is affected, its powers diminished, and its life is shortened. The rules which have been arrived at by the breeders of horses ought to be carefully considered by the teachers of schools, and by the medical advisers who superintend the pupils.

In youth and middle age every organ of the body is adapted for doing more work than it is usually called upon to do. Every organ can, as it is usually termed, "make a spurt" if required; but as old age comes on this capacity disappears, the tissues become less elastic, the arteries become more rigid and less capable of dilating and allowing a freer flow of blood to any part, whether it be the intestine, the skin, the brain, the muscles, or the heart itself. Mere rigidity of the arteries supplying the muscles of the heart will lessen the power of extra exertion, but if the vessels be not only rigid, but diminished in calibre, the muscles of the limbs and the heart itself will be unfit even for their ordinary work, and will tend to fail on the slightest over-exertion. This fact was noticed by Sir Benjamin Brodie, who, when speaking of patients with degenerating and

contracted arteries, such as lead to senile gangrene, said: "Such patients walk a short distance very well, but when they attempt more than this, the muscles seem to be unequal to the task, and they can walk no further. The muscles are not absolutely paralysed, but in a stage approaching to it. The cause of all this is sufficiently obvious. The lower limbs require sometimes a larger and sometimes a smaller supply of blood. During exercise a larger supply is wanted on account of the increased action of the muscles; but the arteries being ossified or obliterated, and thus incapable of dilatation, the increased supply cannot be obtained. This state of things is not peculiar to the lower limbs. Wherever muscular structures exist the same cause will produce the same effect. Dr. Jenner first, and Dr. Parry of Bath afterward, published observations which were supposed to prove that the disease which is usually called 'angina pectoris' depends on ossification of the coronary arteries. . . . When the coronary arteries are in this condition they may be capable of admitting a moderate supply of blood to the muscular structure of the heart; and as long as the patient makes no abnormal exertion, the circulation goes on well enough; when, however, the heart is excited to increased action, whether it be during a fit of passion, or in running, or walking upstairs, or lifting weights, then the ossified arteries being incapable of expanding so as to let in the additional quantity of blood, which, under these circumstances, is required, its action stops and syncope ensues; and I say that this exactly corresponds to the sense of weakness and want of muscular power which exists in persons who have the arteries of the legs obstructed or ossified."*

But the syncope and stoppage of the heart mentioned by Brodie are not the only consequences of impaired cardiac nutrition. The heart may be still able to carry on the circulation, but the patient may suffer intense pain in the process. The outside of the heart was found by Harvey to be insensible to light touches, but the inside of the heart appears to be much more sensitive either to touch or pressure, and the internal pres-

* *Lectures on Pathology and Surgery*, by Sir Benjamin Brodie, London, 1846, p. 360.

sure caused by inability to empty itself produces, as I have already said, intense pain.

A knowledge of the mode of the circulation of blood through the muscles enables us to understand not only the pathology of angina pectoris, but the rationale of various methods of treating patients suffering from angina pectoris or other forms of heart disease. In most cases our object is a two-fold one—to increase the power of the heart, and to lessen the resistance it has to overcome. In some cases we require also to aid the elimination of water, which has so accumulated as to give rise to œdema of the cellular tissue, or dropsy of the serous cavities. In our endeavours to produce these beneficial changes in our patients, we employ regimen diet, and drugs, and it is evident that as in one case the condition of a patient's heart may be very different indeed from that in another, the regimen which may be useful to one may be fatal to the other. We have already seen that sudden and violent exertion may raise the blood pressure, and so lead to intense cardiac pain or to stoppage of the heart and instant death; while more gentle exercise, by increasing the circulation of the muscles, may lessen the pressure and give relief to the heart.

The methods of increasing the muscular circulation may be roughly divided into three, according as the patient lies, stands, and walks. First, absolute rest in bed with massage*; second, graduated movements of the muscles of the limbs and body while the patient stands still; third, graduated exercises in walking and climbing.

The second of these methods has been specially worked out by the brothers Schott, of Nauheim, and the third is generally connected with the name of Oertel.

It is obvious that in cases of heart disease where the failure is great and the patient is unable even to stand, much less walk, where breathlessness is extreme and dropsy is present, the second and third methods of treatment are inapplicable. It is in such cases that the method of absolute rest in bed, not allowing the patient to rise for any purpose whatever, hardly allowing him to feed himself or turn himself in bed, proves advantageous.

* Lauder Brunton, *Practitioner*, vol. li, p. 190.

The appetite is usually small, the digestion imperfect, and flatulence troublesome; and here an absolute milk diet, like that usually employed in typhoid fever, is often most serviceable, being easily taken and easily digested, while the milk sugar itself has a diuretic action, and tends to reduce dropsy. But while simple rest prevents the risk of increased arterial tension and consequent opposition to the cardiac contractions which might arise from muscular exertion, the benefit which would accrue from continuous muscular exertions and increased circulation would be lost were it not that they can be supplied artificially by massage. This plan of treatment, although it has only recently been revived, was known to Harvey, "who narrates the case of a man who, in consequence of an injury—of an affront which he could not revenge—was so overcome with hatred, spite, and passion that he fell into a strange disorder, suffering from extreme compression and pain in the heart and breast, from which he only received some little relief at last when the whole of his chest was pummelled by a strong man, as the baker kneads dough."*

This was a very rough form of massage, but the same kneading movements which Harvey described have been elaborated into a complete system, more especially by Ling in Sweden, and made widely known in America and this country by Weir-Mitchell and Playfair. One might naturally expect that kneading the muscles would increase the circulation through them in somewhat the same way as active exercise, but, to the best of my knowledge, no actual experiments existed to prove this, and I accordingly requested my friend and assistant, Dr. Tunnicliffe, to test the matter experimentally. The method employed was, in the main, the same as that devised by Ludwig, and employed by Sadler and Gaskell under his direction. The results were that, during the kneading of a muscle, the amount of venous blood which issued from it was sometimes diminished and sometimes increased; that just after the kneading was over the flow was diminished (apparently from the blood accumulating in the muscle), and this diminution was again succeeded by a greatly increased flow exactly corresponding to that observed by Ludwig

* *The Works of William Harvey*, Sydenham Society's edition p. 128.

and his scholars. The clinical results are precisely what one would expect from increased circulation in the muscles, and cases apparently hopeless sometimes recover most wonderfully under this treatment.

For patients who are stronger, so that confinement to bed is unnecessary, and who yet are unable to take walking exercise, Schott's treatment is most useful, and it may be used as an adjunct to the later stages of the treatment just described, or as a sequel to it. Here the patient is made to go through various exercises of the arms, legs, and trunk with a certain amount of resistance, which is applied either by the patient himself setting in action the opposing muscles, or by an attendant, who gently resists every movement made by the patient, but graduates his resistance so as not to cause the least hurry in breathing, or the least oppression of the heart. Perhaps the easiest way of employing graduated resistance is by the ergostat of Gärtner, which is simply an adaptation of the labour crank of prisons, where the number of turns of a wheel can be regulated in each minute, and the resistance, which is applied by a brake, may be graduated to an ounce. The objection to it is the uniformity of movement and its wearisome monotony.

Oertel's plan of gradually walking day by day up a steeper and steeper incline, and thus training the cardiac muscle, is well adapted for strong persons, but when applied injudiciously, may lead, just like hasty or excessive exertion, to serious or fatal results. In Schott's method stimulation of the skin by baths is used as an adjunct, and this may tend to slow the pulse as already mentioned. But in all these plans the essence of treatment is the derivation of blood through a new channel, that of the muscular vessels; and the results in relieving cardiac distress and pain may be described in the same words which Harvey employs in reference to diseases of the circulation: "How speedily some of these diseases that are even reputed incurable are remedied and dispelled as if by enchantment."*

There is yet another consequence of the circulation to which Harvey has called attention, although only very briefly, which has now become of the utmost importance, and that is the ad-

* *The Works of William Harvey*, Sydenham Society's edition, p. 141.

mixture of blood from various parts of the body. After describing the intestinal veins, Harvey says: "The blood returning by these veins and bringing the cruder juices along with it, on the one hand from the stomach, where they are thin, watery, and not yet perfectly chylified; on the other, thick and more earthy, as derived from the fæces, but all pouring into this splenic branch, are duly tempered by the admixture of contraries."*

Harvey's chemical expressions are crude, for chemistry as a science only began to exist about a century and a half after Harvey's death, yet the general idea which he expresses in the words which I have just quoted is wonderfully near the truth.

Two of the most important constituents of the blood are chloride of sodium and water. Chloride of sodium is a neutral salt, but during digestion both it and water are decomposed in the gastric glands, and hydrochloric acid is poured into the stomach, while a corresponding amount of soda is returned into the blood, whose alkalinity increases *pari passu* with the acidity of the stomach. Part of this alkali is excreted in the urine, so that the urine during digestion is often neutral or alkaline. Possibly some of it passes out through the liver in the bile, and through the pancreas and intestinal glands into the intestine, where, again mixing with the acid chyle from the stomach, neutralisation takes place, so that neutral and comparatively inactive chloride of sodium is again formed from the union of active alkali and acid. But it is most probable that what occurs in the stomach occurs also in the other glands, and that the liver, pancreas and intestine do not merely pour out the excess of alkali resulting from gastric digestion, but that these glands also decompose neutral salts, pouring the alkali out through their ducts, and returning the acid into the blood.

We are now leaving the region of definite fact and passing into that of fancy, but the fancies are not entirely baseless, and may show in what directions we may obey Harvey's behest to search out and study the secrets of nature by way of experiment. For what is apparently certain in regard to the decomposition of chloride of sodium in the stomach, and probably in

* *The Works of William Harvey*, Sydenham Society's edition, p. 75.

the case of neutral salts in the pancreas and intestine, is also probable in that important, though as yet very imperfectly known, class of bodies which are known as zymogens. Just as we have in the stomach an inactive salt, so we have also an inactive pepsinogen, which, like the salt, is split up in the gastric glands, and active pepsine is poured into the stomach. But is pepsine the only active substance produced? Has no other body, resulting from the decomposition of pepsinogen, been poured into the blood while the pepsine passed into the stomach? Has the inactive pepsinogen not been split up into two bodies active when apart, inactive when combined? May it not be fitly compared, as I have said elsewhere, to a cup or glass, harmless while whole, but yielding sharp and even dangerous splinters when broken, although these may again be united into a harmless whole?*

This question at present we cannot answer, but in the pancreas there is an indication that something of the kind takes place, for Lépine has discovered that while this gland pours into the intestine a ferment which converts starch into sugar, it pours through the lymphatics into the blood another ferment which destroys sugar. Whether a similar occurrence takes place in regard to its other ferments in the pancreas, or in the glands of the intestine, we do not know. Nor do we yet know whether the same process goes on in the skin, and whether the secretion of sweat, which is usually looked upon as its sole function, bears really a relationship to cutaneous activity similar to that which the secretion of bile bears to the functions of the liver. There are indications that such is the case, for when the skin is varnished, not only does the temperature of the animal rapidly sink, but congestion occurs in internal organs, and dropsy takes place in serous cavities, while in extensive burns of the skin rapid disintegration of the blood corpuscles occurs. It is obvious that if this idea be at all correct, a complete revolution will be required in the views we have been accustomed to entertain regarding the action of many medicines. In the case of purgatives and diaphoretics, for example, we have looked mainly at the secretions poured out after their administration

* *Practitioner*, vol. xxxv, August, 1885.

for an explanation of their usefulness, whereas it may be that the main part of the benefit that they produce is not due to the substances liberated through the secretions which they cause to be poured out, but to those which are returned from the intestine and skin into the circulating blood.

How important an effect the excessive admixture of juices from one part of the animal body with the circulating blood may have, was shown in the most striking way by Wooldridge. The juice of the thyroid gland is harmless so long as it remains in the gland, and is probably useful when it enters the blood in small quantities in the ordinary course of life. Yet he found that if this juice be injected directly into the vessels it will cause the blood to coagulate almost instantaneously and kill the animal as quickly as a rifle bullet. But what is powerful for harm is, likewise, powerful for good, and the administration of thyroid juice in cases of myxœdema is one of the most remarkable therapeutic discoveries of modern times.

Since the introduction by Corvisart of pepsine as a remedy in dyspepsia, digestive ferments have been largely employed to assist the stomach and intestine in the performance of their functions, but very little has been done until lately in the way of modifying tissue changes in the body by the introduction of ferments derived from solid organs.

For ages back, savages have eaten raw hearts and other organs of the animals which they have killed, or the enemies they have conquered, under the belief that they would thereby obtain increased vigour or courage; but the first definite attempt to cure a disease by supplying a ferment from a solid non-glandular organ of the body was, I believe, made in Harvey's own hospital by the use of raw meat in diabetes.*

It was not, however, until Brown-Séquard recommended the use of testicular extract that the attention of the profession became attracted to the use of extracts of solid organs. Since then extract of thyroid, extract of kidney, extract of supra renal capsule have been employed; but even yet they are only upon their trial, and the limits of their utility have not yet been definitely ascertained.

* Lauder Brunton, *Brit. Med. Jour.*, February 21, 1874, pp. 221 *et seq.*

Another therapeutic method has been recently introduced which bids fair to be of the utmost importance—viz., the treatment of disease by antitoxins. The discovery by Pasteur of the dependence of many diseases upon the presence of minute organisms may be ranked with that of Harvey, in regard both to the far-reaching benefits which it has conferred upon mankind and to the simplicity of its origin. The germ of all his discoveries was the attempt to answer the apparently useless question, "Why does a crystal of tartaric acid sometimes crystallise in one form and sometimes in another?" From this germ sprang his discovery of the nature of yeast, and of those microbes which originate fermentation, putrefaction and disease.

These minute organisms, far removed from man as they are in their structure and place in nature, appear in some respects to resemble him in the processes of their growth and nutrition. They seem, indeed, to have the power of splitting up inactive bodies into substances having a great physiological or chemical activity. From grape sugar, which is comparatively inert, they produce carbonic acid and alcohol, both of which have a powerful physiological action. From inert albumen they produce albumoses having a most powerful toxic action, and to the poisonous properties of these substances attention was for a while alone directed. But it would appear that at the same time as they produce poisons they also form antidotes, and when introduced into the living organism they give rise to the production of these antidotes in still greater quantity than when cultivated without the body.

The plan of protection from infective diseases, which was first employed by Jenner in small-pox, is now being extended to many other diseases, and the protective substances which are formed in the body, and their mode of action, are being carefully investigated. The introduction of either pathogenic microbes or of toxic products appears to excite in the body a process of tissue-change by which antitoxins are produced, and these may be employed either for the purpose of protection or cure. By the use of antitoxins tetanus and diphtheria appear to be deprived of their terrible power.

But it seems probable that a similar result may be obtained

by the introduction of certain tissue-juices into the general circulation, for it was shown by Wooldridge that thyroid juice has the power of destroying anthrax poison. Increase of the circulation in certain organs will almost certainly increase their tissue-change, will throw their juices or the products of their functional activity into the general circulation, and thus influence the invasion or progress of disease. As I have already mentioned, we are able to influence the circulation in muscles both by voluntary exertion and by massage, and we should expect that both of these measures would influence the constituents of the blood generally. Such, indeed, appears to be the case, for J. K. Mitchell* has found that after massage the number of blood corpuscles in the circulation is very considerably increased. We can thus understand why exercise either of the body or its parts may increase its power to resist infective diseases.

Had time allowed it, I had intended to discuss the modifications of the heart and vessels by the introduction of remedies into the circulation, the power of drugs to slow or strengthen, to quicken or weaken the power of the heart, to contract or relax the arterioles, to raise or lower the blood pressure, to relieve pain or to remove dropsy; but to do this would require time far exceeding that of a single hour. Moreover, the methods and results of such research were admirably expounded to the College by Dr. Leech in his Croonian lecture, and I have therefore thought I should be better fulfilling the wish of Harvey that the orator of the year should exhort the Fellows and Members of the College to search out the secrets of nature by way of experiment by directing their attention to some fields of research which have received at present little attention, but promise results of great practical value.

Lastly, I have to exhort you to continue in mutual love and affection amongst yourselves; and it seems to me that the best way of doing this is to direct your attention to the examples of Harvey and of our late President, whose death we deplore today. They were beloved by their fellows while they lived, their loss was lamented when they died, and they have left

* *American Journal of Medical Science*, May, 1894.

behind them an example not only of goodness, but of courage. Harvey, seated speechless in his chair, distributing rings and parting gifts to his friends while awaiting the approach of death; and Andrew Clark, steadfastly determining to continue at work and die in harness, in spite of the hæmoptysis which seemed to threaten a speedy death, afford us noble examples which ought to encourage us to follow the directions of the venerable Longfellow, who, taking the organ Harvey studied to symbolise such courage as Harvey and Clark showed, says:—

> "Let us then be up and doing
> With a heart for any fate,
> Still achieving, still pursuing,
> Learn to labour and to wait."

ON DIGITALIS, WITH SOME OBSERVATIONS ON THE URINE.

(Thesis presented to the University of Edinburgh, 1836, and to which a Gold Medal was Awarded.)

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Preface.

Encouraged by the distinction awarded to this Thesis by the Medical Faculty of the Edinburgh University, and believing that it contains some facts not altogether without interest or importance, I have been induced to publish it, though fully conscious of its very imperfect condition. Though my time was not only short, but much broken up, the omissions would probably not have been so numerous, and the amount of new material greater, were it not that, fearing lest I should see, not what was actually before me, but what others had seen, and I thought I ought to see, I left myself, during the greater part of the time, purposely ignorant of the literature of Digitalis, only reading it up after most of my experiments had been already performed, and then learning that many of my observations had been already made by various experimenters, whose results they only confirmed.

Here I gladly take the opportunity of acknowledging my great obligation to Dr. Maclagan, who first suggested this subject to me, and by kindly allowing me the use of his laboratory, has enabled me to make experiments I would otherwise have been obliged to leave untried; to Dr. Gamgee, for the great, indeed, essential aid he has afforded me by advice, instruments, and personal assistance; to Dr. Christison, for help given me by books and specimens; to several of my fellow-students, especially to Messrs. Downie, Maclean, and Nicolson, for the assistance they rendered me in the performance of my experiments; and to Mr. Salom, Optician, for the use of his Weather Tables.

March, 1868.

ON DIGITALIS.

As we review the rapid progress made within late years by physiology, pathology, and other departments of medical science, and compare it with the slow advance of therapeutics, we experience a growing dissatisfaction with our present empirical method of treatment, which, consisting, as it does, in the mere tentative administration of drugs without a definite knowledge of their action, must necessarily retard progress, the same medicine being tried time after time by different physicians, and the panacea of one generation being discarded by the next, only to be again resorted to and trusted in by a third.

Turning from this unsatisfactory method, we begin anxiously to look for one of a more rational character, which shall be based not only on a knowledge of the changes induced by disease, but on a minute and accurate acquaintance with the action of the remedies which we prescribe for its cure.

At present, however, our knowledge of their action is extremely vague and superficial, consisting, in the majority of cases, chiefly of the external symptoms manifested by animals under the influence of poisonous doses, and of the changes observed after their administration in disease, when it is often extremely difficult, and sometimes impossible, to say how much is owing to the drug, and how much to the natural course of the malady.

Perhaps no better example of the imperfection of our knowledge can be given than the views entertained respecting digitalis, for although it is in daily and hourly use, and, for several years back, hardly a month has passed without an article upon it in one or other of the medical journals, it is regarded by some as weakening the heart's action, by others as strengthening it, some placing it at the head of the list of diuretics, others denying that it possesses this property at all;

and even when two authorities agree as to the results produced by it, their views as to its *modus operandi* are of the most dissimilar nature. Such being the state of our knowledge of this valuable medicine, I have been induced to make the following investigations with the view of deciding some at least of the disputed points; and if I have not done so much as I would wish, I trust that my labour may not be entirely in vain, but prove, at least, a stepping-stone towards the desired end.

HISTORY.

So striking is the appearance of this elegant plant, with its tall stem rising from the midst of a thick bunch of downy leaves, and gracefully bending at the top under the weight of its beautiful purple bells, that it is imposible to believe the ancient herbalist would have passed it over in silence. As no notice of it is found in their works, we are led to believe that they were unacquainted with it. Its popular name of Foxglove* occurs in Saxon writings of the 11th century; but it seems to have been unknown to the learned till near the middle of the 16th, as it had no Latin name till 1535, when Fuchsius, professor of medicine at Tübingen, gave it that of Digitalis, which it still retains. It seems formerly to have enjoyed a great reputation as an external application† for the cure of wounds and scrofulous ulcers,‡ and for causing the absorption of scrofulous glandular enlargements.§

The internal administration of its juice has been noticed as a remedy for scrofula by Van Helmont,‖ Haller,¶ Fourcroy,** and Merz.††

According to Lobel, digitalis was employed on account of its

* Pereira's *Mat. Med.*

† Ferrein, *Matière Med.*, tome iii, 1770, p. 67. *Vide* Homolle and Quevenne, p. 139.

‡ Geoffrey, *Trait. de Mat. Med.*, 1743, tome vi, p. 202 (H. and Q., p. 140).

§ Ferrein, *op. cit.*

‖ *Apparatus Medicarium*, 1776—1794 (H. and Q., p. 138).

¶ *Hist. Stirpium Indig. Helvetiæ*, 1768 (H. and Q.).

** *Encyclopedie Methodique*, tome v, p. 456 (H. and Q.).

†† *Dissert. Inaugural, Jena*, 1790 (H. and Q.).

emetic and cathartic properties by the peasantry of Somersetshire as a cure for fevers. Ferrein* alludes to these properties, and observes that it was reckoned a cure for inveterate apoplexy, but ought only to be administered to robust persons. It occurs in the list of simples of the London Pharmacopœias for 1650, 1678, 1682, and 1721, is excluded from that of 1746, but appears again in 1788, and in that of 1809 it is not mentioned merely, but the preparation of its tincture and infusion are described, and in all subsequent editions it has held a prominent place. At an early period it seems to have been less used on the continent than in England, as it is absent from the Pharmacopœia of Leyden for 1718. Drake affirms that its action as a diuretic was unknown till 1770, and in 1775 Withering wrote the first monograph on its action as such, noticing also its power of lowering the pulse. From this latter property it began to be used in hæmorrhages, and Ferriar,† giving it for hæmoptyses in the early stages of phthisis thought that it also prevented the farther formation of tubercle—Beddoes,‡ Drake,§ Fowler,‖ Mosman,¶ Barr,** Maclean,†† and Darwin,‡‡ have all recommended its use in phthisis, and Brinton§§ says that it is the best remedy for hæmorrhage from cavities in its advanced stages. Ferriar‖‖ thought it useful in inflammatory fever, and Currie,¶¶ Thomas,*** Rasori,††† Hirtz,‡‡‡

* Ferrein, *op. cit.*

† Ferriar, *On Digitalis.*

‡ Beddoes, *On Consumption, Digitalis, and Scrofula,* 1801 (H. and Q.).

§ Drake, *Letter to Beddoes* (H. and Q.).

‖ Fowler, *Letter* (H. and Q.).

¶ Mosman, *Essay on Scrofula, Glandular Consumption, and Observations on Digitalis* (H. and Q.).

** Barr, *Letter to Beddoes* (H. and Q.).

†† Maclean, *Med. and Phys. Journ.*, lxv, p. 180–201 (H. and Q.).

‡‡ Darwin, *vide* H. and Q., p. 323.

§§ Brinton, quoted by Handfield Jones in *Clinical Remarks on Functional Nervous Disorders.*

‖‖ Ferriar, *op. cit.*

¶¶ Currie, *Medical Reports.*

*** Thomas, *Practice of Physic.*

††† Rasori, *Annales de Therapeutique de Rognetta,* 1845 (H. and Q.).

‡‡‡ *Bulletin de Therapeutique,* February 28 and March 15 (*vide Year Book of Sydenham Society,* 1862, p. 110).

Millet,* Oppolzer,† Schneider,‡ and Traube,§ all hold the same opinion. In continued fever, it has been recommended by Clutterbuck,‖ and in bad cases of typhoid fever by Wunderlich.¶ It has been proposed as an antiperiodic in ague by Davy,** Graffeneuer,†† and Gerard,‡‡ and Bouillaud§§ has treated between 40 and 50 cases successfully by it. It has been recommended in hemicrania by Debout‖‖ and Serre,¶¶ and it was found to be highly efficacious in neuralgia by Boison*** and Hardwicke.††† According to Thomas,‡‡‡ it effects a permanent cure in epilepsy, and Parkinson,§§§ Moll,‖‖‖ Corrigan,¶¶¶ Crampton,¶¶¶ Sharkey,¶¶¶ Neligan,¶¶¶ and Duclos**** have employed it with success. Dr. C. L. Robertson†††† finds it extremely useful in the second stage of general pareses of the insane. Mr. G. M. Jones,‡‡‡‡ of Jersey, employed it in large doses in

* Millet, *Bullet. de Therap. Ann. par Jomain*, 1860, p. 55 (*Sydenham Society Year Book*, 1860, p. 221).

† Oppolzer, *Canst. Jahrb.* vol. iii, p. 273 (*vide Sydenham Society Year Book*, 1860, p. 219).

‡ Schneider, *Annuaire de Thérapeutique*, 1859, pp. 82-88 (*Sydenham Society Year Book*, 1859).

§ Traube, *Deutsche Klinik*, No. 47, 1859, *Canst. Jahrb.*, vol. iii, p. 273 (*vide Sydenham Society Year Book*, 1860, p. 219).

‖ Clutterbuck, *Inquiry on the Nature and Seat of Fever*, 1807 (H. and Q.).

¶ Wunderlich, *Med. Times and Gaz.*, 1862, p. 2040.

** Davy, *vide* H. and Q., p. 324.

†† Graffeneuer, *Merat and Delen's Dict. de Mat. Med.*, tome ii, p. 645-47 (H. and Q., p. 324).

‡‡ Gerard, *Thesis Montpellier* (H. and Q.).

§§ Bouillaud, *Traité de Nosographie Médicale*, 1846, tome iii, p. 471, and *Clinique Medicale de la Charité*, tome iii, p. 236 (H. and Q.).

‖‖ Debout, *vide Sydenham Society Year Book*, 1861, p. 161.

¶¶ Serre, *Bullet. de Ther.*, April 15, 1861, and *Canst. Jahrb.*, vol. iii, p. 29 (*vide Sydenham Society Year Book*, 1861, p. 164).

*** Boison, *Bul. de la Soc. Med. de Gent*, May and June, 1861 (*vide Sydenham Society Year Book*, 1861, p. 164).

††† Hardwicke, quoted by Handfield Jones, *op. cit.*

‡‡‡ Thomas, *op. cit.*

§§§ Parkinson, *Theatre of Plants*, p. 654 (H. and Q.).

‖‖‖ Moll, *Epilepsia Digitali Sanata, Dissert. Bonn*, 1823 (H. and Q.).

¶¶¶ H. and Q., p. 144.

**** Duclos, *Bul. de Ther.*, lix, 1860, *Sydenham Society Year Book*, 1861, p. 161.

†††† Robertson, *Brit. Med. Journ.*, Oct. 3, 1863.

‡‡‡‡ Jones, *Med. Times and Gaz.*, Sept. 29, 1860.

delirium tremens; and Peacock,* Carey,† and Reid‡ record successful cases. It has long been recognised as an excellent diuretic in dropsy depending on disease of the heart, but its administration was sometimes thought dangerous when there was much weakness of that organ. Drs. Handfield Jones,§ Fuller, Germaine, and Wilks§ believe, however, that it strengthens rather than enfeebles the heart, and is, therefore, most useful when that organ is weak, and dangerous only in hypertrophy. Mr. W. H. Dickinson has found it an excellent remedy in menorrhagia, and a powerful oxytoxic. The general poisonous action of digitalis has been examined by Orfila, Bouley and Reynal, Dupuy and Delafond, Bouchardat and Sandras, Stannius, and others. Its action on the arterial tension and the heart has been studied by Blake, Traube, Winogradoff, Briquet, Kölliker, Dybkowsky and Pelikan, Eulenberg and Ehrenhaus, Handfield Jones, Fagge and Stevenson. Its influence on the temperature has been examined by Traube, Dumeril, Demarquay, and Leconte, &c.; on the metamorphosis of tissue by Winogradoff and Stadion.

Chemical History.

Up to the year 1841, when Messrs. Homolle and Quevenne succeeded in obtaining from digitalis a neutral principle in the form of a yellowish powder, presenting the bitterness and possessing the physiological action of the plant, the active principle had been sought for in vain, though several chemists believed they had obtained it in the shape of brownish or yellowish extracts, to which they had accordingly given the name of digitaline, a name afterwards applied to the substance obtained by Homolle and Quevenne.

The results of the analyses given by these gentlemen of digitalis, and their description of the characters of its constituents, are as follows:—

Digitaline.—In scales or masses—pale yellow—easily

* Peacock, *Med. Times and Gaz.*, Aug. 3, 1861.
† Carey, *Med. Times and Gaz.*, Aug. 24, 1861.
‡ Reid, *Edin. Med. Journ.*, 1864-65, p. 112.
§ H. Jones, *Assoc. Med. Journ.*, 1862, 2, p. 181.

powdered, and the powder of a yellowish colour, intensely bitter, with a peculiar faint odour, and causing sneezing if it be carelessly moved, heavier than water, and doubtfully crystallisable. It is unalterable in air, fuses at 100°, and above this becomes coloured and loses its bitterness, which is replaced by an astringent taste. It is neutral to test-paper, but gives off acid fumes when burnt. It contains no nitrogen. It is soluble in nearly 2,000 parts of cold and 1,000 of hot water It is easily soluble in alcohol and wood spirit, in about 100 parts of pure ether, in a considerably larger proportion if the ether contain water, and more especially alcohol, completely soluble in chloroform, partly in almond oil and oleic acid, and insoluble in sulphide of carbon. It forms no compounds with acids. Concentrated sulphuric acid forms a brownish solution, becoming somewhat purple, and depositing olive-coloured flakes on the addition of water. With hydrochloric acid it forms a light green liquid, becoming darker as it stands, and lessened but not changed by the addition of water. Its aqueous solution is not precipitated by bichloride of mercury, acetate, or subacetate of lead, nitrate of silver, perchloride of iron, chloride of gold or platinum, or acetate of copper.

Digitalose.—This has a white crystalline—almost micaceous—aspect. Its point of fusion is 200°, and it is soluble in concentrated sulphuric acid, giving it a pale yellow colour, but forming with dilute acid a rose-coloured solution. It is neutral, tasteless, soluble in alcohol and ether, insoluble in water.

Digitalin.—This is a white neutral powder, soluble in alcohol, insoluble in water, insipid or faintly bitter; furnishing to water a transparent material in which this bitterness resides. Its alcoholic solution is precipitated by caustic potash.

Digitalide.—This occurs in pale, gummy-looking scales, is neutral, soluble in water and feeble alcohol, slightly in strong alcohol, insoluble in ether. Its taste is sweetish, with a bitter after-taste. Is perhaps the bitter part of digitalis, which is soluble in water, along with colouring matter. It is also precipitated by caustic potash, and distinguished from digitalin by its form.

Digitalic Acid.—White, crystallisable, and of an acid taste and peculiar odour, becoming suffocating under heat, soluble in water and alcohol, slightly in ether, decomposes in air, and becomes brown with extreme facility: the decomposition being favoured by light and alkalis.

Antirrhinic Acid.—This is volatile and oily in appearance. Besides these, there are *Digitaloic Acid*, *Tannic Acid*, *Sugar*, *Pectin*, an albuminoid azotised matter, a crystallisable orange-red colouring matter, chlorophyll, a volatile oil, and ligneous fibre.

The process they employed for the extraction of digitaline, was to precipitate a watery infusion of digitalis by subacetate of lead, to remove the excess of lead by a mixture of carbonate and phosphate of soda, and the lime by oxalate of ammonia. To the filtrate they added tannin, and the product of this was mixed with litharge, dried, powdered, and treated by alcohol. This was then evaporated, and the residue was treated with concentrated ether, which dissolved the other principles and left the digitaline. This process, as modified by O. Henry, and adopted in the British Pharmacopœia, consists in treating the syrupy alcoholic extract with acetic acid, decolorising by animal charcoal, precipitating by tannin, decomposing by litharge, and thus freeing the digitaline which is decolorised by animal charcoal and purified by ether.

The composition of digitalis has been examined by many other chemists, especially Radig, Morin, Buchner, Kossman, and Walz.

Walz* has obtained as volatile principles digitalosmin and digitalissic acid (valeric acid), and as non-volatile principles digitalin, digitasolin, digitalacrin, digitaloin, and digitaloic acid. Digitalosmin is the odoriferous principle of digitalis, and is a camphoroïdal substance obtained as a fatty film by distilling with water. When the crude digitaline, obtained after decomposing the tannin precipitate with litharge, is treated with ether to purify it, an acrid matter is dissolved, to which Walz at first gave the name of digitalacrin, thinking it a simple substance; but has since found that from it may be separated digitaline

* Watt's *Dict. Chem.*, Art. "Digitalis."

fat or digitaloin in white crystalline scales, which melt to an oil at a gentle heat, and digitaloic acid in white nacreous laminæ. The residue left by the ether, and which constitutes commercial digitaline, consists of two substances: one of which is much more readily soluble in water than the other. This soluble part is yellowish and amorphous, soluble in 120 parts of cold and 40 of boiling water; is said by Walz to be the active principle, and is called by him digitaline; others call it digitasolin. The insoluble residue is called by him digitaletin, but others called it digitaline. It is still doubtful if all these bodies are really distinct or have been obtained quite pure, but Walz's analyses and formulas agree well. Kossman has given the name digitalic acid to an acid in digitalis, and also to a product of boiling digitaline with soda, lye, or lime.

The name of the active principle has been spelt by Homolle as digitaline with a final e, and by English writers indifferently as digitalin* and digitaline.† It is to be regretted that Homolle gave such similar names to different bodies, and also that other chemists have given different names to the same body, as for example, Walz, who calls the pure active principle digitaletin. I have retained Homolle's orthography.

That digitaline is the active principle, or at least contains it, has been shown by the physiological experiments and clinical experience of various observers, among whom may be mentioned Messrs. Hervieux, Shohl, Sandras, Bouillaud, Andral, and Lemaishe, Corvisart, Laroche, Duroziez, and Mandl, who have found that it produced the same effects as the plant itself, both as a poison and a medicine.

Digitaline is estimated by Homolle and Quevenne as being 100 times as strong as the leaves of the plant; but Stadion reckons it as only 30 times as strong, and from the trials I made on myself I am inclined rather to agree with the latter estimate. In order to determine whether there was no other diuretic principle in digitalis, on account of which it might be preferable to administer the plant itself, or one of its pharmaceutical preparations,‡ M. Homolle made experiments on the

* *Brit. Pharm.* † Garrod, *Mat. Med.*

‡ *Arch. Gen.*, 5 ser., vol. xviii, p. 5, July, 1861 (*vide Sydenham Society Year Book*, 1861, p. 434).

products obtained from the plant by various solvents. The first substance was the residue, after exhausting the leaves with weak alcohol; the second, the substance taken up from the alcoholic solution by ether, consisting chiefly of a nauseous, fœtid, and acid principle, resembling the digitalic acid of Kossman; the third was the alcoholic solution after treatment with ether; the fourth is obtained by treating the result of evaporation of No. 3 with chloroform.

No. 1 he found to be comparatively inert, the result of taking 3 grams, or 46 grains, being only equal to 1 milligram of digitaline, which is, therefore, 3,000 times stronger. After taking 45 centigrams, or about 7½ grains of No. 2, he had no symptoms for eight hours, but was then seized with great nausea, faintness, and vomiting, which continued at intervals of 15 minutes for 30 hours. Next day his pulse had fallen, and, on the fourth day, was as low as 48. Vision was impaired, and he could not look steadily at a bright object. Urine was abundant, but the bladder's contractility was impaired, and external pressure was required to expel the urine. He had pulsation of the abdominal aorta, anxiety, epigastric constriction, and cough, with pneumonic expectoration, lasting for a week: but these, he thought, were caused by the continuous vomiting. About a year after this he took 2 centigrams, or about one-third of a grain of No. 3. He repeated the dose in 40 hours, and again after eight hours more. The symptoms were exactly those of digitaline. No. 4 had exactly the same action, but was much more powerful. M. Homolle concludes that digitaline is the only principle in digitalis which has any therapeutical value, that the greater toleration of the stomach of preparations made by water, is from the absence in them of the nauseating acrid principle (digitalic acid) contained in No. 2, that digitalis owes its sedative and diuretic effects entirely to digitaline, but that its nauseating effect, and probably the impairment of vision it produces, are due to digitalic acid. M. Homolle seems to prove that digitaline is by far the most important and active of the principles contained in digitalis, as the fall of the pulse, noticed after taking No. 2, may have been produced by digitaline contained in it; but as I experienced impairment of vision and nausea

after taking digitaline, which I had got from Mr. Morson himself, who said it had been carefully prepared, and might be relied on, I believe these effects may be produced by digitaline, and are not, as M. Homolle seems to think, entirely owing to digitalic acid.

Physiological Action.

On Plants.—Marcet* found infusion of digitalis in a few seconds caused a slight crisping of the leaves of a haricot plant introduced into it by the root, and next day the plant was dead. On treating a haricot in the same way with solution of digitaline ($\frac{3}{20}$ths of a grain in ℥ii of water), I did not notice the sudden crisping of the leaves, which, however, in the course of a day became dry and rough, in two days were rolled in at the edges, and finally became quite dry and shrivelled, but retained their natural colour.

On Animals.—As the general action of digitalis, in varying doses, has been carefully examined, and the sequence of symptoms accurately noted by Messrs. Bouley and Reynal† in their experiments on horses, I subjoin their account of them.

Six or eight hours after giving a large dose of digitalis to horses, they stand at the stretch of their halter, sad, dejected, and without appetite, and their coat lustreless and rough. Then signs of general excitement appear. The conjunctivæ are injected and of a bright red, the eyes brilliant and fixed, the face pinched, the nostrils dilated and quivering, respiration hurried, the number being 15 to 20 or 25 in a minute, circulation more rapid, the beats of the heart being abrupt, their energy much increased, and accompanied, after a certain time, by a vibratory thrill, with a decided metallic tinkling, and, as poisoning goes on, a distinct bellows murmur becomes audible, and is rendered louder by any exertion; the beats then show a decided intermittence, and the pulse is small, thready, and intermittent. The heat of the body is increased, and hot sweats appear on the ears, nose, shoulders, and flanks. The mouth is hot, and filled with saliva, which is sticky and scanty. The tongue is of a

* *Annals de Chem. et de Physique*, v, xxix.

† *Recueil de Med. Veterin. Pratique*, 3 ser., tom. e vi, p. 207, 1859 (H. and Q.).

purplish-red at its tip and edges, and is covered on the dorsum by a thick coat, which gives it a leaden hue, the fæces are of their normal form or colour. During the first 12 hours the animals often show signs of transitory intestinal pain.

At the end of 24 or 36 hours the stage of excitement has passed, and the animals become comatose, their heavy heads hanging down towards the litter, or kept at the bottom of the manger completely insensible to external noises or stimuli, their eyes fixed, without movement or expression, sometimes half covered by the falling lids, and at other times haggard and ready to start from their orbits, the pupils greatly dilated, and the conjunctivæ, previously of a bright red, are now of a violet brown, and their secretion dried up. The previous acceleration of the respirations is now succeeded by great slowness, their number descending to 8, 7, or even 6 per minute, and being deep, broken, and trembling. The heat of the body is diminished, the sweats stop, and the skin becomes cold. The fæces are now of a browner character, and covered with a layer of mucus more or less thick. The urine is at first suppressed, but at the end of 36 or 48 hours is passed in abundance, pale, clear, and inodorous, voided very frequently, and in small quantity at a time. There is great muscular weakness, staggering gait, oscillation of the posterior extremities, and a kind of paralysis, which slows their movements. In some there are slight vertigoes, in others spasmodic fibrillary contractions of muscles of the face and of the alae nasi. The severity of the symptoms rapidly increases. The muscular weakness becomes extreme, the legs are no longer able to support the weight of the body, and the animal falls *en masse*. The respiration becomes more disturbed, sometimes jerking, difficult, and plaintive, most frequently very slow, but in some instances slightly accelerated. In some it presents a remarkable intermittency, and its time of stoppage coincides with that of the heart when the latter also intermits.* In some cases 24 to 36 hours before death, there has been noticed a paralysis of the lips, chiefly the upper, and a thick and stringy saliva flows from the mouth. Diarrhœa appears, and quantities of a very fœtid, soft, blackish paste

* This also occurs in dogs.—Exp., Appendix.

are discharged, and when the intestinal canal is completely emptied, the diarrhœa becomes serous, the expelled matters being liquid, blackish, and of a repulsive odour. The skin becomes icy cold, the thermometer introduced into the mouth, rectum, or subcutaneous cellular tissue standing in some cases at 31·5° C., or even before death at 25° C. Death generally comes on quietly, but is sometimes accompanied by unconnected movements.

When given in doses less rapidly fatal, so that each dose would only produce slight symptoms, which would soon pass away if the dose were not carefully repeated, the influence which it exerts on the circulation is by far the most prominent phenomenon. At first there is slight excitement of the heart, and its pulsations are a little quickened, then, later on, they undergo a remarkable diminution, falling to 25 or even 20 per minute. If the dose be still repeated, the beats become quicker and more energetic, rising to 55, 60, 65, and 70. The cardiac sounds are more clearly heard, more distinct from each other than normally, and following a different rhythm, there being occasionally intermittences, usually after the same number of beats, but this number varying in different subjects, and in the same subject according to the date of the poisoning. There may be five or six pulsations between the intervals in some, 15 or 16 in others, and in yet others the intermissions are completely irregular. As the poisoning goes on, metallic ringing appears, and becomes more and more distinct and sonorous. Still later, a vibratory thrill appears, and is followed by a bellows murmur. As death approaches the beats of the heart become more and more rapid, being 92, 100, or even 114. The beats of the pulse correspond in time to those of the heart; but as the latter increase in energy, in the same ratio the former become more and more feeble, and less and less perceptible, till at last, when poisoning is complete, it becomes completely imperceptible.

In doses so small as to have no poisonous effect, its action is shown first on the urine and secondly on the circulation. To show this, Messrs. Bouley and Reynal give the following typical case:—

A Hungarian horse of an excellent constitution, employed in the service of the veterinary school of Alfort, aged 10 years.

Normal state at time of experiment:—Respirations 16, pulse 37, full, mucous membranes rosy, digestive functions intact,—all the signs of health.

Jan. 1, 1849, 10 A.M.—6 grams (93 grains) of digitalis powder were given in an electuary, when the animal was completely fasting. 2 P.M.—Respirations 14; passed water, which was clear and plentiful. 6 P.M.—Respirations 13; pulse 35. The water is always passed in abundance, and with the same limpidity. The next day the effects had disappeared.

Jan. 4, 10 A.M.—6 grams given as before. At the time of giving, respiration 16, pulse 37. 3 P.M.—Respirations 14; urine clear, abundant, and odourless. 6 P.M.—Respiration, circulation, and urinary secretion the same. 8 P.M.—Respirations 13; cardiac beats a little diminished in intensity—otherwise quite healthy.

Jan. 5, 7 A.M.—Conjunctivæ pale, pulse 22, small and not well felt; the beats of the heart have diminished in intensity, remain quite distinct, marked intermittence after each beat; respirations 6 to 7. Noon.—Same state. 2 P.M.—Pulse 25, intermittence less sensible; respirations 11; urine always clear, less abundant. 7 P.M.—Lying down quietly, the litter much soaked with urine; pulse 30; intermittence has disappeared; respiration 15.

Jan. 6.—All the symptoms of the medicine disappear, and the functions return to their normal state.

Jan. 8.—6 grams of digitalis. At the moment of administration, pulse 30; respirations 10 to 11; thermometer in rectum 38·75° C., and 31·25° C., in the nasal cavities—all the signs of health. 1 P.M.—Nothing particular. 4 P.M.—Pulse 28; no change in the rhythm of the heart; respirations 10; urine clear, and in considerable quantity, 36·25° C. in rectum; a little tenderness of abdomen. 8 P.M.—Appetite good; pulse 26; cardiac pulsations ringing; respirations 14: urine always abundant.

Jan. 9.—Conjunctivæ pale; pulse 24, small, hardly sensible; beats of the heart enfeebled; respirations 6; temperature 36·25° C. 2 P.M.—Mucous membranes more coloured; pulse 30;

beats of the heart more intense; respirations 12; urine less abundant and less limpid. The functions now began to return little by little to their normal state. In almost every case which they experimented on, the history was exactly the same. In these experiments we note a steady diminution of the respirations, temperature, pulse, and intensity of cardiac beats, with increase of the amount of urine, these effects reaching their maximum in 24 to 36 hours, and then gradually disappearing. The effects of digitalis upon other mammals and man seem, *cæteris paribus*, to correspond closely to those on horses, except that in the latter, and in herbivora generally, there is no vomiting.

Having given this description of its general action, I will now consider its action on various organs more in detail.

On the Blood.—Majendie* states that decoction of digitalis, when mixed with blood, prevents its coagulation, and Thackrah,† that it suspended coagulation, and the clot at length resulting was black. Davy says that ʒss. of extract of digitalis in ʒj of water, added to ʒii of blood as it flowed from the arm, gave it the consistence of paste; after 36 hours it appeared much the same; on the following day, the lower part was more viscid, as if from subsidence of fibrin—it was coagulated on dilution with water. It is impossible to draw any definite conclusion from these statements, as to whether it has any specific action on the blood or not, as the prevention or suspension of coagulation in the first two cases may have been merely from dilution, and the black colour of the clot may be due to the colouring matter of the decoction. In the third case, the prevention of coagulation seems due to the viscosity induced by mixing the sticky extract with the blood, and as soon as this mechanical effect was removed by dilution, the blood coagulated. Orfila† found, that after poisoning dogs with watery extract of digitalis, the blood was fluid in all the five cases in which he mentions its condition. He concludes that "alcoholic (resinous) extract appears to act especially on the heart or blood, since this fluid is *constantly* found coagulated immediately after death, whenever

* Quoted by *Lancet*, 1837.

† *Orfila's Toxicology*, by Waller, 1817, vol. ii, p. 231.

this extract has been applied to the cellular tissue, or introduced into the stomach." This conclusion appears to be rather more general than facts, at least those which he details, warrant, as in five cases he found the blood coagulated in both ventricles only in one case, in the right ventricle completely in one, and partially in another, while it was fluid in the left ventricle in both these cases, and in both ventricles in two others. In four cases in which dogs were poisoned with digitaline, I found the blood coagulated in the right ventricle, the other being empty in one case, partly fluid and as if curdled in both ventricles in another case, and quite fluid in two others.

What is wanted in this subject, however, is not so much loose observations of this sort, but definite experiments on the changes of the chemical relations of the blood in regard to the interchange of gases, such as Bernard made in reference to woorari, and Harley has lately been doing with several of the organic alkaloids.

On the Circulation.—Before considering the effect of digitalis on the circulation, it may be advisable to glance at the cause of the pulse, and the arterial tension and the modifications they undergo.* The pulse is the feeling of a sudden rise experienced by the finger when it presses on an artery, and is caused by the wall of the vessel, which had lost its cylindrical form under the pressure, becoming tense and hard each time that the arterial tension is raised by a systole of the heart, and tending to regain its original form in which all the points in its wall offer an equal resistance to the intense pressure of the blood within.

The arterial tension on which the pulse depends, is the force expended by the heart, put in reserve by the aorta and large arteries, and regulated by the elasticity of these vessels. If the arterial system were empty, and the heart began to beat, the blood which it sent into the arteries would remain there, very little escaping by the capillaries,† as the arteries would have no tendency to contract and press it on between each systole. As

* Marey, *Physiologie Médicale de la Circulation de Sang.*

† Wherever I use the word capillaries, I do so in a general sense, and without entering into the question as to the difference between capillaries properly so called, and small arteries, so that if contractile power be denied to capillaries proper, the word may be read "small arteries."

they became fuller, however, their elastic force or the arterial tension would increase, sending more and more blood through the capillaries, till the quantity escaping through between each systole exactly equalled the amount driven in each time. The arterial tension would then remain nearly fixed, or at least steadily oscillating round one point, becoming somewhat increased as each wave of blood was sent in from the heart, (each wave being equal, not only to the blood escaping by the capillaries during its continuance, but to that escaping during the interval, in addition; this additional amount of blood distends the arteries, and increases their tension), and becoming somewhat diminished as it escaped from the capillaries. The arterial tension may be altered in two ways: (1) If, *while the cardiac pulsations remain the same* (*a*) the capillaries be somewhat dilated, the blood will escape more quickly, and the tension will be diminished. (*b*) If the capillaries be contracted, less blood will escape, and the tension will be increased.

(2) The *capillaries remaining the same*, (*a*) if the beats of the heart be reduced in number, less blood is sent in, and the tension falls; if they be increased, the tension rises. (*b*) If the wave of blood sent in at each pulsation be increased in size, the tension rises; if it be reduced, it falls. The arterial tension or force with which they tend to drive the blood through the capillaries, is easily measured by the hæmadynamometer, and its amount expressed in inches of mercury. It is obvious, then, that the arterial tension is the product of *two* factors, viz.—1. The amount of blood pumped into the arteries by the heart in a given time. 2. The amount of blood escaping through the capillaries in the *same* time. This was clearly enunciated by Blake,* and more fully worked out by Marey. The first factor depends on the amount of blood in each wave, multiplied by the number of waves in the given time. The second, only on the size of the capillaries, and the rapidity of the flow of blood through them, and this latter, again, depends on the arterial tension.

Influence of Respiration on Arterial Tension.—If inspiration and expiration be made with difficulty, as, for instance, by

* *Edin. Med. Journ.*, 1839.

closing one nostril, and thus obstructing the passage of air, the arterial tension *rises* with *ex*piration, and *falls* with inspiration. But if respiration be freely performed as with open mouth, the tension *rises* with *in*spiration, and falls with expiration. This difference is due to the pressure upon the aorta and large vessels of thorax and abdomen.

The enlargement of the thoracic cavity during inspiration causes a vacuum which is at once filled by the external air, if there be no obstacle to its entrance, and thus no great suction is exerted. If the air enter with difficulty, the enlargement of the thoracic cavity by the respiratory muscles acting like the withdrawal of the piston of an exhausting syringe, greatly lessens the internal pressure, and causes much suction, the blood is drawn to the aorta and large vessels of the thorax from the periphery, and the tension is much diminished. During expiration, the contractility of the lung and the expiratory muscles combine to expel the air; but this being done with difficulty, the aorta and large vessels are much compressed, the blood driven towards the periphery, and the tension raised. While this is going on in the thorax, the diaphragm descends into the abdomen during inspiration, lessening its cavity and pressing on the abdominal aorta and increasing the tension, while, during expiration, it ascends, lessening the pressure, and, consequently, the tension. In a normal state, the thoracic and abdominal pressures counteract each other; but when there is any obstacle to the passage of air, the thoracic influence predominates, and the abdominal, when there is any hindrance to expansion of the abdominal parietes. In the normal state of the animal economy, the number of the pulse and the arterial tension are in inverse ratio to each other, the law given by Marey on this point being, "The heart beats so much the more frequently the less the difficulty it has in emptying itself."*

I have entered at length on this question of arterial tension, as a knowledge of the facts I have stated is necessary in order to understand fully the way in which the circulation is modified by digitalis.

On the Pulse.—When given in small doses, digitalis first

* Marey, *op. cit.*

reduces the number of beats without rendering them irregular. If its influence be pushed farther, the pulse remains slow, but now and then a quick beat is interpolated.* These quick beats, as the influence increases, become more numerous, so that the slow beats which now occur only occasionally become intermissions; and in a still further stage, the slow beats entirely disappear, and the pulse becomes regular and extremely rapid.

This slowing, intermission, and final rapidity have been frequently examined in animals, and though I am not aware that the gradual succession of the quick beats to the slow, which occasions the intermittence, has been shown, probably from the readiness with which it would escape the observation of the finger, though at once detected by the eye, yet we see it with great clearness in the case of Daniel G., and though this was not during the increase but the decrease of the symptoms, I think we may infer that these came on very much in the same order in which they went off.

Some have held that there is an acceleration of the pulse before the retardation appears. Bouley and Reynal† noticed this in horses poisoned with large or moderate doses, but never observed it after therapeutical doses had been given. The doctrine of primitive acceleration from medicinal doses was advanced by Sanders,‡ and supported by Joerg§ and Hutchinson.‖ This acceleration is of two kinds—1st, following on the administration of digitalis, and disappearing, or at least diminishing, much within half-an-hour or three quarters; and 2nd, a more permanent acceleration lasting for 24 to 48 hours or longer: the effect of the temporary acceleration not passing quite away during the interval between the doses, so that each succeeding one raises the pulse a little higher than before, till at last the acceleration gives place to retardation, and the number gradully falls, passing even below the normal standard. Though Sanders adduced 2,000 observations in support of his view, yet most succeeding authors have denied it. I have

* Case of Daniel G.

† *Op. cit.*

‡ Sanders, '*On Foxglove.*'

§ Joerg, *Arch. de Med.*, prem. ser., tome xxvii, p. 107 (H. and Q.).

‖ Hutchinson (H. and Q.).

occasionally found my pulse increased after taking digitaline, but sometimes not; and even had the acceleration been frequent, I would not have been able to conclude very much from it, as the pulse varies not only with position but with mental states, and that to a considerable extent in a person of nervous temperament. As to the secondary acceleration, it is perfectly true that you often find, on looking over a table of the pulse, a seeming acceleration of the pulse on the second or third day after beginning to take digitalis, yet it is to no great extent and not greater than we find in health.

Though the primitive acceleration be denied by almost all authorities, few doubt that digitalis causes retardation of the pulse either immediately or in the course of a few days. I have found that my pulse was sometimes quicker, sometimes slower, while I took small doses of digitaline, but that under larger doses there was marked lowering of the pulsations.

This lessening of the number of beats may have two causes:— 1st, it may be central, from the heart being primarily affected by the drug, and contracting more slowly; 2nd, it may be from contraction of the capillaries opposing greater resistance to the passage of blood, and by thus requiring greater propulsive force, slowing the heart's action according to the physical law, that what is gained in power is lost in speed. If the latter were the case, the blood flowing slowly through the capillaries would cause the arteries to become full and tense, the heart would be able only slowly to distend their resisting parietes, and that only to a small extent; so that if we applied a sphygmograph to the artery, we should find the line of ascent very oblique, the height of the curve small, and the line of descent also very oblique. But this is not the case, for if we examine the tracing taken on March 15, we observe that while the pulse is slow and the duration of each beat long, it presents the very opposite characters of those we have mentioned, the line of ascent being sudden and abrupt, the lever rising so rapidly that its *vis viva* carries it too far, so that in its descent it makes a point; the height of the curve is great, and the line of descent is sudden and dichrotic. We see that the pulse in Daniel G. presents the same characters. From these facts I

believe we cannot avoid the conclusion that it exerts a slowing action *directly* on the heart.

In poisoning by digitalis the force of the pulse bears no relation to that of the heart's impulse; for while the latter is strong and hammering, the former is small, thready, and nearly imperceptible. Marey* gives this law, "The force of the pulse is not in correspondence with the energy of the ventricular contraction, but is regulated by the state of the circulation in the ultimate ramifications of the vascular system." The force of the pulse increasing with the arterial tension and diminishing along with it, the weak pulse that occurs in digitalis poisoning is due to the low tension: and this, again, as we shall see hereafter, probably depends on the relaxation of the capillary system, and the rapid transit of blood through it.

On the Heart.—Having seen that digitalis exerts a primary influence on the heart, the question now arises, What is this action? And, first, as to its force. Does digitalis weaken the muscular power of the heart? Does it increase it? or does it do neither, but simply lessen the number of pulsations, either by diminishing its irritability, and so rendering it less sensitive to the stimulus of the blood, or by increasing the power of the regulating part of the nervous system?

Very different opinions have been held on these points by different authors. Stannius† says, that after the injection of a strong dose of digitalis, there is at once a surprising feebleness of the cardiac pulsations, which soon changes into paralysis of this organ, at first partial and then complete; and this he attributes to paralysis of its muscular contractility, rather than to any affection of its nervous arrangements.

Kolliker,‡ Dybkowsky, and Pelikan hold a similar view. On the other hand, many observers have been inclined, by clinical observation and physiological experiment, to think that digitalis acts rather by increasing the power of the heart; and that it causes death not so much by paralysis as by spasmodic contraction. Among others who have held this doctrine of stimulation

* Marey, *Physiol. Med. de la Circ. de Sang*, p. 235.

† Stannius, quoted by Homolle and Quevenne, p. 234.

‡ Carpenter's *Physiology*, p 229.

may be mentioned Kinglake, Briquet, Handfield Jones, Fuller, Winogradoff, and Traube. This opinion has been founded on the observation that digitalis strengthens the weak and dilated heart, and is injurious in hypertrophy, on the increase of the arterial pressure often observed after its injection into the veins, and on the contracted state of the ventricles found after death constantly in frogs, but only occasionally in the mammalia. Mosman thinks that it acts by diminishing the muscular irritability of the heart, and thus lessening the number of pulsations without diminishing their force. Others believe that the slowing of its action is produced through the nervous system, and probably by an increased action of that part of it which exercises a regulating influence.

The settlement of these questions is of extreme importance, in reference to the medicinal administration of digitalis, in cases of weak heart. In order to their solution, let us consider what would be the effect of increasing the muscular power of the heart. Supposing that the size of the capillaries and the number and size of the waves of blood remained the same, but the muscular power of the heart were increased, how would the arterial tension be influenced ?

The power of the heart being greater in proportion to the resistance it has to overcome, it would act with greater abruptness, and force the wave of blood more quickly into the arterial system; and as thus less blood would escape from the capillaries during the time of its systole, the arteries would be more distended and the tension higher. This greater amount of arterial tension, in its turn, would force the blood more quickly through the capillaries at first, and the tension would rapidly diminish; but as the rapidity of the flow of blood would proportionally decrease, the amount passing through the capillaries in a *given* time would be much the same, and the mean arterial tension much the same, but the oscillation much greater. If now the capillaries be contracted, we will have the same phenomena with a higher mean arterial tension, and if relaxed, a lower tension. We would also say that when the capillaries are contracted, less blood escaping by them during the systole, there would be more surplus, and the height of the oscillation

still farther increased; but the reverse when the capillaries were relaxed. But what would be the effect of increasing the size of the wave of blood, the muscular power remaining the same? The increased quantity of blood would take longer to be driven in, the oscillation would not be abrupt, and, in fact, it would merely cause a higher mean tension. The increase of the wave, along with the increase of force, would cause a similar effect.

Intermittence or slowness of the pulse would cause greater oscillation, the long interval allowing the escape of more blood from the capillaries; the tension would fall much. From the length of the interval, the heart would have received more blood than usual, and the succeeding wave would be larger; but there being more room for it in the arterial system, it would not raise the maximum height of oscillation much, if at all, above the normal. If the force of the heart were lessened, the opposite results would take place, and the oscillations be less abrupt and of smaller amplitude.

Let us now see with which of all these conditions the effects observed from digitalis agree.

In experiment 6, a strong well-fed dog was operated on. At 3′ 48″ the respiration was 20, the pulse 84, the mean tension 5·65 inches of mercury, and the oscillation 5—6·5. A grain of digitaline was then injected into the jugular vein. At 59′ 45″ the mean tension is 5·7, or only $\frac{1}{20}$th of an inch higher, but the oscillation is now 4—8, or 4 inches instead of $1\frac{1}{2}$. This increase in oscillation we have seen can be due only to slowness or intermittence of the pulse or increase of the force of the cardiac contractions, as far at least as the circulatory apparatus is concerned, and that in the former case the maximum would not be much above the normal, which in this case it is; and therefore we would consider as proved that the force of the heart is increased, were it not that we observe the remarkable decrease in the number of respirations, and are led to inquire whether it is not to the greater influence of these, rather than to any increase of the heart's force, that the oscillations are due; and this indeed seems highly probable, as the amount of oscillation is so great that we cannot easily imagine

it caused only by a difference in the rapidity with which the blood is impelled into the arteries, and the fact that we notice, that while the average oscillation at the cardiac beats in one case is $\frac{3}{10}$ths of an inch, that at inspiration is 1 inch. Though my own observations are as yet too incomplete to enable me to eliminate the disturbing effect of respiration, and the observations of Winogradoff,* in the short abstract that I have seen of them, are liable to the same fallacy, they yet seem to render the increase of force somewhat probable. It is obvious, however, that by examining a tracing by an instrument such as the registering hæmadynometer of Setschenow, which was employed by Winogradoff, and which registers at once both the cardiac pulsations and the respirations, and comparing its indications with those which we have seen would occur from increase or diminution of the heart's force, the problem might be solved with mathematical accuracy, not only for digitalis but for any other poison.

Though unable at present thus to afford complete proof of the increase of force, there is another line of argument open, viz., the effect of increase or diminution of the contractile power of the heart upon its impulse. If the contractile power be increased relatively to the resistance to be overcome, or arterial tension, the contraction will be rapid, and the heart's impulse abrupt and strong. If the power be lessened, the contraction will be slow, and the impulse consequently weak.

Though this necessarily follows from physical laws, some might yet be inclined to urge as an objection—"But you find this strong and abrupt impulse in nervous palpitations and weakly persons, and is it to be supposed that the power of the heart is increased in these?" But in these cases, though the power of the heart be not absolutely increased, it is relatively to the resistance, for the arterial tension in these cases is low. After the administration of digitalis, we find not only that the impulse is abrupt and strong, showing increased power relative to the tension, but that the tension itself is increased (Exp. V, 3, 25′ 50″), and the absolute increase of contractile power is completely proved.

* *Year Book Sydenham Society*, 1862, p. 452.

From the nature of the impulse generally remaining much the same till the last, or nearly so, the power of the heart appears to be relatively increased all along; but as the arterial tension, though it may be increased at first, greatly diminishes afterwards, the absolute force of the heart may be, and probably is, very greatly diminished before death.

From his observations on the effect of small doses, such as slow the heart's action, Winogradoff found that no change was produced; and as I found (Exp. X, 12, 35′ 20″) that not only was there no change in the mean pressure, but none in the oscillation, and the breathing quiet, though the pulse had fallen from 140 to 78, though not certain, I am strongly inclined to believe that the force of the heart is neither increased nor decreased. Later on, and after a farther dose, as at 1.20′, I am inclined to think that it may be feebler, though possibly it is only because the pulsations are more frequent.

The observation of Stannius, that after a strong dose of digitalis a surprising weakness of the cardiac pulsations becoming finally complete paralysis is observed, may be true in regard to overwhelmingly large doses; and in the sheep, which I killed by 2 grains, the condition of the heart was not noted, but in general the impulse is increased, so generally in fact, that often I have not noted it, looking on it as to be always expected.

(2) *On the Heart's Rhythm.*—Dybkowsky and Pelikan* found in frogs which were poisoned by digitaline (or other cardiac poisons, producing an identical effect), the rhythm of the heart was at first unchanged, but soon after three, five, or ten minutes (according to the poison), irregularity was noticeable. This was of two kinds—(1.) The ventricular contractions became peristaltic, so that after the contraction of the auricles the ventricle did not contract as a whole, but first its upper third, whence the contractions gradually passed down to the apex; but before this had contracted the upper third was again dilated. Two or three minutes before complete paralysis the contractions became still more irregular, so that the upper or

* *Mém. de la Soc. de Biologie* tome iii ser. 3, p 97.

right half was dilated, while the lower or left half was contracted, and sometimes the auricles did not contract simultaneously. Finally, when the ventricle completely stopped, one or more palpitating points could still be observed in it. (2.) The second form, which was especially notable in poisoning by digitaline and green hellebore, consisted in a notable diminution of the number of beats, the heart contracting regularly, but very slowly, just as under galvanisation of the vagi. This sometimes happened before peristaltic movements occurred, or even after their appearance. Fagge and Stevenson* found that the beats are not necessarily diminished, and sometimes the ventricle contracted only once for two pulsations of the auricles, and often one part, generally the apex, continued white, and contracted while the rest dilated regularly. They also observed palpitating points such as Dybkowsky and Pelikan had described, and liken them to little crimson pouches on the white contracted ventricle. All these observers found that the ventricle stopped always in a state of firm contraction.

(3) *Impulse.*—The cardiac impulse seems almost invariably to be increased both in the lower animals and man, and becomes abrupt and hammering.

(4) *Sounds.*—When digitalis is given in poisonous doses, after the pulse becomes intermittent, a change is noticed in the cardiac sounds, there being first a vibratory thrill, and then a blowing murmur with the first sound. The first I have not observed; but Dr. Gamgee felt it in a dog on which I was experimenting. The blowing murmur with the first sound I have noticed several times. It occurs in horses, dogs, and the human subject, and probably in all mammalia. It is probably due to mitral or tricuspid regurgitation from irregular contraction of the musculi papillares. I noticed it in one dog after section of the vagi and before digitaline was injected; but unfortunately, not having listened before dividing them, I cannot say whether or not it was due to their section.

On the Arterial Tension.—In small doses, digitalis, injected into the veins, causes no change, either in the mean tension or

* *Proceed. Roy. Soc.*, vol. xiv, 270.

amount of oscillation. In larger doses it almost invariably increases the tension, sometimes very slightly, at other times considerably; and in one case of Mr. Blake's, where he injected it into the arteries, the rise was enormous, the maximum being 14 inches instead of 5. The tension attains its maximum in three or four to nine or ten minutes, and then gradually diminishes. The oscillation is generally greater at first, and also gradually diminishes. Sometimes there is a rise just before death, and the tension diminishes very slowly after the heart has ceased to beat.

On the Capillaries.—In small doses, digitalis, while it slows the heart's action, seems at the same time to contract the capillaries. If we look at the results of Exp. X, we see that, although the cardiac pulsations were reduced from 140 to 78, yet the mean tension remained the same. This can only be explained by supposing that the capillaries are contracted, or that the heart is sending in at each stroke nearly double the amount it did before. This latter hypothesis seems extremely improbable, for though the blood has longer time to collect in the heart, yet we find when the same time is given by slowing the cardiac pulsations directly, without any action on the systemic capillaries, as we can easily do by galvanizing the vagus, the arterial tension at once falls to a very considerable extent. At other times we find that the tension not only does not fall, but rises to a considerable extent, as in Exp. VI, where, at 3. 41′ the number of pulsations was 85, and the mean tension 5·65, and at 4. 4′ the pulse was 80, with a mean tension of 7 inches—a fall of four beats, with a rise of nearly an inch and a half. Few observers, if any, have noted a higher rise of the arterial pressure than $8\frac{1}{2}$ inches, which was the maximum of oscillation in this case, when they injected preparations of digitalis into the veins, so that they passed through the heart first before getting into the systemic circulation, but on one occasion in which Mr. Blake injected infusion of digitalis into the carotid, pushing it with some force, so that it entered into the systemic circulation and had thus an opportunity of acting on the capillaries before reaching the heart, the pressure rose to 12 or 14 inches. From all these facts, I think we must conclude that it really

possesses the power of contracting the capillaries which Mr. Blake assigned to it.

As the poisonous action of digitalis becomes more fully developed, the capillaries become dilated (and probably paralysed), the arterial tension falls, and, there being less resistance, the heart's action becomes *pari passu* (Bouley and Reynal) more violent, while the arterial pulse becomes more weak and small, and often seems rather a kind of indistinct wavering than decided strokes. The objection may be raised that this is due to the rapidity of the pulse, and the small size of the waves of blood; but we find that the heart is acting powerfully, and if the capillaries were either of the same size or contracted, the impulse being brisk, the waves of blood, however small, would each give a distinct stroke to the finger, as is shown by Marey.* Owing to this dilatation of the capillaries, and the easy transit of blood through them, we find that almost immediately after death the arterial system is empty, and the venous full and turgid. From the patency of the capillaries less of the force of the heart will be expended in forcing the blood through them, and we would expect to find a higher pressure in the veins, at least if the heart be not much weakened. This I have not yet been able to determine. It would be well also to see, in the web of a frog's foot, the changes caused by digitalis when applied locally or generally.

Occasionally, however, at or immediately before death, this relaxed state of the capillaries seems to give place to one of spasm, so that the arterial tension rises and continues at the same height for a considerable time after the heart has ceased to beat, diminishing very slowly as in Exps. IV and VI. This could not possibly be owing to clots forming in the apparatus, at any rate in VI; for if the tube had been stopped by one, the two columns of mercury would have found their level by the higher column decreasing, while the lower rose, and not by the upper one remaining stationary, while the lower one rose up to its own level.

Of the changes in the cranial circulation, caused by digitalis I can say nothing, several trials which I made on animals to trephine and lute in a glass plate having proved total failures.

* Marey, *op cit.*, p. 243.

On the Respiration.—Bouley and Reynal* found that digitalis given to horses in large doses at first caused acceleration of the respirations as well as of the pulse; and after this exciting action had passed away the number became remarkably diminished, falling to 8, 7, or even 6 per minute, being deep, broken, and trembling, and, in some instances, remarkably intermittent, the intermittence coinciding with that of the heart.

Messrs. Delafond and Dupuy† also noticed primary acceleration with subsequent retardation. My own observations on the respiration are extremely imperfect; and though I have no note of previous acceleration in large doses, such may have existed. In most cases, the respiration has become slower and deeper, and, in one case, in a dog (Exp. XII), I noted that it was not only slow (8 in 65 seconds), but distinctly intermittent, the intermissions being of 4 seconds' duration, and coinciding exactly as to time and duration with those of the pulse. At the time I noted this, and for a good while after, I was perfectly unaware of Messrs. Bouley and Reynal's observations.

In smaller doses, the primitive acceleration has not been noticed, and the decrease has gone on gradually from the first. In one case,‡ after injection of a small dose of digitaline, I observed acceleration of the respiration, which might have been accidental; but there was no apparent cause for it, and I had not noted it in the dog before, nor have I since, though he has been under constant observation.

In several sick persons, in whom M. Joret§ noted the respirations before and after taking digitalis there was sometimes acceleration, and sometimes slowing of the respiration; but the results show nothing, and he himself only mentions them in passing. M. Duroziey‖ has not found any slowing of the respiration.

On Digestion.—In small doses, digitalis is said to cause increased appetite.¶ While taking digitaline I have had a good

* *Op. cit.*

† *Bull. de l'Acad. de Med.*, tome xvi, p. 428 (H. and Q.).

‡ Exp. XI, *vide* p. 127.

§ *Archives de Med.*, 2 ser., tome iv, p. 27 (H. and Q.).

‖ *Thesis*, Paris, 1853, p. 36 (H. and Q.).

¶ Germain, *Med. Times and Gaz.*, Sept. 7, p. 250, 1861.

appetite, but I had this as well while I was not taking it; nor do I think my appetite was better after recovering from the sickness caused by the digitaline, than it was before beginning to take the drug, as Withering* found, but his observations had been made on invalids.

Its emetic and cathartic effects, when given in large doses, have been long recognised, and seem to have been the first properties to attract attention. Before these effects appear, however, there are symptoms of digestive derangement of a slighter character, consisting of loss of appetite, bad taste in mouth, borborygmi, abdominal distension, pain in the stomach, occasional nausea, and a vague desire to vomit.† When vomiting occurs, it is violent and painful. Faure‡ describes its characters, as seen by him in dogs, as being peculiar in the expulsive effort of the stomach, far from being the principal circumstances, as in vomiting from other causes is only the result of a series of convulsive contractions, beginning in the limbs, and extending, first to the lower part of abdomen, and then to the upper part and thorax, and under violent contractions the stomach is exposed to pressure, and expels its contents. The vomited matters are mixed with bile, sanguinolent mucus, and fluids of the stomach. The vomitings are intermittent, and the animal rapidly recovers from the effects of one, and seems well till attacked by another fit, the amount vomited after the first fit or or two having emptied the stomach, being very small. This description I think correct in regard to dogs, except the small share which Dr. Faure seems inclined to give the stomach in the act of vomiting; for this must be considerable, if we may judge by analogy from the human subject, as well as by the extreme pressure necessary to make the stomach reject so little as a teaspoonful at a time, unless it were contracting violently itself. The sensation I experienced, while vomiting on the morning of the 16th March, was as if the stomach were contracting with extreme violence as in cramp, much more so than in vomiting in general, and a feeling of soreness continued for some time after. The stomach was entirely empty on that

* Withering, '*On Foxglove.*'

† Appendix, March 17.

‡ *Edin. Med. Journ.*, Nov., 1864, p. 461.

occasion, and nothing (except perhaps a little mucus) was ejected. After taking 30 milligrams more, during the course of the next day, the vomiting recurred on the morning of the 17th; and on this occasion I vomited some bilious matter, liquid, and resembling somewhat yolk of egg, and the crampy contraction was less marked. Dr. Faure says that sometimes the convulsions seem directed towards the intestines, and after contractions of the limbs, &c., such as he describes before vomiting, a glairy, greenish substance, often tinged with blood, is expelled per anum. In horses there is no vomiting,* and the stools are first natural, then covered by mucus, and gradually becoming softer, are first pasty and then liquid, blackish, and fœtid. This blackish colour may be owing, however, to the colouring matter of the digitalis.

On the morning of the 17th March, shortly after vomiting, I had a loose stool, but no persistent diarrhœa, and in small doses it seems to produce constipation, and this is occasionally the case even when there is a fatal result.†

The action of digitalis on the intestinal canal is not merely local, for it produces it quite as certainly when introduced into the subcutaneous tissue or injected into the veins. The pain in the epigastrium, which I felt after the vomiting passed off, remained for several days, and just as it was going away it was succeeded by severe pain in the left side, apparently in the descending colon. At first I was afraid it was inflammatory; but when taken in connection with the peculiar form of the stool passed on the 20th March, which was that of small round pellets, like those of rabbits, I am now disposed to attribute it to spasmodic contraction of some part of the intestines similar to that which I think occurred in the stomach.

On Secretion.—On the Saliva—When digitalis is taken in rather large doses, there is occasionally a feeling of dryness in the mouth,‡ along with some salivation,§ but it is not con-

* Bouley and Reynal, *op. cit.*

† Case related by Dr. Mazel, *Gazette des Hôpitaux* (*vide Edin. Med. Journ.*, 1834–5, p. 170).

‡ Case of Daniel G.

§ Christison, '*On Poisons*,' p. 887, and Henry, quoted by Holland, *Med. Notes and Reflect.*, p. 555.

stantly observed.* I have occasionally noticed the salivation from poisonous doses.† Bouley and Reynal‡ observe that the saliva is rather thick, and flows freely from the mouth.

On the Secretion of the Nasal Mucous Membrane.—Stadion§ found that a peculiar affection of this membrane resembling corriza, was a characteristic symptom of digitaline, and I found that for some days before vomiting came on, clear drops of water were always gathering at my nose;‖ but I had no reason to suppose that I had caught cold, and I believe this increase of the secretion in my case is confirmatory of Stadion's view.

The conjunctival secretion was found by Bouley and Reynal to be dried up in poisoning by large doses.

On the Sweat.—In cases where it has been taken in doses a little too large, for some time there is usually profuse sweating.¶ In poisoning, hot sweats appear at first which, as death approaches, dry up and become cold.

On the Urine.—Since Withering first brought the diuretic properties of digitalis into notice, it has steadily kept its place as one of the best remedies under this class. But though most members of the medical profession believe that it possesses this power, M. Duroziez,** though not entirely denying it, maintains that it is much less frequent than has been alleged, and says that he has not met with a single case clearly proving it. Dr. Germaine†† goes still farther, and boldly declares that "there is no proof that digitalis possesses diuretic properties, the reputation conferred upon it to this effect by Withering having been accepted without discussion; and that the diuresis, which often follows when an amelioration of the condition of the circulation has been produced by it in organic disease of the heart, is only a mediate effect resulting from the return of the circulation to its normal condition." The observations on its diuretic effect, especially in anasarca, and to a less degree in effusion into serous cavities, are so numerous that we can hardly doubt its

* Holland, *op. cit.*, p. 555. † Exp. VI, 4, 42. ‡ *Op. cit.*

§ *Year Book Sydenham Society*, 1862, p. 451.

‖ I was then ignorant of Stadion's observations.

¶ Christison, *op. cit.*, p. 888.

** *Thesis*, Paris, 1853 (H. and Q., p. 296).

†† *Med. Times and Gaz.*, Sept. 7, p. 250, 1861.

existence. Among others who have remarked it, may be mentioned Christison, Andral and Lemaitre, and Hervieux. Several, who admit its diuretic action in disease, entirely deny its possessing this power in health,—as, for instance, Krahmer, Kluyskens, Vassal, and Shohl. Others again, as Pereira, say that it sometimes acts as a diuretic even in health. Joerg,* who experimented on several healthy persons, men, women and children, found the urine increased, with only one exception. Hutchinson, in experimenting on himself, found it increased in three experiments. Hammond, from a three days' observation, says that the amount in health was 1474 c.c., and, after taking 60 drops daily of the American tincture, found it was 1822. The amount of water in the ingesta was not determined. Bouley and Reynal, and Dupuy and Delafond noted the diuretic action in health markedly on horses. In my own case, I found that, with small doses, the urine varied just as my pulse had done, being generally increased to a slight extent while I took the digitaline, but sometimes not, while, with large doses, the diuretic effect was marked, as will appear from the following table:—

Feb. 2—14.....	1304 cub. cent.	or 45·9 oz.		Dose.	
„ 15—24.....	1326	„	46·6	„	Grains. $\frac{3}{20}$ — 10 milligrams of extractiform digitaline.
„ 25—Mar. 2..	1303	„	45·9	„	
Mar. 3—6	1216	„	42·8	„	$\frac{3}{50}$ — 4 milligrams powdery digitaline obtained from Morson.
„ 7—14.....	1421	„	50·0	„	$\frac{5}{50}$ — 12 milligrams.
„ 15&16.....	1137	„	40·0	„	$\frac{2}{20}$ — 30 milligrams, intoxication.
„ 17—22.....	1517	„	53·4	„	

From this we notice, that with the larger doses, especially of the digitaline in powder, there is a marked increase in the amount of urine before intoxication appears, then a sudden fall during its continuance, and another rise of still greater extent after it has passed off, and after the medicine had been discontinued. The actual increase in the amount of urine may to some appear small; but when it is considered that the amount

* Joerg, *Archives de Med.*, prem. ser. t. xxvi, p. 107, H. and Q.

of fluid ingested is the same, and that, in a normal condition, very rarely has a large amount of urine been passed on more than two consecutive days, the distinct and persistent diuresis from the digitaline is remarkable. Winogradoff, from his experiments on moderately large doses of digitaline, concluded that it cannot strictly be called a diuretic, as it was given for five days without marked increase in the quantity of urine. The doses given were from $\frac{3}{10}$ to $\frac{2}{7}$ of a grain. Stadion, subjecting himself to a weighed diet of milk, eggs, bread, and butter, found that during a period of 18 days, during which he took digitaline, beginning with 2 milligrams the first day, and increasing it by one each day, the urine was somewhat diminished. The amount of urine in my own case was markedly diminished during the period of intoxication, when the gastro-intestinal canal was most affected: and in the case of Daniel G., when the pulse was most affected, it fell from an average of between 40 and 50 oz. to 30 oz. on December 2, 25 and 26 oz. on the 3rd and 4th, and 18 oz. on the 5th and 6th, again slowly rising till on the 10th it rose from 25 to 44 oz., and then remained at its normal standard. In very large doses it occasionally causes not only diminution, but total suppression of urine—lasting for three days in a case quoted by Christison,* and one narrated by Mazel.† Bouley and Reynal noticed suppression in horses for about 36 or 48 hours, and then followed by abundant diuresis. In Mazel's case it is not noted whether or not there was diuresis, only that urination was performed freely; but as it was after rising to make water that death occurred, it seems not improbable that it was present. Christison thinks that the sedative and diuretic actions are mutually incompatible; but in horses Bouley and Reynal found them distinctly co-existing; and though my pulse was somewhat lowered at March 13, there was yet diuresis. It is probable, however, that when the action on the pulse is so great as to cause intermittence, the diuresis is diminished. It increases the frequency of micturition.‡

From all these observations, then, we may conclude—(1)

* *Edin. Med. Journ.*, vii, 149; Christison, '*On Poisons*,' p. 889.

† Mazel, *Gazette des Hôpitaux* in *Edin. Med. Journ.*, 1864, p. 169.

‡ *Med. Times*, 1855, p. 381.

That in anasarca, especially from heart disease, digitalis acts as a diuretic. (2) That it sometimes, but not always, acts as such even in health. (3) That when it acts upon the intestinal canal so as to cause vomiting and purging, or when it affects the pulse so much as to cause intermittence, and possibly before this takes place, diuresis is much lessened, though a moderate degree of retardation may coexist with diuresis. (4) That in large doses it causes suppression of urine, lasting in the human subject for three days.

On the composition of the urine, Stadion,* having put himself on a weighed diet of bread, butter, milk, and eggs, and determined the normal amount of his urine and of its constituents, took digitaline for 18 days, beginning with 2 milligrams, and daily increasing the dose by 1 milligram, found that the urine was not only diminished in quantity, but its specific gravity and chief solids were also diminished. The acid reaction was unaltered, but the urea, chloride of sodium, phosphates, and sulphates were lessened, and the uric acid increased. Urea was determined by Liebig's method, after the elimination of phosphoric and sulphuric acid and chorine, and the uric acid by Neubauer's method. He draws the conclusion that it causes rapid wasting of the body, and depression of the exchange of material.

Winogradoff,† from observations made for five days on several healthy persons of all ages, while taking from $\frac{3}{10}$ to $\frac{2}{7}$ of a grain in the 24 hours, found that there was no marked increase in the total quantity of urine, and in one case a diminution. In every case there was a falling off in the quantity of urea and chlorides and salts which resist calcination, but there was invariably an increase of the phosphoric and sulphuric acids. The results which I obtained will be seen from the following table, and the tables in the Appendix:—

* Stadion, *Year Book Sydenham Society*, 1862, p. 451.

† *Year Book Sydenham Society*, 1862, p. 452.

Date.	Urine.	Urea.	Proportion of urea.	Phosph. Acid.	Proportion of PO_5.	Chlorine.	Temp.	Pulse.	Sleep.	Work.		Dose.	
										Hours in laboratory.	Minutes walking.	Grain.	Milligram.
Nov. Dec. 19—12	1048	31·88	30·4	2·67	2·54	6	43·6	68	8	...	...		
13—22	1189	30·90	26	2·75	2·31	7·2	41·2	64·3	7½	5	73	1-200th	
Jan. 4—16	1190	34·46	28·8	3·14	2·74	6	34·3	78	7¼	5	72		
Feb. 17—1	1196	31·63	27·4	3·09	2·734	7·4	41·3	76	8	4½	74	1-16th	
Feb. 2—14	1304	31·90	25·4	3·14	2·577	...	38·5	71	8	3½	65		
15—24	1326	35·77	28·56	3·36	2·69	7	37·6	75·6	7½	3¾	...	3-20th	10 extractiform
Mar. 25—2	1323	33·95	26·1	3·26	2·5	7·6	38·2	71·4	7	4¾			
3—14	1352	35·46	28·5	3·09	2·64	6·6	36·8	68	7⅓	4	...	6-50th	9·6 Morson's
15 & 16	1137	35·18	30·4	3·11	2·75	5·7	38	65	8	2½	85	9-20th	30
17—22	1517	37·49	24·7	2·88	1·9	8·4	37·7	66	8	3			

In determining the amount of urea, chlorine, and phosphoric acid, I used nitrate of mercury for the two first, and nitrate of uranium for the last, according to the processes described by Neubauer and Vogel in their work on urine.

From this table it will be seen, that, like the pulse and the amount of urine, the urinary constituents vary considerably when small doses of digitaline were taken; but that, when the dose was large, the pulse fell, the urine increased, its sp. gr. was diminished, the urea was increased, and the PO_5 and Cl were diminished. For comparison of these results with those of Winogradoff and Stadion, I tabulate them—February 15—24. I do not reckon, as I am not sure of the quality of the digitaline.

Constituent.	Stadion.	Winogradoff.	Brunton.
Water.....	Diminished.	No marked increase.	Decided increase.
Urea	Less.	Less.	More.
Phosphoric acid..	Less.	More.	Less.
Chlorine.....	Less.	Less.	Less.
Sp. gr.....	Less.	.. ..	Less.

With the exception that I experienced diuresis, and had the urea increased instead of diminished, my experience agrees with that of Stadion. From the large increase of urea with less work, I believe that when it acts as a diuretic it increases tissue change; and the diminution of phosphates, I think, is in a great measure due to the dislike to and inability for any kind of mental work.

On the Temperature of the Body.—Messrs. Bouley and Reynal* found that poisonous doses of digitalis produced first increase and then decrease of the animal temperature, but that therapeutic doses caused a steady diminution, without previous increase; Messrs. Aug, Dumeril, Demarquay, and Lecointe,† in experimenting on dogs with digitalis and digitaline, the latter in the dose of 10, 20, and 25 milligrams, and the extract of digitalis 1 to 4 grams in a period of 11 or 12 hours found the temperature rise eight times from 1° to 2°, and in the only case in which it was lowered they used 50 milligrams of digitaline, and death ensued within the hour. Schwelgue says the fall of the pulse is accompanied by a fall in the animal temperature. In Exp. XIII I noticed a remarkable diminution, the animal feeling as cold as if dead for some hours before death actually occurred, and in several cases I have noticed the limbs grow cold a little while before death. Dr. Mazel,‡ in his case of poisoning, noticed that the temperature of the skin in those parts exposed to the air was lower than usual. Hertz§ says that there is first increase and then decrease of the temperature. Traube‖ found that when infusion of digitalis was given in acute rheumatism the temperature fell either with or a short time after the reduction of the pulse appeared. Schneider‖ says that the lowering of the temperature is independent of the slowing of the pulse, and begins from 36 to 60 hours after beginning to give the medicine; while the former begins within from 24 to 48 hours, and they both continue to fall after the

* *Op. cit.*

† *Comptes Rendus*, Mai, 1851, p. 801 (H. and Q.).

‡ *Edin. Med. Journ.*, 1864, p. 168.

§ *Bull. de Therap.*, Feb. 28 and March 15, 1862. *Year Book Sydenham Society*, 1862, p. 110.

‖ *Annuaire de Thérapeutique*, 1859, pp. 82–88.

remedy has been discontinued. Wunderlich* says that when digitalis is given in typhoid fever, in doses of 30 to 60 grains in three to five days, a remarkable diminution of the number of pulsations, simultaneously with marked decrease of temperature, takes place generally about the fourth day, and they fall after the medicine is discontinued; but the effect on the pulse is much more permanent than on the temperature, lasting in many cases for several weeks in succession. It should only be used when the pulse is 120 and the evening temperature is 105°, and with slight remissions; and less of the drug is required to produce its effects than in pneumonia and other acute diseases.

Notwithstanding the opinion of M. Schneider, it seems probable that the diminution of the temperature from therapeutic doses of digitalis depends, at least in the first instance, on the slower circulation of the blood through the periphery; but though the weight of authority is in favour of this opinion, it is possible that the diminution is owing to alteration of tissue change, and that another alteration is the cause of the temperature rising while the pulse remains slow. I think that it is not so much to the change in the circulation that the coldness in poisoning is owing so much as to absolute decrease of the animal heat, for on one occasion the breath felt cold to the hand, and the relaxed state of the capillaries, while it would aid in rapidly cooling the blood and thus the internal parts, would rather tend to keep the periphery warm.

Traube thinks that the lowering of the temperature is due to less rapid oxygenation of the blood from the slower current through the lungs.

On the Nervous System.—In large doses in animals digitalis affects both the sensory and motor system, causing a comatose or semi-comatose state, and insensibility to external impressions, muscular weakness which causes a stumbling, uncertain gait, and an appearance of a kind of paralysis of the hind quarters, so that the animal with difficulty drags them after him. In some cases there are twitchings of the muscles of the face and alæ nasi, or the muscles of the skin over the body, causing an appearance which is sometimes mistaken for convul-

* *Med. Times and Gaz.*, July 12, 1862, and *Arch. d. Heilk.*, 1862, p. 118.

sions;* and in other cases, and perhaps more frequently in dogs, at least there is staggering as if giddy, and convulsive movements of the extremities.

In smaller doses it produces giddiness, headache, tinnitus aurium, disturbed vision, dazzling, weariness, languor and general prostration, and in some cases a kind of intoxication, weakening of the intellectual faculties, and hallucinations and delirium, or even symptoms of acute mania. In some few cases digitalis acts as a soporific. I am not sure whether to attribute it to the digitaline or look upon it merely as a coincidence; but on March 5, after taking 12 milligrams of Morson's digitaline, I experienced a remarkable sleepiness at night, which continued till the 12th, when symptoms of abdominal irritation began to manifest themselves, and these increased till vomiting occurred. On the 14th I felt great languor and prostration, and either on this day, or at least while the languor continued, the mental faculties seemed enfeebled, as, while reading for an examination, the eye glanced over the words, but the mind refused to receive or retain their import. The derangement of sight which I noticed was of two kinds—1st, a general mistiness of objects, such as is seen before fainting; and 2nd, a large bright spot advancing before me, which sometimes resembled a ring showing prismatic colours faintly, and similar in character to, though less distinct than, that seen round a light when digitaline has been introduced into the eye. The headache occasioned by digitalis sometimes, as in the case of Daniel G., persists for some time after the medicine has been disused.

The motor nerves of muscles† have their power impaired by digitalis, as the muscles of the limb of a frog, which was prevented by a ligature from receiving the poisoned blood circulating through the rest of the body, preserved their excitability from eight to sixteen hours longer than the other limbs.

Action on the Eyes.—When digitaline is introduced into the eye, it causes smarting and profuse lachrymation, which passes off in a short time, and nothing more is felt, except perhaps an occasional rough feeling of the conjunctiva, till four or five

* Bernard, *Leçons de la Physiologie.*

† *Mém. de la Soc. de Biologie*, tome 3, ser. 3, p. 97.

hours after, when, on looking at a light, you see it surrounded by a halo, presenting the prismatic colours, and not quite close round the light, but with a dark space between. This halo increases in diameter the farther you move from the light, and becomes smaller and narrower as you approach. I have noticed an appearance exactly similar when light cirrhi were crossing the moon. Homolle and Quevenne say that a slight opalescence is noticeable in the lens (crystalline), and the pupil is somewhat dilated and less contractile. I did not notice any particular difference in the pupil, and the appearance is not due to its dilatation, for I found it quite distinct on looking through a pin-hole in a card. Though on looking I could not detect any opalescence, Messrs. Homolle and Quevenne are probably right as to there being opalescence somewhere, for this would produce the effect noticed.

On the Uterus.—Mr. Dickinson* found that digitalis has a powerful influence in causing the uterus to contract and stop hæmorrhage. A few minutes after the draught of ʒiss. of the infusion is swallowed, the patient complains of acute pain in the back and hypogastrium, like those of the first stage of labour, then blood, solid and fluid, is ejected, and the discharge is absent for some hours, when the pain subsides, and it returns, but less and less, after each dose, till it disappears.

On the Genital Organs.—Stadion† finds that digitalis and digitaline possess the power of temporarily annulling the activity of the sexual organs, and is thus a true antiaphrodisiac; with this conclusion I am disposed to agree. M. Brughmans‡ has stated the same thing, and advises its use wherever turgidity of these organs is to be averted, whether as after-treatment of surgical operations or for other causes.

Mode of Action of Digitalis.—Having considered the general action of digitalis, and the manner in which it affects different parts of the animal economy, we now come to a question of great difficulty, and one on which there has been much dispute —the mode in which it acts.

* *Med. Chir. Trans.*, vol. 39, p. 4.
† *Year Book Sydenham Society*, 1862, p. 451.
‡ *Revue Med. Chir.*, Paris, Dec. 1858. Half-yearly Abst., vol. 24, p. 108.

This question has generally been limited to the mode in which it affects the heart, and the two great theories on this point are—(1) that of Traube,* who thinks that digitalis exerts its influence on the heart through the regulatory (vagus) and musculo-motor system of nerves; and (2) that of Dybkowsky, Pelikan, and Kölliker, that it exerts its action on the regulating and motor apparatus, contained in the heart itself, without the intervention of the vagi. Traube at first proposed the theory that digitalis (1) first stimulated the regulatory nerves, (2) paralysed them, and (3) paralysed the musculo-motor nerves. The musculo-motor nerves are the cardiac ganglia, which can of themselves carry on the rhythmical movements of the heart; but these are aided by the sympathetic, as, according to the theory of Von Bezold, the cardiac ganglia originate continuous excitations, which, meeting with constant resistance in the cardiac nerves, are only able to overcome it periodically, and then to act on the muscular tissue. To these ganglia two sets of fibres pass from the central nervous masses—"One set reaches the heart partly through the cervical, and partly through the dorsal and lumbar portions of the sympathetic cord. The latter fibres originate in the medulla oblongata, and descending to the cervical, and to some extent through the dorsal and lumbar parts of the spinal cord, emerge at many different points to unite with the sympathetic nerve. The function of all these fibres consists in conveying an exciting influence from the medulla to the heart, so that the resistance in the cardiac nerves is more frequently overcome, and the heart beats more vigorously and with greater rapidity. The second set of fibres, when acting, increase the resistance, and they run in the vagi, and probably also originate in the medulla. When strongly excited they can increase the amount of resistance to so great an extent that it becomes superior to the combined influences of the exciting system of the medulla oblongata and of the motor system in the heart itself. After a short interval it diminishes, and the successive discharges of the automatic centres can then reach the heart, though after somewhat longer pauses. By galvanizing the vagus

* *Year Book Sydenham Society*, 1862, p. 453.

this resistance is much increased, and the heart stops in diastole.

The series of experiments on which Traube founded his views were as follows:—He injected infusion of digitalis of such a strength that one syringe-ful was equal to the extract of 8 grains of digitalis leaves, into the veins of dogs, and found that while salt and water produced no effect on the pulse, and one syringe-ful of infusion raised it from 128 to 132, four syringe-fuls brought it down to 32; while after a fifth it suddenly rose to 160, and in 10 minutes more to 174. In another, with a pulse of 108, it was reduced by $2\frac{1}{3}$ syringe-fuls to 33, but with $\frac{2}{3}$ of a syringe-ful more it rose to 202. Several other experiments gave an exactly similar result. To find whether the action was through the vagus or not, he made seven more experiments. In one, for example, after reducing the pulse from 121 to 48, the right vagus was cut, and in two minutes, when again counted, the pulse was 66. On dividing the left vagus it then rose to 204. The same result was obtained by dividing both vagi at the same time. After dividing both vagi, the slowing of the pulse after the injection of digitalis was hardly observable. From these experiments Traube concluded that digitalis operated through the regulating system only. This theory was very generally adopted for some time, but Winogradoff, finding from experiments with the hæmadynamometer, that when the instrument was inserted into an artery, and the vagi stimulated so as to cause slowness of the pulsations, the arterial tension immediately fell; while, when the slowing was produced by the injection of digitalis, there was neither increase nor diminution of the tension, concluded that Traube's view was erroneous, and totally denied that the slowing of the pulse, produced by digitalis, was through stimulation of the vagi or medulla oblongata. Traube being thus induced to re-consider his theory, made some experiments by injecting a weak solution of woorari into the veins of a dog, and keeping up artificial respiration to obviate the disturbing influence which the rise in tension consequent on division of the vagi would have caused, and then injecting infusion of digitalis, he found that the tension rose in one instance from 159 to 260

millimetres, attaining its maximum in two or three minutes, and then gradually declining.

Traube was thus lead to re-mould his theory, and to say that at first there was stimulation of the musculo-motory as well as the regulatory system, that the arterial tension was the product of these two factors, and that digitalis finally paralysed both; and here the theory at present stands (as far as I can find out).

When we look at Traube's first experiments, they certainly seem perfectly conclusively to prove that digitalis acts through the vagus, and this I certainly believe to be the case. Winogradoff's denial of this is based on fallacious reasoning, assuming as he does that because irritation of the vagi does not possess the same action as injection of digitalis, therefore injection of digitalis does not produce the same effect as irritation of the vagi: whereas the action is the same so far as the latter goes, but the former possesses the additional power of contracting the capillaries, as Blake showed so long ago as 1839.

Traube's theory also is very imperfect, for he makes the arterial tension the product of what is really only one factor, leaving altogether out of account the other equally important one, the size of the capillaries, and, as I have stated before, if the capillaries remain the same, and the number of cardiac pulsations be diminished, no amount of force which each may exert from stimulation of the musculo-motory power will do anything whatever towards raising the arterial tension by the diminished quantity of waves and consequent amount of blood.

(2) The second theory, that of Messrs. Dybkowsky and Pelikan, and (Kölliker ?) is that (*a*) digitalis exerts its action directly on the regulating and musculo-motory apparatus in the heart itself, and (*b*) not through the vagi, as their action is not delayed or altered by destruction of the medulla oblongata or division of the vagi, or by the previous administration of woorari. The first part of this theory seems borne out by the experiments of Eulenburg and Ehrenhaus on the extirpated heart of the frog, which, when its lower third was immersed in a solution of digitaline, had its motion completely stopped, if the solution was strong, and if weaker it became slow and intermittent. We see, too, that if we cut the vagus and irri-

tate the distal cut end, the pulsations are slow, and the same result takes place if we apply galvanism to the uncut vagus, and it is only natural to suppose that the poison circulating over the heart's parietes might act either upon the terminal branches of the nerve, or on the apparatus in the heart on which these branches act, and through which they produce their effect, just as upon the central end of the vagus, though probably with less force. The second part (*b*) of this theory I am not inclined to accept, because M. Traube's experiments, I think, prove that the action is altered in mammals by the division of the vagi: and although Messrs. Dybkowsky and Pelikan state that they have found the same results in mammals as in frogs, they do not give definite details like M. Traube; and I am further hindered from accepting it, as in one of the two frogs which I have been able to obtain, and which was poisoned with woorari, its heart laid bare, and first a moderate, and then an enormous dose of digitaline introduced under the skin, the action was not so marked and distinct as Dybkowsky, Pelikan, Fagge, and Stephenson describe it to be.

The hypothesis that I have myself formed in regard to the action of digitalis is as follows:—

Digitalis causes contraction of the small arteries, and at the same time acts on the regulating apparatus of the heart, both directly, and to a much greater extent through the vagus, thus causing slowing of the heart without loss of tension; it stimulates the musculo-motory apparatus, causing increased force of the cardiac contractions. This primary stimulus then gives place to paralysis—first partial, and then complete. The regulating force gradually loses its power, so that the musculo-motory power causes a quick beat to be occasionally interpolated, as the regulating power gets enfeebled, it can only occasionally assert its influence, and the pulse, formerly slow with occasional quick beats, is now a quick one, with occasional slow beats or intermissions; as the regulating power becomes entirely lost, the intermissions disappear, and the pulse becomes regular but very quick, the capillaries have also become paralysed and dilated, but occasionally, just before death, they become spasmodically contracted. The musculo-motor power gets weakened,

the fibres connecting the different ganglia of the heart, and which by keeping up a perfect correspondence between the different ganglia, enable the heart to contract rhythmically, now convey impressions slowly and imperfectly; the different parts of the heart no longer work in unison, and the contractions become irregular and peristaltic; by-and-by the fibres do not transmit impressions at all, and the ganglia working in independence of each other, we see some continuing to make the little area they supply pulsate when the rest has stopped, and finally the ganglia themselves become paralysed, and the heart remains motionless and contracted. But it is probable this stimulating influence is not exerted on the heart and capillaries alone, but on involuntary muscular fibre throughout the body, or on the sympathetic nerves which supply it, since we find it causing contraction of the stomach, intestines, and uterus, and in those organs also, its stimulating effect would probably be followed by paralysis. Not only the nerves are affected, but the power of the muscular tissues themselves is impaired, as shown by Dybkowsky and Pelikan, who found that when two muscles were taken from a frog, one having been taken from a leg which the poison was prevented from reaching by a ligature applied previous to its administration, and the other being taken from the poisoned animal, the curve described by the former in the myographion was much higher than of the latter, showing its greater power.

The cause of death from digitalis seems to be stoppage of the heart's action, and defective supply of blood to the nerve centres. When death occurs from not very large doses, it seems often to be caused by some slight exertion at the time. As in the case of Daniel G., the pulse was of low tension and irregular, and when we know that any exertion still further lessens the tension, we can easily imagine how in such a case there might be syncope ending in death. This seems all the more probable, as I noticed on the 17th of March, besides bright spots, a kind of haziness such as one sees before fainting, though not of so marked a character.

There are several points which I have not yet made up my mind about, such as the remarkable intermissions observed in

the pulse and respiration coincidently, the topical action of digitalis, the points of resemblance and difference between it and other cardiac poisons, and its action on the blood and capillaries, but I hope that I may yet be able to clear up these.

Therapeutic Action.

Soon after Withering announced the property digitalis possesses of slowing the heart's action, physicians began to employ it in hæmorrhages, and Ferriar especially used it in hæmoptysis, in the early stages of phthisis, and thought it might possibly heal ulcerated cavities in more advanced stages. Dr. Brinton thinks it is the best remedy for hæmorrhage from pulmonary cavities, in the dose of 30 to 90 minims every four or six hours. It is also said to be useful in epistaxis, and Mr. W. H. Dickinson found it of the utmost service in menorrhagia, curing in a few days a case thought to be almost at the point of death. He gives the infusion in the dose of ʒss. three times a day. He thinks that as an oxytoxic it is quite as powerful as ergot. It is from the contraction of the uterus itself, and not from the contraction of its vessels, that the benefit is derived; and this idea he supports, not only by showing that it causes pains like labour pains, and expulsion of clots, but that, in a case of fungoid tumour of the os, it did no good whatever; while, if the benefit had been from the contraction of the vessels, it ought to have been as great in this case as it is when the cause of hæmorrhage is within the uterus. Ferriar thought that in inflammatory fever it was useful instead of bleeding and purging, and Currie confirms his observations, saying he had found it useful, not only in acute inflammation of the brain, heart, and lungs, but in acute rheumatism. Several continental authors have borne favourable testimony to its use in acute inflammation. Hirtz gives a case of pneumonia, which he treated first by tartar emetic and venesection; but in two days these produced no amendment, the pulse remaining at 118, and the temperature at 104·6°. Digitalis was then given for two days, and the pulse fell to 82, and the temperature to 98·6°. Although the medicine was now discontinued, on the third day the pulse was 53, and the temperature 97·3°. Returning crepi-

tation was now heard on the eighth day of the attack, and the pulse and temperature began to rise, and three days later the patient was convalescent. He has found the same lowering of the pulse and temperature in acute bronchitis, pleurisy, acute phthisis, and acute rheumatism. He has rarely seen diuresis, and never met with any bad results. The amount taken has varied from 7 to 37 grains. He thinks that venesection may be used with the digitalis. In pneumonia, Millet abjures venesection nearly altogether, but combines the digitalis with kermes giving to adults on the first day $\frac{1}{7}$th of a grain of each every hour, and gradually increasing the dose by $\frac{1}{28}$th of a grain daily, so that on the ninth day the dose is $\frac{3}{4}$ths of a grain. The medicine is not stopped at once, when improvement takes place, but is continued some time longer. Improvement generally occurs about the sixth or eighth days, and the circulation is then affected. Among 87 cases of children, of which 53 were very bad, with much delirium and adynamia, there was but one death. Oppolzer gives it in small doses, along with ipecacuan and cold effusion externally, where the dyspnœa is more from the fever than from local changes. In reference to a case of pneumonia, Traube remarks that the rapidity of action of digitalis varies much in different cases, taking much longer if the person be strong, and the disease at its height, than when it is near a close, or in a chronic case. Schneider says that in acute inflammation digitalis, in doses of $2\frac{1}{2}$ to $3\frac{1}{2}$ grains every two hours, reduces the pulse, and lowers the temperature of the skin. These effects, he says, are independent of each other. Clutterbuck advocated its employment in continued fever. Wunderlich recommends its employment in severe cases of typhoid fever, when the evening temperature rises above 108°, and the pulse one-half in the second week. It has been proposed as an anti-periodic in ague by Davy. Graffeneuer, Gerard, and Bouillaud have treated between 40 and 50 cases successfully by it.

Nervous Affections.—Serre, by the use of Debout's pill of quinine, $1\frac{1}{2}$ grains, and digitalis, gr. $\frac{4}{5}$th, every night for three months, has cured several cases of long standing hemicrania, and, among others, his own, which had lasted 15 years. Boison

has used a pill of musk, 1 grain, ext. digital., 1½ grains, and ext. opii gr. ½, in neuralgia, and its effects he describes as being magical. Mr. Hardwicke gives ½ grain of the powder in the same affection, and with similar results. According to Thomas, it effects a permanent cure in epilepsy; and Parkinson, Moll, Corrigan, Crampton, Sharkey, Nelegan, and Duclos, have all employed it with success. In the second stage of general paresis of the insane, that of mental alienation with maniacal excitement, Dr. C. L. Robertson says, tinct. digit., in doses of ss., is a specific, calming excitement and enabling the patient to pass through this stage without wear or irritation. It steadies the pulse, and thus supplies the brain better with blood, and obviates the tendency to effusion of serum, consequent on inflammation going on in the arachnoid or pia mater.

In delirium tremens, Mr. G. M. Jones recommended ʒss. of tinct. digit. at the first dose, to be repeated if necessary in four hours, and in some cases a third might be given, which did not exceed ʒii. It failed to produce sleep in only three cases out of 70, in 67 it was the only remedy used, and 66 recovered, the fatal case having a tumour of the brain. Peacock thinks this treatment especially useful in young and strong persons, and where the attack has been the immediate result of spirit drinking, and believes that in full doses it does not produce the depression which we would expect. Carey records four successful cases.

In anasarca, especially where this depends on cardiac disease, digitalis is one of our most potent remedies, especially when combined with squill, which is also a cardiac poison of the same class as digitalis. Withering* says it succeeds best when the pulse is feeble or intermitting, the countenance pale, the lips livid, the skin cold, and the swollen belly soft and fluctuating; but it seldom succeeds in men of great natural strength, tense fibre, warm skin, and florid complexion, or those with a tight and cordy pulse. In serous dropsy, its good effects are not so marked, and in encysted dropsy, it is totally useless. By some the infusion is preferred to the tincture as a diuretic, and it is best to give it in half-ounce doses, three times a day.

* Fagge and Stevenson, *Proceed. Roy. Soc.*, May, 1865.

This action may sometimes be induced by cloths soaked in the infusion being laid upon the abdomen.*

As a sedative it requires great care, and, when the circulation fails, the remedy should be remitted; and though Sir H. Holland thinks that doctors are too much afraid of the intermittence caused by digitalis, I think it is a wholesome dread, and that when this sign appears they should at once stop the medicine, and have stimulants at hand in case of need. The tincture in doses of 30 minims is of great service in nervous palpitation, probably, I think, by inducing contraction in the capillaries, and, by thus raising the arterial tension, restoring the normal circulation.

With just one word of warning, I will close this brief summary of the therapeutical applications of digitalis, and that is to those who, thinking that there can be no danger in giving digitalis to those with very weak hearts, and that indeed it is the best thing for them to use it indiscriminately. I believe that I have proved that it increases the force of the cardiac pulsations; but if, while the motor nerves were stimulating it to contract, and the capillaries at the same time were opposing a resistance, the fibres of the heart itself were not composed of sound muscle, but were fatty and friable, some of them would be pretty sure to rupture, and the results would be disastrous. I therefore think that, in cases of fatty heart, great caution is necessary in administering it.

OBSERVATIONS ON THE URINE.

Within late years the attention of physicians has been turned much more than formerly to the observation of the urine for purposes of diagnosis, and physiologists have carefully noted the changes it undergoes in various circumstances, for the purpose of determining the way in which these circumstances affect the interchange of material in the living body.

Having lately made a very extensive series of observations on

* Christison, *Dispensatory*.

the urine and urinary constituents, with a view of determining, if possible, the changes effected in tissue changes under the use of digitalis, I have thought it not out of place to note down the chief facts which I have personally observed, and, in doing this, I will adhere strictly to the order adopted by Mr. Parkes in his excellent work on the Urine.

Amount of Constituents.

In the change of French into English weight, I have reckoned the gramme as equal to 15·43 grains, and the English fluid oz. as equal to 28·4 cubic centimetres.

On an average of 150 observations, chiefly taken during winter, but a few during summer, I find the amount of urine . . 1124 cub. cent. or 39½ ounces.

The maximum amount was 1855 c.c. or 63⅓ „
The minimum „ „ 610 „ or 21½ „

This difference is, however, much more than my normal, the one being in summer and the other in winter; and, moreover, the large number occurred after I had been taking digitalis.

My mean variation, from the lowest to the highest, is about 487 c.c. or 13⅝ oz.

This variation amounts to more than a third of the total amount, and this is therefore considerably above the average, which is ¼.

Urea.—The mean amount of 105 analyses of urea is—

33·44 grams, or 516 grains per day,
1·39 „ 21½ „ per hour.

The mean variation is 9·36 „ 144½ „ or rather more than ¼, while the average amount is ⅕th.

Phosphoric Acid.—From 108 analyses I find the average amount of PO_5, to be 3·1 grams, or 47½ grains daily,
2 „ hourly.

The mean variation is 0·96 „ 14⅘ „ „
which is less than usual, the mean being 35 to 50 per cent.

Chlorine.—From 80 analyses I find the average amount to be

6·8 grams, or 105 grains daily, 4½ grains hourly. This seems much about the average amount.

The analyses of chlorine, however, were not so exact as the others, on account of there sometimes being a difficulty in settling when the point of saturation was reached.

Section II.

Relative Proportions of the Constituents.—The urea seems to be about eleven times greater than the phosphoric acid, and about five times greater than the chlorides. These, however, do not keep their proportions constant, nor is that of the urea to the water so much so as it generally is.

Section III.

On the amount of each constituent excreted in 24 hours by a definite amount of body weight.

Constituent.	In 24 hours. 1 kilogram excretes in c.c. and grams.	In 24 hours. 1 lb. avoir. excretes in drachms and grains.	
			Parkes's average.
Water.....	23 c.c.	2·53 f. oz.	2·93 f. oz.
Urea.....	5 grams.	4·12 grains	3·53 grains.
PO_5.....	0·048 gram.	0·38 grain	0·336 grain.
Cl.....	0·126 „	0·84 grain	0·875 grain.

My weight is at present 134 lbs., and deducting 9 lbs. for clothes, and 1 or 2 lbs. which I feel sure I have gained since the end of the session, I have calculated this table for 125 lbs. weight. I have entered in the last column the average which Parkes gives, showing that the average in my water and chlorine is lower, but higher in the urea and PO_5.

Section IV.

On the acidity I have no observations.*

Section V.

On the Specific Gravity.—The sp. gr. of my urine is notably high, though not more than that observed by Dr. Christison, and a very great increase in it is always seen at night, probably from the solids of dinner passing off.

With this I must at present conclude, but I hope to be yet able to make farther use of the data I have collected; and I would notice that my observations entirely confirm Dr. Bence Jones's opinion that the acidity of the urine is lessened or replaced by alkalinity during digestion, my urine being acid in the morning, neutral at midday (from breakfast), acid before dinner, and alkaline at night.

The close connection between brain work and increase of phosphates in the urine is also well marked, there being almost always an increase on the Saturday, from the effect of the discussions at the Royal Medical Society on the Friday nights, this increase extending over Sunday; and, when I have been attending examinations, or reading hard next day, the amount of phosphoric acid is increased.

[* This statement applies only to quantitative determinations. About six hundred qualitative observations were made, the reaction being usually determined each time that urine was passed. These were all described in the manuscript thesis, but those made from November 14, 1865, to March 16, 1866, were not printed in full on account of the expense, especially as the recapitulatory tables gave the most important facts. In addition to these, however, it may be noted that the urine during digestion was not only neutral or alkaline but was frequently quite milky when passed, from the presence of earthy phosphates. On Sundays, when no work whatever was done, the urine was invariably less in quantity, and was not milky.]

APPENDIX TO THESIS.

Dietary Table.

After some preliminary experiments, the following diet was adopted :—

Breakfast—
Coffee, 170 c.c.
Bread, 7¼ oz.
Butter not weighed, but much the same every morning, as the bread was the same.
1 salt herring—from Jan. 6 to March 22, 1866, 1 egg instead.

Lunch—
4 oz. bread.
2¼ oz. gingerbread.
190 c.c. milk.

Dinner—
Mince collops, 8 oz. The water in which they were cooked was not measured [but was almost exactly the same each day. The weight is that of the raw minced beef before cooking].
Bread, 2 oz.; Nov. 16 to Dec. 2, 1865, 3 oz.
Potatoes, 10 oz.
Water, 320 c.c.

Tea—
Tea, 375 c.c.
Bread, 4½ oz.; Nov. 16 to Dec. 3, 1865, 4¾ oz.
Butter [not weighed but almost the same every day].

[During the whole period of 121 days, from November 21st, 1865, to March 21st, 1866, inclusive, this diet was rigorously adhered to with the slight exceptions noted on March 17th, 18th, 20th, and 21st, when the action of digitalin as an irritant to the stomach and as a powerful diuretic lessened appetite and caused thirst.

The urine was passed into a small bottle which was afterwards emptied into a Winchester flask. From this specimens of the mixed urine of 24 hours were taken for analysis.]

ABBREVIATIONS USED IN APPENDIX.

B..... Breakfast.	Reactn..... Reaction.
L..... Lunch.	ft..... Faint.
D..... Dinner.	c.c. ..... Cubic Centimetres.
T..... Tea.	clr..... Clear.
Amt. ..... Amount.	cld..... Cloud.

L. & H. .... Hours spent in Laboratory and Hospital.
R. M. S. ... Hours spent at the Royal Medical Society, where debates were held every Friday.
prop..... Proportion of the ingredient to the amount of urine.
Under the head *dose* the first numbers are fractions of a grain—the second are milligrams. The dose was actually taken in milligrams, and the fractions of a grain are only reckoned from them.

Date.	Urine.					Pulse.	
	Time when passed.	Amount.	Specific gravity.	Reaction.	Appearance.	Time.	Number.
1865.		c c.					
Mar. 17	8.45	41	1024	Acid	Amber coloured, clouded at bottom	9.25	67 mean, 59–71
	1.30	365	1020	Acid	Straw, clouded at bottom	P.M.	
	7.15	320	1023·5	Acid	Amber coloured, clouded at bottom	10.25	75 mean, 71–76
	12	160	1025	...	Not perfectly clear		
	...	1258	1023	...	Turbid		
„ 18	...	...	...	...	... ...	...	... ...
	...	1200	1022	Acid	Turbid		
„ 19	...	495	1021	Faintly acid	Not quite clear	8·30	61 mean, 60–62 Somewhat cold at the time
	...	390	1019	Alkaline	Very pale coloured at top, clear	9	... ...
	...	398	1022	Faintly acid	Pale, clear, clouded at top		
	1.30	572	1023	...	Pale straw, not quite clear		
	...	1855					
Mar. 20	9.5	348	1019	Neutral	Amber, clear, clouded at bottom	9·55	63 mean, 60–67
	3	525	1020·5	Neutral	Straw do.	P.M. 10·45	80 regular, sitting in dining-room
	7	205	1019·5	Acid	Pale straw do.	11·40	58-60 sitting in bedroom
	11.40	215	1025	Acid	Amber do.	...	... ...
	...	1293					

* Consisting of about a dozen pellets like those of rabbits, and one

Meals.	Sleep.	Exercise. L. & H.	Exercise. R.M.S.	Exercise. Walking.	Bowels.	Dose. Time when taken.	Dose. Amount.	Remarks.
		hrs.	hrs.	min.		No digitalin was taken on these days, which show only the poisonous effects of previous doses.	On March 2nd 1 milligram; on 3rd, 4th, 5th, and 6th 4 milligrams daily; on 7th 6 milligrams; on 8th and 9th 8 milligrams; on 10th and 11th 10 milligrams; on 12th 15 milligrams; on 13th 21 milligrams; on 14th 20 milligrams; on 15th 30 milligrams; and on 16th 30 milligrams—altogether 173 milligrams in 15 days.	
B. 9.40 L. none D. 6.10 T. 7.30	1.45–4 4.30–8.30 6½	1½	1½	200	Open in morning. Stool copious. Quite loose. In the evening, very scanty. A good deal of flatus.			At 4 A.M. I awoke, and vomited at intervals for about ½ an hour. Vomited matter yellow and liquid, somewhat like yolk of egg. Vomited again on rising at 9 A.M. Again at 9.30. Frequent epigastric uneasiness and pain. In forenoon my sight was occasionally not quite clear (just as one sees when about to faint, but somewhat slighter), and a large bright spot occasionally seen, such as is seen after looking at the sun, and then looking away at a dark object. Languor and discomfort all day. Occasional nausea—no more vomiting. Pain in chest on drawing breath, from soreness of diaphragm from vomiting. No lunch, but took 200 c.c. water at 11.30 P.M.
B. 10.25 L. 1 D. 5 T. 7.30	12.30–10 9½	...	...	30	Open ...			Appetite improved, though not very good. Sight somewhat dim, especially after rising up or walking, and bright spots occasionally seen, chiefly after rising or walking. Lunch, 6½ oz. of bread, some cheese, and about 225 c.c. of water, and 25 c.c. of water at bed-time more than usual.
...	10.45–7.45	3½	...	100	Open once ... Stool copious, somewhat soft.			Appetite better to-day. Sight dim, and I see a large bright spot, especially after exertion. This not so bad in afternoon. Slight pain in epigastrium occasionally, lasting some time when it occurs. After dinner constant pain in left side, apparently in descending colon. Much flatus at night.
...	9							
B. 10	3.15–9	8	...	50	Open once, stool extremely scanty*			Sight clear. After looking at a bright sky, and on looking away I see a spot as if I had been looking at the sun. Appetite much better to-day Pain in left side still there on rising, and continued for some hours. Had a slice of bun of about the same weight to lunch instead of the gingerbread I have formerly taken, and for which I at present feel a disgust. Pain in side again to-night. A slight
L. 12.45	5¾							
D. 7								
T. 7.45								

about the size of a walnut. The latter floated, the former sunk in water.

Date.	Urine.					Pulse.	
	Time when passed.	Amount.	Specific gravity.	Reaction.	Appearance.	Time.	Number.
1865.		c.c.					
Mar. 21	8.40	450	1020	Faintly acid	Pale amber colour, clouded at top	9·10	66, 65–67 ...
	1	390	1020	Alkaline	Straw, clear, clouded at bottom	P.M. 10·30	67–68 ... ...
	6	453	1021	Acid	Pale straw do.	...	... ...
	11	230	1025	...	Straw do.	...	... ...
	...	1523					
,, 22	8.35	485	1023	Neutral	... ...	9·10	64 mean, 63–66
	12.20	310	...	...	Straw, clear, clouded at top	Night 1·25	72 regular ...
	5.35	305	1019	Acid	Not perfectly clear ...	...	... ...
	12.20	555	1024	Neutral	Straw coloured, clouded at bottom	...	... ...
	...	1655	1020				

RECAPITULATORY TABLES.

Date.	Temp.	Moist.	Pulse.	Sleep.	Work.			Amount.		Sp. gr.	Reaction.
					hrs.	hrs.	mins	c.c.	oz.		
1865.	°										
Nov. 14	...	...	...	...	...	...	...	1219			
,, 15	...	...	...	...	...	...	...	1161			
,, 16	...	...	...	...	...	...	...	1096			
,, 17	...	...	...	...	...	...	...	1062			
,, 18	...	...	...	...	...	...	...	1164	...	1031·5	acid
,, 19	...	...	...	...	...	...	..	995	35	1032	acid
,, 20	44·2	dry	...	...	...	...	...	1240	43·6	1023·5	neutral
,, 21	48·1	damp	71	...	...	...	...	1005	35·3	1028	...
,, 22	45	wet	67	...	...	...	...	960	33·8	1030	neutral
,, 23	47·2	dry	65·5	...	...	...	...	1010	35·5	1031	acid
,, 24	43·8	wet	71·5	...	...	...	...	1150	40·4	1031	...

Meals.	Sleep.	Exercise. L. & H.	Exercise. R.M.S.	Exercise. Walking.	Bowels.	Dose. Time when taken.	Dose. Amount.	Remarks.
		hrs.	hrs.	min.				threatening of headache before going to bed.
B. 9.15 L. 12.45 D. 6.10 T. 7.45	12-8.30 8½	3½	...	85	Open once, stool scanty, partly from large, partly from small intestine.	...	...	Appetite good Still occasionally see a bright spot like a large bright soap bubble, or like the halo that is seen round a light when digitaline is put into the eye without the central light, which is the cause of the halo in the latter case. It seems to come more after exertion, or after long writing, as in taking notes. I'm not sure whether it is the attention, or looking at the white paper, or the stooping that causes it. Took 1 orange and 100 c.c. of water extra.
B. 9.15 L. 1.30 D. 7 T. 12	12.15-8.30 8½	3½	...	90	Open once, stool copious, well formed.	...	...	Still see a bright spot occasionally. Attended the Royal Medical dinner. Liquids above some soup, 1 glass champagne, ¾ of a glass of claret, about 100 or 150 c.c. of water and 1 cup coffee.

RECAPITULATORY TABLES.

Appearance.	Urea. grms.	Urea. grs.	Urea. amt. in 1000 c.c. of urine.	Phosphoric acid. grms.	Phosphoric acid. grs.	Phosphoric acid. prop.	Chlorine. grms.	Chlorine. grs.	Chlorine. prop.	Dose.	Date.
	grms.	grs.	amt. in 1000 c.c. of urine.	grms.	grs.	prop.	grms.	grs.	prop.		1863. Nov. 14
											,, 15
											,, 16
											,, 17
											,, 18
Clear yellow ...	33·83	522	34								,, 19
Clear yellow ...	35·96	555	29								,, 20
...	31·17	527	34	2·37	36·5	2·35	5·22	80	5·1	...	,, 21
...	29·76	459	31	2·36	36·4	2·35	5·24	81	5·4	...	,, 22
Clear yellow ..	31·81	490	31·5	2·51	38·7	2·48	4·72	93	4·6	...	,, 23
...	35·65	550	31	2·639	40·7	·29	6·27	97	5·4	...	,, 24

Recapitulatory Tables—*continued.*

Date.	Temp.	Moist.	Pulse.	Sleep.	Work.			Amount.		Sp. gr.	Reaction.
1865.	°				hrs.	hrs.	min.	c.c.	oz.		
Nov. 25	40·3	damp	71	...	...	...	...	1010	35·5	1032·5	acid
,, 26	...	...	...	...	...	...	...	1071	37·7	1031·5	acid
,, 27	36·6	damp	69	...	...	...	...	1090	38·3	1030	acid
,, 28	40·1	wet	71·5	...	...	...	...	1170	41·2	1027·5	acid
,, 29	...	...	72·5	...	...	...	...	1055	37·1	1029·5	neutral
,, 30	...	...	73·5	...	...	...	...	806	28·3	1033	neutral
Dec. 1	41·2	dry	68·5	...	...	...	...	1200	42·2	1030·5	alkaline
,, 2	38·9	dry	...	...	...	...	...	738	26	1031	...
,, 3	...	...	...	8¾	...	...	...	1008	35·5	1031·5	neutral
,, 4	40·2	damp	62	8	...	...	...	1026	36·1	1028·5	acid
,, 5	43·8	dry	65	8	...	...	...	1170	41·2	1026	faintly alkaline
,, 6	42·5	damp	66·5	8	...	...	...	1058	37·2	1029	neutral
,, 7	46·5	dry	62·5	8	...	...	...	1110	39	1030·5	alkaline
,, 8	48·8	dry	70	7¾	...	...	...	1130	40	1028·5	alkaline
,, 9	46·3	dry	62·3	7	...	...	...	1120	39·4	1028·5	neutral
,, 10	...	...	...	8	...	...	...	1000	35·2	1031	faintly acid
,, 11	38·6	damp	67	8½	...	...	...	1300	45·7	1024	acid
,, 12	42	dry	66·5	7½	...	...	...	1150	40·5	1028	neutral
Daily mean, not excluding Sundays,	43·6	68	8								
Daily mean, excluding Sunday's urine					...	...	...	1048	36·9	...	...
Mean on Sundays					...	...	...	1018	35·8	...	...
Maximum					...	...	...	1300	45·7	...	...
Minimum					...	...	...	738	26	...	...
Difference					...	...	...	562	19·7	...	...
Dec. 13	40·5	dry	67·7	7	5	...	50	1075	37·8	1026·5	neutral
,, 14	41·5	dry	67·5	7½	5	...	60	1054	37·1	1029	neutral
,, 15	34	dry	66	...	4½	4¾	80	1464	51·5	1026·5	faintly alkaline
,, 16	37·3	dry	62·5	6	4½	...	75	1175	41·3	1025	acid
,, 17	...	...	...	8	...	...	50	1120	39·4	1028	neutral
,, 18	42·5	dry	62	8½	5	...	60	1128	39·7	1028	acid
,, 19	39·4	dry	59·5	7½	5	...	65	1450	51	1022	neutral
,, 20	42.2	damp	60·5	7¼	7¼	...	75	1094	38·5	1029	neutral

Recapitulatory Tables—*continued.*

Appearance.	Urea.			Phosphoric acid.			Chlorine.			Dose.	Date.
	grms.	grs.	prop.	grms.	grs.	prop.	grms.	grs.	prop.		1865.
...	32·82	506	32·5	3·41	52·6	3·37	5·77	89	5·7	...	Nov. 25
Clear yellow ...	37·48	578	35	3·33	51·3	3·11	6·68	103	6·2	...	„ 26
Clear yellow ...	31·06	479	28·4	2·75	42·4	2·52	7·23	111	6·6	...	„ 27
Clear yellow ...	31·59	487	27	2·35	36·2	2	5·54	85	4·7	...	„ 28
Clear yellow ...	30·38	469	28·8	2·52	38·8	2·39	5·76	89	5·4	...	„ 29
Clear yellow ...	29·01	447	36	2·18	33·6	2·70	4·86	75	5	...	„ 30
Great deposit of phosphates	...	...	...	1·95	30	1·62	7·14	110	5·9	...	Dec. 1
Not quite clear ...	...	...	...	2	30·9	2·71	4·79	74	6·4	...	„ 2
Clear yellow ...	...	...	...	2·98	35·9	2·95	5·24	80	5·1	...	„ 3
Large deposit of phosphates	31·39	484	30·5	2·48	38·2	2·41	5·46	84	5·32	...	„ 4
Not quite clear ...	29·62	457	...	2·42	37·3	2·06	5·93	91	5·06	...	„ 5
Not quite clear ...	29·62	477	28	2·46	37·9	2·32	5·63	86	5·32	...	„ 6
Considerable deposit of phos.	30·63	492	27·6	2·84	45·8	2·55	7·07	109	6·36	...	„ 7
Large deposit of phosphates	31·86	491	28·2	2·94	45·3	2·63	7·34	115	6·5	...	„ 8
Turbid deposit of phosphates	...	...	...	3·56	54·9	3·18	7·42	114	6·6	...	„ 9
Clear, clouded at bottom	...	...	...	3·3	50·9	3·3	5·46	84	5·4	...	„ 10
Clouded at bottom	28·6	441	22	2·76	42·5	2·125	6·76	104	5·2	...	„ 11
Large deposit ...	28·29	436	24·6	2·58	39·8	2·25	5·98	92	5·2	...	„ 12
...	31·88	492	30·4	2·67	41	2·54	6	92	5·7		
...	35·65	550	35	3·2	49	3·1	5 79	89	5·6		
...	37·48	578	...	3·56	55	...	7·42	114			
...	28·29	436	...	1·95	30	...	4·72	73			
...	8·19	142	...	1·61	25	...	2·7	41			
Clouded at bottom	27·95	431	26	2·74	42·2	2·55	6	92	5·5	1/200	„ 13
Flocculent cloud	28·88	445	27·4	2·68	41·2	2·55	...	...	...	1/200	„ 14
Large precipitate of phosphates	38·06	587	26	3·16	48·7	2·16	8·8	135·6	6	1/200	„ 15
Turbid throughout	27·96	431	23·8	2·7	41·6	2·3	...	...	...	1/200	„ 16
Clouded at bottom	32·14	496	25·7	2·63	40·5	2·35	8·36	129	7·1	1/200	„ 17
Clear, clouded at bottom	28·76	443	25·5	2·76	42·5	2·45	6·74	104	5·9	1/200	„ 18
Clear, faint cloud at bottom	30·45	470	21	2·64	40·7	1·82	7·06	109	4·8	1/200	„ 19
Clear, clouded at bottom	30·90	476	28·2	2·72	42	2·49	...	...	...	1/200	„ 20

Recapitulatory Table—*continued.*

Date.	Temp.	Moist.	Pulse.	Sleep.	Work.			Amount.		Sp. gr.	Reaction.
					hrs.	hrs.	min.	c.c.	oz.		
1865. Dec. 21	45·8	dry	60	7¾	6	...	60	985	34·6	1030·5	faintly acid
,, 22	48·2	dry	63·5	7½	4	...	80	1278	45	1029	faintly alkaline
Daily mean,	41·2	...	64·3	7½	5	4¼	73				
Mean								1189	41·8	...	...
Amount of Sunday's								1120	39·4	...	...
Maximum								1464	51·5	...	...
Minimum								985	34·6	...	...
Difference								479	16·9	...	...
1866. Jan. 4...	46·2	damp	...	7	4½	...	50	1100	38·7	1029·5	alkaline
,, 5...	36·5	dry	74	7½	4½	5	110	1383	48·7	1028	alkaline
,, 6...	37	dry	78	6½	3½	...	80	1655	58·2	1019	acid
,, 7...	...	...	...	8½	...	...	20	1176	41·4	1026·5	acid
,, 8...	37	damp	75	8	5	...	60	1111	39·1	1026	acid
,, 9...	34·7	damp	77	7½	6	...	70	989	34·8	1031	faintly acid
,, 10...	33·1	damp	73·5	7½	8	...	65	1005	35·3	...	...
,, 11...	24·1	fine	78·5	7¾	5	...	55	1305	45·9	1026·5	faintly acid
,, 12...	26·5	fine	88	8	4½	5	90	1398	49·2	1027	acid
,, 13...	...	...	82·5	7¾	3½	...	50	987	34·7	1029·5	acid
,, 14...	...	...	...	8½	...	...	20	980	34·5	1031·5	neutral
,, 15...	33·5	damp	78	8¼	5	...	60	1156	40·7	1227·5	faintly acid
,, 16...	...	...	77·2	7½	4½	...	65	1002	35·3	1027	faintly acid
Daily mean, excluding Sunday's urine	34·3	...	78	7¾	5	5	72	1190	41·9	...	...
Sundays								1078	37·9	...	...
Maximum...								1655	58·2	...	...
Minimum								980	34·5	...	...
Difference...								675	23·7	...	...
Jan. 17	39·7	damp	79·2	7½	4½	...	60	1073	37·7	1029·5	faintly acid
,, 18	44·2	dry	77·6	6¾	6¼	...	90	1202	42·3	1025·5	faintly acid
,, 19	43·1	damp	83	8¼	4½	5	90	1266	44·5	1025·5	alkaline
,, 20	40·5	damp	76	7	4	...	60	1164	40·9	1024·5	acid

Recapitulatory Table—*continued.*

Appearance.	Urea.			Phosphoric acid.			Chlorine.			Dose.	Date.
	grms.	grs.	prop.	grms.	grs.	prop.	grms.	grs.	prop.	grains.	1865.
Not quite clear ...	33	509	33·5	...	...	...	...	...	...	1/200	Dec. 21
Large deposit ...	...	...	...	...	...	...	...	...	...	1/200	,, 22
...	30·9	476	26	2·75	42·4	2·31	7·4	114	6·2		
...	32·1	496	28·7	2·63	40·5	2·35	8·3	129	7·1		
...	38·06	587	...	3·16	48·7	...	8·8	135			
...	27·95	431	...	2·63	40·5	...	6	92			
...	10·11	156	...	0·53	8·2	...	2·8	43			
											1866.
Clear, clouded at bottom	37·56	580	34·1	...	...	...	...	...	...	...	Jan. 4
Phosphate at bottom	40·79	630	29·5	4·92	75·9	3·92	9 8	151	7		,, 5
Slightly turbid throughout	33·97	524	20·5	3·60	55·5	2·18	...	...	...	...	,, 6
Clear, faintly cld. at bottom	36·05	556	30·6	3·42	52·7	2·91	...	...	...	...	,, 7
Clear, faintly cld. at bottom	34·41	531	31	2·34	36·1	2·11	...	...	...	...	,, 8
Clear, faintly cld. in lower half	33·62	518	34·2	2·98	46	3·02	...	...	...	...	,, 9
...	30·75	474	30·6	2·51	38·7	2·5	...	...	...	...	,, 10
Pale, clear ...	33·27	513	25·5	3·2	49·3	2·7	...	...	...	...	,, 11
Turbid, pale orange yellow	40·38	623	26	3·45	53·2	2·47	...	...	...	...	,, 12
...	32·57	502	27·5	2·98	45·9	3·02	...	...	...	...	,, 13
Clear	32·34	499	33	2·98	45·9	3·05	...	...	...	...	,, 14
Slightly turbid, phosphate	34·68	535	30	2·84	43·8	2·46	8·79	135·6	7·6	...	,, 15
Clear, clouded at bottom	27·65	419	29·6	2·54	34·1	2·54	...	...	...	1/50	,, 16
...	34·46	531	28·8	3·14	48·4	2·74					
...	34·19	527	31·7	3·2	49·3	2·9					
...	40·79	630	...	4·92	75·9						
...	27·65	419	...	2·34	36·1						
...	13·14	111	...	2·48	39·8						
Somewhat turbid	30·25	466	28·2	2·89	44·5	2·7	8·36	129	7·7	1/25	Jan. 17
Do.	31·01	478	25·1	2·76	42·5	2·3	8·98	138·4	7·4	1/25	,, 18
Not quite clear ...	31·65	487·5	25	3·22	49·6	2·55	9·4	146	7·4	1/25	,, 19
Turbid flocculent phosphate	30·26	466·9	26	...	...	...	7	108·4	6	1/25	,, 20

Recapitulatory Table—*continued.*

Date.	Temp.	Moist.	Pulse.	Sleep.	Work.			Amount.		Sp. gr.	Reaction.
1866.	°				hrs.	hrs.	min.	c.c.	oz.		
Jan. 21	...	...	...	10½	...	...	...	990	34·8	1027·5	neutral
,, 22	40·1	dry	76·5	8	5	...	60	1119	39·4	...	...
,, 23	42	dry	78	7	7	...	50	1029	36·2	...	...
,, 24	0·2	dry	78	8½	4½	...	60	992	34·9	...	...
,, 25	44·4	dry	76·5	7¾	4	...	60	1193	42	...	...
,, 26	46·5	dry	77·6	7¾	3	4	90	1327	46·7	...	...
,, 27	45·5	dry	77	7	2	2	85	1515	53·3	...	...
,, 28	...	...	...	9	...	...	...	827	29·1	...	...
,, 29	34·8	damp	70·5	8¾	4	...	90	1177	41·4	...	...
,, 30	33·1	damp	76·2	7	4	...	120	1537	54·1	...	...
,, 31	38·7	damp	76·5	7¼	5	...	60	977	34·4	...	...
Feb. 1	45·5	damp	65·5	7¾	4½	...	60	1177	41·4	...	...
	41·4	...	78·6	8	4½	4½	74	1196	42·1	...	...
Daily mean, excluding Sundays				...	...	...	...				
On Sundays	...	...	...	...	...	...	...	908	31·9	...	...
Maximum ...	...	...	...	...	...	...	...	1537	54·1	...	...
Minimum ...	...	...	...	...	...	...	...	827	29·1	...	...
Difference ...			...	...	...	...	...	710	25	...	...
Feb. 2	44·7	dry	72·5	7	3½	4½	110	1341	47·2	...	...
,, 3	39·7	dry	74	7¼	5½	...	25	1440	50	...	...
,, 4	...	...	...	8¾	...	...	20	915	30·2	...	...
,, 5	40·1	wet	67	8½	2½	...	80	1204	42·2	...	...
,, 6	41·9	wet	72·5	8	4½	...	60	1196	41·4	...	...
,, 7	39·9	wet	67	7	3	...	100	1203	30·2	...	...
,, 8	36·1	damp	73	7¾	4	...	60	1315	46·3	...	...
,, 9	39·1	damp	73	7½	4½	1½	120	1446	50·9	...	...
,, 10	39	damp	70	7¾	1	2*	30	1145	40·3	...	...
,, 11	...	...	...	7¾	...	...	60	...	...	...	...
,, 12	38·1	dry	79	8¾	2½	2*	40	1685	59·3	...	...
,, 13	36·5	dry	72	7½	2	...	90	1246	43·8	...	...
,, 14	28·3	snow	69	7¾	4	...	50	1129	39·7	...	...

* In railway.

Recapitulatory Table—*continued.*

Appearance.	Urea.			Phosphoric acid.			Chlorine.			Dose.	Date.
	grms.	grs.	prop.	grms.	grs.	prop.	grms.	grs	prop.	grains.	1866.
Clear, clouded at bottom	29·7	458·2	30	2·90	44·7	2·93	5·8	90	5·8	4/100	Jan. 21
...	34·68	475·1	31	3·20	49·3	2·86	4·7	73	4·2	4/100	,, 22
...	29·32	451·4	28·5	2·76	42·5	2·69	8·4	30	8·1	5/100	,, 23
...	...	...	27·6	3·03	46·7	3·06	6·1	94	6·1	6/100	,, 24
...	34·6	533	29	3·14	48·4	2·64	7·3	113	6·1	6/100	,, 25
...	33·44	515	25·2	3·39	52·3	2·56	5·6	86	4·2	6/100	,, 26
...	28·78	444	19	3·29	50·7	2·39	...	...	...	6/100	,, 27
...	26·71	412·1	32·3	3·08	47·5	3·73	4 8	74	5·8	6/100	,, 28
...	32·36	499·3	27·5	3·00	46·2	2·55	5·7	89	4·8	7/100	,, 29
...	38·88	599·9	25·3	3·56	54·9	2·32	7·7	120	5	8/100	,, 30
...	29·31	452·2	30	2·90	44·7	2·97	5·5	85	5·6	10/100	,, 31
...	33·54	517·5	28·5	3·23	49·8	2·75	7·8	120	6·6	10/100	Feb. 1
...	31·63	488	27·4	3·09	47·6	2·73	7	108	5·8	1/16	
...	28·2	435	31	2·99	46·1	3·29	5·3	82	5·8		
...	38·88	600	...	3·56	55	...	8·98	138			
...	26·71	412	...	2·76	42·5	...	4·7	73			
...	12·17	188	...	0·80	12·5	...	4·28	65			
...	32·85	506·8	24·5	2·91	44·9	2·18	...	...	...	...	Feb. 2
...	31·32	483·2	21·75	3·31	51	2·3	...	...	...	...	,, 3
...	27·45	423·5	30	3·68	56·7	4·02	7·7	119	8·4	...	,, 4
...	33·11	510·8	27·5	3·04	46·9	2·52	7	108	5·8	...	,, 5
...	31·09	479·7	26	3·18	49	2·66	6·6	102	5·5	...	,, 6
...	27·66	426·7	23	2·77	42·7	2·3	8·4	130	7	...	,, 7
...	35·50	450·7	27	3·12	48·1	2·61	6·2	96	4·7	...	,, 8
...	34·70	535·4	24	3·16	48·7	2·41	8·5	132	5·8	...	,, 9
...	34·35	516·9	30	3·35	51·7	2·93	5·3	82	4·6	...	,, 10
...	...	...	...	...	...	...	...	...	...	...	,, 11
...	33·01	509·3	19	2·91	44·9	1·73	...	...	...	...	,, 12
...	30·52	470·9	24·5	3·15	48·6	2·53	6·7	103	5·3	...	,, 13
...	31·36	482·3	27·7	3·07	47·3	2·72	5·5	85	4·6	...	,, 14

Recapitulatory Table—*continued.*

Date.	Temp.	Moist.	Pulse.	Sleep.	Work.			Amount.		Sp. gr.	Reaction.
1866.	°				hrs.	hrs.	min.	c.c.	oz.		
	38·5	...	71	8	3½	3	65				
Daily mean, excluding Sundays				...	...	...	...	1304	45·9	...	...
On Sundays				...	...	...	...	915	32·2	...	...
Maximum				...	...	...	...	1685	59·3	...	...
Minimum...				...	...	...	...	915	30·2	...	...
Difference				...	...	...	...	770	29·1	...	...
Feb. 15	35·3	damp	70·2	7¾	5	...	65	1329	46·7	...	...
„ 16	35·3	...	79	7½	5½	4½	100	1812	63·8	...	...
„ 17	34·2	dry	88·5	7	½	...	225	1118	39·3	...	...
„ 18	...	...	...	9	...	...	30	920	32·3	...	...
„ 19	35·1	damp	73·5	8¼	5½	...	60	1158	40·7	1026·5	
„ 20	38·6	dry	76·5	7½	1¾	3½*	50	1430	50	1023	...
„ 21	37·8	dry	72·5	7¾	4½	...	60	1249	40·4	1027	...
„ 22	39·6	damp	...	7½	3½	...	90	1302	45·8	1025	...
„ 23	42·8	damp	74	8	3¾	5	80	1296	45·6	1025	...
„ 24	38	dry	70·5	5½	4	2†	90	1245	43·8	1025	...
	37·6	...	75·6	7½	3¾	4¾ 2¼	85				
Daily mean, excluding Sundays				...	...	...	...	1326	46·6	...	...
On Sundays				...	...	...	...	920	32·3	...	...
Maximum...				...	...	...	...	1812	63·8	...	...
Minimum				...	...	...	...	920	32·3	...	...
Difference				...	...	...	..	892	31·5	...	...
Feb. 25	...	...	...	7¼	...	...	20	925	32·5	1031	...
„ 26	38·8	snow	70·5	8	4	...	60	1287	45·3	1022	...
„ 27	36·3	dry	72	8	4½	...	90	1228	43·2	1025	...
„ 28	31·2	snow	69·5	7¼	5	...	60	1305	45·9	1026	...
March 1	33·2	snow	75	6¼	5	...	90	1488	52·3	1022	...
„ 2	35·7	dry	70	5¾	5	5	95	1209	42·2	1025·5	...
	38·2	...	71·4	7	4¼	5	69				
Daily mean, excluding Sundays				...	...	...	...	1303	45·9	...	...
On Sundays				...	...	...	...	925	32·5	...	...
Maximum				...	...	...	..	1488	52·3	...	...
Minimum...				...	...	...	...	925	32·5	...	...
Difference				...	...	...	...	563	19·8	...	...

* Reading and examination. † Examination.

Recapitulatory Table—*continued.*

Appearance.	Urea.			Phosphoric acid.			Chlorine.			Dose.	Date.
	grms.	grs.	prop.	grms.	grs.	prop.	grms.	grs.	prop.	gr. mill.	1866.
...	31·9	492	25·4	3·14	48·4	2·57	6·8	105	5·2	...	
...	27·4	423	30	3·68	56·7	4	7·7	119	8·4	...	
...	35·5	450	...	3·68	56·7	...	8·5	132	...	...	
...	27·45	423	...	2·77	42·7	...	5·3	82	...	...	
...	8·05	27	...	0·91	14	...	3·2	50	...	...	
...	32·71	504·7	24·6	3·50	54	2·64	8	108	6	3/200 1	Feb. 15
...	39·00	601·7	21·5	3·31	51	1·83	9	140	4·9	6/100 4	„ 16
...	34·97	539·5	31·2	3·24	50	2·9	7	108	6·2	6/100 4	„ 17
...	35·71	551	39·7	3·40	52·4	3·7	6	94	6·5	6/100 4	„ 18
...	33·84	522·1	29·2	3·17	48·9	2·74	6·5	100	5·6	6/100 4	„ 19
Not quite clear ...	35·2	543·1	24·6	3·23	49·8	2·26	8·4	130	5·8	9/100 6	„ 20
Not perfectly clear	35·86	553·3	28·7	3 62	56·8	2·9	7·3	114	5·8	9/100 6	„ 21
...	36·05	556·2	27·6	3·33	51·3	2·56	7·6	118	5·8	18/100 12	„ 22
...	39·87	615·1	30·7	3·36	51·8	2·6	7·7	119	5·9	30/100 20	„ 23
...	34·47	531·8	27·6	3·43	52·9	2·76	7·8	121	6·2	52/100 35	„ 24
...	35·77	552	26·9	3·36	51·8	2·69	7·5	117	5·6		
...	35·71	551	39·7	3·4	52·4	3·7	6	94	6·5		
...	39·87	615	...	3·62	56·8	...	9	140			
...	32·71	504	...	3·17	48·9	...	6	94			
...	7·16	111	...	0·45	8	...	3	46			
Clear, clouded at bottom	31·30	482·9	33·8	3·55	54·7	3·84	6·1	95	6·6	...	Feb. 25
Ditto	34·31	529·4	26·7	3·03	46·7	2·36	8·5	131	6·6	...	„ 26
Clouded at bottom	32·11	495·4	26·1	3·07	47·3	2·5	8·5	131	6·9	...	„ 27
Clear, clouded at bottom	34·8	536·9	25·9	3·13	48·2	2·4	9·3	145	7·1	...	„ 28
Clear, clouded at bottom	35·81	621·6	24·1	3·75	57·8	2·52	6·4	100	4·3	...	Mar. 1
...	35·33	545·1	29·2	3·05	47	2·53	7·0	109	5·7	3/200 1	„ 2
...	34·07	524	26·1	3·26	50·3	2·5	7·6	118	5·8	Morson's Digitaline	
...	31 3	483	33·8	3·55	54·7	3·84	6·1	95	6·6		
...	35·86	621	...	3·75	57·8	...	9·3	145			
...	31·30	483	...	3·03	46·7	...	6·1	95			
...	4·56	138	...	0·72	11	...	3·2	50			

Recapitulatory Table—*continued.*

Date.	Temp.	Moist.	Pulse.	Sleep.	Work.			Amount.		Sp. gr.	Reaction.
1866.	°				hrs.	hrs.	min.	c.c.	oz.		
March 3	33·5	damp	...	6½	3¼	...	50	1057	37·2	1031	...
„ 4	...	...	...	8	...	...	20	1090	38·3	1030	...
„ 5	...	...	74	8¼	4½	...	70	1371	48·2	...	...
„ 6	33·4	damp	70	6¾	4¼	...	60	1221	43	...	...
	33·4	...	72	7½	4	...	50				
Daily mean, excluding Sundays			...	...	...	...		1216	42·8	...	...
On Sundays			...	...	...	...	...	1090	38·3	...	...
Maximum...			...	...	...	...	...	1371	48·2	...	...
Minimum...			...	...	...	...	...	1057	37·2	...	...
Difference			...	...	...	...	...	314	11	...	...
March 7	33·8	snow	68·5	9½	4	...	60	1102	38·8	...	...
„ 8	36	damp	67·5	7½	3½	...	80	1228	45	...	...
„ 9	40·2	dry	66	7½	5½	4½	80	1313	46·2	...	...
„ 10	39·8	dry	67	9¼	5	...	40	890	31·3	...	...
„ 11	...	...	...	10	...	...	20	1123	39·5	1031·5	...
„ 12	42·2	dry	65·5	9¾	3½	...	50	1259	44·3	...	...
„ 13	41·2	dry	64	7½	3½	...	120	1488	52·3	...	...
„ 14	37·4	dry	68·5	5½	2	...	80	1607	56·5	...	...
Mar. 14	38°·6	...	66·3	8½	4	4½	66				
Mean, excluding Sundays			...	...	...	...	...	1421	50	...	...
On Sundays			...	...	...	...	...	1123	39·5	...	...
Maximum ...			...	...	...	...	...	1607	56·5	...	...
Minimum ...			...	...	...	...	...	890	31·3	...	...
Difference			...	...	...	...	...	717	25·2	...	...
Mar. 15	36	damp	65·5	8	3½	...	80	1090	38·3	...	...
„ 16	40·1	damp	64	8	2	4½	90	1184	41·7	...	...
	38°	...	64·7	8	...	...	...				
Mean			...	...	...	...	...	1137	40	...	...
Mar. 17	41·4	dull	71	7¼	1½	1½*	200	1258	44·2	1023	...
„ 18	...	...	...	9½	...	...	30	1200	42·2	1022	...

* Examination.

Recapitulatory Table—*continued.*

Appearance.	Urea.			Phosphoric acid.			Chlorine.			Dose.	Date.
	grms.	grs.	prop.	grms.	grs.	prop.	grms.	grs.	prop.	gr. mill.	1866.
...	34·14	526·8	32·3	3·40	52·4	3 22	3·1	49	2·9	6/100 4	Mar. 3
...	...	...	...	3·48	53·7	3·2	...	...	...	6/100 4	„ 4
...	37·96	585·5	27·6	3·05	47	2·23	6·2	96	4·6	6/100 4	„ 5
...	35·80	552·3	29·3	3·06	47·2	2·52	5·5	77	4	6/100 4	„ 6
...	35·96	555	29·5	3·25	50·1	2·82	4·3	74	3·9		
...	...	...	...	3·48	53·7	3·2					
...	37·96	585	...	3·48	53·7						
...	34·14	527	...	3·05	47						
...	3·82	58	...	0·43	6·7						
...	29·38	453·3	26·6	2·44	37·6	2·22	7·5	116	6·8	9/100 6	Mar. 7
...	37·6	580·1	30·6	3·10	47·8	2·41	10	155	8·1	12/100 8	„ 8
...	37·51	578·7	28·5	3·30	50·9	2·52	9·3	145	7	12/100 8	„ 9
...	30·57	471·6	34·3	3·09	47·6	3·47	4·3	67	4·8	15/100 10	„ 10
Somewhat turbid	39·73	613·3	35·3	3·30	50·9	2·97	7·2	113	6·4	15/100 10	„ 11
...	34·21	527·8	27·1	2·41	37·1	1·96	7·1	111	5·6	22/100 15	„ 12
...	37·31	575·6	25	3·27	50·4	2·2	7·1	110	4·3	30/100 21	„ 13
...	35·43	446·6	22	3·21	49 5	2	6·5	101	4	31/100 20	„ 14
...	35·21	543	24·7	3·01	46·4	2·46	7·3	114	5·1		
...	39·73	613	35·3	3·3	50·9	2·97	7·2	113	5·6		
...	39·73	613	...	3·30	50·9	...	10	155			
...	29·38	453	...	2·41	37·1	...	6·5	101			
...	10·35	160	...	0·89	13·8	...	3·5	54			
...	35·77	551·9	32·8	3·18	49	2·92	5·4	84	5	45/100 30	Mar. 15
...	34·60	533·8	29·2	3·05	47	2·58	6·1	95	5·1	45/100 30	„ 16
...	35·13	542	30·9	3·11	48	2·75	5·7	89	5		
... ...	35·5	547·7	28·2	3·09	47·6	2·46	7·2	112	5·7	...	Mar. 17
Turbid	30·66	473	25·5	2·65	40·8	2·2	1·5	24	1·2	...	„ 18

Recapitulatory Table—*continued.*

Date.	Temp.	Moist.	Pulse.	Sleep.	Work.			Amount.		Sp. gr.	Reaction
1866.					hrs.	hrs.	min.	c.c.	oz.		
Mar. 19	39·6	damp	63·5	9	3½	...	100	1855	65·3	...	...
„ 20	34·2	dry	61	5¾	6	...	50	1293	45·5	...	...
„ 21	35·6	snow	67	8½	3½	...	85	1523	53·6	...	...
„ 22	37·6	snow	68	8¼	3½	...	90	1655	58·2	...	...
„ 23	37·8	wet	71	6¾	2½	1¼	80	1194	42	...	...
„ 24	37·3	damp	73	8	3	2½*	110	1219	42·9	...	...
„ 25	...	...	...	9	...	...	...	1080	38	...	...
Daily mean, excluding Sundays	37°·6	...	68	8	3½	1¼	105	1428	50·2	...	...
On Sundays...	...	...	...	...	...	...	...	1140	40·1	...	...
Maximum...	...	...	...	...	...	...	...	1855	65·3	...	...
Minimum ...	...	...	...	...	...	...	...	1080	38	...	...
Difference			...	...	...	...	...	775	27·3	...	...

Recapitulatory Table—*continued.*

Appearance.	Urea.			Phosphoric acid.			Chlorine.			Dose.	Date.
	grms.	grs.	prop.	grms.	grs.	prop.	grms	grs.	prop.	grain.	1866.
...	43·70	674·2	23·5	3·06	47·2	1·65	12·6	195	6·7	...	Mar. 19
...	29·83	460·2	23	2·43	37·4	1·88	7·9	123	6·1	...	,, 20
...	35·14	542·2	23	2·61	40·2	1·71	5·9	91	3·8	...	,, 22
...	43·28	667·8	26·1	3·24	50	1·96	8·4	131	5	...	,, 22
...	38·34	591·4	32·1	3·25	50	2·72	3·8	60	3·1	...	,, 23
...	40·00	617·2	32·8	2·99	46·1	2·45	5·4	84	4·4	...	,, 24
...	36·00	555·8	33·3	3·38	52·1	3·14	5·6	86	5·1	...	,, 25
...	36·9	569	25·8	2·95	45·5	2·24	6·4	100	4·4		
...	33·33	514	20·2	3·23	49·8	2·83	6·4	100	4·4		
...	43·70	674	...	3·38	52·1	...	12·6	195			
...	30·66	473	...	2·61	40·2	...	1·5	24			
...	13·04	201	...	0·77	12	...	11·1	171			

RECAPITULATORY TABLE.

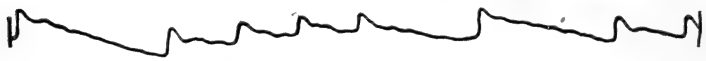
Date.	Temp.	Pulse.	Sleep.	Exercise.	Amount.		Urea.			Phospho ic acid.			Chlorine.		
					C.C.	Oz.	Grams	Grains	Prop.	Grams.	Grains.	Prop.	Grams.	Grains.	Prop.
1865.	°														
Nov. 14—Dec. 12	43·6	68	8	...	1048	36·9	31·88	492	30·4	2·67	41	2·54	6	92	5·7
Dec. 13— ,, 22	41·2	64·3	7½	5 —4¾—73	1189	41·8	30·90	476	26	2·75	42·4	2·31	7·4	114	6·2
1866.															
Jan. 4—Jan. 16	34·3	78	7¾	5 —5 —72	1190	41·9	34·46	531	28·8	3·14	48·4	2·74			
,, 17—Feb. 1	41·4	78	8	4½—4½—74	1197	42·1	31·63	488	27·4	3·09	47·6	2·73	7	108	5·8
Feb. 2— ,, 14	38·5	71	8	3½—3 —65	1304	45·9	31·90	492	25·4	3·14	48·4	2·57	6·8	105	5·2
,, 15— ,, 24	37·6	75·6	7½	3¾—4¾—85	1326	46·6	35·77	552	26·9	3·36	51·8	2·69	7·5	117	5·6
,, 25—Mar. 2	38·2	71·4	7	4¾—5 —69	1303	45·9	34·07	524	26 1	3·26	50·3	2 51	7·6	118	5·8
Mar. 3— ,, 6	33·4	72	7½	4 — 50	1216	42·8	35·96	555	29·5	3·25	50·1	2·82	4·8	74	3·9
,, 7— ,, 14	38·6	66·3	8¼	4 —4½—66	1421	50	35·21	543	24·7	3·01	46·4	2·16	7·3	114	5·1
,, 15— ,, 16	38	64·7	8	2¾—4½—85	1137	40	35·18	542	30·4	3·11	48	2·75	5·7	89	5
,, 17— ,, 22	37·7	66	8	3½ — 62	1517	53·4	37·49	578	24·7	2·88	44·4	1·9	8·4	129	5·5
,, 23— ,, 24	37·5	72	7½	2¾ — 95	1206	42·4	39·17	586	32·4	3·12	48	2·58	4·6	72	3·7

CASE OF POISONING BY INFUSION OF DIGITALIS —RECOVERY.

Daniel G., aged fifty-two. Admitted into Royal Infirmary, October 4, 1865. The patient, who is a tall and powerful man, had an attack of pleurisy more than three months before admission, and, after the acute symptoms were relieved, he was unable to resume his occupation of using the fore-hammer on account of shortness of breath, loss of appetite, and general weakness. On applying to a medical man, it was discovered that there was effusion into the left pleura, reaching up to the third rib; and after being treated by mercurials, &c., for some time, he was admitted into the hospital, and the effusion was found to be still at the same level. On admission, there was dulness over the left front from base of lung to above the level of third rib, and on left back partial dulness from above the scapula to its inferior angle, and thence downwards absolute. There was frequent cough, but no expectoration. The apex beat was most distinct at left side of ziphoid cartilage. Heart sounds natural; pulse 70, of moderate strength; tongue furred; appetite moderate; bowels regular; urine in good quantity, natural in character. He was at first ordered acetate of potash, 20 grs., three times a day; but this producing little benefit, he was ordered half an ounce of infusion of digitalis three times a day.

After being ordered infusion of digitalis, he at first measured it, but soon began to guess it, and had gradually increased the amount. Shortly after doing this, his appetite began to fail, and, at the same time, he had a bad taste in his mouth, and his tongue felt very dry. He felt also a dull sickening pain over the stomach, rising up the line of the sternum to the throat. Occasionally this was like to make him sick. He felt weaker every day. This was about the middle of November, about three weeks before the symptoms attracted attention. He went on gradually increasing the dose. When he lost his appetite he also got occasional headache and, along with the pain in epigastrium, he had palpitation. His bowels were costive. About the third week of November he vomited once or twice after meals when seized by a severe fit of coughing. The vomiting he attributes entirely to the cough. These symptoms grew worse, and he felt weaker and weaker, and less able to walk. About the 1st or 2nd of December he noticed his sight becoming dim, and when he looked at his own hands, or another person's face, they seemed blue. The pain in the stomach was now almost constant; but the headache was not much worse—it was worst in the afternoon. On the morning of the 5th December he complained of weakness and want of appetite. His pulse was found weak and very irregular. At the visit in the middle of the day the cardiac action was found increased, and the pulse distinctly dichrotic. The general rhythm was about two beats in one second, and then an interval of about two seconds. The pulse was 58—somewhat feeble. The pupils were natural and skin moist. Urine deposits a considerable amount of lithates, otherwise normal. He got three ounces of brandy before I saw him, which I did about 5.20 P.M. At that time the cardiac impulse was very abrupt and felt strong, the impression to the hand being exactly what I had felt in experimenting with dogs. The pulse was 66, but very irregular. I took the following tracing with the sphygmograph:—

FIG. 1. 6 P.M.—December 5.—Right radial; patient lying.



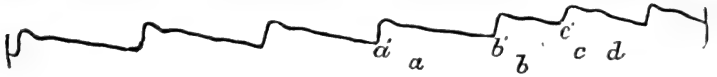
From this we see that the pulse is irregular and intermittent. The *ligne d'ensemble*, or line which would connect the tops and bases of each beat, instead of being straight, is curved, showing that the arterial tension is more influenced than usual by respiration. The pulse is dichrotic, this being especially marked in the last pulsation on the tracing. This dichrotism is not perceptible, or only to a very slight extent in subsequent tracings, showing that the tension of the pulse, when the present tracing was taken was not only low in itself, but much below the ordinary arterial tension of the patient.* He got 3 ozs. more brandy, and a diaphoretic mixture (spt. ammon. aromaticus), which lessened the dimness of vision.

FIG. 2. December 6.—Tracing taken from right radial about 6 P.M. Patient lying.

The *ligne d'ensemble* is much more nearly straight than yesterday, showing that the arterial tension is less variable. Pulse very slow, and irregular as to time; but while yesterday it was as it were a quick pulse with occasional intermissions, or perhaps it might be termed a quick pulse, becoming occasionally a slow one, to-day it is a slow pulse with an interpolated beat or beats; or a slow pulse, becoming occasionally, and for a brief period, a quick one.

The arterial tension is distinctly higher than yesterday, the line of ascent being more oblique, the top of the curve, instead of being sharp, is rounded, and the line of descent gradual instead of sudden, and only the faintest trace of dichrotism.

FIG. 3. December 7.—Tracing taken from right radial at 1 P.M. Patient lying.



The pulse is still irregular, and its characters are almost identical with that of yesterday. We see the distinct interpolation of a beat in the case of the pulsation *b*, which, if the line of descent prolonged to the same length as that of *a*, would reach to the point *d*. If we join the bases *a'* and *b'* of the lines of ascent of the waves *a*, *b*, and *c*, and prolong the line, we find that it passes through the point *d*, and also that the distance between *a'* and *b'* is the same as between *b* and *d*, showing that the rate of lowering of the arterial tension is the same in both; or, in other words, that the blood has been escaping with the same degree of rapidity through the capillaries in both cases. So, when the

* Comparing the suddenness with which the wave attains its maximum height, and its sudden descent, with a tracing after recovery, we see that the cardiac systole is very much more abrupt and short than normally.

next wave *c* was impelled into the arteries before its usual time, the base *c'* of the wave *c* found the arterial tension greater than usual, and in consequence is on a higher line. We notice also, that though the amount of blood sent in by this wave, as indicated by its height, is less than usual, yet coming so close upon the last, it has raised the arterial tension higher than usual, as is shown by the height of the top of *c* being above that of the others.

FIG 4. December 8.—Tracing taken at 3 P.M. Pulse, 93. Patient lying.

This tracing was taken about half an hour after patient had had his dinner, and the rapidity of the pulse is probably due to this.

The pulse is much more regular, and the *ligne d'ensemble* nearly straight. The line of ascent is comparatively abrupt, and then presents an ascending plateau. This latter is probably due to loss of elasticity of the arteries from commencing senile degeneration, which it is evident that patient has, from the nature of the tracings after his return to health. The line of descent is tremulous.

The dimness of sight and pain in epigastrium has been gradually diminishing. This afternoon he had rigors, and went to bed complaining of intense frontal headache.

FIG. 5. December 9.—Tracing from right radial, 8 P.M. Patient lying. Pulse, 64.

Pulse much slower than yesterday. *Ligne d'ensemble* of bases pretty nearly straight. The waves vary slightly in height and length, each third one being smaller, and the line of descent straighter, than the others. This is probably due to the influence of respiration. The ascent is comparatively oblique at first, and after ascending some way becomes still more so, and the line of descent gradual, showing high arterial tension. To-day the headache is better, and the shiverings have not returned.

December 10.—Being Sunday, I did not examine the case.

FIG. 6. December 11.—12.30 P.M.

Ligne d'ensemble is not quite straight. The line of ascent almost perpendicular, then a well-marked ascending plateau. From the little modification that the cardiac impulse has undergone, one would be inclined to say that the elasticity of the arteries was more impared than usual.

Headache almost gone; patient much better.

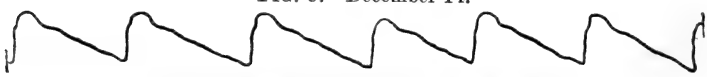
FIG. 7. December 12.—Tracing taken at 1.50 P.M.

Plateau less marked; tops more rounded.

FIG. 8. December 13.—Appetite slightly improved; still slight headache; pulse 60; quite regular; seems now to have returned to its normal state completely.

Tracing taken at 6.30 P.M. Pulse then 66.

FIG. 9. December 14.



Tracing at 5.45 P.M. Pulse 56. Respiration, 20.
Tension slighly higher than yesterday, and pulse slower.

FIG. 10. December 15.—Patient was sitting up but went to bed, and had been lying about forty minutes before the present tracing was taken.

1.28 P.M. Pulse, 60. Respiration, 24.
In this there is a nearly horizontal plateau, and the tension is considerably affected by the respiration.

FIG. 11. December 16.—Tracing taken at 6 P.M. Pulse, 64. Respiration, 23.
Headache to-day only occasional.

Patient still complains of headache, which up to this time has been constant.

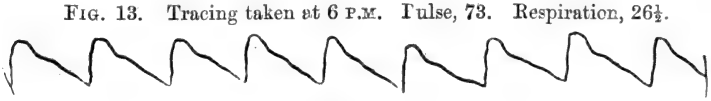
December 17.—Sunday.

FIG. 12. December 18.—Between 1 and 2 P.M. Pulse 63. Repiration, 27½.

Appetite improving. For the last two days headache has not been so bad.

December 19.—Appetite still improving; headache only occasional. The headache over the right or left parietal bones and frontal bone, chiefly about the parietal protuberances; never on the vertex or occiput. It goes from side to side—being to-day over the left, and yesterday over the right, parietal bone. Some pain in back to-day.

FIG. 13. Tracing taken at 6 P.M. Pulse, 73. Respiration, 26½.



Pulse rather quicker; tension rather less.

FIG. 14. December 20.—Tracing at 5.30 P.M. Pulse, 68. Respiration, 32.

My observations were now stopped, as I was going to the country; but from the constancy of the characters of the pulse during the last four days, we may suppose that it had now returned to its normal condition.

EXPERIMENTS ON THE INFLUENCE OF DIGITALIS ON THE PRESSURE OF BLOOD IN THE ARTERIES.

IN order to determine the influence exerted by digitalis, or digitaline, on the arterial pressure, the carotid of a dog was exposed; the nozzle of a hæmadynamometer inserted, and the height to which the column of mercury rose was noted. After waiting a short time to see if the pressure was constant, digitaline suspended in water, or infusion of digitalis, was injected into the jugular vein, and the pressure again noted.

The instruments which were commonly used consisted of a glass flask, partly filled with mercury, into which two tubes dipped, and were held firm by being cemented air-tight into a brass cap. The mouth of the flask is closed by an india-rubber stopper, through which were passed a brass tube, provided with a stop-cock, and having a funnel at its upper end, and a curved glass tube, by means of which the instrument was connected to the artery. This brass nozzle is small at the end, and grows rapidly wider, and is roughened at the small end to prevent its being dragged out of the vessel by giving a better hold to the ligatures securing it. By means of a piece of glass tubing, with a bulb upon it, and india-rubber tubing, the nozzle was connected to the hæmadynamometer. A clip was placed on the tubing, so as to restrain the flow of blood at pleasure. The whole apparatus having been filled up to the end of the nozzle with a solution of bi-carbonate of soda, to prevent coagulation of blood, poured in by the funnel, the stopcock was turned, and the apparatus ready for use. A graduated scale was applied to the tubes to show the height to which the mercury rose. As the volume of mercury in the flask was so much greater than that in the tube, no corrective was employed for the lowering in the flask as it rose in the tube, as would have been necessary had a simple bent tube been used. An apparatus of this kind, with a plain tube, gives trustworthy indications so long as the pressure is constant: but when it is variable, the indications become fallacious from the mercury at each oscillation acquiring a rapidity which carries it above and below the true maximum and minimum points.

To obviate this, the compensating tube of Marey was used. This consists of a tube, whose bore is reduced to a capillary size near the lower end. The mercury can only pass through this very slowly, and the influence exerted by each oscillation on the height of the mercury in it being very small, the true mean pressure of the blood is thus obtained.

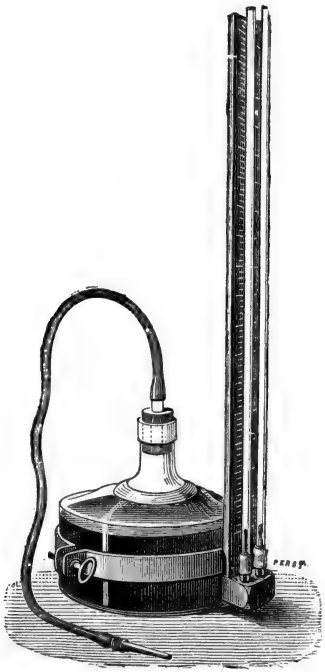


FIG. 15. Marey's Hæmadynamometer. This figure was not in the original Thesis, and I owe its appearance in this volume to Professor Marey's kindness.

EXP. I.—*Nov.* 25, 1865.—The dog experimented on was a pointer of the usual size. It was tied down to a table, and chloroform administered while the carotid was being exposed.

Time.	Mercury. Min. & Mx.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
2.25′	..	..	..	..	The first incision was made, Dr. Gamgee kindly performing the experiment for me.
2.51′	..	..	..	..	Nozzle introduced into carotid.
2.55′	4—5	..	..	..	Stopcock turned on—the mercury rose immediately.
2.57′ 45	5*				
2.59′	..	4·4			
2.59′ 30	4·95	4·25			

* Little oscillation. Probably clots already present.

Time.	Mercury. Min. & Mx.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
3.2′	4·8—4·9	..	..	..	Slight irregularity of heart. Never
3.5′	..	4·4	..	..	sinks, when animal struggles:
3.5′	5	..	..	..	below 4·6; never rises above 4·9 during struggle, but fell immediately.
..	..	..	..	..	1 centigram of digitaline suspended in distilled water.
3.9′	..	..	..	..	The first part injected into jugular vein.
3.13′ 15	4·8	..	..	..	The fourth part injected.
3.14′ 20	..	..	..	..	Injection completed.
3.17′ 40	..	..	..	..	Pulsation faint—tube probably plugged.
3.20′	4·7—4·8	..	..	..	Not above 4·8.
3.22′ 15	4·85	..	..	..	Oscillations barely perceptible.
3.26′	..	..	..	..	Cardiac pulsations, 100—extremely irregular both in number and force.
3.29′ 30	..	..	..	..	A solution of another centigram of digitaline was now injected into the cellular tissue of the upper part of right thigh—completed at 32′ 10″.
3.31′ 40	..	..	..	..	Heart's action weaker, and more irregular.
3.35′	..	..	..	..	It was ascertained that there was obstruction at some point in the apparatus, and on examination, the nozzle and the greater part of the india-rubber tubing, were found filled with clots. These were removed, and the instrument again readjusted at 3.44′.
3.45′ 45	3·2—6	..	..	..	Oscillates with extreme irregularity.
3.47′	4·3—4·4	..	..	..	Hardly perceptible.
3.50′ 45	..	..	..	..	Clip placed on india-rubber tube, and nozzle twice cleaned by suction.
3.53′ 30	3·8—5·7	..	..	..	The mercury soon again became stationary, and after another ineffectual attempt to clear the
4	..	..	90*	..	apparatus, the nozzle was finally withdrawn at 4 P.M., and the wound stitched up. The femoral pulse was 90′, and, though still very irregular, was less so than when last estimated.

4.4′.—Dog released from the table. Seemed a little stiff at first, but soon ran about as if nothing had happened, and made water on the floor. In this

* Less irregular.

experiment, instead of the nozzle which I had before described, a straight one was used of a much smaller bore, which was farther diminished by a stopcock upon it.

Exp. II.—*Nov.* 29.—In this experiment the nozzle was wider, and the apparatus was just as described at the beginning, the hæmadynamometer showing the mean only being employed. The same dog was used which had been experimented on on the 25th. Chloroform was given as formerly.

Time.	Mercury. Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.			
1.58′	..	..	..	I made the first incision.
2.5′ 30	..	..	..	Carotid exposed, and ligatured at distal end.
2.11′	..	..	..	Nozzle inserted.
2.14′	..	120	..	Clip relaxed.
2.17′	5·55			
2.19′	5·4	125	..	5·4 appears to be about the average.
2.20′ 45	5·3	..	..	External jugular vein tied.
2.22′ 30	5·15			
2.23′ 15	5·4	..	..	Half a grain of digitaline in water was injected into the jugular vein. Mercury immediately indicated 5·4.
2.25′	5·45			
	5·5—5·55			
2.25′	5·3	..	..	Suddenly fell to 5·3.
	5·5	..	..	As suddenly rose to 5·5. Then fell again.
2.26′	5·1—5·3	..	..	Heart's action extremely irregular.
2.26′ 30	4·8—5	..	..	Still extreme irregularity in the pulsations.
2.26′ 40	4·7			
2.26′ 55	4·6—4·55			
2.27′	4·4	..	..	Breathing extremely rapid.
2.27′ 45	4·5			
2.28′ 15	4·4			
2.29′ 40	4·8	..	26	Mercury rose to 4·8. Respirations are not so rapid as they were at 27′.
2.30′	4·7	172	..	Pulse more regular.
2.30′ 15	4·8			
2.30′ 30	..	..	..	Respiration much quieter.
2.30′ 45	4·6	148	..	Pulse still regular. Oscillations slight. Column is, on an average, at 4·6, and is less violently affected than before injection.
2.32′ 30	..	200	..	Regular.
2.33′	4·3	..	..	Pupils dilated, and imperfectly contractile to light.
2.34′ 15	4 3			
2.34′ 45	4·1			
2.35′	4·0			
2.35′ 45	3·8	..	..	Pulse weaker.
2.36′ 10	3·6			
2.36′ 30	3·5	180	..	Pulse very weak.

Time.	Mercury. Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.			
2.37′ 30	3·35	..	..	Pupils contract more perfectly. Breathing, abdominal laboured. Intercostal muscles do not act properly. Chiefly the accessory muscles of respiration act. Thorax is raised as it were as a whole.
2.38′ 45	3·4			
2.39′ 20	3·25			
2.40′ 10	3·2			
2.40′ 40	3·3			
2.41′	3·25	154	..	Pulse weak, and rather irregular.
2.42′	3·2			
2.42′ 10	3·3	..	..	Thermometer in axilla of dog 96·5° F. Pupils smaller than at the beginning of experiment, and continue to contract on the application of light.
2.44′	3·2	..	..	Pulse cannot well be estimated. Very irregular.
2.45′ 15	3—3·1	150	..	Pulse irregular. Thermometer 99°.
2.47′ 30	3	..	21	Slimy saliva issuing from the mouth.
2.49′ 30	2·9	150	..	Pulse irregular. Thermometer 99·3° F.
2.53′	2·9	..	18 or 19	Dog appears to be sick, but does not vomit; the muzzle preventing him from opening his mouth at all.
..	2·95	..	..	Dog moans.
2.55′ 10	..	..	..	Groaning much increased, and louder.
2.56′ 15	2·85	155	..	Appears to be endeavouring to vomit.
2.57′ 15	3·1			
2.58′	3·2	..	..	Steadily rising.
2.58′ 10	3·3—3·5			
2.58′ 45	3·1			
2.59′	3·0	..	..	Gradual sinking.
2.59′ 10	2·5	..	..	Convulsions. Passage of fæces.
	2·4	..	..	Stoppage of heart's action.
	2·2			
	Down	..	..	Dog dead.
3				

After this tremors were noticed. Spasmodic twitching of the penis was noticed after heart's action and femoral pulse had ceased, and a fluid resembling, and supposed to be, semen, was emitted; but on its being at once examined microscopically, no spermatozoa were to be found, and only an abundance of large cells like mucus or pus corpuscles were seen. Post-mortem examination was made immediately. The thorax was opened, and the great veins tied. They were much engorged. At 3.16′ the thoracic viscera were removed. A great gush of fluid blood took place from the lower part of the vena cava inferior on cutting it. The veins and right side of the heart were engorged and swollen, stuffed like sausages, as Casper describes it. Right auricle distended. ʒiii. of perfectly fluid blood of a very dark colour was got from the right ventricle. At 3.21 the left ventricle was examined, and found firmly con-

tracted, containing a clot. It was not white from contraction. The blood, on flowing from the body, coagulated in three minutes. The blood from the vena cava inferior coagulated very quickly into an extremely firm clot in the thoracic cavity. The contents of the left side of the heart weighed 1 oz. 4⅓ drachms.

Exp. III.—*Nov.* 29.—A full-grown sheep was experimented on—the hæmadynamometer, showing the maximum and minimum, being employed.

8.35′ P.M.—Respirations 56 per minute; the sheep being at this time tied down on the table. No chloroform was given. Carotid exposed.

Time.	Mx. & Min.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
8.49′	..	..	..	..	Distal end of carotid tied, and tube inserted.
8.56′	..	..	..	..	The clip removed; tube then broke from the artery.
9.12′	..	..	..	..	Tube replaced, and clip removed.
9.14′	3·5—5	4·2			
9.16′	3·5—5·2	4·2			
9.19′	3·5—5				
9.22′	3·5—3·6	..	78	..	Animal excited by examining the wound.
9.24′	4—5	4·3			
9.25′	..	..	..	..	Half a grain of digitaline in water was injected into the cellular tissue of the thorax.
9.26′	4·1—4·6				
9.28′	4·7	..	..	..	On slight agitation.
9.30′	5·0	..	82	36	Breathing more laboured.
9.32′	4·2—4·4	..	80	..	Pulse steady at 80.
9.42′	3·8—4·8	4·3			
9.45′	7·5	5·4	..	..	Sheep struggling.
9.47′	4·1—4·4	..	104		Sheep struggles. After this the oscillations stopped, and clots were suspected in the artery.
9·52′	..	..	..	..	Clip applied, and tube removed. Again applied at 10.6′, but at 10.10′ the india-rubber stopper came out, and the experiment thus interrupted was not resumed.
10.10′	..	..	93	39	The sheep was loosed from the table. Seemed very unsteady on its legs. There was some amount of venous oozing from the wound.

Exp. IV.—*Nov.* 30.—This morning the sheep seemed still much depressed; it had made a good deal of water during the night. Between 1 and 2 P.M. it was again tied on the operating table. Chloroform administered, and the other carotid opened.

Time.	Mercury. Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.			
2.	..	166	..	Hæmadynamometer connected with the artery.
2. 1′	..	..	21	Clip removed. Thermometer in vagina 101·5° F.
2. 3′	2·1—3	..	..	Till this time the mercury in the tube has oscillated between 2·1 and 3, neither steadily nor regularly.
2. 5′	..	..	..	The pupils have become contracted. At the beginning of the experiment they were dilated.
2. 6′ 40	3·5	..	..	Pretty steady at 3·5. The sheep at this moment made a slight struggle, and mercury rose to 3·6 at once, then to 3·7.
	3·6	..	..	
	3·7	..	..	
2. 8′	3·45—3·5	..	..	Thermometer 102·9° F.
2. 8′ 35	3·2			
2. 9′ 45	3·5	..	20	Steady at 3·5.
2.10′ 45	3·95	..	..	Thermometer 102°.
2.11′	3·8	..	..	Sheep appears completely free from the effects of the chloroform.
			..	
2.14′	3·05	..	..	Very feeble pulse.
2.14′ 10	3·4	..	..	During violent struggles which now take place.
..	3·05	..	..	Then fell to 3·05.
..	3·4	..	..	During another struggle.
..	3·1	..	..	Then fell to 3·1.
2.16′ 15	3·4	..	..	An apparently convulsive movement of the head.
2.17′ 10	3·4	..	..	Pretty steady.
..	4·2	..	..	Violent struggle. Mercury rises to 4·2, 4·3, 4·4.
..	4·3			
..	4·4			
..	4·5	..	..	Another struggle.
2.20′	3·7			
..				
2.20′ 10	..	..	..	Injected the first half of 2 grains of digitaline suspended in water (into the jugular vein—this from memory).
2.21′ 10				
2 21′ 25	..	..	..	Injected the remainder of the digitaline.
2.22′ 10	5·2	..	..	Animal violently struggling.
..	5-5	..	..	During another struggle.
2.23′ 10	..	..	..	Pupil obviously contracted.
2.24′ 50	4·9			
2.25′	4·8	..	..	Mercury stands at 4·8. Animal struggles.
..	..	..	..	Pupil has become more dilated. Convulsive movement.
2.26′ 10	..	..	..	Another convulsion.
2.26′ 30	4·7			
2.27′	..	..	..	No perceptible pulsation in the carotid.
..	4·6	..	..	Cornea scarcely sensible to touch. Pupil more dilated.
2.28′ 10	..	..	..	Cornea insensible. Respiration just perceptible.

Time.	Mercury. Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.			
2.29′ 45	4·4	..	..	*Very* faint pulsation in the artery.
..	4·3			
2.31′ 30	..	..	..	Pupil widely dilated. Respiration imperceptible.
..	..	..	..	Pulse inappreciable. Thermometer 101°.
2.33′	..	..	..	Sheep allowed by all to be dead. Had made water since it was placed on the table. Mercury gradually fell.

The slow fall of the mercurial column was at first attributed to clots, but on examination none were found to account for it.

Post-mortem examination made immediately.

On opening the thorax, the veins were found much congested. The vessels were then ligatured, and the thoracic viscera removed. The left ventricle was firmly contracted. Left auricle flaccid. The right auricle and ventricle were both distended with blood. Pulmonary artery was full and turgid; the pulmonary veins empty, or nearly so. Right ventricle contained no clot, but 2½ ozs. of dark fluid blood. Left ventricle contained no clot or blood, but was markedly contracted, without any whiteness, however. Blood returning from lungs was quite fluid, and very dark. Descending aorta contained no clot, so the slow descent of the mercury could not thus be accounted for. Bladder was firmly contracted and empty.

Exp. V.—*Dec.* 20.—A large dog—a kind of bloodhound, or a cross between that and a mastiff, was experimented on. It took about 2 oz. of chloroform, which was applied on a thick towel before it was anæsthetised, though no doubt the greater part of this was lost in the application. The time when it began to get the chloroform was not noted. I cut down on and cleaned about 1½ or 2 inches of the jugular vein, and tied it. After exposing the carotid, which lay very deep, the dog was seized with convulsive tremors, which lasted a short time. Dr. Gamgee then finished the cleaning of the artery, and inserted the nozzle of the hæmadynamometer. The instrument showing the mean only was used.

Time.	Mercury. Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.			
2.44′	..	..	..	Clip removed.
2.44′ 30	5·4			
2.44′ 40	..	..	..	The tube of the hæmadynamometer was forced out by the pressure.
2.55′	..	..	..	Tube re-inserted.
2.56′	5·5			
2.56′ 40	5·7			
2.58′ 30	5·7—5·9	..	..	The dog being quiet.
2.59′ 20	5·5—5·6	..	..	Dog quiet.

Time.	Mercury. Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.			
3.	5·7—5·75			
3. 0′ 45	5·6	..	..	Dog whines and barks as if dreaming.
3. 2′ 30	5·4—5·6			
3. 3′	5·35	..	..	Dog whines loudly.
3. 3′ 30	5·5—5·7			
3. 5′	5·9	..	..	Continuous barking, as if in a dream, more loudly than before.
3. 5′ 6	5·8	..	..	During inspiration, or attempts to bark, the mercury falls. During expiration it rises.
3. 7′	..	..	..	Still attempting to bay. By a jerk, a drop of blood got above the mercurial column.
3. 9′	5·5—5·7			
3.12′	..	156		
3.14′ 30	..	..	..	The injection of one grain of digitaline suspended in about 2½ fluid drams of water. into the jugular vein, was begun.
3.16′	5·9—6·1	..	..	The dog struggling and crying.
3.17′	6·3			
3.18′	5·8—6·1	..	..	The dog cries loudly.
3.18′ 30	6·4	..	..	Still crying louder than ever.
3.18′ 40	6·2			
3.19′	5·8—6			
3.20′	5·5—5·7	..	..	Continuous crying.
3.20′ 20	5·35—5·55			
3.21′ 5	5·2—5·4	120	..	Pulse irregular.
3.21′ 35	5·4	..	..	During a long howl.
3.22′ 10	5·5			
3.22′ 15	5·0			
3.22′ 20	5—5·1	..	..	Respiration slow laboured, abdominal.
..	5·3	..	..	Stops crying.
3.23′	5·6	..	..	Deep, slow, abdominal respiration.
3.23′ 30	5·5	..	..	Breath very laboured.
3.24′	5·2	..	..	Pulse small and irregular.
3.24′ 30	5—5·15			
3.24′ 35	5·3			
3.24′ 45	5–5	..	..	The dog is quite quiet, and there is no struggle whatever to cause the mercury to rise.
3.25′	5·8			
3.25′ 15	5·9	..	..	No struggle whatever.
3.25′ 25	6·0	..	..	Pulse is weak and jerking. (Hæmorrhagic pulse, Maclagan).
3.25′ 40	6·1			
3.25′ 50	6·2	..	..	Action of heart, violent thumping.
3.26′	6—6·2	..	..	Dog crying. Iris is sensitive, slightly contracted.
3.26′ 40	6·3	..	..	During a deep howl.
3.27′ 20	5·8	..	..	Saphena veins tense, and femoral artery feels as if it were contracting against the heart. (Dr. Maclagan.)
3.27′ 50	5–9			
3.29	5·6—5·8	..	..	Howling loudly as if suffering much.

Time.	Mercury. Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.			
3.29′ 30	5·5—5·7			
3.30′ 30	5·5—5·7			
3.30′ 35	5·3	..	..	From 5·3, mercury rose straight to 5·7.
3.31′ 20	5·7—5·6			
3.31′ 35	5·5—5·8			
3.32′ 40	5·5	..	..	Dog struggles, howls loudly, shakes his tail; femoral pulse very small.
3.33′	5·7	..	..	During the loudest howls, the mercury only rises to 5·8.
3.34′	5·5—5·7			
3.34′ 30	5·4	..	..	During a short but very violent struggle.
3.35′	5·7	..	..	During a long struggle.
3.39′	5·3—5·5	..	..	Pupils rather more dilated.
..	5·8	..	..	During a very strong struggle.
3.40′ 55	5·9	..	..	Half a grain of digitaline, suspended in about 1½ drams of water, was now injected into the subcutaneous cellular tissue of the abdomen.
3.41′ 35	5·4			
3.43′	5·5	..	..	Deep groans. Pulse very irregular.
..	5·0			
3.43′ 5	5·2			
3.43′ 10	5·4			
..	5·2			
3.43′ 30	5·5			
3.43′ 33	5·3	..	..	Great irregularity.
..	5·2			
3.43′ 40	..	..	..	Pupil somewhat contracted.
3.44′ 10	5·5			
3.44′ 20	5·2			
3.44′ 25	5·4	136	..	Pulse extremely irregular. Pupil somewhat contracted. Iris sensitive.
3.45′ 30	5·3—5·4			
3.46′ 20	5·3	..	..	The dog howls.
3.47′	4·9	..	..	In a struggle, the mercury now never rises above 5. The dog cries loudly.
3.47′ 30	4·6			
..	4·7	..	..	Only rises to 4·7 during a long struggle.
3.48′ 20	..	..	..	Loud moans, deep and frequent abdominal respiration.
3.49′	4·8	..	..	Extreme irregularity of pulse. Weak moans. Deep sighing respiration.
3.50′	4·3	120	..	Pulse extremely irregular, intermits completely with inspiration. The heart seems to be going all right, and not intermitting.
3.51′ 40	4·2	..	..	Pulse less intermittent.
3.52′ 10	4·7			
3.52′ 30	4·0			
3.52′ 40	3·8			
3.52′ 55	4·3	..	..	Pupil less contracted. Seems normal. Sensitive.
3.53′ 40	4·4			

Time.	Mercury. Mean.	Pulse	Resp.	Remarks.
P.M.	Inches.			
3.53′ 50	4·1			
3.54′ 5	4·4			
3.54′ 10	4·1	..	10	Dog groans. Long deep howls.
3.55′ 30	4·3	..	..	There is intermitting of femoral pulse, but not of heart's action.
3·56′ 15	4·1			
3.56′ 25	4·3	..	..	Intermittency of pulse is distinctly heard during inspiration. Dog moaning.
3.57′ 30	4·2			
3.58′ 5	3·9			
3.58′ 20	3·5	..	..	Gradual fall from 3·9.
3.58′ 30	3·8	..	..	Pupils as before.
3.59′	3·4			
3.59′ 5	3·3	..	..	Dog whining.
3.59′ 40	3·8			
3.59′ 45	3·9			
3.59′ 50	3·6			
4.	4·0			
4. 0′ 5	4·1			
4. 0′ 10	4·2			
4. 0′ 20	4·0			
4. 0′ 25	3·5			
4. 0′ 30				
4. 0′ 35				
4. 0′ 45	3·3	..	24	Gradual fall from 3·5.
4. 0′ 55	3·8	..	..	Mercury rose suddenly to 3·8.
4. 1′	4·0			
4. 1′ 5	4·1	..	..	Dog whines.
4. 1′ 25	3·5			
4. 1′ 30	3·7			
4. 1′ 45	3·4	..	..	Respiration slightly convulsive.
..	3·6	..	..	Dog struggles.
4. 2′ 15	3·4	..	..	Moaning slightly.
4. 2′ 20	3·7	..	..	Falls during inspiration.
4. 3′ 40	3·2			
4. 3′ 45	3·5			
4. 4′	3·4			
4. 4′ 20	3·5			
4. 4′ 25	3·7			
4. 4′ 50	3·6	..	..	Whines and struggles.
4. 5′ 15	3·3			
4. 5′ 20	3·5			
4. 5′ 27	3·3			
4. 5′ 30	3·6			
4. 5′ 35	3·45			
4. 5′ 40	3·75			
..	3·45	..	24	
4. 5′ 55	3·7			
4. 6′ 45	3·8			
4. 7′ 5	..	..	..	The dog snores. Pupil normal.
4. 7′ 25	3·8			
4.11′ 30	4·1	..	..	Pulse intermits during a long inspiration, and the femoral pulse gives a peculiar

Time.	Mercury. Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.			thrilling feeling to the finger when compressed firmly.
4.15′	..	..	..	Dog whines.
4.16′ 30	4·1	216	20	Breathing is quiet. Heart's impulse, 216 in a minute—(Dr. Gamgee). 18 beats in 5 seconds. In half a minute I counted 100 beats, strong, irregular. Dr. G. feels a purring tremor over the cardiac region.
4.25′	..	..	..	Loud double blowing murmur on auscultation, which, I think, is regurgitant.
4.27′	5·7	..	..	On auscultation over the carotid, no murmur is audible Dog breathes very quietly. The double murmur varies much in intensity, the diastolic is far more prolonged. The hæmadynamometer was now stopped by a clot, so the nozzle was taken out of the artery, and the apparatus cleaned. A jet or two of blood issued from the artery before the nozzle was re-inserted.
4.50′	4·0	..	..	Re-inserted. Mercury stood at 4.
4.52′	4·0			
4.53′	..	..	..	Convulsive movement. Head turned over. There was a clot in the artery, just at the end of the nozzle, and this was broken up by pressure.
4.53′ 20	..	..	..	Dog dead. His heart was going pretty regularly, and the beats were apparently of good strength just before the dog died. On looking at the penis, no tremors were observed, and no prostatic mucus was seen. There was a good deal of water about the point of penis, from dog's having emptied its bladder. This might have possibly concealed a drop or two, if such were there.

At 4.59 there were a kind of convulsive snorts.

Post-mortem examination made immediately.

The tongue seemed somewhat pale. On opening the thoracic cavity, the veins were found very full, and perfectly turgid. The right side of the heart was distended by dark fluid blood, and the veins on its surface were dark and full. The left heart contained a little fluid blood, and was flaccid. On the surface were one or two milk spots. The ventricle was opened before the competency of the aortic valves was tried, and then they were scarcely competent, but on examination seemed perfectly healthy. The trachea and larger bronchi contained no mucus, but there was some frothy mucus in the smaller bronchi. At 5.21′ the œsophagus contracted rhythmically when laid along with the heart and lungs on a plate. It continued to do so briskly when stimulated on its mucous surface, after being cut open.

Exp. VI.—*Jan.* 10.—A dog of middle size was laid on the table, and chloroform administered. While this was being done, the dog salivated profusely and passed urine. The heart sounds at the time were perfectly normal. The operation of exposing the carotid was begun at 2.57′ P.M.

Time.	Mercury. Mx. & Min.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
2.57′	..	..	108	20	First incision made.
3.41′ 30	..	..	..	..	Clip removed. Mercury rose.
..	5—6·5	..	84		
3.45′	5—6·5	5·65	..	20	
3.48′	5—6·5	5·65	..	..	The jugular vein was now tied. No very marked effect on the mercury.
3.55′	5—8	6·3	..	..	The injection of 1 grain or digitaline in about 2 ozs. of water was begun into jugular vein. It filled the syringe four times.
3.55′ 20	..	..	..	..	Injection completed. Dog moans.
3.56′ 30	4·7—8·6	6·1–6·2	..	12	
3.59′ 30	3·8—7·7	5·8	..	..	Dog cries.
3.59′ 45	4—8	5·7			
4. 0′	4·2—8·3				
4. 0′ 15	5—8				
4. 0′ 45	6·9—7·2				
4. 1′ 20	4·8—8·2	6·4			
4. 1′ 50	6·2—7·4				
4. 2′ 15	..	6·7			
4. 2′ 30	..	6·8			
4. 2′ 45	6·3—7·5				
4. 3′ 25	6—8	6·95			
4. 4	5·2—8·2	7·0	80		
4. 4′ 45	6·3—7·6				
4. 5′ 15	5·8—8				
4. 5′ 30	6—7·8	6·9	..	12	
4. 7′	6—7·8	6·7	..	..	Pulse irregular.
4. 7′ 20	6·1—7·7				
4. 8′	5·8—7·6	6·6			
4. 8′ 15	5·5—7·2	6·5			
4. 8′ 40	6·3—8·0				
4. 8′ 50	6·1—6·9				
4. 9′	5·8—6·8	6·4			
4. 9′ 40	5·8—7·2	6·35			
4.10′ 20	5·5—6·7	..	..	30	
4.10′ 30	5·5—7·4	6·2			
4.10′ 40	5·3—6·7	6·15			
4.11′ 40	5·5—6·5	6·0			
4.12′ 5	5·5—7·0				
4.12′ 25	5·3—6·2				
4.12′ 40	5·0—6·7	5·8			
4.13′ 30	4·5—6·3	5·7	..	38	Pulse irregular.
4.13′ 45	4·5—6·2	..	..	..	For about three pulsations, or so, the mercury oscillates within 0·2 of an inch, and then there is a sudden rise or fall.

Time.	Mercury. Mx. & Min.	Mean.	Pulse	Resp.	Remarks.
P.M.	Inches.				
4.14′ 40	4·5—8·0	5·4			
4.15′ 5	4·3—5·2	5·3			
4.15′ 10	4·5—6·0	5·25			
4.15′ 45	4·2—5·9	..	..	..	With inspiration.
4.16′	5·0—7·0	5·3			
4.16′ 10	4·0—5·8	5·0			
4.16′ 35	4·2—6·0	5·1			
4.16′ 45	4·5—6·7	5·2			
4.16′ 50	4·0—6·8				
4.16′ 55	3·3—6·0	5·1			
4.17′ 10	3·7—7·0	5·0	..	..	Dog very restless. Struggles.
4.17′ 40	4·0—6·2	4·9			
4.18′ 10	4·5—5·9	5·1			
4.18′ 35	4·7—6·2	5·35			
4.18′ 45	5·0—6·0	5·3			
4.19′ 15	..	..	..	..	A blowing murmur is heard with one of the heart's sounds, but it is difficult to distinguish with which.
4.19′ 45	..	5·4			
4.21′ 10	4·0—6·0	5·0			
4.21′ 30	4·3—5·7	5·0			
4.22′	3·8—6·0	4·9			
4.22′ 25	3·5—6·0	4·7			
4.23′ 30	3·2—5·8	4·5			
4.24′	3·1—5·5	4·4			
4.24′ 10	3·2—5·2	4·35			
4.24′ 15	2·9—5·1	4·3			
4.24′ 25	3·2—5·0				
4.24′ 30	2·9				
4.24′ 45	3·3—5·0				
4.25′	..	4·25			
4.25′ 10	3·2—5·0				
4.25′ 15	5·6	..	..	..	Dog attempts to bark.
4.26′	4·2—5·3				
4.26′ 7	..	4·4			
4.26′ 25	..	4·5			
4.26′ 45	..	4·6			
4.27′	4·2—5·3	4·65	..	22	
4.27′ 40	4 0—5·8	4·6			
4.28′	3·8—5·8	4·6			
4.28′ 30	3·3—5·4	4·5			
4.28′ 59	3·2—5·2	4·3			
4.29′ 10	3·3—5·8				
4.29′ 30	2·9—5·4				
4.29′ 45	..	4·1	..	..	Dog howling.
4.30′ 20	..	3·95			
4.30′ 55	3·0—5·5	4·0			
4.31′	..	..	..	..	Heart's impulse strong. Loud blowing murmur, which almost seems to be with both sounds, and certainly is with one—I think the first.

Time.	Mercury. Mx. & Min.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
4.32′ 40	3·0—5·2	3·9			
4.33′	2·9	..	..	..	Very irregular.
4.33′ 10	2·8—4·7	3·8			
4.34′ 20	3·2—4·0	3·8			
4.34′ 40	3·0—4·8	..	..	26	The mercury goes up suddenly, and falls, as it were, by several short steps.
4.35′ 40	3·1—4·5				
4.35′ 50	3·3—4·7				
4.36′ 15	2·8—4·2	3·8			
4.36′ 50	2·9—4·5	3·75			
4.37′ 15	..	3·7			
4.37′ 30	3·1—4·4				
4.38′ 10	..	3·65			
4.38′ 20	..	3·6			
4.38′ 40	..	..	..	..	Heart's impulse felt distinctly and apparently increased. Murmur still present. Pulse cannot well be counted, it is so quick, small, and irregular.
4.39′ 15	3·2—4·3	3·55			
4.40′ 30	3·1—4·2	..	..	18	Breathing quiet.
4.41′ 10	..	3·4			
4.41′ 20	2·8—3·7	3·3			
4.41′ 50	3·0—3·7	3·15			
4.42′ 35	2·7—3·4	..	..	..	White frothy saliva flows freely from the mouth. Dog lies quiet.
4.43′ 20	2·8—3·7	3·15			
4.44′ 30	2·7—3·3	3·0			
4·45′	2·6—3·6	..			
4.45′ 40	2·4—3·2	2·9			
4.46′	2·5—3·3	2·9			
4.47′	2·6—3·1	..			
4.47′ 20	2·7—3·7	..	..	..	Breathing quite quiet.
4.48′ 10	2·7—3·6	..			
generally	2·8—3·2	.			
4.49′ 20	..	2·8			
4.49′ 45	..	2·75			
4.49′ 50	2·4—2·7				
4.50′ 10	..	3·1	..	..	Moans slightly.
4.50′ 50	..	2·65			
4.51′ 10	2·4—2·8	..	..	..	Moans, and makes slight effort.
4.51′ 40	3·56	2 8	..	..	The oscillating column stopped quite still at 3.56. The mean column steadily rose till they both attained the same height, and there they remained. Thinking that there was a clot formed, the nozzle was removed, but there was none in the instrument. The artery was then pressed to break up any clots

Time.	Mercury. Mx. & Min.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				that might be in it, though none were felt.
4.54′	..	..	..	..	Both have stopped.
4.57′	..	..	..	..	The artery opened.
4.58′	..	..	..	..	The dog threw back his head, made several convulsive respirations, and died.

Post-mortem examination made immediately.

On opening the thorax, air rushed in. The lungs were natural in colour, and very much collapsed. Both sides of the heart were full of blood. The vena cava and venous system generally turgid. The veins of intestines and viscera congested. The venous blood was dark in colour. On pinching the phrenic nerve, the diaphragm contracted; and on pinching the left phrenic, the contraction was not confined to the left side, the fibres of the right half visibly and plainly contracting. On tying the vena cava inferior, and cutting it beyond the ligature, the fluid blood, which issued from the lower end into the thoracic cavity, and which was very dark coloured coagulated in about a minute. (This is by guess, not by a watch.) The heart seems quite normal. Bladder was full. No emission of semen or mucus was observed. Half a grain of the digitaline used in this experiment had been dissolved in a small quantity of spirit for another purpose, but not used. The spirit had evaporated, and the digitaline was in a resinous-looking mass—not in powder.

Exp. VII.—*Jan.* 23.—The dog operated on was a large mongrel. It was thin and weak, and had had loose and sometimes bloody stools for some days back. It was tied down and chloroformed. I then exposed both vagi, and passed ligatures under them, so as to pull them nearer the surface, when they were wanted for section. The hæmadynamometer was then inserted into the left carotid. The mean tube seemed somewhat choked at the capillary part, so as not to work freely, and its indications were therefore not quite trustworthy.

Time.	Mercury. Min. & Mx.	Mean.	Pulse	Resp.	Remarks.
P.M.	Inches.				
2.56′ 45	3·44				
..	3·4—3 9	2·6			
2.59′	3·3—3·8	..	..	..	The mercury oscillates steadily.
3.	..	..	..	..	Both vagi were cut.
..	2·5—4·5	..	..	..	Mercury fell to 2·5.
..	3·5—4·5	3			
3.1′	2·9—3·3				
3.1′ 30	2·3	3·4			

Time.	Mercury. Min. & Mx.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
3.2′ 10	3·0—4·0	..	..	..	Pulse slower.
3.2′ 30	3·3—4·0				
3.2′ 40	..	..	..	..	The dog's breathing is gasping.
...	4·0—4·5				
..	3·3—4·2	..	..	..	Gasping.
3.3′ 30	2·8—3·5	3·4	..	..	Ala nasi are working.
3.4′	3·2—3·6				
3.4′ 20	4·0—4·5				
3.4′ 40	3·8—4·2				
3.5′	4·0—4·3	3·4			
3·5′ 10	4·0—4·3				
3.5′ 40	4·2—4·5	3·4			
3.6′ 15	4·2—4·5				
3.6′ 30	4·2—4·5				
3.10′	4·1—4·4				
3.10′ 30	4·1—4·3	..	..	..	Mucus runs from nose.
..	4·1—4·4	..	..	20	Respiration becomes more jerking.
3.12′	3·9—4·3				
3.12′ 15	3·8—4·2				
3.13′ 45	3·7—4				
3.14′ 15	3·5—3·9				
3.15′	3·5—4				
3.17′	3·4—3·9	..	..	..	Cheeks puff out with every respiration. Whole chest and abdomen heaves up *en masse*.
3.17′ 15	3·4—3·7				
..	3·9—4·1	..	..	..	Breathing suddenly very gentle.
3.19′	4·25—4·3	..	..	14	Inspiration is made by a series of little jerks—expiration made at once.
3.21′ 40	..	..	..	..	Distinct blowing murmur with the sound.
3.24′ 30	4·0—4·25	..	..	..	The mercury rises suddenly with expiration, and falls by a series of little jerks. Breathing stronger—a kind of coughing or snorting respiration.
3.26′ 10	..	..	..	..	Dog throws back head. Mercury falls.
..	4·2—4·3				
..	3·9—4·1				
3.28′ 20	4·2—4·3				
3.28′ 30	4·0—4·2	..	..	..	Dog snorting.
..	3·5—3·9	..	..	..	Convulsive movement.
3.30′ 35	3·9—4·3				
3.31′	4·3—4·5				
3.32′ 15	4·4—4·5				
3.33′ 30	4·2—4·3				
3.37′	4·0—4·2	..	..	..	Jugular vein cleaned. Dog snores.
3.38′	..	..	..	..	Jugular vein tied, and ½ grain of digitaline in water injected into it. (The time of the injection is from memory.)

Time.	Mercury. Min. & Mx.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
..	4·0—4·1				
3.39′ 30	4·5—5	..	..	..	Convulsive movement.
..	4·4—4·9	..	..	..	Low sighs.
..	—5·5				
3.40′ 10	4·7—5·5				
3.40′ 30	—6				
..	—5·8	5			
3.41′	4·9—5·4	5·1			
3.41′ 10	4·9—5·7	5			
..	4·2—5·6	5			
..	4·7—5·1	..	..	..	Stops.
3.43′	..	..	..	..	Heart acts very irregularly. The sounds are like toot-toot-toot-toot-toot-toot-toot-too. Heart very weak. Loud snorting.
3.47′	..	..	..	..	Convulsive movement.
3.48′	..	..	..	..	Coughing.
3.59′ 30	5·3—5·4	..	..	..	Breathing very slow. Heart thumping against the ribs. Breath laboured.
4.5′	4·5—4·6	..	..	..	Heart irregular. Breathing, sighing. Dog put back head convulsively but gently.
4.7′ 30	3·7—4·5	..	..	10	Respirations long, and sighing.
..	4·1—4·7				
4.8′ 5	3·5—4·4				
4.9′ 10	4·0—4·5				
..	3·7—4·3				
4.10′ 10	3·8—4·4				
4.11′ 10	3·5—4·4	..	..	..	Breathing very quiet.
4.12′	3·6—4·3				
4.13′	3·2—4				
4.14′	3·2—4·5	..	..	..	Dog moans.
4.14′ 45	3·4—4·7	..	..	..	Convulsive movements.
4.15′	4·3—5				
4.16′ 50	3·9—4·5				
4.17′ 30	..	..	..	..	Oscillations stopped.
..	4·0—4·1				
4.18′	4·1—4·4	..	..	..	Strong beat of heart.
..	3·5—4·2	..	..	..	Very irregular. Mercury ascends with expiration, and occasionally stops.
4.20′	3·5—4	..	..	..	Snoring, respiration, and a quick weak moaning.
..	3·0—4				
4.22′ 50	..	..	..	..	Oscillations stopped, blowing murmur at heart still present. After trying to dislodge the clot, without effect, the apparatus was removed.
4.35′ 30	..	..	..	..	Dog moans. Convulsive breathing. Heart strong and regular.

Time.	Mercury. Mx. & Min.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
4.50′	..	..	..	..	As the dog did not seem about to die, and we could not wait any longer, his spinal cord was severed just between the occiput and atlas. Post-mortem made immediately. On opening the chest the lungs collapsed. The heart was beating vigorously. At 4.55′ the heart stopped, but could be re-excited to contract. The venous system was much congested. Both sides of the heart contained fluid blood.

Exp. VIII.—*March* 9.—A middle-sized dog was put under chloroform, and the hæmadynamometer applied to the carotid.

Time.	Mercury. Mx. & Min.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
3.20′	6·0—6·7	6·5			
3.26′	5·5—6·7	5·9	..	..	Mercury sinks markedly with expiration (inspiration?). Dog appears to be free from chloroform, and seems to feel pain as he groans.
3.30′	..	..	116	18	
..	5·5—6·5	6·0			
3.35′	..	..	..	..	Injected $\frac{1}{8}$th of a grain of digitaline in water into the jugular vein.
3.36′	..	..	..	..	Dog micturated and voided fæces.
3.40′	5·5—7	6·4	114	14	Pulse regular and stronger than before.
..	5·2—7	6·4			
3.42′	..	..	110		
3.45′	..	..	116		
3.49′ 35	..	..	..	..	Injected $\frac{1}{4}$ of a grain more.
3.50′	5·7—7·8	..	106	..	Pulse regular.
3.55′	4·8	..	..	..	Mercury went down as low as 4·8.
3.56′ 30	5·0—7	..	108	..	Pulse markedly smaller, irregular, and with occasional intermissions. With respiration the mercury falls more markedly than before.
4.	5·7—7·5				

Time.	Mercury. Mx. & Min.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
4.4′	..	..	..	..	Pulse very markedly intermittent, and the mercury falls at each intermission as low as 4.
..	4·0				
4.8′	..	..	..	..	Pulse gives one strong beat and then 3 or 4 feeble ones.
4.10′	..	..	..	..	A drop of prostatic mucus exudes from the point of the urethra.
4.16′	..	..	..	..	Pulse very intermittent. Animal shivers every minute, or even more frequently.
					The hæmadynamometer stopped working.
4.24′	..	..	..	..	Readjusted the apparatus.
..	5·0—7·7	6·0			
4.26′	..	..	104	..	Pulse intermittent.
..	5·8—7·5	6·5–6·6	..	..	Animal continues to tremble.
4.29′	..	6·65	..	..	Oscillations more steady.
4.29′ 30	..	..	..	..	Clot again formed. Almost constant tremors.

The apparatus was cleaned, and again adjusted at 4.40, but the nozzle came out, and there was a gush of blood, and as this would have thrown some fallacy into the future reading of the mercury, the artery was ligatured, the wound stitched, and the dog released from the table. It lay for a few minutes, and then began to try and get off the muzzle. When this was removed, the dog rose and walked about. It seemed rather stiff at first.

Exp. IX.—*March* 20.—The dog operated on on the 9th, having recovered, was put under chloroform, and the carotid exposed. The dog was then allowed to come out from the chloroform, which it did at 2.15 P.M. Instead of digitaline, the extract obtained from commercial tincture of digitalis was employed; the tincture being gently evaporated, and the extract then dissolved in water and injected. The hæmadynamometer giving the mean was employed.

Time.	Mercury. Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.			
2.	..	104		
2.37′	5·5	..	..	Hæmadynamometer set working.
2.37′ 20	5·7	..	..	Prolonged sigh.
2.38′	5·1			
2.39′	5·1—5·3			
..	5·4	..	..	During a long sighing inspiration.
2.41′	5·3			
2.42′	5·0			

Time.	Mercury. Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.			
2.42′ 10	5·2			
2.42′ 25	5·5	100		
2.44′	..	..	14	Pulse slightly intermittent. Respiration very sighing.
2.44′ 30	5·4—5·5			
2.45′	5·9	..	..	Injection of extract equal to ½ dr. of tincture.
2.46′	4·5			
2.46′ 45	3·9			
2.47′	3·7			
2.47′ 5	3·9	..	..	Injection of extract of 1 dr. of tincture.
2.47′ 25	4·8	108		
2.47′ 40	5·4			
2.48′ 20	5·5			
2.49′	5·7	..	..	Under the strongest expiration.
2.49′	5·9			
2.49′ 15	6·0			
2.49′ 30	6·3			
2.50′ 15	6·15			
2.51′ 45	6·0	102		
2.53′	5·6—6·1			
..	5·7—5·8	..	..	When lying quiet.
..	..	..	..	At every expiration there is intermittence of pulse.
2.54′	5·9—6·0			
2.55′	5·6—5·7			
2.56′	5·5	76	..	Intermittence and irregularity both as to the length and strength of pulsations.
..	..	..	12	
2.57′ 20	5·4—5·5	98		
2.59′	5·8			
3.	5·5	100	14	
3.2′	5·8	..	..	Dog howling.
3.3′	5·5—5·7			
3.4′ 30	5·9	..	..	During a struggle.
3.4′ 45	6·0	..	..	During another.
3.5′	6·1	..	..	Still another.
..	6·0			
3.7′	5·7	..	..	Steady. A clot was suspected, so the instrument was removed and examined.
3.11′ 30	5·3	..	..	Instrument replaced.
3.12′	5·5	131	..	Heart's action against the ribs is strong.
3.12′ 15	5·7			
3.13′	5·6			
3.14′	6·5	..	..	Steady. Clot again suspected. Instrument removed.
3.16′ 40	5·8	..	..	Pulse is more regular.
3.24′ 15	..	..	..	Instrument again replaced. The mercury rises in a jerking fashion.
3.25′ 30	5·5			
3.25′ 45	5·8	..	..	Injected part of extract of 1 dr. of tincture. No struggle.
3.26′	5·9	96	..	Respirations few and slight, quite quiet.

Time.	Mercury. Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.			
3.26′ 15	4·5	100	..	Injected the remainder of the water and extract.
3.26′ 30	4.7			
3.27′	5·0	..	..	Dog's breathing is loud and whistling.
3.27′ 5	5·3	..	..	During a great struggle.
3.28′	5·35—5·5	..		
..	5·1—5·3	64		
3.28′ 45	4·8—5·0			
3.29′	4·5—4·7	..	..	Pulse very intermittent. Dog quite quiet.
..	..	..	12	Gasping respirations.
..	4·5—4·6	..	..	Respiration much less deep.
3.31′ 25	4·7—4·8	44		
3.31′ 40	4·9	50	..	Movement of mercurial column barely perceptible.
3.34′ 50	4·95—5·0	..	..	Heart's action weak.
3.35′ 20	..	80	..	Pulse feels rather a wavering than distinct beats.
3.43′ 5	..	..	..	Hæmadynamometer stopped.
3.48′ 20	3·3	116		
3.48′ 50	3·2	..	..	Dog perfectly quiet.
3.50′	3·2	180		
3.52′	3·3			
3.54′	3·2	172	..	There are variations in the quickness of the pulse without variations in arterial tension.
3.57′ 15	3·1	140		
4.0′ 30	3·2			
4.1′ 30	3·2	196		
4.3′ 40	3·25	170		
4.15′	..	..	..	Breath feels distinctly cool on the hand.
..	..	..	..	Clot again formed. In adjusting the instrument again, the blood from the artery was noticed not to be very florid.
4.26′ 20	2·8			
4.27′ 10	2·6			
4.27′ 30	2·8	156		
4.31′ 20	..	..	..	Injected extract of 1 dr. more. Mercury rose 0·3 during injection, and then fell down 0·4 below former level.
4.32′ 10	2·4			
4.32′ 40	2·4	174	..	Whistling respirations.
4.33′ 40	2·7	..	..	Dog struggling.
4.34′ 40	3·4	156	..	Quiet again.
4.38′ 30	3·0	..	12	
4.40′ 10	2·9			
..	3—3·1	175		

At 4.50 the experiment stopped, and dog released from the table at 5 o'clock, the wound having been sewed up. It walked about, but was weak, stiff, and staggering, and almost immediately began to vomit, and did so several times. It died several days afterwards.

Exp. X.—*April* 5.—A large dog was operated on. No chloroform was given, as after I had seen an operation conducted on a dog without chloroform, I concluded that the uneasiness they suffered while getting it was worse than they seemed to experience from the operation. The first incision was made about 11.38, cleaned a part of jugular vein and carotid artery, and inserted the hæmadynamometer. The mean tube of the double instrument having been partly choked, and not working well, I had another made, but not being drawn to a fine enough bore, the mercury oscillated too much in it.

Time.	Mercury. Mx. & Min.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
12. 2′ 20	5·5—6·3	5·9–6·2	132	..	Clip restraining blood removed, mercury at once rose.
12. 7′	5·9—6·5	..	..	..	Dog moaning.
12.11′	5·5—6·5	5·9–6·2	134	..	Mercury rises with expiration, falls with inspiration.
12.15′	5·5—6·5	5·8–6·2	..	..	From groaning its respiration is quick.
12.20′	5·4—6·4	5·9–6·1	..	..	Maximum on a deep inspiration descends to 5, and mean to 5·3.
12.24′ 30	5·4—6·4	5·9–6·1	..	..	Jugular vein tied.
12.24′ 50	6·0—6·5	..	..	..	Injection of one syringe-full of infusion of digitalis completed.
..	5·8—6·4				
12.26′ 30	5·8—6·2	..	140		
12.27′	5·5—6·2	..	120		
12.30′	..	5·9–6·2	86	..	Pulse intermittent.
12.31′	5·6—6·3	5·8–6·2			
12.32′	..	5·9–6·3	78	..	Dog quiet, not moaning.
12.34′	..	5·9–6·3	..	14	
12.35′ 20	5·5—6·5	5·9–6·3	78	..	Oscillating very steadily.
12.38′	..	5·7–6·2			
12.40′	5·5	5·9–6.2	..	..	Pulse varies from 22—27 in $\frac{1}{4}$ of a minute, not intermittent.
12.41′	5·5—6·3	5·9–6·1	88		
12.42′	..	..	84	..	For about four or five beats it is very slow, and then quick for a few more. Dog has passed some prostatic mucus.
12.45′	5·5—6·3	5·8–6·2	..	..	Mean occasionally descends to 5·6, and then rises. Dog whining and whistling slightly.
12.48′	5·5—6·2	5·7–6·0	90	..	Mercury descends on inspiration to 5·4, and next pulsation goes up to 6·2, $\frac{8}{10}$ths of an inch of oscillation. Then there are several small pulsations of about $\frac{3}{10}$ths of an inch oscillation each.
12.51′ 30	..	5·8–6·1			
12.53′ 30	5·5—6·0	5·5–5·7	104	..	Dog whining. Average oscillation of maximum column is $\frac{2}{10}$ths of an inch.

Time.	Mercury. Mx. & Min.	Mean.	Pulse.	Resp.	Remarks.
P.M.	Inches.				
..	..	..	..	20	But dog whining more loudly, and respiration thus disturbed.
12.56′ 15	5·5—6·0	5·9-6·2			
12.58′	5·5—6·0	5·5-5·7	100	..	Pulse has continued irregular since that was noted first. Dog quite quiet. Maximum column goes down to 5 on inspiration.
1. 6′ 15	..	5·8-6·0			
1. 6′ 35	..	5·5	..	..	Injection of one syringe-full more.
1. 6′ 50	..	5·5-6·1			
..	5·5—6·4	5·7-6·1			
1. 8′	5·4—6·0	5·6-5·9	84	..	Maximum occasionally descends to 5. General oscillation is $\frac{2}{10}$ths of an inch.
1. 8′ 30	..	..	..	..	Dog moans loudly.
..	4·8—6·0	4·9-6·0	..	..	During long inspiration it descended.
..	5·5	5·5	..	..	During long expiration.
1.10′	4·5—5·0	4·8-5·0	..	..	Dog tries to vomit.
1.11′	..	7·5-7·7	..	..	During vomiting.
1.12′	5·5—6·5	6·0-6·3	70		
1.13′	5·0—6·0	5·5-5·8			
1.13′ 15	..	5·5-5·7	100		
1.15′	5·0	5·0	124	..	Pulse regular. Again tries to vomit.
..	5·0—5·7	5·0-5·7			
1.20′	5·3—5·5	5·0-5·3	..	..	Mean oscillation of maximum column $\frac{3}{20}$ths of an inch.
1.25′	5·0—5·7	5·3-5·5	112	..	Both tub ccasionally descend to 4·9.
1.26′	..	..	..	..	Again vomits.
1.27′ 15	5·5—6·0	5·5-5·8	..	..	In ordinary pulsations the oscillations are $\frac{5}{20}$ths of an inch.
1.28′ 15	..	5·3			
1.29′ 15	5·2—5·6	5·3-5·6	116		
1.40′	5·3—5·5	5·4 5.5	116		
1.45′ 15	4·5	4·5	..	..	Injected one syringe-full more—mercury at once fell.
..	5·5—5·6	5·3-5·6			
1.48′	5·0—5 5	4·9-5·5	118		
..	At 5.	5·0	..	..	Breathing very rapidly and deeply.
1.50′	4·0—6·0	..	..	..	Tries to vomit.
1.50′ 15	..	..	..	..	Again vomits.
1.50′ 30	..	5·0-7·0			
1.50′ 45	..	5·0-6·5			
1.52′	5·0 - 6·0	5·5-5·8	66	..	Oscillation of max. column, after a deep inspiration, is about 1 inch, and then about $\frac{4}{10}$ths each after.
1.56	..	..	..	..	No cardiac murmur. Dog whines.
2.13	..	..	102	..	Dog loosed.
..	..	..	..	..	He walked steadily, and recovered in a few days.

The infusion used in this case was made by infusing 2 drachms of powdered digitalis leaves in 4 ozs. of water.

Exp. XI.—*Nov.* 25, 1864.—At 10.12 A.M. I injected 4 milligrams of digitaline, about $\frac{1}{16}$th of a grain, suspended in about 30 minims of distilled water into the subcutaneous cellular tissue of the lumbar region of a Skye terrier. Three minutes after he began to lick the part, and when the injection was made, showed signs of irritation. In $4\frac{3}{4}$ minutes he seemed a little confused, and began to lick the corresponding part on the opposite side. In 5 minutes his tongue began to loll out (which I have hardly ever observed in him before or since), and he continued restless till $7\frac{1}{2}$ minutes, when he lay down, his breathing being rather hurried, and his tongue still out. In another minute he rose, and sat apparently intently listening, and as there was no particular sound at the time, I thought this probably indicated ringing in his ears. With the exception of some restlessness he seemed well till 25 minutes after the injection, when he sat down panting and lolling his tongue, as if he had had a smart run, though he had made no particular exertion to account for this. Soon after he seemed quite in his usual, and was none the worse.

Exp. XII.—*Dec.* 12.—A mongrel dog had some blood drawn from one jugular for examination, about the 6th, and on the 9th one of its carotids was exposed, and the hæmadynamometer applied under chloroform, but clots formed immediately, and the experiment was abandoned. On the 12th the dog was very weak.

At 2.5′ P.M., I began to inject ½ a grain (from memory) of digitaline in water into the subcutaneous cellular tissue in the lumbar region.

2.12′ Injection finished. The dog seemed uneasy and lay down.

2.16′ Till now he has been rising, turning round, and lying down again constantly. He now seems unable to stand well—grumbles.

2.17′30 Up again, grumbles, shakes his head listlessly about, seems uneasy.

2.18′ Seems inclined to vomit.

2.19′ Shakes his head and licks his foot.

2.20′ Paws his bed.

2.21′ Opens and shuts jaws.

2.23′ Sits up. The light is shining in his eyes, and his pupils are much contracted. Seems livelier. Shakes his head and paws his bed. I was then called away, and returned at 2.35′.

2.35′ Dog lying quite still, but there is a tremor all over and twitchings of the subcutaneous muscle of limbs, causing the movement of skin to be distinctly visible, but causing no movement of the limb. Breathing slow and laboured. Respirations are 8 in 65 seconds.

2.43′ Pulse 30 per minute, 2 or 3 beats coming close together during inspiration and expiration, and then an interval of 4 seconds between the beats, as well as one of exactly the same length between the end of one expiration and the beginning of another.

At 2.55′ Much the same—grumbling.

3. I now had to go to a class, and did not see the dog again till I returned at 5.30′. The dog was then stiff and cold. The tongue was protruded at the side of the mouth; the jaws shut; saliva on the chops; some prostatic mucus at the orifice of the urethra (not examined microscopically). Post-mortem—Lungs were of a light pink colour, much collapsed. Vena cava and venous system generally, full of black blood, and very turgid. Right auricle and ventricle distended with black blood, which was somewhat curdled—not in firm clots. Left side of heart natural in colour; contained a little blood, also somewhat curdled. Liver congested. Gall-bladder distended. Bladder firmly contracted, and empty.

Exp. XIII.—*Jan.* 16.—A small English terrier, very thin, was taken for experiment.

2.29′ P.M.—The dog was shivering; the heart sounds normal in character, but altered in rhythm, being very slow between the rigors, but during their continuance the beats were very rapid. The shiverings lasting each for about 4 seconds, and the interval about 1 minute. There was no murmur with the cardiac sounds. In the back room in which the dog had been kept, there was a bag of digitalis leaves on which it had lain, and a good many were scattered on the floor, so that the dog may have taken some along with its food before, and this possibly may have been the cause of the curious rhythm of the heart, and of the shiverings.

2.36′ P.M.—I injected ½ a grain of digitaline suspended in rather less than 1 oz. of water into the cellular tissue at the side of the lumbar vertebra.

2.37′ 15.—The dog suddenly started up, and ran to the end of his tether.

2.37′ 40.—Sat down on haunches. 2.38′ 30.—Rose again. 2.39′.—Straddles and whimpers, and jumps about. In attitude of attention; then runs about, and again stands, apparently listening intently.

4.40′ 20.—Whines and licks the place where the injection was made. On being loosed he shook himself, ran off, and sat down. Was restless, and seemed thirsty, so I gave him some water.

2.50′.—Heart sounds as before. 3.30′.—As before; no murmur.

3.50′.—Vomiting. 4.—Purging. 4.10′.—Vomiting. 4.20′.—Again vomiting, and again at 5.30′. I then left for the night.

On the following day (the 17th) the dog lay curled up on the floor for the greatest part of the day, but could stand or walk. At 5.35′ P.M. the dog had refused food, so to kill it at once I poured into its mouth some alcoholic solution of extract of digitalis, most of which it swallowed. 5.37′.—The dog vomited some white mucus, then lay quite quiet. 5·40′.—Again vomiting. 5.44′.—Seems livelier. 5.45′.—Again vomiting. 5.46′.—Purging.

On the 18th, at 10 A.M., the dog was lying curled up; it rose once or twice, but with some difficulty, and straddled very much when standing. Gait tottering and unsteady. 10.30′.—Struggles in vain to rise. Progresses along the floor, partly on its side and partly on its belly. Ineffectual efforts to rise. Heart's action very weak, but seems more regular. Surface cold. Respirations 7¼ per minute. Pupils contracted. The dog lay so, occasionally making slight vain efforts to rise for about an hour more, and then till 3.20′ P.M. it lay as if

quite dead, only very feeble respiration being seen, and the eyelids contracting when the finger touched one of them or the cornea. The caruncula lachrymalis covered almost one-fourth of the eye. At 3.20′ it was lying as if quite dead; the surface quite cold; the limbs flaccid; and the pulse inappreciable when it gave one or two yawns. At 3.23′ it gave a short, weak, low howl, and immediately after the cornea was found insensible. Post-mortem was made between five and ten minutes after death. On opening the body, a small quantity of urine trickled from the urethra, probably from pressure on the bladder, which was quite full. The lungs were of a natural colour. The heart was well filled with blood in both cavities. The venous system turgid. The heart contracted readily on irritation. At 4 P.M. the dissection was interrupted. It was resumed at 5.7′. The pericardium, when opened, contained a small quantity of serum, about one or two drachms. The heart still showed signs of contractility. At 4 P.M. the diaphragm contracted readily on irritation of the phrenic nerve; the œsophagus and thoracic duct contracted on pinching them.

Jan. 26.—One centigram of digitaline was injected into the cellular tissue of the loins of a rabbit. It produced no apparent effect.

SPHYGMOGRAPHIC TRACINGS.

The following are fac-similes of sphygmographic tracings of my own pulse, taken from 6th December, 1865, to 24th March, 1866:—

FIG. 16. 1865—Dec. 6—10.45 P M.

FIG. 17. Dec. 8—Right radial—12.35 midnight.

FIGS. 18 AND 19. Dec. 9—Right radial—11 P.M.

FIG. 20. Dec. 11—10.40 P.M.

FIG. 21. Dec. 12—10.30 P.M.

FIG. 22. Dec. 13.

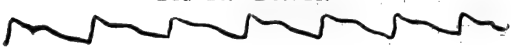


FIG. 23. Dec. 14—9.45 P.M.

FIG. 24. Dec. 15—12 midnight.

FIG. 25. Dec. 16—11.10 P.M. Pulse 75.

FIG. 26. Dec. 18—11 P.M.

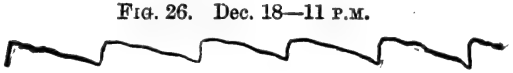
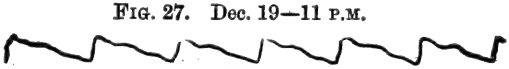


FIG. 27. Dec. 19—11 P.M.



FIGS. 28 AND 29. Dec. 20—10.35 P.M.

1

2

(1) Not tied very tightly; (2) Tied very tightly on the arm.

FIG. 30. Dec. 21—10.50 P.M.

FIG. 31. Dec. 28—10.40 P.M.

FIG. 32. Dec. 29—10.20 P.M.

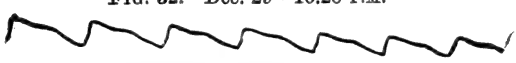


FIG. 33. Dec. 30—10 P.M.

FIG. 34. 1866—Jan. 1—11 P.M.

FIG. 35. Jan. 2—1.5 at night.

FIG. 36. Jan. 3—11 P.M.

FIG. 37. Jan. 4—10.45 P.M.

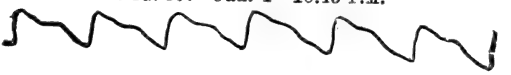


FIG. 38. Jan. 5—1.2 at night.

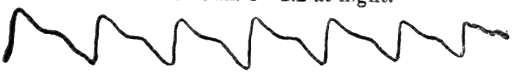


FIG. 39. Jan. 9—11 P.M.

FIG. 40. Jan. 10—11 P.M. Had had a little exercise just a few minutes before.

FIG. 41. Jan. 11—10.30 P.M.

FIG. 42. Jan. 12—1.10 at night.

FIG. 43. Jan. 13—11 P.M.

FIG. 44. Jan. 15—10-11 P.M.

FIG. 45. Jan. 16—10-11 P.M. Pulse 80.

FIG. 46. Jan. 17—10.20 P.M. Pulse 82.

FIG. 47. Jan. 19—12.45 midnight.

FIG. 48. Jan. 20—10.20 P.M. Pulse 80.

FIG. 49. Jan. 22—10 P.M.

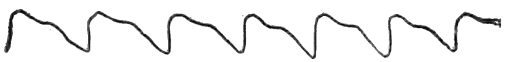


FIG. 50. Jan. 23—10-11 P.M.

FIG. 51. Jan. 24—10.55 P.M.

FIG. 52. Jan. 25—10.17 P.M.

FIG. 53. Jan. 26—12.18 midnight.

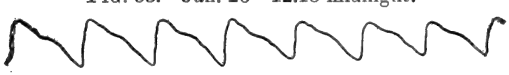


FIG. 54. Jan. 27—11.27 P.M

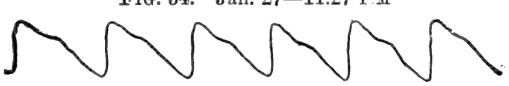


FIG. 55. Jan. 29—11.15 P.M.

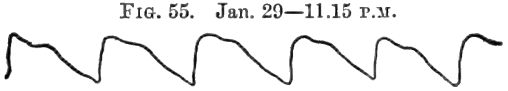


FIG. 56. Jan. 31—10.30 P.M.

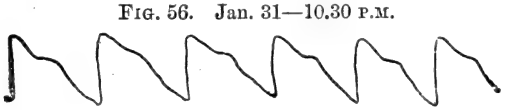


FIG. 57. Feb. 1—11.30 P.M.

FIG. 58. Feb. 2—1 at night.

FIG. 59. Feb. 3—11.30 P.M.

FIG. 60. Feb. 5—10.25 P.M.

FIG. 61. Feb. 6—10.50 P.M.

FIG. 62. Feb. 7—10.50 P.M.

FIG. 63. Feb. 10—about 12 P.M.

FIG. 64. Feb. 17—10.50 P.M.

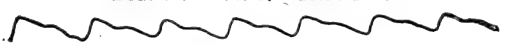
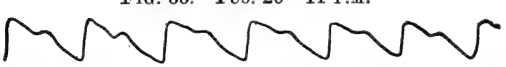


FIG. 65. Feb. 19—10.30 P.M.

FIG. 66. Feb. 20—11 P.M.



FIGS. 67 AND 68. Feb. 21—11.30 P.M. Sphygmograph not so tightly tied in No. 2 as in No. 1.

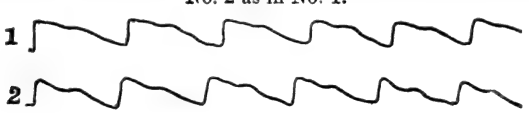


FIG. 69. Feb. 22—11 P.M.

FIG. 70. Feb. 23—1 at night.

FIG. 71. Feb. 24—11.20 P.M.

FIG. 72. Feb. 26—11.30 P.M.

FIG. 73. Feb. 27—12.30 midnight.

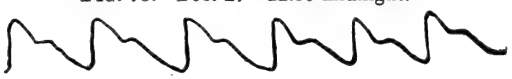


FIG. 74. Feb. 28—10.30 P.M.

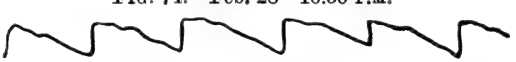


FIG. 75. March 1—1 at night.

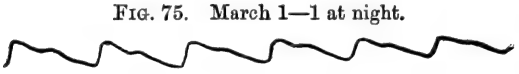


FIG. 76. March 2—1 at night.

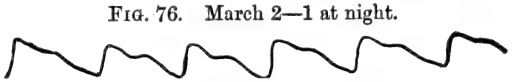


FIG. 77. March 3—11 P.M.

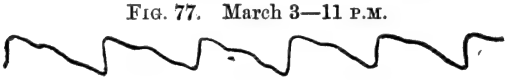


FIG. 78. March 5—11 P.M.

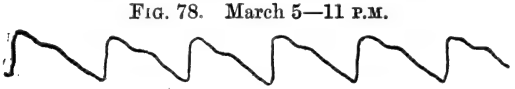


FIG. 79. March 6—11.25 P.M.

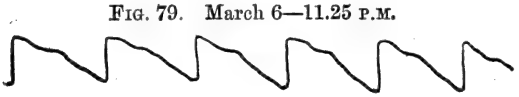


FIG. 80. March 7—11.30 P.M.

FIG. 81. March 8—11.30 P.M.

FIG. 82. March 9—11.50 P.M.

FIGS. 83 AND 84. March 10—11.15 and 11.30 P.M. No. 1—11.15 P.M. The sphygmograph not so tightly tied as in No. 2.

FIG. 85. March 12—11.45 P.M.

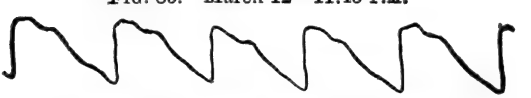


FIG. 86. March 13—2.50 at night.

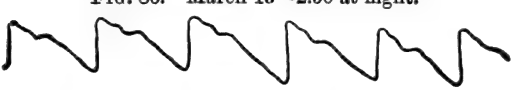


FIG. 87. March 14—11.15 P.M.

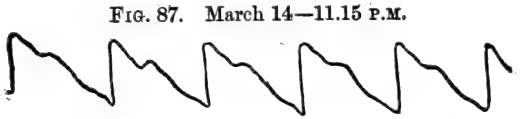


FIG. 88. March 15—11.20 P.M.

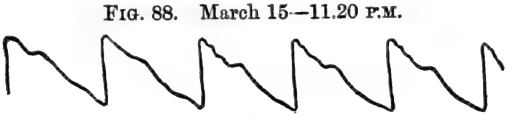


FIG. 89. March 16—5 A.M.

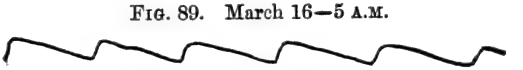


FIG. 90. March 16—1 at night.

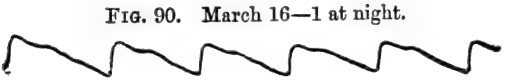


FIG. 91. March 17—11 P.M.

FIG. 92. March 17—about 11 P.M.

FIG. 93. March 19—2.30 at night.

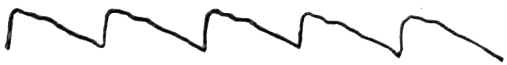


FIG. 94. March 20—11.23 P.M.

FIG. 95. March 23—12 midnight.

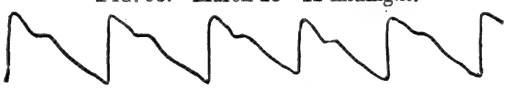


FIG. 96. March 24—10.40 P.M.

FIG. 97. March 24—10.40 P.M.

ON THE USE OF NITRITE OF AMYL IN ANGINA PECTORIS.

(Reprinted from *The Lancet* for July 27th, 1867.)

FEW things are more distressing to a physician than to stand beside a suffering patient who is anxiously looking to him for that relief from pain which he feels himself utterly unable to afford. His sympathy for the sufferer, and the regret he feels for the impotence of his art, engrave the picture indelibly on his mind, and serve as a constant and urgent stimulus in his search after the causes of the pain, and the means by which it may be alleviated.

Perhaps there is no class of cases in which such occurrences as this take place so frequently as in some kinds of cardiac disease, in which angina pectoris forms at once the most prominent and the most painful and distressing symptom. This painful affection is defined by Dr. Walshe as a paroxysmal neurosis, in which the heart is essentially concerned, and the cases included in this definition may be divided into two classes.

In the first and most typical, there is severe pain in the precordial region, often shooting up the neck and down the arms, accompanied by dyspnœa, and a most distressing sense of impending dissolution. The occurrence and departure of the attack are both equally sudden, and its duration is only a few minutes.

In the second class, which, from its greater frequency, is probably the more important, though the pain and dyspnœa may both be very great, the occurrence of the attack is sometimes gradual, and its departure generally so; its duration is from a few minutes to an hour and a half or more, and the sense of impending dissolution is less marked or altogether absent.

Brandy, ether, chloroform, ammonia, and other stimulants

have hitherto been chiefly relied upon for the relief of angina pectoris; but the alleviation which they produce is but slight, and the duration of the attack is but little affected by them.

In now publishing a statement of the results which I have obtained in the treatment of angina pectoris by nitrite of amyl, I have to observe that the cases in which I employed this remarkable substance belonged rather to the second than the first of the classes above described.

Nitrite of amyl was discovered by Balard; and further investigated by Guthrie,* who noticed its property of causing flushing in the face, throbbing of the carotids, and acceleration of the heart's action, and proposed it as a resuscitative in drowning, suffocation, and protracted fainting.

Little attention, however, was paid to it for some years, till it was again taken up by Dr. B. W. Richardson, who found that it caused paralysis of the nerves from the periphery inwards, diminished the contractility of the muscles, and caused dilatation of the capillaries, as seen in the web of the frog's foot.

Dr. Arthur Gamgee, in an unpublished series of experiments, both with the sphygmograph and hæmadynamometer has found that it greatly lessens the arterial tension both in animals and man; and it was these experiments—some of which I was fortunate enough to witness—which led me to try it in angina pectoris.

During the past winter there has been in the clinical wards one case in which the anginal pain was very severe, lasting from an hour to an hour and a half, and recurring every night, generally between 2 and 4 A.M.; besides several others in whom the affection, though present, was less frequent and less severe. Digitalis, aconite, and lobelia inflata were given in the intervals, without producing any benefit; and brandy and other diffusible stimulants during the fit produced little or no relief. When chloroform was given, so as to produce partial stupefaction, it relieved the pain for the time; but whenever the senses again became clear, the pain was as bad as before. Small bleedings, of three or four ounces, whether by cupping or venesection, were, however, always beneficial; the pain being completely

* *Journal of the Chemical Society*, 1859.

absent for one night after the operation, but generally returning on the second. As I believed the relief produced by the bleeding to be due to the diminution it occasioned in the arterial tension, it occurred to me that a substance which possesses the power of lessening it in such an eminent degree as nitrite of amyl would probably produce the same effect, and might be repeated as often as necessary without detriment to the patient's health. On application to my friend Dr. Gamgee, he kindly furnished me with a supply of pure nitrite, which he himself had made; and on proceeding to try it in the wards, with the sanction of the visiting physician, Dr. J. Hughes Bennett, my hopes were completely fulfilled. On pouring from five to ten drops of the nitrite on a cloth, and giving it to the patient to inhale, the physiological action took place in from thirty to sixty seconds; and simultaneously with the flushing of the face the pain completely disappeared, and generally did not return till its wonted time next night. Occasionally it began to return about five minutes after its first disappearance; but on giving a few drops more it again disappeared, and did not return. On a few occasions I have found that, while the pain disappeared from every other part of the chest, it remained persistent at a spot about two inches to the inside of the right nipple, and the action of the remedy had to be kept up for several minutes before this completely subsided. In almost all the other cases in which I have given it, as well as in those in which it has been tried by my friends, the pain has at once completely disappeared. In cases of aneurism, where the pain was constant, inhalation of the nitrite gave no relief, but where it was spasmodic, or subject to occasional exacerbations, it either completely removed or greatly relieved it. It may be as well to note that in those cases in which it failed small bleedings were likewise useless.

From observations during the attack, and from an examination of numerous sphygmographic tracings taken while the patients were free from pain, while it was coming on, at its height, passing off under the influence of amyl, and again completely gone, I find that when the attack comes on gradually the pulse becomes smaller and the arterial tension greater as

the pain increases in severity. During the attack the breathing is quick, the pulse small and rapid, and the arterial tension high, owing, I believe, to contraction of the systemic capillaries. As the nitrite is inhaled the pulse becomes slower and fuller, the tension diminished, and the breathing less hurried. On those occasions when the pain returned after an interval of a few minutes, the pulse, though showing small tension, remained small in volume, and not till the volume as well as tension of the pulse became normal did I feel sure that the pain would not return.

As patients who suffer from angina are apt to become plethoric, and greater relaxation of the vessels is then required before the tension is sufficiently lowered, I think it is advisable to take away a few ounces of blood every four weeks. When the remedy is used for a long time, the dose requires to be increased before the effect is produced. A less quantity is sufficient when it is used with a cone of blotting-paper, as recommended by Dr. Richardson, than when it is poured on a large cloth. From its power of paralysing both nerves and muscles, Dr. Richardson thinks it may prove useful in tetanus; and I believe that, by relaxing the spasm of the bronchial tubes, it might be very beneficial in SPASMODIC ASTHMA. I have tried it in a case of EPILEPSY, but the duration of the fit seemed little affected by it. It produces relief in some kinds of HEADACHE and in one of NEURALGIA of the scalp it relieved the severe shooting pain, though an aching feeling still remained.

While cholera was present in Edinburgh during last autumn, Dr. Gamgee proposed it as a remedy during the stage of collapse, a condition in which there are good grounds for supposing that the small arteries, both systemic and pulmonic, are in a state of great contraction. No well-marked case afterwards occurring in the town, he was deprived of an opportunity of putting it to the test; but it is a medicine well worthy of a trial, and, should another epidemic unhappily occur, it may prove our most valuable remedy.

ACTION OF DIGITALIS ON THE BLOOD-VESSELS.

In conjunction with ADOLPH BERNHARD MEYER, M.D.

(Reprinted from the *Journal of Anatomy and Physiology*, vol. vii, 1873.)

INDEPENDENTLY of each other, and in different ways, we both arrived at the conclusion that digitalin causes contraction of the small blood-vessels.* Wishing to support our views by still more conclusive proofs, we took advantage of the opportunities afforded to us in the physiological laboratory of the Berlin University to perform together, in January, 1868, some experiments on the subject. We are perfectly aware of their incompleteness, but circumstances having prevented us from continuing them, and the departure of one of us for a distant land rendering it improbable that we shall be able to resume them together, we now publish their results.

We believed that by a comparison of the form of the curves indicating the blood-pressure before and after the injection of digitalin into the circulation, we should be able to determine exactly whether it caused contraction of the arterioles or not. The kymographion we employed was that of Ludwig, as modified by Traube, and the experiments were conducted on dogs in the following manner. The animal being narcotised by hydrochlorate of morphia, a cannula was inserted into the crural artery, and a curve (fig. 98) showing the normal blood-pressure was described. Digitalin, suspended in a small quantity of distilled water, was then injected into the carotid artery, and pressure-curves again described. Injection into the artery was

* T. Lauder Brunton *On Digitalis: with some Observations on the Urine*, London, 1868, p. 52 (*vide* p. 55), and A. Bernhard Meyer, *Zur Lehre von den Herzgiften in Untersuchungen aus dem physiologischen Laboratorium der Züricher Hochschule* herausgegeben von Professor Fick. Wien, 1869, p. 71.

employed because Blake* found that digitalin produced a much greater effect on the blood-pressure when introduced into the circulation in this way than if injected into a vein. A comparison of the tracings thus obtained, after the injection, with that of the normal pressure and pulse (fig. 98), showed a slow-

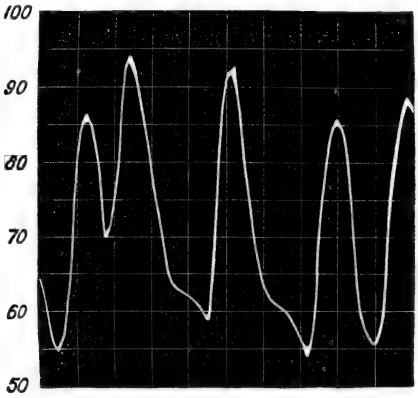


FIG. 98.

ing of the pulse, accompanied by an increase in the mean blood-pressure, while the height of the wave occasioned by each cardiac pulsation remained much the same (fig 99). The pres-

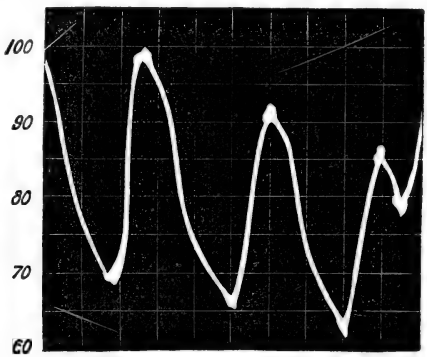


FIG. 99.

sure continued to rise gradually although the pulse not only became slower and slower, but the oscillations of the mercurial

* Blake, *Ed. Med. Journ.* 1839.

column at each pulsation diminished in extent (fig. 100). This rise could be due either to the heart propelling a greater quantity of blood into the aorta at each pulsation, or to the arteries, contracting so as to hinder it from escaping from the arterial into the venous system. The diminished height of the pulse-wave seems sufficient of itself to negative the former idea and to show that the increased pressure can only be due to contraction of the arterioles, but we think that a still clearer proof is afforded by the form of the wave. The time occupied in the ascent of the pressure-wave (indicated by the horizontal distance between the lowest and highest parts of the ascending limb) is nearly the same in figs. 98 and 100, but the descending limb of the latter sinks very gradually indeed, while in the

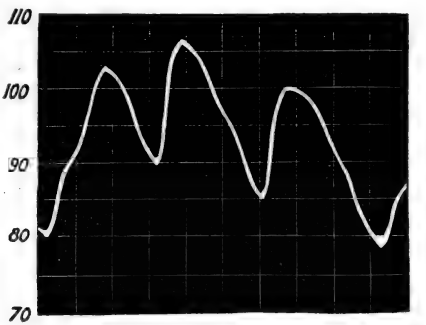


FIG. 100.

former it falls almost as quickly as it rises. What then is the explanation of this phenomenon? During the diastole of the heart, the sigmoid valves when healthy, as they were in this case, completely close the cardiac end of the aorta. The whole arterial system may then be compared to an elongated elastic vessel, from which fluid is issuing by a narrow opening. The greater the pressure of fluid in the vessel the more rapidly will it escape by the opening, the more quickly will the pressure consequently fall, and the more abrupt will be the descent of the pressure-curve. Now, the mean blood-pressure in the normal tracing is somewhat over 70 millimetres,* and the maxi-

* The true heights are of course nearly double these, but for convenient comparison with the tracings we have taken the numbers as they stand in the

mum height of the wave 44, while in that taken when the action of the digitalin was greatest, the mean pressure is somewhat over 90 millimetres, and the maximum 104. The fall of pressure ought, therefore, to be more abrupt, but instead of this it is more gradual. This alteration cannot, we think, be explained by any oscillations of the mercurial column independently of the blood-pressure, and can only be due to contraction of the arterioles retarding the flow of blood from the arterial into the venous system during the cardiac diastole. In a recent paper,* Boehm considers that the rise in blood-pressure produced by digitalis, is chiefly due to the increased action of the heart, and that the condition of the arterioles has little or nothing to do with it. He seems, however, to interpret tracings of the blood-pressure in the arteries of mammals in the same way as those obtained from the excised heart of the frog, and apparently forgets that while in the latter the form of the diastolic as well as of the systolic curve depends on the heart alone, in the former the heart can have but little or no influence on the pressure in the arterial system during the diastole, since all communication between them is prevented by the closure of the sigmoid valves. The curves which he gives confirm our views, for they show the same gradual fall in the pulse-wave, after the injection of digitalis, that ours do, and being traced with Fick's spring-kymographion, are free from any fallacies due to oscillations of the mercurial column. The continued high pressure he observed during prolonged stoppage of the heart, which he attributes to continuous cardiac systole, we would ascribe to contraction of the vessels so far as it is not due to changes in the respiration. If the arterioles were not contracted the pressure would fall, as, *e.g.*, in the experiments of Ludwig and Hafiz.†

We next attempted to ascertain whether the slowing of the

figures. (These curves only show the *ascent* of the mercurial column above the level in one limb of the U-tube of the manometer, whereas the true height is got by adding to this the descent of the mercury below the level in the other limb with a slight correction for the weight of the carbonate of soda solution in the descending limb.)

* *Pflüger's Archiv*, vol. v, p. 190.

† Ludwig's *Arbeiten*, 1870.

pulse is due to a direct specific influence of the drug on the roots of the vagus as supposed by one of us,* or to the stimulation of these roots by the increased pressure of blood in the cranium produced by the contraction of the arterioles, as supposed by the other.† In order to do this we diminished the blood-pressure by the inhalation of nitrite of amyl after it had become high and the pulse slow from the injection of digitalin. If the slowing of the pulse were due to a specific action of the digitalin on the vagus roots, it ought to continue although the pressure falls, but if due to stimulation of these roots by the high blood-pressure, it should disappear whenever the pressure is reduced. Our experiments showed that whenever the pressure fell after the inhalation of the nitrite of amyl the pulse became quick. It might thus appear that the slowing is due in part at least to the high pressure, and not altogether to a direct influence of the digitalin on the vagus; but this must be decided by farther experiment.

Lastly, we tried to discover whether digitalis causes contraction of the vessels by acting directly on their walls or on the vaso-motor centre. This we sought to do by observing whether the injection of digitalin into the circulation caused any alteration in the calibre of the vessels of the rabbit's ear after the sympathetic nerve of the same side as well as both vagi had been divided in the neck. The vagi were divided in order to prevent the digitalin from slowing the heart, and thus disturbing the circulation, and the sympathetic to prevent any influence being transmitted to the vessels of the ear from the vaso-motor centre. The results of these experiments were not constant, and we are unable to draw any definite conclusions from them; but the fact that the vessels of the ears were occasionally seen to empty themselves more quickly after the injection of digitalin than before, seems to us to indicate an action upon the walls of the vessels themselves.

The conclusions to which we have arrived are shortly, 1st, that digitalin causes contraction of the arterioles. This is proved by the small height of the pulse-wave, and by its descent

* Brunton, *Op. cit.* (*vide antea*, pp. 71 and 72).

† Meyer, *Op. cit.*

becoming more gradual after the injection notwithstanding the increased blood-pressure. 2nd, that the slowing of the pulse is probably due in part to the increased blood-pressure which results from the contraction of the arterioles. We gladly take this opportunity of expressing our obligations to Professor Rosenthal for the assistance and advice which he so constantly and kindly afforded us, and to Herr Merck, of Darmstadt, to whose kindness we owe the digitalin we employed.

[The kymographion employed was of the same kind as the one figured on p. 281.]

ON THE CHEMICAL COMPOSITION OF THE NUCLEI OF BLOOD CORPUSCLES.

A Research carried on in Professor Kühne's Laboratory, in Amsterdam, in the Winter of 1868–69.

(Reprinted from *The Journal of Anatomy and Physiology* for November, 1869.)

During the course of last summer (1868) Professor Kühne discovered that the chief constituent of the nuclei of blood corpuscles agreed in its reactions with mucin rather than fibrin or albumen. It had previously been found by Hoppe-Seyler,* associated in the nuclei with a small amount of paraglobulin, and, previous to Professor Kühne's discovery, had been supposed to be an albuminous substance, resembling fibrin. I was informed by Professor Kühne, while working in his laboratory in Amsterdam, of the observations he had already made, and having repeated them, I publish the result with his permission. The observations are not complete, but I give them now, as I am unable to prosecute them further at present.

The nuclei of the blood corpuscles of eels and frogs yield a substance similar to that obtained from the blood of fowls; but as the latter could be much more readily obtained in considerable quantity, it alone was used in studying the reactions in detail.

To obtain the nuclei, the defibrinated blood, mixed with ten or twelve times its volume of NaCl solution of 3 per cent., is filtered through linen, and the corpuscles allowed to subside in a flat tray. The supernatant fluid is then removed by a syphon, and the corpuscles, thus freed from serum, are either washed repeatedly with much water in the same manner, or after being allowed to settle in the salt solution for at least twenty-four hours, when they form a kind of film, are scraped together, and washed on a linen filter. In the former case, the nuclei or

* Kühne, *Lehrbuch der Physiologischen Chemie.*

rather zooids of the blood corpuscles are obtained as a white powder, which sinks very slowly in water; in the latter, as a mass resembling fibrin in appearance. Microscopic examination shows this powder to consist of the nuclei in the form of small round bodies containing several dark granules, surrounded by a ring of transparent colourless substance, apparently a remnant of stroma, whose breadth is about equal to the diameter of the nucleus, and whose edge is so delicate as to be scarcely perceptible. On the addition of aniline red or blue, dissolved in dilute alcohol, the nucleus becomes deeply coloured, the stroma slightly so, and its edges much more distinct. Weakly alkaline solutions of carmine and solutions of iodine also colour the nucleus deeply, but the stroma very slightly, or not at all. The nucleus is generally in the middle, but, occasionally, is more or less eccentric, and sometimes sticks quite close to one side of the surrounding substance. This last may possibly be its constant situation, and its central one only apparent, and it may thus correspond to the point in mammalian blood corpuscles, which was found by Roberts* and Rindfleisch† to become deeply coloured by magenta. If the powder be then shaken with ether and water it forms a layer between the two; and when this is microscopically examined, the nuclei alone are seen, the stroma formerly surrounding them being no longer perceptible even after the addition of aniline. The nuclei may be got at once by treating the corpuscles with ether, separating the nuclear layer by a stoppered funnel, and then washing in water. Alkalis cause the nuclei to swell, to run together in clumps, become indistinct, and finally disappear. Dilute mineral acids or acetic acid cause them to shrink and become more sharply defined. A small, strongly refracting point, resembling a nucleolus, and seeming to take up the colouring matter more strongly than the rest, also becomes visible; but this appearance may be due to a change of shape in the nucleus, occasioned by the acid. Concentrated mineral acids cause them to shrink much, to run together, become indistinct and disappear. The stroma surrounding the nuclei swells and shrinks somewhat,

* *Proceedings of Royal Society*, 1863.

† *Experimental Studien über die Histologie des Blutes.*

but not so markedly as the nuclei. If ferrocyanide of potassium be added to the nuclei shrivelled by acetic acid they swell up and become so indistinct as to be hardly visible. A solution of taurocholate or glycocholate of soda dissolves both nuclei and stroma. A little concentrated NaCl solution also causes the nuclei to disappear. When the corpuscles are washed on a linen filter, a fibrinous-looking mass is obtained, which, on microscopic examination, is seen to consist of shreds of fibrous membrane, or of bundles of fibres, studded with darker spots, and arranged in a manner resembling those of fibrin, though more regular and with less intercrossing. These spots seem to be the nuclei, but their outline is not so distinct, nor do they take the deep tint with aniline which they do in the powdery condition, the fibres becoming quite as deeply tinted as they.

The zooids are insoluble in water, and when suspended in it sink very slowly, but do so much more quickly after the addition of alcohol, concentrated acetic or oxalic acid, or dilute mineral acids. The mixture with water is quite mobile, and does not foam when shaken; but does so after the addition of a little NaCl solution, becoming at the same time somewhat tenacious and much clearer, the nuclei being partly dissolved and partly suspended. A concentrated mixture with NaCl solution gives a white flocky precipitate when much diluted. Salt solutions, of even one-fourth per cent., dissolve them to a considerable extent. The solubility in NaCl solution varies much, diminishing when the zooids stay long in water, but more slowly when the temperature is low. The same is the case with mucin obtained from tendons.

When many zooids are suspended in water, one drop of concentrated solution of potash or soda is sometimes sufficient to convert 40 cubic centimetres of the mixture from a milky mobile liquid to a clear gelatinous mass, resembling albuminate of potash in appearance, though not quite so firm. When this is thrown on a filter, the filtrate gives no precipitate with acetic acid. When more potash is added, a tenacious ropy fluid is produced, which filters very slowly; the filtrate is mobile, and though generally more or less alkaline, is sometimes neutral.

Alkaline carbonates dissolve them, but much more slowly,

nor do they form a jelly like the caustic alkalis; sometimes, however, they cause the zooids to stick together and form flocks, which, rising to the top, form a sticky mass. Lime and baryta water leave them apparently unchanged, and, after standing on them some time, give no precipitate with acetic acid, but an immediate turbidity if ferrocyanide of potassium be then added. Concentrated mineral acids dissolve the zooids, and give a precipitate on the addition of alkalis or much water.

Dilute mineral acids, such as HCl of 10 per cent., cause the mixture with water to foam on shaking, but when the filtered fluid is made alkaline by potash it gives no precipitate with acetic acid, but a turbidity when ferrocyanide of potassium is then added. The filtered solutions of the zooids in alkalis give the reactions of albumin, but the precipitate by acetic acid is generally insoluble in excess. Sometimes, however, not only the mucin from nuclei, but that from glands and tendons, appears quite soluble in large excess of glacial acetic acid. If the zooids be treated with HCl of one-tenth per cent., or acetic acid or NaCl solution of 10 per cent., and the filtered solution be precipitated by acetic acid and again filtered, the clear fluid in each case gives the reactions of albumin. The HCl solution is precipitated on neutralization, and the precipitate is insoluble in NaCl solutions of 10 per cent.

The albuminous body thus belongs to that class which includes, according to Hoppe-Seyler, fibrinogen, fibrinoplastic substance and myosin.

That the zooids contain fibrinoplastic substance or paraglobulin, as stated by Hoppe-Seyler, is shown by the distinct fibrinoplastic action which they exert when well washed. Sometimes they possess none at all; and this is probably due to the removal of the substance in the washing, the salt solution with which the corpuscles were washed not having been sufficiently carefully removed, and rendering the first water a dilute salt solution. This dissolves a certain amount both of albuminous substance and of mucin, becomes milky after standing or passing CO_2 through it, and possesses a slight fibrinoplastic effect. The fibrinoplastic effect was tried in all cases with a mixture of horse plasma and sulphate of magnesia.

From the way in which fibres are formed when the zooids are washed on a linen filter, it seems probable that fibrinogenic substance may also be present; but whether this be the same as mucin, or what the relation between mucin and the generators of fibrin or myosin, if any such relation exists, is still to be investigated.

When the precipitate from solutions in alkalis or NaCl by acetic acid is washed with acetic acid, then with dilute alcohol, and afterwards dissolved in a *small* quantity of potash and filtered, the filtrate is generally alkaline, but sometimes neutral. It is unchanged by boiling, gives with mineral acids a precipitate soluble in excess, and with acetic acid a precipitate insoluble in excess. On exceptional occasions, I have seen it, as well as mucin from tendons dissolved by excess of glacial acetic acid, give with acetic acid and ferrocyanide of potassium no turbidity, the ferrocyanide of potassium causing any turbidity from the acetic acid to become less and disappear; but after standing a considerable time a precipitate forms. Chloride of mercury causes no precipitate; with tannin, acetate of lead, or dilute sulphate of copper or chloride of iron it gives a precipitate. Added to potash and sulphate of copper it prevents the precipitation of the hydrated oxide of copper, but the solution remains blue even after boiling.

Nuclei, freed from stroma by ether and water and then dissolved in potash, give the same reactions. These reactions differ from those of mucin as given by Eichwald (Kühne, *Lehrbuch der Physiologischen Chemie*), inasmuch as tannin, sulphate of copper and chloride of iron give a slight precipitate or turbidity, but on treating nuclei and mucin from glands and tendons in the same way they give the same reactions. When a salivary gland is treated by potash, and the solution precipitated by acetic acid, the precipitate is sticky, and seems to differ much from that given by acetic acid in solutions of nuclei in potash, which is flocky, and gathers on a linen filter into a mass looking like boiled fibrin; but if the strongly acid and sticky precipitate from the gland be allowed to stand some time in water, it becomes exactly like that obtained from the nuclei.

The zooids and their solution in NaCl act briskly on peroxide

of hydrogen; the nuclei, after treatment by ether and water, do so also but less vigorously.

When boiled with dilute sulphuric acid they gave no trace of sugar.

I have never succeeded in obtaining them free from sulphur even after repeatedly dissolving in potash, and precipitating and washing by acetic acid; but the more carefully they were cleaned the less sulphur was found; and Professor Kühne on one occasion obtained no trace of sulphur after burning with nitrate of potash and adding chloride of barium. This trace of sulphur may possibly depend on a little albumen carried down with the mucin; more especially as one sees that if the hæmoglobin be not entirely removed by washing before dissolving in potash and precipitating by acetic acid, hæmatin is constantly carried down with the precipitate, and cannot again be separated.

When chicken blood is treated by NaCl solution of 10 per cent., as in Professor Heynsius' experiments lately published, the nuclei are dissolved and form a large portion of the fibrinous-looking substance he describes.

Whether mucin exists in mammalian blood or not I cannot certainly say, though the substance got by treating dogs' blood with salt solution of 10 per cent., and then washing the slimy mass, seemed, after solution in potash, to give a precipitate with acetic acid insoluble in excess. The quantity obtained pure was, however, so small that I was unable to try any other reaction.

Shortly, then, the substance of the nuclei, both with and without the stroma, agrees with mucin, and differs from albumin in its insolubility in HCl of 0·1 to 1 per cent., in its alkaline solutions being precipitated by nitric, hydrochloric or sulphuric acid, and the precipitate dissolved without difficulty by excess; in being precipitated by acetic acid, and the precipitate insoluble in excess, ferrocyanide of potassium causing no further turbidity, but clearing up any formed by the acetic acid; in neutral solutions being unchanged by boiling, and giving no precipitate with chloride of mercury, and when boiled with caustic potash and sulphate of copper remaining clear blue. It agrees with albumin and with mucin as I found

it (though differing from it, as described by Eichwald) in giving a turbidity or slight precipitate with tannin, chloride of iron and sulphate of copper. It differs from mucin in being insoluble in lime or baryta water, or in HCl of 10 per cent. Its most remarkable reaction is the change it undergoes by the addition of a very small quantity of caustic potash to the water in which it is suspended. It is then much more closely allied to mucin than to albumin. From the solubility and reactions of mucin being somewhat variable it is not improbable that, like albumin, it may occur in several forms, of which this may be one; but its composition and relations must be determined by analyses, which I hope at a future period to be able to make.

Öffentliche Gesammtsitzung am 12 December, 1869, zur feier des Geburtstages Seiner Majestät des Königs.

Dr. T. Lauder Brunton, *Ueber die Wirkung des salpetrig-sauren Amyloxyds auf den Blutstrom.* Aus dem physiolcgischen Institute zu Leipzig. Vorgelegt von dem wirklichen Mitgliede Prof. C. Ludwig. (Mit. 6 Holzschnitten.)

(Aus den *Berichten der Mathem.-Phys. Classe der Königl.-Sächs. Gesellschaft der Wissenschaften*, 1869, s. 285, und *Ludwig's Arbeiten 4ter Jahrgang* für 1869, s. 101.)

Auf das salpetrigsäure Amyloxyd hat *Guthrie* zuerst die Aufmerksamkeit der Aerzte und Physiologen gelenkt; bei einer chemischen Untersuchung dieses von *Balard* entdeckten Stoffes bemerkte er, dass sich nach Einathmung seiner Dämpfe das Gesicht lebhaft röthe, dass die Carotiden heftiger klopfen und dass der Herzschlag beschleunigt werde. Einige Jahre nachher behauptete *Richardson*, dass das salpetrigsaure Amyloxyd die Nerven von der Peripherie nach dem Centrum hin lähme, die Contractilität der Muskeln vermindere und Erweiterungen der Blutcapillaren in der Schwimmhaut des Froschfusses herbeiführe. Diese Mittheilung gab Professor *Arthur Gamgee* Veranlassung neue Versuche zu unternehmen. Aus seinen noch nicht veröffentlichten Beobachtungen war der eben genannte Gelehrte so freundlich mir das Folgende mitzutheilen: Ein Einfluss auf die Lebenseigenschaften der motorischen und sensiblen Nerven ist nicht zu finden, ebenso wenig gelang es, eine Erweiterung der Gefässe in der Schwimmhaut zu sehen. Athmet der Mensch die Dämpfe der Verbindung ein, so röthet sich das Gesicht, und die Pulscurve der *art. radialis*, welche der Sphygmograph aufzeichnet, nimmt eine eigenthümliche Form an; die bedeutendste Abweichung von der normalen Gestalt bietet der absteigende Curvenschenkel, insofern er statt des allmäligen einen sehr plötzlichen Abfall zeigt. Wird in die Carotis des Kaninchens ein Manometer eingesetzt und werden darauf die Dämpfe des salpetrigsauren Amyloxyds durch die Nase einge-

führt, so mindert sich die Häufigkeit des Herzschlags und der mittlere Blutdruck nimmt ab.

Auf Grund dieser Beobachtungen habe ich selbst das salpetrigsaure Amyloxyd zuerst mit Erfolg bei Kranken angewendet, die an gewissen Formen von *Angina pectoris* litten.* Hierdurch für das neue Arzneimittel interessirt, ergriff ich während meines Aufenthalts in Leipzig die Gelegenheit um in dem physiologischen Institute dieser Stadt einige Versuche darüber anzustellen, wie die Erscheinungen zu erklären seien, die man mittelst desselben im Blutstrom erzeugt hatte.

Als Versuchsthiere dienten Kaninchen. Im Anschluss an den bisherigen Gebrauch verleibte ich ihnen die Dämpfe des Amylpräparates ein, welche durch die künstliche Respiration in die Lungen geblasen wurden. Zu dem Ende schaltete ich in das Verbindungsrohr zwischen dem Blasebalg und der Trachea eine Nebenschliessung ein; mit andern Worten der an der Trachea und dem Blasebalg einfache Luftkanal war auf einem beschränkten Abschnitt in zwei Zweige zerlegt. In jedem der beiden Zweige sass ein Hahn, durch welchen die Lichtungen eines jeden Röhrenschenkels nach Belieben verschlossen werden konnten. Das Hauptrohr ging unmittelbar aus dem Blasebalg in die Luftröhre, in dem Nebenzweig war dagegen eine kleine Spritzflasche eingesetzt, deren Boden mit salpetrigsaurem Amyloxyd bedeckt war. Je nach der Stellung der Hähne konnte man also der Lunge die atmosphärische Luft rein oder im Gemenge mit den Dämpfen der Amylverbindung zuführen. Die eben geschilderte Einrichtung zog ich der unmittelbaren Anwendung der Dämpfe auf die Nase darum vor, weil es mir darauf ankam, die Wirkung derselben auf den Herzschlag festzustellen. Das Herz des Kaninchens, beziehungsweise die betreffenden Vagusäste desselben sind bekanntlich ungemein empfindlich gegen jede Aenderung in dem O-Gehalt des Arterienblutes; jede merkliche Abminderung des letztern hat sogleich eine Abnahme der Schlagzahl zur Folge. Nun ereignet es sich aber gewöhnlich, dass die Kaninchen die Athembewegungen einstellen, wenn so stark riechende Dämpfe wie die des salpetrigsauren Amyloxydes vor ihre Nase gehalten werden und dass sie erst mit der

* The *Lancet* for July 27, 1867.

beginnenden Athemnoth die Bewegungen wieder ausführen Damit aber ist auch schon eine Vagusreizung ganz unabhängig von den zugeführten Dämpfen eingeleitet. Zur Anwendung der künstlichen Respiration griff ich diesmal um so lieber, weil der Blasebalg, welcher mir hier zu Gebote stand, durch eine sehr regelmässig arbeitende Maschine getrieben ward, somit konnte ich sicher sein vor Störungen, welche durch ein ungleichförmiges Athmen eingeführt werden.—Das Manometer, mit welchem ich den Druck mass, wurde in die Carotis eingesetzt.

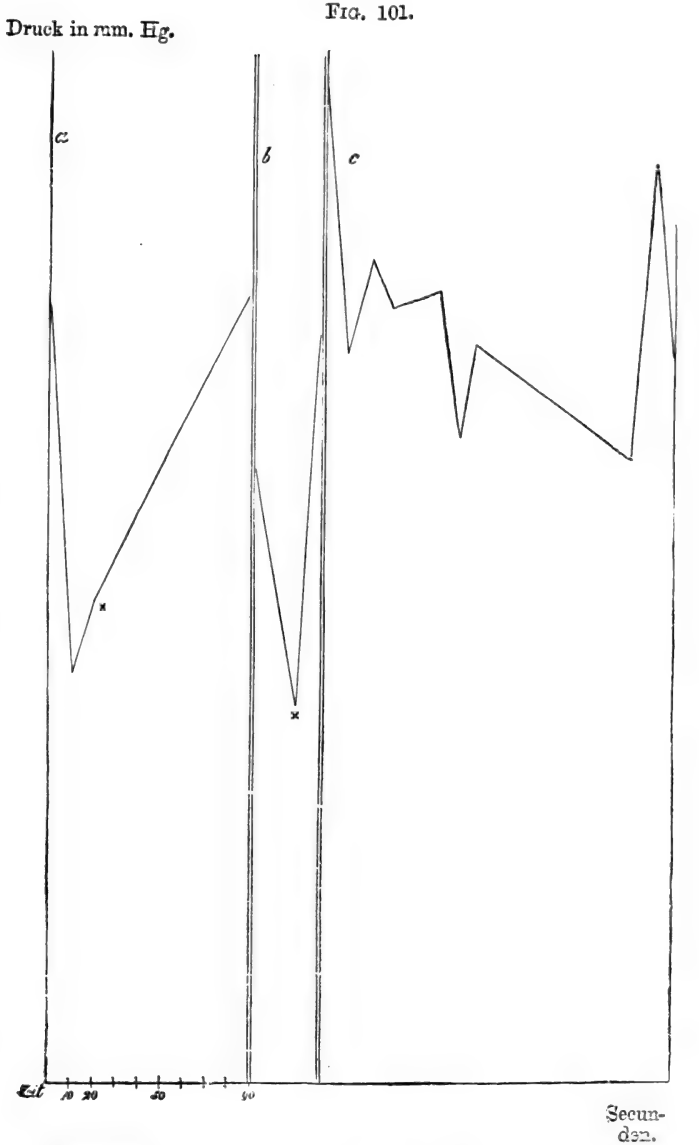
Mit diesen Hülfsmitteln sah ich zunächst, dass der Blutdruck, unmittelbar nachdem die Dämpfe des Amyloxyds eingeblasen waren, rasch absank, ohne dass sich die Zahl der Herzschläge merklich gemindert oder gemehrt hätte. Mit dem Absinken des Drucks stellten sich zugleich Krämpfe in allen Muskeln des Rumpfs und der Gliedmaassen ein, wodurch die von der Amylverbindung eingeleiteten Aenderungen des Blutstroms getrübt wurden. Denn mit dem Eintritt der Krämpfe hob sich der Blutdruck wieder und es wurden zugleich an der aufgeschriebenen Druckcurve die Herzchläge gar nicht oder ungenau zählbar. Um die Krämpfe und damit, wie ich glaubte, auch die Störungen zu vermeiden, welche sich dem reinen Hervortreten der Amylwirkung entgegensetzen, griff ich zur Vergiftung mit Curare. Hiernach schwanden allerdings die Krämpfe; aber es trat ein neues störendes Element ein, was, wie ich vermuthe, in dem Reizungszustande gelegen ist, in den die Gefässmuskeln durch das Curare verfallen.

Allerdings sank auch am curarisirten Thiere der Druck alsbald nachdem das Einblasen der flüchtigen Amylverbindung seinen Anfang genommen hatte, und der Druck erreichte seine ursprüngliche Höhe nicht wieder, während mit der Zuführung des Dampfes fortgefahren wurde: aber das Sinken war kein stetiges, sodass schliesslich der Druck dauernd auf einem bestimmten Minimalwerth angelangt wäre. Im Gegentheil die Quecksilbersäule hob sich und senkte sich und dieses zwar etwa so, wie es *L. Traube* an der Druckcurve des curarisirten Thieres gesehn hat.*

Diese Schwankungen sind jedenfalls der Ausdruck zweier

* L. Traube, *Centralblatt für die med. Wissenschaften*, 1865. 881.

Fig. 101.



Unvergiftet. Curarevergiftung.

× Einblasen beendet.

im entgegengesetzten Sinne wirksamer Einflüsse. Dieselben könnten gefunden werden einerseits in der Anwesenheit der unzersetzten Moleküle des salpetrigsauren Amyloxyds und anderseits in den aus dem letztern enstandenen Umsetzungsproducten, sodass Alles auf die dauernde Anwesenheit der Amylverbindung zu beziehen wäre, aber nach den vielfach bestätigten Erfahrungen von *L. Traube* konnte auch das Curare, also eine der Amylverbindung fremde Wirkung, für die Ursache der Druckvariation gehalten werden.

In Ermangelung einer andern unverfänglicheren Methode, durch welche auch am unvergifteten Thiere die Wirkung des während einer längern Zeit eingeflössten Amyldampfes sichtbar zu machen wäre, muss ich mich darauf beschränken, die Folgen seiner sehr vorübergehenden Einwirkung vorzulegen. Zu diesem Ende, namentlich aber um dem Umfang und den zeitlichen Ablauf der Druckerniedrigung zu versinnlichen, theile ich die in Figur 101 dargestellten Curven mit, welche durch die ihnen beigegebene Erklärung verständlich sein werden. Beim Beginn jeder der drei hintereinander ausgeführten Beobachtungen, *a*, *b*, *c* fängt das Einblasen an; schon 10 Secunden nach demselben ist der Blutdruck sehr tief herabgegangen. Traten Krämpfe ein, wie dieses in der Curve *a* und *b* der Fall ist, welche vor der Curarevergiftung von dem Thiere gewonnen wurden, so stieg der Druck wieder an, trotzdem dass das Einblasen noch fortgesetzt wurde. Wenn aber mit dem Einblasen 20 Secunden nach Beginn desselben aufgehört wurde, so stieg der Druck rasch wieder empor, sodass er in höchstens einer Minute seinen früheren Werth wieder erreicht hatte. Diese Erscheinungsreihe habe ich so oft bestätigt gefunden, als ich die Beobachtung anstellte. Sie weist darauf hin, dass schon minimale Mengen unsres Stoffes von der grössten Wirkung sind; und sie zeigt ausserdem, dass das in das Blut gekommene Gift sehr bald wieder unwirksam gemacht wird, entweder weil dasselbe innerhalb des Körpers zerstört wird oder weil es aus demselben verdunstet.

Die Erniedrigung des Blutdrucks kann nun herrühren entweder von einer Verminderung der Herzkräfte oder von einer solchen der Widerstände. Für die zweite dieser Unterstellun-

gen spricht die beträchtliche Erweiterung der peripherischen Gefässbezirke, wie man sie nicht allein am Ohr des Kaninchens, sondern auch in auffallendster Weise an der menschlichen Gesichtshaut sieht, namentlich wenn ein Individuum mit sehr reizbarem, leicht erröthendem und erblassendem Gesicht einige mit dem Dampf geschwängerte Athemzüge ausführte. Immerhin erschien es mir noch nothwendig die Frage durch einen Versuch zu entscheiden, um so mehr, als ich dabei auch zu erfahren wünschte, ob die eintretende Gefässerweiterung abhängig sei von einer unmittelbaren Aenderung der Gefässwand oder von einer solchen, die herbeigeführt ist durch die Abschwächung des Tonus, den die Gefässnerven im verlängerten Marke empfangen.

Um verständlich zu machen wesshalb sich mir diese Fragestellung aufdrängte, will ich hier in der Kürze einige Resultate einer andern Versuchsreihe einschalten, die ich ebenfalls in Leipzig begonnen aber leider noch nicht vollendet habe.

Durch die bemerkenswerthen Beobachtungen von *M. Schiff*, welche eine allseitige Bestätigung erfahren haben, ist es bekannt, dass der Durchmesser der Arterien des Kaninchenohres sehr häufig in Schwankungen begriffen ist. Ich habe nun gefunden, dass diese Erscheinung dem Ohr der Kaninchen keineswegs allein eigenthümlich ist, sondern dass man sie in gleich ausgesprochener Weise auch an allen andern freigelegten Arterienzweigen der Haut und des Bindegewebes beobachten kann. Diese Schwankungen des Durchmessers zeigen anderwärts grade so wie am Kaninchenohr grosse Unregelmässigkeiten, indem sie an demselben Ort bei dem einen Thiere deutlicher und häufiger auftreten als bei einem andern und als sie zu verschiedenen Zeiten bei demselben Thier fehlen und vorhanden sein können.

Diese Veränderungen des Arteriendurchmessers sind mindestens zum Theil vollkommen unabhängig von den Erregungen, welchen die Gefässnerven im Hirn ausgesetzt sind; denn sie bestehen an den Arterien des Ohrs und an denen der übrigen Körpertheile unverändert fort, wenn man auch sämmtliche Nerven, sympathische und cerebrospinale durchschnitten hat, die in dem zu beobachtenden Orte sich verbreiten, ja sie ver-

schwinden nicht nach der Durchschneidung des Halsmarkes trotz des sehr niedrigen Blutdruckes, der dann noch übrig bleibt. Die beschriebenen Bewegungen der grossen und kleinen Arterien treten, wie erwähnt, nicht bei jedem Thiere und nicht zu jeder Zeit gleich deutlich ein. Fehlen dieselben, so kann man sie in der Regel hervorrufen, entweder durch Vergiftung mit Curare oder durch Unterbrechung der Athmung. Sind dieselben einmal geweckt, so pflegen sie sich auch dann noch fortzuerhalten, wenn selbst nachträglich die Athmung auf das Sorgfältigste geregelt wird. Da durch die Untersuchungen von *L. Traube*, *Thiry* und *Kowalewsky** bekannt ist, dass in Folge der Curarevergiftung und der gestörten Athmung der Blutdruck in den Arterien erster Ordnung sehr grosse Variationen erfährt, so muss der Gedanke erwachen, es seien diese letztern Schuld an den Veränderungen der Durchmesser der kleinsten Arterien. Diese an und für sich annehmbare Erklärung erweist sich aber als unhaltbar wegen des Ganges, den die Verengerungen und Erweiterungen in den kleinen Arterien darbieten. Sehr häufig stellt sich nämlich plötzlich im Verlauf einer kleinen Arterie mitten zwischen zwei mit Blut erfüllten Stücken eine Einschnürung ein, sodass ein Verhalten zum Vorschein kommt, wie man es schon seit langer Zeit am ausgeschnittenen Dünndarm kennt.—In den Bezirken, deren Nerven sämmtlich durchschnitten sind, erhalten sich die Arterienwände auch noch in einer andern Beziehung dem ausgeschnittenen Darme ähnlich. Jede leiseste Berührung einer beschränkten Stelle ruft eine Bewegung hervor, die sich meist auf den getroffenen Ort beschränkt. Diese durch den unmittelbaren Einfluss erzeugte Veränderung besteht jedoch, so weit ich gesehen, nicht vorwiegend in einer Verengerung der Lichtung wie beim Darm, sondern vorzugsweise in einer Erweiterung derselben, welche sehr lange als eine partielle Ausbuchtung bestehen bleibt und die sich nur allmählig ausgleicht. Da schon *Gunning* und *Cohnheim* Aehnliches an der Schwimmhaut und der Zunge des Frosches beobachtet haben und da *Sadler* auch an den Gefässen der Skeletmuskeln der Hunde auf Thatsachen gestossen ist, die sich nur durch Eigenbewegung der Gefässwand erklären

* *Centralblatt für die med. Wissenschaft*, 1868. 579.

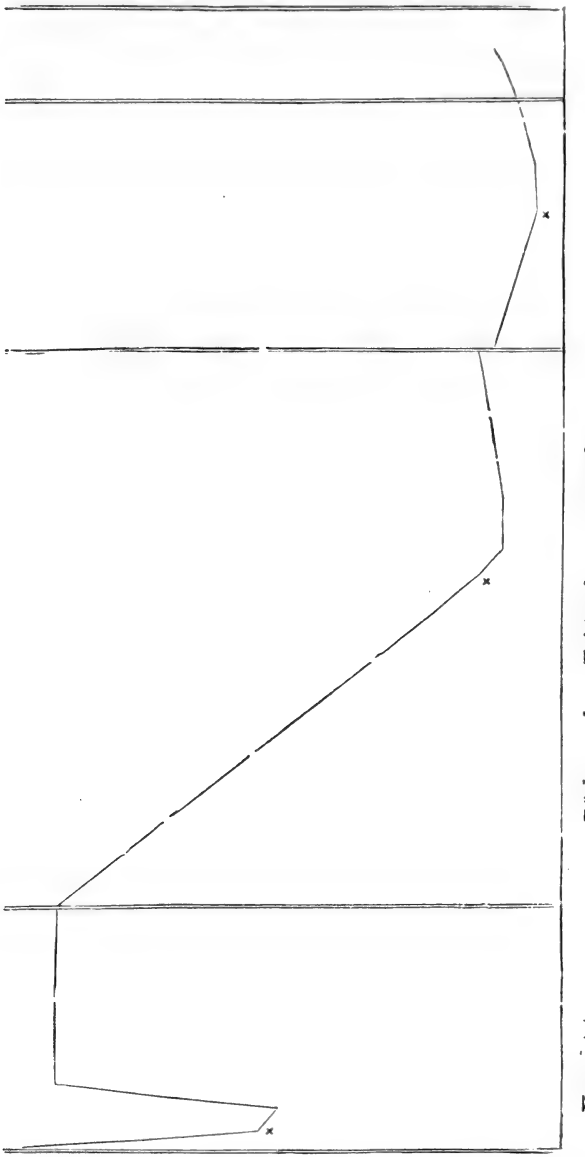


Fig. 102.

lassen, so scheint die selbstständige Veränderung dieser letztern ein weit verbreitetes und darum wichtiges Ereigniss zu sein.

Wenn ich nun zu den Versuchen mit salpetrigsaurem Amyloxyd zurückkehre, so wird es einleuchten, warum ich den

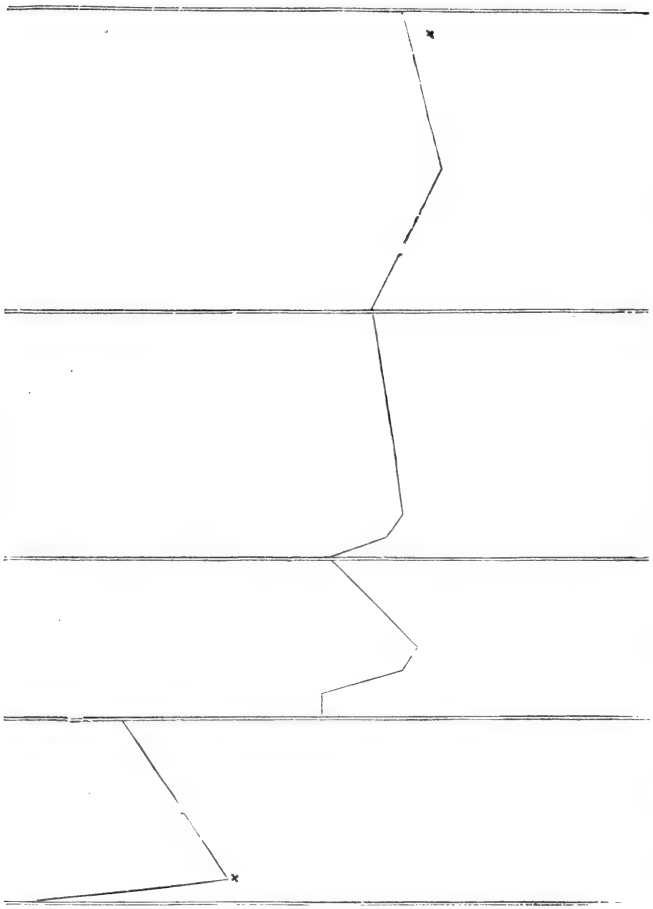


Fig. 103.

Dampf der genannten Verbindung auch solchen Thieren einblies, deren Rückenmark vorgängig durchschnitten worden war.

Meine Vermuthung, dass an den Thieren, die dieser Operation unterworfen worden waren, die Druckminderung in Folge der Amylwirkung nicht ausbleiben werde, hat sich vollkommen bestätigt. Als Beispiele für den Befund mögen die in

Fig. 102 und 103 wiedergegebenen Beobachtungen an zwei verschiedenen Kaninchen dienen.

Jedem der beiden Thiere wurden vor der Durchschneidung des Halsmarks die Dämpfe des salpetrigsauren Amyloxyds eingeblasen. In diesem Stadium des Versuchs trat das schon bekannte Resultat zu Tage. Nach der Durchschneidung des Halsmarks, welche unmittelbar unter dem Atlas geschah, sank bei dem Thier II der Druck ungewöhnlich tief herab; als er constant geworden war, bewirkte das Einblasen der Dämpfe ein neues Sinken des Blutdruckes, das also auf die Rechnung des salpetrigsauren Amyloxyds zu setzen war. Der Werth des Abfalls war nach absolutem Maasse gemessen allerdings ein geringer; nach relativem Maasse war dagegen die Aenderung noch eine sehr bedeutende. Die Erscheinungen des Sinkens eines schon an und für sich niedern Druckes sind hier denen analog, welche man zu sehen pflegt wenn der zweite *n. splanchnicus* noch durchschnitten wird, nachdem vorher schon der erste durchtrennt war.

Als das Einblasen ausgesetzt wurde erhob sich der Blutdruck nicht alsbald wieder auf seine frühere Höhe, sondern er sank vorerst noch tiefer um sich dann erst ganz allmählig zu erholen. Dieser Erfolg kann zwei Erklärungen finden. Aus andern Versuchen, die im hiesigen Laboratorium unternommen wurden, ist mir bekannt, dass die Geschwindigkeit des Blutstroms sehr stark heruntergeht, wenn das Halsmark durchschnitten ist. Da die Zuführung und die nachfolgende Entfernung der Amylverbindung in Abhängigkeit von der Stromgeschwindigkeit des Blutes stehen muss, so wäre der langsame Ablauf der Druckschwankung vielleicht hieraus zu erläutern. Möglich ist aber noch ein anderer Grund. Bei dem vorliegenden Thiere sank nämlich die Pulszahl in der Zeiteinheit von 9 auf 4 herab. Dieses Herabgehn, welches wohl die Folge des sehr verminderten Druckes gewesen ist, kann ebenfalls an der langsamen Erholung Schuld sein.—Eine Wiederholung der Einathmung bei dem Thier ergab dasselbe Resultat.

Bei dem zweiten Kaninchen (Fig. 103) erniedrigte sich nach Durchschneidung des Halsmarks der Druck nicht so bedeutend als im vorhergehenden Fall. Auch bei ihm sehen wir durch

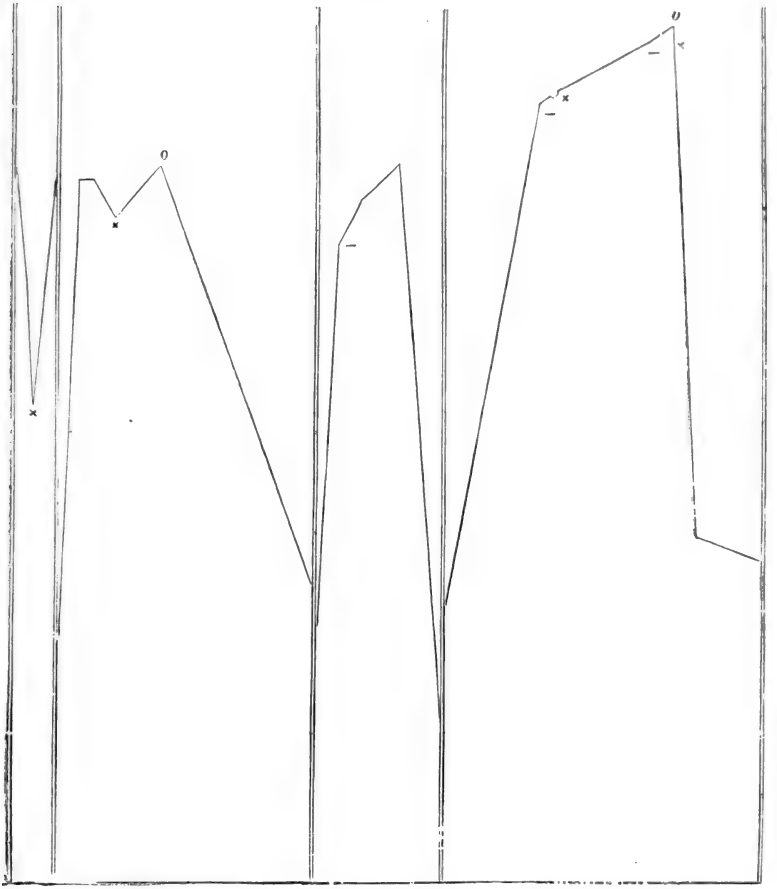
die Einathmung der Amylverbindung den Druck noch weiter heruntersteigen. Da das Thier wegen seines höhern Blutdrucks eine öftere Wiederholung des Versuchs vertrug, so benutzte ich die Gelegenheit, um statt der bis dahin geübten kurzdauernden Einverleibung eine längere 87 Secunden anhaltende stattfinden zu lassen. Während dieser langen Einblasung ging der Druck nicht tiefer herab als während der kürzern, ja gegen Ende des Einblasens erhob er sich sogar wiederum ein Kleines. Diese Thatsache ist mit Rücksicht auf die frühere Bemerkung das curarisirte Kaninchen betreffend nicht ohne Bedeutung. Dieses Thier (3) zeigte von dem vorhergehenden auch insofern ein abweichendes Verhalten, als sich die Pulszahl während und nach der Einblasung nicht änderte; trotzdem trat auch hier die Wiederherstellung des höhern Druckes sehr langsam ein und als die Lungen des Thiers den Amyldämpfen sehr anhaltend ausgesetzt gewesen waren erhob sich zwar der Druck nach Beendigung des Einathmens der Amyldämpfe, aber er kehrte nicht mehr zu seiner frühern Höhe zurück. Dieser Umstand muss es sehr wünschenswerth erscheinen lassen, eine Methode zu finden, die an dem unversehrten Thier eine längere Einwirkung des salpetrigsauren Amyloxyds erlaubt.

Nach diesen Versuchen, denen ich noch einige gleichbeschaffene zufügen könnte, wird es keinem Zweifel unterliegen, dass das salpetrigsaure Amyloxyd zu den Stoffen gehört, welche unmittelbar auf die Gefässwand lähmend wirken. Zweifelhaft bleibt es nur noch, ob die Nervenendigungen oder die Muskeln selbst ergriffen werden. Zudem werden weitere Versuche darüber anzustellen sein, ob die Gefässwand die einzige unter den aus glatten Muskeln hergestellten Häuten ist, welche der Vergiftung durch salpetrigsaures Amyloxyd zugänglich ist.

Um auch den letzten Einwand wegzuräumen, der gegen das soeben mitgetheilte Ergebniss erhoben werden könnte, habe ich mich um den directen Beweis dafür bemüht, dass die Erniedrigung des Blutdruckes in Folge des salpetrigsauren Amyloxyds unabhängig ist von einer Schwächung der Herzkräfte. Der Plan, nach welchem ich die hierauf zielenden Versuche ausführte, bestand darin, den Thieren die a. aorta unmittelbar unterhalb des Zwergfells zusammenzupressen und sie während-

dess den Dämpfen dor Amylverbindung auszusetzen. Wenn das salpetrigsaure Amyloxyd eine schwächende Wirkung auf das Herz ausübt, so hätte nun der Druck, auf welchen sich das

Fig. 104.

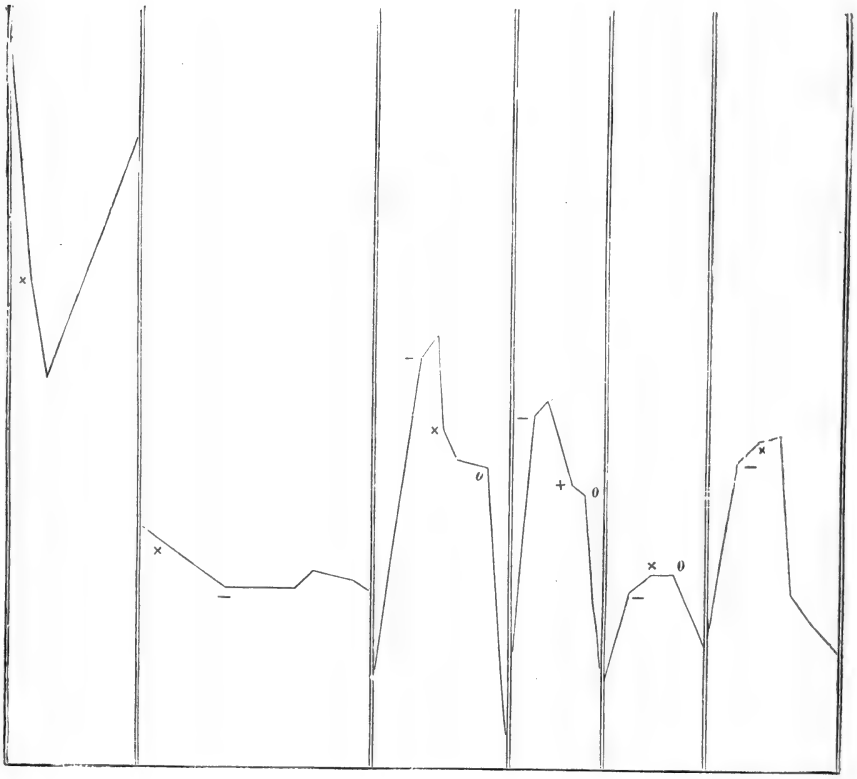


– Einblasen begonnen ; + Einblasen beendet; im Beginn der drei letzten Beobachtungen Aorta comprimirt ; 0 Aorta geöffnet.

Blut nach der Verschliessung der Aorta erhoben hatte, alsbald wieder absinken müssen, nachdem mit dem Einblasen der genannten Verbindung der Anfang gemacht worden war. Dieses Absinken hätte sich selbstverständlich in einem um so höheren

Grade einstellen müssen, je bedeutender das Herz unter der Einwirkung unseres Giftes gelitten hätte. Aus einer nähern Ueberlegung der Bedingungen, unter welchen der soeben skizzirte Versuch ausgeführt wird, ergiebt sich jedoch sogleich,

Fig. 105.

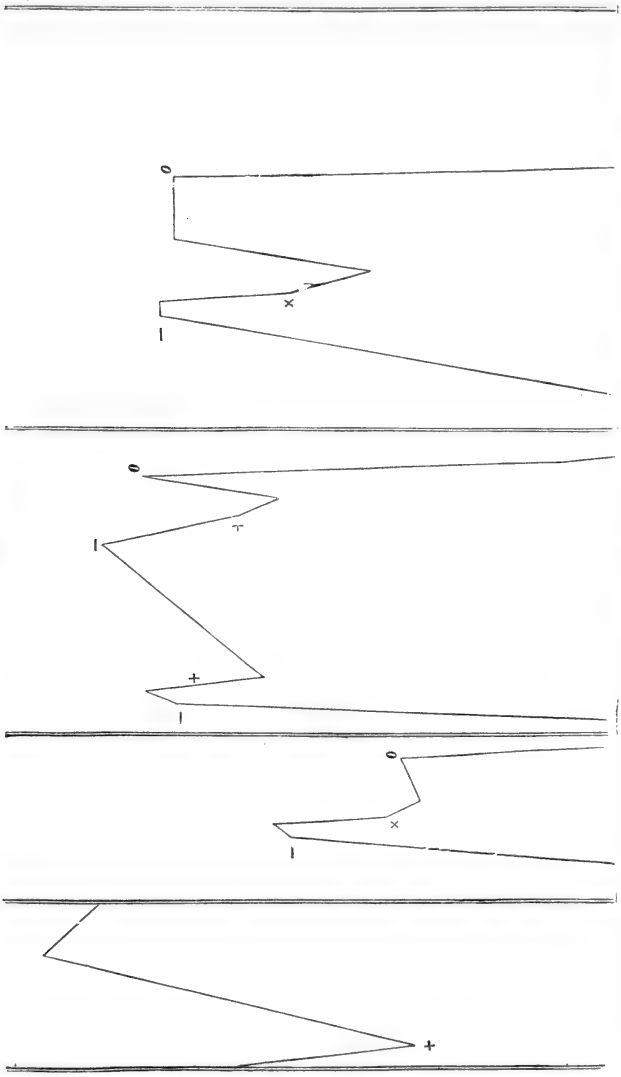


Halsmark durchschnitten.
In den 4 letzten Beobachtungen Aorta comprimirt; bei 0 Aorta geöffnet;
— Einblasung begonnen; + Einblasung beendet.

dass man nicht immer auf ein vollständiges Ausbleiben der Drucksenkung rechnen könne; dieses darum nicht, weil ja durch die Verschliessung der Bauchaorta nicht alle Wege abgeschnitten sind, durch welche das Blut aus der Brustaorta entweichen kann. Diese noch offen gelassenen Wege werden sich unter

dem Einflusse des Amyloxyds erweitern und hierdurch wird eine Druckerniedrigung möglich werden. Um den Werth dieser

Fig. 106.



Die Ordinaten, welche den Druck angeben, beginnen 50 mm. über der Abscisse. In den drei letzten Beobachtungen Rückenmark durchschnitten und Aorta comprimirt; bei 0 Aorta geöffnet; − Einblasung begonnen; + Einblasung aufgehört.

letzteren in engere Grenzen einzuschliessen, unternahm ich die Aortencompression nur an solchen Thieren, denen das Hals-

mark zerschnitten war. Durch diese Operation war auch die Wandung der nicht verschlossenen Gefässe erschlafft und ich hatte somit zu erwarten, dass die durch die Wirkung des Amyloxyds hinzutretende Abspannung von einer geringern Folge für das beschleunigte Abfliessen des Blutes sein werde, als wenn das Amyloxyd auf die noch dem normalen Tonus ausgesetzten Gefässwandungen wirksam geworden wäre.

Die Resultate dieser Versuche sind repräsentirt durch die Figuren 104, 105 und 106. Zum Verständniss derselben führe ich an, dass die erste Einathmung an jedem der drei Thiere geschah, bevor das Rückenmark verletzt oder die Aorta comprimirt war. Diese Versuche wurden in der Absicht vorausgeschickt um die Empfänglichkeit des möglichst normalen Thieres gegen das Gift zu prüfen. Nachden hierauf das Rückenmark durchschnitten war, wurde entweder noch vor der Compression der Aorta ein Versuch angestellt, wie ihn Fig. 105 zeigt, oder es wurde auch sogleich die Bauchaorta mit dem Finger zusammengedrückt. Als in Folge dieses Eingriffs der Blutdruck hoch angewachsen war, wurde nun mit dem Einblasen der giftigen Dämpfe begonnen. Ueberblickt man die Folgen, welche hierdurch in zweien der vorgeführten Versuche (Fig. 104 und 105) eintraten, so gewahrt man ein veränderliches Verhalten. Oefter hält sich während des Einblasens der Druck unverändert oder er steigt sogar, statt wie sonst zu sinken. Zuweilen aber stellte sich während desselben auch ein Sinken des Drucks ein, das jedoch viel geringer ist als es während der ersten Einathmung am unverletzten Thiere gewesen. Bei dem dritten Versuche (Fig. 106) findet sich während der Aortencompression und des gleichzeitigen Einblasens jedesmal ein Absinken des Druckes ein, das auch rasch wieder verschwindet, wenn mit dem Einblasen der giftigen Dämpfe aufgehört wurde. Aber auch diese Druckverminderung ist um ein Beträchtliches geringer als die vor der Markzerschneidung und der Aortencompression aufgetreten war.

Aus diesem Resultate dürfte man zu der Ueberzeugung gelangen, dass das salpetrigsaure Amyloxyd, wenn überhaupt, doch zum mindesten nicht mächtig genug auf das Herz wirke um das beträchtliche Abfallen des Druckes zu erklären, wel-

ches seine Einathmung vor der Aortencompression herbeiführt. Ueberlegt man nun, dass es Fälle giebt, in welchen der Druck gar nicht absinkt nachdem er durch die Verschliessung der Aorta emporgetrieben wurde, und bedenkt man ferner, dass die schwächern Druckabfälle, welche während des Aortenschlusses eintraten, ihre genügende Erklärung durch die Erweiterung der Schlüsselbein- und Kopfarterienzweige finden; erwägt man endlich, dass die Zahl der Herzschläge durch das Einblasen des giftigen Dampfes keine Veränderung erfährt, so dürfte man zu der Ueberzeugung gelangen, dass das salpetrigsaure Amyloxyd auf das Herz überhaupt keine unmittelbare Wirkung übt.

Ein Symptom, welches eine besondere Erklärung bedürfte, sind die Krämpfe der Skeletmuskeln, welche ausnahmslos beim Kaninchen eintreten, das nicht mit Curare vergiftet und dessen Rückenmark nicht durchschnitten ist. Ich habe es einstweilen unterlassen, nach einer Erklärung für dieselben zu suchen, da ich ihren Eintritt niemals bei den Menschen beobachtet habe, welche salpetrigsauren Amyloxyd einathmeten.

Schliesslich lasse ich noch die Zahlen folgen aus denen die Figuren der vorstehenden Abhandlung construirt sind.— Ich bitte bei der Durchsicht die Pulszahlen zu beachten.

Datum des Versuchs und No. der Beobachtung.	Zeit in Secunden.	Einathmen von salpetrigs. Amyloxyd.	Blutdruck in Mm. Hg.	Puls-Zahl in der Zeiteinheit.	Bemerkungen.
Juli 9, 1869.					Zu Fig. 101.
1.	0	begonnen	104·5	9	
	10		57	9	Krämpfe.
	22	aufgehört	65		
	59		90		
	87		108		
2.	0	begonnen	83	9	
	19	aufgehört	52	9	Krämpfe.
	33		102		
	36		92		
3.	3		141	11,5	
	6		157	11,5	Mit Curare vergiftet
	12	angefangen	139	11,5	
	19		99		

Datum des Versuchs und No. der Beobachtung.	Zeit in Secunden.	Einathmen von salpetrigs. Amyloxyd.	Blutdruck in Mm. Hg.	Puls-Zahl in der Zeiteinheit.	Bemerkungen.
Juli 9.					Zu Fig. 101.
	30		112		
	44		106		
	59		108		
	72		88		
	77		101		
	151		85		
	159		126	11,0	
	165		101		
4.			75	12?	
	1	angefangen	38		
		aufgehört	67		
	3	angefangen	78		
	6		67		
	14		62		
	21	aufgehört	64		
	36		64		
Juli 24.					Zu Fig. 102.
1.	0	angefangen	72	10	
	8	aufgehört	41		Krämpfe.
	17		38	11	
	30		68		
	108		68		
2.	0	angefangen	18	9	Rechte Hälfte des Rückenmark durchschnitten.
	20	aufgehört	11	5	
	25		8,5	4	
	53		8	4	
	114		11	8	
3.	0	angefangen	9	9	
	4	aufgehört	3,5	6	
	20		4	4	
	46		6	8	
	später		9	9	
Juli 23.					Zu Fig. 103.
1.	0	angefangen	81	9 u. 11	
	14	aufgehört	56	11	
	87		70		
2.	0	angefangen	43	8	Rückenmark am occiput durchschnitten.
	6		43	8	
	25	aufgehört	32	8 u. 7,5	
	33		30	8	
	64		42		

Datum des Versuchs und No. der Beobachtung	Zeit in Secunden.	Einathmen von salpetrigs. Amyloxyd.	Blutdruck in Mm. Hg.	Puls-Zahl in der Zeiteinheit.	Bemerkungen.
Juli 23.					Zu Fig. 103.
3.	0	angefangen	42		
	7		34		
	20	aufgehört	32		
	112		36		
4.	0	angefangen	38		
	42		29		
	87	aufgehört	31		
5.	0		32		
	56	fing an	27		
	123		32		
Juli 31.					Zu Fig. 104.
1.			95		
	7	angefangen	65		
	12	aufgehört	95		
			36		Rückenmarkdurchschnitt. zwischen atlas u. occiput.
2.	0	angefangen	95	6,5	Aorta comprimirt.
	8	aufgehört	95	6	
	16		90		
	33		97	6	
	100		40	8	Aorta losgelassen.
3.			36		
		angefangen	86	5,5	Aorta comprimirt.
	12		92	5	
	31		97	5	
	50		22	6	Aorta losgelassen.
4.	0		38	6	
	28	angefangen	105	7	Aorta comprimirt.
	42	aufgehört	107	7	
	70	angefangen	112	6	
	84	aufgehört	114		
	92		116		
	106		47		Aorta losgelassen.
	134		44		
Aug. 9.					Zu Fig. 105.
1.	0	angefangen	67		
	8	aufgehört	65		Krämpfe.
	14		52		
	56		85		
2.	0	angefangen	32	6	Rückenmark durchschnitten.
	8	aufgehört	30	6	

Datum des Versuchs und No. der Beobachtung.	Zeit in Secunden.	Einathmen von salpetrigs. Amyloxyd.	Blutdruck in Mm. Hg.	Puls-Zahl in der Zeiteinheit.	Bemerkungen.
Aug. 9.					Zu Fig. 105.
	36		24		
	70		24	6	
	76		26	6	
	92		25		
	98		24		
3.	0		13		
	17	angefangen	55		Aorta comprimirt.
	24		58		
	27	aufgehört.	45		
	33		41		
	47		40		
	53		7		Aorta losgelassen.
	67		3		
4.			14	6. 5 u. 7	
	11	angefangen	47	6, 5	Aorta comprimirt.
	16		49	6	
	23	aufgehört	38	6	
	28		37	8	
	33		14	7	Aorta losgelassen.
5.			13	6	
	12	angefangen	23	6	Aorta comprimirt.
	22	aufgehört	26	5, 5	
	33		26	5, 5	
	47		17	7	Aorta losgelassen.
6.			19	5	
	12	angefangen	41	6	Aorta comprimirt.
	19	aufgehört	44	6	
	26		45		
	32		23	6	Aorta losgelassen.
	50		16	6, 5	
Aug. 12.					Zu Fig. 106.
1.	0	angefangen	97		
	5	aufgehört	76		Krämpfe.
	47		126		
	110		119		
2.			20	8	Rückenmark durchschnitten.
	25	angefangen	92	7	Aorta comprimirt.
	31		95	8	
	33	aufgehört	80	6, 5	
	38		75	8	
	61		78	7, 5	
	72		20		
					Aorta losgelassen.

Datum des Versuchs und No. der Beobachtung.	Zeit in Secunden.	Einathmen von salpetrigs. Amyloxyd.	Blutdruck in Mm. Hg.	Puls-Zahl in der Zeiteinheit.	Bemerkungen.
Aug. 12.					Zu Fig. 103.
3.			24	7	
	14	angefangen	107	7	Aorta comprimirt.
	21		113	7	
	22	aufgehört	105	6, 5	
	25		96	7	
	84	angefangen	118	7	
	86		114	7	
	98	aufgehört	99	7	
	103		94	8	
	115		113	7	
	127		26	7	Aorta losgelassen.
	140		24	7	
4.			23	8	
	0	angefangen	110	7	Aorta comprimirt.
	6		110	7	
	8	aufgehört	92	7	
	18		82	7	
	34		108		
	67		108	7	
	70		33	7, 5	Aorta losgelassen.
	77		20	7	
	137		17	7	
5.			18		
	5	angefangen	106		Aorta comprimirt.
	10		108		
	15	aufgehört.	92		
	24		85		
	82		104		
	84		27		Aorta losgelassen.
	93		17		

ON THE ACTION OF NITRITE OF AMYL ON THE CIRCULATION [AND ON ACTIVE DILATATION AND CONTRACTION OF ARTERIOLES INDEPENDENTLY OF NERVE-CENTRES].*

(From the *Journal of Anatomy and Physiology*, vol. v, 1871, pp. 92 to 101.)

THE property of causing flushing of the face and throbbing of the carotids, which nitrite of amyl possesses, was first observed by Guthrie in 1859, but no further notice of it was taken till Dr. Richardson, in 1866, again drew attention to it. His experiments led him to conclude that it paralysed the nerves from the periphery to the centre, lessened the contractility of the muscles, and dilated the capillaries in the web of the frog. They were shortly afterwards repeated by Drs. Gamgee and Rutherford, who, however, found no action on the nerves, either sensory or motor, and rarely any on the capillaries of the frog. In some other experiments, also unpublished, but whose results they have kindly communicated to me, they found that the sphygmographic tracing of the radial pulse underwent a remarkable change, the waves becoming much more frequent, and their ascent, but especially descent, much more rapid; and the pulse-rate and pressure in a mano-

* The chief research on which I was engaged in Professor Ludwig's laboratory during the summer of 1869 and winter of 1869–70 was that relating to the local dilatation and contraction of arterioles independently of nerve-centres. This was the research which Professor Ludwig had suggested and on which he worked with me, while that on nitrite of amyl was only carried on at those times when Professor Ludwig was engaged with other students. As time did not allow me to finish the research on the arterioles, that on nitrite of amyl was published and only a brief abstract given of the results obtained during the research on the arterioles, both Professor Ludwig and I hoping that circumstances might allow me to return to his laboratory and finish it. This was unfortunately not the case, and he continued to work at the subject with Hafiz, Lépine, A. Mosso, Von Frey, and Gaskell.

meter connected with the carotid of a rabbit falling, when the vapour of the nitrite was inhaled. Previous division of the depressor nerves did not affect the result.

The diminished blood-pressure which it produces, led me to apply it in angina pectoris, and the good results I obtained made me anxious to investigate more closely the nature of its action. An excellent opportunity for doing so was afforded me by the kindness of Professor Ludwig, in whose laboratory at Leipzig the experiments, the result of which I am about to give, were carried on. With the exception of one or two on dogs, they were made upon rabbits; and instead of allowing the animals simply to inhale the vapour, artificial respiration was employed, the apparatus being so arranged that the air could be either sent direct from the bellows, through a tube in the trachea, to the lungs, or passed through a vessel containing the vapour of the nitrite. The advantages of this arrangement were that the bellows being worked by an engine with great regularity, the disturbing influences of unequal respiration on the blood-pressure were to a great extent avoided. One of the chief of these is that any strongly smelling vapour, and nitrite of amyl among others, acting on the nose of rabbits, causes suspension of the respiration for a short time; and the alteration in the condition of the blood thus produced causes irritation of the vagus and slowing of the heart's action; such as Drs. Rutherford and Gamgee found accompanying the sinking of the blood-pressure in rabbits.

When air charged with the vapour was passed directly into the trachea of a rabbit the blood-pressure almost immediately sank very much, but the pulse-rate remained nearly unchanged. As the pressure sank general convulsions took place and the pressure immediately rose, notwithstanding the continued inhalation of the vapour, the pulse curves becoming at the same time indistinct, so that the rate could not be well ascertained.

When the vapour was discontinued after twenty seconds the pressure rose still more quickly, and in a minute at most attained its normal height, as is seen in Fig. 107, where the distance along the abscissa indicates the time, and the ordinate the pressure in millimètres of mercury. This shows that very

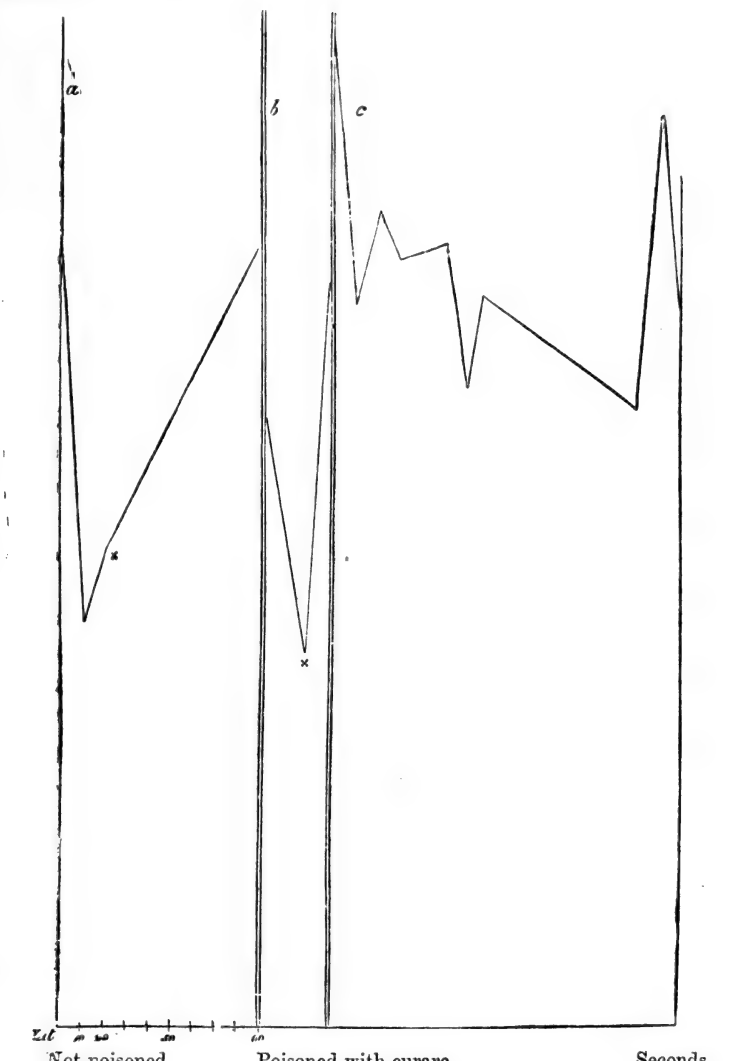
small quantities of the drug produce a great effect, and that its action speedily passes off, the vapour being either excreted or destroyed in the body.

In order to avoid the disturbance occasioned by the convulsions, the animals were then poisoned by curare and the vapour administered. The pressure, as before, sank immediately and did not return to the normal amount so long as the inhalation was continued. It did not, however, sink constantly, and then remain at a definite minimum, but oscillated up and down, just as Traube observed it in curarised animals, and as is shown in the last two curves of Fig. 107.

It is possible that the convulsions which occur readily in rabbits, but which I have only once, and that to a very slight extent, seen in man, are suffocative, like those produced by CO, for Dr. Gamgee has shown that nitrites acting on the blood prevent hæmoglobin from giving up its O. This is the more probable as the respiration is first affected, and if a drop of nitrite of amyl be mixed with water and the vapour thus diluted be administered, the limbs remain quiet, but the animal begins to make respiratory movements independently of the bellows, and when the vapour is less diluted these become more and more marked till general convulsions take place.

The diminished blood-pressure might be due either to a lessened power of the heart, or a dilatation of the arteries and a consequently diminished resistance. That the latter is the true cause is rendered probable by the flushing which the vapour causes, both in the human face and the rabbit's ear, and is shown by what might at first seem an anomalous action in some dogs. When the pulse in dogs is slow, the inhalation of amyl produces comparatively little effect on the blood-pressure; and it might be thought that its action was different in them from rabbits, but the reason is that the pulse, which in rabbits is naturally rapid, and remains unchanged by the vapour, becomes in these dogs remarkably quick, almost as much so as in rabbits. If the vagi be first divided, so that the pulse in the dog becomes quick like that of the rabbit, and the nitrite be then inhaled, the pressure falls just as in rabbits. In order to confirm this view, and at the same time to decide the question,

FIG. 107.



whether the dilatation of the vessels was due to a direct action of the substance upon them or to a diminution in the tone which

the vaso-motor nerves derive from the medulla oblongata, another series of experiments was undertaken. This question was the more interesting from its connection with another research which I began under Professor Ludwig's direction, but unfortunately have not yet finished. Professor Ludwig observed, and directed my attention to the fact, that the alterations in the lumen of arteries noticed by Schiff in the rabbit's ear, may be seen also in all exposed arterial twigs in the skin and connective tissue They vary in amount and rapidity in different animals, and in the same animal at different times. They are sometimes absent, but in such cases may be generally produced by poisoning with curare, or by suspending the respiration; and when once aroused, they continue some time, although the respiration be afterwards most carefully performed.

That these alterations are, at least in part, completely independent of the vaso-motor nerves in the brain is shown by their occurrence in the ear and other parts, after all the nerves, sympathetic and cerebrospinal, going to the part have been divided, and after division of the cord in the neck notwithstanding the low pressure which then remains.

The form of the variation shows that they do not depend on varying blood-pressure in the large arteries; for sometimes a contraction suddenly appears between two parts of the artery filled with blood, and in one case in the rabbit's ear I noticed such a contraction take place in a small artery at the point where it branched off from a larger one, and proceed peristaltically downwards.

The lightest touch on an artery after division of the nerves causes a movement generally limited to the part, and consisting not in a contraction, but in dilatation, which remains for some time, and gradually disappears. As Gunning and Cohnheim have made similar observations on the tongue and web of the frog, and some facts in Sadler's research (*Ludwig's Arbeiten*, 4ter Jahrg.) can only be explained by an independent motion of the vascular walls, it seems to be a widely extended and therefore important phenomenon. If the nitrite acts through the vaso-motor centres in the brain, it should have no effect if these be separated from the vessels by dividing the cord in the neck,

but if its action be exerted directly on the vessels, the division of the cord will not prevent it, and that it in fact does not do so, will be seen from figs. 108 and 109. The blood-pressure, which

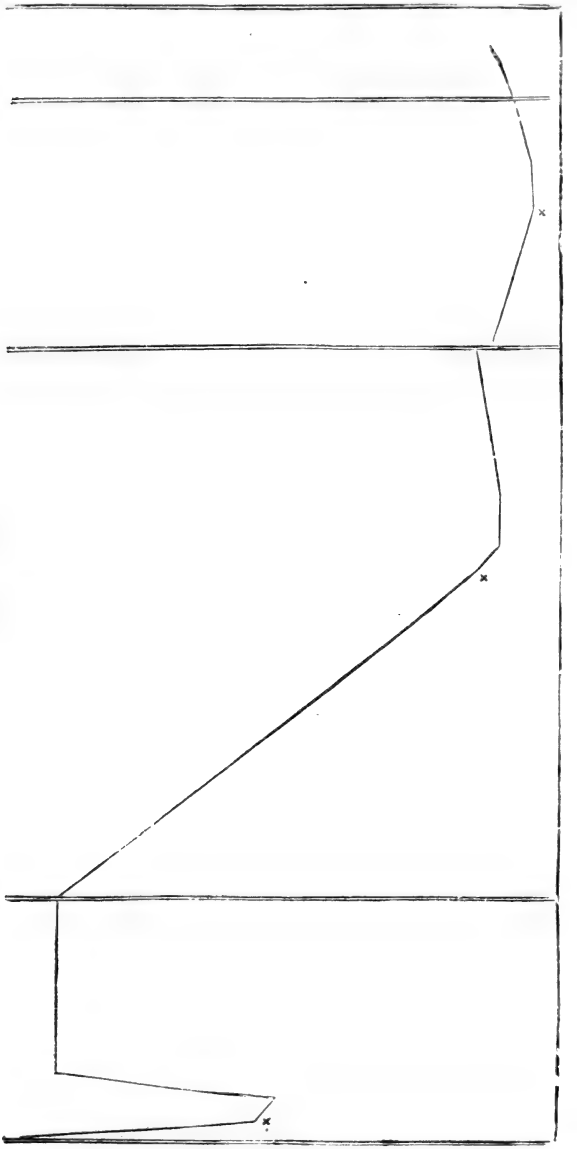


FIG. 108.

N 2

had sunk very low after division of the cord, sank yet farther when the nitrite was inhaled. Although the sinking was not absolutely great, it was so relatively to the very low pressure already existing, and was analogous to that observed on the

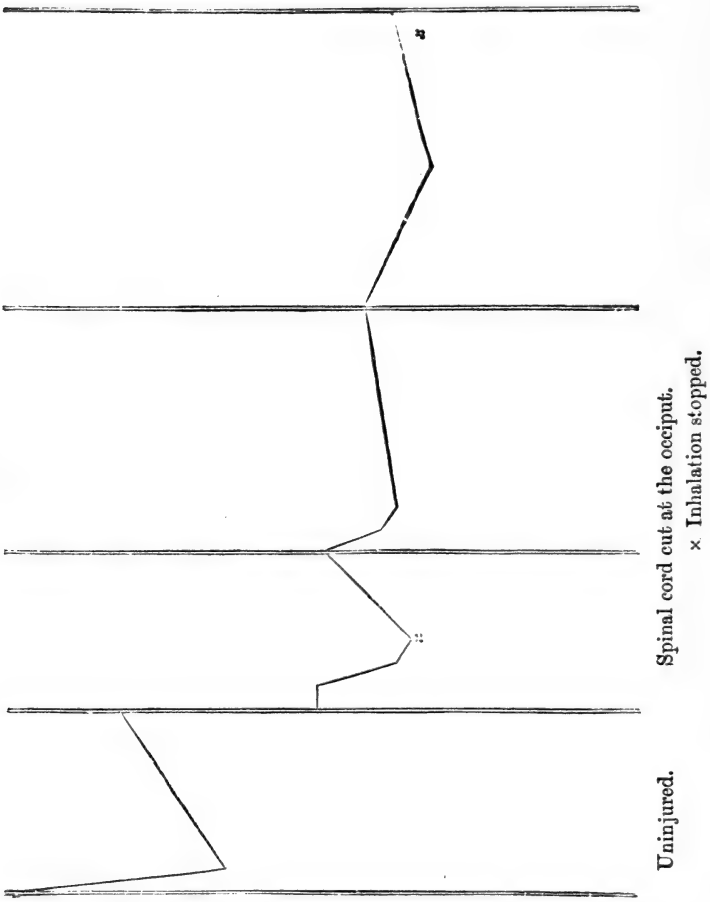
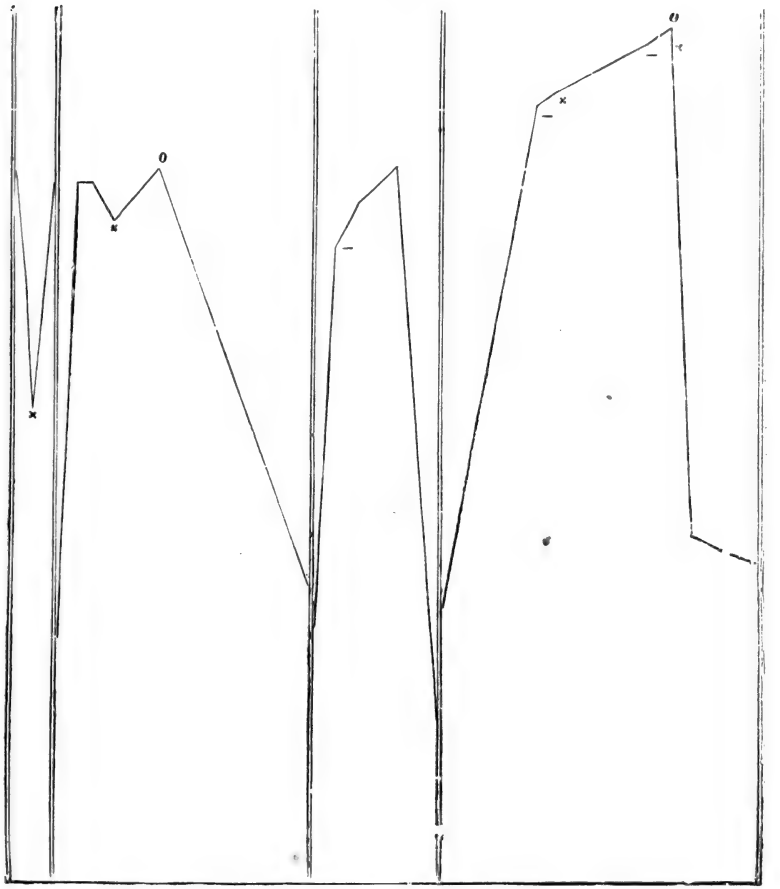


FIG. 109.

section of a second splanchnic nerve after division of the first. The other experiments, to prove that the diminished blood-pressure after inhalation is due to dilatation of the vessels, and not to a weakened heart, consisted in compressing the aorta below the diaphragm and then administering the nitrite. If

the diminution in pressure was due to a weakened heart, the inhalation of the nitrite should at once cause a diminution in the pressure to which the blood had attained after compression of the aorta. As only the circulation in the lower part of the body was in this way cut off, we cannot expect that no sinking should take place, but only that it should be less than the normal. In order to diminish the error from this source, these

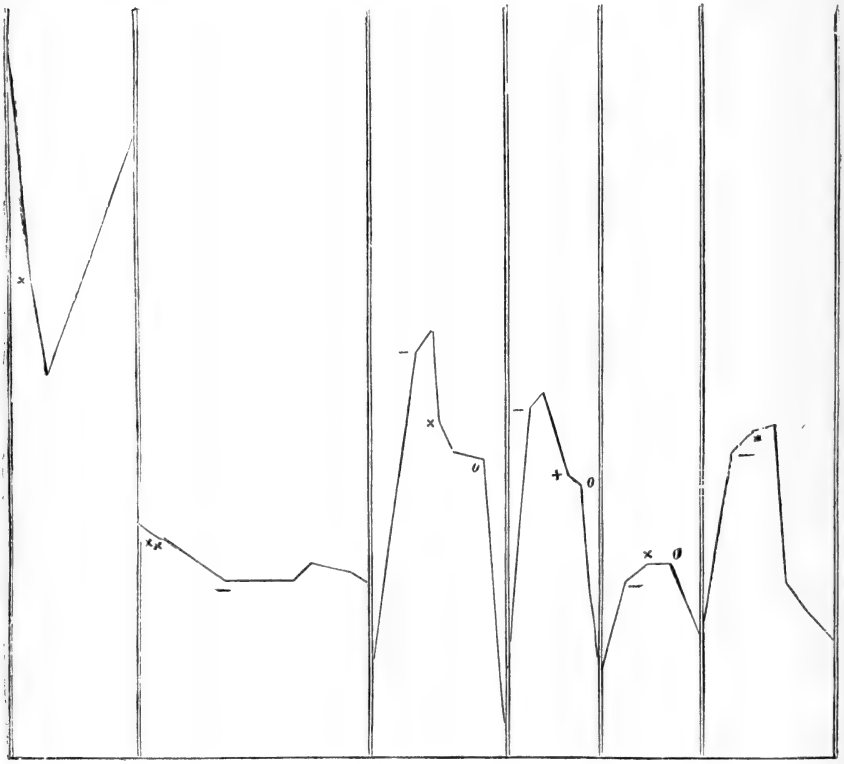
FIG. 110.



—Inhalation begun. × Inhalation stopped; at the beginning of the last three observations the aorta was compressed. *o* Aorta opened.

experiments were made after previous division of the cord in the neck so that the vessels should become relaxed, and the difference produced in their calibre by the vapour being thus less. The results obtained were, as shown in figs. 110, 111 and 112

Fig. 111.



Cord cut in the neck.
In the last four observations the aorta was compressed ; at *o* the aorta was opened. — Inhalation begun. + Inhalation stopped.

that sometimes a rise took place during the inhalation, but generally a sinking, much less, however, than in the normal condition.

We may therefore conclude that the diminution in the blood-pressure is not due to weakening of the heart's action, but to a

dilatation of the vessels, and that this depends on the action of the nitrite on the walls of the vessels themselves. Whether

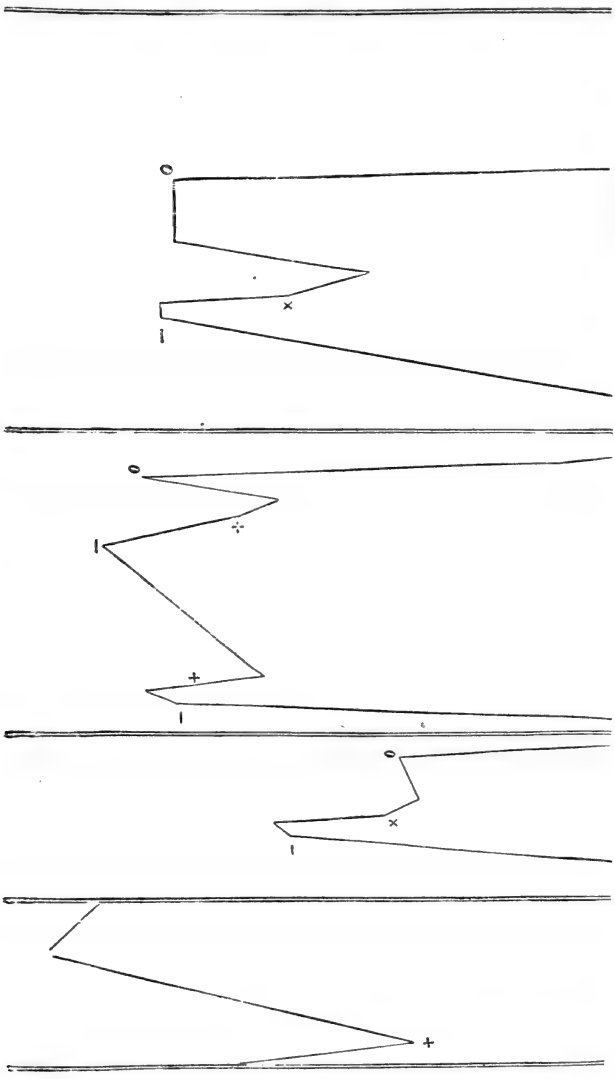


FIG. 112.

The ordinates indicating the pressure begin 50 mm. above the abscissa. In the last three observations the spinal cord was divided, and the aorta compressed; at *o* the aorta was opened. − Inhalation begun. + Inhalation stopped.

this is due to its action on the muscular walls themselves, or the nerve-ends in them, cannot at present be with certainty said;

and further experiments must be made to determine whether the walls of the arteries are the only structures consisting of unstriped muscle which are affected by it.

The further dilatation which takes place after the usual tone of the vessels has been destroyed by division of the cord, seems to indicate that it is of an active nature analogous to that in the vessels of the penis after irritation of its nerves; and this would point rather to an affection of the nerves than of the muscular fibres. In conclusion, I desire to express my warmest thanks to Professor Ludwig for the great kindness he has shown me, and for his invaluable advice and assistance in this investigation.

NITRITE OF AMYL IN ANGINA PECTORIS.

(Reprinted from the *Clinical Society's Reports*, vol. iii, 1870.)

WILLIAM H—, æt. 26; formerly a blacksmith, now a toll-keeper, admitted to Ward I, Royal Infirmary, Edinburgh, December 7th, 1866.

Antecedent History.—Patient was strong and healthy till his tenth year, when he was confined to bed for six months by a severe attack of rheumatism. During the next twelve years he had four other less severe attacks, and after recovering from the last of these his feet began to swell during the day.

In April, 1866, he had a seventh attack, which lasted for a month, and six weeks after it was over he noticed an unusual palpitation of his heart, for which he entered the infirmary, and remained there three weeks, but left unrelieved. The palpitation gradually increased till he felt it along the line of the carotids as high up as the ears; and in November last he began to feel besides a dull heavy pain about the left nipple. At first this came on every three days, usually during the night, and lasted half an hour. During the day he felt little inconvenience from the palpitation unless he exerted himself.

On admission, the pain was no longer confined to the region of the left nipple, but was worst along the right border of the sternum, and extended up to the right arm. This pain was more severe if he walked about much, otherwise he felt well. Professor Maclagan had charge of the clinical wards at this time, and the patient was treated for six weeks with tincture of aconite, and then with tincture of digitalis; but under these remedies the pulse became intermittent, and the pain was not relieved by either, and rather aggravated by digitalis. They were therefore discontinued, the digitalis being stopped on January 31st. During their employment wet cupping over the cardiac region to the extent of ʒiv temporarily relieved the pain.

February 1st, Professor Maclagan's term of office having expired, Professor Bennett took charge of the clinical wards.

On February 6th the patient began to complain of pain in the back, neck, head, thighs, and elbow-joints; he had no appetite, was perspiring profusely, and his pulse was 116, full and strong. Next day the pain was most severe in the shoulders, back, hip, and knee-joints.

On the 8th he was examined by Professor Bennett and the clinical class, and the following was found to be the condition of his circulatory system:—Apex beat $2\frac{1}{4}$ inches below and $2\frac{1}{2}$ inches to the outside of the left nipple. On palpation, pulsation is felt over the whole left front and side of thorax, most strongly between the fourth and sixth ribs, and faintly over the supra-clavicular region.

Cardiac dulness commences at the middle line of the sternum and extends laterally outwards for 5 inches.

A loud, double, blowing sound is heard over the whole of the cardiac region, but is loudest at the base. Over the right sterno-clavicular articulation a single blowing is heard. Pulse 104, strong and jerking. The respiratory system was normal, the skin covered with an acid sweat, the tongue furred, no appetite, urine high-coloured and slightly albuminous. The pain in the joints continued along with pain in the neck in the line of the carotids, but the pain in the cardiac region was absent.

On the 11th the pulse fell to 80, and the pain in the joints diminished, but the patient was still troubled by pain in the left ear, and along the line of the carotids, with violent pulsation in them at night.

On the 18th the rheumatic pains in the joints and shoulders had entirely disappeared, but the pain in the cardiac region came on during the night.

On the 19th four ounces of blood were taken from the arm, with immediate relief from the pain and violent pulsation, and the pain over the heart, which usually came on at 3 a.m., was much less on the ensuing night.

25th.—Patient's appetite remains unimpaired by the pain, and he takes all his food, consisting of steak diet, beef tea,

potatoes, and bread. Pil. Colocynth. c. Hyoscy. every other night. Ordered Tinct. Lobeliæ, 20 drops three times a day.

27th.—The pain continued to come on during the night. ℥iv of blood were taken from the arm at 10 p.m. An hour after patient went to sleep, had a good night, and the pain did not come on.

March 3rd.—Pain felt at 11 p.m. in breast and ears. A poultice applied over the breast gave some relief.

6th.—Pain severe at 3 a.m., lasting for about one hour. At 9 a.m. ℥iij of blood were taken from the arm. At 10 a.m. pulse 76, not so forcible as yesterday.

7th.—No pain during the night.

8th.—Pain came on as usual during the night. Tinct. Lobeliæ to be stopped.

9th.—℥j of brandy to be taken when the pain comes on.

10th.—The pain came on in the night and was not relieved by the brandy.

12th.—The pain came on as usual at 3 a.m. A few drops of nitrite of amyl were put on a towel and inhaled by the patient. The primary effect noticed was a suffusion of the face, and the patient felt a glow over his face and chest. The pain disappeared almost simultaneously with the occurrence of these phenomena, but returned in three minutes. He then inhaled 5 drops more; the pain again disappeared and did not return.

16th.—The pain has recurred each night and been relieved by the inhalation of 10 drops of nitrite of amyl. Last night it came on about 10·30 p.m., the same in position and character as before. On the patient's taking 10 drops of nitrite of amyl in ℥ss of brandy, the pain went away, but returned in three minutes; 5 drops were then inhaled from a towel, and the pain disappeared. He went to sleep in an hour and slept till 3 a.m., when he was awakened by a return of the pain. He drank 10 drops in a little brandy, but, no effect following, he inhaled a few drops. The pain disappeared and did not return.

17th.—Pain came on at 1 a.m.; 10 drops were given internally. The pain was relieved, but returned in a few minutes; 10 drops were then inhaled. The pain disappeared and did not return.

Dr. Bennett, thinking the relief of pain by the amyl might be due to anæsthesia, ordered chloroform to be tried during the attack.

18th.—About 2 a.m. the pain came on as usual, and chloroform was inhaled by the patient. He was only partly put under it, and as soon as he again became completely conscious the pain was found to be present as before; 6 drops of nitrite of amyl were then given by inhalation. The pain disappeared and did not return.

25th.—The pain came on at 1.58 a.m., but was not very bad. While it was present the pulse was 100, respirations 32. After amyl was given, but the pain was not quite gone, the pulse was 130, it fell with the disappearance of the pain to 100, and twelve minutes after was 80, and the respirations 24.

April 6th.—The pain had come on about 2.35 a.m., and the patient was relieved by a whiff of amyl, but it began to return at the end of the sternum, right ear, and right shoulder. The chest was auscultated, but no abnormal sounds could be detected to indicate any coincident spasm of the bronchial tubes.

10th.—Patient continues to have the pain every night, and instead of inhaling the nitrite of amyl from a cloth, does so from the bottle. Two or three inhalations usually suffice to relieve the pain. Up to the 8th he used pure nitrite made by Dr. Gamgee, but this being finished, he then began to use some made by Macfarlane & Co., but the smell of it was not so agreeable, and it sometimes occasioned headache, which the pure amyl never did.

14th.—The pain has been coming on several times during the night, is most intense at a spot two inches inside of the right nipple, remains there after it has gone from the rest of the chest, and is only removed by repeated inhalation. Last night it came on three times, and was relieved by amyl each time, but five or six inhalations were required. To-day at 11 a.m. ʒiv of blood were taken from the patient's arm, and he was ordered Potass. Iod. gr. viij, three times a day.

17th.—Pain came on during the night and continued uninterruptedly for one hour and a half. By Dr. Bennett's order

no amyl was taken, in order to determine whether the relief of the pain was due to it or to some change in the symptoms independent of it. Three dry cups were applied over the cardiac region. They did not relieve the pain.

18th.—No pain during the night. No amyl taken.

19th.—Very little pain, lasting half an hour. Took no amyl.

May 9th.—Has had the spasmodic pain every night. Last night it came on five times at intervals of about an hour, and was in each case relieved by inhalation.

15th.—Pain has been rather less during the past two nights. Attention was called to-day to purpuric spots upon both legs, which the patient had noticed some days previously. The gums were neither swollen nor tender. His diet for some time past has been beef-steak and potatoes, with porridge and milk for breakfast. The use of iodide of potassium to be suspended.

17th.—Pain came on severely in the chest a little after midnight. It was worst 2 inches inside of the right nipple.

Tracing 1 (fig. 117).—Oh. 22′ a.m. Pulse 104 small, resp. 36. There is a thrill to be heard and felt with the second sound at the apex.

22′ 40″ 13 drops inhaled from a cloth.

Tracing 2 (fig. 118).—Oh. 24′ 0″ The lever of the sphygmograph has risen very much. The pain has gone, except at a point 2 inches inside of right nipple.

25′ 30″ 5 drops more given; pulse 112.

Oh. 28′ 0″ Pain almost gone; patient now inhaled from the bottle; pulse 100.

Tracing 3 (fig. 119).—Oh. 34′ 0″ Pain has been gone for 4 minutes, but at 37′ it began to return inside the right nipple, and a little more was inhaled.

Oh. 40′ 0″ Pain quite gone; pulse 92; resp. 28.

Tracing 4 (fig. 120).—Oh. 47′ 0″ Pain did not return.

In these tracings, like the others, the patient's position was unchanged, and neither the band nor pressure screw of sphygmograph was touched.

18th.—Pain came three times last night, and was very severe. He has had it during the day three times. The purpuric spots on the legs are much paler. To recommence iodide of potassium.

21st.—The purpuric spots have reappeared on both legs. To stop the Pot. Iod. He had pain last night, but none during the day.

24th.—Bled to ʒiv on account of general uneasiness and powerful pulsations of the heart. The bleeding was immediately followed by a sense of relief.

28th.—The pain has only been absent one night since the bleeding, but it has been much less severe than before it. The sphygmograph was fixed to his arm to-night in order to take a normal tracing for comparison with one to be taken during the attack. This had scarcely been done when the pain unexpectedly came on. The tracing (fig. 121, p. 195), though unfortunately very imperfect, shows the diminished volume and increased tension of the pulse. In 2 (fig. 122) the pain was severe, and 3 (fig. 123) was taken after inhalation of amyl.

June 1st.—Condition remains the same, spasmodic pain in the cardiac region occurring every night, but not severe, and easily relieved by a few inhalations of nitrite of amyl. Patient wished to resume his former occupation of toll-keeper, and was to-day discharged at his own request. Recommended to have occasional small bleedings.

Remarks.—In this case of Dr. Bennett's, which by his kind permission I now publish, we have a history of numerous attacks of rheumatic fever, followed by cardiac lesion, which was accompanied by palpitation of the heart, throbbing in the carotids extending as high as the ears, and a spasmodic pain in the chest. This pain was sometimes most severe near the left nipple, and sometimes at the right border of the sternum, but extended over the whole cardiac region, and shot up to the right ear and down the right arm. It used to come on suddenly

during the night, generally between midnight and 3 a.m., was accompanied by little or no feeling of dyspnœa, and was somewhat relieved by the patient's sitting up. It generally came on every third night at first, but latterly every night, and was worse when the patient had used much exertion during the day. It was not relieved by tincture of aconite, tincture of lobelia inflata, brandy, or dry cupping over the cardiac region. It was made worse rather than better by tincture of digitalis. It was temporarily relieved by chloroform, but whenever the stupefying effect passed off the pain was as bad as before. It was somewhat relieved by warm poultices to the chest, and was generally absent for one night after a small bleeding, either from the arm or by cupping the chest. Under the use of iodide of potassium the attacks became less frequent, but purpuric spots appeared on the limbs, and each attack was at once relieved by the inhalation of nitrite of amyl. During an attack of rheumatic fever it disappeared completely, again returning with the departure of the rheumatic pains.

Angina pectoris is defined by Dr. Walshe as a paroxysmal neurosis, in which the heart is essentially concerned, and he divides it into pseudo and true angina, which differ mainly in the intensity of the symptoms. Friedreich and others divide it into functional and organic, according as it is accompanied by cardiac lesion or not. From the absence of a sense of impending death, the present case might be reckoned as one of pseudo-angina, but in the intensity of the pain and the manner of its radiation it more closely resembles true angina. As a cardiac lesion was present, it belongs to the class organic angina.

Various opinions have been advanced as to the pathology of this disease, some saying it is a mere brachio-thoracic neuralgia, but most holding that it is a neuralgic affection of the cardiac plexus. Some are of opinion that it is associated with cramp of the heart, others with weakness of that organ.

Eichwald* thinks that there is not only weakness of the heart, but a mechanical impediment to its action, produced by irritation of its regulating nerves, and that the pain is caused

* *Würzburg. med. Zeitschr.*, vol. iv, 249; *Cblt. f. med. Wiss.*, vol. i, 877.

by unavailing efforts to overcome this obstacle. Nothnagel* states that during angina there is pallor and coldness of the extremities, small pulse, and other symptoms of a cramp-like contraction of the systemic arteries, and that the spasm is relieved by remedies which cause their relaxation, such as warm baths and friction.

It is quite possible that the pathology of all cases classed under angina pectoris is not the same, and that the differences of opinion are not due merely to the want of exact methods of observation. What the nature of the attack was in the present case may be learned to some extent from an examination of the sphygmographic tracings, which were begun by direction of Dr. Maclagan, and continued during the time the case was in the wards under the care of Dr. Bennett. In taking these tracings, the instrument, which was one of Marey's, without any means of estimating the pressure employed, was applied to the arm above the end of the radius, as it was found to cause pain when applied over the bone for any length of time. The amplitude of the curve thus obtained is greater, and it did not occur to me, till after studying the physiology of the circulation under Professor Ludwig, that in such cases as the present, where sudden changes occur in the vessels, I was increasing the fallacy which the variation in the height of the lever from turgescence of the tissues produces, and which may be confounded with a rise from increased tension in the vessels. Except where marked otherwise, the tracings were all taken with the patient in a recumbent position, and neither the cord by which the instrument was attached to the arm, nor the screw regulating the pressure, was touched during the observation.

The case excited considerable interest, and was carefully observed and commented on by Professor Bennett to the clinical class, and the cardiac lesion was diagnosed by him from the physical signs to be aortic obstruction and regurgitation, with dilatation of the aorta, but no sacculated aneurism.

The tracings confirm this diagnosis, showing in a typical manner the abrupt ascent, terminating in a hook, of each wave, characteristic of the unfilled arteries, which aortic regurgitation

* *Deut. Arch. f. klin. Med.*, vol. iii, 309; *Cblt. med. Wiss.*, vol. v, 715.

produces, and the long and rounded apex of aortic obstruction. There is, however, a marked difference between the tracings from the two radials, the ascent of the wave being more abrupt, the top flatter, and the descent distinctly dichrotic in the right, while in the left the ascent is less abrupt, as shown by the smaller hook at the top; the maximum height is not attained till near the end of the systole, and there is generally little or no dichrotism in the descent. This might be due to aneurism; but there were no physical signs to show its presence, and in the absence of a *post-mortem* examination, or experiment with a schema, hypotheses as to the cause of difference are of little value.

The tracings taken during an attack were chiefly from the right radial. The only one I got while the pain was actually coming on is unfortunately an imperfect one (No. 1, May 28th, Fig. 121). From this tracing, and from those taken when the pain was becoming worse (Nos. 1 and 2 of May 17th, Figs. 117 and 118), it will be seen that as the pain increased the curve became lower, both the ascent and descent more gradual, and the dichrotism disappeared. This form of curve clearly indicates that the arterial tension is much increased, and this increase can, I think, be due only to contraction of the small systemic vessels, so sudden and so great as well to deserve the name of spasmodic. As I have stated in a former paper,* this increased tension led me to suggest nitrite of amyl to relieve the spasm.† The rapidity with which this increase in tension takes place is shown by the great change which the form of the pulse has undergone in Tracing 1, May 28th, during the short time occupied in re-inking the pen. It would seem from Tracings 3 and 4 (Figs. 115 and 116) of the plate that the tension in the right radial was raised more than in the left, and farther experiments with simultaneous tracings are necessary to decide whether the spasm extends to all systemic vessels or to all alike.

At the same time that the tension increases the pulse becomes somewhat quicker, which shows that there is some dis-

* *Lancet*, July 27th, 1867, *cf. antea, p.* 137.

† Dr. Bennett, on being informed of the successful result of the first experiment, ordered the inhalation to be continued.

turbance of the regulating apparatus of the heart, as normally the increased tension acting on the roots of the vagus should slow the pulse. It has been suggested to me (by Professor Ludwig) that the pain in the heart may be due to irritation of its sensory nerves by the great pressure of the blood, and that in the right arm and neck may be due to the same cause acting on the arteries, those of the right side being possibly contracted more than the left. Whenever the tension was lowered by nitrite of amyl the pain disappeared from the greater part of the cardiac region, the neck and the arm, but sometimes remained persistent at a point about 2 inches to the inside of the right nipple. This I think indicates that the tension in the right ventricle was not yet relieved, and the small volume of the pulse (see Tracing 3, May 17th, Fig. 119) seems to show that the amount of blood passing through the small pulmonary vessels at each systole was small, probably from contraction of their lumen. So long as this condition remained the pain was almost certain to return. It is possible that the right ventricle might not be able to empty itself completely at each systole, was therefore quickly refilled, and consequently contracted frequently, forcing the left ventricle to contract with it, and producing the rapid pulse with small volume seen in Tracing 3 of May 17th, Fig. 119. The influence of the small vessels of the lungs over the circulation, though in all probability of extreme importance, is a subject of which we know as yet almost nothing.

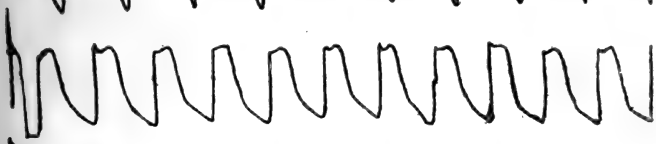
The question whether the contractile power of either ventricle is lessened during the attack is one which cannot be decided with certainty from the present tracings. Digitalis which has been recommended on the supposition that the heart is weak during the attack, proved productive in this case of more harm than good, contracting, as it does, the small vessels.

We may, I think, conclude that (1) the attack in the present case consisted in a spasmodic contraction of some, if not all, of the small systemic, and probably of the pulmonary vessels, causing great increase in the blood-pressure in both sides of the heart, such as is found in animals after division of the vagi;

TRACINGS OF THE PULSE.

In Angina Pectoris.

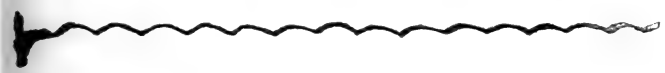
Normal Pulse.
Right radial.
Fig. 113.



Left radial.
Fig. 114.

During Angina.
Right radial.
Fig. 115.

Left radial.
Fig. 116.



May 17th.
1. Pain severe.
Fig. 117.

2. Pain gone, except near the nipple.
Fig. 118.

3. Pain quite gone, but afterwards returned.
Fig. 119.

4. Pain gone, and did not return.
Fig. 120.

May 28th
1. Pain coming on.
Fig. 121.

2 Pain severe.
Fig. 122.

3. Pain relieved by Amyl.
Fig. 123.

(2) that this was probably due to a derangement of the vaso-motor system, and accompanied by a derangement of the cardiac regulating apparatus, producing quickened instead of slowed pulsation; (3) that the pain was not primarily due to irritation of the nerves composing the cardiac plexus, but produced by the pressure of the blood on those of the heart and arteries; and (4) from the alternation of the attacks with rheumatic pains in other parts of the body, that they were of rheumatic origin.

EFFECT OF WARMTH IN PREVENTING DEATH FROM CHLORAL.

(From the *Journal of Anatomy and Physiology*, vol. 8, May 1874, pp. 332 to 3 9)

SINCE chloral was first brought into notice, and its action investigated by Liebreich, it has been made the subject of numerous experiments, and has not only proved a most useful medicine but a valuable aid to physiological research. During the stay made in this country by Professor Stricker four years ago he used chloral frequently as an anæsthetic while making some experiments with Dr. Burdon Sanderson on the circulation in mammals. At his suggestion I made the following experiments as well as many others which it is quite unnecessary to give at length, as they simply confirm the observations of Liebreich and others. The general results were that the subcutaneous injection of a solution of chloral induced sleep, which was light and readily broken if the dose were small, but passed into coma if the dose were large. In dogs considerable restlessness was observed before sleep came on. The power of muscular co-ordination was affected in dogs before sopor was induced, so that they staggered and fell when attempting to walk either of their own accord or in obedience to a call. A similar loss of co-ordination was observed in rabbits, but in general they and guinea-pigs sat quietly after the administration of the chloral, and thus the motor affection was less perceptible in them than in dogs. In dogs the respiration occasionally became very rapid immediately after the subcutaneous injection of chloral, but it became slow after the animal began to exhibit symptoms of drowsiness. In rabbits and guinea-pigs the number of respirations was also diminished, but a preliminary acceleration was not observed in them. The pulse was not affected to the same extent as the respiration, and the heart always continued to beat after the respiratory move-

ments had ceased. One of the most important phenomena, and the one to which I wish to call particular attention at present, is the diminution of temperature which chloral induces, and the extraordinary effects of warmth in hastening recovery from its action, and preventing death from an overdose. The fall of temperature has been noticed by Liebreich and most other writers, but the effect of warmth applied to the animal's body has not, I think, received sufficient attention, although Dr. Richardson has pointed out its usefulness in preventing death. The diminution of animal heat is partly due in all probability to greater loss from the surface caused by the vessels of the skin becoming much dilated under the influence of the drug, and allowing the blood to be cooled more readily by a low external temperature. It is partly due also to the diminished production of heat which cessation of muscular action always causes, whether it be induced by simply tying down an animal so as to prevent motion, or by the administration of curare or narcotics.

Professor Stricker having noticed that the animals on which he experimented often required a second dose of chloral to maintain anæsthesia, when they were wrapped in cotton-wool so as to prevent loss of heat, and still more when they were laid in a warm place, I made the following experiments at his suggestion. They show clearly that an animal wrapped in cotton-wool may recover perfectly from a dose of chloral which is sufficient to kill it when exposed to the cooling action of the air (which in the laboratory was about 20° C.), and that recovery from the narcotic action is much quicker when the temperature is maintained in this way, and still more rapid when the animal is placed in a warm bath. If the temperature of the bath is too high the animal may die from excessive heat, as I have shown in a former paper.*

The bearing of these experiments on the treatment of persons suffering from an overdose of chloral is so obvious as hardly to require any observations from me. The patient should be put to bed, and the temperature of the body main-

* "On the Effect of Temperature on the Mammalian Heart and on the Action of the Vagus," *St. Bartholomew's Hospital Reports*, vol. 7, 1871 (*vide* p. 209).

tained by warm blankets and hot-water bottles to various parts of the body, and especially the cardiac region. Warmth over the heart is an excellent stimulant to the circulation, which, like the respiration, is enfeebled by chloral, the heart, according to Rajewsky, being more or less paralysed by the drug. If respiration threatens to fail it should be maintained artificially so as to allow time for the chloral to be excreted and the normal functions to be restored.

Expt. I. Into two guinea-pigs of nearly equal size 0·6 c.c. of a 50 per cent. solution of chloral (equal to about 5 grains or 0·3 gramme of chloral) was injected subcutaneously.

	Temp. of animal.		
	No. 1.	No. 2.	
Before injection..	103·8° F.	104·6° F.	
After injection— 5 min.	..	..	No. 1 was almost motionless, and was rolled in cotton-wadding.
	..	..	No. 2 was left uncovered.
27 min.	99·7	101·5	
1 hr. 20 min.	96·0	92·6	
1 hr. 40 min.	95·2	91·0	
2 hr. 33 min.	94·3	about 80°	The graduation of the thermometer did not extend so low as 80°, and the temperature was calculated approximately, or guessed, by the height of the mercury.
2 hr. 57 min.	93·8	..	The legs of No. 2 are shivering.
4 hr. 0 min.	87·3		
4 hr. 42 min.	88·4	..	No. 1 was now deprived of its covering. It shivered and grunted but lay in whatever position it was put, and was still completely narcotised.
5 hr. 27 min.	88·8		
5 hr. 42 min.	..	..	No. 1 awakened.
			No. 2 remained as before, motionless, except for the shivering.
5 hr. 52 min.	95·8	..	It did not recover, and died some little time afterwards.

Expt. II. Into two guinea-pigs, No. 1 weighing 655 grammes, and No. 2 weighing 670 grammes, 1·1 c.c. of 50 per cent. solution of chloral hydrate was injected.

	No. 1.		No. 2.		
	Temp.	Resp.	Temp.	Resp.	
	102·4°				
After injection—					
7 min.	101·8	89	101°	..	Both animals nearly narcotised. No. 1 put into a warm-air bath. No. 2 allowed to lie without cover.
1 hr. 53 min.	..	..	91·8	24	
2 hr. 7 min.	102·9	78			
2 hr. 20 min.	102·4	50	..	..	Kicks vigorously when pinched.
2 hr. 34 min.			abt. 87	12	Does not kick when pinched.
8 hr. 0 min.	98·8	..	..	13	No. 1 is now awake.
24 hr. 0 min.					Temperature of No. 2 cannot be taken or estimated, as it is so low that the mercury does not rise from the bulb of the thermometer. No respiration is visible, but occasionally the animal opens its mouth convulsively. No reflex. It was put in the warm bath, but respiration did not become re-established, and all signs of life shortly disappeared.

Expt. III. Into a guinea-pig, No. 1, weighing 272 grammes, was injected 0·65 c.c. of a 50 per cent. solution of hydrate of chloral. Into another, No. 2, weighing 330 grammes, the same quantity of the solution was also injected.

	No. 1.		No. 2.		
	Temp.	Resp.	Temp.	Resp.	
At injection.....	100·9°	..	100·8°		
After injection 7 min.	..	..	..	..	No. 1 fast asleep. It was put into a warm-air bath. No. 2 not quite asleep.
12 min.	..	..	..	..	No. 2 nearly quite asleep. Lies as it is placed. Reflex movements are slight.
26 min.	..	..	93·1	46	
50 min.	107·0	62			
1 hr. 26 min.	..	..	..	28	Shivers very much with expiration, so that the respirations are difficult to count. Grunts slightly when the thermometer is introduced into the rectum.
2 hr. 4 min.	102	104	about 89·5	30	Both animals are chewing.
2 hr. 38 min.	101·8	..	88·5	..	No. 1 is awake. Though still somewhat sleepy, it will no longer lie on its back. No. 2 cries when pinched. It was put into the warm bath.
4 hr. 6 min.	..	..	95·6	..	No. 2 is now awake.

In this experiment (No. III) the dose was small, and guinea-pig No. 2 recovered although it was not kept warm, but not till an hour and a half after No. 1, although the latter was the smaller animal, and the dose it received was therefore much greater in proportion to its size.

Expt. IV. Into each of three guinea-pigs 1·1 c.c. of 50 per cent. solution of hydrate of chloral was injected subcutaneously. No. 1 weighed 640 grammes, No. 2, 670 grammes, and No. 3, 717 grammes.

	No. 1.		No. 2.		No. 3.		
	Temp.	Resp.	Temp.	Resp.	Temp.	Resp.	
	101·6°	..	102·5°	..	101·4°	..	No. 1 was put at once into a hot-air bath after the injection.
After injection 19 min.	..	..	..	..	..	..	No. 2 was quite narcotised and was wrapped in cotton-wool.
9 min.	..	..	..	..	..	..	No. 3 was narcotised and was left lying on table.
2 hr. 20 min.	..	..	..	..	85	17	
2 hr. 40 min.	..	..	97	36			
2 hr. 50 min.	104·4	74					
3 hr. 0 min.	..	..	95·3	..	83	20	Saliva runs from mouth.
	103·5	70					
5 hr. 30 min.	..	..	..	..	?	10	
5 hr. 50 min.	..	..	94·6	..	..	..	Begins to show signs of reflex when pinched.
6 hr. 0 min.	100·6	76					
7 hr. 50 min.	..	..	..	..	..	8	
8 hr. 10 min.	..	..	93·2	..	..	..	Is beginning to awake.
8 hr. 20 min.	100·8	..	..	..	..	..	No. 1 is dead. It appeared to have had convulsions, for some of the cotton-wool lining the bath was caught in its teeth.
22 hr. 0 min.	..	..	..	..	..	..	No. 3 is still alive. On pinching one hind foot he moves both it and the other one. Occasionally opens its mouth in a convulsive manner and paws with its feet while it lies on its side. It died a short while after.

In this experiment the animal No. 1 died in consequence of too high a temperature of the bath.

Expt. V. Into the flank of a guinea-pig, No. 1, weighing 392 grammes, was injected 0·75 c.c. of a 50 per cent. solution of chloral, and into the axilla of another, No. 2, weighing 335 grammes, 0·9 c.c. of the same solution.

	Temp. of animal.		
	No. 1.	No. 2.	
After injection—			
3 min.	..	..	No. 1 lies quite quiet. No. 2 put into a warm-air bath at 98·6°.
5 min.	98·2	98·0	
12 min.	..	98·3	No. 1 is dead. The heart beat after the respiration stopped. The respirations of No. 2 became very rapid and deep after it was put in the air bath.
2 hr. 26 min.	..	111·4	No. 2 was heard to give a grunt, and on taking it out almost immediately after it was found to be dead.

The dose was here either too large or the temperature of the bath rose too high.

Expt. VI. Into each of three guinea-pigs, No. 1 weighing 490 grammes, No. 2 weighing 425 grammes, and No. 3 weighing 415 grammes, 1·1 c.c. of a 50 per cent. solution of chloral hydrate was injected subcutaneously.

	No. 1.		No. 2.		No. 3.		
	Temp.	Resp.	Temp.	Resp.	Temp.	Resp.	
A minute or two after injection ..	100°	90	99·4°	96	100°	84	
	..	..	..	..	..	..	Nos. 2 and 3 quite narcotised.
5 min.	..	..	..	..	..	..	No. 1 quite narcotised. No. 1 left exposed. No. 2 rolled up in cotton wadding, and No. 3 put into a warm-air bath at 86°.
31 min.	..	26	..	..	..	..	No. 1 shows some reflex action of foot when it is pinched.
1 hr. 13 min.	about 87	13	..	..	..	..	Respirations of No. 1 are very deep.
2 hr. 15 min.	..	..	96·8	36			
2 hr. 26 min.	..	..	..	..	105·4	90	
2 hr. 35 min.	?	8					
3 hr. 35 min.	..	4	..	..	..	..	Pulse of No. 1 is 80 per minute.
3 hr. 56 min.	..	..	93·6	27			
4 hr. 7 min.	..	..	..	..	102·6	94	No. 3 grunts when pinched.
4 hr. 16 min.	..	..	..	..	..	..	No. 1 is dead.
6 hr. 45 min.	..	..	92·5	36	..	..	No. 3 is awaking.
6 hr. 56 min.	..	..	..	..	103·6	..	No. 3 is running about.
10 hr. 0 min.	..	..	85·0	34			
20 hr. 30 min.	..	..	93·0	..	..	..	No. 2 has just been delivered of a young one, which is dead. No. 2 can run about.
22 hr. 0 min.	..	..	..	..	..	..	No. 2 seems quite well; eats heartily.

This experiment shows the effect of warmth in preventing death, and the rapidity of recovery when the animal is put in a warm bath, compared with that which it makes when encased in cotton-wool.

All these experiments were made in August, 1870, in the laboratory of my friend, Dr. Burdon Sanderson, and I gladly take this opportunity of returning him my most hearty thanks for the facilities and aid he afforded, and the kindness which he then and ever has shown me.

INFLUENCE OF TEMPERATURE ON THE PULSATIONS OF THE MAMMALIAN HEART AND ON THE ACTION OF THE VAGUS.

(Reprinted from *St. Bartholomew's Hospital Reports*, vol. vii, 1871, pp. 216 to 228.)

THE influence of warmth in quickening the pulse has been long known, but the hypothesis put forward by Budge,* and again by Liebermeister,† that the quickness of the pulse in fever is due to the increased temperature of the body, gives it an interest to physicians which it would not otherwise possess. This hypothesis is grounded on the fact that increased temperature, within certain limits, causes the hearts of frogs and mammals to beat more quickly, both when they are in the body and after they have been separated from it. This has been observed in the frog's heart by Humboldt,‡ Pickford,§ Weber,‖ Budge,¶ Tigger,** Panum,†† Calliburces,‡‡ Schelske,§§ and by Cyon,‖‖ in Ludwig's laboratory. As the experiments of the last-mentioned observer were more complete and extended than those of the others, I shall give the results which he obtained. His experiments were performed by removing the heart entirely from the body of the frog, filling it with serum through the vena cava, and connecting the aorta with a manometer, by which the number and force of the pulsations could be measured and registered. The heart was then enclosed in a vessel whose temperature could be altered at will. Any

* Budge, quoted by Panum.
† Liebermeister, *Deutsch. Arch. f. klin. Med.*, vol. i, 464.
‡ Quoted by Panum.
§ Pickford, Henle u. Pf. *Zeitsch.*, vol. xi, 2, 1851.
‖ Weber, quoted by Panum.
¶ Budge, *Arch. f. phys. Heilk*, vol. v, 590.
** Tigger, *Dissertation*, 1853, quoted by Panum.
†† Panum, *Bibliothek für Läger*, Bd. x, p. 46, and Schmidt's *Jahrb.*, 1858.
‡‡ Calliburces, *Gaz. hebd.*, 1857, p. 468.
§§ Schelske, *Ueber die Veränderung der Erregbarkeit durch die Wärme*, 1860.
‖‖ Cyon, *Ludwig's Arbeiten*, 1866.

change in the number of the heart-beats which was produced by an alteration of temperature was of course due to its action on the nerves or muscular substance of the heart itself, as it had been severed from all connection with other structures. In this way he found that it is only within a certain limited range of temperature that the frog's heart pulsates at all, the lower limit being from 32° to 28·8° F., and the upper one between 86° and 104° F., the limits varying somewhat with each individual heart. When it is cooled down, its beats become slower and slower till it reaches the lower limit, and then they stop altogether. When it is slowly warmed, they become quicker and quicker till they reach their maximum rapidity, within a few degrees of the upper limit. They then become slower and slower, and finally stop when the limit itself is reached. During the time the heart is being warmed, the number of its beats does not steadily increase throughout in the same proportion to the rise of temperature. From the lower limit the number of beats increases at first very slowly, and then more and more quickly for each increment of temperature, till the maximum rapidity is attained, and then, with each degree of rise in the temperature, the pulsations diminish in number, rapidly though irregularly, and soon cease. In the two or three degrees which precede complete stillstand the beats become not only slow but irregular, so that almost no two intervals between them are of the same length.

At the under limit of temperature the heart contracts only to a small extent, but a few degrees above it the maximum amount of contraction is reached, and this amount continues the same up to from 57·2° to 66·2° F., when the contractions again begin to get smaller and smaller.

Just before it is stopped altogether by the heat, the ventricle no longer contracts as a whole, but does so in a peristaltic manner, so that it sometimes seems to be contracting vigorously, and yet not a drop of the fluid it contains is expelled, but it is merely moved about from place to place in the ventricular cavity, one part expanding as another contracts, and *vice versâ*.

When the heart is beating regularly, at moderate tempera-

tures, irritation of the venous sinus causes cessation of the beats; but during stillstand from cold, each irritation of it produces a single contraction, and during stillstand from heat produces tetanus of the heart. The inhibitory centres through which the irritation of the sinus acts, at ordinary temperatures in producing slowing and stoppage of the heart, seem therefore to be completely paralysed by heat, as otherwise they would prevent the contraction from becoming tetanic, and would only allow it to be intermittent.

Schelske also found that if the vagus, which usually causes slowing, be irritated by a strong electric current, while the heart is in this condition of stillstand from heat, an undulating contraction is produced.

This may be due, as Cyon thinks, to the current being partly conducted to the heart, and irritating it directly; but it seems to strengthen the supposition that the inhibitory centres in the heart, and through which the vagus usually produces slowing, are paralysed.

Pickford, Budge, Tigger, and Panum found that the hearts which were exposed to a high temperature soon ceased beating and lost their irritability, so that they no longer contracted on the application of a stimulus either mechanical or electrical, while those exposed to a moderate temperature continued to beat, and retained their irritability for a very much longer time.

Budge and Tigger had assumed that the action of temperature on the mammalian heart was the same as on that of the frog; but as Nysten had not noticed temperature to exert any particular influence over the time that the mammalian heart retained its irritability after separation from the body, while its action was so marked in frogs, Panum thought it well to test this assumption by experiment.

He took three rabbits of exactly the same age, and as nearly as possible of the same size and strength, killed them by dividing the spinal cord in the neck, and at once removed the heart and lungs. These were then placed in vessels in which the air was kept moist so as to prevent the irritability of the heart being injured by drying. The temperature in one vessel was 42·8° F., in a second 61·7° F., and in the third 91·4° F. The

heart which was put into the warmest vessel beat much more rapidly, and that in the coldest vessel more slowly, than the one which was exposed to a moderate temperature. He also found, although Nysten had failed to observe it, that, just as with the frog's heart, the rabbit's heart which had been put in the warm vessel, and thus caused to beat more quickly, stopped pulsating and lost its irritability by tactile or electrical stimuli much sooner than that in the temperate one. The heart which was put in the cold vessel lost its irritability even sooner than that which was warmed, or rather it seemed to lose it, for the irritability was not destroyed but was merely dormant, and when moderately warmed the heart again became irritable, and remained so for a considerable time.

I have made several experiments on the effect of temperature on the rabbit's heart while it still remained in the body, sometimes leaving all its nervous connections untouched, and sometimes dividing the vagi. These experiments were made by narcotising the animal with opium or chloral, and laying it in a tin vessel about 20 inches long by 6 inches broad, and 3 inches deep in the inside, and well padded with cotton wool. The vessel was double, and by pouring hot water into it, the temperature of the rabbit was gradually raised. The belly of the animal was also covered with cotton wool, and sometimes with an india-rubber bag containing hot water. To make respiration easier, a cannula was introduced into the trachea, and in some experiments the inspired air was passed over warm water, so as to warm it and saturate it with moisture and lessen the loss of heat from the lungs. The pulsations of the heart were counted by pushing a fine needle through the thoracic walls into the heart, so that it vibrated with each pulsation, and connecting its outer end, by means of a fine thread, with the lever of one of Marey's cardiographs, which registered the beats on a revolving cylinder covered with smoked paper. (*Vide* p. 294.) By means of this arrangement, which I owe to Professor Stricker of Vienna, it is possible to count the pulsations with great exactitude, even when the heart is beating at the rate of 470 in a minute, as it did in one instance. The temperature was measured by a thermometer in the rectum. As the animals

were completely narcotised, and remained perfectly motionless, the thermometer remained undisplaced in the rectum from the beginning to the end of the experiments.

The results are shown in the following table :—

Temperature.	Pulsations in 15 Seconds.							
	No. of Experiment.							
	I.	II.	III.	IV.	V. vagus cut.	VI.	VII. vagus cut.	VIII.
99° F.	..	..	..	76	..	..	98	
100	..	..	..	71	..	78		
101	..	..	..	73	..	81		
102	..	..	..	76	..	86	83	82
103	..	..	85	77	78	87	84	83
104	..	..	..	82	81	89	87	89
105	..	..	85	85	85	86	91	118
106	..	..	..	89	87	58	91	103
107	..	..	88	91	88	..	97	91
108	..	..	..	94	90	..	97	89
109	..	..	97	96	..	..	101	102
110	..	..	97	97	..	..	110	102
111	..	..	101	102	..	..	108	105
112	..	..	99	..	..	..	109	103
113	..	..	85	..	..	..	90	112
114	..	..	..	..	..	..	..	17
115								
116								

From this table it will be seen that the heart beats more quickly as the temperature of the animal rises, till it reaches its maximum, and then becomes slower, and finally stops. The increase in the number of beats is not the same for each degree of rise in the temperature, and the number of beats at the same temperature, and also the amount of quickening for each degree of rise of temperature, differs in the different animals.

The upper limit of which the heart stands still varies in different animals, but in the stronger animals it is between 113° and 114° F., or even above it. It must be remembered, however, that this was the temperature of the rectum, and as the back of the animal lay on the warm cotton wool covering the tin vessel, and its belly was covered with cotton wool as well, while the thorax was not covered, so as not to interfere

with the working of the cardiac needle, it is probable that the temperature in the rectum was higher than in the thorax. In Experiment VIII the heart became markedly irregular just before it stopped.

The effect of increased temperature on the pulse of healthy men has been studied by Lemonnier, Currie, Bartels, Liebermeister,* and others, and they all agree that the pulse rises with the temperature.

From an analysis of 280 cases, Liebermeister found that the pulse became quick as the temperature rose, although the amount of quickening was not the same for each degree of increase. The regularity of the quickening was, however, quite as great as that which I have found in rabbits, as is evident from the numbers which he gives. and which I append here:

Temperature	98·6° F.	99·5	100·4	101·3	102·2	103·1	104	104·9	105·8	106·7	107·6
Mean pulse rate ..	78·6	84·1	91·2	94·7	99·8	102·5	108·5	109·4	110	118·6	137·5
Increase for each ·9° F.		5·5	7·1	3·5	5·1	2·7	6·	·9	·6	8·6	18·9

We see then that the number of pulsations increases with the temperature in the hearts of frogs and rabbits, both when exercised and when in the body; that it does so in healthy men, and also in exactly the same way in a fever patient.

In view of all these facts, even although we find so high an authority as Wunderlich† stating that it is by no means certainly shown that the cardiac contractions are determined by the temperature, it seems to me that we can hardly avoid the conclusion that the quickness of the pulse in fever is mainly due to the higher temperature of the heart.

Another question, however, now arises. Although the higher temperature be the chief, is it the only cause of the quickened pulse?

Liebermeister says that the rise of temperature can be occasionally observed to precede the rise of the pulse; but Wunderlich states, on the other hand, that it is more common to find that the changes in the pulse have slightly preceded

* Liebermeister, *Deutsch. Arch. f. klin. Med.*, i, 463.

† Wunderlich, *Medical Thermometry*, Syd. Soc. Trans., p. 440.

the alteration of temperature, and, as it were, announced the occurrence of the latter.

Here, then, at the very beginning of fever, we have a quickening of the pulse which cannot be due to temperature. It might be produced by stimulation of the motor ganglia in the heart itself by some cause yet unknown, by stimulation of the quickening centres in the brain and cord, or by diminution of the power of the vagus, either through some impression made directly on the brain, or indirectly through some change occurring in the arteries and altering the blood pressure. The first cause seems very unlikely, and it is more probably due to either the second or third, but this must be decided by future investigations. On this point I have made no experiments, my attention having been attracted rather to the effect which high temperatures in fever would have upon the vagus, and to the way in which this might modify the action of the remedies then employed.

Thomas* found that digitalis sometimes had no action on the pulse when given in pneumonia, and as digitalis acts chiefly through the vagus it seemed to me possible that its want of action might be due to paralysis of the inhibitory apparatus in the heart through which the vagus acts upon it.

This appeared all the more probable since Schelske and Cyon had found that a high temperature paralysed it in the heart of the frog, and the rapid increase in the pulsations noticed by Liebermeister between the temperatures of 105·8° and 107·6° F., seemed to indicate that the same thing occurred in the mammalian heart. In order to test the truth of this supposition, I performed the Experiments I, III, IV, V, and VIII, which are given in detail below.

The animals were narcotised, the vagi exposed, and their power tested by irritating them by an induced current from one of Du Bois Reymond's coils. The temperature of the animal was then raised, and the power of the vagus tested from time to time with a current of the same strength as that used at first. From these experiments, and especially from No. VIII, it will be seen that as the temperature was raised and the pulse quick-

* Thomas, *Arch. f. Heilk.*, vi, 4, p. 329, 1865.

ened the power of the vagus diminished; but when the temperature had risen nearly to the upper limit, and the pulsations were becoming slow, the power of the vagus again increased, and, contrary to my expectation, was strongly marked just before the heart ceased to beat. Few as these experiments are, the results are so definite that we may, I think, conclude that in the heart of the rabbit, and probably other mammalian hearts, a temperature sufficiently high to produce stoppage of the heart does not paralyse the vagus or the inhibitory apparatus through which it acts. It is possible that a longer exposure to a high temperature, such as occurs in fevers, may produce this result; but it seems probable that it is not so, and that if digitalis, or other similar drugs, should not act on the pulse during fever, we must seek for some other explanation of their failure than paralysis of the structures through which they act. Unfortunately I did not carefully look for clots in the vessels after death; but on dividing the carotids and jugulars the animals bled freely, and in one which I examined no trace of a clot could be found in the heart or vena cava. I am inclined, therefore, to reject Weikart's* hypothesis that death from heat is due to coagulation of blood in the vessels, and rather to look on the impairment of the muscular power of the heart by the heat, possibly from coagulation of the myosin in its muscular substance, as the cause of death, as suggested by Bernard,† and to regard the rapid loss of irritability, noticed by Panum, in the heart exposed to a high temperature, and therefore beating quickly, as an indication of the great importance of keeping down the temperature and pulse-rate in fever patients by every means in our power.

I gladly take this opportunity of expressing my thanks to Professor Burdon Sanderson for the kindness with which he placed his apparatus at my disposal and allowed me the use of his laboratory in which the greater number of my experiments were performed.

Experiment I.—A young rabbit was fastened in the apparatus and narcotised by the injection of 1½ cub. cent. of laudanum

* *Arch. d. Heilk.*, p. 193, 1863.

† Bernard, *Compte-rend. de la Soc. de Biologie*, p. 51, 1859.

into the jugular vein. A cannula was then put into the trachea, and a thread passed under the right vagus. The temperature in the rectum was 94·8° F. Hot water was then poured into the apparatus; an india-rubber bottle containing hot water was placed on the belly, and the cannula in the trachea was connected with a flask containing warm water, so that the inspired air should be warm and moist. The temperature gradually rose, and the power of the vagus over the heart was tested by irritating it from time to time.

Temp. 105·2° F.	Irritation of vagus stops the heart.
106	" " acts, but not so strongly.
109·2	" " causes slowing, but no stoppage.
115	" " " " " "

The pulse became slow and weak, and the animal was removed and put under a tap of cold water, but its pulsations were not restored. On post-mortem examination the venous system was found much congested.

Experiment II.—A rabbit, weighing about 3½ lbs., was narcotised by injecting a solution of chloral subcutaneously. An hour and a half after it was put in the apparatus, a cannula put in the trachea, and a thread passed under the right vagus; but the nerve was not cut. Temperature in rectum 100·2° F. Hot water was poured into the apparatus, and the inspired air passed over hot water. The temperature sank to 100° F.; it then began to rise, but the animal died before it rose much above 104° F.

Experiment III.—A young rabbit, weighing about 3 lbs., was narcotised by the subcutaneous injection of about 30 grs. of chloral. It was fastened in the apparatus; a fine needle was thrust into the heart, and connected with one of Marey's cardographic levers. The needle was removed at the end of each tracing. Cannula in trachea.

	Temp.	Pulse in 15″.
		85
Right vagus irritated		6
		85
	103·6° F.	85
Right vagus irritated		5
		82
	105·4	85

	Temp.	Pulse in 15″.
Right vagus irritated		34
		91
A piece of wood had been placed under it the previous time to isolate it, and not removed, so it was probably weakened by exposure to air.		
	107·2	88
Right vagus irritated		28
		94
	109	97
Right vagus irritated		38
		99
Right vagus irritated	109·2	26
	110	97
Right vagus irritated		34
		99
		101
Right vagus irritated	111·2	48
		103
	112·2	99
Right vagus irritated		38
		103
	113·2	85
Heart has almost ceased to beat	113·6	

Respiration had entirely ceased. Artificial respiration was tried, but it did not stimulate the heart in the least. The tracheal cannula was found to be full of moisture. The animal was allowed to lie in the apparatus.

The heart stopped at	5 h.	8 m.	P.M.	Temp.	113·6° F.
"	"	" 8	"	"	114·6
"	"	" 11	"	"	115
"	"	" 20	"	"	115·8
"	"	" 30	"	"	116·4

The animal was now removed from the apparatus. In taking off the head-holder, the animal's jaws were found to be so firmly locked together that it was with considerable difficulty that the bar of the holder could be removed from between the teeth. On opening the abdomen the muscular walls were found to be somewhat congested; the viscera were rather pale. Behind the right kidney, in the cellular tissue, over the psoas muscle, there was an extravasation of blood, about 2 inches long by about ½ an inch broad. Lungs natural. Left ventricle was firmly contracted; right ventricle nearly empty. The left ventricle

was quite hard, and the septum seemed to have contracted so firmly that the apex of the heart had a cleft appearance. Both auricles were moderately filled; the bladder contained a good deal of urine. During the experiments the muscles of the neck seemed somewhat œdematous.

Experiment IV.—A young rabbit was narcotised by the subcutaneous injection of chloral. The amount seemed insufficient; and after the animal was placed in the apparatus, the right jugular was exposed for the purpose of injecting some into it. The vein had several irregular branches, one of which was unfortunately wounded, and the animal lost some blood. The vein was then tied, and the choral injected into the carotid artery. No cannula was placed in the trachea. A thread was passed under the right vagus, but it was not cut. No hot-water bottle was placed on the abdomen, but only a piece of cotton wadding.

	Temp.	Pulse.
		70
Right vagus irritated		30
7 seconds after		72
		72
Vagus irritated		13
	99° F.	76
	100	71
	101	73
	102	76
	103	77
	104·2	82
	105	85
	106	89
	107	91
	108	94
	109	96
	110	97
	111	102
	111·5	102
Vagus irritated	111 5	37

The animal now awoke, so I removed it from the apparatus and administered a fresh dose of chloral. Unfortunaely, however, I injected it into the abdominal cavity, and the rabbit died in a few minutes.

Experiment V.—A rabbit was chloralised and placed in the apparatus, a cannula put in the trachea, and both vagi exposed.

	Temp. 103·5° F.	Pulse 78
Right vagus cut	102·9	79
Left vagus cut	102·6	80
Right irritated		40
Afterwards		76
Left vagus irritated		26
7½″ afterwards		78
Temperature rising rapidly, about 0·3° in a minute	103·3–103·8	78
	104·5–104·8	81
	105·5–105·8	85
	106·5–106·7	87
	107·5–107·6	88
	108·5–108·6	90
Heart suddenly became slow and weak	109·2	stopped

Experiment VI.—A young rabbit, weighing about 1½ lbs., was narcotised by the injection of 4 c.c. of 50 per cent. chloral solution under the skin of the flank. Shortly after it was placed in the apparatus the respiration stopped, but the carotids were seen vigorously pulsating. The trachea was quickly opened, a cannula inserted, and artificial respiration begun. The heart, which had begun to get weak, soon pulsated normally again. A thread was passed under the right vagus, but it was not cut

	Temp. 104·4° F.	Pulse 82
	100·1	78
	101–101·2	81
	102–102·2	86
	103–103·1	87
	103·5–103·8	87
	104	89
	105	86
	106	58
	106·2	42
Began artificial respiration ..	106·2	64

Respiration began to go on again naturally, but soon stopped; and on again beginning artificial respiration the animal did not recover. On post-mortem examination, blood was found to have extravasated into the pericardium from the heart.

Experiment VII.—A young rabbit, weighing about 1½ lb., was narcotised by injecting 3 c.c. of a 50 per cent. chloral solution subcutaneously. An hour afterwards a cannula was introduced into the trachea.

	Temp. 99·8° F.	Pulse 76
	99·5	73
Both vagi cut.....	99·5	98
Animal was now warmed....	102·4	83
	103	84
	104	87
	105	91
	106	91
	107	97
	107·5	97
	108-108·2	97
	109	101
	109·5-109·7	102
	110·3-110·4	110
	111-111·1	108
	111·6-111·7	107
	112-112·1	109
	112·5-112·7	106
	113	90
	113·2	35
	113·5	18
	113·8	10

The beats of the heart now became imperceptible. The thorax was quickly opened, and the heart seen to be at rest and moderately contracted. On irritating the left vagus in the neck by a strong induced current a slight undulating contraction began in the heart and lasted for a few seconds. After stopping, it was again excited by direct irritation of the heart. After stopping a second time, it could not be excited to move by irritating either vagus, but slight movement occurred on irritating the heart directly. The abdominal parietes were slightly, but the viscera were not, congested. The blood was fluid.

Experiment VIII.—A strong rabbit, weighing between 3 and 4 lbs., was narcotised by the subcutaneous injection of 5 c.c. of a 50 per cent. solution of chloral. Three-quarters of an hour afterwards a cannula was placed in the trachea, and a thread passed under each vagus, great care being taken to injure the nerve as little as possible.

Temp. 100·9° F. Pulse 76.

Right vagus irritated. The secondary coil had been placed by mistake over the primary one, and convulsive movement of the thorax occurred, which obscured the pulse. It was then pushed back 120 mm. during the irritation, but the movements still continued

After irritation 73

Left vagus irritated. Slowing and stillstand of heart, and irregular contractions of the thorax occurred.

Right vagus again irritated. Similar result as before.

Afterwards 77

Left vagus irritated 29

Afterwards 79

Right vagus irritated; distance of secondary coil 100 mm. ..... stillstand

Afterwards 79

Left vagus irritated; distance of coil 100 mm. ..... stillstand

In ½ of a minute it was again perfectly regular.

102 82
103 83
104–104·4 89
105–105·5 118
106 103
107 91
108 89
109 102
110 102

Left vagus irritated; distance of coil 100 mm. 40

In 3 seconds after 102

Left vagus again irritated 38

In 7½ seconds after 106

Pulsations are now very small 113 112

Left vagus irritated 22

15 seconds after 108

113·4 106
113·5 87

Left vagus irritated ..... slowing and stillstand

Convulsive movement of the thorax occurred, and lasted nearly ½ a minute. The pulse then became regular 82

It continued so for 35 seconds, and then suddenly fell to 30

114·4 17

The pulse now became irregular, 4 beats occurring together in one second, followed by a

Temp. 100·9° F. Pulse 76.

pause of another second, and then 3 or 4 beats occurring together again.

114·5 ..... 14½

Left vagus irritated ..... stillstand

Afterwards 18

The beats now became slow and almost imperceptible ..... 114·8 ..... stopped

The thorax was quickly opened. The heart was still. On irritating the left vagus in the neck by a strong induced current, a slight vermicular movement occurred in the heart. After stopping it could be again excited by direct irritation of the heart.

The viscera were not congested; there was no extravasation; the blood was fluid; and there was no trace of a clot in the heart or vena cava.

EXPERIMENTAL INVESTIGATION OF THE ACTION OF MEDICINES.

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I.—The Standard of Health.

British Medical Journal, 1871, April 22nd, p. 413, and April 29th, p. 439.

Modes of Investigation.—Pathology.—Pharmacology.—Life.—Conditions of Health and Disease.—Effect of Drugs.—Direct and Indirect Action.—Local and Remote Action.—Dose.—Modification of Dose.—Cumulative Action.—Effect of Habit, Climate, Fasting.—Form of Administration.—Effect of Large and Small Doses.—Homœopathy.—Constitution and Idiosyncrasy.—Explanation of these from Experiments on Animals.—Connection of Chemical Constitution and Physiological Action.

The usual mode of investigating the action of a remedy is to give it to a patient during an illness and observe what changes occur in the symptoms after its administration. But it not unfrequently happens that medicines are given without any distinct change in the symptoms ensuing. Even when one does take place, we very often cannot be sure that it is due to the medicine, and not to the course of the disease or some other modifying cause. For, if the remedy and the disease are both at work together, it is obviously impossible for us to decide what part of the result is due to the one and what part to the other, unless we know what the course of the disease would have been without the medicine, and what action the medicine would have had if the disease had not been present. Any attempt to investigate the action of a remedy by giving it under such circumstances is like that of a rifleman who should attempt to learn shooting by practising only at dusk, when he could not see the butt, much less the bull's eye. He might go on practising for ever in this way without making any improvement; for, when he missed, he would never know whether it was because he had not seen the mark properly or had not aimed steadily at it. If he wish to learn, he must practise by daylight, when he can clearly see the mark, and can thus be

sure that every miss is due to unsteady aim. He must fire high or low, to one side or the other, as he finds necessary, and, by gradually correcting every error, his aim will at last be sure. Should he then be called on to stand sentry on some dark night, and shoot at some suspicious object without hitting it, he would know that his failure was due to his not having seen the object distinctly, and having consequently aimed in a wrong direction. And just as the rifleman, before he stands sentry in the dark, must learn to shoot by daylight, when he can note the effect of each alteration in the position of his rifle on the course of the bullet, so ought we to investigate the action of our remedies in circumstances and under conditions which we know and can vary at will, marking the effect of each variation upon their action till we thoroughly and exactly understand what it is, before we proceed to give them in disease, when not only the conditions under which they operate are at present in a great measure unknown, but the effects they produce cannot be definitely ascertained from insufficient knowledge of what the result would have been had they been withheld. Of late years, it is true, vigorous efforts have been made to determine what course diseases run when not interfered with by medicines; and, although it is often difficult to say what the sequence of symptoms will be in any particular case, depending as it does not only on the general course of the disease but on individual peculiarities of the patient and on the varying circumstances in which he is placed, we may nevertheless ascertain with tolerable accuracy whether or not our treatment is beneficial in a general way, even when we cannot determine its effects in detail.

Very inexact and very unsatisfactory as such a knowledge of medicines as this necessarily is, it must for the present be our guide in practice in a large number of instances; and our treatment at present and for some time to come will be chiefly empirical, because our knowledge of pharmacology, and perhaps still more of pathology, is not yet sufficiently advanced. For there is hardly any disease in which we know the exact nature of the morbid changes which are occurring, or the precise organs or tissues which are their seats; and, with some exceptions, we

are but very imperfectly acquainted with the structures on which our remedies act, and the exact mode in which these are affected by them. Day by day, however, our ignorance is diminishing; and we may hope that ere long rational treatment will to a great extent supersede blind empiricism. It not unfrequently happens at present that we meet with a case which bears a very close resemblance to others which we have treated successfully, and which nevertheless obstinately resists the remedies which we had previously found serviceable. Our failure astonishes and vexes us; but we are ignorant of its cause, and we can only select some other drug by guess and try it: we cannot at once choose the one which will have the desired effect.

Pathology.—In order to choose a drug which will have the effect that we desire to obtain, we must know where the morbid changes are taking place, and what their nature is; and we must be sure that our medicine will act on the affected part, and in such a way as to counteract the disease. We must trace every symptom which we see, back to its unseen source; every flush on the cheek, every quickening of the pulse, back to the vaso-motor or cardiac nerves, which have allowed the capillaries to become dilated, and thus produced the redness, or have permitted the heart to beat more rapidly than its wont. We must then inquire what has produced this alteration in the nervous system, and so on, till at last we discover, if possible, the hidden cause of the mischief. We will then give that remedy which will act in the proper way on the part which we believe to be the seat of the morbid process; and, if the expected result does not ensue, we shall, at any rate, have discovered what the pathology of the disease is not; and, by trying a remedy which will act in a different way or on a different structure, we may find out what it really is.

When I speak of the pathology of a disease, I do not mean those obvious alterations in the structure of an organ which we meet with in *post mortem* examinations, but the so-called functional changes which precede and are the cause of both them and the symptoms. For example, the disorganisation of a man's liver by the presence of an abscess, or of his kidneys by fatty degeneration, is not the disease from which he suffered, any

more than a field strewn with slain or crowded with heaps of wounded is a battle. The disease was the alteration in the nervous and vascular systems, and in the nutrition of tissues, which we call the inflammatory process, and which produced the abscess and degeneration, and the disturbance of the same systems, to which these lesions in their turn give rise; just as an army may not only lose the battle for want of the assistance which its slain and wounded would have given, but its retreat may be embarrassed by their presence.

The insufficiency of present modes of treatment, and the urgent necessity which exists for an accurate knowledge of pathology and pharmacology, are shown by the manner in which any new remedy is seized upon and applied in all sorts of cases, even in those where a knowledge of the morbid processes going on, and of the action of the remedy itself would at once have indicated that harm, and not benefit, must ensue from its application. It is unnecessary to discuss here the manner in which pathology must be studied in order that an accurate knowledge of it may be obtained: I may merely indicate as examples the works of Cohnheim, Brown-Séquard, Sanderson, Stockvis, Stricker, and many others.

Pharmacology.—In studying pharmacology, our first object is to find out on what structures a remedy acts. For this purpose, it is of no use to give it to a man either sick or well. We may do so in order to find out what general symptoms it produces; and from these symptoms we may guess at the structures affected; but, in order to convert our hypothesis into certainty, we must have recourse to an experiment which may be of two kinds. Firstly, we may apply the drug to those structures or organs which we suppose to be affected by it, and to them alone, and see whether the general result is the same. This we generally do either by immersing them in a solution of it, or by causing blood containing it to circulate through them.

Secondly, we may prevent the drug from reaching these tissues or organs while it is applied to all other parts of the body, and observe whether the effect is absent. For this purpose, we cut off from one or other parts of the body the supply of blood which carries the drug along with it, or we may so

injure the part that its function is abolished, and no action exerted upon it can produce any effect. But it is impossible to do this in man, and so we must have recourse to the lower animals, in which we can produce at will the conditions we desire. Although the administration of a medicine to a patient is really an experiment, we vary the conditions in which it acts to so much greater extent in animals that it is convenient to call the latter mode of investigation the *experimental method*, and the former that of *clinical observation*.

Now pathology and pharmacology may go on hand in hand both in teaching and study, but they must always be preceded by physiology; for, unless we know the processes which take place in the healthy organism, it is impossible to understand the changes they undergo in disease, or the effect of drugs upon them. I will, therefore, here say a few words regarding the processes in which life consists, before proceeding to speak of the mode in which they may be modified by the action of remedies.

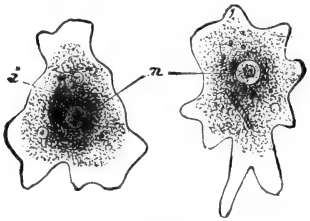
Life.—We meet with life only in certain bodies composed of carbon combined in a very complicated manner with oxygen, hydrogen, and nitrogen; and it may, generally speaking, be said to be the power which these bodies possess of assimilating to themselves other substances, of decomposing them, and of evolving energy, which is shown in active motion, active growth, &c. Evolution of energy in this way is the distinguishing mark of life. When we look at a grain of wheat, an egg, or a dried wheel-animalcule, we are unable to say whether or not it is alive; it is only when it begins to evolve energy, either by moulding other substances into conformity with its own constitution in active growth, as in the seed or egg, or by active motion, as in the animalcule, that we are able to decide the question. We cannot say how these bodies originally came to possess their complicated constitution and wonderful powers; but the evolution of energy by which we recognise the continued presence of life seems to be more intimately associated with chemical affinity than with other forms of energy, such as light, heat, or electricity. All these forms of energy modify the processes which occur in living beings, both those which are

chemical and those which we term vital, and apparently in much the same degree; but whether they modify the vital only through the chemical, we are at present unable to say. Instances may readily be found in which life continues active, although one or other of the forces mentioned is not supplied to the living body from without, and is only secondarily present as a result of chemical changes going on within. Thus a seed in the earth, a fungus in a cellar, or a proteus in its dark cave, live and thrive without a ray of light; and the whale and walrus in the Arctic seas are independent of any external heat, their temperature being only maintained by combustion taking place within their own bodies. But there seems to be no instance of vitality alone continuing active when a stop has been put to the occurrence of chemical changes. Sometimes both chemical and vital processes are suspended together for a time, as in a grain of wheat or a rotifer when it is kept dry, or in an egg when kept cool and coated with varnish to exclude air. So long as chemical activity remains dormant, no other form of energy can awake the latent vitality. Only when the conditions necessary for chemical transformation of the proper kind and amount are supplied, does it again become manifest. Thus light or heat may be applied in any amount or any proportion to an egg, a seed, or a dried rotifer, and still they will not grow or move if the air be withheld from the former or the moisture from the two latter, which is essential for the production of chemical changes within them.

Conditions of Health and Disease.—These changes of which I have been speaking consist in the assimilation of certain substances, their decomposition within the organism, and the rejection of waste products. A due proportion between these constitutes health. Just as a fire can only be kept bright by raking out the ashes and supplying fresh fuel as that in the grate burns away, so an organism can only be kept healthy by removing the products of waste and supplying fresh nutriment as its tissues get decomposed during action. The conditions necessary for this purpose are secured in the simplest forms of life, such as the amœba, by the little mass of protoplasm moving about in a fluid, which can not only supply

the oxygen to keep up combustion and evolve energy, and the nourishment necessary to replace the material thus used up, but can at the same time remove the products of waste. In higher

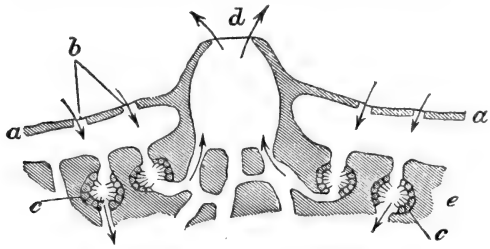
FIG. 124.—Amœba Princeps.



An amœba figured at two different periods during movement.
n, nucleus; *i*, ingested bacillus.

organisms, the little masses of living material of which they are composed, and which are for the most part fixed, are nourished by a fluid in which they are bathed, fresh portions of it being supplied by its constantly flowing over them, instead of their moving like the amœba through it. In sponges, for example, where amœba-like bodies are attached to a framework, as shown in the diagram (Fig. 125), a current of water is kept flow-

FIG. 125.—Hypothetical Section of Spongilla.



[After Huxley.] It consists of a number of particles, each resembling an amœba, and supported by a fibrous framework. It is divided into a superficial layer (*a*) and a deeper part (*e*), separated by a cavity. The particles of which *e* is composed would not get enough nourishment were it not that a constant current of water is kept flowing over them by the action of the cilia with which some of them (*c*) are provided. These move constantly in one direction, and thus draw the water in at *b* and cause it to flow out again at *d* in the direction of the arrows.

ing over them by ciliary action. If we imagine this sponge placed in a vessel of water we will have no very unfair picture of the body of a mammal. The little masses of protoplasm in the sponge may be compared to the cells which form our bodies, the vessel to our skin, the water to the intercellular fluid or lymph in which our tissues are bathed, and its surface whereby oxygen is absorbed from the air to our lungs. Just as the sponge cannot be said to live in air, so we do not really live in air. We—that is, the tissues which compose our bodies—live in what Claude Bernard* has termed an internal medium, viz. the intercellular fluid which exudes from the blood-vessels, gives nutriment and oxygen to the tissues, and returns again to the general circulation by the lymphatics and veins.

It will simplify our conception of this subject if we fix in our mind's eye one little mass of protoplasm or cell, and consider what changes will be produced in it by different conditions. Any alteration in the amount of the nutrient fluid, or in its composition, will necessarily produce a change in the nutrition of the living matter to which it is supplied. If nutriment be withdrawn, the cell will begin to burn away. If oxygen be withheld,† or the products of waste be not removed, combustion will cease, and the cell will die. If nutriment or oxygen be supplied in insufficient quantity, or the products of waste only partially removed, the cell may adapt itself to the altered circumstances, and its nutritive and functional processes go on in the same way, but to a less extent than before; or they may become deranged—that is to say, the cell becomes diseased. The limits within which the cell can adapt itself to changes in nutrition are the limits of its health. The higher animals, however, are no mere aggregation of cells, each nourishing itself independently of the others; for each cell has its own peculiar function, each its special kind and amount of nourishment; and none must do either too much or too little work, none must have too much or too little nourishment, or the nutrition and functional activity of the body as a whole cannot be properly maintained. This delicate adjustment of the several parts to one

* Bernard, *Revue des Cours Scientifiques*, 1863–4, p. 278.

† Kühne, *Untersuchungen über Protoplasma u. Contractilität*, p. 53.

another is secured by means of the nervous system, which regulates at once the activity of any organ, the quantity of nutritive fluid supplied to it, and the amount of material it shall take up. The means by which it acts are, its direct influence on the nutrition of cells themselves,* as is seen in the salivary glands;† or its indirect action through the circulation in slowing or quickening the heart, which propels the blood; in contracting or dilating the vessels which convey it to any part;‡ or, on the capillaries which allow the actual nutritive fluid or lymph to filter out and bathe the tissues. Besides thus regulating the supply, it also regulates the composition of the nutritive fluid by maintaining a due relation between the activity of the body, the supply of new material by digestion, and the separation of effete products by the excreting glands. On account of this mutual dependence of all the parts of the body on one another, if one gets wrong it puts the others out of order. Thus a sudden chill may act on the vaso-motor nerves, and cause contraction of the vessels of the skin; the blood they contain is thus thrown back on the internal vessels§ and congestion and inflammation of the kidneys ensue. In consequence of this, they no longer excrete as they ought the effete products, which then accumulate in the blood, react on the nervous system, and this again on the muscles; and so the circle goes on. In the case supposed, the vaso-motor nerves of the kidneys have also been reflexly affected by the chill, and in consequence the renal arteries have not contracted sufficiently to resist the increased pressure and prevent congestion; while in another they might have done so, only allowing so much blood to pass as to increase secretion, and, by thus lessening the flow in the renal vessels have counteracted the effect of vascular contraction in the skin, restored the normal pressure in the kidneys and preserved health. When all the organs are able to accommodate their nutrition and function to great alterations, we say the health is strong; but when they can only do so to slight ones, we say

* Ludwig, *Physiologie d. Menschen*, vol. ii, p. 346.
† Heidenhain, *Studien aus d. Physiolog. Institut zu Breslau*, Heft iv, 1868.
‡ Ranvier, *Compt. rend.*, 1869, vol. ii, p. 1326.
§ *Vide* Johnson, *British Medical Journal*, Dec. 6th, 1873, p. 664.

the health is weak; and when this is the case with one organ alone, we say that it is specially weak.

Effect of Drugs.—The nutrition of a cell may not only be altered by changes in its supplies of nutriment and oxygen, but it may be modified or destroyed by the addition of certain substances to the nutrient fluid. Thus a weak solution of alkali may increase or diminish the rapidity of the changes which it undergoes, by hastening the removal of waste products if they be acid, or retarding it if they be alkaline; while a weak acid will have an opposite effect. Certain metallic salts may stop them altogether by forming a firm compound with the substance of the cell, while other bodies may enter into combination with it for a time (possibly replacing some ordinary ingredient of its nutriment), again passing out and leaving it in its primitive condition, but altering during their stay its physical characters and functional properties. Such seems to be the case with curare, which, when injected into the blood, paralyses the peripheral ends of motor nerves; but, if life be preserved by artificial respiration, the poison is excreted, and its effect passes off.* No change can be noticed in the nerve-fibres, either by the naked eye or microscopically, during the paralysis; and this was supposed to show that great functional alterations may occur without any structural change. But this is not the case; for Kühne† has ascertained that, when the ends of motor nerves in muscles are examined microscopically, their outline is found to be more distinct during the action of the poison. It is possible that the change in physical properties shown by this distinctness of outline may be only the indication of some more important alteration in their chemical composition; but, whether it be more chemical or physical, a change at any rate takes place; and to this, I believe, we must attribute the alteration in function.

Whatever be the composition of protoplasm, the substances which are associated with it in the composition of different cells are at any rate different; and, although the same nutritive fluid is supplied to them, they do not all take out from it, or give out to it the same substances in the same proportions, but some take

* Brodie, *Phil. Trans.*, 1812, p. 205.

† Stricker's *Histology*, Power's translation, vol. i, p. 221.

up more of one thing and some more of another. And they do just the same with drugs added to the nutritive fluid. Thus lime salts naturally exist in the blood, and are carried by it to every part of the body; but while the bone-cells take them up in large amount, nerve-cells assimilate an almost infinitesimal quantity.* And if we feed an animal on madder, which has an affinity for lime-salts, the bones become deeply stained, while the nerves and fat retain their normal colour. It is possible, too, though experiments on this point are wanting, that a substance added to the nutritive fluid may be taken up by two structures, but may have a very different effect on the one from what it has on the other; just as a grain of sand, which would have no effect on the machinery of a locomotive, may totally stop the movements of a watch. We do not know whether sulphocyanide of potassium and curare are taken up equally by nerves and muscles or not; but the former salt will paralyse the muscles without affecting the nerves, while curare will paralyse the nerves, but leaves the muscles intact.†

The cells composing one structure, then, take up and are acted on by some drugs, and not at all by others; while other structures are much affected by the very substances which had so little action on the first.

Direct and Indirect Action.—When any drug is taken up by a structure and acts upon it as curare on the ends of motor nerves, we term this its *direct* action. Thus paralysis is due to the *direct* action of curare on the motor nerves. But, as all parts of the body are dependent on one another, some other structure may be affected, not by the action of the drug upon it but by that which it has exerted on the first part. This is its *indirect* action. Thus, when curare has been given to an animal, it occasionally happens that the nerves going to the respiratory muscles become paralysed before those which go to the extremities.‡ The muscles of respiration then cease to act, the blood is no longer arterialised, carbonic acid accumulates, and, by irri-

* Buchheim, *Arzneimittellehre*, p. 25.

† Bernard, *Leçons sur les Effets des Substances Toxiques*, p. 314.

‡ Hermann, "Ueber eine Bedingung des Zustandekommens von Vergiftungen," *Du-Bois Raymond und Reichart's Archiv*, 1867, p. 64.

tating the nerve-centres, produces convulsions, which cease when the action of the poison extends to other nerves. In this case neither the muscles, the blood, nor the nerve-centres, are acted on directly by the curare. The muscles will contract if stimulated, and, if the lungs be artificially supplied with air, the blood will be arterialised as usual, the convulsions will cease, and life may be preserved. These asphyxial convulsions, which are produced by the circulation of venous blood in the nerve-centres, are thus due to the *indirect* action of curare.

Local and Remote Action.—Before curare could reach the nerves on which it acted directly, it was necessary for it to enter the circulation, but it had no marked action on the spot whence it was absorbed. Other substances, however, produce an effect on the spot to which they are applied, and this may be independent of any effect which they produce after absorption. This is termed their *local* action. Thus strong sulphuric acid taken into the stomach combines with its tissues and forms a slough: this is its local action. But besides this, the irritation in the stomach produces through the nervous system a weakening effect on the heart, the circulation stops, and the person dies. It is not the sulphuric acid which has found its way into the circulation and acted on the heart that arrests its pulsations, but the irritation in the stomach which has influenced it through its nerves. This is the *remote* effect of the acid.

Dose.—The effect produced by any remedy depends on several conditions. The first of these is the *amount existing in the blood* at any given time, which we may call the *actual dose*, to distinguish it from the usual dose administered by the stomach or otherwise, a part of which may not be absorbed, but remain inert at the point of introduction. The action which a drug has on the body is not dependent on its absolute amount, but on the proportion it bears to the body on which it is to act, so that an amount which is a small dose for one person is a very large one for another.* Thus if a grain of some active substance be injected at the same time into the veins of a full-grown man and into those of a boy of only half his weight, it will be distributed through twice as much blood in the man as in the boy, and

* Buchheim, *Arzneimittellehre*, p. 65.

each tissue will only receive half as much of it. The dose of a drug must therefore be regulated by the weight of the patient; and thus women, being lighter, require a smaller amount than men, and children less than adults. Though it would be more exact, it is not always convenient, to weigh patients; but in experiments on animals the weight of the animal should always be carefully ascertained, as well as the amount of the drug administered. If a substance be injected into the veins, the whole of it mixes with the blood and becomes active immediately, and the maximum effect is thus at once obtained and will again diminish as the substance is excreted. But the case is different if it be injected subcutaneously, and if it be given by the stomach or any other mucous cavity the difference is still greater; for as soon as some of it is absorbed excretion begins, and thus part of the drug is passing out of the blood while another part is being taken in. The amount in the blood is, then, *only the difference between that absorbed and that excreted in a given time*, and absorption may be so slow or excretion so quick that there is never a sufficient amount of the substance in the blood to produce any effect. Thus Bernard found that a dose of curare which would certainly paralyse an animal when injected into the veins or even subcutaneously, would have no effect when introduced into the stomach;* and showed that this was due to the kidneys excreting the poison as fast as it was absorbed from the stomach, by extirpating the kidneys,† when the animal became paralysed as surely as if the poison had been introduced at once into the veins, though not so quickly. Hermann also discovered, without being acquainted with Bernard's observations, that curare taken into the stomach would produce paralysis if excretion were prevented by ligature of the renal vessels.

The more rapid the absorption, or the slower the excretion, of any drug, the greater will be its effect. Thus the effect produced by the same dose of a medicine will be in proportion to the rapidity of its absorption from the different parts to which it has been applied, unless the differences be so slight or the excre-

* Bernard, *Leçons sur les Effets des Substances Toxiques*, p. 282.

† Bernard, *Revue des Cours Scientifiques*, 1865.

tion so slow that there has not been sufficient time for the removal of any considerable quantity from the blood. On this account we must diminish the dose of a medicine in order to obtain the same effect, according to the rapidity of absorption from the place to which we apply it. Absorption is quickest from a serous membrane, then from intercellular tissue, and lastly, from mucous membrane. The vascularity and rate of absorption from intercellular tissue is greater on the temples, breast, and inner side of the arms and legs than on their outer surfaces or on the back.* It should not be forgotten that any drug introduced into the stomach but not absorbed into the blood is as much outside the body as if it were in the hand, for any effect it will have on the system, provided always it have no local effect on the gastric walls. For if it act directly on the walls of the stomach, it may have an effect which it would not have when held in the hand or applied to the skin. Thus mustard, which would produce redness and burning of the skin, will cause vomiting when swallowed; but opium, which does not act on the stomach itself, produces no effect until after it has been absorbed.

By the difference between absorption and excretion under different circumstances or in different individuals,† the cumulative action of drugs, the effect of idiosyncrasy, habit, climate, condition of body, as fasting, etc., disease, and form of administration, can to a great extent, though not entirely, be explained; but experiments on some of these points are deficient, and the explanations now given are to some extent theoretical.

Cumulative Action.—If a substance be naturally so slowly excreted from the body that the whole of the dose in ordinary use is not excreted before another is given, the amount present in the body will gradually increase, just like the curare in Hermann's experiment, and will produce an increasing or cumulative effect. Examples of this are to be found in metallic preparations, such as those of mercury or lead, which are excreted very slowly; or in some of the organic alkaloids, if given in

* Eulenburg, *Hypodermatische Injection der Arzneimittel*, 3rd edition, p. 65.

† Children absorb more quickly than adults, so opium is more dangerous to them. Marx, *Lehre von den Giften*, vol. ii, p. 117.

sufficiently large and frequent doses. The size of the dose and the frequency with which it must be repeated in order to produce a cumulative effect will differ according to the rapidity with which the drug is excreted; for, if excretion be rapid, a larger dose, or more frequent repetition, will be required. The long time which elapses before a dose of opium takes effect on some individuals is probably due to its being very slowly absorbed; and the power of one man to take, without apparent effect, an amount of alcohol or opium which would intoxicate another, to its either being more slowly absorbed from the stomach or intestine, or more quickly excreted by the lungs, skin, or kidneys, so that the amount present in the blood at any one time is never sufficient to produce toxic effects. There are two vegetable active principles, digitalin and strychnia, to which an especial cumulative action is ascribed. After moderate doses of these drugs have been taken for some time, it is found that instead of the effects they produce increasing gradually, as we would expect from a gradual accumulation in the blood, the symptoms of poisoning become suddenly developed in somewhat the same way as if the dose had been suddenly increased. It is evident that a diminution in the quantity excreted will produce this effect as readily as an increase in the quantity taken, and this is probably the true cause of the phenomenon. When digitalin has been taken for some time and accumulated to a certain extent in the blood it causes a diminution in the amount of urine excreted, and this diminution is either accompanied or quickly followed by the other symptoms of poisoning.* The effect indeed seems exactly the same as Hermann would have obtained in his experiment if he had only partially compressed the renal arteries instead of ligaturing them completely. For digitalin appears to diminish the secretion of urine by exerting a powerful action on the renal vessels,† and in large doses may completely arrest the secretion of urine,‡ and probably also the circulation through the kidneys.

* Brunton, *On Digitalis, with some Observations on Urine*, p. 39 (*vide antea*, p. 61).

† Brunton and Power, *Proc. Roy. Soc.*, 1874, No. 153, and *Centralblatt d. Med. Wiss.*, 1874, p. 497 (*vide postea*, pp. 410 and 412).

‡ Christison, *Edin. Med. Journ.*, vol. vii, p. 149. *Mazel, Gazette des Hôpitaux* 1861–74.

Effect of Habit, Climate, Fasting, and Form of Administration.—The effect of habit in lessening the action of drugs may be due to increased power of excretion or diminished absorption; and that of a warm climate in increasing the action of narcotics, such as hyoscyamus, to their excretion being hindered by the diminution in the amount of urine consequent on the increased cutaneous transpiration. A medicine taken by a fasting person is generally more rapidly absorbed and has a greater effect than if the stomach be full, as is well known in the case of alcohol. The form of administration has also an effect on the rapidity of absorption. When a drug is given in a soluble form in small bulk it is more quickly absorbed, and will have greater effect than when given in an insoluble form or much diluted. Thus two glasses of raw brandy may intoxicate a man, especially if taken on an empty stomach when the person is thirsty and absorption therefore rapid. The same quantity diluted with two quarts of water would have little or no effect, for before the stomach could get the whole absorbed, the alcohol which had first found its way into the blood would have been in great part either excreted or consumed.

Large and Small Doses.—The effect produced by a small dose of a drug is sometimes exactly the opposite of that produced by a large one. We cannot say exactly why it is so; but we very generally find that any substance or any condition, whether it be acid or alkali, heat or electricity, which in moderate amount increases the activity of cells, destroys it when excessive.*

Homœopathy.—This opposite action of large and small doses seems to be the basis of truth on which the doctrine of homœopathy has been founded. The irrational practice of giving infinitesimal doses has of course nothing to do with the principle of homœopathy—*similia similibus curantur:* the only requisite is that mentioned by Hippocrates, when he recommended mandrake in mania; viz., that the dose be smaller than would be sufficient to produce in a healthy man symptoms similar to those of the disease. Now in the case of some drugs this may be exactly equivalent to giving a drug which pro-

* Kühne, *Untersuchungen über Protoplasma und Contractilität*, pp. 49, 31, 33, and 43.

duces symptoms opposite to those of the disease; and then we can readily see the possibility of the morbid changes being counteracted by the action of the drug and benefit resulting from the treatment. For example, large doses of digitalis render the pulse extremely rapid, but moderate ones slow it.* In this instance its moderate administration when there is a rapid pulse is homœopathic treatment, and this has sometimes been beneficial. But it is not proved that all drugs have an opposite action in large and small doses, and homœopathy, therefore, cannot be accepted as an universal rule of practice.

Constitution and Idiosyncrasy.—Variations in the action of a drug cannot be entirely explained, however, by the varying amount in which it may be actually present in the circulation and acting on the body. Another modifying element of great power is *constitution.* In animals generally we have certain motor arrangements in the bones and muscles, regulating arrangements in the nervous system, and yet other arrangements in the circulatory system for supplying them with the material necessary for the performance of their functions. But the parts which enter into each of these are not equally developed in all animals; in some one part preponderates; in others, another. Even in animals of different species, and in individuals of the same species where the relative size of organs seems the same, differences nevertheless exist; and the presence of a few cells more or less in a ganglion, and a few fibres more or less in a nerve, may alter to a very great extent the action of any substance on the organism. When a medicine given to one person produces an effect slightly differing from that which it generally causes, the difference is said to be due to *constitution;* when its difference is great, it is said to be due to *idiosyncrasy.* Now, these effects may be merely due to differences in absorption and excretion, as has been already explained, or to the different *relative development* of other parts, especially parts of the nervous system. It is easy to understand the altered effect which may be thus produced, and to perceive the ambiguity of such terms as "nervous stimulant," when we recollect that

* *Vide* Traube, *Med. Centr. Ztg.*, vol. xxx, p. 94, 1861, and Brunton *On Digitalis*, p. 21 (*vide antea*, p. 47).

different parts of the nervous system act exactly in the opposite way to others; and if anything should act on both of these, it will produce an opposite effect according as one or other part is more developed and more powerful. Thus, the vagus nerve has the power of rendering the heart's action slow, and the accelerator nerve of quickening it; and any drug which irritates them both will make the heart's action slow if the vagus be more developed, or quicken it if the sympathetic be stronger. Thus, two horses of unequal strength, pulling in opposite directions, may counterbalance each other; but if both be struck with a whip at the same moment, the power of the stronger becomes evident and he pulls the weaker after him.

A good example of this action is given by muscarin, an alkaloid obtained from a poisonous mushroom, *Agaricus muscarius*. Professor Schmiedeberg, of Strassburg,* has shown that this alkaloid produces great irritation of the vagus nerve, so that in frogs the heart will stand still for hours together. When given to dogs, it sometimes makes the pulse slow, but sometimes quickens it; and one might therefore be inclined to say that when it produces quickening it cannot be acting on the vagus. But the explanation of this phenomenon is, that muscarin does not act on the vagus alone, but has also an effect on the vasomotor nerves, producing dilatation of the vessels and diminution of the blood-pressure in them.† Now, lessened pressure acts as a stimulant to the accelerator, and quickens the heart. In this way muscarin stimulates both vagus and accelerator, and the pulse is rendered quick or slow according as the power of the one or other is greater in the particular dog to which it is given. In frogs, the blood-pressure has no great action on the heart, and in them the effect of the vagus is not interfered with.

Another instance may be given where an apparent difference in the effect of a drug on two animals may be removed by reducing their organs to the same condition. In most animals, the slowing action of the vagus on the heart is constantly exerted during health; and when it is cut the heart beats much

* Schmiedeberg und Koppe, *Das Muscarin*, p. 28.

† Schmiedeberg, *op. cit.*, pp. 43 and 48.

faster. But in the rabbit, its power is comparatively small, and the increased rapidity of the pulse after its division is but slight. In most dogs, on the contrary, its power is great, and if it be cut, the heart beats very much quicker, and sends more blood into the arteries, so as to raise the pressure in them. If we measure the pressure of the blood in the arteries of a rabbit and of a dog, and then cause them to inhale nitrite of amyl, we find that the small vessels have become widened and allow the blood to pass easily out of the arterial system into the veins, so that the pressure sinks considerably in the rabbit, but it sinks only slightly in the dog. The effect seems at first sight different; but when we examine it more closely, we find that the heart of the dog is no longer beating slowly, but very quickly, so as to keep up the pressure, notwithstanding the rapid flow of blood through the widened vessels, while the heart of the rabbit was going so fast before that it could not go much more quickly. If we cut the vagi in the dog, so that the heart goes as quickly as in the rabbit before it begins to inhale, the blood pressure sinks during the inhalation, just as it does in the rabbit.*

I have given these examples at length, because of their important bearing on the question how far conclusions as to the action of medicines on man may be drawn from those which they exert on the lower animals. Now, the action of curare in paralysing the ends of motor nerves is one of the simplest and least complicated examples that we can take, as the very nature of its action prevents disturbances in other systems from showing themselves; and we find that it is exactly the same in the Indian who accidentally wounds himself with his poisoned arrow, in the game which he shoots, or in the frog on which we experiment.

Motor nerves, the structure on which curare acts, are alike present, and in all are its results the same.

As we have seen that in the lower animals, differences in the action of drugs are produced by differences in the structure of the animal, and that the former disappear when the latter

* Lauder Brunton, "Action of Nitrite of Amyl on the Circulation," *Journal of Anatomy and Physiology*, vol. v, p. 95 (*vide antea*, p. 176).

are removed, we are, I think, justified in concluding that, when the organs or structures on which a drug acts are similar in man and the lower animals, the action will be alike, and that variations will be observed just in proportion to the difference between his structure and theirs. But as it may be difficult or impossible to detect these differences except from the effects, we ought to test our conclusions as to the action of remedies by giving them to a healthy man, and observing whether their effects are such as we have been led, from our experiments on animals, to expect.

Disease.—The different effects of a medicine in health or disease may be partly due (1st) to alterations in the relative amount of absorption or excretion produced by the disease and consequent changes in the quantity of the drug actually present in the blood. Thus, enormous quantities of opium have been given during the collapse of cholera without producing any effect, because no absorption took place, and the opium remained in the stomach so long as the collapse persisted. When it passed off and absorption again began, the opium was taken into the circulation and exerted its usual action, so that persons have died of the remedy after recovering from the disease.

The difference in action is due (2nd) to the alterations produced by disease in the organs and tissues of the body which may interfere with both the indirect and direct actions of the drug. Thus, digitalis usually slows the pulse by acting on the heart through the vagus. But in febrile diseases it sometimes has little or no perceptible action on the pulse. This is probably due to the fact, that the accelerating ganglia of the heart are stimulated by the high temperature to such an extent that the vagus can no longer restrain them. For irritation of the vagus trunk by galvanism, which has a stronger action on the heart than digitalis and usually stops its pulsations entirely, ceases to do so when the temperature of the animal is raised, and yet the vagi are not paralysed, for when the motor power of the heart diminishes they can again stop it, although the temperature may still be high.* What the alterations in each

* Lauder Brunton, "On the Action of Heat upon the Mammalian Heart," *St. Bartholomew Hospital Reports*, vol. vii, p. 221 (*vide* p. 212).

disease, and the ways in which they will modify either the direct or indirect action of remedies, really are, can only be determined by an increased knowledge of pathology and by actual clinical observation.

Chemical Constitution and Physiological Action.—I have spoken thus far only of the changes in the body and the various effects which they produce; but I must not leave this subject without mentioning the wide field of research which has been opened up by the remarkable discovery made by Drs. Crum Brown and Fraser,* of the relation which exists between chemical constitution and physiological action. It was known before that one drug would act only on one part of the body, another on another; but they have shown that changes in the chemical composition of a drug may not only alter its action, but transfer it to a different structure: so the addition of sulphate of methyl to strychnia, brucia, or thebaia, causes them to act on the terminal branches of motor nerves instead of on the spinal cord, while a similar addition to other alkaloids removes some of their actions but leaves others unchanged. Further researches of this kind may enable us to determine what parts will be acted on by a drug after a definite change has been effected in its chemical constitution; and the progress of physiological chemistry in ascertaining the composition and properties of the tissues renders it not impossible that such knowledge may yet be acquired as that spoken of by Locke in the following words: "Did we know the (mechanical) affections of the particles of rhubarb, hemlock, opium, and a man, as a watchmaker does those of a watch, whereby it performs its operations, and of a file, which by rubbing on them will alter the figure of any of the wheels, we should be able to tell beforehand that rhubarb will purge, hemlock kill, and opium make a man sleep." And even though our knowledge should never reach this extent, the rapid advances which it has made of late years, the power which we now possess of altering the chemical composition of the organic alkaloids, and along with it their physiological action, and the fact that two of them (conia and muscaria) have already been made synthetically, incline us to

* *Transactions of the Royal Society of Edinburgh*, vol. xxv, pp. 1 and 693.

believe that we may by-and-by make the substances which will produce the physiological effects which we desire, and that a future lies before therapeutics of which at present we can hardly dream.

II.—Action of Drugs on Protoplasm: General Directions for Experimental Investigation.

British Medical Journal, 1871, May 13th, p. 405, and May 20th, p. 521.

Modes of Experimenting.—Caution.—Action of Drugs on Protoplasm.—Action on Vibriones and Bacteria.—Contagium Vivum.—Action on Fungi; on Fermentation; on Putrefaction; on Oxidation; on White Blood Corpuscles; on Inflammation.—Action of Gases.—Steps of an Investigation.—Administration of Drugs.—Observation of Effects.—Interpretation of Results.—Minimum Fatal Dose.—Various Channels of Administration.—Excretion.—Mode of Securing Animals.—Instruments required.—Mode of making Cannulæ, T-tubes, and Pens.—Narcotising Animals.—Action of Narcotics.—Introduction of Cannulæ into Vessels—Injection of Fluids.—Division and Irritation of Nerves.—Artificial Respiration; in Mammals; in Frogs.—Administration of Gases or Vapours.

Gentlemen,—In experimenting on the effect of drugs, our great object must be to *localise* their action—to be able to say with certainty, This is the organ on which this medicine acts, and such and such is the action which it exerts upon it. There are two ways in which this might be done.

1. We might give the medicine to animals of all kinds, from those consisting of one simple cell upwards to the highest forms of life, and mark how its action became modified as we advanced farther and farther from the simple mass of sarcode, and organ after organ became differentiated and developed. Unfortunately, however, the knowledge of comparative anatomy and physiology which is required to interpret the effects that we might thus obtain is so great, and possessed by so few, that this method is at present of little use.

2. We might take a highly organised animal, not very unlike man in its general structure, and, by operative procedures, allow the medicine to act now on one and now on another part of the body, but never on all at once, till we find out those parts for which it has a particular affinity.

This second method is the one which we chiefly employ, but

sometimes we may very conveniently use them both, as in the case of protoplasm, the physical basis of life.

Caution.—As I intend not only to describe the ways in which experiments on the action of medicines are to be performed, but also to give examples of the conclusions drawn by various observers from the experiments which they have made, and of the way in which these conclusions have been applied, I take this opportunity of strongly warning you, once for all, that you must distinguish very carefully between the observations actually made by any one and the conclusions which he draws from them. Observations on the effect of a drug may be correct, and yet the theory of its mode of action be erroneous; and both of these may be right, and still the proposed application of it to a disease may be valueless from ignorance of its real pathology. All observations, too, are not to be taken as facts: they must be confirmed by frequent repetition either by the first observer himself or by others before they can lay claim to this title. Their value depends to a great extent on the observer, and is in proportion to his power of seeing correctly what is before him, and the exactness of his description of what he has seen. Perhaps erroneous statements are due in great measure to the results of experiments not being noted at the time when they were done, but written down from memory some time afterwards. When this is the case, they lose in a great measure their claim to the name of observations, and they become merely thoughts or ideas of the observer. *All experiments should be noted down at the time when they are performed;* and if they are not, the time which elapsed before they were written should be stated, that future workers may know what value to attach to the observation, and not be put to the unnecessary trouble of disproving it if it be erroneous. Before beginning an investigation, it is convenient to write out the questions which we propose to ourselves, and to note down what experiments will be necessary to answer them. We are thus less likely to make experiments at random, and to waste time without coming to any certain conclusion.

Action on Protoplasm.—We may study the action of drugs on protoplasm either in unicellular organisms like the Infusoria, in

cilia, in white blood-corpuscles, or in those minute bodies—bacteria and vibriones—to which attention has of late been so much directed, and which, despite their minuteness, possess so much importance from their power of producing fermentation and decomposition in dead organic matter, and not improbably of causing disease in living beings. For the purpose of studying it in Infusoria, we prepare an infusion of hay some days before we wish to experiment, and a solution in water of the drug which we wish to investigate. We then heat a piece of glass tubing in the middle, draw it out and cut it across, so as to obtain two little pipettes, which will deliver drops of nearly equal size. From one of these we let fall a drop of infusion of hay on a glass slide, and examine it under a low power of the microscope without a covering glass. We then let fall a drop of the solution of our drug upon it, mix the two drops well with a glass rod, and again examine them microscopically to see whether or not the infusorial animalcules are still moving. If they be moving, and continue to do so for some time, we prepare a stronger solution of the drug; but if they have completely stopped when we looked, we make a weaker one, and again mix a drop with one of hay infusion, repeating the experiment till we have got a solution of such a strength that a slight movement of the animalcules can be observed just after mixing the drops, but ceases almost immediately, and cannot be brought back by adding water. We can then compare the action of different drugs by observing of what strength the solution of each must be, in order to produce precisely this effect.

Professor Binz of Bonn has found in this way that certain substances, such as common salt, chlorate, chloride and bromide of potassium, alum, &c., appear to stop the movements of Infusoria by altering the amount of water which they contain, as strong solutions cause them to shrivel at first, and then to swell up and become motionless. Weaker ones make them swell likewise; but their effect at first is different, as they do not shrivel up the animals, but, on the contrary, render their movements more lively.

Other substances kill them in a way which we do not understand, stopping the movements at once without producing any

apparent change in the animal's body to account for it. The most active of these substances are chlorine, bromine, corrosive sublimate, iodine, permanganate of potash, and creasote. After these comes quinine, less powerful than they, but far more so than other organic alkaloids. Even strychnia, so fatal to higher animals, has barely one-fourth the power over these lower organisms which is possessed by quinine, a substance which is dangerous to mammals only in such large doses that we are accustomed to look upon it as a remedy, but hardly at all as a poison.

Action on Vibriones and Bacteria.—If a piece of boiled meat or white of egg be allowed to lie in water for a few days, or a little of Pasteur's solution be exposed in a glass, the fluid becomes milky, and vibriones and bacteria are formed in large numbers. Pasteur's solution is made by dissolving 10 grams of sugar, 5 decigrams of tartrate of ammonia, and 1 decigram of yeast-ash, in 100 c.c. of water; or a little white of egg may be added to the hay infusion, when the Infusoria soon disappear, and it remains full of bacteria and vibriones. A drop may now be taken, diluted with another drop of water, and the action of drugs on vibriones examined in the same way as on Infusoria.

In this way it is found that the same substances which kill Infusoria also prove destructive to vibriones and bacteria: and if they kill these organisms when outside the animal body, they should do so likewise when they are inside, and thus cure diseases that may be caused by their presence. Now, bacteria have been said to be the cause of malignant pustule, and they are at all events frequently present in large numbers in the blood of animals affected by it, and their destruction can hardly fail to be advantageous. We are, therefore, not at all surprised to learn that Bouley and the French Commission found* that, while all animals which they inoculated with this disease died when left to themselves, four recovered out of five to which they had given carbolic acid, and that other cases treated in the same way by others gave a like favourable result. The striking correspondence between the effect actually produced on the

* *Compt. rend.*, vol. lxviii, p. 82.

disease and that which we should expect from its action on bacteria, which we suppose to be the cause of it, seems also to be an evidence of the truth of the hypothesis that bacteria are the cause of the disease, and that carbolic acid cures it by killing them. Before we accept this as a fact, however, we should test it by adding to one portion of the blood of a diseased animal, carbolic acid in the same proportion as was likely to be present in the blood of the one cured, and comparing it with another portion to which none had been added, and see whether the amount was sufficient to have any action on the bacteria. If it were not sufficient, we should have to look for some other action of the acid to explain its effect.

As cases of malignant pustule or other diseases in which bacteria and vibriones are found in the blood happily do not present themselves every day, Binz produced fever in dogs artificially by injecting infusion of hay or putrid animal matter into their veins, and then tested the action of quinine by injecting it either at the same time or shortly afterwards. The quinine diminished the effect of the infusion, but not to the extent which he expected; and this he thinks due to the infusion not containing vibriones alone, but gases and other products of decomposition, whose action would not be affected by quinine. Whether this be so or not, must be decided by further experiments. He believes also that hay-fever is due to vibriones; and he cured Helmholtz, who had suffered from it for several years, by injecting a solution of quinine into his nostrils.

Action on Fungi.—When spores of the ordinary penicillium or mould-fungus are thrown into Pasteur's fluid or syrup, they grow and develop new spores. Two portions must be taken, and the drug to be tested added to one and not to the other, and the amount of it necessary to prevent the formation of spores must be noted. If carbolic acid, corrosive sublimate, or very strong solutions of quinine be added to them their growth is prevented.

Action on Fermentation.—As butyric fermentation depends on the presence of vibriones and alcoholic on the yeast-fungus, we should expect that substances which kill these would

prevent fermentation. To test this, two glass-tubes or flasks are filled with a mixture of milk-water, grape-sugar, and chalk (from which carbonic acid will be set free by the lactic acid formed), or with a solution of grape-sugar or yeast. To one of them a certain amount of the substance to be tested is added, and both are then inverted over mercury and kept in a warm place for several days. The amount of gas developed is then measured; and, if the addition of the substance have hindered the production of gas, we know that it has hindered fermentation in the same proportion. It has thus been found that quinine, amounting to $\frac{1}{180}$th part of the mixture, completely stopped the development of vibriones or the production of gas; and other substances have a similar effect.

As many cases of indigestion, acidity, flatulence, vomiting, and summer diarrhœa, more especially in children fed by hand, are most probably due to the fermentation of starchy and saccharine food caused by vibriones, Binz thinks that creasote, quinine, &c., are serviceable in their treatment by stopping this. As it is the local action that is wanted, the longer the medicine remains in the intestine before being absorbed, so much the better will its effect be; and thus the greater benefit derived from bark than quinine in some such cases might be explained.

Action on Putrefaction.—The antiputrescent action of drugs is tested by putting a square of boiled white of egg into each of two vessels containing water and setting them in the sun. To the liquid in one vessel the drug is added, and the rapidity with which the edges of the square of white of egg on it become decomposed and soft is noted and compared with that in the other vessel. Instead of white of egg, a piece of meat or bread may be used. The relative power of different drugs in stopping putrefaction does not always correspond to the ideas which we would be inclined to form; for who would think that quinine would be more powerful than such antiseptics as creasote, chloride of lime, or arsenic? and yet such is said to be the case. So powerful is quinine, that a piece of meat placed in a solution of $\frac{4}{5}$ per cent. of the sulphate, with a little dilute acid, remained in summer without decomposition till the fluid was dried up.

Action on Oxidation.—If fresh leaves of lettuce or dandelion are triturated with five or ten times their weight of water, with free access of air, the fluid filtered, and fresh guaiac tincture added to it, a blue colour is produced, showing that ozone is present in it. To test the action of a drug on the formation of ozone, two portions of the filtered fluid are put in test-glasses, and the drug added to one. Both are allowed to stand for one or two hours, with occasional shaking, fresh guaiac tincture is dropped cautiously into both, and by the greater or less depth of blue produced in each fluid we judge of the amount of ozone present in each. In this way it is found that quinine diminishes or stops the formation of ozone in these fluids, and at the same time the little protoplasma-granules with which they abound are rendered motionless and altered in appearance. There seems to be some connection between these protoplasma-granules and the formation of ozone, as the stoppage of the one runs parallel with the alteration in the other.

Quinine seems to have the power of diminishing oxidation within the body as well as out of it, since when injected into the blood it lessens the excretion of urea and diminishes the temperature both in health and disease during life, and hinders its rise after death, and this action is apparently not due to nervous centres regulating temperature, or to changes in the circulation allowing quicker cooling by the skin.

Action on White Blood-Corpuscles.—To examine this, we take a drop of blood from the finger, put it on the under surface of a thin glass, and lay it over the opening in Stricker's warm stage,* and examine it with a high power of the microscope, such as Ross's $\frac{1}{12}$ or Hartnack's No. 10, at a temperature of 98° F. After satisfying ourselves that the white corpuscles are in active motion, we take a solution of the drug in fresh serum, or in half per cent. solution of common salt; mix a drop of it with the blood and examine again. Or we may use Max Schultze's warm stage, which consists of a flat piece of brass covering the stage of the microscope, and having a long arm projecting at each side and a thermometer in front. When a lamp is placed under one or both arms, they conduct the heat

* Stricker's *Histology*, New Sydenham Society's translation, p. 13.

to the middle part on which the object lies, and thus warm it to any desired temperature. The drop of blood must be placed on a piece of glass $3\frac{1}{2}$ inches long and $2\frac{1}{2}$ broad, which is then laid on the warm stage. The drop is next covered by a thin glass, and over all is put the lower part of a lamp-cylinder, through whose upper end the tube of the microscope slides, and round whose interior is put a piece of moist blotting-paper to prevent evaporation from the blood. The drug is applied as with Stricker's stage. Solutions of corrosive sublimate and veratria, even in very minute quantity, stop the movements of the white blood-corpuscles, but neither is so active as quinine. Strychnia is rather less powerful than any of these, and many other alkaloids much less so.

Action on Inflammation.—During inflammation, the white blood-corpuscles are very active, and crawl through the walls of the capillaries in much greater numbers than usual. It is, therefore, interesting to inquire what will be the effect on this of any drug that stops their motions. For this purpose we curarise a frog, and lay it on a large plate of cork with a hole at one side and another piece of cork $\frac{1}{2}$ inch high at the other. We fix the body of the frog to the raised piece, open its abdomen with a pair of scissors, draw out the intestines, and fasten the mesentery with very fine pins over the hole. In an hour and a half or two hours afterwards white corpuscles come rapidly out of the vessels and wander over the field. We may then inject our drug into the circulation or apply it locally to the mesentery.

Binz states that, when he injected quinine into the circulation, the number of corpuscles in the vessels became diminished, and they ceased to wander out, while those already out continued to wander further, so that, instead of being evenly distributed over the field, they left a clear space round the outside of the vessel, in which few were to be seen. If, on the other hand, it be applied locally, the corpuscles which are already out stop moving, while those in the vessel continue to migrate, and thus, instead of a clear space, a dense accumulation of corpuscles forms round the vessel. In order to produce this effect, $\frac{1}{25000}$th to $\frac{1}{20000}$th of the animal's weight of quinine

is necessary; and, if it were given to a man weighing 150 lbs., in order to stop the exit of corpuscles from the vessels in such a disease as peritonitis, 3 or 4 drachms of the medicine would require to be given within a short time. Binz's observations as to the effect of quinine on the white corpuscles have been confirmed by Martin, but have been denied by Schwalbe, so that further investigations on this point are very desirable.

Action of Gases.—This is examined by putting the cells to be examined on Stricker's warm stage, and bringing the gas into contact with them in the manner described by him.*

Steps of an Investigation.—The animals which we chiefly use in experiments are frogs, rabbits, guinea-pigs, and dogs. In investigating the action of a drug, we examine—

1. What the symptoms are which a large dose produces.

2. Taking the most prominent symptom, we inquire (*a*) On what organ does the production of this symptom depend? (*b*) How has it been affected by the drug? (*c*) Has this affection been primary or secondary?

3. We examine other organs which we think may have been also affected.

Administration of Drugs.—To examine the general effect of a drug, we weigh the animal and then give it a large dose in our first experiment, in order to get exaggerated symptoms. It may be given by the mouth or by subcutaneous injection. In frogs, the substance may be injected either under the skin of the back or into the abdominal cavity. In rabbits, &c., it is most conveniently injected under the skin of the flank. In guinea-pigs, the abdominal parietes are very thin; and, if we wish to compare experiments with different doses, care must be taken not to push the point of the syringe into the abdominal cavity, as the absorption will be then more rapid, and the same dose produce a greater effect. If we wish to give the medicine by the mouth, we either put it well back on the root of the tongue and then hold the animal's jaws together till we think it has swallowed it, or we put a perforated cork between its teeth, push an elastic catheter through the hole in the cork down the œsophagus into the stomach, and inject the drug in solution

* Stricker's *Histology*, Sydenham Society's edition, p. 8.

through the catheter. Orfila used to introduce the drug into an opening in the œsophagus, which he then ligatured to prevent vomiting; but since subcutaneous injection was introduced this method is rarely employed.

Observation of Effects.—After the drug has been administered, we allow the animal to move freely about, but prevent frogs from escaping by covering them with a large bell-jar. We then see whether the animal is restless or disinclined to move; whether its movements are perfectly performed or unsteady; whether or not its legs seem weak and paralysed, or convulsive movements or involuntary twitchings be present; whether its heart-beats or pulse, and respirations, are quick or slow, strong or weak, regular or irregular; whether there is vomiting or purging, diuresis, salivation, dryness of the mouth, flow of tears, or dry conjunctiva, and whether the pupil be contracted or dilated. If the animal seems asleep, we pinch it to ascertain if reflex action continue after voluntary motion is gone; and if respiration cease, we ascertain if the heart still continue to beat. As soon as possible after death, we open the animal and see if the heart still be beating. If it have stopped we note whether its cavities are full or empty, its walls flaccid or firm, and try whether it will contract or not on pinching or scratching it, or on irritating it by an electric current. We observe whether the veins are turgid or empty, the lungs pale or congested, the stomach and intestines quiet or in active peristaltic movement, the spleen large or contracted, the bladder full or empty; and the urine may be tested for sugar.

Interpretation of Results.—If we find in the course of these experiments that voluntary motion is increased or lessened, we may naturally conclude that the activity of the cerebrum is increased or diminished, unless the increase of motion should depend on pain, or its diminution on impairment of the motor apparatus. Unsteady movements, paralysis or convulsions, impaired reflex action on pinching, or stoppage of respiration before the heart, point to the spinal cord, to the nerves, or to the muscles; while quick or slow, strong or weak pulse, or stoppage of the heart before the respiration, point to the vasomotor system or cardiac nerves; increased or diminished secre-

tion, to secreting nerves; and full or empty bladder, and diminished or increased peristalsis, to the motor nerves of the bladder or intestine. We then try the effect of a small dose and note in what respect it differs from that of a large one. We thus ascertain in a general way what the organ is, which is chiefly acted on by any drug, and afterwards proceed to investigate the nature of the action by a farther series of experiments.

Minimum Fatal Dose.—If the drug be poisonous, we then try to ascertain the minimum fatal dose. For this purpose we weigh an animal and inject into it a dose which we think will not prove fatal, wait a short while, and then inject more till death is produced. We then reckon how much of the drug has been injected for every pound weight of the animal. We take another animal, and inject into it *at once* a quantity which will be somewhat smaller for its body-weight than that given to the first. The reason why a somewhat smaller quantity should be taken is, that some time was allowed in the former experiment for the excretion of part of the poison between each dose. If this amount prove fatal, we must give a still smaller quantity to another animal; but, if not, we must give more till we find the smallest quantity which will kill.

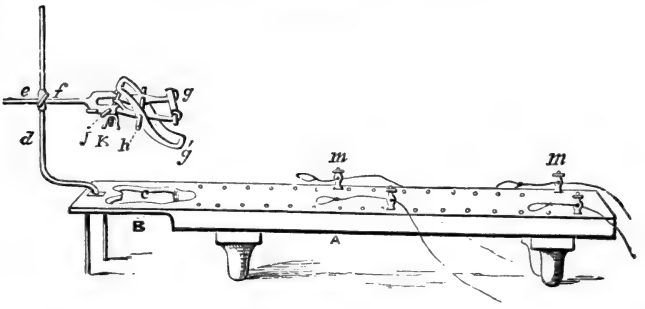
Various Channels of Administration.—The next point to be determined is, whether the effects are the same when given by the mouth or rectum, or other mucous surfaces, as by subcutaneous injection. If we should find, as Bernard did with curare, that a substance which is active when injected subcutaneously or into a vein, has no effect when introduced into the mouth, rectum, eye, or bladder, we must determine whether this is due to want of absorption or to decomposition of the drug by the secretions with which it becomes mixed. This is done by mixing it with these secretions, such as urine or gastric juice, allowing it to stand some time at the temperature of the body, and then injecting the mixture subcutaneously, and observing whether the usual effect is produced or not; or by ligaturing the ureters to prevent excretion.

Excretion.—Lastly, we examine in what manner it is excreted from the body. As most solids are excreted by the kidney, we

generally restrict this process to evaporating the urine, or testing it either chemically or by injecting some of the extract into another animal.

Mode of Securing Animals.—In order to determine in an exact manner what organs or parts are affected, we are obliged to make use of apparatus of various kinds; and, before these can be applied to an animal, it must be prevented from moving. Frogs are fastened to a frog-board by a piece of cord with a noose at the end, slipped over each elbow and ankle. The frog-board may consist of a piece of mill-board about 9 inches long by 3 inches broad, with four slits at the sides to keep the cords in position, or of a piece of wood the same size, and from a quarter to half an inch thick, with holes, through which the cords are passed. They may be fastened by simply tying them together or by sticking a small wooden pin into each hole, or by four screws, such as are used by fastening the wires of galvanic batteries, placed in the edges of the board. The last way is, I think, the most convenient. Rabbits are best secured by Czermak's holder and board (shown in Fig. 126). The best cord is strong window-cord. The one end should be flattened with a hammer, and turned over so as to make a small loop, whose two sides are then firmly bound together with waxed thread. Through this loop the other end is passed, and the noose thus made is ready to be drawn tight at any moment. The other end of the cord should be cut to a point and also bound with waxed thread to prevent the strands unravelling. The rabbit is placed on the board, the nooses slipped over the legs and drawn tight, and the ends of each cord passed through the screw which will be nearest it when the animal lies on its back. The rabbit is then turned over, and the cords drawn through the screws and fastened. The bar *h* is then put between its teeth, and the screw *l* turned till *g* and *g'* fit tightly over its muzzle, and the projecting ends of *g* fixed into the ends of *f*. Dogs may be fastened by Bernard's holder (Fig. 127A), or by a simple bar of iron put behind their canine teeth. A piece of cord is first tied round the upper jaw, the bar put into the mouth, and the two jaws tied firmly over it. A split trap may be used instead of the cord. I have had a bar made with a hole at each end, into

FIG. 126.

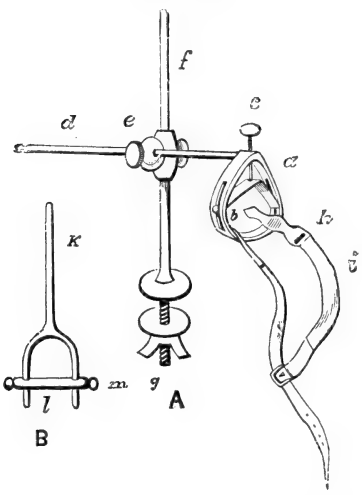


Czermak's Rabbit Holder and Board. A, The board. B, A bent piece of iron forming the upper part of the board. *c*, An open space through which instruments can be introduced from below to divide the spinal cord. It is generally covered by an iron plate. D is an upright rod fixed by a screw into a slit in B. *f* is a forked rod, which can be moved back or forward, up or down, by the nut *e*. The forks are hollow, so that the ends of the holder can be passed into them and fastened by the screw *j*. *h* is a bar which passes behind the incisor teeth of the rabbit. *g* and *g'* are two bent bars which pass under the chin and over the nose of the animal, and are brought together by the screw *k*. From the upper end of *g'* hangs a screw, which passes between two projections on *g*, and has a mother-screw *k*. The screw *k* works against the projections on *g*, and draws the ends of *g'* and *g* together. These press on the rabbit's nose and under jaw and keep the teeth firmly locked over the rod *h*. *m m* are screws for fixing the cords which confine the legs. They are a remarkably convenient sort, consisting of an outer part with a horizontal hole, and an inner ring with a stalk on which a milled screw plays. When the milled head is at the top of the stalk, the inner ring and outer holes correspond, and the cord can then be easily pushed through; but when the milled head is turned, the stalk and ring are drawn up and the cord nipped between it and the outer part. The cords may either be fastened directly in the screw or passed first through one of the holes in the edge of the board. The board should be covered with a large pad of india-rubber stuffed with horse hair, and there should be another round pillow to put under the animal's neck.

which a fork of steel passes, and is secured by a screw. The fork may then be fastened by a nut to an upright rod, as in Czermak's holder (Fig. 127B). Cats and guinea-pigs may be fastened by Czermak's holder. For guinea-pigs, a little padding must be placed between *g* and *g'* in order to make them catch the head. A simple bar and cord may also be used for rabbits, cats, and guinea-pigs, as well as for dogs.

Instruments required.—The instruments which we generally require for operations are—sponges, one pair of large scissors

FIG. 127.



A is Bernard's dog-holder. *a* is a metal ring, within which a bent piece of metal, *b*, is moved up and down by the screw *c*. *h* is a straight piece, which is fastened by a screw to *a*, and can be moved nearer to or farther from a corresponding piece at *b*. These two pieces lie under the lower jaw of the dog; the bent piece *b* is screwed down on its nose, and the strap *i* buckled behind its head, which is thus firmly fixed. It may be moved back or forward by sliding the rod *d* through the nut *e*, or up and down by moving *e* on *f*, which is a strong iron rod fastened to a table or board by the screw *g*.

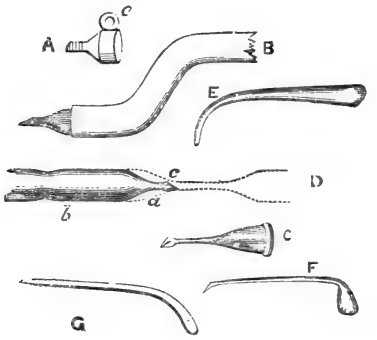
B, Brunton's holder for dogs or rabbits. A loop of cord is tied round the upper jaw, the bar *l* passed behind the canine teeth of the dog or cat or incisors of the rabbit, and the two jaws then tied together to prevent its slipping out. This mode of fastening animals has been long used, and my modification simply consists in the addition of the forked bar *k*. After *l* is fastened in the mouth, the forked ends of *k* are pushed through holes in *l*, and fastened by the screws *m*. *k* may then be fastened to an upright bar by means of a nut in the same way as Bernard's or Czermak's holder.

and one small pair, cutting well at the points, scalpels, forceps, small bull-dog forceps with smooth points, blunt hooks, a small aneurism-needle, flattened sidewise and with a rounded point (Fig. 128G), ligatures, finder (a kind of probe set in a handle to open up the lumen of a divided vessel), syringe, cannulæ, a piece of card, small whalebone-probe, and one or two swine's bristles. As these are very apt to be mislaid during an operation, I find it convenient to have a small wooden tray about three-quarters of an inch deep, with thin upright sides, and

divided into compartments, one for each kind of instrument. It is advisable, also, to have an extra instrument or two of each sort.

Way of Making Cannulæ.—Cannulæ for injecting into vessels may be made of metal (Fig. 128C) or of glass. Glass ones can be easily made of any size required by heating a piece of glass-

FIG. 128.



A is a metal cannula with an ear *e*, by which it can be fastened to any tube connected with its large end. B is an instrument for introducing A into a vessel. It consists of a piece of metal tubing, with a pointed piece of wood at one end, over which A is put. The point projects through the small opening in A, so as to enter the lumen of the vessel readily. C is a metal cannula which fits on the end of a syringe for injecting fluids into vessels. D is a glass cannula. The dotted line shows the original tube drawn out in the blow-pipe flame; the darker line shows the finished cannula. E and F are two pieces of glass tubing drawn out to make pens. They may be attached by pieces of cork to any writing apparatus. G is an aneurism-needle.

tubing over the flame of a blow-pipe, and drawing it out in the middle, as represented by the dotted line (Fig. 128D). It is then heated at *a* and slightly drawn out, so that a bulging piece is left between *a* and *c*; it may then be heated and very slightly drawn out at *b*, then cut with a three-cornered file at *c*, and the point ground obliquely off on a hone. If the point be at all sharp, its edges may be rounded in a gas-flame. When the cannula is introduced into a vessel, a ligature at *a* prevents it from coming out: it may be connected with a syringe or with any piece of apparatus by a piece of india-rubber slipped over

the other end and tied at *b*. A cannula for connecting an artery with a kymographion may either be of this sort, or may be made of metal of the shape shown in Fig. 128A. As it is difficult to hold it with forceps, it should be put on a piece of wood or whalebone of the shape shown at B. This both holds it firmly, and the point entering the vessel allows the cannula to be more readily pushed on into the lumen. A few notches on the side of the cannula prevent the vessel and ligature with which it has been tied from slipping off the end. By means of the little ear at *e*, it can be tied to the tube, on to which it is fitted.

Mode of Making Cannulæ, T-tubes, and Pens.—Cannulæ for the trachea are made by closing one end of a tube, directing a small blow-pipe flame against a point in its side till it is quite soft, and then suddenly blowing into it. The soft part expands into a thin bulb, which is scraped off, and a hole remains in the side of the tube. The object of this hole is to allow the air to escape during expiration. Instead of a hole in the cannula, one may be cut in the side of the india-rubber tube to which it is connected; but this is more apt to be accidentally closed. The tube is then drawn out into the form seen at Fig. 129A, p. 262, cut off at both ends, and one end ground obliquely off on a sandstone with some water.

A knob may be made at the ends of other cannulæ for various purposes, by heating the end and striking it against a piece of glass or iron, or by heating the end in a flame, continuing to blow steadily through the tube while you do so.

T-tubes are made by blowing a hole in the side of one tube, in the same way as for a respiration-cannula; and then putting the heated end of another tube over it while the first is still hot, so that the two stick together. The joint must then be annealed by heating it in an ordinary gas-flame, reducing the size of the flame gradually, so that the glass may cool very slowly.

Pens for use with a kymographion are made by drawing tubes to a point, as shown in Fig. 128, E and F, and grinding the point on a fine hone, and rounding it, if necessary, in the flame.

Narcotising Animals.—Narcotics cannot be given in all cases

to animals on which we experiment, as their action must to a certain extent complicate that of the drug which we wish to investigate. We cannot use them when we are observing what are the general symptoms which a medicine produces. But, when we are investigating its action on particular organs, we may often use them, not only with safety, but with advantage, when they have no action on the particular organ which we are studying, or so little that its disturbing influence is more than compensated by the diminished muscular action, and consequent ease in performing the experiment, which narcotics produce.

It is almost unnecessary to say that, in all cases which admit of it, narcotics should be used, as we have no right to inflict any unnecessary pain, although we may be justified in taking the lives of the lower animals in order to preserve the more valuable life of man, either by supplying him with food by means of those killed in the slaughter-house, or by obtaining the knowledge which shall enable us to cure disease by means of those killed in our experiments. The narcotics which we use are opium and chloral. Chloroform is inadmissible, as its administration generally seems to cause dogs more pain than the experiment itself, and rabbits are very easily killed by it.*

A convenient form of giving chloral is a solution containing half a grain in 1 minim or 1 gram in 2 c.c. of water. The dose for a frog is 2 to 5 centigrams, or about 1 to 5 drops. The dose for guinea-pigs is about 12 minims of this solution for an animal half a pound weight; and more or less may be given, according to the weight of the animal, 18 minims being given to one weighing three-quarters of a pound, and 24 to one weighing a pound. About the same proportion of dose to weight may be employed for rabbits.

Opium may be given in the form of laudanum, or of solution of acetate or hydrochlorate of morphia. Much as it is used, the proper dose for different animals has not been exactly determined. We do not often employ it to narcotise guinea-pigs or rabbits, but frequently for dogs. The dose for a medium-sized dog is about 40 minims or $2\frac{1}{2}$ c.c. of laudanum, or

* This statement is erroneous, *vide* p. 336.

2 drachms of liquor morphiæ, which is equal to 1 grain or 5 centigrams of morphia. This dose is for injection into a vein: when injected subcutaneously, rather more should be given. If the dog be above or below middle size, the dose must be proportionately increased or diminished. We must be careful not to give too much opium to old dogs, or they will die. Opium is preferred by some to morphia, as producing more certain narcosis, and being less likely to produce the excitement and hyperæsthesia which sometimes follow the administration of morphia.

When we wish to render the animal absolutely motionless, or to observe what effect any drug will produce after the motor nerves have been paralysed, we give curare. Small doses of this remarkable substance paralyse the motor nerves of muscles, but leave the vagi and vaso-motor nerves unaffected. Large doses of it seem also to cause paralysis of the vagi. It affects the blood-pressure to a certain extent, moderate doses contracting the vessels and raising the pressure, while large ones lower it. The dose of curare for a frog is about 1 to 5 drops or more of a solution of 1 part in 1000. The dose varies with the size of the frog and the purpose for which we wish it. If we wish to observe the circulation microscopically, we must not give too large a dose, or the heart may stop. To rabbits, $\frac{1}{2}$ to 1 c.c. or 8 to 15 minims, and to dogs, 4 to 6 c.c. or 1 to 2 drachms, of such a solution, may be given.*

Definite rules cannot be laid down as to the experiments in which narcotics may or may not be used. The experimenter himself must judge in each case whether their action is likely to disturb that of the drug to be experimented on or not. For this purpose, he must know the action which the narcotics themselves produce; and I will, therefore, mention in a few words what that of each is.

Action of Narcotics.—Chloral acts on the brain, producing deep sleep, during which there is no sensation or voluntary motion. The reflex function of the spinal cord is first increased and then diminished in frogs; in guinea-pigs and rabbits, it is

* Curare may be obtained from Messrs. Hopkin and Williams, New Cavendish Street, London; or from Brückner and Lampe, Leipzig.

diminished for thermal irritations, but not for tactile ones—pinching producing reflex action, but burning or pricking none. It leaves the motor nerves, vagus, and muscles unaffected; but diminishes the activity of the respiratory nervous centre, rendering the breathing slow, and of the cardiac ganglia, somewhat weakening the heart. It lessens the blood-pressure and temperature, probably by dilating the vessels at the surface, as the ear of a rabbit becomes hot and its vessels dilated, while the general temperature is falling.

Opium is a mixture of several alkaloids, some of which are purely narcotic, while others produce tetanic spasms just like strychnia, and others partake of both characters. This is the case with morphia, in which, however, the narcotic qualities predominate. In small doses it first slightly increases, and then diminishes the irritability of motor and sensory nerves, the reflex action of the cord, the irritability of the vagus (ends and central roots), the musculo-motor apparatus of the heart, and the temperature. If the dose be large, those functions may be at once lessened. The blood-pressure varies, but is generally raised.

The advantage of giving either a narcotic or the drug to be investigated by injection into a vein rather than subcutaneously is, that the action is immediate, and we know that the whole of the dose has taken effect; whereas, after subcutaneous injection, a part may remain for some time in the cellular tissue before it enters the blood and becomes active. The most convenient vein is the external jugular. In dogs, however, it is sometimes more convenient to inject the narcotic into a vein which runs obliquely across the outside of the hind knee-joint. Before injecting, we must introduce a cannula into the vein; and the introduction of a cannula into a vessel is an operation on the proper performance of which the success of many an experiment depends.

Introduction of Cannulæ into Vessels.—First the hair must be cleanly clipped or shaved away, and loose hairs removed by a moist sponge. The skin, subcutaneous cellular tissue, and cutaneous muscles, are divided with a scalpel, and any bleeding vessels are twisted or ligatured. If the vessel lie deep, the

muscles are separated from each other by the finger of the operator, or by a blunt aneurism-needle, and any unyielding connective-tissue may be cut by a pair of scissors. That surrounding the vessel itself should be separated from it by the aneurism-needle. A closed pair of forceps may be pushed under the vessel and then opened. This both raises it from its bed, and lays bare a considerable part of its course. A couple of ligatures are now caught between the jaws of the forceps and drawn through. The proximal end of the exposed part of the vessel is now compressed by a pair of smooth-pointed bull-dog forceps, or a ligature laid in a simple slip-knot; one ligature is firmly tied round the distal end, and the second ligature is tied in a loop round the middle, but is not drawn tight. A small piece of calling card, about an eighth of an inch broad, is then slipped under the vessel, so that it may rest on it and remain steady: its walls are then snipped by a sharp-pointed pair of scissors just on the distal side of the loop. The finder, or aneurism-needle, may be introduced so as to make the opening more distinct, and, if necessary, this may be enlarged by the points of the forceps being introduced, and then separated. One lip of the divided vessel is seized by the forceps, the cannula introduced, and the loop drawn tight over it so as to tie it firmly into the vessel. The cannula is then filled by a small glass pipette with the fluid to be injected, the syringe is fitted on, the bull-dog forceps removed, and the requisite amount injected. The bulldogs are again put on, and the syringe removed.

Injection of Fluids into Vessels.—First, we prepare the solution to be injected in a test or a watch-glass, and see that the syringe is in working order. The most convenient is one for subcutaneous injection, with a glass barrel and a graduated piston. On the piston-rod a small nut screws up and down, so that it can be set to any figure on the rod, and thus prevents it from being any further pushed in, so as to allow the exact amount required to be given at once, but prevent the accidental injection of more than this amount. The end of the barrel must either fit directly into a cannula of the shape shown in Fig. 128, c, or it may be adapted to a glass cannula by tying a small piece of india-rubber tubing to the cannula. The cannula is then

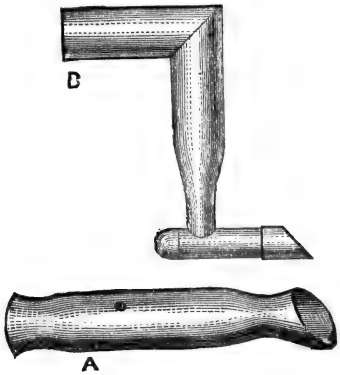
introduced into the vessel as already described. A fine pipette must be at hand, made by drawing a piece of glass tubing to a point, and by this the cannula, or cannulæ with the attached india-rubber tubing, must be carefully filled with the fluid, so that no air-bubbles remain. The syringe is then connected to it, the slip-knot of the ligature untied, or the bulldogs compressing the vessel in front of the cannula removed, and the necessary amount injected. The slip-knot is then re-tied, or the bulldogs replaced, if a second dose is to be given. If no more is to be injected, the vessel may be firmly ligatured.

Division and Irritation of Nerves.—The nerve must be laid bare, and separated from the surrounding connective tissue in the same way as a vessel, especial care being taken never to seize the nerve itself with the forceps. Blood must be removed by a sponge squeezed quite dry, and the nerve must on no account be touched with water. If we wish to remove any adhering clot, or if the nerve happen to get dry through long exposure, it may be moistened with a little saliva or serum. A director is then pushed under the nerve, or we raise it up by a ligature passed below it, so as to secure the adjoining vessels from injury, and we then divide it by a pair of scissors. Very often we wish to have the nerve prepared for section some time before we actually divide it. We then pass the ligature under it and tie the two ends together, so as to prevent the ligature from being pulled from below the nerve, and thus form a loose loop by which we can at any moment raise and divide the nerve.

Nerves may be irritated by pinching, the application of strong saline solutions, or heat; but more generally we use Pulvermacher's galvanic forceps, which are made of alternate wires of copper and zinc, and dipped in acetic acid, or, still oftener, the interrupted current from Du Bois Raymond's induction coil. The most convenient electrodes for this purpose consist of two wire points, about a quarter to half an inch long, and an eighth to a quarter of an inch apart. They may either be set in an ivory handle, or they may be simply fixed in a piece of glass tubing by means of cement or sealing-wax, or simply pushed through a piece of cork.

Artificial Respiration in Mammals.—Artificial respiration is chiefly used to keep an animal alive after it has been poisoned with curare, for the purpose of rendering it perfectly still during an experiment: or after the thoracic cavity has been opened for observation or experiment on the viscera it contains. It is performed by introducing a cannula into the trachea, and inflating the lungs by means of a bellows connected with it by india-rubber tubing.

FIG. 129.



A is a glass cannula for artificial respiration, large enough for a small dog. A hole for the exit of expired air is seen in the side. B a metal one for a rabbit. The hole for expiration is at the top, and not visible in the figure. The lower part of the cannula can be turned round upon the upper at a joint about one-third of the way from the top, not marked in the figure. The tube which conveys air can thus be brought from the side instead of the front.

To introduce the cannula, an incision is made in the middle line below the cricoid cartilage through the skin and cutaneous muscles; the larger muscles lying along the side of the trachea are separated from it by an aneurism-needle or the handle of the knife, and a strong ligature is passed under it by an aneurism-needle or forceps, care being taken to avoid the veins which lie close to its posterior wall. A round or oval piece must then be cut out of the front of it by the scissors or knife, and the cannula introduced, and tied firmly in by the ligature.

When the knee-shaped metal cannula is used, it is advisable to push the heel of the cannula into the trachea, so that the tube lies quite in its lumen. After the cannula has been tied

into the trachea, the ends of the ligature may be fastened round the upright bend of the knee, to ensure that it do not slip out. The bellows may be simply held in the hand, or fastened to the under side of a table by means of a piece of board screwed to its upper side and larger than the bellows itself, so that there is a rim of board all round. A few screws passed through this projecting rim into the under side of the table hold the bellows fast. A small pulley (one used for window-blinds will do) is then screwed into the under side of the table, and a cord passed over it. One end of the cord is fastened to a piece of board a foot and a half or two feet long, which serves as a treadle; and the other end to the under board of the bellows, so that it may be drawn up when the treadle is pressed down by the foot. A weight must be attached to the under board of the bellows, in order to draw it down again after it has been raised. The respiration is kept regular by depressing the treadle in accordance with the beat of a metronome set to beat the proper number in a minute.

The apparatus may be rendered more complete by the introduction between the bellows and trachea of a valve which will allow the air to pass readily towards the trachea, but hinder its return. Such a valve may be readily made by passing two pieces of glass tubing through the cork of a wide-mouthed bottle, and partially filling it with mercury or water. The tube nearest the bellows must descend nearly to the bottom of the bottle, while the other just passes through the cork. The air from the bellows passes easily through the mercury or water in which the end of one tube dips; but any attempt to return simply raises the mercury in the tube. If water be used, the tube must be longer, so that it may contain a column of water sufficiently high to afford the necessary resistance to the return of the air. This sort of valve is termed Müller's valve. (Fig. 130, v.)

Artificial Respiration in the Frog.—Although the frog can live perfectly well for some time without breathing, it may be desirable in some experiments to employ artificial respiration. A cannula for this purpose is best made by heating the end of a glass tube about one-eighth of an inch in diameter (more or

less, according to the size of the frog), and then suddenly pressing it down on a metal plate, so that a broad rim is formed round the end. The sides of the larynx are seized by two artery forceps, the cannula introduced, and tied firmly in. A Richardson's spray-producer, from which the tubes have been removed, is then connected with it and used as a bellows.

Introduction of Gases or Vapours into the Lungs.—Gases or vapours may be introduced into the lungs either by simple inhalation or by artificial respiration. For the inhalation of a gas, a conical bag of oilskin, india-rubber, or bladder, must be made to fit the snout of the animal, and connected with a bag, bladder, or gas-holder containing the gas. Or a tube may be put into the trachea and connected with the gas-holder.

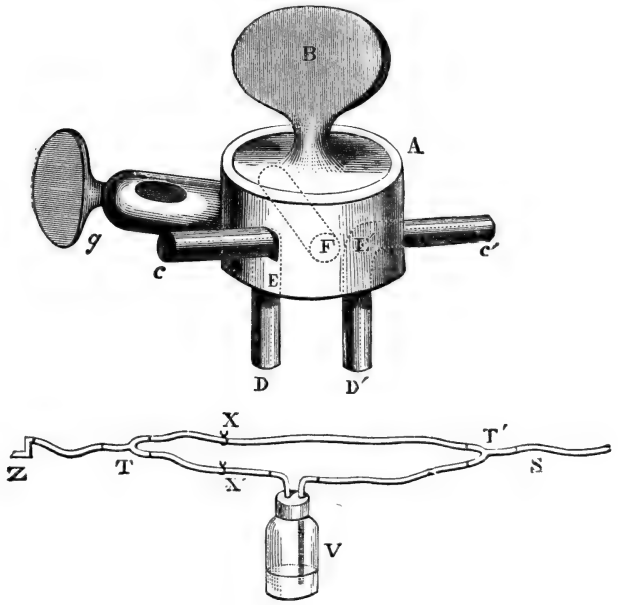
For the inhalation of a vapour, a cone of strong paper or cardboard may be used, the wide end being put over the muzzle, and the liquid, the vapour of which is to be inhaled, dropped on a piece of blotting-paper and put on the small end. Or the whole cone may be made of blotting-paper.

Many different kinds of apparatus have been used for the artificial respiration of gases, among which may be mentioned the ingenious instrument of Thiry and the beautiful respiration-pump of Ludwig. The simplest method probably is to have the gas in a bag, connected by means of the bottle or Müller's valve with the tracheal cannula. The gas may then be forced into the lung at intervals, by alternately compressing and relaxing the bag.

Air may be loaded with the vapour of any kind of fluid before it is sent into the lungs, either by mixing the fluid with the water in the bottle-valve, or by emptying out the water and putting a little of the fluid alone on the bottom of the bottle. Pure air or air loaded with vapour may be sent into the lungs alternately by the arrangement shown in Fig. 130. A stream of air is sent from the bellows through the india-rubber tube S, and divided into two by the T-tube T′. When the clip X is removed, and X′ put on, the air passes straight through to the tracheal cannula Z. If X be now put on, and X′ removed, the air passes through V (Müller's valve), and becomes loaded with the vapour of any fluid placed in the bottle.

The alternation may be effected still more rapidly and conveniently by a stopcock which I have had made for this purpose. Two tubes, C and C′, pass from its sides, and two others D and D′, from its bottom. The interior is perforated with three holes. Two of these, E and E′, are L-shaped, and one (F) passes straight through from side to side. When the handle B is in a line with C and C′, their lumen corresponds with that of

FIG. 130.



A. Brunton's stopcock. V. Müller's valve.

the hole F, and air passes straight through. When B is transverse, the hole E corresponds with C and D, and E′ with C or D′, so that air passing in through C′ passes down through D′, and may pass up through D and out at C. When B is neither in a line with C nor yet transverse, but half-way between, the holes in the interior do not correspond with those on the exterior of the stopcock, and no air can pass at all, and it may thus be used for experiments on asphyxia. When such experiments are made, the hole in the tracheal cannula must be carefully

stopped with white wax. By means of the screw G the stop-cock may be fastened to the rod E of the rabbit-hold in Fig. 1. The tubes D and D′ may either be attached by pieces of india-rubber tubing to tubes of a bottle such as V, or they may be themselves passed through the cork and a small piece of glass tubing long enough to reach the bottom of the bottle attached to D′. By then simply turning the stopcock, pure air may be passed direct to the lungs through C′, F, and C, or it may be loaded with vapour by passing it through D′ into the bottle, and then up through D and C to the lungs.

III. Artificial Circulation: Investigation of Blood-Pressure.

(*British Medical Journal*, 1871, June 3, p. 581.)

Artificial Circulation of Blood.—Circulation of Warm and of Cold Blood.—Fever.—Mode of Conducting Artificial Circulation.—Application of this Method to Pharmacological Investigations.—Schema of the Circulation.—Circulation in the Living Body.—Importance of the Arterial Elasticity.—Arterial Tension or Blood-Pressure.—Oscillations in it produced by the Heart and Respiration.—Causes of Variation in the Blood-Pressure.—Influence of Nerves upon it.—Cardiac Ganglia.—Inhibitory Nerves of Heart.—Quickening Nerves of Heart.—Vaso-motor Nerves.—Vaso-inhibitory Nerves.—Action of Counter-irritants.—Tabular View of the Causes of altered Pulse-Rate and Blood-Pressure.—Application of this to Pathology.—Experimental Examination of Blood-Pressure.—Forms of Manometer.—Kymographion.—Mode of using the Kymographion.—Reduction of the Kymographion Tracings.—Mode of recording Experiments.—Graphic Method of representing Experiments.

Artificial Circulation of Blood.—A constant supply of arterial blood to all parts of the body is necessary to preserve their vitality; and if the supply to any part be cut off by stopping its circulation, that part will die. Thus, if the circulation be stopped in an arm or leg by tying its arteries, or through their becoming plugged by emboli, mortification, or death of the part, ensues; and if the heart cease to beat, and the circulation be thus stopped in all parts of the body, they all die. But, if we supply arterial blood artificially to any one part, we may keep it alive at least for a certain time after the rest of the animal is dead; and the muscles may be made to contract, the lungs to excrete carbonic acid, the lymphatics to pour forth

lymph, and the excised liver to secrete bile, for hours after the rest of the animal has been consigned to the dust-bin.

Circulation of Warm and Cold Blood.—For this purpose, blood may be used either at the temperature of the room or of the body; but these have not exactly the same effect, and experiments made with blood at one temperature must not be compared indiscriminately with those made with blood at another. Professor Ludwig, to whom we owe this method, has discovered by its means the curious fact that the muscles of a warm-blooded animal may be artificially endowed with the properties of those of a cold-blooded one. Those of a frog or other cold-blooded animal retain their irritability, and contract, when stimulated, for a long time after they have been removed from the body; while those of warm-blooded animals quickly lose theirs, and will no longer contract on the application of a stimulus, no matter how powerful it may be. But if the muscle of the warm-blooded animal be quickly cooled by passing a stream of *cold* blood through its vessels immediately after it has been excised from the body, and before it is stimulated, it will retain its irritability for a long time, and respond to stimuli again and again, like that of the cold-blooded frog.

Fever.—In the same way, by supplying the heart of a mammal with cold blood, it may be made to resemble that of a frog or turtle; while, on the other hand, if the heart of a frog be supplied with warm blood, it will become like that of a mammal; and if the temperature be still further raised the quick and weak beats of fever are produced.

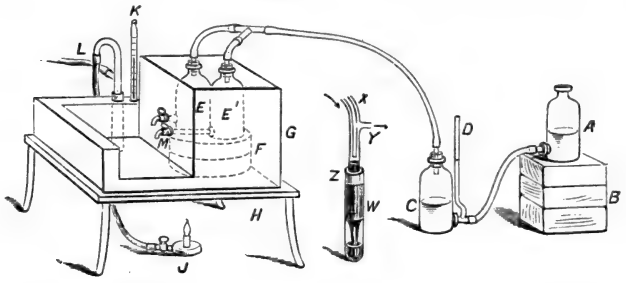
Mode of Conducting Artificial Circulation.—When we wish to pass blood, at the ordinary temperature of the room in which we are working, through any organ, we defibrinate the blood of the animal itself from which the organ has been obtained, or the blood of an animal of the same species; dilute it somewhat with salt solution of 1 per cent.; and put it into a flask with two necks, one of which is near the bottom of the flask, as seen at A, Fig. 131. We then introduce a cannula into the principal artery of the organ, and ligature, if necessary, the smaller arteries and branches; fill it carefully with blood by means of a fine pipette, so that no air-bubble remains in it, and

connect it with the lower neck of the flask. By then simply raising the flask, the blood flows out of it through the cannula into the vessels, and out again by the veins, from which it may be collected, shaken with air, and used over again. As the lips of the divided veins are sometimes apt to fall together and hinder the exit of blood, it is advisable to put a cannula into them as well; and great care must be paid to the adjustment of these, in order that they may be fairly in a line with the lumen of the vein, and not form an angle with it, which would present an obstruction to the flow of blood from it.

For the purpose of passing a stream of blood at the temperature of the body, we use the same apparatus; but the flask containing blood (E, Fig. 131) is then placed in a water-bath, kept constantly heated to 98° F. As this prevents us from conveniently raising the flask high enough to obtain the pressure required to carry on the circulation, we supply the want by compressing the air in the upper half of the flask, E, by means of two other bottles, A and C, containing mercury or water. On raising A, the fluid which it contains runs into C, and compresses the air in its upper half; and as this communicates with E by an india-rubber tube, the pressure is freely transmitted to it, and exerted on the surface of the blood which it contains.

Application of this Method to Pharmacological Investigations.—Besides its use in the experiments of Ludwig and his pupils on the secretion of bile and the formation of lymph, this method has been used by Cyon to show that urea is formed in the liver; but, so far as I know, no experiments on the action of medicines have yet been made by its means. It may seem, then, a strange thing that I should mention, in a course of experimental pharmacology, a mode of research which as yet has only been tried in physiology; but the good service it has already done the physiologist, and the splendid promise it gives to us, are, I think, a sufficient excuse. For we can thus take two similar organs, or two parts of the same organ, and supply them with the same blood, at the same temperature and the same pressure—in short, we may put them under exactly the same external conditions; but to the blood supplying the one we may add any drug whose action on the organ we wish to

FIG. 131.



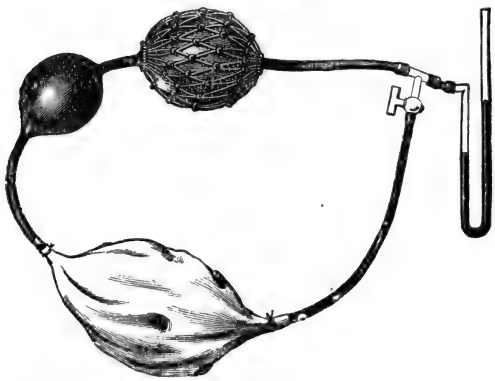
A and C, Bottles containing mercury or water. B, Wooden blocks, by which A may be raised to the required height. If water be used, it is easier to suspend it from a pulley in the ceiling, so as to get sufficient pressure. D is a manometer, to estimate the pressure in C and E. E is a bottle containing blood, F is a small stand to raise the bottle E from the bottom of G, as it is otherwise apt to become too warm, and the bottom of the bottle cracks, or the blood is decomposed. G, a tin water-bath. At one side of it is a trough with hollow sides, into which the warm water freely passes, and in which the organ to be experimented on may be laid. H is an iron stand supporting G. J is a Mitscherlich's burner. K is a thermometer, by which the temperature of the water-bath is examined. L, Bunsen's gas regulator, as modified by Geissler. This apparatus consists of a wide glass tube, W, divided into two parts by a septum, from the middle of which a tube runs down nearly to the end of W. The upper part is filled with mercury, which, of course, runs down the inner tube and fills the bottom of W, compressing the air in it. A perforated cork, Z, is then put into the upper part of W, and the tube Y pushed through the hole in its centre. Inside Y, and shorter than it, is a second tube X, and the two are sealed to one another at their upper ends. The tube Y is then connected to a gas-pipe, and X to Mitscherlich's burner, by india-rubber tubing. So long as Y is not pushed so deeply into W that the point of X dips into the mercury, the gas enters through Y, passes down between Y and X, comes up again through X, and goes to the burner. The apparatus is now set by dipping it into the water-bath, and heating the water to 98°, or any other temperature desired, and then pushing Y down till the point of X is just covered by the mercury. The passage of gas through it is at once stopped, and the flame would go out were it not that a very small hole in the side of X admits just enough gas to keep it alive. As the flame gets low, the temperature of the water-bath above it diminishes, the air and mercury in W contract and leave the end of X open, so that the gas again passes freely to the burner, and the flame becomes larger. The water-bath now regains its former temperature, the air and mercury expand, the end of X is again closed, and again the flame becomes small. By this apparatus a water-bath may be kept for a very long time without varying more than half a degree.

test. We can analyse the blood flowing into, and that flowing from, the substance of the organs before and after the experi-

ment, the lymph produced, or the secretion poured forth; and by comparing the results when the drug was added with those obtained when it was withheld, we may, I think, gain such a knowledge of its action as could be got in no other way.

Schema of the Circulation.—In the living body, a constant stream of blood is kept up in the vessels, in exactly the same way that a constant current of air is produced in Richardson's spray-apparatus. By removing the glass or metal tube from

FIG. 132.



Simple schema of the circulation, consisting of a spray-producer, bladder, and mercurial manometer. The elastic ball represents the heart; the elastic bag, covered with netting to prevent too great distension, represents the aorta and arterial system; and the bladder represents the venous system.

one of these, and attaching a nozzle with a small stopcock to the india-rubber tube in its stead, we obtain a very good schema of the circulation; and, by imitating on it the changes which occur in the heart and vessels, we may form a much clearer idea of them than we could otherwise do. The india-rubber ball will represent the heart; the elastic bag, surrounded by netting, will represent the elastic aorta and larger arteries; and the stopcock, which regulates the size of the aperture through which the air escapes, will represent the small arteries and capillaries, whose contraction or dilatation regulates the flow of blood from the arteries into the veins. If we turn the stop-

cock so as to present some resistance to the escape of air, and then compress the india-rubber ball, very little air will issue from the stopcock even while we are squeezing the ball; the greater part of it goes to distend the bag; and, when we cease to compress the ball, no air at all comes out from the stopcock. At the next squeeze, the bag becomes a little more distended; and a little air issues from the stopcock, not only while we are compressing the ball, but even when we relax our grasp. At each squeeze of the ball, the elastic bag becomes tighter, till it is so tense and contracts so strongly on the air inside, that it can press all the extra amount of air forced into it when the ball was compressed, out through the stopcock, during the time when the ball is relaxed. When this is the case, every time we squeeze the ball we see the bag become a little fuller, and air issue more quickly from the nozzle. At each relaxation, while the ball is refilling, the bag gets a little slacker, and the air passes out of the nozzle a little more slowly, but never stops entirely. During the time the ball is filling, the valves between it and the bag and nozzle are closed, and cut it off from any connexion with them. All this time, then, the stream of air from the nozzle must be entirely independent of the ball; it is produced by the contraction of the elastic bag, and by it alone. The bag may be stretched, and the tension of its walls increased in consequence, in two ways: first, by working the ball more quickly; second, by lessening the opening of the nozzle, and thus hindering the passage of air through it. One trial will, I think, be enough to show you how much easier it is to alter the pressure by changing the size of the nozzle than by any alteration in the working of the ball, and thus convince you that alterations in blood-pressure probably depend much more on alterations in the lumen of the small arteries than on changes in the action of the heart.

But our schema, as it at present exists, is not a perfect representation of the heart and vessels; for it draws its air from an inexhaustible reservoir, the atmosphere, and is not obliged each time to use that amount alone which it had previously driven through the nozzle; while the heart can only use the blood which has been forced by it through the capillaries and returned

to it by the veins. In order to make our schema complete, we must connect its two ends by tying them into a bladder or large thin caoutchouc bag (such as is used, after inflation, as a toy for children), so that the air shall pass into it from the nozzle and be sucked out of it by the elastic ball. This will represent the veins. If we then repeat the experiment just described, we shall find that, when we begin to work the ball and stretch the elastic bag representing the arteries, the bladder, representing the veins, becomes empty and collapsed; and just in proportion as we fill the bag do we empty the bladder. If we now stop, the air will gradually escape from the bag to the bladder, till both are equally filled as they were at first.

Circulation in the Living Body.—The phenomena of the circulation in the heart and vessels are very much the same as in the spray-producer. When the heart stands still (as when the vagus is strongly galvanised), the blood flows from the arteries into the veins till they are nearly full and the pressure inside both is about the same. If the heart now begin to beat, it forces blood into the elastic aorta and arteries at each systole, and distends them, just like the elastic bag of the spray-producer; while at the same time it takes blood from the veins, and they become empty in proportion as the arteries become full. At every diastole, the elasticity of the distended aorta causes it to contract on the blood it contains, and keeps it flowing on through the capillaries till another systole occurs. During the diastole, the heart is completely shut off from the aorta by the sigmoid valves (just as the ball of the schema was shut off from the elastic bag), and the blood is kept flowing during this time by the elastic contraction of the aorta and large arteries. In general, the diastole is longer than the systole; so that for the greater part the circulation is carried on by the elasticity of the arteries, and not directly by the heart. The arteries become distended by the heart, just as the elastic bag was by the ball, and press more and more on the blood in them (so that it would spout higher and higher, if one of them were cut), till they are able during the diastole to press the same amount of blood through the capillaries into the veins as had been pumped into them during the systole. The more

these are stretched, the greater is the pressure they exert on the blood they contain; and the amount of this is termed the *arterial tension* or *blood-pressure*. These two terms mean the same thing, and we use one or other just as the fancy strikes us. At each systole, the fresh supply of blood pumped in by the heart stretches them more; that is, the arterial tension rises. During each diastole, the blood escapes into the wide and dilatable veins, and the arteries become relaxed; that is, the arterial tension falls.

Besides the oscillations which take place in the blood-pressure at each beat of the heart, a rise and fall in the form of a long wave occurs at each respiration. The wave begins to rise just after inspiration has begun, reaches its maximum just after the beginning of expiration, and then begins to fall again till a new wave succeeds it. The heart-beats are generally quicker during inspiration, and slower during expiration.

The blood-pressure thus oscillates up and down at each heart-beat and rises and falls with each respiration, and the average between the highest and lowest points is called the mean arterial tension or mean blood-pressure.

Causes of Variation in the Blood-Pressure.—The pressure of blood in the arteries depends on two circumstances: first, the amount of blood pumped into them in a given time; and second, the amount that flows out of them into the veins in the same time. If more be pumped in, or if less flow out, it will rise; if less be pumped in, or if more flow out, it will fall. It may, therefore, be raised—1. By the heart beating more quickly; 2. By a larger amount of blood being sent into the aorta at each beat; 3. By contraction of the small vessels. It may be lowered—1. By the heart beating more slowly; 2. By the heart sending out less blood at each beat; 3. By dilatation of the small vessels, allowing the blood to flow more quickly into the veins; 4. By contraction of the pulmonary vessels, or obstruction to the passage of blood through them.

The influence on the pressure exerted by the amount of blood sent out by the heart at each beat, and by the number of beats, to a certain extent, though by no means completely, counteract each other; for, when the heart is going quickly, it has not

time to fill completely, and so sends out little blood at each beat; but, when going slowly, it becomes quite full during each diastole, and sends out a larger quantity of blood at each contraction.

It must be remembered that we measure the blood-pressure in the systemic arteries; and, before the blood can get into them from the veins, it must come through the pulmonary vessels. Any contraction of the lumen of these vessels, by lessening the entrance of blood into the systemic arteries, will cause the pressure in them to fall.

Influence of Nerves on Blood-Pressure.—Both the quickness of the heart's beat and the contraction of the arteries are regulated by the nervous system; and it is generally by acting on different parts of it that drugs alter the blood pressure, though they may also do so by acting on the muscular walls of the heart and arteries themselves. The parts of the nervous system chiefly concerned in regulating the circulation are:

I. The *cardiac ganglia* which lie in the walls of the heart, and are, in all probability, the cause of its rhythmical action.

II. *Inhibitory nerves,* which render the heart's action slow, and, if irritated very strongly, may stop its beating altogether, and produce still-stand in *diastole.* The inhibitory fibres have their origin or roots in the medulla, and proceed in the vagi to the heart. In man and in dogs, they are normally in constant action; and, after they are cut or paralysed, the heart beats in the dog three or four times as quickly, and in man twice as quickly, as before. In rabbits and cats they act less, and their division only makes the heart go one-half or one-fourth faster. A drug may irritate them, and render the heart's action slow—

1. By acting *directly* on (*a*) their roots in the medulla, (*b*) their fibres, (*c*) their ends in the heart;

2. *Indirectly,* through its action on other parts, producing (*a*) increased blood-pressure, or (*b*) accumulation of carbonic acid in the blood, both of which act as irritants to the vagus-roots;

3. *Reflexly,* (*a*) through irritation of sensory nerves, (*b*) irritation of the intestines, (*c*) of the sympathetic nerve, (*d*) of the

depressor, or (*e*) of the vagus of the other side. Reflex irritation is only likely to be caused by drugs having a powerful local action.

Drugs may also paralyse the inhibitory fibres, and thus quicken the heart.

III. *Quickening Nerves.* These belong to the sympathetic system. They have their origin in the brain or medulla, pass down through the cervical part of the spinal cord to the last cervical and first dorsal ganglion (which are often united), and thence through the third branch of the ganglion to the heart. Quickening fibres are said by some to run also in the cervical part of the sympathetic cord. Unlike the vagus, the quickening nerves are not normally in constant action. They may be irritated—

1. By the *direct* action of drugs upon them.

2. *Indirectly* by the drugs producing a diminished blood-pressure, which acts as a stimulus to them.

IV. *Vaso-motor Nerves,* which cause the smaller arteries, and probably also the capillaries, to contract. These belong to the sympathetic system; and the most important of them are the splanchnics, which produce contraction of the intestinal vessels. As these vessels can, under certain circumstances, hold all the blood in the body, the influence of the splanchnics over the blood pressure is very great; and division of these can lower it, or stimulation of them increase it very much. The centre for the whole vaso-motor system, however, seems to be in the medulla oblongata; and it is generally in constant action, keeping up a certain amount of contraction or tone in these vessels. Its activity may be increased, and the vessels made to contract—

1. By *direct* irritation of the centre.

2. By *reflex* irritation through (*a*) the cervical sympathetic (*b*) the vagus, when the brain is intact, and the animal not narcotised, (*c*) sensory nerves. When the medulla is separated from the rest of the body by dividing the spinal cord at the atlas, it can, of course, no longer exert any influence over the vessels; and they consequently become dilated throughout the whole body, and the blood pressure sinks very low. If the

lower end of the divided cord be then irritated, the vaso-motor nerves which pass through it from the medulla to the body are stimulated, and the blood-pressure rises.

V. *Vaso-inhibitory Nerves.* Irritation of these nerves is conducted to the vaso-motor centres, and acts on them in such a way as to cause a reflex dilatation of the small vessels, either (1) throughout the whole body, or (2) in one particular part of it.

1. The chief nerve which causes dilatation throughout the whole body is one which runs from the heart to the medulla, and is called, from its power of diminishing blood-pressure, the depressor nerve. Its fibres seem to be included in the vagus in the dog; but in the rabbit it generally runs separate from the heart to the level of the thyroid cartilage; here it divides into two so-called roots, one root going to the superior laryngeal, and the other to the vagus nerve. These are generally called roots, though, as the nerve conveys impressions *from* the heart *to* the brain, they are, physiologically, really branches. There seem to be also depressor fibres in the vagus itself; but this nerve contains fibres of many kinds, and, among others, some which cause contraction of the vessels and rise of blood-pressure — hence called pressor-fibres. The former seem to act on the vaso-motor system through the medulla itself, while the latter affect it through a centre in the brain, so that, when the brain is perfect, irritation of the central end of the vagus causes increased contraction of the vessels and raised blood-pressure; but, when the brain is removed or its functions abolished by opium, it causes dilatation of vessels and diminished pressure.

2. When a sensory nerve is irritated, the action of the vaso-motor centre is suspended in the part supplied by the nerve, and in those which immediately adjoin it, so that their vessels become dilated, while at the same time contraction of the vessels in other parts of the body is produced. The blood-pressure is thus increased generally, and produces in the locally dilated vessels a very rapid stream of blood. This fact was first discovered, and its importance in therapeutics indicated, by Ludwig and Lovèn.

Action of Counter-irritants.—The application of an irritant, whether mechanical, chemical, or thermal, injures the tissues of the part to which it is applied; and what better means of removing the injury and restoring health could be imagined than a copious supply of blood, and the removal of every hindrance to its free flow which contraction of the vessels might present?

Experiments are still wanting to decide how far the vascular dilatation will extend in the neighbourhood of the irritated part when more or less powerful irritants are applied, or which the vessels are (if any) that especially contract, when certain others dilate; so that at present, when we apply a mustard plaster to the chest to relieve bronchitis, we are unable to say with certainty whether the relief is due to a more full flow of blood through the vessels of the bronchi, or to contraction of their lumen diminishing congestion, or (though this is unlikely) to some unknown action independent of the vessels altogether. The experiments of Sinitzin, however, (detailed by a recent writer in the *British Medical Journal*, 1871, p. 535) which show that ulcers of the cornea, eyelids and lips, occurring after division of the fifth nerve, rapidly heal when dilatation of the vessels of these parts is produced by extirpation of the superior cervical ganglion, render it in the highest degree probable that it is to the increased flow of blood that healing is due. As a general rule, too, the vascular dilatation seems to extend more widely the stronger the irritant applied; and we may thus see how a strong irritant, or one applied over a large extent of surface, may prove beneficial in a deep-seated inflammation when a weak one or one applied to a small surface has no effect.

For convenience of reference, I have put together the causes of alteration in the blood-pressure in the following table (p. 278).

Application to Pathology.—The brief sketch of the circulation which I have given, will enable you to understand and appreciate the meaning of the changes produced in our circulation by any drug, and to explain the facts we may meet with in the course of an investigation. I may remind you that the altera-

Causes of Alterations in Blood-pressure and Pulse-rate.

Blood-pressure may be diminished.

- **By slow action of the heart**
  - Irritation of vagus-roots
    - Directly, by the action of the drug on them.
    - Indirectly, by increased blood-pressure.
    - „ by accumulation of CO^2 in the blood.
    - Reflexly, by irritation of some other nerve.
  - Irritation of vagus-fibres?
  - Irritation of vagus-ends in the heart.
  - Increased excitability of vagus-ends in the heart.
  - Paralysis of sympathetic ends in the heart?
  - Weakness of the heart
    - Paralysis of the cardiac ganglia.
    - Paralysis of the cardiac muscular fibres.
  - Weakness of the heart.
- **By smallness in the amount of blood sent into the heart at each systole**
  - Contraction of the pulmonary vessels.
  - Great dilatation of the venous system.
- **By dilatation of the small arteries**
  - Paralysis of the vaso-motor centre
    - Direct, by the action of the drug.
    - Reflex, through the depressor.
    - Reflex, through vagus and sensory nerves, when brain is removed or animal poisoned by opium.
    - In operations, by division of cord or of splanchnics.
  - Paralysis of the arterial walls.
  - Paralysis of vagus-roots.

Blood-pressure may be increased.

- **By quick action of heart**
  - Paralysis of vagus-fibres.
  - Paralysis of vagus-ends in heart.
  - Stimulation of sympathetic roots
    - Directly
    - Indirectly, by lowered blood-pressure.
  - Stimulation of sympathetic fibres?
  - Stimulation of sympathetic ends in heart?
  - Stimulation of the cardiac ganglia
    - Directly.
    - Indirectly, by causing increased temperature of body.
- **By larger amount of blood at each beat**
- **By contraction of small arteries**
  - Irritation of vaso-motor centre
    - Direct.
    - Indirectly, by accumulation of CO^2 in the blood.
    - Reflex, through the cervical sympathetic.
    - Reflex, through the vagus, when the brain is present and the animal is not narcotised.
    - Reflex, through sensory nerves. In operations, this may be seen to occur by irritation of the peripheral ends of the divided spinal cord or splanchnics, as well as from irritation of cerebro-spinal nerves.
  - Direct irritation of vascular walls.

tions in the pulse-rate and blood-pressure which we meet with in disease, as well as those produced by drugs, are due to some one or other of the causes mentioned in the previous table; and whenever you meet with a quick, slow, weak, or irregular pulse, you must try to find out to which of these causes it is due, in order that you may be able to apply scientifically the proper remedy.

Experimental Examination of Blood Pressure: Forms of Manometer.—As the life and health of the body and of the organs comprising it depend on the supply of blood to them—and this, as we have already seen, is closely associated with the arterial pressure—the observation of the effects of drugs on it naturally forms one of the most important parts of an investigation into their action. The first to measure the blood-pressure was Hales, who simply connected a glass-tube with an artery, and noted the height to which the blood rose in it. Poiseuille improved upon this method by substituting a bent tube, partially filled with mercury, for the straight tube, and estimating the pressure from the difference in the level of the mercury in the two limbs. A solution of carbonate or bicarbonate of soda was introduced into the tube between the mercury and the blood in order to prevent its coagulation. The bent tube, partly filled with mercury, is called a hæmadynamometer, or, more generally, a manometer. The height of the mercury is read off from a scale fixed behind the tube. Usually both limbs of the tube are of equal diameter, and the blood-pressure is then ascertained by doubling the height of the mercury above zero in one limb and subtracting a fraction, which varies with the specific gravity of the solution of soda used. The height must be doubled, because the mercury descends as much below zero in the one limb as it rises above it in the other; and a fraction of the whole is subtracted for the additional weight of the column of soda solution, which enters one limb as the mercury rises in the other.

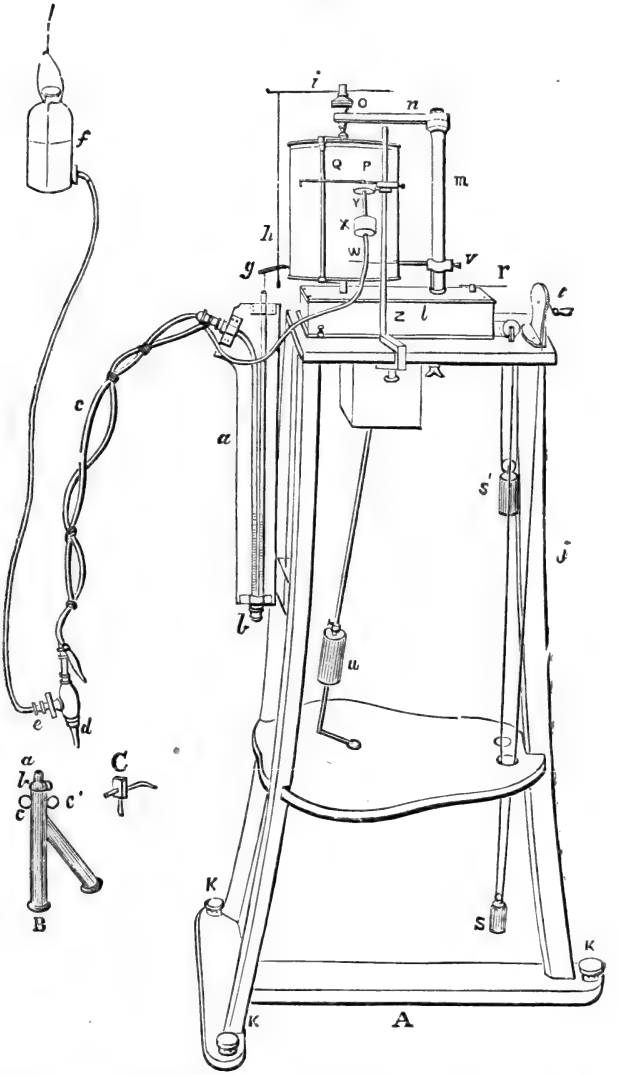
A very simple manometer, which will show the mean blood-pressure as well as the maximum and minimum between which it oscillates, may be made by passing two straight glass-tubes about 16 inches long through the cork or india-rubber stopper of a small wide-mouthed bottle, and fixing behind them a

graduated cardboard scale. The lower end of one tube must be nearly closed in the blow-pipe flame, and both pushed down till they almost touch the bottom of the bottle. A third bent tube is inserted into the stopper, reaching only to its under surface, and a piece of india-rubber tubing is attached to its upper end for the purpose of connecting it with the artery. Some mercury is then poured into the bottle, so as to stand a little above the ends of the tubes, and both it and the india-rubber tube are filled with a saturated solution of bicarbonate of soda and connected with the artery. The mercury rises and falls in the open tube with every pulsation; but in the one with the constricted end the resistance to its movement is so great that it can only rise and fall slowly, so that, before its upward oscillation has had time to show itself, its descent has begun, and *vice versâ*. The upward and downward oscillations thus balancing each other, the mean pressure only is shown (*vide* pp. 103 and 104).

The oscillations in the unconstricted tube are so rapid that it is impossible for the eye to follow them exactly; and this difficulty led Ludwig to conceive the idea of making them register themselves by means of a slender rod swimming on the surface of the mercury, and bearing at its upper end a pen which moved up and down on a piece of paper fixed on a revolving cylinder. The vertical height of the tracing thus produced showed the blood-pressure, while the horizontal distance from one point to another on it indicated the time between them.

This instrument is called a kymographion; and, in devising it, Ludwig introduced for the first time into physiology that method of self-registration which is now generally applied to all kinds of vital phenomena, and has already done much to render our knowledge exact. That form of it which is used by Traube, and made by Sauerwald, of Berlin, is shown in Fig. 133. It consists of a metal cylinder (*p*) supported on a wooden frame (*j*), and caused to revolve at a steady rate by clockwork and pendulum (*l* and *u*). The manometer is fixed to the wooden frame and connected with the artery by tubing of lead and india-rubber. On the mercury in one limb floats a rod or swimmer of glass, to whose upper end is attached a glass

FIG. 133.



A, Ludwig's Kymographion. *a'*, the manometer. Instead of one simple bent glass tube, it consists of two tubes fixed on a piece of wood and joined by a piece of metal *b*, which may be unscrewed for cleaning the tubes. *c* is a tube of soft lead, for connecting the manometer with the artery. One end of it is screwed to the manometer and the other is attached to a stopcock *d*. *d* is a stopcock

attached to *c*, and may be connected with the tube B in the artery by a piece of india-rubber tubing. It is bored in a T-shape, and is perforated in the centre by an additional perpendicular hole, into which is put a hollow plug *e*. *f* is a flask containing saturated solution of bicarbonate of soda, and connected by india-rubber tubing with *e*. When the clip on the india-rubber tube just above *e* is removed, and the stopcock turned longitudinally, soda solution will flow into *c* as well as out of *d*. By turning it transversely, the opening towards *c* may be closed, and soda will then only run out through *d*. This is done when we wish to wash out the cannula with soda without altering the level of the mercury in *a*. *g* is a glass pen attached to the top of a glass rod or swimmer, which rests on the surface of the mercury in *a*. *h* is a thread of unspun silk, with a small weight attached to it. It rests against the pen *g*, and keeps it constantly applied to the paper without impeding its movements. *i* is an iron wire, from which the thread *h* is suspended. *j* is the wooden frame bearing the clockwork and revolving cylinder. *k* are three screws to level the frame. *l* is the clockwork. *m* is an upright, and *n* a horizontal bar, which support a pivot *o*. *p* is a metal cylinder, which carries the paper. *q* is a small metal bar for holding the paper on the cylinder. It is hinged to the lower edge of the cylinder, and caught by a spring at its upper edge. It lies in a hollow in the cylinder, so that its outer surface does not project above it. When a new paper is to be put on, the spring catch at the upper end of *q* is raised, *q* pulled out, the old paper removed, and the edges of the new one placed under *q*. It is then pushed down, its upper end is caught by the spring, and the paper is securely held. *r* is a catch for stopping the movement of the clockwork. *s* and *s'* are two weights to drive the clockwork. *t* is a rack for winding up the weight *s'*. *u* is a pendulum, with a movable bob, to regulate the motion of the clockwork and cylinder. By moving the bob up or down, the motion may be made quicker or slower. *v* is a pencil stuck through a piece of cork and fastened to the upright *m*, so as to draw a line on the paper at the same level as *g*, when there is no pressure on the mercury in the tube. The blood-pressure is estimated by the height of the curve traced by *g* above the zero line thus drawn. *y* is one of Marey's tympana, which is supported on a movable rod *z*, and may be used for registering either the respiration or the form of the pulse-wave. It consists of a shallow cup of metal, over whose top a piece of india-rubber is tightly stretched. A metal tube passes into the interior of the cup, and a light lever lies over the upper surface of the india-rubber and is firmly connected with it. When air is blown into the interior of the cup, the india-rubber bulges and raises the lever; when air is sucked out, it becomes depressed and draws the lever down. When used to register the respirations, it is simply connected with a tube in the trachea of the animal, or with a mask fitted before its nose. As the piece of india-rubber stretched over *y* is thin, it would be blown out, and perhaps burst, by the pressure, if we were to connect it directly with the artery. One of Marey's sphygmoscopes is, therefore, introduced between them when we wish to measure the blood-pressure. The sphygmoscope consists of a little bag of strong india-rubber, enclosed in a piece of glass tubing, connected with the tympanum. The bag is filled with soda solution and connected with the artery. Each time that the pressure rises in the artery, the bag becomes distended and forces some of the air out of the glass tube into the tympanum, and raises the lever; and when the pressure diminishes, the bag collapses again and the lever falls. *x* is a modification of this, designed by my friend Dr. Burdon Sanderson. Instead of

a bag enclosed in a tube, it consists of a metal box, across the interior of which a septum of strong india-rubber is stretched. One side of the box is filled with soda solution and connected with the artery; the other with air and connected with the tympanum. *w* is a piece of lead-tubing for connecting the sphygmoscope *x* with the tube in the artery.

B is a forked tube of German silver or brass for connecting the artery with the kymographion. *a* is a cannula, which is inserted into an artery (see fig. 3A). *b* is a small ring, soldered to it, by which it may be tied to the rings *e* on B, to prevent it from slipping off. *e* and *e* are two rings soldered to B. By means of ligatures passed through these, B may be fastened to the skin or hair of the animal, to prevent its being displaced by any sudden movement. The oblique limb of B may be connected to A *d* alone by a piece of india-rubber tubing, or to both A *d* and A *w* at the same time by means of a Y glass tube and india-rubber tubing. Another piece of india-rubber tubing is attached to the straight limb *d*, and closed by a clamp or clip. When a clot forms, the clip is taken off and the clot removed, the tube washed out by a stream of soda solution, and the clip again replaced.

C is the tracing-pen (see fig. 3E). It is stuck horizontally through a piece of cork; another small piece of glass tubing, about three-fourths of an inch long, closed at its upper end, and about one-twelfth of an inch in diameter, or just wide enough to admit the end of the swimmer, is stuck vertically into the same piece of cork.*

pen (*g*), which registers the movements of the mercury on the revolving cylinder.

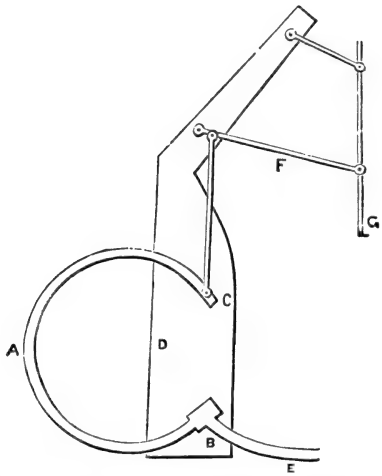
The disadvantage of the mercurial manometer is, that it does not give the true form or extent of the variations of blood-pressure, the inertia of the mercury causing it to oscillate above and below the true value. We may, however, obtain the true form of each oscillation along with the mean pressure by connecting the artery at the same time with the manometer and one of Marey's sphygmoscopes and levers (Fig. 133, *x* and *y*) by means of a Y-tube, one end of which is connected to *d* and the other to *w*. In order to obtain the mean pressure, we turn the stopcock (*e*) till, on blowing through it, only a slow rise and fall of the mercury can be produced, but no sudden oscillation. On then connecting it with the artery the mercurial column shows the mean pressure, while the sphygmoscopic lever registers each oscillation (*cf.* Brunton and Cash, *Phil. Trans.*, vol. clxxxii (1891) B, pp. 547–550 and 601–632).

Besides this form there are various others on the same principle, some of which have cylinders which wind off a con-

* The instrument figured here was made by Sauerwald for Von Bezold, but as Von Bezold did not require it on account of illness it was sold to the author by Sauerwald in 1867.

tinuous roll of paper from a bobbin, so that a tracing may be taken uninterruptedly for an hour or two without renewing the paper. In order to avoid the inconveniences of the mercurial manometer, Fick has constructed one (Fig. 134) in which the pressure is not measured by the movements of a column of mercury, but by those of a bent hollow tube (A) fixed at one end and free at the other. The tube is filled with alcohol, and

FIG. 134.



Fick's spring kymographion. A is a flat tube of German silver, fixed at one end B to a piece of board D. The other end C is freely movable. E is a tube connecting A with the artery. F is a lever made of reed, connected to C. G is the writing point, moved up and down by F, and kept perpendicular by another short lever above. The tube A is filled with alcohol, and the tube E with a soda solution, and B is then connected with the artery. Whenever the pressure rises, the tube A tends to straighten itself, but it is firmly fixed at the end B, and so the end C alone moves upwards, and pushes up the lever F and the writing-point G. Whenever the pressure relaxes, the tube bends back again to its original shape, and the point G consequently again descends. The tracing is taken by allowing G to rest against a revolving cylinder, covered with a piece of paper, which has been smoked either over a gas flame or a paraffin lamp.

its fixed end connected with an artery. At every rise of pressure this tube tends to straighten itself, and this motion of the free end is communicated by it to a lever (F) and writing-point (G), which records it on a smoked cylinder.

The advantage of this form of kymographion is that it gives

the exact form, duration and extent of each pressure-variation. Its disadvantage is that the tracings it gives are on a small scale, so that it is not so well adapted for showing small oscillations of pressure like those at each heart-beat in the rabbit, although it answers admirably for dogs. Another disadvantage is that the tracing must be taken on smoked paper, and this is more troublesome to manage than white paper and ink.

Mode of using the Kymographion.—The kymographion must first be rendered perfectly level by the screws K K (Fig. 133). The upper part of the outer tube of *a* and the tube *c*, the india-rubber tube connecting it with B, and B itself, are then filled with soda solution and the clip at *e* put on. A fresh sheet of paper is put on *p*, the pen (*g*) filled with ink, and the pencil (*v*) adjusted at the same level. A piece of cotton-thread should be drawn through the pen, so that the end projects just beyond the pen's point; this makes the pen write better. The animal is next fixed, a vein exposed for injecting, the cannula (*a*) introduced into an artery in the way already described, the blood being prevented from entering the cannula by a clip placed on the artery. A drop of carbonate of soda solution is placed in the cannula (*a*), the tube (B) fitted into it and tied to it by a thread through the ears *b* and *c*. Two other threads through *e* and *e* fasten the tube (B) to the skin or hair of the animal. The flask (*f*) is raised several feet above the apparatus, and the clip at *e* opened, so as to make the pressure in the manometer and tubes nearly equal to that of the blood in the vessels so as to prevent the blood from filling the tubes. It must not be greater, or the carbonate of soda will pass into the vessels and produce convulsions. The clip at *e* is then replaced and that on the artery removed, the cylinder set in motion, and a tracing of the normal blood-pressure taken.

The drug in solution is now injected into a vein and a fresh tracing taken. At the time the injection is begun, a cross should be made on the tracing opposite the pen of the kymographion, and a O should be made when the injection is finished. The time at which these were made should be noted on a separate piece of paper, and afterwards copied on to the tracing itself. Instead of putting on a fresh piece of paper each item,

two or three may often be taken on one paper by having two or three exactly similar glass pens of the form shown filled with inks of different colours. Each is stuck through a small piece of cork, and into the under side of the cork a small glass tube is put, which will just fit the top of the swimmer. By simply dropping the glass tube on the end of the swimmer, the pen is in its place at once, and can be changed with great facility. A small sable brush may also be substituted for the glass pen.

After the experiment has gone on for some little time, a clot is apt to form in the cannula. When this is the case, the clip must be replaced on the artery, the stopcock (*d*) turned transversely, so as to keep the mercury at the same height, the clip on the india-rubber tube at *d* B and at *e* A removed, and the tube washed out by a stream of carbonate of soda. Any clot in the cannula is removed by a spill of twisted paper, by a hog's bristle, or by a piece of whalebone. The whalebone-probes are most convenient, as they can be made of any size. A single jet of blood should now be allowed to escape from the artery, so as to make sure that there is no clot in it, the tube again washed out with carbonate of soda, the clips at *e* B and *e* A replaced, that on the artery removed, and the stopcock turned and tracings taken as before.

Reduction of the Kymographion Tracings.—It is not only impossible to publish the tracings as they are taken from the kymographion for the benefit of others, but it is extremely difficult to draw any except very general conclusions from them for one's self. Before they can be of much use they must be reduced to tables, or, what is still better, the tables themselves may be graphically represented. In making the tables, we must first fix the time at which the different parts of the tracing were made. The time when the tracing was begun and when the injection was made must be noted down at the time in a separate note-book, or, still better, on the tracing itself. In the first tracing it is convenient to take the time when the injection was made, as a starting-point from which to reckon the other periods.

Beginning at this point, then, we divide the abscissa or zero line into parts corresponding to five seconds each, or any other period we think convenient. If the circumference of the

cylinder be 60 *millimètres*, and it revolve once in a minute, each 5 *millimètres* of paper will correspond to five seconds' revolution.

Secondly, we must ascertain the blood-pressure at different times. At the point where the injection took place, we draw from the tracing a perpendicular to the abscissa, and another, 5, 10, or 15 seconds further back. The mean pressure is most readily and exactly got by means of a planimeter; but, as this is an expensive instrument and possessed by few, we usually employ ruder methods. The first is to determine the square superficies of the irregular figure contained by the abscissa, the two perpendiculars and the curve, and then divide it by the length of the abscissa; this gives the mean height of the pressure-curve. The size of the figure is ascertained by placing over it a piece of tracing-paper or glass ruled in square *millimètres*, and counting the number of squares contained in it. Volkmann cuts the figure exactly out in paper of uniform texture and weighs it. By then comparing its weight with that of a square of given size, the superficies of the figure is easily ascertained. The second method is still simpler, and, though not so exact, takes much less time, and is, therefore, frequently employed. It consists in drawing a straight line from one perpendicular to the other along the curve, so as to cut the pulse- and respiration-waves as nearly as possible in their middle, and leave as much of their surface above as below it. We then measure the height of this line above the abscissa, double it, and subtract from it the fraction of the whole, which represents the column of carbonate or bicarbonate of soda solution which entered one limb of the manometer and pressed on the mercury in it as the mercury rose in the other limb. For a solution of carbonate of specific gravity 1018, this fraction will be about $\frac{1}{27}$ of the whole.

Passing along the curve taken after the drug has been injected, we note the place where any change in pressure has occurred, and here we draw another perpendicular and proceed as before.

Thirdly, we obtain the number of pulsations and respirations in a minute by counting the pulse- and respiration-waves

between each two perpendiculars, and reckoning from the time between them what the rate of pulse or respiration will be in a minute. As the rate of both may change several times in a minute, and a calculation of this sort would lead to considerable error, we not unfrequently take 15 seconds as the unit of time instead of a minute.

The way in which the numbers thus obtained may be tabulated, is shown by the following examples of supposititious experiments. These examples have been made by piecing together several experiments of Von Bezold, and show generally the action of atropine, but must not be regarded as accurate descriptions of any one experiment.

Even when a continuous roll of paper is employed, instead of several separate pieces, it is often convenient to divide it by lines, and tabulate each part separately, just as when separate pieces of paper are used.

Mode of Recording Experiments.

Experiment I, November 5, 18—.

Young rabbit. Weight 1540 *grammes*. Jugular vein exposed and 1 cubic *centimètre* of tincture of opium, containing 2 *grammes* in 25 cubic *centimètres*, injected into it. Cannula in the left carotid. Animal otherwise uninjured.

	Time after injection.	Blood-pressure.	Pulse in 15 s.	Respiration in 15 s.	Remarks.
Tracing I.					
Tracing begun 2.39 P.M...	..	78	60	23	2½ *milligrammes* of sulphate of atropine, dissolved in 2 cubic *centimètres* of water, injected into the jugular vein towards the heart.
Injection begun 2.39.15 ..	..	78	60	23	
„ ended 2.39.25 ..	..	80	63	18	
At 2.39.35.....	10 s.	83	65	19	
At 2.40.0	35 s.	87	70	20	
Tracing II.					
At 2.40.30	1.5	92	92	22	

Experiment II, November 9, 18—.

Old rabbit. Weight, 1764 *grammes*. Jugular vein exposed. Animal not narcotised. Cannula in the left carotid. Animal otherwise uninjured.

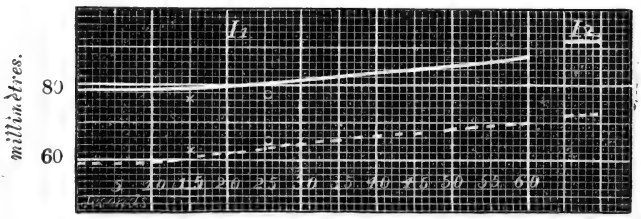
	Time after injection.	Blood-pressure.	Pulse in 15 s.	Respiration in 15 s.	Remarks.
TRACING I.					
Tracing begun 3.50.0 P.M.	..	92	64	26	2 *centigrammes* of sulphate of atropine, dissolved in 2 cubic *centimètres* of water, injected into the jugular vein towards the heart.
Injection begun 3.50.10 ..	..	92	64	26	
At 3.50.13.....	..	73	..	..	
Injection ended 3.50.15 ..	..	73	70	24	
At 3.51.0	45 s.	72	70	26	
TRACING II.					
At 3.58.0	7.45	78	68	25	

Graphic Method of Representing Experiments.—In looking over a column of figures such as the tables we have now obtained, it is by no means easy to see at once what it really indicates ; and it is still more difficult when we have to compare several tables together. For this reason it is of great advantage to convert the tables into curves, from which the result of any experiment can be learned at a glance, and the points of resemblance, or difference in the results of a whole series compared with the greatest ease.

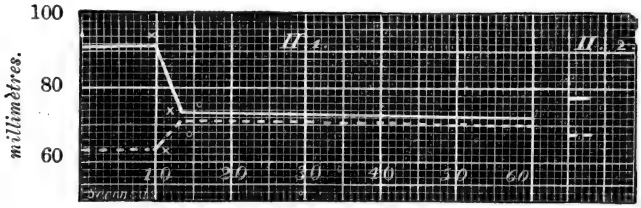
To obtain these graphic curves, we reverse the process by which we formed our tables. We first take a piece of paper ruled in squares, and on it we draw a horizontal line or abscissa, and then a perpendicular to one or both ends, and number the spaces along both the abscissa and the perpendicular or ordinate. Those along the abscissa represent periods of time to which we may assign any value which is convenient, seconds, minutes, hours, or multiples of these. The numbers along the ordinate may represent blood-pressure, pulse-rate, number of respirations, or degrees of temperature ; and we may describe curves representing all of these on the same paper, distinguishing them from

one another by the use of different coloured inks. Fig. 135 represents graphically the tables of blood-pressure and pulse-rate in Experiments I and II. We begin the pressure-curve by making a dot on the first perpendicular, at a height corresponding to the number 78. Passing along horizontally from this for a space corresponding to 15 seconds to the abscissa, we make another dot; and at 10 seconds further, at a height corresponding to 80, we make a third dot, and so on. We then connect the dots by lines, and thus obtain the curves we wish.

FIG. 135.



Exp. 1. The straight line shows the blood-pressure, and the dotted line the pulse-rate.



Exp. 2.

IV.—DETERMINATION OF THE EXACT STRUCTURES THROUGH WHICH DRUGS AFFECT THE HEART AND VESSELS.

(*British Medical Journal*, 1871, December 9, p. 659, December 16, p. 687, and December 30, p. 749.)

Comparison of the Effects of Drugs on different Animals in different Doses.—Mode of determining the exact Cause of Symptoms.—Mode of raising Blood-pressure.—Modes of counting the Beats of the Heart.—Causes of Quickened Pulse.—Direct Stimulation of the Sympathetic.—Stimulation of Cardiac Ganglia.—Paralysis of the Vagus-roots and Fibres, and of its Ends in the Heart.—Causes of Slow Pulse.—Irritation of Vagus-roots.—Mode of supplying the Head and Body with different kinds of Blood.—Indirect Irritation of Vagus-roots through the Blood-pressure: mode of lowering and raising it.—Reflex Irritation of Vagus-roots.—Indirect Irritation through the Respiration.- Irritation of Vagus-fibres.—Increased Conducting Power of Fibres.—Stimulation of Vagus-ends.—Paralysis of the Sympathetic.—

Paralysis of the Cardiac Ganglia.—Part of the Ganglionic Apparatus affected.—Nervous System in the Heart.—Motor Ganglia.—Stimulating Ganglia.—Inhibitory Ganglia.—Connecting Apparatus.—Action of Drugs on the Inhibitory Apparatus.—Nicotia, Muscaria.—Antagonism of Atropia and Physostigma; bearing of this on Therapeutics.—Paralysis of Co-ordinating Apparatus.—Paralysis of the Muscular Fibres of the Heart.—Blood-pressure: mode of determining whether Changes in it are due to Alterations in the Heart or Vessels.—Elimination of the Action of the Heart: Division of its Nerves.—Irritation of Vagus.—Ligature of Aorta.—Artificial Circulation; in Mammals, in the Frog.—Observation of Vessels.—Action on Vaso-motor Centre; on Vascular Walls.—Influence of the Action of Parts surrounding the Vessels upon them.—Action of the Pulmonary Circulation on the Blood-pressure.—Use of the Sphygmograph.

Comparison of the Effects of Drugs.—Before proceeding to examine separately the different structures through which a drug may act on the blood-pressure, it is advisable to compare the effects which it produces on animals of different kinds, such as dogs and rabbits, as well as the action of larger and smaller doses on animals of the same kind. Continuing to take as an example the action of atropia, admirably investigated by Von Bezold, we find the following results.

With a small dose of atropia injected into the jugular vein towards the heart:

The blood-pressure rises in both rabbits and dogs:

The pulse becomes quick, rising in rabbits from 256 to 288; in dogs, from 80 to 240.

With a larger dose:

The blood-pressure, in both rabbits and dogs, falls at first and afterwards rises to the normal.

The pulse becomes quick in both.

With an additional dose:

The blood-pressure in rabbits falls very low as the poison reaches the heart; afterwards rises; and falls again below the normal.

The pulse becomes slower, and then quicker.

With a very large dose:

The blood-pressure sinks instantly in both rabbits and dogs.

The pulse in rabbits becomes slower and weaker, and then stops; in dogs it becomes quick.

This comparison between the effects which atropia produces in different animals, and in large and small doses in the same animal, shows us that it sometimes raises and sometimes lowers the blood-pressure, but that it always quickens the pulse, except when a large quantity of the poison is introduced at once into the heart of the rabbit. On consulting the table already given (p. 278),* it will be seen that quickening of the heart may be due to stimulation of the sympathetic, either directly by the drug or indirectly by diminution of the blood-pressure; to stimulation of the cardiac ganglia; or to weakening or paralysis of the vagus. Any one of these conditions may cause quickened pulsation; and, in order to determine which of them really does it, we must test each one of them separately by farther experiment.

Mode of determining the exact cause of Symptoms.—The plan which we follow is this: we suppose for the time being that the cause which we are testing is the true one, and consider what effects it will produce under certain conditions. We then supply these conditions experimentally, and see whether or not the results we obtain correspond with those which we should find if our supposition were correct. So in the present instance we first ask, Is the quickening of the pulse due to indirect stimulation of the sympathetic roots by diminished blood-pressure or not? We suppose for the moment that it really is so, and we consider that if we raise the blood-pressure we shall remove the cause of quickening and bring the pulse down again to its normal rate. We then proceed to raise the pressure, and see whether or not the pulse is rendered slow, as we expect it to be. In the case of atropia, a special experiment is not necessary for this purpose, as we have seen that small doses do not *lower* but *raise* the blood-pressure, at the same time that they quicken the pulse; consequently the quickening cannot be due to indirect stimulation of the sympathetic. Other drugs, however, such as nitrite of amyl, even in small doses, lower the blood-pressure at the same time that they quicken the pulse, and in their case we must raise the blood-pressure artificially.

* *British Medical Journal*, June 3rd, page 538.

Mode of Raising Blood-pressure.—This may be done either by injecting a sufficient quantity of the defibrinated blood of another animal of the same species, warmed to 98° Fahr., into the carotid or crural artery towards the heart, or by compressing the aorta. The aorta may be either compressed by the thumb of the operator, or by a narrow pad of cork laid over it and pressed upon it by a tourniquet, of which the strap has been passed round the animal's body.

Mode of Counting the Beats of the Heart.—Now, if we wish to determine the blood-pressure at the same time with the pulse-rate, we may count the latter from the oscillations which each beat of the heart produces in the tracing of the kymographion, or from the sphygmoscope attached to it; but this is not always necessary, and we may wish to ascertain the pulse-rate without going to the trouble of opening an artery and using a manometer. We may do this in three ways:—1. By feeling the pulse in one of the large arteries, such as the crural, with the finger; 2. By listening to the beats of the heart with a stethoscope; 3. By the motion of a needle stuck into the ventricles. For this purpose a fine harelip-needle is inserted at the point where the apex beats, and is pushed upwards into the substance of the ventricle. At its upper end it may have either a knob, or a loop to which a thread can be attached, and a barb at the point will prevent it from changing its position in the heart when traction is made upon it. In rabbits, the point where the needle should be inserted is in about half an inch to the left of the sternum in the third intercostal space, and the length of the needle used should be about 3 inches. Various means have been proposed for counting the oscillations more readily than can be done by simply watching the movements of the needle itself. The knob of the needle may be allowed to strike against a wine-glass, and the pulsations may thus be counted by the ear; or a needle without a knob may be used, and a rice-straw with a piece of bright-coloured paper attached to it may be slipped over it, so that its vibrations, amplified by the long straw, and made more visible by the bright-coloured paper, may be readily counted by the eye.

A convenient way of registering the oscillations on an upright

cylinder is one devised by Professor Stricker. One of Marey's cardiographic levers is fixed on a rod close to the side of the animal and some distance above it, and a small piece of cork attached to the lever. One end of a fine thread is then fastened to the needle, and its other end pulled through a slit in the cork till it is sufficiently tight to make the lever vibrate with each movement of the needle; it is then fastened by twisting it round the lever, or by a little sealing-wax. If the lever be not raised several inches above the needle, it is pulled too much to a side and not sufficiently downwards to give a good tracing. The tracing may be taken either on plain paper with a glass pen or camel's-hair brush attached to the lever by a piece of cork, or with a dry point on smoked paper. Instead of a vertical cylinder a horizontal one may be used, and is perhaps still better. In this case the lever should be nearly on a level with the needle, and not raised much above it (*cf. antea*, p. 208).

Is the Quickening of the Pulse due to direct Stimulation of the Sympathetic?—If so, the injection of the drug should cause an increase in the pulse-rate after the vagi have been divided as well as when they are intact. We therefore divide the vagi, inject the drug into the veins, and see whether or not the pulse-rate is increased. On doing this with atropia it is found that the pulse becomes slower rather than quicker, showing that the drug does not stimulate the quickening nerves of the heart. The increased rapidity of the pulse which it produces when the vagi are intact is, therefore, not due to this cause.

Is the Quickening due to Stimulation of the Cardiac Ganglia?—The experiment just mentioned shows that it is not, for, if it were, injection of atropia should cause quickening after division of the vagi. Supposing, however, that it had caused quickening, the question whether the acceleration was due to the ganglia or the sympathetic would have to be decided by dividing all the nerves going to the heart with a platinum-wire heated by electricity, and then injecting the drug, or by applying it to the heart of the frog in a way which I shall afterwards describe. If it quickened the beats of a heart thus separated from all other nerves, it could only do so by acting on the cardiac ganglia themselves.

Is the Quickening due to Paralysis of the Vagi?—The exclusion of the other causes leads us to believe that it is due to this; but, in order to avoid the possibility of error, we must try to confirm our conclusion by other experiments; and, moreover, we have still to find out which part of the vagus is affected—its roots, its fibres, or its ends in the heart.

Are the Vagus-roots Paralysed by the Drug?—We are enabled to answer this question by our knowledge of the fact, that poisons only act on the parts to which they are carried by the blood, and that when introduced into the circulation they do not reach every part of the body at once, but are carried on with the blood-stream first to one part and then to another, and will reach a part near the point where they were introduced before one which is farther off. Thus, if we inject a drug into the carotid it will be carried direct to the head, and will act on the medulla oblongata and the roots of the vagus before it reaches the heart; but if we inject it into the jugular vein it will reach the heart and act on the vagus-ends in it before it reaches the roots in the medulla. If atropia paralyse the vagus-roots, then its injection into the carotid towards the head should be followed by rapidity of the pulse more quickly than its injection into the jugular; but if it act on the vagus-ends in the heart, the pulse should become rapid more quickly after injection into the jugular vein towards the heart than after injection into the carotid. On testing this experimentally, it is found that, when atropia is injected into the jugular vein towards the heart, the pulse at once becomes quick, even before the injection is finished; but, when it is injected into the carotid towards the head, the pulse is not quickened for a quarter of a minute or more, or, in other words, till the poison has had time to pass through the capillaries of the head and go through the veins to the heart. This, then, shows that it is the vagus-ends in the heart, and not the roots in the medulla, that are paralysed by it.

Are the Vagus-fibres Paralysed?—From the rapidity with which paralysis of the vagus occurs after atropia reaches its ends, we have already come to the conclusion that the ends are the part affected rather than the roots or fibres; but it is well to

substantiate our conclusion by further experiment. We divide the vagus and galvanise its peripheral extremity. If we do this to a normal vagus, the heart will beat more slowly or stand still altogether; but if either the fibres or ends of the nerve have been paralysed, no change will be produced in the heart's rhythm by the application of galvanism to its trunk, and this we find to be the case after the administration of atropia. But this experiment does not enable us to decide which part of the nerve is paralysed—the fibres or the ends, for in either case the effect would be the same. We may do this, however, by observing the effect which irritation of the vagus-trunk produces on such of its fibres as do not go to the heart. If it were the fibres which were paralysed, we should expect that those which go to the heart would not be the only ones affected, but that those going to other parts would be paralysed likewise.

I have hitherto spoken of the vagus as if it were a simple nerve containing only inhibitory fibres for the heart, but it is really a most complicated bundle, containing centripetal fibres having probably no fewer than eleven different functions, and centrifugal ones having nine or ten; so it is little wonder that it has long been a puzzle to physiologists, and even yet its functions are not completely investigated. Among these fibres are some which produce contraction of the œsophagus and muscles of the larynx; and if we find that irritation of the vagus continues to produce contractions in these parts after it has ceased to render the heart's action slow, as is the case after injection of atropia, we conclude that its fibres are not paralysed. Dr. Rutherford has shown that the best mode of observing the effects of irritation of the vagus on the muscles of the larynx, is to open it in front and place the animal in such a position that the light may be reflected from the inner surface of the arytenoid cartilage, as the slightest movements can then be readily detected. In this way it is found that atropia produces complete paralysis of the cardiac branches of the vagus, while the motor fibres supplying the muscles of the larynx remain unaffected; and we are therefore forced to conclude that it acts not on the fibres but on the ends in the heart. A more direct method is to apply the drug dissolved in an indifferent

fluid, such as half per cent. solution of chloride of sodium, to the vagus itself, and then to irritate the nerve about this point. This may be done by dropping the solution on the nerve after placing a piece of gutta-percha tissue below it, so as to keep the fluid from reaching the tissue below and being absorbed. If the drug paralyse the fibres, the irritation which is applied to the nerve above the part which is moistened by the solution will not be conveyed by the paralysed part of the nerve, and will consequently have no effect on the heart.

How does a Drug render the Heart's Action Slow?—We have now gone over the experiments which are necessary to determine what the structure is through which a drug quickens the heart's action, and we have now to consider those which we require when investigating the action of a drug which renders it slow. It may do so by irritating the vagus-roots, fibres, or ends; by increasing their excitability, so that they act more strongly when stimulated; or by paralysing the sympathetic, the cardiac ganglia, or the muscular substance of the heart itself.

Does it act by irritating the Vagus roots?—In order to answer this question, we divide both vagi and then inject the drug. We thus separate the heart from the vagus-roots and deprive them of any influence over it, so that, if they have been the cause of slowness of the pulse in previous experiments, it will not occur in this; but if the slowness have been due to other causes it will, with one or perhaps two exceptions, be noticed in this experiment, just as it would had the vagi been intact. These exceptions, which we will consider afterwards, are increased excitability of the vagus-fibres and ends. The vagus-roots can only act on the heart through the medium of the fibres and ends; if the drug itself should affect these structures, its action on the heart may be much altered or even destroyed. If the vagus-ends be paralysed, the roots can exert no more action on the heart than they can after we have cut through the trunks; and if the excitability of the ends be increased, the power of the roots over the heart will be greatly augmented, so that the heart's action may be made slow without there being any actual irritation either of the roots or ends. In order, then,

to find out what effect the drug has on the vagus-roots themselves, we must inject it into the carotid, so that it may reach them before it reaches the fibres or ends; and note what change occurs in the pulsations of the heart immediately after the injection. Any change which occurs immediately is due to the effect of the drug on the roots themselves; and, by comparing the number of pulsations at this time with that which is found a quarter of a minute or so afterwards, when the drug has reached the vagus-ends, we may discover whether their excitability has been increased or diminished. Thus, in the experiment already mentioned for ascertaining whether or not the vagus-roots are paralysed by atropia, we find that, when we inject it into the carotid, we get immediate slowness of the pulse, showing that the vagus-roots are irritated by the drug; but whenever it gets round to the heart it paralyses the vagus-ends, and the slowness at once disappears. If we were to keep the head alive by supplying it with an artificial stream of blood containing atropia, and prevent any of the poisoned blood from reaching the heart, the slowness might be continued indefinitely.

Mode of supplying the Head and Body with different kinds of Blood.—In his researches on respiration Hering employed a method of this sort, at one time supplying the brain with blood loaded with carbonic acid while the blood of the body was richly arterialised, and at another sending arterial blood to the brain while respiration was stopped and the blood circulating in the body was intensely venous. For this purpose he opened the thorax and tied the left carotid and innominate close to the aorta, and the vena cava superior close to the heart in a cat; he then introduced one cannula into the innominate artery, and another into the vena cava, and injected dog's blood, defibrinated and warmed, into the innominate artery, while he allowed it to flow out by the vein.

In atropia we have an example of a drug which acts on more than one part at once, and whose action on one part completely neutralises the effect which its action on the other would produce. In the case of others, however, we have the action on the different parts strengthening each other, as in veratria

which, like atropia, stimulates the vagus-roots, but, instead of paralysing the ends, increases their sensibility, and thus greatly augments the effect which the excited roots would have exercised over the heart, even had the ends remained unaltered.

Are the Vagus-roots Irritated directly by the Drug or indirectly through increased Blood-pressure?—Along with the slow pulse, produced by the injection of atropia into the carotid, a rise occurs in the blood-pressure; and how are we to determine whether the irritation of the vagus-roots is due to this increase, or to the direct action of the drug itself? This is a question very difficult to solve in the case of atropia, on account of the rapidity with which the vagus-ends are paralysed and all influence of the root over the heart destroyed. In the case of other drugs, however, where time is allowed, the question might be settled by diminishing the blood-pressure and seeing whether or not the slow pulse returned to its normal rate, and then raising it again and observing whether the pulse again became slow.

Mode of Lowering and Raising the Blood-pressure.—The blood-pressure may be lowered by opening a large artery, such as the carotid or crural, and allowing the blood to flow out into a vessel warmed to 98° Fahrenheit, and again raised by injecting the warm blood back into the artery. Or we may adopt Ludwig and Asp's plan, of inserting into the central end of the carotid a straight tube with a stopcock in its middle, and the moist bladder of a small animal, well emptied of air, tied to its free end. When the stopcock is opened, the blood rushes from the carotid into the bladder, and the tension in the arteries is diminished; but, when we press the blood out of the bladder back into the arteries, the tension on them is again increased.

Are the Vagus-roots Irritated Reflexly from some other part of the Nervous System?—There are two ways of deciding this: the first is to inject the poison in such a manner that it shall reach the vagus-roots before it reaches the other nervous structures through which we suspect it to act reflexly; the second is to remove these nervous structures themselves, or to destroy their function by means of some other poison. Thus, if we think that atropia, when injected into the carotid, acts on the medulla through the cerebrum, we may either remove the latter, or

abolish its function by opium or chloral. The application of irritating vapours, such as ammonia or tobacco-smoke, to the nasal mucous membrane of a rabbit, produces still-stand of the heart. We ascertain that this is due to irritation of the vagus by cutting it and finding that the vapour then has no effect; and we next decide that the irritation is conducted to the nervous centres through the trigeminus and not through the olfactory nerve, by observing that section of the former likewise prevents the action of the vapour on the heart, while section of the latter does not affect it.

Are the Vagus-roots Irritated indirectly by the Drug impairing Respiration, and thus allowing Carbonic Acid to accumulate in the Blood?—In the experiment just mentioned, we have ascertained that the vagus is irritated, and that irritation is conducted to the nerve-centres through the trigeminus, but we do not know that the irritation is directly reflected from the trigeminus to the vagus. It might be due to irritation of the vagus-roots by carbonic acid, which has accumulated in the blood from impeded respiration; for the irritating vapour applied to its nose causes the rabbit to close its nostrils and stop breathing for a while if the trigeminus be intact, but when it is cut no irritating impression can be conveyed to the brain, and so no closure of the nostrils takes place, either voluntarily or reflexly. The rabbit, therefore, continues to breathe freely: no carbonic acid accumulates in the blood, and no irritation of the vagus occurs. Other drugs, such as strychnia and curare, &c., impede respiration—not by causing closure of the nostrils and consequent obstruction to the passage of air to the lungs, but by acting on the muscles and nerves and diminishing the respiratory movements. Strychnia does this by producing tetanic contraction of the respiratory muscles, curare by paralysing them, and chloral by diminishing the excitability of the respiratory nervous centre. In all such cases, in order to ascertain that indirect irritation of the vagus from impeded respiration is not the cause of the slowing of the pulse, we insert a cannula into the trachea and begin artificial respiration; we then note the rate of the pulse and blow the irritating vapour into the nostrils, or inject the drug into the veins, and see whether or not the pulse is

rendered slow, taking care to keep up artificial respiration all the time. If the drug cause convulsive movements which interfere with the proper performance of artificial respiration, curare should be given so as to prevent their occurrence, and the experiment should be again repeated.

Are the Vagus-fibres Irritated?—To ascertain this we apply the drug dissolved in an indifferent fluid, such as a solution of half per cent. of chloride of sodium, or serum, to the nerve, and notice whether any change occur in the heart-beats. Care must be taken that the solution of the drug be not applied in too concentrated a solution, as false conclusions might thus be arrived at, for it might then have an irritant action, which it could not have if it reached the part through the circulation and became diluted by the blood before reaching the nerve.

Is their Conducting Power Increased, so that the Roots can act through them on the Heart more readily and powerfully?—If their conducting power be increased, other stimuli as well as those from the roots will act more powerfully on the heart. We therefore divide the vagi and apply a stimulus to the peripheral end of one or both by irritating them with one of Du Bois Reymond's induction-coils, and note at what distance from the primary coil the secondary one must stand in order to produce stoppage or slowness of the heart; we then apply the drug to the nerve below it and again irritate. If the excitability of the nerve be increased, stoppage or slowness should be produced when the distance between the primary and secondary coils is greater—that is, when the current is weaker than before. It is generally assumed that the fibres are not likely to be affected, and these experiments are rarely performed.

Are the Vagus-ends Excited?—We may test this in the same way as the action on the roots, by injecting the drug at one time into the jugular and at another into the carotid. If it increase the excitability of the ends without affecting the roots, we should find it produce, when injected into the jugular vein, an immediate slowing of the pulse, which does not become greater in a quarter of a minute afterwards, when the drug has reached the roots. When injected into the carotid, no slowness should occur till sufficient time has elapsed for it to pass round to the heart.

If it increase the excitability of both roots and ends, immediate slowness should occur, whether it be injected into the jugular or carotid, and this should become more marked after 15 or 20 seconds. If, like physostigma, it increase not only the excitability of the vagus-ends, but that of the quickening centre in the head, injection into the jugular should be followed by immediate slowing, which would become less marked when the drug reached the head, and injection into the carotid by an immediate quickening, which would become less or give place to slowness when the drug reached the heart.

At first sight one might think that, after time had been allowed for the drug to pass round the circulation and be applied both to the vagus-roots and ends, its action on the heart would be the same whether it had been originally injected into the jugular or into the carotid; but this is not the case, for that organ towards which the drug was injected gets a larger dose, and its action is more strongly excited than that of the other. Thus when physostigma is injected into the carotid, the quickening centres are stimulated and the pulse-rate rises; and, although the pulse falls somewhat after the vagus-ends have also been acted on, it nevertheless continues above the normal, the stimulation of the vagus-ends not being able to counteract the still more excited quickening centres. When it is injected into the jugular, the vagus-ends get the largest dose; and although the pulse, which is at first made very slow, may afterwards become quicker when the drug reaches the brain, it nevertheless does not reach the normal rate, the quickening centres being unable to counteract the more strongly excited vagus. If the vagus be then cut, however, the pulse becomes quicker than it would have done had no physostigma been given; or, if the vagi be first cut and the drug injected, the pulse is quickened at once. One might think that, since the drug acts on the vagus-ends, its action should remain after the nerves themselves have been divided; but since it is by increasing the excitability of the ends that it acts, if we separate these ends from the roots, and thus remove their normal stimulus, their increased excitability can have but little effect. In order to measure the amount of increase in the excitability of

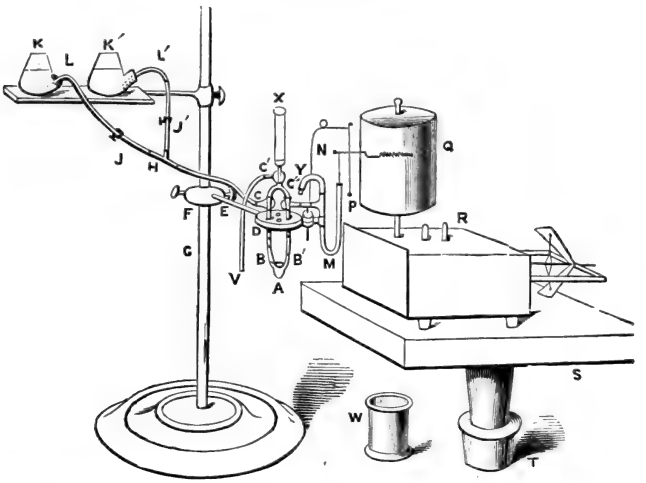
the nerves, we divide the vagi and irritate them by an induction-coil, noting the strength of current required to produce still-stand or slowness of the heart before and after injection of the drug into the veins.

Is the Sympathetic Paralysed?—This is tested by cutting the vagi and dividing the spinal cord between the first and second cervical vertebræ, so as to exclude the action of those centres in the head which quicken the heart and raise the blood-pressure; the drug is then injected, and the sympathetic irritated by an induced current and the pulse counted. If it be quickened by the irritation, the sympathetic is not paralysed.

Are the Cardiac Ganglia Paralysed?—To see whether or not the nervous structures contained in the heart itself are acted on by a drug, we must separate it from all other nerves passing to it from without, and prevent its being acted on by anything other than the drug, such as altered blood-pressure or temperature. This is done in mammals by dividing the vagi, the sympathetic cord, the depressor, and the spinal cord between the first and second cervical vertebræ. The heart is thus separated from the quickening and retarding centres, so that any alteration in its beats must be due to the nerves contained in its walls, or the muscular fibre of these walls themselves: at the same time the vessels are separated from the vaso-motor centre, and the heart is thus protected from the effects of any change in the blood-pressure, except the generally unimportant ones produced by the action of the drug on the vascular walls. The number and amplitude of the heart's contractions are then registered by a needle placed in the ventricle, and the blood-pressure by the manometer; poison is injected into the jugular, and the tracings taken afterwards are compared with those taken before. If we find that the heart-beats have become slower and weaker, while the pressure they have to overcome has not been increased, we may conclude that the motor nerves or the muscular substance of the heart have become paralysed. If the blood-pressure have risen, blood should be allowed to flow from an artery till it falls to its previous level, and then tracings should be taken with the needle for comparison with the previous ones.

The action of drugs on the heart can be studied still better in the frog than in mammals, as the heart of the former can be completely separated from the body, so that the drug can be applied to it alone. After its removal it continues to pulsate just as before, and, consequently, any action of the drug on the rhythm or force of its beats can be very easily noticed. The usual way of making experiments on this subject formerly was to take out the heart and lay it in a solution of the poison, or, what was better, to take two glasses containing solution of chloride of sodium (half per cent.) and add a little of the drug to one of them. A frog's heart was then laid in each, and the beats of the poisoned compared with those of the unpoisoned one. Both of these plans are inferior to that of Ludwig, who supplies the heart with serum so as to keep it as nearly as possible in a normal condition, and attaches to it a manometer, so that it may itself register the number and form of its beats, and give more exact indications than could be obtained by merely looking at it. The apparatus which he and Cyon first used, and which is figured in his *Arbeiten* for 1866, has been considerably modified by Dr. H. P. Bowditch, and is shown in Fig. 136. It consists of a bent glass tube (C C′ C″), which is supported by a glass plate (D). The frog's heart (A) is connected to the ends of this tube by means of india-rubber tubing and two glass cannulæ, one of which (B) is tied into the vena cava and the other (B′) into the aortic bulb. The tube has three openings, each of which is furnished with a three-way glass stopcock. By means of one of these (C) it can be filled with serum from a reservoir (K or K′), and the stopcock may be so turned as to allow serum to enter the part of the tube above it, the part below it, or both together, or the communication with K may be shut off while the lumen of the tube remains open. By C′, the serum which has been already used is allowed to escape, when a fresh supply is given, and C″ allows the tube to communicate with a manometer (M), on the mercury in which a fine pen floats and registers its oscillations on a revolving cylinder (Q). Each time the heart contracts it drives the serum with which it is filled out of the ventricle, round the tube, and back through the vena cava into the auricle, and at the same time raises the mercurial column in M.

FIG. 136.—Dr. H. P. Bowditch's Apparatus for Experiments on the Heart of the Frog.



A is the frog's heart. B is a cannula tied into the vena cava, and B′ one into the aortic bulb. C, C′ and C″ are three glass stopcocks. By C fresh serum is supplied, by C′ old serum is let out, and C″ allows the communication between the bent tube B C′ B′ and the manometer M to be opened or shut at will. D is a glass plate, through which the bent tube B C′ B′ passes. E is a rod ending in a ring into which D is fitted. F is a nut by which the whole apparatus can be moved up and down on the stand G. H is a T-tube. J and J′ are two clips to stop the flow of serum from K or K′. K and K′ are two fountain-bottles for supplying serum to the heart. K contains pure, and K′ poisoned serum. L and L′ are bent tubes which convey the serum out of K and K′. M is a small manometer. N is the pen or point which swims on the mercury. The horizontal part is made of glass; the vertical rod of esparto grass, with a small piece of sealing-wax at its lower end. The tracing may be made with ink, or with a dry point on smoked paper. P is a small weight which hangs by a piece of unspun silk from a bent wire, and keeps the pen resting on the paper. Q is the revolving cylinder. R is the clockwork, which is provided with one of Foucault's regulators. S is a table, which can be raised or lowered at pleasure, and fixed at any height by the screw T. V is an india-rubber tube, through which the serum is emptied from X. X is a graduated tube, into which the serum is allowed to pass after it has circulated some time. Y is an india-rubber tube, which is generally closed by a clip, but is opened when the apparatus is to be filled, or when we wish to let down the mercury to zero, in order to draw an abscissa. W is a glass vessel, which fits tightly to the under side of D, and protects the heart from external irritation. Into the two holes seen in D tubes may be fitted air-tight, and the heart made to pulsate in an atmosphere of any sort of gas.*

* This apparatus is made by Geisler, Blume's Hof, Berlin. Mr. Hawksley,

The height of the curve traced by the pen depends very much on the amount of serum which the heart contains, being very much higher when the heart is full; and it must, therefore, be equally filled each time, or very different tracings will be obtained. For this purpose I use, as reservoirs for the serum, fountain-bottles, in the mouth of which it always stands at the same level, and, consequently, always fills the heart at the same pressure. One of them (K) is filled with pure serum, and the other (K′) with serum to which a certain amount of the drug to be tested has been added.

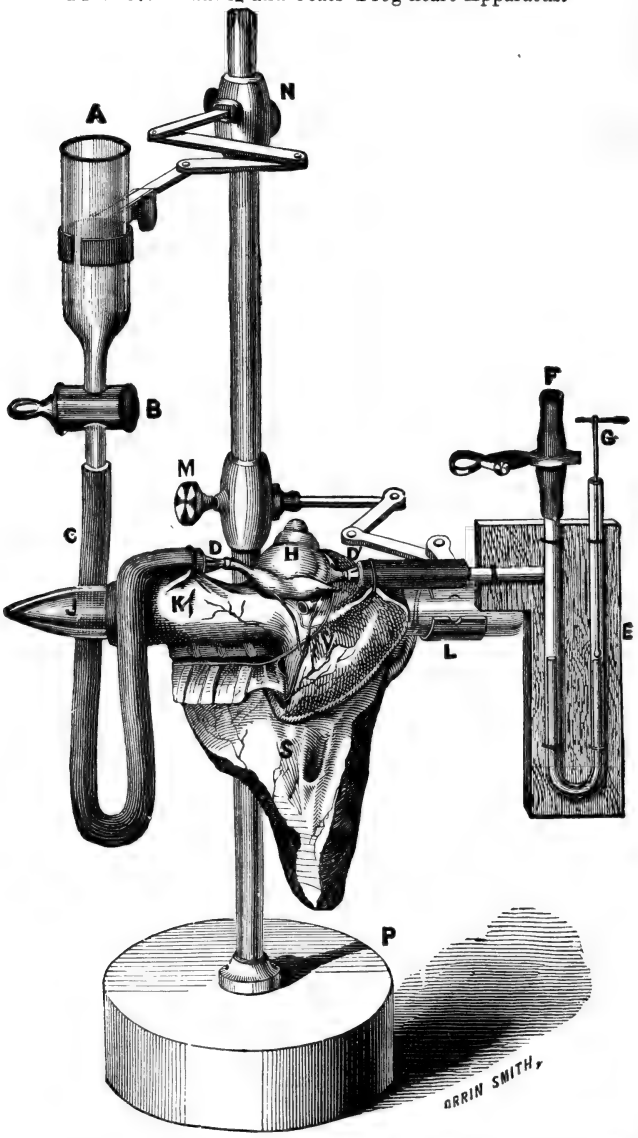
For the purpose of introducing the cannula into the heart, the brain and cord of the frog are destroyed by a piece of wire, and the animal fixed on its back to a board. A V-shaped incision, with its apex at the lower end of the sternum, and its limbs extending upwards and outwards towards the forearms, is then made in the skin, and the flap turned back or cut off. The sternum is then removed in a similar way. The pericardium is next opened, the cut being made while the heart is contracted, so as to avoid injuring it. The apex of the heart itself is then turned upwards, and two ligatures are passed underneath a small vein which runs from its posterior surface to the pericardium. The ligatures are tied, and the vein is cut between them. The pericardium must now be removed entirely from the heart, and the vena cava superior and the right branch of the aorta tied. The vena cava inferior is carefully isolated; a ligature is passed under it, a short and wide cannula tied into it, and another into the left branch of the aorta. The heart is then cut away from the body. Both cannulæ are filled with serum, and connected by india-rubber tubing to the ends of the tube C C′ C″, care being taken to exclude air-bubbles. The end of the manometer nearest C is filled with serum by opening the clip at Y, and allowing all the air and a little serum to escape. The clip is then replaced, and the heart allowed to beat once or twice, with the stopcock C and the clip J freely open, so that it may

of Blenheim Street, Oxford Street, has adapted a bobbin and rollers to the revolving cylinder figured above, so that it will carry a continuous roll of paper, and may be conveniently used instead of the kymographion shown in fig. 133. The instruments which I have already described as necessary for experiments may be obtained from him or from Oswald Hornn, Schiller Strasse, Leipzig.

become full of fresh serum. The stopcock C is then turned so as to cut off the tube C C′ C″ from all communication with K; and tracings are then taken, an abscissa or zero-line being drawn under each. The heart is next supplied with poisoned serum from K′, and the tracings which it gives are compared with the normal ones. By slightly turning the stopcock C, a greater or less resistance may be opposed to the circulation of fluid, and the effects thus imitated which contraction or relaxation of the vessels would produce in the living animal.

Another apparatus has been invented by Ludwig, and used by Coats in his research on the vagus, in which there is no circulation, the serum being simply forced out of the ventricle at each systole, and falling back at each diastole. It gives, however, very good tracings of the number and form of the heart-beats, and is extremely well adapted for observations on the effects of drugs on the vagus. It consists of a manometer, E, and a reservoir, A, with which the frog's heart is connected by two cannulæ, D and D′. The frog's heart is prepared by destroying the brain and spinal cord, removing the sternum and fore-legs, but leaving a large flap of skin, S, to cover the heart with, and then introducing a cannula into the vena cava and aorta, as in the former experiment. Instead of then cutting out the heart, the liver and lungs are removed, and the stomach is cut through the middle; and a glass tube, sealed at both ends, and as thick as the œsophagus will admit, is pushed through it till one end projects at the mouth and the other from the cut end of the stomach. The vagus is thus clearly displayed; and, in order to isolate it more perfectly, all other nerves should be cut away, as well as a part of the pharynx, so that no soft parts may touch it from its exit from the bone to the place where it crosses the aorta. From this point to the heart, it should be left untouched; and the jugular vein should not be tied, so as to leave it undisturbed. The glass tube J is then fixed firmly in a holder L, and the cannulæ, D and D′, connected with the reservoir A, and the manometer E. Instead of the reservoir A shown in the figure, it is perhaps better to use two fountain-bottles. The apparatus is used just like that shown in Fig 136; and the heart should in this case also be filled so full that a

FIG. 137.—Ludwig and Coats' Frog-heart Apparatus.



A is a reservoir for serum. B, a stopcock to regulate the supply to the heart. C, a piece of caoutchouc tubing connecting A and D. D, a glass cannula in the vena cava inferior. D′, another in the aorta. E, a manometer. F, a piece of tubing closed by a clip, to allow of the escape of serum. G, a fine pen, floating on the mercury in E. H, the frog's heart. J, a sealed glass tube, passed through the œsophagus K, and firmly held by a holder L. M, a nut which allows L to be moved up and down. N, a second holder to support A. P, a stand with upright rod. S, a flap of skin to cover the heart and prevent drying. V, the vagus.

certain tension exists within it even during diastole. The amount of this is shown by the height of the diastolic curve above the zero-line. When the vagus is irritated, the tension during the diastole sinks; but, if its inhibitory fibres be paralysed by atropia, which leaves its quickening ones unhurt, irritation has then the opposite effect, and the tension during the diastole becomes greater and greater till the heart may stand still in firm contractions.

What Part of the Ganglionic Apparatus in the Heart is affected?—In dealing with this part of the subject, we tread on very unstable ground, for here pharmacology has almost run ahead of physiology; and even with our physiological knowledge of the nervous structures of the heart a great deal of speculation is mixed. We know that the heart contains ganglia scattered through its substance, but found in the greatest numbers in the septum between the auricles and in the auriculo-ventricular groove of the frog's heart, in which they have been chiefly investigated. As the heart, long after it has been separated from the body, or the apex after it has been cut off from the ventricle, will still continue to beat rhythmically, the cause of the contractions must be contained in itself; and we assume the cause in each part to be the cardiac ganglia, and suppose that they are connected by some apparatus which keeps them working harmoniously together, as the different parts of the heart all contract in a definite order so long as it is uninjured. Their action may be rendered slow or quick by nerves passing to them from without, both the retarding and the quickening nerves being contained in the vagus in the frog while in mammals the retarding ones are found in the vagus, and the quickening ones chiefly in the third branch of the ganglion stellatum (or first dorsal generally joined to the last cervical), although some may also be found in the vagus.

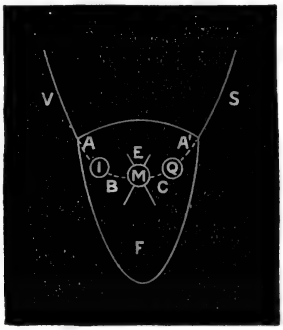
Some physiologists consider that the function of all the ganglia is simply to keep up rhythmical movements in the heart. Others hold that only some of them, found chiefly in the venous sinus and ventricle, have this function: while others are inhibitory, and restrain the action of the former. These inhibitory ones exist chiefly in the septum

between the two auricles. The reason of this supposition is that, when the venous sinus is separated from the rest of the heart, it continues to pulsate; but the auricles and ventricles stand still. When the ventricle is cut off from the auricles, it begins to beat again, but the auricles do not; so that it would seem as if the motor apparatus in the venous sinus and ventricles together could overcome the inhibitory apparatus in the auricles, and keep the heart going; but that this is too strong for the motor ganglia in the ventricle alone, and will not let them go on till they are separated from it, or till it becomes exhausted, which it seems to do after a little, and then both auricles and ventricles begin anew. The physiologists who hold the simpler view, say that this stoppage is only due to the irritation of the vagus-fibres which run along the venous sinus, and that the renewed cardiac contractions are simply due to the irritation passing off. The pharmacologist, however, is not contented even with the more complicated of these mechanisms, but demands a still more elaborate nervous apparatus in order to explain the action of poisons on the heart. The necessity for this has been clearly shown and a plan of the nerves drawn up by Professor Schmiedeberg. I have endeavoured to represent the supposed nature of this apparatus in the accompanying diagram. (Fig. 138.) It consists of a ganglion M, which keeps up a rhythmical contraction of those muscular fibres of the heart to which it is connected by the fine nervous filaments E. This ganglion is connected by an intermediate apparatus, B, with an inhibitory ganglion I, which can retard or stop the muscular contractions which M produces; and by another apparatus C, with another ganglion Q, which quickens the contractions. I is connected by an intermediate apparatus, A, with the retarding fibres V, of the vagus, and Q by A′ with the quickening nerves S, of the heart.

Inhibitory Ganglia of Heart.—We have hitherto included under the terms vagus-ends all the inhibitory apparatus in the heart; but, when we begin to experiment with the heart alone, we find that poisons which such experiments as have already been described would lead us to class together as acting on the vagus ends, really act on very different parts of the cardiac nervous system. Thus nicotia, when injected into the

blood after the vagi and cord have been divided, renders the pulse slow; but this soon gives way to quickening; or, if the dose be large, quickening may occur at once; and, if we then irritate the vagus, we find that we cannot render the heart beats slow any more than we can after poisoning by atropia. We thus see that, after the irritation which nicotia first occasions in the vagus-ends has passed off, it paralyses them; and we might thus be inclined to think that they acted on the same structures. But, if we give nicotia to a frog, and instead of

FIG. 138.—Diagram of the hypothetical Nervous Apparatus in the Heart.



M, motor ganglion. I, inhibitory ganglion. Q, quickening ganglia. V, inhibitory fibres; and S, quickening fibres from the medulla. A, A', B and C, intermediate apparatus. E, fibres passing from the motor ganglia E, to the muscular substance F. For simplicity's sake, only one set of motor ganglia has been represented, but other similar ones are to be supposed to be present in other parts of the heart, and so connected with this set that they all work in unison. It must be remembered that this diagram is purely hypothetical; but if this be carefully borne in mind, the sketch will be found of service in remembering and comparing the action of different poisons on the heart.

irritating the vagus, we irritate the venous sinus, still-stand of the heart is at once produced; while, if atropia be given, and the venous sinus then be irritated, the pulsations are not slowed at all—showing us that there is some inhibitory apparatus in the venous sinus which has been paralysed by atropia, but left untouched by nicotia. We may substantiate this conclusion by another and extremely useful method of investigation—viz., by administering another poison, and seeing how its action is affected by each of the other two. If we allow a little muscaria

to reach a frog's heart, its beats become slower and slower, and at last cease altogether, the ventricles remaining widely distended, just as they would do if the vagus were strongly galvanised. If nicotia be then injected into the frog or mixed with the serum supplying an excised heart, no alteration is observed; and if nicotia be injected before the muscaria, the latter poison stops the heart just as usual, although the nicotia may have so paralysed the vagus that no irritation whatever applied to its trunk could act on the heart. But, if atropia be used instead of nicotia, the effect of the muscaria is at once destroyed, and the heart, which was standing quite still, immediately begins to beat. If the atropia be applied first, and muscaria given afterwards, it has no effect. Hence we see that nicotia has paralysed some part of the inhibitory apparatus farther away from the motor ganglia than that on which muscaria acts, while atropia has acted either on the same part as muscaria, or on some other one which lies between it and the motor ganglia.

Now, as the inhibitory effect produced by muscaria is not developed all at once, but goes on slowly increasing till it makes the heart stand still in diastole, it seems probable that its stimulating action is exerted on a ganglion, rather than on a nerve-fibre, and we therefore suppose that it acts on the inhibitory ganglion I. As the action of nicotia is exerted on something farther from the heart than I, our first idea is that it must be the nerve-fibres V. But on applying nicotia to the trunk of the vagus, after fixing the heart in Coats' apparatus, we find, on irritating the nerve above the point, that it still conducts impressions and causes stoppage of the heart. We are thus led to suppose the existence of an intermediate apparatus on which nicotia acts; but, whether or not this intermediate part simply consists of nerve-fibres less protected from the poison than those in the trunk, we cannot say. As atropia destroys the action of muscaria, it may act like muscaria on I; but the fact that muscaria does not destroy that of atropia would lead me to refer the action of the latter to a part between I and M, which is represented by B. Of what nature this part is we know nothing; but that such a part exists is rendered

all the more probable by the mutual antagonism of atropia and physostigma. Although this latter poison renders the vagus very sensitive, so that the power of any irritation applied to its trunk to stop the heart is immensely increased, yet it has not the extraordinary power of producing still-stand of the heart possessed by muscaria. Unlike muscaria, however, it has the power of removing the paralysis of the vagus produced by atropia, and, though an additional dose of atropia will again cause paralysis, a second dose of physostigma will again remove it. This difference of action between muscaria and physostigma seems to show that they act on different nervous structures; while the mutual power that atropia and physostigma possess to neutralise each other's effects, indicates that atropia acts on the same structure as physostigma, and consequently on a different one from muscaria.

Antagonism of Atropia and Physostigma.—Atropia and physostigma are thus physiological antidotes to each other; and Fraser has shown that a dose of physostigma large enough to kill an animal may be given to it with impunity if atropia be administered along with it, and that the animal may be afterwards destroyed by a small dose given alone. It is true, they do not completely counteract each other's action, each one seeming to produce several effects, some of which, and these the most deadly, are neutralised by those of the other drug, while others are not so neutralised; and, if enormous doses be administered, those active effects which are not neutralised may become so powerful as to cause death, although they are comparatively unimportant when the dose is small.

Importance of this in Therapeutics.—Nevertheless, within certain limits these poisons do antagonise each other most successfully; and this observation seems to me to have a most important bearing on the treatment of such diseases as have their origin in morbid matter introduced into the system, for it shows that it is not always necessary to eliminate a poison in order to remove its effects, but that it may be neutralised and rendered innocuous while still present in the organism; and seems to indicate that, for the treatment of zymotic diseases, we should seek to discover such remedies as will counteract the

effects of the poisons on which they depend, and not merely endeavour to quicken their elimination.

Action of Various Drugs on the Inhibitory Apparatus.—From experiments which he has made on the excised hearts of frogs with Ludwig and Coats' apparatus, Boehm has come to the conclusion that conia paralyses the terminal filaments of the vagus; nicotia the intermediate structure between them and the inhibitory ganglia; and that others, such as atropia, hyoscyamia, daturia, physostigma, aconitia, delphinia and veratria, diminish or destroy the irritability of the inhibitory ganglia themselves. It is rather extraordinary to find physostigma in this list; and it would thus seem that the pure alkaloid which Boehm used had a different action from the tincture used by Von Bezold, unless it be that the result depends simply on a difference in the amount of the poison used.

Accelerating Ganglia in the Heart.—We infer the presence of quickening ganglia in the heart from the effects produced by irritating the vagus after its inhibitory power has been destroyed by the administration of nicotia or atropia. When irritation is then applied to the nerve, it no longer produces retardation, but, on the contrary, a decided acceleration of the cardiac pulsations. This shows that the vagus contains fibres which quicken the heart, and that these are unaffected by the drugs which have paralysed the others. The quickening, however, does not take place till some time after the application of the irritant, and, if it be applied only for a short time, no acceleration may take place till after its removal; but, after it does occur, it remains for a considerable time. If we irritate the heart directly, instead of irritating the nerve, its beats are quickened at once, and the acceleration does not last long after the irritation is discontinued. This shows that, when we stimulate the quickening nerves, we do not act directly on the motor ganglia M (Fig. 138), as we do when we irritate the heart itself, or as we should do if the quickening fibres ended directly in them; and we therefore infer the existence of the accelerating ganglia Q between the quickening nerves S and the motor ganglia M. The accelerating apparatus seems to be stimulated by veratria, for we find that the cardiac pulsations are increased by its

administration to mammals in which the spinal cord, vagi, sympathetics and depressors have all been divided, or when it is applied to the excised heart of a frog.

Is Quickening of the Excised Heart due to Paralysis of Inhibitory or Stimulation of Accelerating Ganglia?—It is possible that the quickening may be due to paralysis of the inhibitory ganglia in the heart, and not to stimulation of the quickening ganglia. This can be decided by paralysing the inhibitory ganglia by means of atropia, before applying the poison to be tested—*e.g.*, veratria. If the latter poison exercise a stimulating action on the quickening ganglia, it will quicken the heart after atropia has been applied. If it simply paralyse the inhibitory ganglia, it will have no further effect after their power has been destroyed by atropia. In the diagram, I have figured intermediate structures C and D between the quickening nerves and ganglia, so as to correspond with those of the inhibitory apparatus; but whether they really exist or not, we cannot at present say.

Is the Co-ordinating Apparatus of the Cardiac Ganglia Paralysed?—Regarding this apparatus we know almost nothing. When the heart is dying its rhythm is often disturbed, and two or three contractions of the auricles may occur for every contraction of the ventricle. When laudanum is poured into the heart, the rhythm is quite reversed; for after each pause the ventricle contracts first, and contraction of the auricle follows it. Digitalis and some other poisons cause peristaltic movements in the ventricle; and occasionally some spots in the ventricle continue to pulsate while the rest of it remains firmly contracted and motionless. These effects are probably due to disturbance of the apparatus which connects the different motor ganglia in the heart and causes them to work in unison.

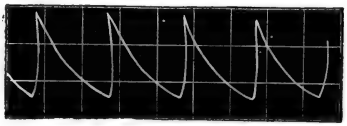
Are the Muscular Fibres of the Heart Paralysed?—We test this by applying an irritant to them directly, and seeing whether or not they contract. If the motor ganglia be uninjured, the application of an irritant generally produces a rhythmic contraction of the whole heart; but, if they be paralysed while the muscular fibre is healthy, the irritation only causes a local contraction of the part to which it is applied.

Blood-Pressure.

The blood-pressure depends on two things—1, the activity with which the heart pumps the blood into one end of the arterial system; 2, the rate at which it flows out at the other end into the veins. The rate is regulated by the small arteries and capillaries, which dilate and contract so as to quicken or slow it. The power of contraction is denied to the capillaries by many physiologists; but Stricker has, I think, conclusively shown that they do possess it.

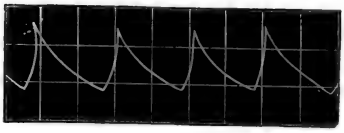
The rapidity with which the blood flows through them does not depend entirely on the width of the capillaries, but also on the pressure in the arteries which is forcing the blood into them. The higher this is, the more rapidly does the blood flow; and in proportion as it diminishes does the current become slower. From this circumstance we can judge of the force of the heart-beats from the form of the curve which we obtain with the sphygmoscope. When the heart contracts with great force, it drives the blood out of the ventricle into the arteries so quickly that there is no time for much to escape from the capillaries while the systole lasts, and so the tension rises high. This increased tension makes the blood run quickly out of the capillaries, and we have a fall of pressure, rapid at first, but gradually becoming slower as the tension diminishes. This is shown in Fig. 139. When the heart contracts less forcibly, it

FIG. 139.



sends in the blood more slowly, and there is time for a greater quantity to escape by the capillaries during the systole; and the tension does not rise so high. From the tension being lower, the outflow of blood is not so quick, and the pressure therefore sinks more gradually than in the former case. This is represented in Fig. 140. Both of these figures were obtained

FIG. 140.



by connecting a sphygmoscope with a schema of the circulation such as I have already described, and compressing the india-rubber ball which represented the heart with greater or less force and suddenness, care being taken, however, to empty it completely each time, so that the amount of air sent out should always be alike.

As variations in the blood-pressure may be due to alterations in the activity of the heart or the size of the capillaries, or to both together, we cannot say when it is due to the one and when to the other, unless we can keep one of them constant while we allow the other to alter, or unless we examine them both separately.

Elimination of the Action of the Heart.—We may keep the action of the heart tolerably constant, and thus ascertain with considerable exactitude the action of any drug on the exit-tubes —whether they be arterioles or capillaries matters not—by separating the heart from the nerve-centres, and then injecting the drug into the circulation.

Division of Cardiac Nerves.—This separation can be effected to a considerable extent by dividing the sympathetics, vagi and depressors in the neck; but it is done much more effectually by dividing the nerves near their entrance into the heart by a fine wire heated by means of a galvanic battery.

As poisons generally produce their most marked effects on the heart of mammals through the nervous centres whose connexion with the heart we have thus severed, alterations in the blood-pressure will be due to changes in the vessels, except in so far as the drug may have affected the cardiac muscle or ganglia. But, just as we obtained the most exact results when we examined the heart altogether apart from the blood-vessels, so we shall probably come to the most satisfactory conclusions regarding the vessels by observing them apart from the heart.

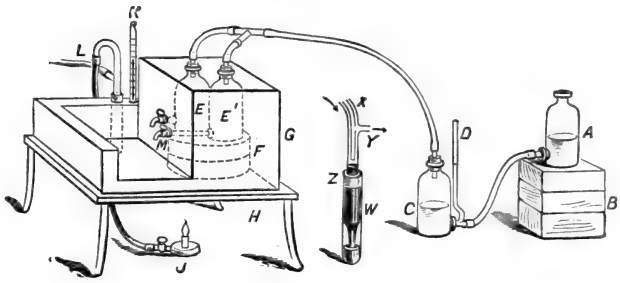
You will remember that, during the diastole, the circulation is carried on entirely independently of the heart by the pressure of the blood in the arteries; and, if we can prolong the diastole sufficiently, we shall be able to tell whether the vessels are dilated or contracted by simply seeing whether the pressure sinks quickly or slowly.

If we prevent any blood from being pumped into the aorta by the heart, the arterial system will come to resemble a bottle with a hole in it, from which the fluid which it contains is running. The larger the hole, the more quickly will it run out and the bottle become empty, and *vice versâ*; and, in the same way, the more dilated the capillaries are, the quicker will the blood run out of them into the vein, and the pressure sink in the arteries; the more contracted the capillaries are, the more slowly will the blood flow through them, and the more gradual will be the fall of pressure. In the case of many poisons, we may do this by irritating the vagi before poisoning, and seeing how quickly the pressure falls while the heart is standing still; and then repeating the experiment after injecting the poison. If the pressure fall more quickly in the second case, we know that the vessels have become dilated; and if more slowly, that they have contracted. Of course, only those parts of the tracings in which the pressure has been the same are to be compared with each other; but, if we stop the heart long enough, we can always get parts in both which are capable of comparison.

When the poison paralyses the vagus, as atropia does, this method fails; and then we must open the thorax, perform artificial respiration, and put a ligature round the aorta.

Artificial Circulation in Mammals.—As an animal quickly dies when the aorta is ligatured, it is better to carry on artificial circulation by a syringe through a cannula inserted into the aorta, as Hering has done in his researches on the connexion between arterial movement and respiration. After the blood has circulated once, it may be defibrinated, shaken with air, warmed to 40° Cent., and re-injected. Instead of using a syringe, the cannula in the aorta may be connected with the nozzle M, Fig. 141, and the blood put in the flask E. It can thus

FIG. 141.



be kept at a constant temperature more easily than when a syringe is employed. The pressure may be alternately increased and diminished so as to imitate the beats of the heart by raising and depressing the flask A. This may be done by passing a string over a pulley, and attaching one end to the flask and the other to a treadle worked by the foot. Warm blood has the disadvantage, that it undergoes change and becomes decomposed quickly; and cold blood may, therefore, be sometimes preferred. When cold blood is employed, only the flask which contains the blood is necessary; and it may be raised or lowered in the same way as the other.

Artificial Circulation in Frogs.—Artificial circulation may be kept up in frogs by simply inserting a cannula into the aorta, and allowing blood to flow into it from a raised reservoir, as done by Rollett. By using two, as in the experiments on the frog's heart, normal blood may be allowed first to circulate through the vessels; and, the web being put under the microscope, their diameter may be measured; and then poisoned blood may be allowed to flow through them, and any change in their diameter noticed.

Observation of Vessels.—The parts best adapted for observing changes in the size of vessels in mammals are the ear in rabbits and the mesentery. When the mesentery is chosen for observation, the abdominal parietes should be divided; but the peritoneum should not be opened, as changes in the diameter of the mesenteric vessels may be observed through it, and they are thus protected from the disturbing element which the irritation

produced by the access of air to them would introduce into the experiment. The vessels in the rabbit's ear are readily measured by a micrometer used with one of Brücke's magnifiers, which is simply a telescope with an extremely short focus. The ear should be held up so as to allow the light to shine directly through it, and the magnifier placed horizontally.

The area of the capillaries may be lessened, and the flow of blood through them retarded in two ways: 1, by contraction of their walls; 2, by pressure exerted on them from without. They may be made to contract by irritation, 1, of the vaso-motor centres, 2, of the vaso-motor nerves, or, 3, of their muscular walls; and pressure may be exerted from without by the motions of muscles or of organs composed of involuntary muscular fibre such as the intestines. The movements of respiration also, as already mentioned, exercise an important influence on the pressure.

Elimination of Respiration and Muscular Movement.—The influence both of respiration and of muscular movement may be eliminated by giving the animal curare, and keeping up artificial respiration, before beginning to experiment with the drug whose action we wish to examine.

Elimination of Vaso-motor Centre.—For the purpose of ascertaining whether the drug has acted on the vascular walls or on the vaso-motor centre, we divide the vaso-motor nerves going to a part before injecting it, and see whether it acts as it would have done had they been undivided. Thus, when we are observing the rabbit's ear, we divide the sympathetic in the neck; and, when looking at the mesentery, we cut the splanchnics before the injection, and see whether the vessels contract or dilate as we have previously seen them do under influence of the poison in animals in whom the nerves were intact.

For the purpose of ascertaining whether the drug acts on all the vessels in the body in the same way that it does on those of the ear or mesentery, we first cut the vagi, sympathetics and depressors, and then divide the spinal cord between the occiput and atlas, or atlas and axis, so as to sever the connexion between

the vaso-motor centre and vessels, and begin artificial respiration. We next note the blood-pressure, inject the poison, and see what alterations it produces. Experiments may also be made by irritating the vagus or ligaturing the aorta.

Action of Surrounding Parts.—It sometimes happens, as in the case of physostigma, that the drug produces no contraction in the vessels of the ear or mesentery when their nerves are cut —a fact which shows that it acts on them through the vaso-motor nerves, and not directly on their walls; and nevertheless, when injected into a vein after the cord has been cut, it may cause the blood-pressure to rise very considerably. At first sight, this would seem to indicate that the drug acted on the walls of some vessels in the body, if not on those of the ear or mesentery, directly, and not through their vaso-motor nerves. On examination, however, it is found that the obstruction to the flow of blood through the capillaries does not depend on their contraction, but on the occlusion of a large number of them in the intestine by spasmodic contraction of the intestinal walls in which they are imbedded.

Influence of the Pulmonary Capillaries.—It has lately been pointed out by Holmes that when a drug such as ergot, which acts on the walls of the vessels and causes them to contract, is injected into the jugular vein, it has to pass through the pulmonary capillaries before it reaches the systemic ones; and, by contracting them, it will lessen the amount of blood sent into the aorta from the left ventricle, and will at first produce a fall in the arterial pressure, succeeded by a great rise when time has elapsed for the drug to reach the systemic capillaries and cause them likewise to contract.

Use of the Sphygmograph.—For a description of the sphygmograph and the mode of applying it, we must refer to the special works on that subject, such as those of Marey and Sanderson. The indications which it gives are the following: 1. The greater or less pressure which is requisite to compress an artery and stop its pulsations enables us to estimate approximately the amount of pressure within it. 2. The amount of pressure and the rapidity of the pulse help us to form conclusions regarding the motor and inhibitory apparatus of the heart, in the same way as

in the experiments already mentioned, though, of course, to a much more limited extent and with much less certainty. 3. The form of the curve, like those in Figs. 13 and 14, shows, in the same way as those of the sphygmoscope, Figs. 13 and 14, the rapidity with which the pressure falls during the diastole, and from this curve and the amount of blood-pressure we can judge of the size of the capillaries.

LECTURE V.—*See* APPENDIX, p. 643.

VI.—RESPIRATION.

(Reprinted from the *British Medical Journal*, Feb. 13, 1875, p. 201.)

Position of the Respiratory Centre; chiefly situated in the Medulla Oblongata, but extends also to the Spinal Cord.—Effect of Strychnia upon it.—Influence of Nerves upon it.—Influence of Vagus.—Vagus contains two sets of Fibres, Accelerating or Inspiratory, and Retarding or Expiratory.—Cause of Rapid Breathing in Pneumonia.—Influence of the Superior and Inferior Laryngeal Nerves.—Nasal and Cutaneous Nerves.—Local Action of Vapours when inhaled.—Action of Ammonia.—Methods of Registering Respiratory Movements.—Acceleration of Respiration by Drugs.—Is it due to (1) Excitement of the Voluntary Nerve-centres, (2) Increased Temperature, (3) Increased Venosity of the Blood?—Increased Venosity may be due to (A) Prevention of Blood from reaching the Air; (B) Prevention of Air from reaching the Blood. Blood may be prevented from reaching Air—(*a*) By Stoppage of the Heart: Action of Quinine.—(*b*) By Embolism of the Pulmonary Vessels; Action of Condurango.—(*c*) By Contraction of the Pulmonary Capillaries; Action of Muscarine.—Observation of the Pulmonary Capillaries in the Frog under the Microscope.—Effect of Heat and Cold upon them.

IT used to be supposed that the respiratory centre was not only situated in the medulla oblongata, but was confined to it. Legallois found that the cerebral hemispheres, cerebellum, and even a part of the medulla itself, could be removed without arresting respiration; and thus showed that the respiratory centre was either in the medulla or in the spinal cord. (*Expériences sur la Principe de la Vie.* Paris, 1830, tome i.) Flourens noticed that injury to a point named by him *nœud vital*, at the lower end of the calamus scriptorius, instantly arrested respiration, and thus caused death (*Comptes Rendus*, vol. xxxiii, page 437); and all experimenters have found that division of the cord just below the medulla also arrested breathing. These experiments seem to show most conclusively that the respiratory centre is situated in the medulla, and does

not extend to the spinal cord; but the recent researches of Prokop Rokitansky (Stricker's *Medicinische Jahrbücher*, 1874, p. 30) on this subject show how careful we must be in drawing conclusions from experiments. Like all others, he has found that, under normal conditions, breathing ceases as soon as the influence of the medulla is destroyed by division of the cord just below it. But if strychnia be given to the animal, so as greatly to increase the excitability of its respiratory centre as well as of other reflex centres before the cord is divided, respiration will go on after the section has been made; and strychnia injected into the veins after the section will restore the respiratory movements, which the cut had arrested. This shows that the respiratory centre is not confined to the medulla, but extends into the spinal cord. The part contained in the cord is, however, too weak to keep up respiration alone under ordinary circumstances, though it can do so when its power is increased by strychnia. These remarkable effects of this poison give promise of future benefit from its use as a restorative in cases of death from drowning, &c.; but further experiments on animals are necessary before we dare employ such a powerful remedy in man.

Rokitansky's experiments enable us to demonstrate the presence of a respiratory centre in the spinal cord, as well as in the medulla of adult animals; but it is only fair to say that this was shown long ago by Brown-Séquard in the case of young ones. In young mammals and adult birds, he found that the thorax continued to execute rhythmical respiratory movements for a short time after the cord had been divided transversely at the level of the first or second pairs of cervical nerves, so that there must needs be a part of the respiratory centre in the cord below that level (*Journal de la Physiologie*, vol. i, 1858, p. 223, and vol. iii, 1860, p. 153). Besides this, he considers that there are what we may term peripheral respiratory centres—viz., ganglia in the substance of the diaphragm itself analogous to those in the heart, which enable it to contract rhythmically after its connections both with the medulla oblongata and with the spinal cord have been destroyed (*op. cit.*, vol. ii, 1859, p. 115).

Although the excitement of the respiratory centre and the amount of work done by the respiratory muscles depend on the venosity of the blood in the medulla oblongata, yet this work may be differently distributed by the respirations becoming quicker but shallower, or slower but deeper, without the quantity of air respired being at all altered. This is effected by the action of various afferent nerves, of which the chief are the vagus, the superior laryngeal, and the nasal nerves; though others, such as the cutaneous nerves generally, have considerable influence.

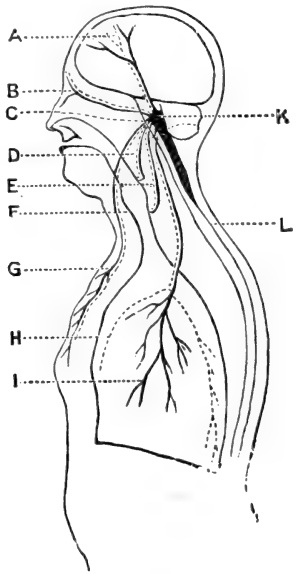
Irritation of the vagus, or of its central end when divided, lessens the resistance in the respiratory centre, and quickens the respiration, but makes it shallower. Stronger irritation causes prolongation of inspiration. A very strong excitation annihilates the resistance in the centre, and causes inspiration to be almost indefinitely prolonged, so that the breathing is completely arrested.

The ends of the vagi in the lung are normally in a state of constant excitation, and therefore division of these nerves renders the respiration slow.

Irritation of the vagi, on the contrary, causes, as we have said, considerable acceleration of the respiration; and the quick breathing which we observe in pneumonia is probably due to the irritation of the pulmonary branches of the vagus which the inflammation produces. It can hardly be caused by the venous condition of the blood alone, nor yet by increased temperature; for the blood may be very much more venous in bad bronchitis, and the temperature higher in fever, without the respiration becoming anything like so rapid as in a case of pneumonia. But, although I thus speak of the vagus as an inspiratory or accelerating nerve alone, I do this only for the sake of simplicity, as this is its chief function. It really contains, however, both inspiratory and expiratory fibres, although the former predominate. (Hering and Breuer, *Wiener Acad. Sitzungs-ber. Math.-Naturwiss. Cl.*, vol. lvii, Ab. 2, page 672.) The inspiratory fibres are excited by collapse, and the expiratory fibres by distension, of the lung. Thus, these nerves form a sort of regulating mechanism for the respiratory movements.

As soon as a deep inspiration is taken, the distension of the lungs excites the expiratory fibres, and leads to the consequent expulsion of the air; as soon as expiration takes place, the collapse of the lungs excites the inspiratory fibres, and thus leads to renewed inspiration.

FIG. 142.—Diagram showing the position of Respiratory Centre, and the Afferent Nerves which influence it. Inspiratory Nerves are indicated by plain, and Expiratory by dotted, lines.



A. Inspiratory and Expiratory Fibres for voluntary alterations in Respiration.
B. Cutaneous Nerves of Face.
C. Nasal Branch of Fifth Nerve.
D. Superior Laryngeal Nerve.
E. Inferior Laryngeal Nerve.
G. Cutaneous Nerves of the Chest.
} chiefly expiratory.
F. Larynx.
H. Expiratory Fibres of Vagus excited by distension of Lung.
I. Inspiratory Fibres of Vagus excited by collapse of Lung.
K. Respiratory Centre in Medulla and Cord.
L. Spinal Cord.

As the effect of irritating other nerves as well as the vagus is not always alike (Bert, *Leçons sur la Respiration*, page 490), it is probable that the laryngeal, nasal, and cutaneous nerves

may also contain both inspiratory and expiratory fibres. It has already been mentioned, that the accelerating fibres of the vagus in the lungs are probably irritated in pneumonia, but in bronchitis the expiratory ones are chiefly irritated, and give rise to the expiratory efforts in coughing, which serve to expel any irritating substance in the bronchi. When these fibres are exhausted, or the respiratory centre is feeble or irresponsive, the mucus will remain, and consequently strychnia suggests itself as an auxiliary in such cases. If the irritation depend on something which cannot be removed by coughing, such as miliary tubercle, we employ opium, chloral, &c., which lessen the excitability of the respiratory centre.

Moderate irritation of the superior laryngeal nerve renders the respirations slower but deeper; a stronger irritation prolongs expiration; and a very strong one causes the respiration to stop entirely in the state of expiration (Rosenthal, *Athembewegungen*, p. 244) until the increasing venosity of the blood greatly stimulates the respiratory centre, and causes respiration again to commence.

Irritation of the inferior laryngeal nerve (Burkart, Pflüger's *Arch.*, vol. i, p. 107), and of the supramaxillary (Kratschmer, *Sitzunges-ber. der Wien. Acad., Math.-Nat. Cl.* 1870, vol. lxii, Abt. 2, p. 24), and nasal branches of the fifth nerve, acts in a similar way to irritation of the superior laryngeal nerve, as well as irritation of the cutaneous nerves generally, and especially of those of the face and chest. (Schiff, *Compt. Rend.*, 1861.)

We have then to find out whether the alteration in respiration produced by any drug is due to its action on the respiratory centre, or on some of the nerves which influence it; and the following table may help us to do so more readily, by showing at a glance the chief ways in which the respirations may be accelerated or retarded.

The respiratory movements may be quickened by	Excitement of nerves.	Increased irritation of the vagus. By action of voluntary centre.
	Greater excitement of resp. centre.	Increased temperature of blood. Increased venosity of blood. Action of drugs.

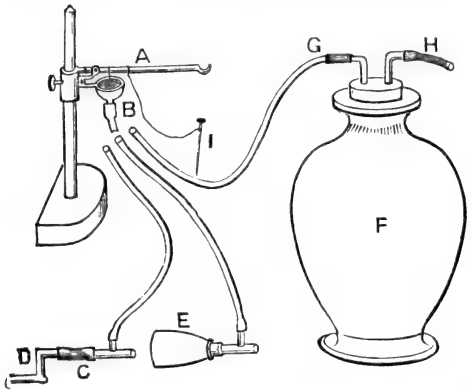
- The respiratory movements may be rendered slow by
  - Diminished excitement of respiratory centre.
    - Diminished venosity of blood.
    - Action of drugs.
  - Nervous influences.
    - Slight irritation of cutaneous nerves.
    - Action of voluntary centre.
    - Paralysis of vagi.
    - Irritation of superior laryngeal nerves.
    - Irritation of inferior laryngeal nerves.
    - Irritation of nasal nerves.

If the drug to be experimented on be injected subcutaneously or into the veins, the actions on the respiratory centre and on the vagi are the chief points which require attention; but if we are experimenting with a vapour, its local action on the nasal, laryngeal, and possibly, also, on the pharyngeal nerves (Brown-Séquard, *Archives of Scientific and Practical Medicine,* p. 94) must be carefully attended to, as it may greatly modify its general action on the respiratory centres. Thus Kratschmer has found (*op. cit.*) that tobacco smoke inhaled by a rabbit through its nostrils, or blown upwards into the nasal cavity from an aperture in the trachea, will cause arrest of breathing in a state of expiration from the irritating effect of the vapour on the nasal branches of the fifth, while it has no such effect when blown into the lungs. Ammonia, when inhaled, also arrests the respiratory movements in the same way; but Knoll (*Sitzungs-ber. der Wien. Acad.*, vol. lxviii, Abt. 3, p. 255) has observed that, if it be blown into the lungs, while the nostrils are carefully protected from its influence, it causes accelerated and shallow breathing, alternating with slow and deep respirations, and occasional stoppages in the position of expiration, obviously from its action on the different fibres of the vagi. When injected into the blood, it causes, according to Funke (Pflüger's *Archiv.*, vol. ix, p. 436), various alterations in the respiration, which are not easy to analyse, but it certainly seems to excite the respiratory centre; but the use of carbonate of ammonia in bronchitis has long been familiar to the medical profession.

The movements of respiration are not only more easily counted than in any other way, but their depth, and the

relation of inspiration to expiration, best noted by causing them to register themselves on a revolving cylinder. Various means of doing this have been suggested by different authors. One of the simplest consists of a needle pushed into the diaphragm, and connected by a thread with one of Marey's levers (see I, Fig. 143). Marey's pneumograph consists of a cylinder

FIG. 113.—Methods of Registering Respiration.



A is the lever of Marey's registering apparatus; B is a hollow drum, with open tube below, and covered at the top with a piece of thin caoutchouc, on which rests a tin plate connected with the lever A. When the air is blown into B, the caoutchouc is lifted, and the lever rises. When air is drawn out, the caoutchouc sinks, and the lever falls. The tube of B may be connected by india-rubber tubing with the respiratory passages in several ways. C is a T-tube, open at one end and connected at the other with a cannula (D), which is placed in the trachea of the animal and brought into communication by its upright limb with B. Instead of D, an india-rubber catheter may be placed in the animal's nostril. E is a caoutchouc bag, which is tied over the animal's muzzle and used instead of the tracheal cannula. F is a large vessel, from which two tubes (G and H) proceed. G is connected with the lever B, and H with the respiratory passages of the animal. I is a needle, which is simply connected with the lever by a thread: when pushed into the diaphragm, it registers the respirations.

of soft india-rubber, enclosing a spiral spring, whose extremities are connected with two pieces of metal which form the ends of the cylinder. A band is passed round the thorax of the animal, and attached to the ends of the cylinder. The interior of the cylinder is brought into communication with one of

Marey's levers; and as each respiratory movement draws the ends of the cylinders wider apart, or allows them to approach, the air is rarefied or compressed, and a corresponding movement is transmitted to the lever. Bert has modified this, and made it more sensitive by making the cylinder itself of metal, and its ends of india-rubber. Another method—one more ordinarily employed—is to introduce one limb of a T-tube into the nostril or trachea of an animal, or to connect it with a tracheal cannula. The respired air passes through the other end, and the third limb is connected with one of Marey's levers.

Is Quickening of Respiration due to Irritation of the Vagi?—When the respiratory movements become quickened by the injection of a drug into the circulation, the first cause to which it may be due, mentioned in the preceding table, is irritation of the ends of the vagus in the lung. In order to discover whether this be the cause or not, the vagi must first be divided and the drug injected. If it acts only on the ends of the vagus, the respiration which was quickened by injection when the vagi were intact, will not be quickened by it when these nerves are divided.

Is the Quickening due to Excitement of the Voluntary Nervous Centres?—This cause of quickening is eliminated by narcotising the animal with opium or chloral, or by removing the cerebrum. For the method of doing this, see Sanderson, *Handbook for the Physiological Laboratory*, p. 295.

Is it due to Increased Temperature?—If the temperature of the animal has risen above the normal—the fact can readily be ascertained by the thermometer—it may then be reduced by the application of cold water or ice, or by a stream of cold air directed on the surface of the skin. Unless the cooling be effected very gradually, these applications cause reflex disturbance of the respiratory movements through the cutaneous nerves.

Is it due to Increased Venosity of the Blood?—The drug may produce this by its action on the blood; and this is to be determined by the means already described. Generally we let a little blood issue from an artery; and if its colour be of normal brightness, we conclude that the gases it contains are also normal.

But external respiration may be arrested or diminished, the blood rendered venous, the respiratory movements consequently increased, and dyspnœa and asphyxia produced by preventing the blood from reaching the air, as well as by preventing the air from reaching the blood. The blood may be prevented from coming into relation with the air: (*a*) By stoppage of the heart; (*b*) By embolism of the pulmonary artery; (*c*) By contraction of the capillaries of the lung.

(*a*) *By Stoppage of the Heart.*—When respiration is suddenly impeded in any of these ways, the breathing becomes panting; and when it is suddenly stopped altogether, asphyxial convulsions occur. When the jugular vein is chosen for the introduction of drugs into the circulation, they come very quickly and without much previous dilution with blood nto contact with the heart and pulmonary vessels, and thus affect them more strongly than they would do if injected subcutaneously, or into one of the veins of the extremities. When a large dose of quinine is thus injected, the heart may be stopped at once, and convulsions ensue. Any alteration of the heart's action produced by a drug is easily noted by means of a needle fixed in the ventricle.

(*b*) *By Embolism of the Pulmonary Artery.*—This cause of interrupted respiration may easily lead an inexperienced observer to very erroneous conclusions regarding the action of a drug. Supposing him to inject an unfiltered solution of some extract into the jugular vein, he may find the respiration almost immediately afterwards become panting; the eyes start from their orbits, the limbs become convulsed, the head drawn back, and after one or two quivering contractions, life becomes extinct. He at once concludes that the substance he has injected is one of extreme activity, whereas it may be really quite inert; the violent symptoms which followed its injection being due to the extract being imperfectly dissolved, and the suspended particles producing embola in the pulmonary vessels.

In some experiments which I made on condurango, I was at first misled by this circumstance, and believed that the drug had a tetanising action, like that of strychnia, as convulsions came on immediately after injecting a solution of the extract

into the jugular vein. The same mistake has probably been made by Gianuzzi,* who attributes a convulsive action to the drug. By injecting the solution into the peritoneal cavity, however, I found that it had no action whatever even when used in large quantities, while a solution of strychnia applied in the same manner would have acted nearly as strongly as when injected into a vein.

(*c*) *By Contraction of the Pulmonary Capillaries.*—When contraction of the pulmonary capillaries is produced by a drug injected into the veins, the venous blood is hindered from reaching the left side of the heart, and the left ventricle and arterial system become empty, and the arterial pressure sinks while the right ventricle and venous system become swollen and turgid. The alteration of the blood-pressure in the arterial and venous systems may be measured by manometers connected with them; but while the arterial fall in the pressure is easily observed, there is considerable difficulty in measuring that in the veins, due to the rapid formation of coagula in the tube which is pushed down the jugular vein into the vena cava.

Another method is, to open the thorax and note the colour of the lungs and the comparative fulness of the right and left sides of the heart, and of the venous trunks, before and after injection of the drug. The animal is first narcotised, and a cannula placed in the trachea. The skin and cellular tissue are then divided along the middle of the sternum and reflected on each side. The muscles are then divided along the line of the costal cartilages, and artificial respiration is begun. The abdominal muscles are then separated from their attachment to the sternum and costal cartilages; the latter are cut through, except the first, which is left untouched in order to avoid wounding the internal mammary artery, and the sternum is bent upwards and retained in its position by a hook. In the rabbit, it is generally unnecessary to tie any vessels, as the bleeding stops quickly of itself; but if any one should bleed

* Gianuzzi and Bufalini, *Ricerche eseguite nel Gabinetto di Fisiologia della Universita di Siena*, pp. 71–86; abstracted in the *Centralblatt für die Med. Wiss.*, 1873, p. 824.

much, it ought to be laid hold of and ligatured. Artificial respiration being carefully and regularly kept up by means of a metronome, the colour of the lungs, the size of each ventricle, and the number of cardiac pulsations is observed, the drug injected, and the observation repeated. The pulsations must be counted, because slowness of the heart's action, by affording time for the accumulation of venous blood in the right ventricle, would cause it to become distended, although there were no obstruction to the pulmonary circulation. When the drug to be experimented on is not a solution but a vapour, it must be passed into the lungs by the method already described (*British Medical Journal*, May 20, 1871).

In this way, I have found that muscarin causes contraction of the pulmonary vessels, and produces dyspnœa (see *British Medical Journal*, November 14, 1874), although the heart continues to beat, and artificial respiration is vigorously kept up. The lungs become pale, the right side of the heart swells up, and the left side and arteries become empty, as represented diagrammatically in Fig. 145. The vapour of chloroform blown

FIG. 144. FIG. 145.

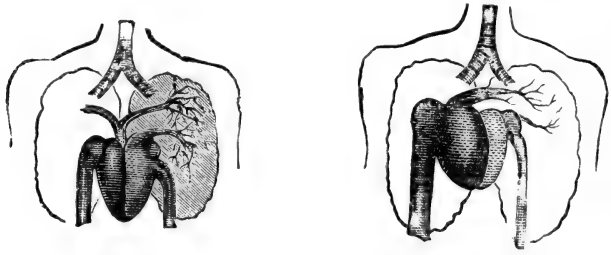


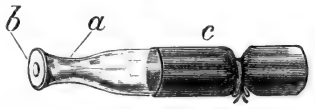
FIG. 144.—Diagram representing the normal condition of the circulation. Both the veins and arteries are moderately full; the two sides of the heart are of much the same size, and the circulation through the lungs is free.

FIG. 145.—Diagram representing the condition of the circulation after the administration of muscarine. The veins are distended, the arteries empty; the right side of the heart is much enlarged, the left side collapsed, and the circulation through the lungs almost entirely arrested.

into the lungs causes a similar appearance, but it arrests the cardiac pulsations more or less completely at the same time.

The action of the drugs on the pulmonary capillaries in the frog may be observed directly by means of the microscope. A frog is curarised, and a glass cannula, to which a short piece of india-rubber tubing is attached, is tied into its larynx. An incision is then made into the side of the frog a little below the arm, care being taken not to injure the lung in dividing the thoracic wall; and, the lungs being inflated through the cannula, one of them protrudes through the opening. The piece of india-rubber at the end of the cannula must then be clamped, so as to prevent the air from escaping and the lung from collapsing (Fig. 146). The whole frog is then placed on a

FIG. 146.—Form of Tube for insertion into the Larynx of the Frog.



It is made by drawing out a piece of tubing to the size marked *a*, heating the end and pressing it against a piece of metal, so that it assumes the shape *b*. *c* is a piece of india-rubber tubing, which must be closed, either by a ligature, as shown in the drawing, or, what is still better, by a clip, so as to prevent the escape of air from the lung.

glass plate, which is fixed with a clip to the stage of the microscope. The lung is brought under the objective, and supported, if necessary, by a cork ring fixed to the glass plate with sealing-wax. Any changes in the calibre of the pulmonary vessels are then readily observed by means of a micrometer placed in the eye-piece.

Four years ago I attempted to ascertain by this method (Fig. 147) the effect of sudden changes from heat to cold on the lungs; and I have found that, if a stream of warm moist air be first directed on the lung, and immediately afterwards a stream of cold moist air, the capillaries sometimes contract as much as one-third of their diameter under the influence of the cold.

Dr. Sharpey informs me that the lung of the toad, unlike that of the frog, does not collapse even when no obstruction is offered to the escape of air; and therefore, if toads be used, the india-rubber tube and clamp on the cannula are unnecessary.

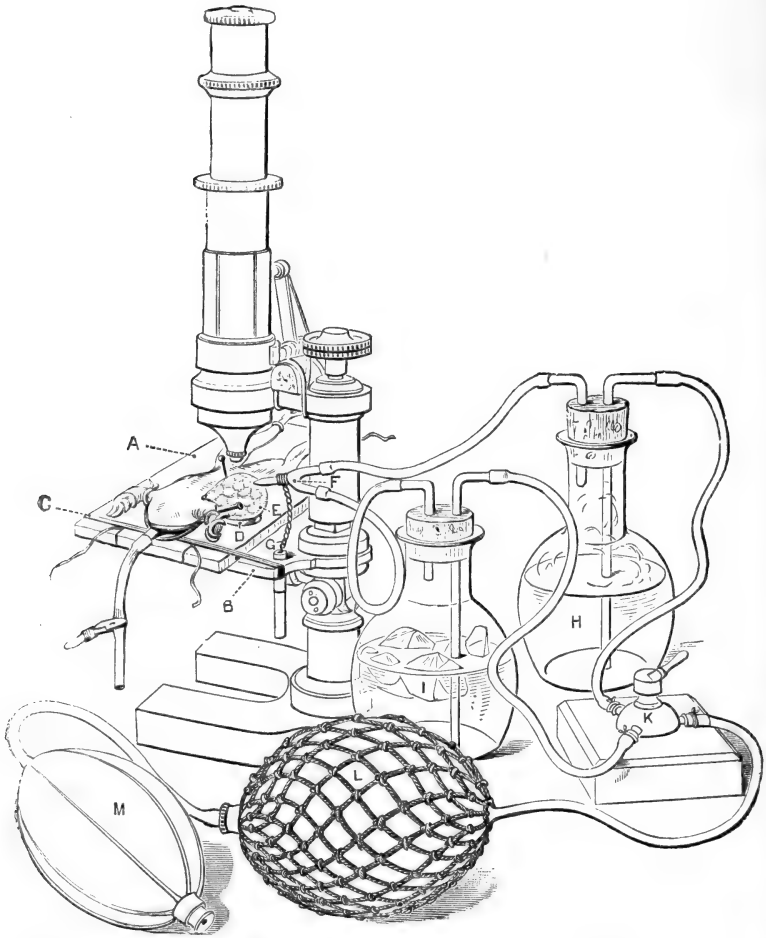


FIG. 147.—Apparatus mentioned on preceding page, and which I employed in my experiments made in 1871 for ascertaining the effect of heat and cold on the vessels of the frog's lungs. A, a piece of cork to which the frog is fastened, is laid on B, the stage of a microscope, and attached by an india-rubber strap, C. D is a small ring of cork covered with a thin circle of glass. E is the inflated frog's lung. F is a tube by which a current of air can be directed on the frog's lung. It is held in position by a piece of wire, G, which can be bent to any position. I is a flask containing ice and water. H, a flask containing hot water. K is a three-way stopcock, by which a current of air may be sent from the spray-producer, L and M, through either I or H at will, and thus cold or hot air may be applied alternately to the lung. (Reprinted from my *Text Book of Pharmacology, &c.* London: Macmillan & Co.)

APPENDIX

Artificial Circulation through Isolated Organs.—In order to study the effects of alterations in the blood, and the action of various poisons upon the walls of the vessels themselves, with entire exclusion of the nervous system, Ludwig and Mosso have kept up artificial circulation in the kidney and the liver. In removing these organs great care is taken not to wound them, and the diaphragm is removed along with the liver. In experimenting on the kidney large dogs were employed. The carotids were first opened, and blood allowed to flow until convulsions began. The artery was then closed for some time, during which the blood was defibrinated and part of it put into a flask, so as to be ready to wash out all the coagulable blood from the kidney. The carotids were now opened a second time, and as much blood as possible got from them by pressure on the abdomen, &c. As soon as the animal became insensible the abdomen was opened, the renal artery was then compressed just above its bification, so as to prevent any air getting into it, and a glass cannula was introduced into the main artery; another cannula was put into the renal vein. All the small vessels which communicate with adjacent parts were ligatured, and the kidney was then removed. Before connecting the cannula in the renal artery with the apparatus for artificial circulation, it was carefully filled by means of a fine pipette with defibrinated blood, and the utmost care employed to prevent any air bubbles from getting into the vessel. After the communication between the renal artery and the flask has been opened, it sometimes happens that blood does not flow until a considerable time has elapsed, owing, apparently, to a tetanic contraction of the vessels in the kidney.

After the blood has begun to flow it does not do so in an equable stream, as it would do through glass tubes, but its velocity is alternately greater and less, owing to periodic contractions of the walls of the renal vessels, independently of any nervous influence. If the circulation is arrested for some time and then allowed to go on, the rapidity is much greater after than before the stoppage, but it gradually falls again to normal.

Blood containing much carbonic acid and little oxygen (*erstickungsblut*), causes the vessels to contract and the stream to become slow, while blood containing much oxygen and little carbonic acid causes them to dilate. When different sorts of blood are allowed to circulate after each other through the kidney, and each successive kind contains less CO_2 than the one preceding it, the rapidity of the flow from the vein goes on increasing; or, as it might be expressed, each kind of blood in this series seems to diminish the amount of contraction of the vascular walls which the greater amount of CO_2 in the preceding kind had occasioned. The order would be this—suffocation—blood—venous—arterial—apnœic, *i.e.*, saturated with oxygen by agitation with air. This dilatation, however, was only temporary.

When nicotine was mixed with blood in the proportion of 1 to 10,000 it seemed, at first, to cause contraction of the vessels, for it produced a diminution in the flow of blood, and also in the size of the kidney; but both soon returned to the normal. One per cent. of nicotine, on the contrary, seems to cause immediate dilatation of these vessels, for it immediately causes an increase in the velocity of the current and the size of the kidney. The increased velocity is not to be entirely ascribed to contraction of the vessels, for a solution of nicotine of this strength alters the blood, and will diminish the friction in the vessels.

Atropia has a powerful action, and different doses of it produce different effects. In the proportion of 1 in 100,000 it causes diminished rapidity in the flow of blood and in the volume of the kidney, but both soon return to their normal. One in 10,000 causes diminished, followed by increased rapidity, but this soon disappears. One in 5,000 soon kills the kidney, but before doing so causes first diminution, and then acceleration of the current through it. Chloral hydrate first causes diminished and then greatly increased velocity, but it also has a very peculiar action on the vessels, increasing the rhythmical contractions in them when they are present, and causing them to appear when they were previously absent.

The shocks of an induction coil, or Faradaic currents, do not

alter the velocity of the circulation, but constant currents do. During the time they are passing, both the rapidity of the current and the size of the kidney increase, and after the irritation ceases they diminish. When the circulating blood contains a small quantity of chloral, this action is altered. At first, when the chloral has not altered the current much, it becomes slightly diminished during the irritation, and slightly increased after its removal. When the chloral has acted longer and increased the velocity of the current to five or six times its normal, no alteration is noticed during the application of the current, but a still further increase occurs after its removal.

After the kidney has been removed from the body for 24 hours, and kept in a cool place, its vessels still retain their irritability, but small doses of chloral in such a kidney only cause contraction, and larger doses of 0·3 to 0·5 per cent. are requisite to induce dilatation. The effect is not due to the action of the chloral on the blood, for it is produced when the blood is replaced by serum. One of the most extraordinary things about the action of chloral is that, in the dead kidney, instead of increasing the rapidity of the current, or leaving it unaltered, chloral greatly diminishes it—exactly the opposite to its effect on the living organ. When the blood used in the artificial circulation is saturated with carbonic acid, chloral no longer produces any effect on the vessels, so its action would seem to be abolished by this gas.

Induction of Anæsthesia.—At p. 257 I have stated that chloroform is inadmissible as a narcotic, as its administration seemed to cause dogs so much pain, but farther experience has shown me that this statement is incorrect. Chloroform can be readily administered to all animals by placing them under a glass bell-jar, along with a sponge or piece of blotting-paper, saturated with the anæsthetic. The advantage of the glass jar is that the movements of the animals can be distinctly seen, and they can be removed immediately on their becoming insensible, thus avoiding the danger to which they would be exposed by longer inhalation of air saturated with the vapour. The vapour being heavier than air sinks to the bottom of the

jar, and, when the animal falls unconscious, the air it then respires is much more heavily charged with the vapour than that which it breathed while still erect. On account of the density of chloroform vapour, anæsthesia is more quickly produced when the bell-jar has an opening at the top which can be plugged with cotton-wool saturated with chloroform, than when the sponge is laid at the bottom of the jar; as in the former case, the vapour falling down is more rapidly diffused through the air of the jar than in the latter. Instead of a bell-jar a deep milk pan may be used, the rabbit or cat being placed in it and the top covered by a towel stretched tightly over it. The chloroform is sprinkled on the towel. Anæsthesia is thus rapidly induced, but care must be taken not to allow the animal to remain too long in the vessel. For large dogs an inverted packing-case, without the lid, may be used instead of a bell-jar.

After the animals have been rendered insensible and the operation has been begun, the anæsthesia may be kept up by putting a piece of cloth round the animal's nose and pouring chloroform upon it, a drop or two at a time, as often as is necessary. In this way less chloroform is required, and there is not so much danger of killing the animal by giving it the vapour in too concentrated a form.

Instead of keeping up the anæsthesia by the continued administration of chloroform, it is often more convenient to open a vein and inject opium or chloral.

In operations on the abdominal viscera in dogs, *e.g.*, in making a gastric fistula, death sometimes occurs from shock, although the animals are completely under the influence of chloroform. For such operations ether is preferable, as it increases rather than diminishes the power of the heart. If given in the same way as chloroform, however, much time and a very large quantity of ether are required to produce anæsthesia. Professor Schiff has found,* however, that it can be readily done by pouring a quantity of ether into a bladder, and holding this tightly around the dog's muzzle, so that it respires ether vapour almost pure. As dogs do not like to be tied down, the muzzle shown at fig. 127,

* Professor Schiff, verbal communication to the author.

p. 254, should be put on, and the operator, sitting on a low stool, should put the dog's fore paws on his knee and hold them with one hand, while with the other arm passed round the dog's body he restrains its movements, and an assistant holds the bladder with ether over the dog's nose.

PHYSIOLOGICAL ACTION OF CONDURANGO.

(From *Journal of Physiology*, vol. v, pp. 17—34.)

ALL the experiments which I have performed for the purpose of ascertaining the physiological action of Condurango were made with a watery extract prepared for me by Mr. Jeffs. Dispenser to St. Bartholomew's Hospital.*

Characters of the Extract of Condurango.

One ounce of the extract was obtained from one pound of the root. It was of a dark brown, almost black colour, slightly aromatic odour, and a bitter taste. It was very soluble in water, and formed a dark brown opaque solution.

General Action of the Extract on Frogs.

Some of the experiments here detailed were made with the double purpose of ascertaining the influence of Condurango on reflex action as well as its general action, and the animals were therefore in these experiments suspended, instead of being allowed to move freely on a level surface.

Experiment I.—Five grains of the extract of Condurango were suspended in six minims of water and $\frac{7}{8}$ths of the mixture ($4\frac{3}{8}$ grains) injected under the skin of the back of a large frog, tolerably strong but not so active as most of the others. It was then covered by a glass jar. The frog remained quiet when left to itself, but moved actively when touched. No effect seemed to be produced by the Condurango for an hour afterwards.

Twenty-four hours after the frog was again examined and seemed totally unaffected. Four days afterwards it was found

* The experiments recorded in this paper were all made in the autumn of 1871.

to be somewhat languid, and five days after the injection it was dead.

Experiment II.—A strong frog was suspended by the fore legs and two grains of solid extract were introduced under the skin of the abdomen. Immediately afterwards the frog seemed somewhat more restless than before, and drew up its legs more quickly when they were touched. Its movements were performed in the same way after the injection as before it. When placed on a level surface it seemed quite unaffected by the Condurango, and continued to be so for the next ten days during which it was observed.

Experiment III.—One grain of extract mixed with a few drops of water was injected under the skin of the back of a strong frog suspended in the same way as the other. Immediately afterwards it became restless, and seemed also uneasy when touched. Otherwise it remained unaffected, and no effect of the Condurango could be observed during the next ten days.

Experiment IV.—Two grains of the extract mixed with a few drops of water were injected under the skin of the back of a frog suspended like the others. The result was the same as in Experiment III.

Experiment V.—Five grains of the extract were suspended in water and injected under the skin of the back of a strong frog. The frog was suspended by the head. It seemed somewhat restless after the injection, but no other effect could be observed. Next day it seemed in its normal condition, and on the third day also.

Experiment VI.—The same experiment as in V was repeated with a like result.

Experiment VII.—The same as in V and VI. No result was observed at first. Next day the frog seemed weak, and when laid on its back could not turn over so readily as the others. It was a smaller frog than the others. On the third day it seemed well.

These experiments show that the extract of Condurango when injected under the skin of frogs produces no effect even when such a large dose as 5 grains is administered.

The restlessness which is noted in those hung up was in all

probability due to the injection of the fluid, and not to the action of the drug, as it occurred immediately after the operation and before there had been time for much to be absorbed.

The death of one frog after the injection can hardly be attributed to the Condurango, as the animal was observed to be less active than the others previous to the injection, and death did not occur till several days afterwards.

General Action on Mammals.

The experiments on this point were made exclusively on rabbits.

Experiment VIII.—One gramme (15·4 grs.) of the extract was dissolved in 20 cub. cent. of a solution of one part NaCl in 200 of water. It was dissolved in ½ per cent. NaCl solution in preference to water, in order to avoid the irritation which water itself produces when brought in contact with the tissues of the body. Ten cubic centimetres of this solution were injected into the peritoneal cavity of the body weighing 936 grammes (2 lb. 1 oz.).

No effect whatever was observed.

Thirty-four minutes afterwards the remaining 10 cub. cent. were injected. No effect was produced. The solution had not been filtered.

In order to test the effect of the injection of saline solution itself, 10 cub. cent. were injected into the peritoneal cavity of a rabbit weighing 425 grammes (1 lb. 15 oz.).

It produced no effect.

Next day both animals were perfectly well and lively. They seemed to have passed a good deal of water during the night, but as they were both in the same cage it was impossible to say how much had been passed by each. Both animals were kept under observation for several days, but no further effect of the injection was noticed. The increased urination was probably only due to the water which had been injected.

Experiment IX.—One gramme (15·4 grs.) of extract was mixed with 10 cub. cent. of water. The solution was not filtered, and contained little particles. A cannula was placed

in the jugular vein of a rabbit weighing 1,030 grammes (2 lb. 4 oz.), and 1¼ cub. cent. of the solution were injected into it. No apparent effect was produced.

Fifteen minutes afterwards 1 cub. cent. more was injected; three minutes after the second injection the respiration was much quicker; and five minutes afterwards 1 cub. cent. more was injected.

One minute after the last injection the animal's hind legs spread out laterally, and it sank down on its fore paws.

In half a minute more it turned on its side, its head became drawn backwards on its shoulders so as to form almost a right angle with the body, and it gave one or two convulsive kicks. Its eyes then became very prominent and the cornea insensible to the touch.

Post-mortem Examination. — The body was immediately opened. When the abdominal muscles were divided the legs gave a twitch. The heart was still found pulsating, though only feebly. The right cavities were full, but the left cavities were empty

In this experiment the injection of about one-third of a gramme (5 grs.) of the extract into the jugular vein was followed by death, whereas in Experiment VIII the injection of three times this dose into the peritoneal cavity of a smaller rabbit produced no effect. As drugs are generally absorbed with great rapidity from the peritoneal cavity the difference between the results of the two experiments could hardly be due to non-absorption of the Condurango in Experiment VIII, and it was therefore in all probability due to something not connected with the action of the drug.

The hurried breathing, convulsions, and death which followed the injection of the unfiltered solution of the extract into the jugular vein, as well as the distension of the cavities on the right side of the heart and the emptiness of those on its left, seemed to indicate that the death of the rabbit in Experiment IX was due to the production of emboli in the pulmonary artery by the undissolved particles of extract.

In order to test this conclusion the following experiment was made :—

Experiment X.—One gramme (15·4 grs.) of the extract was dissolved in 20 cub. cent. of warm water and filtered. When first thrown on the filter it passed rapidly through, but in the course of a minute or two it began to pass through very slowly. As soon as it began to do this the fluid was emptied out of the first filter and thrown upon a fresh one. In this way the filtrate was obtained quickly, but might contain very fine particles which had passed through the filter and might have been removed by it afterwards.

A cannula was placed in the jugular vein of a rabbit weighing 680 grammes (1½ lb.), and 10 cub. cent. of the filtrate were slowly injected into it. During the injection the respiration became hurried, and occasionally a convulsive twitch of the limbs occurred. A few minutes afterwards 5 cub. cent. more were injected. The animal was then released. It tumbled much and seemed weak, but could move about perfectly well. Its respiration was laboured. Twenty hours afterwards it seemed weak and languid and its respiration somewhat hurried.

In this experiment nearly ¾ of a gramme were injected into the jugular vein of a rabbit weighing 680 grammes with the effect of producing hurried respiration and weakness. In Experiment IX the injection of ⅓ of a gramme was followed by the death of a rabbit weighing 1,030 grammes.

The difference between these experiments consisted in the solution of Condurango being filtered in Experiment X and *not* in Experiment IX, and we must therefore conclude that the fatal result in the latter case was due to the presence of large particles in the fluid.

The hurried breathing in Experiment X might be due to the small particles which had passed through the filter but were yet large enough to become impacted in the pulmonary capillaries.

Results of Experiments on the General Action of the Extract of Condurango.

Condurango has no poisonous action.

The extract produced no apparent effect on frogs when given in doses of ⅓ of a gramme (5 grs.), or on a rabbit in a dose of 1

gramme (15½ grs.), an amount which is equivalent to 72 grammes (2½ oz.) of the extract, or 2½ lb. of the root for a man weighing 150 lb. The convulsions which occurred in Experiment IX were in all probability due to embolism of the pulmonary artery and not to the action of the Condurango. The statement of Gianuzzi and Bufalini* that Condurango has a convulsant action like strychnia probably depends on a mistaken misinterpretation of the results of experiments like that of Experiment IX, although I cannot be certain on this point, as I have never been able to see their original paper.

It has no paralysing action, and apparently no action of any kind on voluntary muscles or motor nerves, as the movements of the animals were unaffected by its administration.

Effect of Condurango on Reflex Action.

As Condurango produces no *apparent* effect, and as Dr. Joseph Xavier Eguigusen states that "it cannot be administered many days in succession because in some persons nervous phenomena of importance supervene," it seemed possible that its action might resemble that of quinine.

The following experiments were therefore undertaken in order to ascertain whether it had, like quinine, the power of diminishing reflex action.

They were performed in the usual way, by suspending a frog by the fore-arms or head and noting by the aid of a metronome the time which elapsed before it drew its foot out of a very dilute mixture of sulphuric acid and water. Extract of Condurango was then injected under the skin, the foot again dipped in dilute acid, and the time till it was pulled out compared with that which had been noted before the injection.

To show that the mere suspension of the frog and the successive irritations applied to the feet had no effect on the time required for reflex action, a frog into which nothing was injected was suspended at the same time as the others.

* *Ricerche eseguite nel Gabinetto di Fisiologia della Universita di Siena*, pp. 71—86, abstracted in the *Centralblatt de Med. Wissenschaften*, 1873, p. 824.

Experiment XI.—Four frogs were suspended by their arms, and their feet irritated by a very dilute sulphuric acid. After each application of the acid the foot was carefully washed.

In the following account *R* stands for right foot, *L* for left foot, and the numbers under each indicate the number of seconds before the foot was drawn out of the dilute sulphuric acid.

Time.	Frog I.		Frog II.		Frog III.		Frog IV.		Remarks.
	R.	L.	R.	L.	R.	L.	R.	L.	Frog I was tested first, but on dipping its right foot into the acid, it became apparent that it was too strong. It was therefore diluted and again applied.
3h. 20′		12″	5″	15″	7″	6″	5″	5″	
,, 35′	12″	10″	12″	12″	12″	16″	6″	6″	
,, 38′	12″	10″	13″	6″	13″	20″	4″	8″	
,, 45′	13″	13″	12″	13″	13″	17″	6″	10″	
	15″	25″	11″	12″	20″	20″	8″	10″	
4h. 0′									Two grains of extract of Condurango were suspended in a few drops of ¾ per cent. NaCl solution, and injected under the skin of the back of Frog IV.
,, 3′									
,, 5′							uneasy		
,, 10′	quiet		uneasy		quiet		quiet		
,, 12′					uneasy		uneasy		On touching the feet of Frogs II, III, and IV, they drew them away much more readily than Frog I.
	26″	28″	12″	30″	18″	46″	4″	8″	Reflex action again tested by acid.
	32″	40″	10″	12″	18″	25″	6″	8″	
	46″	34″	8″	8″	11″	22″	9″	7″	

Frog I was not so lively as the others, and it will be seen from the next experiments that the diminution of reflex action which occurred in it during this experiment is not a general rule but due to an individual peculiarity.

Experiment XII.—Two frogs were suspended by the head and reflex action tested by dilute sulphuric acid (one part acid to 250 of water).

During the experiment both frogs struggled a good deal, and when a severe struggle occurred just before the acid was applied to the foot reflex action seemed to be somewhat diminished.

Time.	Frog I.		Frog. II.		Remarks.
	R.	L.	R.	L.	
1h. 33′	10″	49″	26″	42″	Acid of 1 in 300 was here used. Frog I struggled much after acid had been applied to the right foot.
	8″	14″	10″	11″	Acid of 1 in 250 here used.
	13″	14″	11″	11″	
	14″	14″	4″	7″	
2h. 57′					Five grains of extract of Condurango suspended in water was injected under the skin of the back of Frog II.
abt. 3h.	9″	11″	54″	26″	
5h. 53′	10″	8″	17″	30″	
Twenty hours afterwards	4″	10″	36″	62″	
	20″	16″	41″	35″	
	12″	?	15″	20″	Frog II very restless.

During the night they were taken down and had rested.

Experiment XIII.—Two frogs suspended, and reflex action tested with sulphuric acid (1 to 250 water).

Time.	Frog I.		Frog II.		Remarks.
	R.	L.	R.	L.	
	1″	3″	4″	6″	
	2″	3″	2″	5″	
	2″	1″	5″	6″	
2h. 58′					Five grains of the extract of Condurango suspended in a few drops of water were injected under the skin of the back of Frog II.
			Frog uneasy		
abt. 3h. 5′	2″	3″	8″	10″	Frog I remained untouched.
5h. 58′	1″	1″	5″	6″	
Twenty hours afterwards	4″	2″	5″	7″	They were taken down at night and not left suspended.
	2″	1″	11″	12″	

Experiment XIV.—Two frogs were suspended by the head, and reflex action tested by applying dilute sulphuric acid (1 part acid in 250 of water) to the feet.

Time.	Frog I.		Frog II.		Remarks.
	R.	L.	R.	L.	
2h. 26′	11″	8″	8″	5″	
,, 32′	9″	8″	11″	7″	
,, 52′	10″	6″	6″	4″	
,, 59′					Five grains extract of Condurango, suspended in a few drops of water, were injected under the skin of the back of Frog II.
					Frog I was untouched.
3h. 10′	12″	10″	9″	8″	Frog II became uneasy and restless immediately after the injection.
abt. 6h.			8″	10″	Frog I had escaped and could not be found.
Twenty hours afterwards			11″	17″	
			12″	18″	

For greater convenience in comparing the results of these experiments I subjoin the mean number of seconds required for reflex action in each of the frogs during the time they were suspended before Condurango was injected into some of them, and the number of seconds required during the time they hung after the injection had been made.

Experiment XI.

	Frog I.		Frog II.		Frog III.		Frog IV.	
	Uninjured.		had $2\frac{1}{2}$ grs. extract.		had 2 grs. extract.		had 2 grs extract.	
	R.	L.	R.	L.	R.	L.	R.	L.
In the time before injection	$12\frac{3}{4}$	14	$10\frac{3}{5}$	$11\frac{3}{5}$	13	$15\frac{4}{5}$	$5\frac{4}{5}$	$7\frac{4}{7}$
After	$34\frac{2}{3}$	34	10	$16\frac{2}{3}$	$15\frac{2}{3}$	31	$6\frac{1}{3}$	$7\frac{7}{7}$
Difference	$21\frac{11}{12}$ more	20 more	$\frac{3}{5}$ less	$5\frac{1}{15}$ more	$2\frac{2}{3}$ more	$15\frac{1}{5}$ less	$\frac{8}{15}$ more	$\frac{2}{15}$ less

Experiment XII.

	Frog I.		Frog II.	
	Uninjured.		5 grs. extract.	
	R.	L.	R.	L.
In the time before injection	$11\frac{2}{3}$	14	$8\frac{1}{3}$	$9\frac{2}{3}$
After	$10\frac{3}{4}$	$11\frac{1}{4}$	$32\frac{3}{5}$	39
Difference	$\frac{11}{12}$ less	$2\frac{3}{4}$ less	$24\frac{4}{5}$ more	$29\frac{1}{3}$ more

Experiment XIII.

	Frog I.		Frog. II.	
	Uninjured.		Got 5 grs. of the extract.	
	R.	L.	R.	L.
In the time before injection	$1\frac{2}{3}$	$2\frac{1}{2}$	$3\frac{2}{3}$	$5\frac{2}{3}$
After	$2\frac{1}{4}$	$2\frac{3}{4}$	$7\frac{1}{2}$	$8\frac{3}{4}$
Difference	$\frac{7}{12}$ more	$\frac{5}{12}$ more	$3\frac{7}{12}$ more	$3\frac{1}{12}$ more

Experiment XIV

	Frog I.		Frog II.	
	Uninjured.		Got 5 grs. of extract.	
	R.	L.	R.	L.
In the time before injection	10	8	$8\frac{1}{3}$	$5\frac{1}{3}$
			10	$10\frac{3}{4}$
			$1\frac{2}{3}$ more	$5\frac{5}{12}$ more

Difference between the number of seconds required for reflex action during the time the frogs were suspended before the injection of Condurango, and in the time after the injection.

Uninjured Frogs.

	R.	L.
Frog I, Expt. XI	$21\frac{11}{12}$ more	20 more
	In the time after injection	
Frog I, Expt. XII	$\frac{11}{19}$ less	$2\frac{3}{4}$ less
„ „ XIII	$\frac{7}{12}$ more	$\frac{5}{12}$ more

Frogs which received Condurango.

R.	L.				
$\frac{3}{5}$ less	$5\frac{1}{15}$ more	Frog II	Expt. XI	2 grs. solid extract	
$2\frac{2}{3}$ more	$15\frac{1}{5}$ more	„ III	„ „	2 grs. in water	
$\frac{3}{15}$ more	$\frac{2}{15}$ less	„ IV	„ „	2 grs.	„
$24\frac{4}{15}$ more	$29\frac{1}{3}$ more	„ II	„ XII	5 grs.	„
$3\frac{7}{12}$ more	$3\frac{1}{12}$ more	„ II	„ XIII	5 grs.	„
$1\frac{2}{3}$ more	$5\frac{5}{12}$ more	„ II	„ XIV	5 grs.	„

In only one of these experiments (Experiment XII) does any marked diminution of reflex excitability occur after the injection of Condurango. Nearly as great a diminution is to be observed in Experiment XI, Frog I, where nothing had been injected, and it is therefore probable that the exceptional diminution in Experiment XII as well as in Experiment XI, Frog I, is to be ascribed to an individual peculiarity of the frog and not to the action of the Condurango.

In most of the other experiments we find a slight diminution of reflex excitability, but it is very slight and might be due to the exhaustion produced by the struggles of the animal after the injection of the drug.

Conclusions regarding the Effect of Condurango on Reflex Action.

Unlike quinine Condurango has very little effect on reflex action. A slight diminution of reflex excitability was observed after the injection of the extract into frogs in doses of 2 or 5 grains, but the number of experiments is insufficient to show whether or not this was due to the exhaustion produced by the struggles of the frog.

Effect of Condurango on Circulation and Respiration.

Experiment XV.—A cannula was placed in the trachea of a rabbit and connected by india-rubber tubing with a T-tube, to

one limb of which was attached a stopcock, which allowed of more or less free communication with the atmosphere and the other limb of which was in connection with one of Marey's cardiographic levers which registered the respirations on a revolving cylinder. By increasing or diminishing the resistance which the stopcock opposed to the entrance of air into the tracheal cannula the amplitude of the excursions of the lever could be altered at will.

The blood-pressure was registered by a kymographion connected with a cannula in the left carotid of the rabbit. The number of cardiac pulsations was estimated from the undulations produced by them in the blood-pressure tracings.

Time.	Blood-pressure.	Pulse.	Respirations.	Remarks.
	in millimetres of mercury.	in 7½″	in 7½″	
abt. 4h. 15′	120	21	6¾	Each 6th respiration became larger than the others when the injection was made.
				5 cub. cent. of a suspension of 4 grammes extract in water was injected into the peritoneal cavity.
	120	18	6½	The respirations became deeper and the undulation in the tracing of the blood-pressure corresponding to every 6th respiration becomes very distinct, while previously it was very slight.
				This seems due to the pain of the injection and the excitement of the animal after it.
abt. 4h. 23′	120	17	6	
				Injected about 2½ cub. cent. more. The undulations in the pressure curve again became more distinct and the respirations much more forced.
4h. 32′	114	20	6½	
5h. —	108	?	7	
				Attempted to inject more solution into the peritoneum, but the tube seemed stopped up and the solution would not enter. A clot now formed in the cannula in the carotid, so it was cleaned out. In order to prevent the blood from

Time.	Blood-pressure.	Pulse.	Respirations.	Remarks.
	in millimetres of mercury.	in 7½″	in 7½″	
				passing too far into it after readjustment, the bicarbonate solution of soda was passed into it at a pressure nearly equal to that at which the blood had formerly stood.
				When the artery was again connected with the manometer it was found that the blood-pressure had fallen, and therefore some of the bicarbonate of soda in all probability passed into the artery.
5h. 21′	86			
	70	16	8	
	66			
5h. 21′ 45″				Injected 4 cub. cent. of saturated solution of extract of Condurango in ¾ per cent. solution which had been filtered while hot into the jugular vein.
5h. 22′	60	14	8½	
5h. 22′ 15″	50	12½	8	Cardiac pulsation larger.
5h. 22′ 30″	56	13	8	
5h. 23′	64		8	
5h. 24′ 30″	64	14		
5h. 30′	48	15½	9	

The animal was then killed.

Experiment XVI.—A cannula was placed in the trachea of a rabbit and connected as in the previous experiment with one of Marey's levers by a T-tube and a stopcock.

The movements of the registering lever were increased or diminished according to the greater or less resistance which the stopcock opposed to the entrance of air into the T-tube.

A second cannula was placed in the left carotid and connected with a kymographion which registered the blood-pressure. The number of cardiac pulsations was ascertained by counting the undulations which they produced in the blood-pressure.

The Condurango was injected through a cannula in the jugular vein.

	Time.	Blood-pressure.	Pulse.	Respirations.	Remarks.
		in millimetres of mercury.	in 7½″.	in 7½″	
Tracing I.		102	35	7½	
					Right vagus irritated by an interrupted current.
After irritation	7½′	46	7?	15?	Respiration trembling and imperfect. Irritation stopped after continuing for 7½″. The pulse immediately became quick and the blood-pressure rose.
	15′	122		11½?	
	22½′	107		12?	
	30′	106	30	14½	
	37½′	98	36	11½	
Tracing II.					
Some minutes after Tracing I		104		9½	5 cub. cent. of a cold saturated solution of Condurango were filtered and injected into the right jugular vein.
After injection	10½′	96	34	9½	
		96	33	9½	
Tracing III.		87			
	after beginning of tracing				
	15′	83	33	10	
	22½′	74		10	
	30′	77	30	10	
	37½′	75		9½	
	45′	75	30	9½	
	52½′	78		10	
	60′	75		10	
	1h. 7½′	75		9½	
	15′	75		9	Right vagus irritated.
	22½′	63			—The nerve was not
	30′	73	14	5	divided.
	37½′	83	12½	7?	Irritation continuing.
	45′	88	13	12?	
	52½′	93	13	15	
	2h.	95	13	14	Irritation stopped.
	7½′	122	30	13½	
	15′	124	28	11	
	22½′	113		11	

	Time.	Blood-pressure.	Pulse.	Respirations.	Remarks.
		in millimetres of mercury.	in 7½″	in 7½″	
Tracing III (*continued*).	30′	106	30	11½	
	37½′	101		10½	
	45′	99		11	
	52½′	98		11½	
Tracing IV.		93			
	7½′	94			
	15′	102	12		Right vagus irritated.
	22½′	102	10½		Irritation continuing.
	30′	102	10½		Respiration very weak. Irritation stopped.
Tracing V.	7½′	99			Both vagi divided. The pressure curve shows large undulations which do not correspond with the respiratory or pulse wave, but extend over a period nearly equal to that occupied by 2½ respirations.
	15′	103		5	
	22½′	102		4	
	30½′	101		4	
	37½′	100	34?	5	
	45′	95		4½	Peripheral extremity of the right vagus irritated.
	52½′	94	11	4½	
	1h.	98		5	Irritation stopped.
	1h. 7½′	94		4½	

The animal was now killed.

Experiment XVII.—A strong rabbit weighing 6 lb. was experimented on. The respirations, pulse, and blood-pressure were recorded as in the previous experiments.

	Time.	Blood-pressure.	Pulse.	Respirations.	Remarks.
		in millimetres of mercury.	in 7½″	in 7½″	
Tracing I.	7½′	131			
	15′	131	30	8	
	22½′	131	30	8½	
Tracing II.					Both vagi cut.
	7½′	128	34	6	
	15′	129	34	5	
	30′	128	33	5	
	37½′	128	33	5	
	45′	126		5½	
	52′	127	34½	5½	
Tracing III.	1h.	129		5½	
	7½′	128		5½	
	15′	127	33	4½	
	15 5/7′				Vagus irritated and heart stopped. Blood pressure fell during the first stoppage 38 mm. in 8/34 of a second.
	18½′	46			
	22½′	150			The electrodes were then less closely applied to the nerve, and the pressure rose.
	30′	142	34½	6	
					After the irritation ceased three respirations succeeding it were much smaller than the others.
	33′				Vagus again irritated. The blood-pressure sank 48 mm. in 9/34 of a second.
	37½′	47	2 ?	7	
	39½′	36	0		Irritation stopped.
	43½′		0	7½	
	45′	92			
	47′	186			Respiration very small.
	52½′	162		6	
	2h.	160	32½	5½	
	7½′	126			
	15′	123	36	6	
Tracing IV.	7½′	123			
	15′	122	35	5½	
	22½′	124		5½	
	30′	120	27	5½	
Tracing V.	7½′	120	28	6	

	Time.	Blood-pressure.	Pulse.	Respirations.	Remarks.
		in millimetres of mercury.	in 7½″	in 7½″	
Tracing V *(continued).*	11′				Began to inject a solution of Condurango (filtered into the jugular vein. Injected 10 c.c. containing 25 grammes of extract.
	15′	122	31	7	
	22½′	127		6	
	30′	125	31	5½	
	37½′	123	32	5½	
	45′	123		6	
	52½′	123	32½	6	
	55′				Injection finished.
	1h.	123	33½	5½	
	7½′	122		6	
	15′	119	32	5½	
	16½′				Left vagus irritated. Blood-pressure fell 38 mm. in $\frac{6}{34}$ths of a second.
	21′	61			
	1h. 22½′	99			
	27′	106	8½	6	Irritation stopped.
	30′	136			
	37½′	118		5½	

At this time peculiar curves began to appear in the blood-pressure tracing. I could not understand in the very least what their cause was at the time, but when the experiment was finished I found that a clot of blood had formed in the tracheal cannula, which would obstruct the breathing, and was in all probability the occasion of these curves. As this would complicate to a great extent the effects observed I have not noted this part of the experiment.

Results of Experiments XV, XVI, and XVII.

	Blood-pressure.	Pulse.	Respiration.	Remarks.
Expt. XV.	unaltered	slightly slower	slightly slower	Injection of 1 gramme of extract into the peritoneum.
	somewhat less	quickened to normal	quickened to normal	½ gramme more.
	less	slower	no effect	Injection into the jugular.
Expt. XVI.	less	no effect	quicker	do. do.
Expt. XVII.	unaltered	quicker	quicker	¼ gramme into jugular;—vagi cut.

These experiments show that Condurango has no action on the pressure of the blood when it is injected into the peritoneum in large doses. The diminished blood-pressure noticed in some instances might be due to the animal's strength being diminished by its position on the board and the effects of the operations. Its effect on the pulse and respiration is not constant, the injection being sometimes followed by quickening and sometimes by slowing, and moreover the results which followed its injection into the jugular might in some degree be due to the presence of fine particles in it having a mechanical effect.

The whole subject of the pulmonary circulation, the action of drugs upon it and the effect which changes in it produces upon other parts of the body, is at present very imperfectly known, and it is therefore extremely difficult or impossible to say what the effect of such fine particles as were contained in the solution of extract might be when they once enter the pulmonary vessels.

For the purpose of ascertaining whether Condurango had any effect in contracting or dilating the arterioles and capillaries, the vagus was irritated so as to stop the heart, and the rapidity with which the blood-pressure fell during the stoppage of the heart before the injection was compared with that which was found after it.

Experiment XVII. Tracing II.

Blood-pressure fell	38 mm.	in	$\frac{3}{4}$ths of a second	}	*before* injection of $\frac{1}{4}$ gramme.
„ „	48	„	$\frac{9}{3\,4}$ „ „		
„ „	24	„	$\frac{5}{3\,4}$ths in one pulse wave		
„ „	38	„	$\frac{6}{3\,4}$ths of a second	}	*after*.
„ „	18	„	$\frac{5}{3\,4}$ths in one pulse wave		

These numbers show that with the instrument employed no definite conclusion can be drawn regarding the state of contraction of the arterioles, but indicate that no extensive alteration was produced in them by the Condurango.

It may seem strange that I have not made any experiments on the effect of Condurango on tissue change as indicated by the amount of urea and salts in the urine more especially, as it

has been recommended especially in cases where a drug possessing an influence over tissue change would be likely to be serviceable. The experiments of Boeck have, however, shown that those drugs, such as iodine, morphine, and quinine, which have some effect upon tissue change, produce but very slight alterations compared with those which result from variations in food, and Toldt and Nowak have found that the amount of nitrogen varies even in the flesh of the same animal, so that it would be almost necessary to analyse the flesh eaten every day as well as rigorously to fix its amount, and this would be more than anyone could well undertake who could not devote his whole time to the work.

General Summary.

Watery extract of Condurango has no action on frogs even when injected into the dorsal lymph-sac in doses of 5 grains. On rabbits it has no poisonous action when injected into the peritoneal cavity. When a solution containing fine particles in suspension is injected into the jugular vein the animal dies with symptoms of opisthotonos. When the coarser particles are removed this does not occur although the breathing is quickened. It is not improbable that the quickening of the breathing is due to the lodgments of fine particles in the pulmonary capillaries, and that the opisthotonos which I noticed in one experiment (Exp. IX) and which has been supposed by Gianuzzi and Bufalini to be due to the direct action of Condurango on the nerve centres was really due to asphyxia caused by pulmonary embolism.

Unlike quinine Condurango has very little effect on reflex action.*

Condurango when injected into the peritoneum even in large doses has no action on the blood-pressure.

It does not exert any definite action on the arterioles nor does it paralyse the peripheral terminations of the vagus.

* Since the preceding experiments were made Mr. Pardington and I have found that the diminution in reflex excitability which Chaperon described as caused by the injection of quinine into the lymph-sac of the frog probably depends on the local irritation produced by the acid in which the quinine is dissolved.

ON THE EMPLOYMENT OF NITRITE OF AMYL IN THE COLLAPSE OF CHOLERA [WITH EXPERIMENTS UPON THE PULMONARY CIRCULATION].

(Reprinted from the *British Medical Journal*, January 13th, 1872; with references.)

In two papers which have recently appeared in this Journal,* and in the *Practitioner*,† Dr. Talfourd Jones very ably advocates the use of nitrite of amyl as a remedy in the collapsed stage of cholera. His proposal is, however, by no means a new one; for it was made by Dr. Chapman in 1866, as he mentions in a letter to this Journal,‡ and also by Dr. Gamgee about the same time. At the time that I mentioned the suggestion of the latter in a paper on the "Action of Nitrite of Amyl in Angina Pectoris," in the *Lancet* for July, 1867, I was unaware that this medicine had been already tried unsuccessfully by Drs. Hayden and Cruise of Dublin. Shortly after the publication of my paper, I obtained, through the kindness of those gentlemen, a copy of their Report of the Cholera Epidemic of 1866, as treated in the Mater Misericordiæ Hospital, Dublin; and from this§ I now extract the following notices of the action of nitrite of amyl in that disease.

"When inhaled for a few minutes, he (Dr. Richardson) showed that it is capable of so exciting the circulation, that the face becomes flushed, accompanied by a thrilling sensation. It occurred to us that, in virtue of this remarkable property, the nitrite of amyl might be useful in re-establishing the circulation in the collapse of cholera. In one case, that of a man forty-two years of age, admitted in incipient collapse, the pulse rose from

* *British Medical Journal*, September 30th, 1871, p. 378.
† *Practitioner*, October 1871, p. 213.
‡ *British Medical Journal*, October 7th, 1871, p. 426.
§ *Report of the Cholera Epidemic*, p. 56.

102 to 114, and the temperature in the axilla rose from 95$\frac{1}{5}$° to 96$\frac{3}{5}$° F., after inhalation of the nitrite of amyl for three minutes. The inhalation appeared to aggravate his thirst. In another case, that of a woman aged thirty-four, also in collapse, the pulse became perceptible after inhalation for a few minutes; and the patient seemed otherwise improved. Thirst seemed aggravated by the inhalation in this case also. A boy aged four, in collapse, inhaled the amyl for a few minutes, after which there was a slight appearance of colour in the face. The boy strenuously resisted its further administration, owing to the obstruction to free respiration which it occasioned. In several other cases the amyl was tried; but although, when inhaled for a few minutes, it usually heightened in some degree the colour of the face and surface-temperature, the difficulty of inducing patients to continue the experiment for a sufficient length of time, owing to its interference with respiration and the increased thirst which it occasioned, caused it to be abandoned."

As the results of their trial of oxygen are very interesting, I subjoin them also.

"Inhalation of oxygen by means of Dr. Richardson's apparatus was also made trial of. In one case, that of a woman in collapse, the pulse became perceptible for a few minutes. A woman aged forty-four, in collapse, inhaled oxygen for eighteen minutes. The pulse, previously all but imperceptible, increased in strength; and the temperature of the surface was slightly elevated. In a third case, that of a girl aged twenty-four, oxygen was administered on three several occasions. The temperature rose slightly after the first administration, and the patient requested that she might have it again, as it gave her relief. The oxygen, like the amyl, though of temporary advantage, was found to produce no permanent benefit, and was therefore abandoned."

Both these remedies seem to offer fair promise of success, and their use is certainly indicated by the symptoms; that of nitrite of amyl by the contracted state of the vessels which is almost certainly present in the collapse of cholera; and that of oxygen by the cyanotic appearance of the patient, and by the diminished combustion in the body, which is indicated by the small amount of carbonic acid given off from the lungs during this state. It

is, therefore, rather disheartening to find from this Report that they produced no permanent benefit; and that the use of the nitrite of amyl, from which one would have been inclined to expect still more advantage than from that of oxygen, had to be abandoned, because it increased the distress of the patient by impeding still more the already difficult respiration, and rendering more intense the tormenting thirst. It is, however, better to know that they have been tried and found unsuccessful, than to cherish a false hope in their efficacy, only to be undeceived and disappointed when we come to try them; and a careful consideration of the cause of their failure may possibly help towards a more successful plan of treatment. In order to understand why the oxygen and amyl did not fulfil the expectations which had been formed regarding them, it will be necessary to take a glance at the conditions which are found in the collapse of cholera, their probable causes, and the mode of action of the remedies employed.

The most striking symptoms in the collapse of cholera are generally the excessive purging; the peculiar nature of the stools, which are liquid and colourless, resembling rice-water in appearance; and the large amount of fluid which is evacuated from the bowels. The extreme thirst of the patient, and his urgent calls for water; the shrivelled and pinched look of the surface, and its bluish colour and coldness; the cramps in the muscles; the husky voice; and occasionally the difficult respiration, also attract immediate attention. A closer examination shows that the pulse is small, or even imperceptible; and that the proportion of carbonic acid excreted by the lungs is not more than a third of that given off in health.*

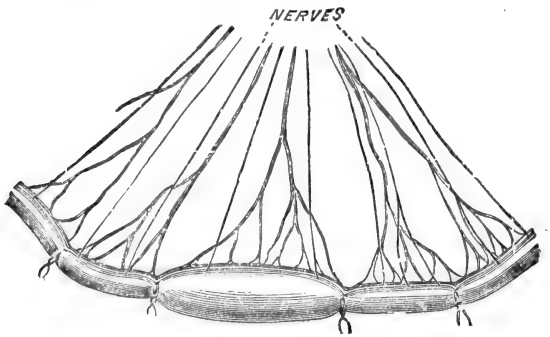
In attempting to trace each of these symptoms back to its origin, we do not deal with certainties, but only with probabilities more or less strong. We cannot say with any approach to certainty what the cholera-poison is, by which all these symptoms are occasioned; but we may assign a proximate cause to each one of them—to some with a probability almost amounting to certainty; to others, only with hesitancy and doubt.

The rice-water stools, which form so prominent and charac-

* Davy, quoted by Rayer, *Gazette Médicale*, 1832, p. 278.

teristic a symptom, have naturally attracted much attention; and numerous analyses of them have been made by Kühne,* Parkes† and others, with a view to ascertain their nature and probable origin. It has thus been found that their composition is like that of the intestinal juice, except that they contain a much larger proportion of water than it does. Under ordinary circumstances, the secretion from the mucous membrane of the intestine is never so dilute as the stools of cholera; but a very dilute juice, which is almost identical in composition with the rice-water stools,‡ is secreted by the intestine when the nerves going to it are paralysed, as in the well-known experiment of Moreau.§ This gentleman took a large dog, which had not been fed for at least twenty-four hours, and, after putting it under chloroform, made an incision through the abdominal walls, and drew out a loop of intestine. Round this he put two ligatures,

FIG. 148.—Diagram showing the effect of section of nerves on secretion from the intestine. The nerves going to the middle loop have been divided, and it is distended with the fluid secreted.



about 4 or 5 inches apart from one another, so that the piece of bowel between them was completely tied off from the rest of the intestine; he then cut all the nerves going to this

* Kühne. Paper read before the Medical Society of Amsterdam in the winter of 1868–9. Unpublished.

† Parkes, *London Journal of Medicine*, vol. i, p. 134.

‡ Kühne, *op. cit.*

§ Moreau, *Comptes Rendus*, 1858, p. 554.

part, but took care to leave all the blood-vessels uninjured. He next tied off in the same way a piece of intestine about the same length as the first on each side of it, but did not cut the nerves going to them. All the three parts were thus completely empty; they were all equally isolated from the rest of the intestine, and were all in exactly the same condition in regard to their vascular supply; but the nerves of the middle piece were cut, and therefore paralysed, while those of the pieces at each side of it were not. He then put the intestine back into the abdomen, and sewed up the wound. After four or five hours, he killed the dog, and examined the intestine. The two pieces which had been ligatured off from the rest, but whose nerves had not been cut, were found empty, just as they were when they were put into the abdomen: but the third piece, which lay between the two others, and whose nerves had all been divided, was found distended like a sausage with a fluid whose composition, as I have already said, was almost identical with that of cholera-stools. Now, in this experiment, all the nerves going to the intestine were cut, and therefore paralysed; but we do not know whether or not the same effects would have been produced if only some of them had been paralysed, and it is not improbable that it might have been so.

We have, then, in cholera, the same profuse secretion as in Moreau's experiment; and from identity of effect we may fairly infer identity of cause, and are, therefore, justified in concluding that the great outpouring of fluid into the bowel is due in both cases to paralysis of some, at least, of the nerves of the intestine. The probability that only some of the nerves, and not all of them, are paralysed in cholera, is strengthened by a consideration of the circumstances which induce a paralytic secretion of saliva in the submaxillary gland. Whenever a difficult question regarding secretion arises, we are always obliged to refer to this gland, because in it the process of secretion has been most fully investigated, and the conditions under which it takes place are best understood. When some of the nerves connected with the submaxillary gland* are paralysed by dividing them, a continuous and profuse secretion is poured out by it. When some addi-

* The fibres connecting the submaxillary ganglion and the lingual nerve.

tional nerve-fibres,* however, are divided, instead of the secretion becoming still more profuse, it becomes diminished. We do not possess sufficient knowledge regarding secretion from the intestine to be certain that it can be modified in the same way as that from the submaxillary gland; but if, as seems very probable, this analogy subsists between them, we can easily understand that, while a profuse flow of liquid into the intestine indicates a certain amount of paralysis of its nerves, a more moderate flow might be due to two opposite causes—viz., either to a less degree of paralysis or to a still greater one. When I speak of the choleraic discharges as a consequence of nervous paralysis, I refer only to the rice-water stools, and do not at all include the preliminary diarrhœa; for that may depend only on irritation of the intestinal nerves without paralysis, just as an abundant secretion of saliva may be obtained from the submaxillary gland by irritating some of the nerves connected with it,† without division or paralysis of any one of them.

In consequence of such a large amount of water being abstracted from the blood by the intestinal glands in order to form the rice-water stools, the blood itself becomes much thicker, and the proportion of solid matter it contains much greater.‡ The intense thirst during life, and the dryness of the tissues which is found after death, appear to be directly due to the loss of water from the blood.

The other symptoms have also been ascribed by some persons to the effect of the thickened blood; while others attribute them partly to this, and partly to the reflex action of the intestinal lesions on the nervous system; and yet others to the direct action of the cholera-poison itself.

As Dr. Parkes§ and Dr. George Johnson have clearly pointed out, all the other symptoms can be referred to the blood being

* The fibres connecting the ganglion and the chorda tympani. Kühne, *Lehrbuch der Physiologischen Chemie*, p. 4.

† *E.g.*, as by irritation of the chorda tympani, either directly by irritation applied to its trunk, or reflexly through the lingual by acids applied to the tongue.

‡ Herrmann, Wittstock, Dittel, Thomson, &c., quoted by Griesinger. Virchow's *Pathologie*, Bd. ii, Abt. 2, p. 334.

§ *Parkes on Cholera*, London, 1847, p. 105.

hindered from passing through the lungs. In consequence of the obstruction in front, the blood accumulates in the right side of the heart, and distends the large veins. It passes so slowly through the pulmonary vessels, that, although it is laden with carbonic acid, and is quite able to give off this gas and to take up oxygen,* the air which is expired contains but a small proportion of the carbonic acid which it would do in health.† So little blood reaches the left ventricle, that all that it can send out at each systole hardly causes a wave in the arteries. The pulse therefore becomes weak and imperceptible, not only in the radial, but in large vessels like the brachial; and the arteries, when cut across, hardly bleed at all.‡ The arterioles, and probably the capillaries, become empty; or, as some term it, the vital turgor disappears; and this empty state of the vessels, along with the drying of the tissues already alluded to, causes the face to become pinched and shrunken, the fingers shrivelled, and the skin to lose its wonted elasticity.§ From the want of any fresh blood from behind to force it on, rather than from the obstruction in front, the blood stagnates in the venous radicles, and becomes almost completely deoxygenated, giving a livid hue to the surface;‖ and when a vein is opened,

* I have not been able to find direct experiments on the amount of carbonic acid contained in the venous blood in cholera, nor on its power to give off this gas and absorb oxygen, but I infer that it contains much carbonic acid, from its extremely dark colour; and that its power of undergoing respiratory changes is not destroyed, from the fact that it becomes red on exposure to air. See *Parkes on Cholera*, p. 113.

† Rayer, *Gazette Médicale*, 1832, p. 278, and several authors quoted by him.

‡ Dieffenbach, quoted by Griesinger, Virchow's *Handbuch der Pathologie und Therapie*, Bd. ii, Abth. 2, p. 327, and by Magendie, *Gazette Médicale*, 1832, p. 253. Magendie attributes the emptiness of the arteries, and Griesinger the slow passage of blood through the lungs, to weakness of the heart; but it seems much more probable that they are due to obstruction of the pulmonary circulation, as Parkes has shown that the heart sometimes continues to beat with considerable vigour during collapse, and the *second* sound of the heart becomes inaudible while the first can still be heard. Now the first sound is caused almost entirely by the contraction of the muscular walls of the heart (Ludwig and Dogiel, *Ludwig's Arbeiten*, 1869, p. 78), and it disappears *first* in cases of weakness of the organ, as in fever; but the second sound is caused by the closure of the sigmoid valves.

§ Niemeyer, *Practice of Medicine*; translation. London, 1871, vol. ii, p. 637.

‖ Griesinger, *op. cit.*, p. 328.

and the thick blood which distended it is emptied out, no more will flow. From the blood, which in health acts as the diffuser of heat to the extremities, and the equaliser of temperature in the body, being thus pent up in its interior, and no longer circulating through the skin or lungs, and becoming itself cooled as it warms them, the surface and the expired air both become cold, while a thermometer in the rectum may show a temperature higher than any observed even in the most intense fever.*

All the symptoms are thus easily and satisfactorily explained by the hypothesis of Parkes and Johnson, that the circulation is obstructed in the lungs; and even cases which at first sight might seem to militate against it, on closer examination serve, I think, only to confirm it. Such cases are those observed by Mackinnon,† where, after a check had been put to the vomiting and purging, the voice, breathing, and warmth of the skin became natural; the face had none of the peculiar character of the disease; the patients walked about and called for food, saying that they felt well; but their pulse was imperceptible, and in one or two days they died of coma. In these cases, it is true, the imperceptible nature of the pulse might be partly due to feeble action of the heart; but it seems not improbable that it was owing in great measure to persistent obstruction in the pulmonary circulation. It would appear almost impossible for men to live in such a condition; but Sir James Paget has shown‡ that persons may have their pulmonary circulation obstructed to an enormous extent, and yet hardly present a symptom of anything wrong, so long as the systemic vessels contract in unison with the pulmonary ones, and do not allow any more blood to pass through them in a given time than is able to flow through the obstructed arteries in the lungs during a similar period.

While the hypothesis of obstruction to the pulmonary circulation readily explains the symptoms in collapse, it is not easy to ascertain how this obstruction is occasioned, and several

* Güterbock, *Virch. Arch.*, vol. xxxviii, p. 30.
† Reynolds' *System of Medicine*, vol. i, p. 163.
‡ *Medico-Chirurgical Transactions*, 1845, p. 359.

causes might be assigned to it, and much might be said in favour of each of them. It might be due only to the thickened condition of the blood, which hindered it from passing through the pulmonary capillaries, although they were not contracted beyond their normal calibre, or the thickened blood itself may act as an irritant to them and cause them to contract. It is very probable that the thickened state of the blood is one cause, and by no means an unimportant one, of the retarded flow of the blood; but it appears also likely that contraction of the pulmonary capillaries is present in addition, and also that it does not depend on the condition of the blood, for, as Niemeyer and others have pointed out, the symptoms of collapse may disappear so quickly that it can hardly be supposed that time enough has elapsed to allow of the absorption of sufficient fluid to restore to the blood its normal amount of water.*

The blood in cholera has the colour of bilberry juice, and this might be supposed to indicate changes in it which would cause it to act as an irritant to the pulmonary vessels, and cause them to contract independently of any change in the amount of water it contained. This, however, can hardly be the case, as Krukenberg† has found this condition continue for weeks. This peculiar colour of the blood is probably due to some of it having become so completely deoxidised in the capillaries, that the hæmoglobin has passed out of the corpuscles into the plasma, and this view is confirmed by the dark red colour which the serum sometimes presents (*Parkes on Cholera*, p. 124). When blood has undergone deoxidation to such an extent that this occurrence takes place, it ceases to become red when exposed to air, but it nevertheless takes up oxygen and gives off carbonic acid in the usual way. This fact explains the statement made by Rayer, that blood in cholera does not become red when exposed to air; and the observation of Searle (*Searle on Cholera*, p. 62), that the blood drawn from the arteries in cholera is often dark coloured.

Besides the causes already mentioned, there are two others to which the contraction of the pulmonary vessels might readily be

* Niemeyer, *Symptomatische Behandlung der Cholera*, p. 14.

† Niemeyer, *op. cit.*, p. 13.

attributed; viz., reflex action from the intestines, and the direct action of the cholera poison, whatever that may be, on the vessels themselves. The occurrence of symptoms almost exactly resembling those of cholera-collapse in cases of perforation of the intestines, or of intense gastro-intestinal irritation by arsenical poisoning, would seem to favour the first view. On the other hand, the fact that there is no great lesion of the intestinal tube in cholera during life—the denudation of epithelium, on which Niemeyer laid much stress, being chiefly, if not entirely, a post-mortem phenomenon—as well as the occurrence of symptoms of collapse after intense malaria poisoning, as mentioned by Goodeve,* is in favour of the second view, and between them I cannot pretend to decide. Whatever be the cause of the contraction of the pulmonary vessels in cholera, we may, I think, assume that the obstruction to the circulation is due partly to it and partly to the thickened condition of the blood.

The indications for treatment in cholera-collapse, then, are—1. To remove the paralysis of the intestinal nerves. 2. To dilute the thickened blood. 3. To dilate the pulmonary capillaries. 4. To oxygenate the blood passing through them.

How the paralysis is to be removed I for one do not know. That the copious secretion from the bowel eliminates the poison from the blood is, I think, doubtful, and any benefit that may result from it in this way is, I believe, more than counteracted by the alteration which it produces in the condition of the blood. That many cases in which the discharge has been profuse have ended in recovery, and that others in which it has been scanty have terminated fatally, may simply show (if the analogy between the secretion in the intestine and the submaxillary gland be correct) that the nervous paralysis has been more complete in the latter than in the former case, while the accumulation of fluid in the intestine without purging, in the so-called cholera sicca, would indicate paralysis not merely of the secreting, but also of the motor, nerves of the bowel. What I have just said, however, is no argument against the use of castor-oil in the treatment of collapse. When we know so little of the pathology of the disease, or of the action of the

* Reynolds' *System of Medicine*, vol. i, p. 17.

remedies we employ, our treatment must be empirical, and successful results must be our warrant for employing one method rather than another. The second indication, viz., to dilute the blood, is generally fulfilled by giving ice and ice-cold water by the stomach. The wonderful effects which immediately follow injection of salt solutions into the veins show what an important share the loss of water from the blood has in the production of collapse. The ultimate benefit resulting from this mode of treatment has hitherto not been commensurate with the immediate relief to the symptoms which it affords, but this should only lead us to try whether we cannot, by employing different proportions of salts, or using medicines in addition to them, find some method of rendering the immediate effects of the injection permanent.

For the purpose of relaxing the contraction of the pulmonary capillaries, nitrite of amyl would seem, as Dr. Jones says, to be the very remedy. In this Journal for October 14th (1871), Dr. George Johnson observes that nitrite of amyl may not act on the pulmonary capillaries as it does on the systemic ones. I have, however, tried it on animals, and find that it does. When given to rabbits, it causes the systemic capillaries to dilate enormously, the blood flows rapidly into the veins, and the pressure on the arterial system sinks in a corresponding degree. If it did not produce dilatation of the pulmonary as well as of the systemic capillaries, the blood which pours rapidly into the veins could not pass with equal rapidity out of them through the pulmonary vessels, and it would consequently accumulate in, and distend the right side of the heart. In order to see whether this was the case or not, I thoroughly narcotised a rabbit with chloral, put a cannula into its trachea, and kept up artificial respiration. I then opened the thorax, and, after carefully noting the appearance of the heart, passed the vapour of nitrite of amyl, mixed with air, into the lungs. When this was done, the cardiac pulsations became a little quicker, but not the slightest distension of the right side of the heart or of the jugular vein could be observed. I repeated the experiment several times with the same result. There is no reason to suppose that the chloral with which the animal was narcotised altered in any way the

action of the nitrite of amyl on the pulmonary vessels, for I have found that other vapours, as well as certain poisons, injected into the jugular vein, cause accumulation of blood in the right side of the heart after the animal has been completely narcotised. I have also observed that this accumulation of blood, which I believe to be due to contraction of the pulmonary vessels caused by the poison or vapour, has disappeared in the case of one poison at least,* after the injection of another drug which had been previously found to be an antidote to it in other respects. With the prosecution of these experiments I am at present engaged; and I take this opportunity of thanking Dr. Burdon Sanderson for his kindness in allowing me the use of his laboratory and apparatus.

Dr. Johnson also says that, even if nitrite of amyl were shown to possess the power of relaxing the pulmonary capillaries in health, it might not do so in disease, or at any rate not to the same extent. Some observations which I have made on its action in angina pectoris lend probability to this idea. In the paper already referred to, which I published in 1867, I mentioned my belief that angina was due to spasmodic contraction of the capillaries; and in a paper in the *Clinical Society's Transactions* for 1870, I gave copies of one or two of the sphygmographic tracings which led me to form this belief. In it I noticed that occasionally after the anginal pain had disappeared from every other part of the cardiac region, it remained persistently at a spot two inches inside the right nipple. This local persistence of the pain was accompanied by a peculiar condition of the pulse, which seemed to me to indicate that the pulmonary capillaries had not become relaxed to the same extent as the systemic ones. As sphygmographic tracings, especially when taken with an instrument like the one I used, in which the pressure exerted by the spring could not be estimated, sometimes admit of different interpretations, I append copies of some of them. I may mention, however, that these tracings are strictly comparable with each other, although they

* Muscarin, the active principle of amanita muscaria, discovered by Professor Schmiedeberg, seems to produce contraction of the pulmonary capillaries, and this is at once removed by atropia.

may not be so with tracings taken at a different time; for while these were being taken, the instrument remained attached to the arm of the patient, and the pressure of the spring which rested upon the artery remained unaltered. In the normal condition of the patient, his pulse presented the characters seen in Fig. 149.

Fig. 149.

During the attack of angina, the capillaries become contracted, and the arterial tension rose as seen in Fig. 150. When

Fig. 150.

the nitrite was inhaled, the pulse in most cases quickly regained its normal character; but when the pain remained in the region of the right nipple after the inhalation, the arterial tension fell as usual, indicating dilatation of the systemic capillaries, but the volume of the pulse remained small, as shown in Fig. 151. The

Fig. 151.

small volume is, I think, due to the pulmonary capillaries not dilating, or only imperfectly, under the action of the nitrite; and if I discontinued the inhalation before the volume of the

pulse became normal, as well as its character, I felt nearly certain that the spasmodic pain would speedily return with all its former intensity.

The observation of Drs. Hayden and Cruise that the pulse became perceptible in their patients after the inhalation, seems to show, however, that the nitrite did relax the pulmonary vessels during the collapse, and allowed a fuller stream of blood to pass into the left ventricle, and thence to the body. Why, then, did it increase the difficulty of breathing? One would have thought that by allowing more blood to flow through the lungs, it would at least have alleviated this symptom, if it did not remove it altogether. The experiments of Dr. Arthur Gamgee at once enable us to answer this question. In a paper in the *Royal Society's Transactions*,* he showed that nitrite of amyl combines with hæmoglobin, the oxygen-carrier of the blood, and prevents it from giving off oxygen after it has taken it up. When the blood is exposed to the vapour of the drug as it passes through the lungs, the oxygen becomes locked up in it, and cannot be given off to the tissues for their use, so that however much oxygen the blood in the arteries may contain, it acts very much as if it were venous. In consequence of this, I have found that when the vapour of the nitrite is passed into the lungs of rabbits, they are seized with suffocative convulsions. The greater part of the blood which passed through the lungs having been acted on by the vapour, it affects the brain just as it would have done if the trachea had been closed, and no air allowed to come near it during its passage through the pulmonary vessels, and therefore convulsions occur as soon as it reaches the brain. Professor H. C. Wood, of Philadelphia,† who has lately written a valuable paper on the action of the nitrite, found no convulsions after injecting it subcutaneously. By giving it in this way, the blood was not acted on during its passage through the lungs, and asphyxia was prevented. This, I think, shows that if nitrite of amyl is to be used at all as a remedy in cholera, it must be given internally or by subcutaneous injection, and not by inhalation. This mode of admini-

* *Philosophical Transactions*, 1868, p. 589.

† *American Journal of Medical Sciences*, July, 1871.

stration seems to me to be indicated also in spasmodic asthma, when the arterialisation of the blood is also impaired. In angina pectoris it will act when given internally, but a larger dose is required than when inhaled; and it remains to be seen whether it can be given in cholera in sufficient doses to relax the capillaries without, at the same time, injuriously impairing the respiratory changes in the blood and tissues.

ON THE USE OF ARTIFICIAL RESPIRATION AND TRANSFUSION AS A MEANS OF PRESERVING LIFE.

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In his admirable *Lessons in Physiology*, Huxley says that "the brain, the lungs, and the heart, have been fancifully termed the tripod of life; but, in ultimate analysis, life has but two legs to stand upon, the lungs and the heart, for death through the brain is always the effect of the secondary action of the injury to that organ upon the lungs or the heart." This conclusion is founded on the experiments of many observers, among the most interesting of which are those of the Abbé Fontana and Legallois.* The former found that the brain was not necessary to life; for he could cut off the heads of rabbits and guinea-pigs, and yet keep their bodies alive by connecting a pair of bellows with the trachea, and keeping up artificial respiration. As he himself says, an animal can live quite well without a head: artificial respiration and the circulation of the humours in the various parts are quite sufficient. The headless trunks evidenced their vitality by displaying sensitiveness to impressions, and executing what the Abbé considered to be voluntary movements, but which we would now term simply reflex actions. Legallois went even further than Fontana; for, not content with cutting off the rabbit's head, he tied the aorta and vena cava, and then cut away the whole of the posterior part of the body, leaving only the headless thorax. This fragment of the body, mutilated as it was, still remained alive; the fore paws showed sensibility when irritated, and the thorax twisted when the skin over it was pinched, or more distinctly still if

* Fontana, *Traité sur le vénin de la vipère, sur les poisons Américains, sur le laurier cerise, et sur quelques autres poisons végétaux*, Florence, 1781, tome 1, page 317; Legallois, *Expériences sur le principe de la vie*, Paris, 1830, tome 1, p 130.

the lower end of the spinal cord were touched. Even when the experiment was carried farther, and the whole of the cervical with part of the dorsal spinal cord was destroyed, evidences of life could be observed in the posterior two-thirds of the thorax. These experiments demonstrated beyond doubt that, if the lungs and heart could perform their functions with any other fragment of the body as they do with the thorax, it might be kept alive. As Legallois himself says, "if the place of the heart could be supplied by a sort of injection, and if at the same time a supply of arterial blood, either natural or artificial, if such a formation of blood were possible, could be obtained, life might be maintained indefinitely in any fragment of the body whatever; and consequently a severed head might be kept alive and in possession of all the faculties pertaining to the brain. Not only could life be maintained in this manner, either in the head or in any other isolated part of an animal's body, but it might be recalled after its entire extinction; it might even be recalled to the whole body, and a veritable resurrection, in every sense of the word, might be effected." Perhaps it may seem that the success of his experiments rendered Legallois too sanguine; but his anticipations have already in great part been fulfilled, and a severed head has been partially at least restored to life by M. Brown-Séquard. His experiment, as related by M. Vulpian,* consisted in cutting off the head of a dog immediately after it had been killed, and connecting the carotid and vertebral arteries with an apparatus for artificial circulation. After eight or ten minutes had elapsed, and all signs of excitability in the medulla oblongata and the rest of the encephalon had been gone for several minutes, defibrinated and arterialised blood was injected simultaneously into the vertebrals and carotids. In a few seconds, signs of life began to appear, and the muscles of the eyes, in fine, acted in such a way as seemed to prove that the cerebral functions were re-established.

Hardly less astonishing than Brown-Séquard's experiments are those of Preyer,† who has succeeded in restoring their vital properties to a frog's muscles after they have been brought into

* *Revue de Cours Scientifiques*, 1864-65, tome 2, p. 217.

† *Centralblatt für die Med. Wissenschaft.*, 1864, p. 769.

the state of rigor mortis by dipping them into warm water. This condition depends on coagulation of the muscular substance or myosin; and circulation of blood alone through muscles in this state is of no use, for it cannot soften the hardened myosin. Something more is therefore necessary. Coagulated myosin is soluble in a solution of common salt; but, though a muscle dipped in such a solution may lose its hardness and again become soft and pliable, it does not regain its vitality. By combining the two methods, however, the difficulty has been overcome; and, by first dipping the rigid muscle in a solution of salt, and then allowing blood to stream through it, Preyer has had the satisfaction of seeing frogs jump and swim by the aid of muscles which had been almost as hard and stiff as a piece of wood only a short while before.

Nor are nerves and muscles the only parts which can be kept alive by artificial circulation. Glands also preserve their vitality; and Ludwig and his pupils,* by maintaining artificial circulation in them, have succeeded in making livers secrete bile, and lungs excrete carbonic acid, for hours after they have been excised from the body.

More examples might be given, but the above are sufficient to show the power of artificial circulation to keep any part of the body alive after the death of the rest. The converse of this is also true; and, if blood be prevented from circulating through any part of the body, that part will die, although the rest may remain healthy. So generally known is this, that no one ever thinks of tying a bandage so tightly as to stop the circulation, and leaving it thus, as he well knows that death, or, as we usually term it, mortification of the ligatured part would be the result. It is easy for any one, indeed, to observe for himself the destructive effects of want of blood and the vivifying power of renewed circulation, by repeating the experiment devised by the Danish physiologist Steno, or Stenson, more than 200 years ago. A gentle steady pressure with the thumb on the abdominal aorta of a rabbit, so as to stop the circulation for a couple of minutes, is all that is necessary to produce complete paralysis of the hind legs of the animal; and a few minutes

* Ludwig's *Arbeiten*, 1868, p. 113, and 1870, p. 38.

more of renewed circulation suffice to restore them to their normal state. It might almost seem that the tripod of life had been reduced to one leg—viz., a circulating apparatus or heart; but this is not the case, for it must be remembered that the blood which circulates must be oxygenated or arterial; and if, as in the case of artificial circulation, there be no lungs to effect its oxygenation, their place must be supplied by agitation with air, though this is at best but a poor substitute. Indeed, it is rather because the blood carries oxygen than nutriment to the tissues that arrest of circulation causes them to die so speedily; for Kronecker found* that, after he had exhausted the muscles of a frog by constant irritation, he could restore their contractility by passing through their vessels a solution of permanganate of potash, which, like the blood, could supply them with oxygen, although it could yield them no nourishment.

The body is made up of a number of parts; and if the heart stop, the circulation ceases; or, if the lungs fail to perform their duty, so that the circulating blood is no longer arterialised, all the parts, and therefore the whole body, will die. But the parts will not all die at the same time; and this is a point of great practical importance. The brain and spinal cord generally die first, and the heart may be pulsating as regularly as ever when all respiratory movements have ceased, and no irritation, however intense, will evoke the faintest indication of consciousness, or excite the slightest reflex action. The muscles retain their irritability still longer than the heart, and they continue to possess their power of contraction, and the lungs their ability to oxygenate the blood, even after the cardiac pulsations have entirely ceased. Here, then, we come to the third leg of the tripod of life—viz., the brain—for want of which the other two cannot stand. The whole body, in fact, may be, and often is, alive, with the exception of the nervous centres. The heart is alive, the lungs are alive, but the brain is dead, and, without it, the respiratory muscles will not work. The want of oxygen weakens the heart; it gradually stops, and then the other parts of the body die, each in its turn. But, if the respiration can only be kept up artificially, the heart will go on

* Ludwig's *Arbeiten*, 1872, p. 182.

beating; the circulation of arterial blood through the brain may gradually restore its power; the rhythmical movements of natural respiration will again begin, and the life of the animal once more be securely established. This is no mere fanciful dream, but sober fact, as the successful efforts of the Humane Society to resuscitate persons apparently dead abundantly prove. It has, moreover, been lately demonstrated in a striking manner in some experiments of Schiff.* These were made for the purpose of ascertaining what the use of artificial respiration would be in concussion or compression of the brain, or in cases of apoplexy where a clot has formed in the medulla oblongata, and, by pressing upon that part of it which presides over the innervation of the muscles of respiration, has put a stop to these movements. In order to imitate the effect of an apoplectic extravasation, Schiff anæsthetised a dog with ether, and, after exposing the medulla oblongata, destroyed a considerable part of it with a scalpel or sound, though he always left one lateral column at least intact. Immediately after the injury the respiration ceased, the tongue became swollen and livid, convulsions occurred, and the animal appeared to be dying. The heart became weaker and weaker; but, when it had almost ceased to beat, artificial respiration was begun. Very shortly the pulsations regained their normal strength, and the death-like lividity of the tongue gave place to the rosy hue of health. After respiration had been kept up for a few hours it was discontinued, and then, if the injury to the medulla had not been too great, spontaneous respiratory movements commenced, but they were still feeble. They became much stronger if artificial respiration were again renewed for half an hour longer—strong enough, indeed, to keep the animal alive without any artificial assistance. It is true that, when the lesion had destroyed the one side of the medulla, only one-half of the thorax took part in the respiratory movements; but this was in many cases quite sufficient for the wants of the animal. In the only case in which Schiff attempted to keep the animal alive permanently he was perfectly successful. The beneficial effects of artificial respiration were equally encouraging when natural respiration

* *La Nazione*, 1872, No. 102.

was arrested by compression of the brain through the injection of tepid water under high pressure into the cranial cavity. From these experiments it is evident that we may hope for the best results from the use of artificial respiration in some of those cases of apoplexy where an extravasation almost instantly arrests the respiratory movements, either directly by destroying a part of the medulla, or indirectly by causing compression of the brain. It may be thought that there is a considerable difference between the compression produced by the injection of tepid water and that which is due to an extravasation of blood, inasmuch as the water will be rapidly absorbed, while the blood will not. To a great extent this is true, and we can hardly expect very much good from artificial respiration in cases of apoplexy where the clot is large and the affection of the respiration is gradual. In those cases, however, where a small extravasation only has taken place in or near the medulla, the respiratory movements are abolished, just as in Schiff's experiments, by what may be termed the shock, although the medulla could carry on respiration well enough if time were given it to recover from the immediate effects of the injury. The employment of artificial respiration for a few hours would give the time required.

In another class of cases—that of poisoning by woorara, hydrocyanic acid, &c.—artificial respiration is invaluable. In his *Travels** Waterton tells a melancholy story of a poor Indian who, when shooting at a monkey sitting in a tree straight above him, was wounded near the elbow by his own arrow as it fell down. He immediately became convinced that it was all over with him. "I shall never," said he to his companion in a faltering voice, and looking at his bow as he said it, "I shall never bend this bow again." Having said this, he took off the little bamboo poison-box which hung across his shoulder, and putting it, together with his bow and arrows, on the ground, he laid himself down beside them, bade his companion farewell, and never spoke again.

It is not true, as some persons formerly supposed, that the minutest quantity of woorara in the blood is sufficient to cause

* *Travels in South America*, 1825, p. 71.

death. It is a very powerful poison, certainly; but there is a limit to its virulence; and, if there be too little of it in the blood, it will have no action. On this account it is not usually poisonous when swallowed, for it is excreted by the kidneys as quickly as it is absorbed from the stomach, and so there is never enough in the blood at any one time to produce any effect whatever on the body. The result is very different, however, when the kidneys are prevented from acting, by ligatures applied to the ureters. Then the poison, which is gradually absorbed from the stomach, goes on accumulating in the blood, and by-and-by, when it has reached the necessary amount, it produces exactly the same effects as if it had been injected directly into the veins. When the poison is applied to a wound, it is usually absorbed more quickly than the kidneys can excrete it, and so poisoning occurs. But, if a ligature be applied above the wound so as nearly to stop the circulation, the absorption of the poison may be hindered so much that it is not taken up from the wound any faster than the kidneys can excrete it. Thus the whole of it may be got rid of, without its ever being able to produce any toxic effects whatever. If the circulation be allowed to go on at all in the wounded part, it is rather difficult to regulate it exactly enough to ensure that too much poison shall not be absorbed at once. It is, therefore, better to apply the ligature so tightly as to stop the circulation altogether, and only remove it occasionally for a few seconds at a time. In this way it is easy to control the absorption of the poison by removing the ligature with more or less frequency, and leaving it off for a longer or shorter period, as seems advisable. But it is not by regulating the absorption of woorara only that we are able to prevent its toxic action. Even when a large quantity is circulating in the blood, and the animal seems perfectly dead, recovery is still possible.

The woorara, curare, or ticunas poison—for it has all these names and several more—has little or no action on either the brain or the muscles; but, as Bernard has shown, it paralyses the motor nerves; and so the rhythmical nervous impulses which the medulla usually sends to the muscles of respiration cannot be transmitted, and breathing ceases. Many years before

Bernard's experiments, however, Sir Benjamin Brodie* observed that, in animals apparently killed by this poison, the heart continued to beat for a long time; and the idea occurred to him that, if he could keep up respiration for a sufficient length of time, the poison would be eliminated, and the animal completely restored. His first attempts were unsuccessful, but after a little while he succeeded completely; and since then his experiment has been so frequently repeated, that no physiologist can doubt that the complete restoration of an animal poisoned in this way is merely a matter of time, unless the dose has been so overwhelmingly great as to paralyse the heart. I have myself twice restored to life rabbits which a dose of woorara had apparently completely killed, by keeping up artificial respiration in the one case for one, and in the other for four hours; and in foreign laboratories I have seen them partially restored, and only rendered motionless by repeated doses of woorara, oftener than I can well recollect. Hydrocyanic acid is a much more dangerous poison than woorara; for it seems not only to arrest respiration by paralysing the brain, spinal cord, nerves and muscles, but also to stop the circulation by destroying the power of the heart. The heart, however, is not so soon affected as the respiratory organs; and Brodie succeeded in restoring animals poisoned by small doses of it given in the form of oil of almonds.

The poison of the cobra di capello resembles prussic acid rather than woorara in the universality of its action; for some experiments which I made about a year ago in the laboratory of Dr. Burdon Sanderson seem to show that it paralyses the spinal cord, the motor nerves and the muscles themselves. The heart also, as Dr. Fayrer and I have found, seems to be paralysed if the dose be very large, as it may be also by an excessive dose of woorara; but it almost always continues to beat for a long time after respiration has ceased. To this fact I have drawn particular attention in my appendix to Dr. Fayrer's admirable work on the *Thanatophidia of India*. The same thing was observed by Fontana (*op. cit.*, tom. i, p. 80) in poisoning by the bite of the viper, and by Weir Mitchell in poisoning by the

* *Phil. Trans.*, 1812.

rattlesnake. Weir Mitchell* found that the heart might be kept pulsating for a long time by means of artificial respiration; but his results do not seem to have been so encouraging as to lead him to propose it as a means of saving life. Dr. Fayrer and I have been more fortunate, and on one occasion we have succeeded in keeping the heart of a rabbit beating for eight hours after the animal was apparently dead. Nor had the heart ceased to pulsate even then; but the hour was late, the room was cold, the assistant was no doubt tired, and the experiment was consequently given up. Although respiration had been continued for a much longer time than is usually necessary with woorara, the animal gave no signs of returning sensibility. This seems to indicate a difference between the poisons. On the probable cause of this, I shall have something to say in a later part of this paper.

The service which artificial respiration renders in cases where breathing has ceased in consequence of asphyxia, whether due to drowning, strangling, or poisoning by carbonic acid in brewer's vats or close rooms, is so generally recognised, that it is unnecessary to say anything about it here. Its use in poisoning by strychnia is not so well known, and, so far as I am aware, has only been tested upon animals. Before I proceed to speak of this, it may be well to say a few words in explanation of the term apnœa, which I shall have to use, as it is employed by physiologists in a different sense from that which is attached to it by many physicians. On the meaning of dyspnœa, both physicians and physiologists are agreed; and both apply it to the violent respiratory efforts which occur when the blood is imperfectly aërated. Apnœa, however, is not unfrequently used by physicians in the sense of extreme dyspnœa, where there is excessive difficulty of respiration. Physiologists apply it to a very different condition—viz., that in which the blood is so excessively aërated that there is no need for breathing at all. This will be much better understood by the reader if he will try a simple experiment on himself. Let him note how many seconds he can hold his breath, and he will find that he can only do so for a very short time. Let him then quickly take

* *Researches on the Venom of the Rattlesnake*, 1861, p. 81.

several deep breaths, and repeat the experiment. He will now notice that for several seconds more than on the first trial he does not feel any inclination to breathe at all. This is the state of apnœa as understood by physiologists. A few years ago, Rosenthal and Leube* discovered that, when rabbits were kept in this condition by means of artificial respiration, a fatal dose of strychnia might be injected subcutaneously without producing any effect. When the respiration was discontinued, and the animal was allowed to pass from the state of apnœa, convulsions came on even after the respiration had been kept up for as much as three hours. If it were continued for three and a half or four hours, however, the strychnia seemed to have been destroyed or excreted, and respiration might be discontinued without the occurrence of any convulsion whatever. That the lives of the animals had really been saved by artificial respiration was shown by the fact that they died when a similar dose of strychnia was given to them some time afterwards, and respiration was not used. A year afterwards, another of Rosenthal's pupils—Uspensky—showed† that strychnia was not the only poison the action of which could be prevented by artificial respiration. The convulsive action of brucia, thebaia, and caffeïne was abolished in an exactly similar manner; but no influence could be observed upon that of picrotoxin and nicotia.

The examples already given are sufficient to prove that life may often be preserved by means of artificial respiration alone, both in injury and in poisoning. If a man be found lying insensible in a close room, poisoned by the fumes of a charcoal fire, he can generally be restored by respiration if his heart be still beating. But this is not always the case; for the charcoal-fumes contain carbonic oxide, which unites with the colouring matter of the blood, and prevents it from taking up oxygen; so that it may pass time after time through the lungs, and yet remain venous. It is true, that after a while the carbonic oxide will be expelled from the blood, which then will become capable of taking up oxygen as usual; but the heart may stop, and all hope of recovery be lost before this can be effected, if the

* Reichert and Du Bois Reymond's *Archiv.*, 1867, p 629.

† *Op. cit.*, 1868, p. 522.

blood have been much changed by the deadly gas. In such cases, the only hope lies in removing the poisoned blood, and replacing it by healthy.

This does not by any means always succeed; but occasionally the recovery from impending death is almost miraculous, as in a case where it was employed by Dr. Hueter (*Berlin. Klin. Wochensch.*, 1870, p. 341). The patient, who was a strong young man, was living in a hotel, and one night had a fire lighted in the stove of his room. Next morning he was found perfectly unconscious, his iris and cornea quite insensible, and his pulse small and rapid. His respiration was weak and intermitting. Just as everthing was ready, and transfusion of blood was begun, it failed altogether. Notwithstanding this, fresh blood was allowed to stream into the patient's radial artery; the poisoned blood was drawn from a vein, and respiration was kept up artificially. Gradually the pulse became stronger, spontaneous respiratory movements again began, and the cornea became sensitive. In about five hours consciousness returned, and in a few days health was completely restored. Excepting the veritable resurrection of which Legallois speaks, what can be more wonderful than the recovery from impending death just related? And, if the joint use of artificial respiration and transfusion is so successful in one case of poisoning, there seems to be no reason why it should not be so in all. In strychnia-poisoning, for instance, where the quantity absorbed has been too great, and death is impending, notwithstanding the use either of chloroform or of artificial respiration, part of the poison might be removed by abstracting some of the blood in which it was circulating, and fresh blood supplied. If convulsions were occurring constantly, transfusion would be nearly impossible, but they might be stopped either by much chloroform or by woorara. I have already mentioned that woorara is excreted rather quickly by the kidneys; and, consequently, artificial respiration for a few hours is usually sufficient to restore animals which have been poisoned by it.

Let us suppose it, however, to be slowly excreted. Many hours, or even days might then elapse before the whole of it could be got rid of; and the maintenance of artificial respiration

for such a length of time might be impossible. In such a case as this, the obvious plan of treatment would be, of course, to remove the poison along with the blood in which it was circulating, instead of waiting for its slow removal by the emunctories.

Now, it appears to me that this is the case in poisoning by the bites of snakes, and this the treatment which must be adopted. We must combine artificial respiration with transfusion. The experiments of Dr. Fayrer show that the poison of the cobra is circulating in the blood of an animal which has been bitten by it; for this blood will kill another animal when injected into it. From those of Fontana, it would seem that the poison of the viper is eliminated from the body; for pigeons did not die if a ligature were placed on the bitten limb, above the place where the wound had been inflicted, and removed after some time. Fontana thought that the poison had been destroyed in the limb, but was evidently puzzled about it, for some of his other experiments had shown him that mixing it with blood did not destroy its virulence. He imagined that he had completely stopped the circulation in the injured limb; but it is more probable that he had only partially done so, and that the poison was thus slowly absorbed from the limb, and, being excreted equally quickly, did the creature no harm. If this explanation of his experiments be not correct, it is difficult to understand why poisoning did not occur when the ligature was removed, as Waterton found to be the case in some similar experiments which he had tried with woorara. So long as the ligature was tight, the woorara remained confined to the limb; but as soon as the circulation was allowed to go on, the poison was absorbed, and the animal died. This may seem to be in direct contradiction to what I have already said regarding the probable comparative slowness of the excretion of snake-poison to that of woorara; but it must be observed that Fontana waited a much longer time before he untied the ligatures than Waterton did, and would thus allow a much larger proportion of the poison to be excreted. It must be noted also that the poison with which he experimented was that of the viper and not of the cobra, and there may be considerable differences in the facility

with which they are excreted. It is, however, possible that I am mistaken in supposing that cobra-poison is more slowly excreted than woorara, as the facts on which I base the supposition are simply that the poison of the cobra, introduced into the stomach, seems to produce death more readily than woorara would do, and that animals poisoned by it may be kept alive for a longer time by artificial respiration without ultimately recovering. The poison of the viper, on the other hand, according to Fontana, may be swallowed, in moderate quantity at least, with impunity, though it also occasionally kills when taken in this manner, as woorara likewise does when the quantity is great and the stomach empty, so that absorption is rapid.

Enough has now been said to show the possible use of transfusion, combined with artificial respiration, not only in poisoning by carbonic oxide, but by strychnia and other poisons. Its employment in collapse from hæmorrhage requires no remarks at present. But, in order to make such a method serviceable, it must be easily performed, and a supply of blood easily got. Now, I believe that a very simple apparatus indeed will serve the purpose of transfusing defibrinated blood. But how is a sufficient supply to be got? for it is evident that a considerable quantity may be required. The requisite quantity of human blood in most cases can hardly be obtained; but it has been experimentally shown that the blood of lambs and calves may be transfused into the blood-vessels of man without doing him any harm.

Two hundred years ago, an objection was raised to this method of proceeding by Laury (*Revue des Deux Mondes*, January, 1870, p. 393), who said that, as the blood of a calf or of any other animal whatever is composed of several different particles fitted to nourish the different parts of the body, what is to become of the particles which were destined to produce horns? And, if the blood of a calf be transfused into the veins of a man, as the disposition and habits usually accord with the temperament, will the blood of the calf not give the man the stupidity and brutal inclinations of this animal? Here we almost seem to have Darwin's theory of pangenesis; and, if

this theory be true, are not Laury's objections well founded? As far as man is concerned, it may be difficult to give a positive answer either in the affirmative or the negative; but the experiments which Mr. Galton has made on rabbits, for the express purpose of testing Darwin's theory, show that in these animals transfusion has no effect either on the animals themselves or on their progeny. We may therefore, I think, safely conclude that the risk of injuring a man's character, or that of his descendants, by transfusion of an animal's blood, is not for an instant to be weighed in the balance against the chance of saving his life in those cases where alone the operation would be performed.

VERANDERTE WIRKUNG ZWEIER ARZNEIMITTEL, WENN SIE GLEICHZEITIG IN DEN ORGANISMUS EINGEFÜHRT WERDEN.

(From the *Centralblatt der medicenischen Wissenschaften*, September 27, 1873, p. 689.)

Die ausgezeichneten Untersuchungen von Crum Brown und Fraser haben dargethan, dass ein Alcaloid, welches vor seiner Einführung in den thierischen Organismus eine Verbindung mit einem anderen Körper eingegangen ist, eine veränderte Wirkung äussert. So weit mir bekannt, ist bis jetzt von einer ähnlichen Modification, hervorgebracht durch die vereinigte Wirkung zweier Arzneimittel innerhalb des Organismus, Nichts veröffentlicht worden.

Ich habe eine solche in letzter Zeit an salpetrigsaurem Amyloxyd und Strychnin beobachtet. Diese 2 Arzneimittel bringen, wenn sie gleichzeitig wirken, Lähmung der motorischen Nerven hervor. Das betreffende Experiment wird in folgender Weise ausgeführt. Ein Frosch, in dessen Rückenlymphsack Strychninlösung injicirt worden, wird, sobald Tetanus eingetreten, in ein mit Dämpfen des salpetersauren Amyloxyds gefülltes Gefäss gebracht. In dasselbe Gefäss wird ein gesunder Frosch als Vergleichsthier eingeführt. Beide Frösche verbleiben daselbst, bis sie bewegungslos sind. Wenn hierauf der Nv. ischiadicus blosgelegt und gereizt wird, so treten in dem nur durch salpetrigsaures Amyloxyd vergifteten Frosche heftige Contractionen der Extremität ein, während in dem anderen Frosche dies nicht der Fall ist, obgleich seine Muskeln auf directe Reize sich contrahiren. Ein ähnliches Resultat wird beobachtet, wenn vor der Vergiftung mit Strychnin und salpetrigsaurem Amyloxyd die Circulation der Extremität durch eine oberhalb des Kniegelenks angebrachte Ligatur, mit Ausschluss des Nv. ischiadicus, aufgehoben wird.

Obgleich nach Paralyse der motorischen Nerven die Muskeln

ihre Reizbarkeit beibehalten, so waren sie dennoch sehr rasch todtenstarr, sowohl nach der gleichzeitigen Anwendung beider Arzneimittel, als auch, wenn salpetrigsaures Amyloxyd allein angewendet wurde. Salpetrigsaures Amyloxyd sowie andere salpetrigsaure Verbindungen sind deshalb als Muskelgifte zu betrachten. Es ist nicht leicht zu entscheiden, wie viel von der Paralyse der directen Wirkung auf das Ende der motorischeo Nerven und wie viel der Abnahme an Irritabilität der Muskelsubstanz zuzuschreiben ist. Ich hoffe binnen Kurzem in der Lage zu sein, meine Experimente über die Wirkung des Strychnins in Verbindung mit anderen Körpern sowie über die Wirkung der salpetrigsauren Verbindungen zu veröffentlichen.

ON THE APPARENT PRODUCTION OF A NEW EFFECT BY THE JOINT ACTION OF DRUGS WITHIN THE ANIMAL ORGANISM.

(From the *Journal of Anatomy and Physiology*, November, 1873, vol. viii, p. 94.)

THE admirable researches of Crum Brown and Fraser have demonstrated that the physiological action of several alkaloids may be completly altered by their union with such bodies as iodide of methyl. The compounds thus produced sometimes act on organs which do not appear to be affected by either of the components separately, the ends of the motor nerves for example being paralysed by iodide-of-methyl-strychnia, though neither iodide of methyl alone, nor strychnia alone, seems to have much influence over them. Although chemical action outside the body alters in this way the action of alkaloids, I am not aware that any instance has been noticed in which a similar modification appears to be produced by the joint action of two drugs after their introduction into the animal organism. I have lately observed an example of this sort in the case of strychnia and nitrite of amyl. The experiments which I made on this subject were performed in several ways, but I will only describe the two most important. In the first series of experiments a solution of strychnia was injected into the dorsal lymph sac of a frog, and as soon as tetanus came on the animal was put into a vessel filled with the vapour of nitrite of amyl. A second healthy frog was also introduced along with it for the purpose of comparison. They were left in the vessel till both were motionless, when they were removed and the sciatic nerves of both were exposed. On irritating these nerves by the application of a Faradic current, vigorous contractions occurred in the limbs of the frog poisoned by nitrite of amyl alone, but those of the animal poisoned by strychnia and nitrite of amyl together remained motionless. The skin

was then removed from the legs of both and the muscles irritated by the application of the current directly to them. In many instances, those of the frog poisoned by the nitrite and the strychnia together contracted nearly as strongly and readily as those poisoned by the nitrite alone. It is therefore evident that their failure to contract when the nerves were stimulated must have been due to paralysis of the nerves themselves, just as it is in poisoning by woorara. The second series of experiments was made by ligaturing the artery supplying one leg of a frog before injecting strychnia into the lymph sac. The poison was thus carried by the blood to every part of the body except the leg whose artery had been tied. The animal was then placed in a vessel filled with the vapour of nitrite of amyl as before, and after motion had ceased the sciatic nerves were exposed and irritated. It was then found that the muscles of the ligatured leg which had been exposed to the nitrite of amyl, but preserved from the strychnia, contracted vigorously when the corresponding sciatic was irritated, while those of the other leg did not respond at all. When the skin was stripped off, however, and the muscles irritated directly, in many instances no great difference could be noted between their irritability.

The muscles of frogs which had been poisoned either with strychnia and nitrite of amyl, or with nitrite of amyl alone, passed more quickly than usual into a state of rigor mortis; and I therefore regard nitrite of amyl as a muscular poison. It is not improbable that the apparent paralysis of the motor nerves may be partly due to diminution of the irritability of the muscle itself, but the results of direct stimulation show that this is not sufficient to explain it entirely, and we must therefore believe that the nerves themselves are also paralysed. Besides nitrite of amyl, I have tried the nitrites of sodium, ethyl, butyl and capryl; but my researches on these are not yet completed. They seem, however, to show that the nitrites are muscular poisons, but their actions differ according to the bases which they contain.

ON THE PATHOLOGY AND TREATMENT OF SHOCK AND SYNCOPE.

(Address read before the Abernethian Society, St. Bartholomew's Hospital. Reprinted from the *Practitioner*, vol. xi, p. 246, Oct. 1873.)

THE assemblage of phenomena which we designate by the term "shock" is so much more frequently met with in surgical than in medical practice that it may almost seem that in writing a paper on this subject I have left the proper domain of the physician, and trespassed on that which the surgeon claims as his own. We shall hereafter see, however, that shock may occur in the course of diseases for which the physician alone is called into consultation, and it is intimately connected with fainting or syncope, a condition which is usually treated of in medical rather than in surgical text-books. So closely, indeed, are syncope and shock connected that they were considered by the celebrated surgeon, Travers,* to differ in degree rather than in kind, and we shall find it convenient to take a glance at the conditions which we find in syncope, before we proceed to examine those of shock.

I shall divide this paper into three parts. First, the injuries or impressions on the nervous system which occasion syncope and shock, and the symptoms which are observed in these conditions; Secondly, the causes of each symptom; and Thirdly, the remedies used and their mode of action. To put them shortly, these three heads are: 1. *The symptoms and causes;* 2. *The pathology;* and 3. *The treatment of shock and syncope.*

As I have already said, it will be convenient to consider the symptoms of syncope before those of shock. Having had little surgical experience myself, I shall quote very freely from the works of others; and the first case I shall give is one taken, not from a scientific work, but from the pages of a popular religious periodical. I cannot even vouch for the historical

* *Treatise on Constitutional Irritation*, 1826, p. 466.

truth of the narrative, and yet I choose this case because we have records of numerous other ones which resemble it so much in one or more particulars, that we can hardly doubt the substantial accuracy of the description; and owing to the peculiar circumstances under which the events are said to have taken place, we find in this one instance all the phenomena which we would otherwise have to seek for, some in one case, some in another.

During the reign of Charles or James the Second, one of the Scottish Covenanters, named John Bruce, concealed himself from the dragoons who were in search of him at some little distance from his cottage, and his little daughter Alice was accustomed daily to visit him with a supply of provisions. One day, while on this errand, she was unhappily discovered and seized by the dragoons, who at once guessed her purpose from the food she was carrying, and declared that unless she informed them of the place of her father's concealment they would torture her with thumb-screws. She refused, and the instruments were accordingly applied. Scarcely, however, had a few turns of the screw been made, when her face became deadly pale, and she fell back insensible. The screw was at once undone, water from a neighbouring rivulet was dashed in her face, and after a deep sigh or two the paleness disappeared and consciousness returned. Again the dragoons demanded her secret, adding the threat that they would not let her off so easily this time. Again she refused, and the dragoons, irritated by her obstinacy, by a few rapid turns of the screw nearly crushed her thumbs between the jaws of the instrument. A second time the deadly pallor overspread her face, and unconsciousness relieved her pain. This did not suit the purpose of the dragoons, and they again sought to restore her as before. But this time all their efforts were unavailing; the heart had ceased to beat, and the poor child was dead.

Here we have a typical instance, first of fainting, then of death by syncope, following the infliction of intense pain alone, without any injury whatever to the vital organs. Sometimes death may occur from an impression on the nervous system without even pain being felt, as in a case recorded by Sir Astley

Cooper in his lectures on surgery.* "A healthy labourer belonging to the India House was attempting to lift a heavy weight, when another labourer came up and said, 'Stand on one side; let an abler man try.' At the same time he gave the former a slight blow on the region of the stomach, when the poor fellow immediately dropped down and expired. On examination of his body there was not any mark of violence discovered." This may be regarded as a typical instance of instant death from shock, but cases like it are comparatively rare. Usually the injury is succeeded by a period of depression of all the vital functions, and this may either end in death, pass into a state of excitement, or gradually disappear and give place at once to health without any intervening excitement.

The symptoms ordinarily observed in shock are well illustrated by a case which Professor Fischer has described in a clinical lecture on this subject.† From this I have made the following extracts:—"The patient, a strong and perfectly healthy young man, was struck in the abdomen by the pole of a carriage drawn by runaway horses. No serious injury was done to any of the internal organs, at least we have not been able after a careful examination to find any trace of one. Nevertheless, the grave symptoms and the alarming look which he still presents made their appearance immediately after the accident. He lies as we see perfectly quiet, and pays no attention whatever to anything going on around him. His countenance is sunk and peculiarly elongated, his forehead is wrinkled, and his nostrils dilated. His weary, lustreless eyes are deeply sunk in their sockets, half-covered by his drooping eyelids, and surrounded, by broad, dark rings. The pupils are dilated, and react slowly to the light. He stares purposelessly and apathetically, straight before him. His skin and such parts of the mucous membranes as are visible are pale as marble, and his hands and lips have a bluish tinge. Large drops of sweat hang on his forehead and eyebrows. His whole body feels cold to the hand, and a diminution in temperature is readily detected by the thermometer, which indicates a degree and a half in the axilla,

* *Lectures on Surgery, from notes by Tyrrell*, 1824, vol. i, p. 10.

† Volkmann's *Sammlung Klinischer Vorträge*, No. 10.

and a degree centigrade in the rectum, below the normal. Sensibility is much blunted over the whole body, and only when a very painful impression is made on the patient does he fretfully pull a wry face and make a languid defensive movement. He does not move a single limb spontaneously, but after being repeatedly and urgently requested, he shows that he can still execute limited and brief movements with his extremities. If the limbs are lifted and then let go, they immediately fall as if dead. The sphincters remain closed in our patient, at least passage of urine and fæces has not been noticed since he came into the hospital. When drawn off with the catheter, the urine is found to be scanty and dense, but free from any traces of sugar or albumen. The pulse is almost imperceptible, irregular, unequal, and very rapid. The arteries are small, and the tension very low While the patient was being brought to the hospital the pulse became quite imperceptible, and the cardiac sounds very irregular and intermittent. The patient is perfectly conscious: he replies very slowly and only when repeatedly and importunately questioned, but his answers are quite to the point. You heard how he gave the details of the accident reluctantly and imperfectly, but in the main correctly Only while he was being brought to the hospital did he refuse to answer at all. His voice is hoarse and weak, but his articulation is good. On being repeatedly questioned the patient complains of cold, faintness, formication and deadness of the extremities. When he shuts his eyes he becomes sick and giddy. His senses are perfectly acute. His respiration appears to be irregular, and abnormally long, deep and sighing inspirations alternate with very superficial ones, which are scarcely visible or audible. While being brought to the hospital he vomited several times, and nausea and hiccup still remain. Anyone who knew the patient, or had seen him shortly before the accident, could hardly recognise him now. His appearance, cold skin, and hoarse voice immediately recall the appearance of a cholera patient to the memory of the attentive observer; the characteristic dejections are alone wanting to make the resemblance complete."

But cases of shock do not always present these appearances. If we call the form just described the torpid one, we can readily

distinguish from it another erethismic form which Travers terms "prostration with excitement."* The countenances of patients suffering from it are distorted, and express a nameless anxiety and excruciating agony. They toss wildly about, groan and scream, and complain of a fearful oppression and want of breath, oppressive presentiments of death, and a feeling of total annihilation. No encouragement is of any use; they lament and behave themselves like madmen. The consciousness of these sleepless and restless patients is unclouded, but seems to be completely engaged by the frightful anguish. On this account they answer no questions, but only sigh and moan. They murmur to themselves, and pay no attention to what is going on around them. Such parts of the mucous membranes as are visible are pale, but the countenance, on the contrary, is slightly flushed, and the forehead hot; the eyes are sunk, but have a peculiar lustre, and the pupils are contracted. The skin of the extremities is generally cool and insensible, but not to the same degree as in the torpid form of shock seen in the case of the patient already described. Occasionally no coldness is perceptible. Vomiting of quantities of mucus and painful retching are constant and very obstinate symptoms of this form of shock. Burning thirst is present, and liquids are greedily swallowed, but no sooner are they down than they are again rejected. Every movement is made hastily and accompanied by a remarkable trembling. Occasionally all the limbs shiver as in a rigor, and the patient has no power to control the movement. A wounded officer in this condition repeatedly requested me, says Professor Fischer, not to consider it as a sign that he was afraid. Convulsive movements, and fibrillary twitchings of the muscles, and especially of those in the face, are observable. The respiration is frequent and superficial, the pulse small, and cannot be counted.

Both these forms of shock may occur independently, but there is a certain connection between them. Patients recovering from the torpid form may come gradually to present the symptoms of the erethismic, and *vice versâ*, when the condition becomes worse, the torpid may be developed from the

* Travers, *op. cit.*, p. 407.

erethismic form. The latter is then to be regarded sometimes as an independent condition, and sometimes as a second stage of the torpid form.

Both forms of shock sometimes terminate in death, while at other times, according to Mr. Travers,* instead of the continuance and fatal increase of the symptoms of prostration, they may gradually give place to a partial and defective reaction, protracting life but scarcely improving the prospect of restoration, which remains doubtful for several days in succession; or, on the contrary, an efficient and healthy degree of reaction may be quickly established consequent upon symptoms threatening the most unfavourable issue. "Again and again," he continues, "I have left the bedsides of patients brought into the hospital pulseless, and apparently moribund without any external injury, having suffered falls or blows so serious as to have induced the symptoms of prostration to an alarming extent, and have found them on the succeeding day, to my great surprise, restored to the tone and tranquillity, comparatively speaking, of health. Reaction has in these cases been spontaneous, or nearly so, although gradual enough to occupy a period of many hours." "Now, had such persons suffered topical injuries of a severe though reparable description, it is to my mind more than probable that reaction would have failed altogether; but had it, by favour of circumstances, been established, it is at least equally probable that it would have taken the form of excitement. In other cases days have elapsed before a perfect reaction and complete relief have been obtained."

Having said so much regarding the symptoms of shock, let us shortly run over its causes. The cases already related show us that it readily follows a blow on the abdomen, sometimes even when the blow is by no means severe. Injury to the genitals is another important cause of shock. Hardly anyone finishes his school days without receiving a blow on the testicles, either at cricket or during the struggles at football, and ever afterwards he bears vividly in mind the dreadful depression, weakness and sickness which instantly overpowered

* Travers, *op. cit.*, p. 409.

him. The same thing takes place in operations, and Mr. Erichsen* has observed that at the moment of division of the spermatic cord in castration the pulse sinks, even though the patient has been fully anæsthetised. Still more striking are the effects occasionally observed on the passage of a catheter or bougie. They are thus described by Sir Astley Cooper:† "A person has a bougie passed into his urethra for the first time; the urethra is irritated by it; he says, I feel faint,' becomes sick, looks pale, and, without care, he drops at your feet. His pulse has nearly ceased, and his body is covered with a cold perspiration. You place him on a sofa with his head a little lower than his body, and as soon as the blood freely enters the brain all his functions are restored. Thus, by irritating the urethra the stomach is influenced, the actions of the head and heart are suspended, and the powers of the mind vanish."

Injuries to bones have a peculiar power to induce shock. It is, perhaps, more frequently observed as a consequence of the crushing of bones in railway accidents than of any other cause whatever. It may be said that in such cases all the textures of the limb, skin, fascia, muscles, vessels and nerves are injured as much as the bones, but two cases of Pirogoff's‡ seem to show that it is to injury of the latter rather than of the former structures that the effect is to be attributed.

In two amputations of the thigh which he performed, before the introduction of chloroform, death occurred on the operating table. One case was for severe traumatic injury, the other for chronic disease of the knee-joint, which had greatly weakened the patient. In both cases the pain and loss of blood during the operation were only a little greater than usual, yet in both, immediately after the bone had been sawn through, the face became pale, the eyes staring, the pupils dilated, a peculiar rigidity of the body occurred and death immediately took place.

Extensive burns frequently cause shock in a marked degree, and such, says Mr. Travers,§ is the effect of the transient bodily

* *Science and Art of Surgery*, 4th edit., p. 6.

† *Lectures on Surgery, from notes by Tyrrell*, 1824, vol. i, p. 9.

‡ Quoted by Fischer, *op. cit.*, p. 10.

§ Travers, *op. cit.*, p. 74.

pain experienced in the extraction of a tooth, or the extirpation of a wart or corn, as in some persons to produce syncope, retching, or convulsions. Nor must the effect of mental emotion be left out of account, as this is sometimes sufficient of itself to cause death without any injury to the body whatever. Many years ago the janitor of King's College, Aberdeen, had rendered himself in some way obnoxious to the students, and they determined to punish him. They accordingly prepared a block and axe, which they conveyed to a lonely place, and having dressed themselves in black, some of them prepared to act as judges, and sent others of their company to bring him before them. When he saw the preparations which had been made he at first affected to treat the whole thing as a joke, but was solemnly assured by the students that they meant it in real earnest. They proceeded to try him, found him guilty, and told him to prepare for immediate death, for they were going to behead him then and there. The trembling janitor looked all round in the vain hope of seeing some indication that nothing was really meant, but stern looks everywhere met him, and one of the students proceeded to blindfold him. The poor man was made to kneel before the block, the executioner's axe was raised, but instead of the sharp edge a wet towel was brought smartly down on the back of the culprit's neck. This was all the students meant to do, and thinking that they had now frightened the janitor sufficiently, they undid the bandage which covered his eyes. To their astonishment and horror they found that he was dead.

Another case is related by Mr. Travers,* who saw a man suffering from strangulated hernia expire suddenly on the table during the steps preliminary to the operation which, from the state of the symptoms and of the bowel as ascertained by examination after death, might be said to afford the fairest prospect of relief.

The cases of shock of which we have so far spoken are perhaps more likely to come under the notice of the surgeon than of the physician. The state of shock, or collapse as it is more frequently called in medical practice, occurs when the

* Travers, *op. cit.*, p. 23.

abdominal viscera are injured from within, just as when they receive a blow from without. Thus the intense irritation which corrosive poisons, such as sulphuric and other mineral acids, or large doses of arsenic, occasion in the stomach, produces, in addition to local pain, coldness and pallor of the surface, sighing respiration and weak or imperceptible pulse. The same thing occurs when perforation takes place in the stomach or intestines, and their contents escape into the peritoneal cavity. The occurrence of shock after parturition, especially in cases of twins, is probably partly due to nervous influence and partly to the removal of pressure from the abdominal vessels by the loss of such a large portion of the abdominal contents, which must almost unavoidably occasion more or less relaxation of the vessels.

To recapitulate shortly what we have said under this head, the *symptoms* of shock are: pallor and coldness of the skin, weak pulse, oppressed and sighing respiration, dilated pupils and sickness.

The *causes* of shock are: painful impressions—more especially extensive burns—injuries to bones, and, above all, injuries to the abdominal viscera and genitals.

We have now to consider our second head, viz.: *The pathology of shock; or, the causes of each symptom.* I ought properly to take up every one and trace it back to its cause, but I shall not attempt to do this, because it would occupy too much time, and I am not sure I could at present succeed in the attempt. I shall, therefore, be content to glance at a few of the principal symptoms only.

And first:—Why should the pulse be small and weak and the tension in the artery low, so that a slight pressure with the finger is sufficient to compress its walls and completely arrest its pulsations? The smallness of the pulse wave under such conditions at once informs us that only a little blood is sent into the arteries at each contraction of the heart. This may be owing to the heart acting so feebly and imperfectly that it only sends out a small portion of the blood with which its cavity was filled, or it may be that it is doing its duty perfectly but has no blood to send out. It would be very hard to say which

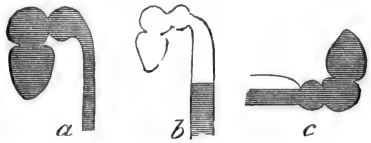
of these two causes is the true one, or whether they do not both share in the production of shock, if we had not experiments on the lower animals to give us some clue to the true solution. Several years ago Professor Goltz, now of Strassburg, found that on striking the abdomen of a frog several times the heart stopped altogether.* After a short pause it again went on, but instead of becoming completely full during each diastole, and sending a large volume of blood into the arteries at each systole, it remained pale and empty; no blood at all, or hardly any, flowed into it during the diastole, and consequently it could not send any into the vessels when it did contract, and it might just as well have remained motionless. On looking for the blood that ought to have been supplying the heart, he found that it was stagnating in the vessels of the abdomen, and especially in the veins. The intestinal vessels are so capacious that when they are fully dilated they can hold all the blood in the body. Normally, however, they are kept in a state of partial contraction by the influence of the vaso-motor nerves which supply them. It used to be supposed that these nerves only went to the arteries, and that these alone were capable of contraction and relaxation, but Goltz found that the veins also were supplied by vaso-motor nerves, and that they too could contract and dilate, though to a less extent than the arteries. Whenever the power of the vaso-motor nerves was destroyed, both arteries and veins dilated and held so much blood that there was not sufficient left to keep up the circulation in the rest of the body. If the frog was held in the upright position no blood at all reached the heart, but if it was laid horizontally a little blood trickled into the heart, and the circulation was thus kept up, though very weakly.

Here, then, we have in the frog the same effects produced by a blow on the abdomen as in the case of the young man who was struck by the carriage pole, with this difference, that in the man we could only feel the weakness of the pulse, while in the frog we can see why it is weak. Professor Fischer says that the best and shortest definition of shock which has yet been given is that of Mr. Savory:—"Shock is the paralysing influ-

* *Virchow's Archiv*, vol. xxvi, 1863, p. 11, and vol. xxix, 1864, p. 394.

ence of a sudden and violent injury to nerves over the activity of the heart." The experiments of Goltz show that this definition is perfectly correct, but you must not forget that there are the two factors in shock as seen in the frog. First, the stoppage

FIG. 152.—Diagram to illustrate the Effects of the Horizontal and Vertical Positions on the Circulation of the Frog in Shock.



a. Normal circulation in the upright position. *b*. Circulation after dilatation of the veins has been produced by a blow on the intestines. The blood does not reach the heart, and it beats empty, so that the circulation stops. *c* shows the circulation in a horizontal position after the veins have been dilated, as in *b*. The veins are still dilated, but the blood reaches the heart, and the circulation is carried on. Fig. *c* is perhaps too diagrammatic, as it appears to show an empty space in the veins. In reality the veins, being very thin-walled, collapse. Fig. *b* is open to the same objection, but if we suppose ourselves to be looking at the vein from the front instead of in section, *b* represents almost exactly what I have seen myself in repeating Goltz's experiment. This diagram was not in the original paper, but is taken from my *Text-Book of Pharmacology*, &c.

of the heart; and second, dilatation of the vessels. *These are quite distinct, and I have frequently observed that blows of moderate severity will produce in some frogs stoppage of the heart without dilatation of the vessels, in others vascular dilatation without arrest of the cardiac pulsations, although severe blows generally produce both.**

The pallor of the surface and the coldness of the skin are the next symptoms which engage our attention, and what we have just learned regarding the circulation will render their explanation easy. The rosy flush of health is due simply to the red colour of the blood shining through the skin as it courses through the capillaries, and whenever the circulation is stopped, either by the vessels contracting as after exposure to cold, or by the blood stagnating in the abdomen as in shock, pallor overspreads the surface. The warmth of the external parts of the body is due to the warm blood from the interior, which heats

* Results of a series of unpublished experiments.—T. L. B.

them in the same way that rooms are warmed by hot-water pipes, and whenever the circulation ceases there is nothing to prevent the surface of the body being cooled down to the temperature of the surrounding medium, and such, in fact, does take place. The lividity or blueness which is occasionally observed is due to the blood in the capillaries becoming dark and venous as it flows sluggishly through them, or even stagnates in them altogether when the circulation is very weak. I shall at present say nothing about the respiration or sickness, but pass on to consider the insensibility which we find in syncope though not in shock, and which distinguishes the former from the latter.

The functions of the brain, on whose failure insensibility depends, require for their performance a constant supply of blood, and when this is cut off they at once cease. A year or two ago Dr. Waller proposed to produce temporary anæsthesia for short operations by compressing both carotids, or, in fact, garotting the patient; and I have been informed by my friend Mr. Image, of Bury St. Edmunds, that in Baron Larrey's Hôpital du gros Caillou, in Paris, it was the usual custom, before the introduction of chloroform, to lay a patient on his back and then to lift him up very suddenly to the standing posture, whenever they wished to induce fainting for the purpose of relaxing muscles in cases of dislocation. The vessels of the patient were carrying on the circulation all right while he was in the horizontal position, but they had not time to adapt themselves to the altered conditions when the man was placed upright, and so the blood ran to the depending parts of the body, and the brain was left without it.

But why should a fainting fit, which, apparently, is more severe than shock, inasmuch as the brain also has ceased to act, and the patient is thus rendered more deathlike, be quickly recovered from, while shock lasts for many hours? This is a question difficult to answer, inasmuch as the necessary data fail, and we are forced to fall back on hypothesis. In attempting to answer it we must remember that it is not really the heart's action which keeps up the circulation directly. It is the pressure of the blood inside the arteries forcing it on through

them, and, as Goltz's experiment shows, the heart may be pulsating and yet the circulation be at a standstill. Now, the arterial tension may be lessened (1) by the heart stopping, or (2) sending little blood into the arteries at each beat, or (3) by the arterioles dilating so as to let the blood easily out from the arteries into the veins, where it may stagnate and be useless. Another point we must remember is that it is the circulation in the brain which is the important factor in producing insensibility. In the patient who was suddenly lifted on his feet the circulation in the rest of the body was going on perfectly well; it only failed in the brain.

Now, it is very easy to bring down the blood-pressure very much by stopping the heart for a few instants, and it may take a little while before it rises to its normal condition. A second way is to dilate the arterioles, and if the arterioles be dilated at the same time that the heart is stopped, the pressure will fall with great rapidity, and, when the heart again begins to beat, it will take a much longer time to raise the pressure sufficiently to carry on the circulation than it would otherwise do. Now, when a painful impression is made on a sensory nerve, it is not unfrequently carried up to the medulla oblongata, where it is transferred to the vagus nerve, which, as you know, has the power of stopping the heart, and by setting this nerve into action arrests the cardiac pulsations. If the arterioles should happen to be dilated, as they almost always are in a warm room, the pressure of blood in the arteries immediately sinks, the brain getting an insufficient supply ceases to act, and the patient falls down unconscious. The very fact of the head being lowered induces more blood to pass to it, and the normal condition is at once in many cases restored.

The condition of the vessels in fainting has not been ascertained, and the only observation bearing on the subject that I can find is one by John Hunter.* While engaged in bleeding a lady she fainted, and during the continuance of the faint he observed that the blood which flowed from the vein, instead of being dark and venous, was of a bright scarlet colour, like that of arterial blood. Now, the only condition in which we know

* *Works of John Hunter*, edited by Palmer, 1837, vol. iii, p. 91.

this to take place is when the arterioles are greatly dilated, and the blood flows so quickly through them that there is no time for it to be deprived of oxygen during its passage. This is seen in the submaxillary gland during irritation of the chorda tympani nerve, and it was observed by Meyer,* the celebrated propounder of the doctrine of conservation of energy, in persons whom he bled in the tropics, and who had their vessels dilated in consequence of the heat; and it was also noticed by Crawford† in animals bled during immersion in a warm bath. It would therefore seem that in fainting the vessels of the external parts of the body are occasionally, at least, widely dilated, and this explains the frequency with which persons faint in warm rooms and crowded churches. I am inclined then to suppose, that in fainting there is dilatation of the vessels in the *external* parts of the body, although the data on which I found my opinion are too imperfect to allow of my speaking very positively on the subject. If you examine the veins on the back of your hand in a crowded assembly, such as people often faint in, you will probably find them very full, indicating that blood is flowing rapidly into them from the arteries, and that their colour is of a lighter blue than usual, showing that the blood they contain is lighter coloured or less venous than usual. This indicates that the cutaneous arterioles are dilated, and this dilatation has doubtless a great deal to do in many

* R. Meyer, *Die organische Bewegung in ihrem Zusammenhang mit dem Stoffwechsel*, 1845, p. 84. Meyer's explanation of the occasional red colour of venous blood is different from the one I have given above. We both agree that the slightness of the alteration it has undergone in its passage from the arteries into the veins is due to the fact that but little oxygen has been taken from it by the tissues as it flowed through the capillaries. Meyer considers that the tissues adapt themselves to the wants of the body, and take little oxygen from the blood when the external air is warm. The oxidation which usually goes on within the body is thus diminished, the production of the heat lessened, and the temperature of the animal prevented from rising too high. This hypothesis, though very plausible, is rendered improbable by the experiments of Bernard (*Revue Scientifique*, 1871–72, pp. 123 and 182), which show that the tissues of animals which have been exposed to a high temperature absorb oxygen (after death at least) much more quickly than usual. I therefore attribute the florid colour of the blood to dilatation of the arteries and capillaries, allowing it to flow so quickly through them that the tissues have not time to abstract much oxygen however great their avidity for it may be.

† Crawford, *Experiments and Observations on Animal Heat*, 1788, p. 308.

instances with the reduction of the blood-pressure and the induction of syncope. As the skin is usually pallid during the fainting fit itself, we can hardly suppose that the blood is then flowing very rapidly through the cutaneous vessels. If the hypothesis I have just advanced be correct, we are driven to the conclusion that it is the blood-vessels of the muscles which undergo dilatation during syncope. This idea likewise receives confirmation from the observation made by Thackrah,* that it is in muscular men that venous blood most frequently presents a florid colour. Such of you as have seen a living muscle cut across, however, know that when it is at rest very little blood indeed flows from the divided ends of the vessels which permeate its substance, and you may be inclined to doubt the possibility of these vessels ever being able to dilate so much as to drain, as it were, the blood from the arteries into the veins and produce syncope. That they can dilate and drain the blood out of the arteries very quickly has been shown by Ludwig and Hafiz,† who found that when the vessels of the intestines and skin were made to contract, the blood which could no longer flow through them poured through the vessels of the muscles, and, notwithstanding the fact that these vessels were at that very time excited to contraction by irritation of their vaso-motor nerves, the blood flowed from the arteries into the veins, and the pressure in the arteries sank nearly as quickly as when the cutaneous and intestinal vessels were patent. If such be the effect of the muscular arteries on the blood-pressure when they are trying to contract, what must it be when they are ready to dilate? Dilatation of the vessels alone may sometimes be sufficient of itself to lower the blood-pressure to such an extent that fainting occurs; but at other times this is combined with the depressing effect of sudden stoppage of the heart. In shock there is great dilatation of the vessels in the *interior* of the body, especially of the veins of the intestine. If this state should be associated with sudden stoppage of the heart, instant death will occur, as in the case of the labourer in the India Docks. In short, then, I consider syncope to depend chiefly on

* Thackrah, *Inquiry into the Nature and Proverties of the Blood*, p. 85.

† *Ludwig's Arbeiten*, 1871, p. 107.

dilatation of the arterioles, especially of those near the surface, though in cases like that of Alice Bruce it may be due entirely to stoppage of the heart; while the chief factor in shock is dilatation of the abdominal veins. The longer duration of shock than of syncope is probably due to the veins recovering their contractility more slowly than the arterioles.

Having thus formed some sort of idea regarding the pathology of syncope and shock, we come to our third head, viz., the question of treatment. In syncope, our first idea is to restore the circulation to the brain, and this we do by laying the head level with the body, or perhaps, still better, as recommended by Sir Astley Cooper, on a level somewhat lower than that of the body.

The next thing is to raise the blood-pressure. Now, this is most easily done by causing the arterioles to contract. We therefore hurry a person who has fainted from the warm room to the cold air, and dash cold water on the face, in order to cause contraction of the vessels on the surface of the body. We also give draughts of cold water to cause contraction of those of the stomach. Besides this we apply ammonia or aromatic vinegar, which is strong acetic acid, to the nose. Why do we do this? Many of you know that when ammonia is applied to the nose of a rabbit it causes the heart to stop instantaneously, and one would therefore think that to hold it before a fainting person's nose was to do the very worst possible thing. But we all know that this is not the case. Some time ago a member of this Society asked me this question, and I could at that time give him no satisfactory answer. I have since made some experiments on the subject, and I find (what has indeed been already noticed by Kratschmer*) that when ammonia or strong acetic acid is held before the rabbit's nose, it causes contraction of the arterioles. Consequently it prevents the blood-pressure from falling quickly, even should the heart become feeble or stop, and is thus useful in preventing syncope. When the blood-pressure has already become lowered by the occurrence of syncope, contraction of the arterioles causes it to rise, and it is by causing this that acetic acid or ammonia are useful as restoratives.

* *Wiener Sitz. Bericht*, 1870, Abt. II, vol. lxii, p. 24.

In shock we have two conditions to remove. The first of these is the feebleness of the heart itself, which is due to the action of the vagus. To counteract this we apply stimulants. Now, one of the most powerful stimulants to the heart is heat. It is true that it dilates the vessels, but in shock we have nothing to fear from dilatation of the vessels near the surface of the body, where circulation is hardly going on at all, nor is it likely that it will increase the dilatation of those in the interior. We therefore pursue a plan of treatment directly the opposite of that which we employ in fainting, and apply warmth instead of cold to the surface, especially to the cardiac region, over which a hot poultice or india-rubber bottle filled with hot water should be placed. At the same time, and for a similar purpose, we give brandy and ether internally. The second and most important indication for treatment is to cause contraction of the great vessels, especially the veins in the abdominal and thoracic cavities, so that the blood, instead of stagnating uselessly in them, may be sent onwards to the heart, and thence to the rest of the body. I have already described the effect of acetic acid and ammonia held before the nose, but this is only one example of the general rule that all powerful impressions on sensory nerves cause contraction of the blood-vessels. Painful impressions made upon the skin, for example, have this effect, and Goltz has shown that pinching the toes of a frog, or irritating them by acetic acid, prevents the vessels from dilating when the abdomen is struck, or causes them to contract and propel the blood to the heart if dilatation has already taken place. If I may judge from my own experience, persons not unfrequently take unconscious advantage of this effect of pain, and medical students occasionally prevent themselves from fainting, when witnessing an operation, by biting their lips or pinching their fingers. Its beneficial action in shock is very great, and my friend Dr. Fayrer informs me that he has succeeded in recovering a patient from a state of collapse by thrashing his feet and the calves of his legs with switches after other means had failed. Mustard plasters are often applied for a similar purpose. Sometimes the performance of an operation during shock is attended by a marked improvement in the patient's condition, and it seems to

me not improbable that this is due to the stimulus thus given to the vaso-motor nerves. At other times, however, the additional injury seems to produce an injurious effect either on the heart or vessels, and the patient succumbs. It is possible that the different effects of operations performed during shock may depend to some extent on the greater or less amount of irritation which is occasioned to the nerves of bones as compared with those of the soft parts; for, as we have already mentioned, injuries to bones tend to cause syncope, while irritation of other nerves, unless it be excessive, tends to prevent it by raising the blood-pressure. This, however, is a question which pertains more especially to surgeons, and with them I will leave it. I must not conclude without mentioning another valuable remedy in cases of shock, viz., digitalis. It has, I think, been conclusively proved by Dr. Adolf B. Meyer and myself,* that this drug possesses the power of contracting the arterioles, and I have shown† that it greatly strengthens the pulsations of the heart. We would therefore expect it to prove useful in shock, and experience does not disappoint our anticipations. This is well shown by a case of shock following parturition, in which it was employed by Dr. Wilks‡ some years ago. My attention was drawn to this by my friend Dr. Milner Fothergill, and I quote the following from his admirable essay on digitalis.§ "The patient was apparently *in articulo mortis*; her limbs were cold, her body in a state of deathly clammy sweat; the face was livid, no pulse could be felt at the wrist, and a mere fluttering was heard when the ear was placed over the region of the heart. Brandy and ether had been tried without any good effect, and as dissolution was imminent, it was determined to try digitalis. Half-drachm doses were given every hour; after four doses a reaction took place, and after seven doses complete recovery occurred." Such a case as this needs no comment, and a consideration of the encouraging results here obtained can hardly fail to gain for digitalis a much more extensive application in cases of shock than it has hitherto received.

* *Journal of Anatomy and Physiology*, Nov., 1872, p. 134, *vide antea*, p. 151.

† *On Digitalis*, London, 1868, p. 28, *vide antea*, p. 52.

‡ *Medical Times and Gazette*, Jan. 16, 1864.

§ *Digitalis: its Mode of Action and its Use*, London, 1871, p. 63.

DIURETISCHE WIRKUNG DER DIGITALIS

In Verbindung mit H. POWER, M.B.

(From the *Centralblatt der medicinischen Wissenschaften*, July 4, 1874, p. 497.)

Max Hermann und Ludwig haben gezeigt, dass die Geschwindigkeit der Harnabsonderung von dem Unterschied des Blutdruckes in den Nierenglomerulis und dem Druck des Harnes in den Harncanälchen abhängt.

Gegenwärtig nimmt man allgemein an, dass die diuretische Wirkung der Digitalis nicht von einer specifisch diuretischen Wirkung dieses Arzneimittels, sondern ausschliesslich von seiner Fähigkeit, den Blutdruck im arteriellen Gefässsystem zu steigern, bedingt ist.

Die Resultate von Experimenten, die wir vor ungefähr einem Jahre angestellt haben, beweisen, dass dies nicht der Fall ist.

Nach Injection einer bedeutenden Dosis von Digitalin in die Venen eines catheterisirten Hundes fanden wir die Harnsecretion bedeutend vermindert und selbst vollkommen schwinden, während gleichzeitig der Blutdruck zuweilen bedeutend gesteigert war. Nach einiger Zeit fiel der Blutdruck wieder und in einigen Experimenten trat die Harnsecretion gerade wieder ein, als der Blutdruck zu sinken begann, während in anderen Fällen dieselbe nicht vor dem Sinken des Blutdrucks unter die Norm auftrat. In einigen Experimenten war die Geschwindigkeit, mit der der Harn abfloss, geringer, in anderen floss er sehr reichlich, obgleich der Blutdruck bedeutend unter die Norm gesunken war. Würde Digitalis seine diuretische Wirkung einzig und allein der Fähigkeit, eine Steigerung des Blutdruckes zu bewirken, verdanken, dann hätte das Fliessen des Harnes bedeutend vermehrt sein müssen unmittelbar nach der Injection und hätte wieder abnehmen müssen, so wie der Blutdruck fiel. Statt dessen fanden wir die Secretion am geringsten während

des höchsten Standes des Blutdruckes, sehr reichlich hingegen, als der Blutdruck unter die Norm gesunken war. Zur Erklärung dieser Erscheinungen sind wir geneigt, anzunehmen, dass Digitalis eine erregende Wirkung auf das vasomotorische Nervensystem im Allgemeinen und auf die vasomotorische Nerven der Niere im Besonderen ausübt. Gleichzeitig müssen wir annehmen, dass es eine mässige Contraction der Gefässe des Körperkreislaufes und eine Steigerung des Blutdruckes in denselben, so wie eine übermässige Contraction der Nierenarterien bedingt, deren nächste Folge eben das Aufhören des Fliessens des Harnes ist. So wie die excitirende Wirkung auf das vasomotorische Nervensystem nachlässt und vorübergeht, erschlaffen die Gefässe der Niere schneller und bedeutender als die übrigen Gefässe, so dass der Blutdruck in den Nierenglomerulis noch über die Norm gesteigert ist, obgleich die Spannung der Gefässe im Allgemeinen unterhalb der Norm ist.

Unterstützt wird diese Annahme noch durch die Thatsache, dass der nach dem Wiedereintreten der Secretion gesammelte Harn Eiweiss enthielt, gerade wie Hermann nach mechanischer Absperrung des Kreislaufes in den Nierenarterien gefunden. Wir wollen die Möglichkeit, dass das Variiren der Secretion theilweise auch von der directen Einwirkung des Arzneimittels auf die secernirenden Elemente der Niere abhängen mag, nicht übersehen; wir sind gegenwärtig mit diesbezüglichen Experimenten beschäftigt, die wir nach deren Abschluss veröffentlichen werden.

ON THE DIURETIC ACTION OF DIGITALIS.

In conjunction with HENRY POWER, M.B., F.R.C.S.

(Reprinted from the *Proceedings of the Royal Society*, No. 153, 1874.)

It has been shown, by Max Herrmann and Ludwig, that the rapidity of the urinary secretion depends on the difference in pressure between the blood in the renal glomeruli and the urine in the urinary tubules.

At present, it is generally assumed that the diuretic action of *Digitalis* is not caused by any specific influence of the drug upon the kidney, but is due exclusively to its power of increasing the blood-pressure in the arterial system.

The results of some experiments made by us nearly a year ago show that this is not the fact. On injecting a considerable dose of digitalin (1—2 centigrammes) into the veins of an etherized dog, we have observed that the secretion of urine was either greatly diminished or ceased altogether, while the blood-pressure rose, occasionally to a considerable extent. After some time the blood-pressure again fell; and in some of the experiments the secretion of urine recommenced at the instant the fall began. In other instances it did not recommence till the blood-pressure had sunk below the normal. Occasionally the secretion did not flow with its original rapidity, but in others it was poured forth copiously, even although the blood-pressure had sunk considerably below the normal.

If *Digitalis* acted as a diuretic only by raising the blood-pressure, the flow of urine should have been greatly increased immediately after the injection, and should have diminished with the fall of arterial tension. Instead of this the secretion was least when the blood-pressure was highest, and most copious when the tension had fallen below the normal.

The explanation we would offer of these phenomena is, that *Digitalis* probably stimulates the vaso-motor nerves generally,

but affects those of the kidney more powerfully than those of other parts of the body. Thus, it causes a moderate contraction of the systemic vessels, and raises the blood-pressure in them, but, at the same time, produces excessive contraction of the renal vessels, so as to stop the circulation in the kidneys and arrest the secretion of urine.

As the action of the drug on the systemic vessels passes off, they relax, and the blood-pressure falls; but the renal arteries probably dilate more quickly and to a greater extent than the others. The pressure of blood in the glomeruli may thus be increased above that normally present in them, although the tension in the arterial system generally may have fallen below the normal.

Additional evidence in favour of this explanation is afforded by the fact that the urine collected after the re-establishment of secretion contains albumen, just as Herrmann found it to do after mechanical arrest of the circulation through the renal arteries.

We do not overlook the possibility that the alteration in secretion may be partly due to the direct action of the drug on the secreting elements of the kidneys, and we are still engaged in experiments on this subject.

CASES OF EXOPHTHALMIC GOÎTRE.

(Reprinted from St. Bartholomew's Hospital Reports, vol. x, 1875.)

THIS disease is characterised by three prominent symptoms—viz., palpitation of the heart, enlargement of the thyroid gland, and protrusion of the eyeballs. It was first observed by Parry, and described by him in a paper on "Enlargement of the Thyroid Gland in connection with Enlargement and Palpitation of the Heart," published in 1825. Parry's work, however, seems to have been little known, and the disease was again noticed by Graves of Dublin, and described by him under the title of "Newly observed Affection of the Thyroid Gland in Females," in his *System of Clinical Medicine*, published in 1843. The attention of the profession having been attracted to the disease by Dr. Graves, it is generally called Graves' disease in this country, and "maladie de Graves" by Trousseau in France. Both Parry and Graves observed the protrusion of the eyeballs, as well as the other symptoms, but they seem to have regarded it as quite subsidiary to the other two symptoms, and perhaps looked upon it as an accidental complication. The equal importance of the exophthalmic with the other symptoms was first insisted upon by Basedow, a practitioner in the German town of Merseburg. He is therefore considered by the Germans to have been the first to give a complete picture of the disease, and they call it after him "die Basedow'sche Krankheit," or Basedow's disease.

In most of the cases described by Graves the paroxysmal nature of the palpitation, and of the increased enlargement of the thyroid, forms a prominent symptom, and appears to have specially attracted his attention. In these cases the protrusion of the eyeballs does not seem to have been at all noticeable; while in most cases where this symptom is prominent, the thyroid gland, although subject to occasional variations in size, generally remains more or less obviously enlarged. The follow-

ing case is one of purely spasmodic exophthalmos, in the intervals of which the symptoms entirely disappeared. Not having witnessed one of the fits myself, I am obliged to rely solely on the testimony of the mother for the accuracy of my facts.

M. M., a girl aged 13, first seen on Wednesday, August 26, 1874, middle height, fair, well nourished, slightly strumous-looking; has a somewhat vacant expression. The eyes are not prominent, nor is the thyroid gland larger than usual. Mammæ not developed. There is a loud systolic murmur at the apex of the heart, faintly audible over the base.

About 20 months ago a large weight fell from a window and slightly grazed her nose. Three days afterwards she had a fit. According to her mother's account, this fit was not preceded by any warning. The first thing noticed was that the eyes became very prominent, or in the mother's own words, "stood out shocking." The hands were clenched, and the arms drawn up towards the head. The body was drawn somewhat to the right side, and the mouth also to the right. This lasted for 4 hours and 20 minutes. She then fell asleep, and slept for four hours more, only awakening once during that time. During this sleep her eyes returned to their ordinary size. About 14 months afterwards she had another fit; a third one on June 21; a fourth one about four weeks ago; and a fifth one last Monday, August 24. During the fit she foams at the mouth: there is also some bleeding from the mouth; in the last fit from the ears also. After the fit she complains of pain in all her limbs; and a fortnight before the fit comes on she complains of being very tired, and of aching in her back and sides. She has never menstruated, the appetite is good, the tongue covered with a thin white fur. Bowels open two or three times a week.

Ordered—Ferri et ammoniæ citrat., gr. viii.; ammon. carb., gr. ii; spt. chloroform, ℥ x.; tinct. nuc. vom., ℥ x.; infus. quassiæ, ad ℥ i.: ter die sumend. Pil. aloes et myrrh, gr. v.: omni nocte sumend.

August 31.—*In statu quo.* Has had no more fits.

Rpt. haust et pil.

October 9.—The same treatment has been continued. There

has been no return of the fits; but the mother says that she thinks one is now coming on, as she sees premonitory symptoms.

Ordered—Potass. bromid, gr. xxv.; spt. chloroform, ℥ xx.; aquæ, ʒ i.: ter die sum.

The next one was admitted into Mary Ward, under the care of Dr. Andrew, in June last. It is a most interesting case, presenting in a typical manner most of the symptoms of exophthalmic goître, although neither the enlargement of the thyroid nor the protrusion of the eyeballs is present to any great extent. It is also remarkable in being complicated by diabetes, a disease which has been shown by the researches of Cyon, Eckhard, Pavy, and others to be closely associated with the third cervical ganglion, and the nerves passing through it; the very part, indeed, to which the nervous disturbances in exophthalmic goître have already been attributed.

Dr. Andrew has not only kindly placed this case at my disposal for publication, but has afforded me every assistance and facility for observing it myself. I have also to acknowledge my obligations to Dr. Andrew's house-physician, Mr. Strugnell, to whom I owe the observations with the ophthalmoscope, and to Mr. Wharry, to whom I am indebted for the analysis of urea. In recording the case here, I have inserted some observations which were made some time after the patient's admission: *e.g.*, the ophthalmoscopic observations, which were made about the end of August. Most of these, however, I have distinguished by brackets from those made at the time of admission.

S. P., aged 43, lady's maid. Patient is of the middle height, and very thin and nervous-looking. Hair thin.

History.—Her mother's family is very rheumatic, but they are all long-lived. Father's family not so rheumatic, and they live generally above middle age. There are none of either family who have suffered from fits, nor is there any history of either diabetes or phthisis. When 17 years of age, she had rheumatic fever. At the age of 25 she became a lady's maid. About 10 years ago she had some family trouble, and some more five or six years ago. About 13 years ago she went to a

family where one of the members was fidgety, and gave her a good deal to do. She remained in this situation for ten years. About five years ago she began to lose flesh, but she grew stronger again. Three years ago she went to a situation where the ladies were very kind, but were often out at balls, so that she was often kept up at night. When she did not get sleep at night, she lost it altogether; for she never could sleep in the day. About two years ago she noticed a pulsation in the epigastrium. About that time she had a severe fall on the back of the head. She was unconscious for some minutes, and did not recover from its effects for several hours. About this time, also, she began to notice that her stools became occasionally very pale. They continued so for about five weeks at a time, and a similar attack has come on every three months since. About six months ago she became very thirsty, felt pain in the back, and began to lose flesh. Two months ago she had diarrhœa and sickness. About three weeks ago one of the ladies whom she served noticed that her right eye was looking strange, and asked if she had a cold in it. Before that time it was natural.

On Admission.—The patient is very thin. There is some œdema of the feet and ankles. The thyroid gland is more prominent than usual: the right lobe is larger than the left. The patient never noticed the enlargement of the gland until it was pointed out to her in the hospital.

Eyes.—Both eyes somewhat prominent; the right eye more prominent than the left. [On pressure, the eyes retreat in the sockets. There is very slight tenderness to pressure on the right eye, more on the left. There is a brown patch on the right side of the right conjunctiva. This has been there ever since she remembers. On making the patient look up and down, the right upper eyelid does not follow the movements of the eye as quickly as normal; so that on looking down, the conjunctiva is exposed, forming a white ring above the cornea. The patient states that she feels as if the right eyelid caught. The left eyelid moves normally.

The pupils are normal in size. The right pupil does not act quite so readily as the left. She is presbyopic, focus being 16 inches. She has noticed that she required to hold objects

further off only since she came into hospital, but the presbyopia may have come on some weeks before, as she had no work, and therefore no opportunity of observing it. The vision of the left eye is $\frac{12}{12}$ of Snellen's types. That of the right eye is $\frac{12}{20}$, with a -48 lens it becomes $\frac{12}{15}$. Her eyes ache if she looks long at any object. They did not use to do so. She is often troubled with muscæ volitantes. She has some subjective visions when her eyes are closed. These are in the form of stars flying about; they are usually of a red colour. On ophthalmoscopic examination, the media are found to be a little hazy. Nothing abnormal in the discs, except that the right disc seems a little smaller than the left. The fundus of both eyes is fairly natural.]

Circulatory System.—The heart's apex beats two inches below and half an inch outside of the left nipple. There is a systolic murmur. The abdomen is retracted, and there is strongly-marked epigastric pulsation. The veins on the arms, legs, and neck are very large, full, and light blue, not dark blue, in colour. When emptied, they fill very rapidly from behind. The face is not flushed, nor are the ears red. The temporal arteries are prominent and tortuous. The pulse is 120, full and regular. The sphygmographic tracing shows a flat plateau and moderately slow descent. This seems to indicate that the arteries have undergone senile degeneration, and that they do not empty with any very great rapidity. There is no marked pulsation in the thyroid gland, nor is there any very obvious increase in the pulsations of the carotid arteries.

Respiratory System.—The voice is soft and pleasant. (She has lately noticed it change, and become weaker and more "clinky." She has only noticed this since she began to recover in hospital. She sometimes has a little pain in her throat when she speaks.) The lungs are normal.

Muscular and Nervous Systems.—The muscles are very small. The thumbs are drawn in upon the palms. She finds difficulty in rising from a sitting posture. She is very neat in her habits, is not quick-tempered, but the contrary. She is very emotional, and is in either very high or very low spirits. When well, she is high-spirited and full of fun; but for three weeks before

admission she has been liable to fits of crying, during which she is miserable without knowing why. These fits are relieved by cold water to the face, ether internally, or ammonia to the nose. She feels very hot, and cannot bear many clothes on during either day or night. She has always had this feeling, and always liked cold weather best. Temperature on admission, 101·9°.

Digestive System.—Tongue very dry and furred. She is very thirsty, and her appetite is bad. Bowels irregular.

Secretions.—Perspires very much in warm weather, or on the slightest exertion. Urine very abundant, sp. gr. 1035, acid. Contains much sugar.

June 2.	Ordered—Bran cakes; beef-tea, 1 pint; brandy, 2 fluid oz.; eggs, 2. Pil. col. c. hyoscyam., gr. x. statim; hst. sodæ citrat. efferv., 6tis horis.			
„ 3.	Feels rather better; ordered fresh greens.			
„ 4.	Urine, 3¼ pints;	sp. gr.	1030.	
„ 5.	„ 2¼ „	„	1028.	
„ 6.	„ 3¼ „	„	1025.	
„ 7.	„ 5 „	„	1025.	
„ 8.	„ 6 „	„	1027.	
„ 9.	„ 4 „	„	1024.	Seems better. Temperature, 99°; pulse, 114. Ordered—Essence of meat, ʒ v. (spt. rect., ʒ i.; aq., ʒ i.), instead of brandy.
„ 10.	„ 3¾ „	„	1024.	
„ 11.	„ 4½ „	„	1022.	
„ 12.	„ 4¼ „	„	1025.	
„ 13.	„ 3¾ „	„	1023.	
„ 14.	„ 4½ „	„	1025.	
„ 15.	„ 4½ „	„	1023.	Is rather hysterical; adde hst. tinct. opii, ♏ v. Temp., 99°.
„ 16.	„ 4¼ „	„	1022.	
„ 17.	„ 3¼ „	„	1023.	
„ 18.	„ 3½ „	„	1022.	
„ 19.	„ 3¾ „	„	1018.	
„ 20.	„ 4½ „	„	1018.	
„ 22.	Diarrhœa.			
„ 23.	„ 2½ pints;	sp. gr.	1013.	Still some diarrhœa; otherwise seems better: less sugar in urine. Ordered—Bismuth subnit., gr. xv.; tinct. catechu., ʒ ss.; decoct hæmatoxyli, ʒ i. ꝑ r. n.
„ 25.	„ ..	„	1012	
„ 27.	„ 3 pints;	„	1014.	
„ 29.	„ 4 „	„	1020.	

June 30. Urine, 4 pints; sp. gr. 1027, alk. Temp., 99°. No diarrhœa; appetite good; sleeps well; less œdema of feet; seems better. Ordered—Acid, nitrohydrochlor. dil., ℥ x.; liq. strychniæ, ℥ iii.; tinct. opii, ℥ v.; aq. menth. pip., ʒ i., ter die.

July 3. „ .. „ 1013.

„ 7. „ 4¾ pints; „ 1013. General condition improved; sugar rather diminished; feet still a little swollen. Ordered—Hst. sodæ cit. efferv. 6tis horis.

„ 13. „ 3¼ „ „ 1030.

„ 16. Ordered—Liq. strychniæ, ℥ iii.; tinct. opii, ℥ v.; acid phosph. dil., ℥ xxv.; aquæ, ʒ ii. 6tis horis.

„ 28. Urine, 5 pints; sp. gr. 1028. Rather hysterical. Weight, 5st. 8lbs.

	Urine. c.c.	Sp. gr.	Reaction.	Percentage of urea.	Total urea. Grammes.
August 26 ..	2565	1030	Acid.	·73	18·7245
„ 27 ..	2280	1030	Acid.	·85	18·96
„ 28 ..	2700	1025	Faintly acid.	·825	22·275

September 1.—Urine, 4 pints, sp. gr. 1030. Nothing abnormal in fundus of eyes.

September 8.—Gained 3¼ lbs. during the last few weeks.

September 23.—Not quite so well last night.

October 4.—Had not been quite so well during the day. Hysterical, and crying a great deal. About seven o'clock she went to bed, and took some beef-tea; about nine she spoke to the nurse; at 10 the sister saw that she was lying quiet, with the curtains of the bed slightly drawn; and at 11 P.M. she was found to be dead. No dyspnœa whatever was observed. The friends of the patient would not allow a post-mortem examination in the hospital, and after some difficulty permission was obtained to examine the body at their house. Owing to the circumstances under which it was made it was exceedingly imperfect and unsatisfactory. The lungs were much congested and œdematous. There was no consolidation, and they were singularly free from pleuritic adhesions. No vegetations were observed on the cardiac valves. The left ventricle was contracted and empty; the right ventricle contained a little blood. The liver was normal. The thyroid gland was enlarged

and hard, and it was firmly attached to the trachea. The eyes were sunken, but not greatly.

The cause of death here has evidently been œdema of the lungs, which has come on rapidly and insidiously.

In this case, the three prominent symptoms of exophthalmic goître, although present, are not so noticeable as in many others; but the collateral symptoms, such as the imperfect consensus between the movements of the upper eyelid and visual plane, on which Von Gräfe laid particular stress, the emotional character, the feelings of heat, the actual high temperature noticed by Teissier, are particularly well marked. To trace the symptoms back to their origin is exceedingly difficult, and, indeed, impossible, in the present state of physiological knowledge. All that we can hope to do at present is to put together the facts already ascertained, so that we may gain a clearer idea of the possible origin of the symptoms, and see more readily what points remain for investigation.

Palpitation.—Three causes of palpitation at once suggest themselves to the mind, and these three are undoubtedly the chief, although there may be, and probably are, others which occasionally come into play. These three are—1. Paralysis of the vagus; 2. Relaxation of the arterioles; 3. Stimulation of the accelerating nerves of the heart. The vagus acts as the regulating nerve of the heart, not only by diminishing the number of its pulsations, but by moderating their strength. Paralysis of this nerve, therefore, causes palpitation of the heart, as well as quickness of the pulse. Palpitation depending on this cause may be compared to the excessive work done by a steam-engine from which the governor-balls have been removed. But a steam-engine may also work with excessive and injurious violence if the resistance it has to overcome is much diminished, especially if this occur suddenly, and the governor-balls, although present, work imperfectly. The same is the case with the heart, which is very liable to palpitate violently when the arterioles become relaxed from weakness of the vaso-motor system, and allow the blood to pour readily through them into the veins, instead of opposing a moderate amount of resistance to its passage.

In anæmic persons, for example, where the vaso-motor system is weak and the arteries relaxed, the heart often beats violently, especially when any additional relaxation is produced in the arteries by some slight exertion. Here, no doubt, there is a disproportion between the action of the heart and the work it has to do. This implies a weakness or disturbance of the nervous arrangement, which ought to regulate the one to the other. The part of this arrangement which is in fault, however, seems to be the vaso-motor system, which allows the vessels to dilate too much, rather than the vagi, whose function is to restrain the heart. Both kinds of palpitation which I have mentioned, depending as they do on a weak or paralysed condition of the vagi or vaso-motor nerves, ought to be relieved by the use of tonics; and in fact we do find that such remedies, and more especially iron, are of the utmost service in the palpitations of anæmia. But the third cause of palpitation, viz. stimulation of the accelerating nerves of the heart, depends not on weakness, but on over-action of that part of the nervous system, and anything that will increase its power will prove injurious rather than beneficial. Now this is exactly the condition which is found in exophthalmic goître. Although persons suffering from this disease are not unfrequently anæmic, the administration of iron is not followed by its usual good effects. On the contrary, Trousseau states that it increases the palpitation to such an extent that its employment can rarely be continued. This is exactly what we should expect on the supposition that the palpitation depended on stimulation of the accelerating nerves of the heart, and I am therefore inclined to believe that the palpitation in exophthalmic goître is due to irritation of these nerves. Their deep origin has not been exactly determined, but they pass out from the spinal cord along the vertebral artery to the third cervical ganglion, and thence to the heart. They might be excited by an irritation applied to either, at their origin or during their course, and thus we might expect them to be called into action by changes in the brain, medulla, spinal cord, third cervical ganglion, the branches accompanying the vertebral artery, or those going to the heart. In order to ascertain where the source of irritation is, we must

discover what other nerves appear to be irritated in exophthalmic goître, and consider what points exist at which application of an irritant might affect all the nerves at once.

Enlargement of the Thyroid Gland.—The great variations which occur in the size of the thyroid gland in exophthalmic goître, and its remarkable pulsation, which has sometimes caused it to be mistaken for aneurism, have led nearly all observers to ascribe its enlargement, in the first instance at least, to dilatation of its vessels and engorgement of the gland with blood, in a manner similar to that which occurs in erectile tissues. After this has continued some time, increased growth may occur in the glandular elements. This dilatation may depend on direct paralysis of the vasomotor nerves of the glandular vessels, or on inhibition of these nerves by others, in the same way as the vaso-motor nerves of the penis cease to act and allow the vessels to become full when the nervi erigentes are irritated. The vasomotor nerves of the thyroid vessels proceed from the second cervical ganglion, but I am not acquainted with any experiment showing whether they pass from the spinal cord to the ganglion through its communicating branches, or pass upwards through the third cervical ganglion. Neither do I know whether these vaso-motor nerves may be inhibited, and the vessels dilated, by irritation of the third cervical ganglion, or other parts of the nervous system.

Protrusion of the Eyeball.—In a case recorded by Laqueur* the protrusion of the eyeballs seems to have been partly due to an increased amount of fat within the orbit, but this may have been only consequent on long-continued congestion. In many cases the protrusion varies at different times, and in the case of M. M. it is only temporary, disappearing in the intervals between the fits. It is therefore usually ascribed, and in all probability correctly, to increased fulness of the blood-vessels, or of the blood-vessels and lymphatics, in the orbit. It may be also due, however, as suggested by Professor Laycock, to contraction of the involuntary muscular fibres stretching across the back of the orbit, which were described by Professor Turner of Edinburgh some years ago. Whatever be the cause

* Dissertation: Berlin, 1861; Canstatt's *Jahresbericht.*

of it, however, Claude Bernard has found that protrusion of the eyeball may be produced by irritating the branches connecting the first and second dorsal ganglia with the spinal cord.

Impaired Movement of the Eyelid.—The loss of consensus between the movement of the eyeballs and the upper eyelid is ascribed by Von Gräfe to disturbed innervation of the lids, and especially of the levator of the upper eyelid, which is partly supplied by the sympathetic.

Diabetes.—The diabetes in this case can hardly be due to imperfect destruction of sugar in the body, as the temperature was higher than normal. It must therefore be due to increased formation. Increased formation depends, according to Bernard, on dilatation of the hepatic vessels, and a quicker flow of blood through the liver. According to Cyon, the vaso-motor nerves of the liver pass from the vaso-motor centre in the medulla through the cervical part of the spinal cord, pass out from it, and proceed along the vertebral artery to the third cervical ganglion, thence to the first dorsal, and along the gangliated cord and splanchnics to the liver. (See figure.) Division of this nervous path causes the vessels to dilate, and produces diabetes; but it would appear that irritation of the cervical ganglia, or at least of the first or the third, also causes diabetes, which does not depend on paralysis, but on reflex inhibition of the vascular nerves of the hepatic vessels.

Pathology of Exophthalmic Goître.—All the symptoms seem to point to an affection of the cervical sympathetic, and post-mortem examination of a case by Peter showed that the lower cervical ganglia, especially the right one, were thicker and redder than normal; that the connective tissue was increased, as well as nuclei and spindle-shaped cells, while there were very few ganglion cells. It seems, therefore, that the third cervical ganglion may be looked on as the seat of the disease. So long as we know so little of the pathology, it is impossible to treat the disease scientifically; but the treatment which seems in practice to have given the best results is the use of digitalis and veratria, and Meyer states that he has obtained great benefit from the application of galvanism to the neck. A weak ascending current was passed through both sympathetics;

FIG. 153.

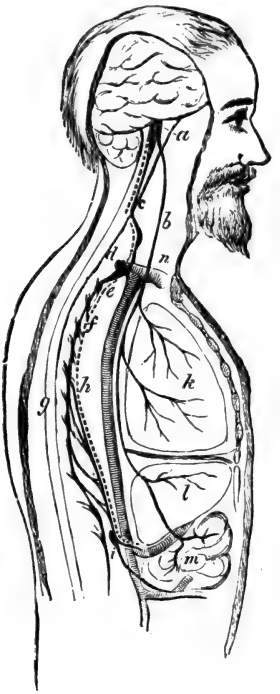


Diagram showing the course of the vasomotor nerves of the liver, according to Cyon and Aladoff. These nerves are indicated by the dotted line which accompanies them *a*, the vasomotor centre; *b*, the trunk of the vagus; *c*, the vasomotor nerves of the liver passing along the vertebral artery from the spinal cord to the third cervical ganglion; *d*, the fibres connecting the third cervical and first dorsal ganglion. They pass on each side of the subclavian artery, and form the annulus of Vieussens. Above *e* is the first dorsal ganglion; *f* the gangliated cord of the sympathetic; *g*, the spinal cord; *h*, the splanchnic nerves; *i*, the semilunar ganglion, from which vasomotor fibres pass to the hepatic and intestinal vessels; *k*, the lungs to which fibres of the vagus are seen to be distributed; *l*, the liver; *m*, the intestine; *n*, the arch of the aorta.

Division of the vasomotor nerves of the liver by partial division of the spinal cord in the neck or section of the fibres *c* or *d* causes diabetes, by allowing the hepatic vessels to dilate, and the flow of blood through the liver to become more rapid. Division of the gangliated cord *f*, or the splanchnics *h*, would probably have a similar effect were it not that the vasomotor nerves of the intestine are contained in them as well as the nerves for the liver, and therefore when they are divided the intestinal vessels dilate. The blood then goes to the intestine, so that the circulation through the liver is not increased although its vessels are dilated. Diabetes, therefore, does not result from section of *f* or *h*.

Irritation of the vagus *b*, or of its branches, causes reflex dilatation of the hepatic vessels and diabetes. A similar result sometimes follows irritation of the first and third cervical ganglia.

Protrusion of the eyeballs was produced by Bernard, by irritating the branches connecting the first and second dorsal ganglia with the spinal cord. The letter *e* lies between these ganglia.

one pole was also laid on the submaxillary region, and the other on the closed eye, or the thyroid gland. The treatment adopted in the case of S. P. was of course modified on account of the diabetes, and alkalies were administered, as experience has shown these to be beneficial in this disease. The benefit probably depends on the action of the alkali on the ferment, by which glycogen is converted into sugar in the body. The action of the ferment is impeded by the alkali, the conversion of glycogen into sugar takes place more slowly than usual, and thus the quantity in the body is diminished.

ONE OF THE CAUSES OF DEATH DURING THE EXTRACTION OF TEETH UNDER CHLOROFORM.

(Reprinted from *The British Medical Journal*, December 4, 1875.)

In a clinical lecture delivered by the late Professor Syme several years ago, he made the somewhat remarkable statement that, nothwithstanding his constant use of chloroform for many years, he had never had a death from it occur in his practice. The reasons he gave for this success were two. "First," said he, "we always use good chloroform; and, second, we always give plenty of it." Now, others besides Professor Syme have used good chloroform—have used, indeed, chloroform by the same makers, and altogether undistinguishable from that employed by him; and yet they have had to deplore the occurrence of deaths during its administration. This fact of itself is sufficient to show that the second reason given by Professor Syme for his success is of great importance; and that, in administering chloroform, it is just as necessary to give plenty of it as to use only the best quality. It is, indeed, very extraordinary to see how timidity in the use of chloroform seems to be associated with a more than ordinary fatality; and how the careless—one would say almost reckless—employment of it is frequently unattended with any inconvenience. In Snow's work on *Chloroform*, p. 151, the following passage occurs: "In Guy's Hospital and St. Thomas's, the medical officers had a strong objection to narcotism by inhalation for the first two or three years after the practice was introduced, and chloroform was used much less generally in these institutions than in any other of the hospitals of London; yet it was precisely in these two hospitals that two deaths from chloroform occurred before any such accident had happened in any other hospital in this metropolis." Dr. Snow seems inclined to attribute both of these deaths to the administration of chloroform; but a careful

consideration of them may lead us to another conclusion. Before attempting to analyse these cases, however, I wish to recall to the memory of some here an anecdote regarding the introduction of chloroform into the Edinburgh Infirmary, which Mr. Syme was accustomed to relate in his clinical course. One of the surgeons of the infirmary, I believe the late Professor Miller, had agreed to Sir James Simpson's request to perform, for the first time, an operation under chloroform. Everything had been prepared, and the tray containing the instruments and bottle of chloroform was being conveyed into the operating theatre, when the bearer stumbled and fell, and the whole contents of the bottle were irretrievably lost. There was no time to get more chloroform, and the operation was performed without it. The patient died on the table. Had chloroform been administered, the death would have been put down to the anæsthetic, and not to the operation; and, in all probability, not another drop would ever have been used.

This case shows us—and it is only one of many—that deaths used to occur from shock during operations before the introduction of chloroform, but they were then put down to their true cause; whereas, since its introduction, one hears little or nothing of death from shock, and much of death from chloroform. Another circumstance which is well worthy of notice, and which ought to be borne in mind, is the frequency with which the remark occurs in the descriptions of these so-called deaths from chloroform, that a fatal result was all the more extraordinary and unexpected because the quantity of chloroform administered had been exceedingly small. Mr. Syme would have said that, instead of being extraordinary, it was the very thing to expect; and if, like him, the operators had given plenty of chloroform, their patients would not have died.

And now let us look at the first two cases of death *under* chloroform—I will not say *from* chloroform—in these two London hospitals, where such a dislike to the anæsthetic was felt.

John Shorter, aged 48, a porter, known to Mr. Solly for some time as a very active messenger, of intemperate habits, but apparently in perfect health, was admitted into George's Ward, under Mr. Solly, on the 9th October, 1849, suffering from

onychia of the left great toe, which had existed some time. It was determined to remove the nail, the man having decided, before entering the hospital, on taking chloroform. On Wednesday, October 10th, at a quarter before 2 P.M., he began to inhale the chloroform, with 1 drachm in the inhaler. It had no visible effect for about two minutes; it then excited him, and the instrument was removed from the mouth, and about 10 drops more were added; he then almost immediately became insensible; the chloroform was taken away, and the nail removed. He continued insensible; and, his face becoming dark, the pulse small, quick, but regular, and respiration laborious, his neckerchief was removed, and the chest exposed to fresh air from a window near to the bed; cold water was dashed in his face, the chest rubbed, and ammonia applied to his nose. After struggling for about a minute he became still, the skin cold, pulse scarcely perceptible, and soon ceased to be felt at the wrist: respiration became slow at intervals, but continued a few seconds after the cessation of the pulse.

The subject of the second case was Alexander Scott, aged 34, a police constable, who died in Guy's Hospital in June, 1850, whilst undergoing an operation for the removal of a portion of the right hand. Mr. Cock, the operator, said that he was certain there was no disease about the patient. He described the accident as follows:—The ordinary machine was used, and, as it had not the effect, witness directed that a napkin should be folded into the shape of a cone, which was applied with chloroform. The removal of a portion of the bone occupied one minute and a half; but, before it was completed, the blood, which was gushing out, suddenly stopped, when witness directed Mr. Lacy to feel the pulse of the patient, and they found that he had expired.

The sudden stoppage of the hæmorrhage shows that, in this case, as in others, the action of the heart was suddenly arrested. The first attempt to cause insensibility failed in this as in some other cases.

Let us take yet another case, the second one ever recorded of death under chloroform. The patient, a healthy woman, 35 years of age, was taking chloroform in order to have several

teeth extracted. The following account of what occurred was given by two female friends of hers who were present at the operation:—"The respiratory movements appeared to be free; chest heaving. Whilst inhaling the face became pale. At the expiration of about one minute the instruments were applied, and four roots of teeth were extracted. The patient groaned, and manifested what they regarded as evidences of pain while the teeth were being extracted, although she did not speak or exhibit any other sign of consciousness. As the last root came out, which was about two minutes from the beginning of the inhalation, the patient's head turned to one side, the arms became slightly rigid, and the body drawn somewhat backwards, with a tendency to slide out of the operating chair. At this instant, Mrs. Pearson states, she placed her finger upon the patient's pulse, observed it was feeble, and immediately ceased to beat. The face, which was previously pale, now became livid, as did also the finger nails; and the lower jaw dropped, and the tongue projected a little at one corner of the mouth, and the arms were perfectly relaxed. The females regarded her as being then quite dead."

In two of these cases death occurred after the inhalation of chloroform had been discontinued, and in the third the chloroform seemed to have no bad effects until the operation was begun. In all of them the death followed the operation, and must, I think, be attributed to the shock caused by it. But what is shock? and is there more than one kind of it? for the symptoms were not the same in all these cases. In two of them the heart seemed to stop suddenly, while in the third it failed gradually, although it ceased before the movements of breathing; and the death must therefore be attributed to arrest rather of the circulation than of the respiration. The circulation is kept up in the body by the heart constantly pumping the blood out of the veins into the arteries. Whenever the heart stops pumping, or whenever it gets no blood to pump, the circulation will stop. It does not matter how much blood is in the vena cava or right auricle waiting to be sent into the arteries, if the heart be not beating; nor is the case a whit better when a wound in the jugular has drained away all the blood, so that no efforts of

the heart, however numerous and however vigorous, can send a drop of blood into the aorta.

It must be recollected that blood is only useful to the tissues when it is in the arteries, just as water is only available for household purposes while it is in the cistern or supply pipes. Once the water gets into the sewer it is of no more use, unless it can be filtered and again pumped back into the cistern; and once the blood has got into the veins, it is no more use unless it can be purified by the lungs and pumped back into the aorta, from which it may once again pass to nourish the tissues. The only difference between blood still in the veins and blood which has run out of them into a basin, is that, when in the basin, it cannot get to the heart, and be pumped by it into the arteries; while, so long as it is in the veins, it generally reaches the heart readily. But although it generally does reach the heart easily, it does not always do so. Sometimes it accumulates in the veins of the abdomen, and never reaches the auricle; so that it might just as well be in a basin for any use it is to the heart or body. This was shown by Professor Goltz, of Strassburg, by a remarkable experiment. After exposing the heart of a frog he noticed that it beat regularly, and at each beat sent a quantity of blood into the aorta, again becoming full of blood in the interval between the pulsations. The frog's heart is partially transparent; so that it is easy to see by its colour when it is empty and when it contains blood. He now struck the frog's intestines pretty hard, and found that the heart stopped. The irritation produced by the blow had been conducted up to the medulla oblongata; and, being reflected down the vagus nerves to the heart, had stopped it. After a little while, the heart seemed to recover, and began to pulsate again. But there was a very remarkable difference between its appearance now and its appearance before the blow had been given. Instead of becoming filled with blood during each diastole, and assuming a deep red colour in consequence, it remained quite pale and empty; and, although it contracted vigorously, the circulation stopped, for the heart had no blood to propel. On looking at the vena cava, Goltz found the cause of this phenomenon. The frog was hanging with its legs downwards, and the vena cava was not

full up to the level of the heart. Usually the vena cava and veins of the intestines are kept in a state of semicontraction or tone by the vaso-motor nerves, but now they had become completely relaxed: so that the blood which usually would have filled them completely up to the heart was not sufficient, and so they were only about half full. On laying the frog in a horizontal position, the blood ran towards the heart. It was thus evident that the blow on the intestines had done something more than stop the heart. It had also stopped the usual action of the vaso-motor centre; so that the veins, instead of remaining in a state of tonic contraction, became widely dilated. And, be it noticed, this dilatation of the veins in Goltz's experiments was more permanent than the stoppage of the heart, and continued after the cardiac pulsations had recommenced. But all frogs are not alike; for sometimes a blow on the intestines will stop the heart without having much effect on the veins; and sometimes it will cause the veins to dilate, and will not stop the heart, although very often, as I have already said, it will do both. The same effects seem to follow blows on the abdomen in man and in the frog, but with this difference: in the frog, the heart may stop for some time, and again go on without much injury to the animal; in man, the stoppage of the heart produces death in not many seconds. A good example of this is to be found in Sir Astley Cooper's *Lectures on Surgery*; where he relates that a healthy labourer belonging to the India House was attempting to lift a heavy weight, when another labourer came up and said, "Stand on one side; let an abler man try." At the same time, he gave the former a slight blow on the region of the stomach, when the poor fellow immediately dropped down and expired. On examination of his body, there was not any mark of violence discovered. Here, no doubt, the blow in the abdomen stopped the man's heart, just as it does in the frog; and death occurred before the organ had time to recover from the shock. In another case, described by Professor Fischer, a young man was struck in the abdomen by a carriage-pole; and, after the accident, lay pale and motionless, with a feeble pulse, empty arteries, deep sighing respirations, and a livid tinge on his hands and lips. In this instance, the

heart had either not been stopped at all, or had speedily recovered itself; but the abdominal veins had been so dilated that all the blood in the body could hardly fill them sufficiently to leave a driblet over for the general circulation, although a little still did trickle into the heart so long as the patient remained in the recumbent posture.

We have, then, two forms of shock, according as the injury produces its effect chiefly on the heart or chiefly on the vessels. But it is not merely blows on the abdomen which have the power of producing shock; irritation of other parts can do so likewise; and this seems to be peculiarly the case with regard to bones. Thus Pirogoff records two cases in which death occurred during operations before the introduction of chloroform. In both, the pain and loss of blood during the operation was only a little greater than usual; yet in both, *immediately after* the bone had been sawn through, the face became pale, the eyes staring, the pupils dilated, a peculiar rigidity of the body occurred, and death immediately took place.

The symptoms in these cases of Pirogoff's are almost exactly the same as those of Mr. Cock's case I have already described; but Pirogoff's deaths were put down to the operation, because no chloroform had been given; while the death in Cock's case was ascribed to the anæsthetic, because some chloroform had been administered; although, on account of the operator's unwillingness to give it at all, the quantity was probably very small.

In all three, it is evident that the heart stopped suddenly; and this in itself was sufficient to cause death, though it is highly probable that dilatation of the abdominal vessels also occurred.

In Mr. Solly's case, the dilatation of the abdominal vessels seems to have been the chief cause of death; for the pulse became gradually, though rapidly, weaker and weaker, and then stopped altogether, just as we would expect it to do if the heart suddenly ceased to be supplied with blood.

In the third case I have described, probably the heart was chiefly affected; for, just as the fourth stump of a tooth was removed, the pulse was felt to be exceedingly weak, and almost immediately afterwards became imperceptible.

Stoppage of the heart's action, then, being of such importance as a cause of death, we must now inquire how it is produced. The heart is kept pulsating rhythmically by the motor ganglia which it contains within itself, and will continue to pulsate for some time after its complete removal from the body. But though it thus shows its power to contract independently of the central nervous system, it is, nevertheless, influenced to a great extent by the nerve-centres within the cranium. It would never do to have the heart acting without reference to the wants of the system, and pumping blood vigorously into the arteries when the pressure within them was already too great, or acting slowly and feebly when the limbs were engaged in severe work, and wanted an abundant supply of blood to enable them to perform it. There are, therefore, nerves, some accelerating and others retarding the heart, which pass to it from the medulla oblongata, and, acting as the spur and reins of a rider do upon his horse, regulate its beats in accordance with the wants of the system. The retarding fibres are contained in the vagus nerve; and, when this nerve is irritated strongly, the heart will either stop immediately in diastole, or will beat very slowly and more feebly. Nor is it only by direct irritation of the vagus that this result can be attained. Just as irritation of a sensory nerve sets motor nerves in action, and produces various muscular movements by reflex action through the spinal cord, so may irritation of a sensory nerve set the vagus in action and produce stoppage of the heart, by acting reflexly through the medulla oblongata. A good many sensory nerves can do this; but there is one which possesses the power in an especial degree. The roots of the fifth nerve are anatomically closely connected with those of the vagus; reflex stoppage of the heart is produced more readily by irritation of the fifth than of any other nerve. In many rabbits, the heart can be instantaneously stopped by irritating the nasal branches of this nerve by a pungent vapour, such as ammonia, held before the nose. In every rabbit, or almost every rabbit, indeed, we can stop the heart by a pungent vapour applied to the nose; but we do not always do it in the reflex manner I have just described. The animal always closes its nostrils to prevent the entrance of the

vapour, and keeps them closed so long, that the carbonic acid accumulating in the blood begins to act on the vagus and stop the heart. But this only occurs after the vapour has been held before the nose for some time: while the reflex stoppage which I have just mentioned takes place at once, almost simultaneously with the closure of the nostrils. This reflex stoppage has been shown by Hering and Kratschmer to be due to the irritation being conveyed along the nasal branches of the fifth nerve to the medulla, whence it is reflected along the vagus to the heart, and stops it.

Yet, notwithstanding the stoppage of the heart, the rabbit does not die; nor is it, indeed, any the worse. Why is this? Usually, when the heart is stopped, as, for example, when a ligature is put round the aorta, the blood all runs out of the arteries into the veins; and then, as I have said, it is useless for nutrition. But there is a nervous arrangement which prevents this when the heart stops in consequence of an irritation applied to the fifth nerve. This nerve not only contains branches which are connected with the vagus and stop the heart or retard it, but it also has branches which go to the cerebral hemispheres, and there excite an action which passes down the vaso-motor nerves, causing the auricles to contract, and preventing the blood from running out of the arteries into the veins, except very slowly indeed; so that, as soon as the irritation stops, the circulation is ready to go on normally. But it is only when the cerebral hemispheres are in good working order that this occurs. When they are removed, or when their function is destroyed by chloroform, morphia, or chloral, irritation of a sensory nerve, such as the fifth, no longer has the same effect; and it then always, according to Cyon, lessens the pressure of blood in the arteries. As it is the pressure of blood within the arteries which keeps up the flow within them, just as it is the pressure of water within the pipes supplying a town which keeps up the supply to the houses, we can readily see that the diminished pressure which occurs on the irritation of a sensory nerve, after the cerebral hemispheres have been rendered useless by a small quantity of chloroform, is a most serious thing for the animal. But here it is a little chloroform which is a

dangerous thing; and a full dose prevents any risk from this reflex stoppage of the heart. For the small dose acts on the cerebral hemispheres first, and destroys the reflex action, which contracts the vessels, while it leaves the ganglia at the base of the brain and the medulla unaffected, and thus allows the reflex stoppage of the heart to go on as usual. A full dose, on the other hand, affects not only the cerebral hemispheres, but the ganglia and medulla, and prevents any reflex action whatever on the heart. I have found that, when a full dose of chloroform has been given to a rabbit, one may hold either strong ammonia or glacial acetic acid before the nose, and not the slightest slowness in the beats of the heart can be observed. Sometimes, indeed, it has seemed to beat rather more quickly than before.

Now let us try to apply these observations on the lower animals, and, by them, try to explain the action of chloroform on man, and the danger of employing it in the extraction of teeth, as well as in other slight but painful operations. For it is precisely in these slight but painful operations—extraction of teeth and evulsion of nails—that death most frequently occurs; and it is just in them that little chloroform is given, because the administrator thinks: "Oh, the operation won't last above a few seconds; and it is no use giving the patient enough to keep him or her snoring for half an hour." We know perfectly well that many and many an one has teeth drawn under chloroform without any bad result; and we have already seen that every rabbit has not the same liability to reflex stoppage of the heart from irritation of its fifth nerve; but every now and then we meet with a peculiarly sensitive animal, and every now and again we meet with a case of death from the extraction of a tooth under chloroform.

If the nervous system in man be at all like that of the rabbit, the violent irritation of the fifth nerve caused by the extraction of a tooth will tend to stop the heart. But it will also cause contraction of the blood-vessels; and thus extraction of a tooth in the waking state is rarely attended with any serious consequences. But if the reflex action on the blood-vessels, which usually occurs in the cerebral hemispheres, be prevented by a

small dose of chloroform, just enough, as in the case I have related, to abolish consciousness without preventing reflex action in the ganglia at the base of the brain, and if the heart of the individual be at the same time peculiarly sensitive to the impression made on the fifth nerve, it may be stopped, and the pressure of blood in the arteries may sink so low that it never rises again. But if, on the other hand, chloroform be given, as Professor Syme recommended, with a free hand, so as to produce total abolition of reflex action, no irritation of the fifth nerve by the extraction of any number of teeth will have any effect; the heart will pulsate as usual, and no danger is to be apprehended from this cause.

I do not at all mean to say that the administration of concentrated chloroform-vapour is free from danger—far from it; but the limits of my paper will not allow me to enter into this subject. All I can attempt to do is to direct attention to the observation of Professor Syme, whose acuteness and accuracy few will question, and to try to impress it, by showing the probable physiological reason why one ought always to induce perfect anæsthesia before beginning any operation under chloroform. At the same time, I would observe that, just as the circulation, which had ceased in the frog in Goltz's experiment so long as it hung vertically, went on again when the animal was laid in a horizontal position so that the blood found its way to the heart, so it may go on in man; and, therefore, the safest position for operations is the recumbent one.

The two rules, then, for preventing death during the extraction of teeth under chloroform are: put the patient thoroughly over, and lay him in a horizontal position.

ON IRRITANTS AND COUNTER-IRRITANTS, WITH REMARKS ON THE USE OF BLISTERS IN RHEUMATISM.

(Reprinted from *St. Bartholomew's Hospital Reports*, vol. xi, 1875.)

UNDER the terms irritants and counter-irritants we include those substances which first cause redness and then inflammation when applied to the surface of the body. When they are used for their effect upon the part to which they are applied, as *e.g.*, a blister to a callous ulcer, they may be termed irritants; when used for their effect on a distant part, *e.g.*, a blister to the chest in pneumonia, they may be termed counter-irritants.

But, before beginning to say a word about their action, it may be advisable to try to clear the way by correcting a common error regarding congestion and its relation to inflammation. Congestion generally means that there is more blood than usual in some part or other of the body; but the blood may be either streaming rapidly through the vessels, or stagnant in them, so that the condition in the two cases is utterly different. When the sympathetic nerve is cut in the neck of a rabbit, the vessels of its ear become dilated, the ear itself becomes rosy-red, and the warm blood coursing rapidly through it raises its temperature. We then say that the ear is congested.* If we tie a ligature round a finger, and leave it there for some time, the finger gets swollen, cold, and blue, and we again say the finger is congested. But the different colour of the parts is enough to show us that there is a great and important difference between the congestion in the ear and that in the finger; and as the colour is due to the blood shining through the vessels and tissues, we at once ascribe the rosy colour of the rabbit's ear to bright arterial

* In his lectures on *Surgical Pathology*, Sir James Paget wise y designates what I have here called congestion, as determination of blood to a part, and limits the term congestion to the condititon which is present after stasis has begun.

blood filling the arteries and capillaries, and the dusky hue of the finger-tip to dark venous blood filling the capillaries and veins. But not only is there a difference in the vessels which are distended in these two kinds of congestion, there is also a difference in the current through them. In arterial congestion the blood is streaming rapidly through the vessels, bringing a constant supply of fresh oxygen and fresh nutriment to the tissues, and removing the waste products as rapidly as they are formed, so that the part in which arterial congestion is present is in the best possible conditions for health and growth, and for repair if it should happen to be injured. This arterial congestion is usually distinguished by the term active congestion. In venous congestion there is no doubt more blood than usual in the part, but it is of no service to it, for it is stagnant. Instead of bringing fresh supplies of oxygen and nutriment, it remains in the vessels until its oxygen is entirely consumed, and its colour becomes almost black; the products of waste accumulate in it, and interfere with the nutrition of the tissues, as the ashes in a grate choke the fire. Nor is its injurious action negative only, it is positive as well; for while it does no good itself, it keeps the vessels filled, and prevents any new blood from entering them. This is venous, or, as it is often termed, passive congestion. Judging by the pictures I have just drawn of the two sorts of congestion, one would say there could be no doubt which was the better, and yet one would look more alarmed at the news that some organ was in a state of active congestion than if one were informed that the congestion was passive. The reason of this is, that active congestion is frequently regarded as almost synonymous with inflammation, whereas the two are widely different. Congestion may, and very frequently does, exist without inflammation, and inflammation sometimes exists without congestion, although generally accompanied by it. Nothing is easier than for any one to convince himself of the fact that arterial congestion may exist without inflammation. Let him put his hand into warm water for a little while, and on taking it out he will find the whole skin of a uniform rosy-red, showing that all the capillaries are dilated and filled with bright blood; the veins will swell up,

become light-blue in colour, and, when emptied by gentle pressure, will fill rapidly, showing that they too are full of bright blood, and that the circulation through them is rapid; the hand will be larger than before, and rings which previously fitted will now be too small for the fingers; the skin will be warmer than before, even when time has been allowed for the warmth due to the water to pass off; in fact, three of the signs of inflammation, *rubor, tumor, et calor* will be present, but instead of the *dolor* there will be a feeling of great comfort, whereby the hand signifies to its possessor that it is for the time being in superabundant health. Perhaps the experiment is even clearer if, instead of putting his hand into hot water, the observer will take a look either at his own or his neighbour's hands after a good dinner and several glasses of wine. The same redness and swelling is noticeable, and the warmth can also be observed, although no extraneous heat has been applied to the surface, as it had in the other experiment. Nobody would think of calling the hands inflamed in either of these two instances, for we all know that in a short time the redness, &c., will pass off, leaving them in their ordinary condition. Some may think, however, that if active congestion were to continue for weeks and months, instead of for a few minutes or hours, it would lead to inflammation in the part, but such is not the case. What it does lead to is hypertrophy of the part, the increased supply of nutrient material furnished by the full current of blood leading to increased growth. This was well shown in a rabbit exhibited by Dr. W. Stirling at the recent meeting of the British Medical Association in Edinburgh. Three months previously, Dr. Stirling had divided the sympathetic in the neck of the animal, which was young and growing. The ear at once became red and hot as usual, and instead of the congestion subsiding more or less after some time, as it not unfrequently does, it continued almost unaltered up to the time of the Association's meeting. The ears at the time when the sympathetic was cut were of the same length, but in three months the increased blood supply had caused the congested ear to grow so much faster than the other, that at the time of the meeting it was a quarter of an inch longer than its fellow on the

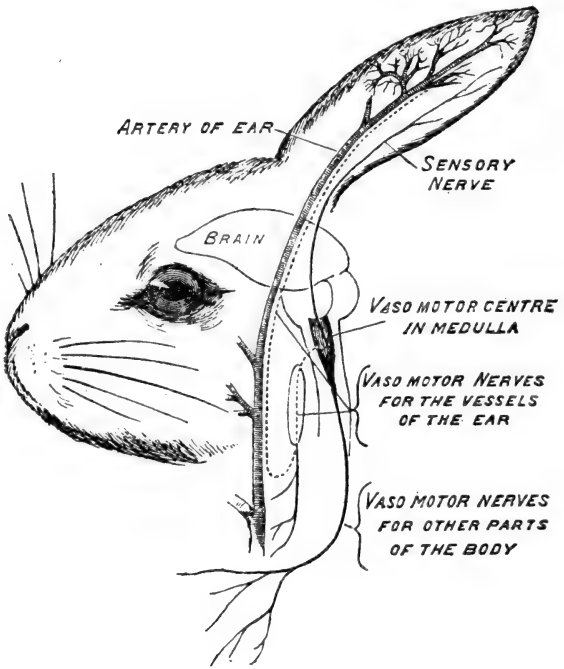
opposite side. It is evident, then, that congestion is not inflammation, and does not cause it even when long continued. That inflammation can take place without congestion, is shown not only by the fact that it occurs in non-vascular tissues, such as the cornea and cartilage, but even more strikingly by the remarkable observation of my friend Dr. Ainslie Hollis, that textural changes similar to those produced by inflammation in higher animals, follow the application of irritants to anemones which have no vascular system whatever.* The two processes of congestion and inflammation are therefore quite different, and each can exist independently of the other. Nevertheless, congestion accompanies inflammation in the great majority of cases, and modifies its progress. While we carefully bear in mind that the two processes are not identical, let us now try to see what the connection is between them, and in doing this, let us begin by inquiring how congestion is produced. From Dr. Stirling's experiment, it is evident that a copious supply of blood is beneficial to the tissues, and that if all the vessels throughout the body were dilated, and blood flowing freely through them, the tissues in general would be much better off than they are. But in order to have these dilated vessels sufficiently full, the body would require twice as much blood as it has; to supply the blood, the digestive organs would need to be larger, and the heart must be more powerful in order to propel it; in short, the individual would require to be re-made on a different plan. The arrangement, which has been found by experiment to exist in animals, is much more economical. The quantity of blood in the vessels is not sufficient to fill them even half full if they were all dilated at once,† but by means of the vaso-motor nerves which have their centre in the medulla oblongata and spinal cord, they are kept in a state of semi-contraction sufficient to enable the blood to fill them. Whenever the vaso-motor nerves are divided, the vessels they supply become dilated, so as to offer little or no resistance to the flow of blood, and the current through them consequently becomes rapid. Thus in the rabbit

* *St. Bartholomew's Hospital Reports*, 1874, p. 267. *Journal of Anatomy and Physiology*, vol. vi, p. 386; vii, p. 80; and viii, p. 124.

† Schiff, *Lo Sperimentale*, 1872, p. 369.

the vaso-motor nerves for the ear pass from the medulla along the cervical sympathetic to the arteries, as shown in Fig. 154. When the cervical sympathetic is cut, the vaso-motor centre can no longer exercise any influence on the arteries of the ear, and they dilate as already described.

FIG. 154.—Diagram of the Vaso-motor Nerves of the Rabbit's Ear.



But there is another way of making them dilate, viz., by causing the vaso-motor centre to cease to exert its usual influence over these vessels, instead of destroying its means of communication with them by cutting the vaso-motor nerves. This can be done by irritating a sensory nerve to the ear. The irritation is conveyed up to the vaso-motor centre, and seems to arrest its action over the vessels supplying the part whence the sensation has come, so that they dilate, and the ear gets red and hot This dilatation, in consequence of irritation applied to a sensory

nerve, is not peculiar to the vessels of the ear—it occurs in all probability in every vessel of the body; and the dilatation from irritation is not confined to the capillaries and small arteries—it extends up to the larger branches, so that the artery of the part is not only wider than usual, but it pulsates forcibly. It is indeed so much greater than that produced by division of the vaso-motor nerve, that some have supposed it to be due to nerves causing the vessels to dilate actively, and not simply to yield to the pressure of the blood in them. But this hypothesis is unnecessary, for Ludwig has found that irritation of a sensory nerve has a double effect: (1) It causes the vessels of the part to which it is distributed to dilate; (2) it causes the vessels in other parts of the body to contract, so that the general blood-pressure is raised, and the blood driven into those vessels which are relaxed. The part supplied by the irritated nerve consequently gets its supply of blood doubly increased by the dilatation of its own vessels, and the contraction of those in other parts of the body. So constant is this contraction, that Ludwig has employed the increased blood-pressure which it causes as an indication that sensory impressions have been conveyed to the nervous centres,* and its great importance in regard to the action of counter-irritants will be hereafter apparent. I ought to say, however, that the contraction really seems to be universal, and to affect more or less the vessels of the part whose nerves have been irritated, as well as those of the rest of the body, but this contraction in them is more than counterbalanced by dilatation. Thus it is that the vessels of this part not unfrequently contract before they dilate, and sometimes the dilatation is transient, and is succeeded by contraction. It may seem strange that the irritation conveyed by a sensory nerve to the vaso-motor centre should arrest its action over some vessels and increase it over others; but this idea only occurs when we forget that what we call the vaso-motor centre is really a collection of ganglionic cells connected with nerves going to different parts of the body, just as a telegraph station may contain numerous instruments, by which messages may be sent to different parts of the country. The adaptation of

* Ludwig and Dittmar, *Ludwig's Arbeiten*, 1870, p. 4.

this arrangement to secure a full supply of blood whenever it is wanted is obvious. Now, as I have already said, a copious blood-supply not only enables the tissues to grow rapidly, but to repair themselves rapidly when injured, and a scanty blood-supply, on the contrary, will cause repair to be slow, and will even induce death and destruction of a part without any other lesion; as, for example, when the circulation is stopped by an embolus. The effects of copious blood-supply in accelerating repair have been beautifully shown by the experiments of Sinitzin.* When the fifth nerve is divided within the skull, ulcers form on the cornea, eyelids, and lips. If the superior-cervical ganglion is torn out, so that the vaso-motor nerves of the vessels of the face are destroyed, and the supply of blood to it increased after these ulcers have formed, they heal up speedily; and if the ganglion is torn out before the fifth nerve is cut, they do not form at all. That the beneficial effect of evulsion of the ganglion is due to the free supply of blood which it produces, is shown by the fact that it has no action whatever if the carotid of the same side is ligatured, so as to prevent the destruction of the vaso-motor nerves from increasing the current. As we have already seen, a still greater supply of blood is secured to a part by irritating its sensory nerves than by dividing its vaso-motor ones, and the utility of this in repairing injured parts is now obvious. When a grain of sand falls into the eye, it irritates the sensory nerves, and immediately the vessels of the conjunctiva fill, as Sinitzin noticed them to do, after evulsion of the sympathetic ganglion, and the free supply of blood is ready to assist the repair of any damage caused by the sand to the delicate structures of the eye, besides supplying materials to the lachrymal gland for the purpose of washing away the offending body. If the grain of sand is now removed, the vessels contract, and the tears being wiped off everything looks as before. There has been congestion, but no inflammation. But if the sand remains longer, inflammation occurs, sero-fibrinous exudation takes place under the conjunctiva, or pus may even be formed.

If we examine the process of inflammation more narrowly by

* *Centralblatt d. med. Wissenschaften*, 1871, p. 161.

using the microscope instead of the unaided eye, we find that irritation, such as a pinch applied to the web of a frog's foot, causes sometimes brief contraction, succeeded by dilatation; at other times, immediate dilatation, first of the arteries, then of the veins and lastly of the capillaries, at the site of irritation, and at the same time, the velocity of the current through them becomes greatly increased.* After a while the arteries contract again, the contraction beginning at a distance from the irritated spot, and progressing towards it. This contraction interferes with the current of blood, and its velocity in the arteries beyond becomes reduced to the normal. Next the capillaries contract, but the veins still remain dilated; the current in them becomes slow, and white blood-corpuscles stick to their sides; but after a little they also contract, and the normal circulation becomes completely restored.

If a piece of caustic is applied to the web, similar changes are produced: all the vessels in the neighbourhood, for some distance around, dilate, and the blood streams through them with great velocity. But here a remarkable condition makes its appearance which was not present in the previous experiment. Although the capillaries of the injured part remain dilated, and the blood is streaming with unabated rapidity in the vessels all around, it begins to get slower in them; the red corpuscles seem to find an impediment in their way, and accumulate in these capillaries, like the vehicles in one of the crowded streets of the City during a block. The current in the arteries and veins likewise becomes slow; the so-called lymph-spaces, which, like sidewalks, run along the interior of the arterial walls, and are usually free from blood corpuscles, become invaded; the corpuscles oscillate backwards and forwards, as if in a vain attempt to proceed, and then, becoming stationary, seem to form an almost solid mass. By-and-by the vessels in the neighbourhood contract again, and the current in them becomes normal; but those vessels which lead directly into the cauterised part—arteries as well as veins—remain permanently dilated. The stasis in the capillaries extends over a wider area; a few red corpuscles pass through the walls of the capillaries, and colourless corpuscles

* Lister, *Phil. Trans.*, 1858, p. 645. Cohnheim, *Neue Untersuchungen.*

FIG. 155.—Blood-vessels in normal condition.

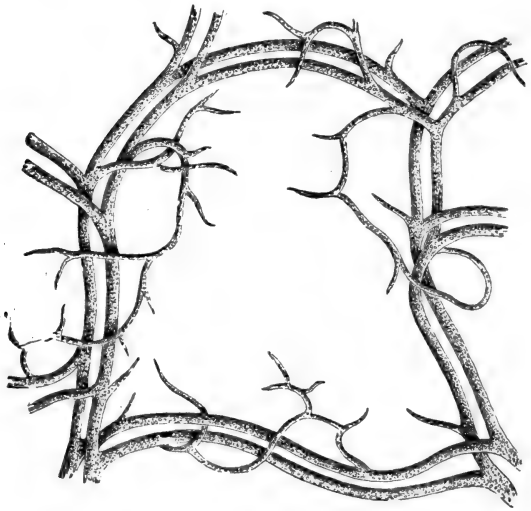
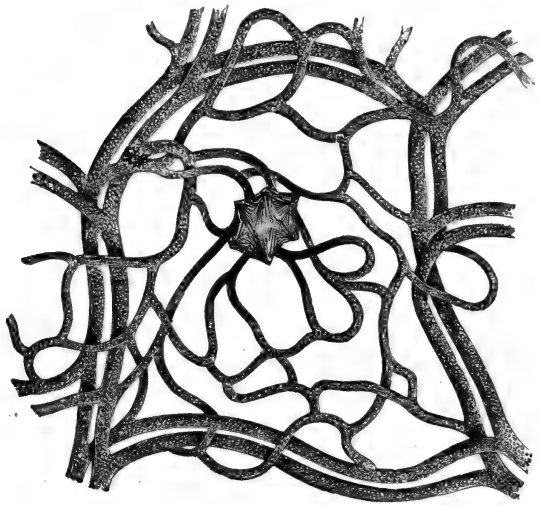


FIG. 156.—Same Vessels after the application of an Irritant and commencement of Inflammation.



emigrate in numbers from both the capillaries and the veins forming in great measure, if not altogether, the pus with which

we are familiar as one of the products of inflammation. After the pinch, then, we have had merely congestion; after the caustic, inflammation. But in both we have had a similar dilatation in the calibre of the vessels, a similar increase in the velocity of the circulation. Where, then, are we to draw the line between congestion and inflammation? This question has been well answered by Sir James Paget, who says that the line appears to be crossed "when the circulation, which was rapid, begins to grow slower without any diminution, but it may be with an increase, in the size of the vessels." According to Cohnheim, the changes which are observed in the diameter of the vessels are mere accessories, and not integral parts of the inflammatory process; and he also makes the slowing of the circulation and stasis coincide with the commencement of inflammation.*

There is no doubt about the fact, but it is difficult to see why the blood corpuscles should stand still in a vessel where there is no apparent obstruction, and many explanations have been advanced to account for the phenomenon. The one which finds most general acceptation at present is that of Cohnheim, who believes that it consists in some alteration in the tissues, which begins in those forming the walls of the blood-vessels, or immediately adjacent to them. This opinion is supported by the observation of Ryneck,† that stasis may be noticed in vessels where the blood has been washed out and replaced by milk. The milk globules accumulate in the capillaries of the irritated part in much the same way as the corpuscles usually do. This would seem to show conclusively that it is the vessel, and not the blood it contains, which obstructs circulation and leads to stasis. Yet it is hard to see how the appearances observed are to be explained thus, and they are exactly those which we should expect from the blood suddenly becoming thicker, and consequently flowing less easily. Both Henle and Wharton Jones have adopted this view, the former supposing that the blood became thicker, both by the plasma losing water by exudation through the walls, and by having the proportion

* Paget, *Surgical Pathology*, 1863, p. 227. Cohnheim, *Neue Untersuchungen.*

† Ryneck, *Rollett's Untersuchungen*, 1870, p. 103.

of its albuminous constituents increased. The two brothers Ernest Heinrich and Edward Weber ascribed it, without more ado, to coagulation of the blood in the capillaries ; and it seems to me that the view taken by those two wonderful men, although long forgotten, is after all the right one.* It does not conflict with that of Cohnheim, for the coagulation, if such be present, no doubt owes its occurrence to changes in the vessels. Brücke† has found that, while blood remains fluid in living and healthy vessels, it coagulates in them when they die, so that we would naturally expect any injury which lessened their vitality would tend to cause coagulation within them ; and Wharton Jones has actually noticed coagula form in the vessels after pressure upon them. The absence of any fibrinous threads in the interior of the vessels of inflamed parts does not in the least disprove coagulation ; for, when experimenting with the plasma from horses' blood, I have seen the contents of a glass tube, from 1 to 2¼ inches in diameter, in which there were three layers, the upper one of pure liquor sanguinis, the middle of liquor sanguinis *plus* white blood-corpuscles, and the third of red corpuscles with liquor sanguinis, all apparently fluid. It was only when I attempted to turn them out that I found coagulation had occurred. Even when turned out, the soft clots showed no sign of structure, until they had been squeezed in the hand, and then fibrinous threads became perceptible. If coagulation thus failed to become visible in such a large tube, the absence of any easily recognised sign of it in a small capillary is not astonishing. The chief difficulty in the way of accepting Weber's theory is the occurrence of stasis, when defibrinated blood or milk is made to circulate through the vessels. But defibrinated blood, when made to circulate in this way, takes up something while in the vessels, which re-imparts to it the power to coagulate, so that it may form a clot after it has issued from the veins. So far as I know, no similar experiments have been made with milk, but it is possible that it too acquires so much coagulating power as to cause stasis. In the absence of the requisite data, it is impossible to look upon

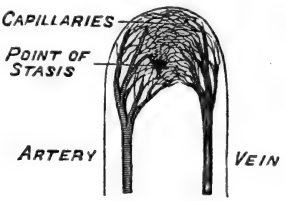
* *Virchow's Archiv*, 1857, p. 152.

† Brücke, *Virchow's Archiv*, 1857, p. 183.

Weber's explanation of stasis as anything more than an hypothesis; but, as I have already said, I am inclined to adopt it, and to consider that inflammation begins in vertebrates when coagulation occurs in the capillaries, and arrests the flow of blood through them.

But whether this view be taken or not, the facts are certain, that stoppage of the circulation does occur in the irritated capillaries, and that the arteries leading to the part are dilated. What the cause of the pain in inflammation is, we do not exactly know; but it seems very probable that it depends to a great extent on the stretching of the vessels, and the nerves surrounding them, at or near the site of stasis, by the blood which is driven into them through the dilated arteries. For, as every one knows, the pain of inflammation is of a throbbing character; it is increased at each time the vessel is distended by a beat of the heart, and relieved by lessening the supply of blood. Now, the supply of blood can be lessened in several ways, and several means, apparently of an entirely opposite nature, are used to relieve pain. Supposing that we take as an example an inflammation of the tip of the finger, it is easy to understand how it may be relieved by pressure on the radial artery, or by raising the hand to the level of the shoulder, and may be aggravated by allowing the arm to hang dependent by the side. But how is it that the pain in the finger may be relieved by dipping it in cold water, and also by the application of a warm poultice? I believe the answer to this question to be that the cold causes the arteries above the point of stasis (Fig. 157) to contract—and thus lessens the force of the current of blood which is being pumped upon that point. The warm poultice, on the other hand, dilates those capillaries in which circulation is still going on, and by thus offering another channel to the blood, lessens the force of the current against the point of stasis. It is well known, too, that the pain of a burn can be greatly lessened by holding the burnt part before a fire. But, as I can testify from personal experience, the pain is first greatly increased before it is relieved. I placed a red-hot coal on the back of my hand until the skin was corrugated and glazed. I then held it before a brisk fire for some time. At

first the pain became so severe that I was tempted to withdraw my hand; but by-and-by the pain became easier, and almost entirely disappeared shortly after I had finally taken my hand away. The explanation of this I fancy to be, that at first the burn caused stasis in the capillaries of the part to which I



applied the coal, and that the irritation to the sensory nerves caused the vessels to dilate, as in Loven's experiment. The blood being driven down on the obstructed vessels, produced distension and pain, which was increased when the warmth of the fire caused the larger arteries to dilate still further. But after the warmth began to dilate the capillaries of the hand, the blood passed through the newly enlarged channels, and its impact on the obstructed vessels being thus removed, the pain ceased.

In the days when blood-letting was much in vogue, it was found to be a matter of every-day experience that the pain of inflammation was removed for a time by opening a vein; and although the pain again returned, the abstraction of a further quantity again relieved it. The relief is explained by the general diminution in the blood-pressure after phlebotomy lessening the tension of the vessels of the inflamed part; while the return of the pain is in all probability due to the fact that after the abstraction of blood the vessels contract, so as to accommodate themselves to their diminished contents, and thus raise the pressure again. Unluckily, however, blood-letting does something more than diminish the tension within the vessels of the inflamed part in common with those of the rest of the body; it drains away the vital fluid, and seriously impairs the power of restoration. It is evident, therefore, that

if we can lessen the tension in the vessels of an inflamed part, either by causing the arteries to contract or the capillaries to dilate, we shall do more service to the body than if we weaken the whole of it to relieve a part. This, I believe, we can do by means of counter-irritants. I have already mentioned that the application of an irritant causes contraction of the vessels of other parts of the body, at the same time that it induces dilatation in those of the injured part, but this action will not afford us much help, if all the vessels are contracted alike, for then the blood would pour with increased pressure into the dilated vessels of the inflamed part, and the pain would be worse than before. But clinical experience shows that irritation to the surface of the body will relieve internal pain, and a mustard poultice or blister to the side in pleurisy frequently, indeed generally, gives more or less relief. And there are several facts which tend to show that just as irritation applied to different portions of the skin will induce definite reflex movements distinct from each other,* so irritation applied to different parts of the surface will induce contraction in different sets of vessels, a definite correspondence existing between the part irritated and the set of vessels which contract. Ludwig and Loven† observed that when the sensory nerve of one ear was irritated, dilatation of the vessels was sometimes observed in the other ear also, although it was much less, and generally was replaced by contraction sooner than on the side operated upon; and Callenfels‡ noticed that pinching one ear caused contraction in the vessels of the other. Plunging one hand into cold water has been observed to cause cooling of the opposite hand, an effect which must be due to contraction of the vessels. But the most important experiments on this point are those of Zülzer,§ who painted cantharides collodion repeatedly over a part of the back of a rabbit for 14 days. At the end of this time he found that the vessels underneath the skin were much dilated and filled with blood, and the superficial muscles were

* Sanders-Ezn, *Ludwig's Arbeiten*, 1867, p. 11.
† *Ludwig's Arbeiten*, 1866, p. 11.
‡ Callenfels, *Zeitsch. f. rat. Med.*, 1855; Bd. vii, p. 191.
§ Zülzer, *Deutsche Klinik*, 1865.

hyperæmic. Those of the deeper layers, on the contrary, as well as the thoracic wall, were much paler than on the uninjured side, and even the lung itself was anæmic. When a hair seton was left in the knee of a rabbit for four weeks, suppuration was induced immediately around it, but the muscles around the joint, and the joint itself, were very anæmic when compared with the corresponding parts on the uninjured limb.

Supposing that the effects of blisters on man are similar to those upon rabbits, we can understand the benefits derived from their use in inflammation of internal organs. If the pericardium, pleura, or lung itself is inflamed, the application of a blister to the chest will cause contraction of the arteries in them, and lessen the pain, just as pressure on the radial or brachial would do in inflammation of the finger. Their beneficial action in pericarditis is well illustrated by two cases which, in the absence of Dr. Church, I lately had under my care. J. E., a male aged 25, was admitted into John Ward on September 13, suffering from a first attack of rheumatism. Both wrists and knees were swollen and painful. At 11 o'clock on the morning of admission the heart sounds were normal. At 2 P.M. a distinct pericardial friction was heard. A blister was applied over the cardiac region, blisters to both wrists, and poultices to the knees. Next day the friction had entirely gone, and the pain in the wrists disappeared, although it still continued in the knees. On the succeeding day a friction sound was again audible, but the pain in the wrists never returned. A blister was again applied to the cardiac region. Next day the friction had disappeared, and did not return. No increased dulness in the cardiac region could be detected. E. B., a female aged 16, was admitted for scarlatina into Elizabeth Ward, on September 6. On the 13th an acute attack of rheumatism came on, with swelling and pain in the wrists, and distinct pericardial friction. In this case also a blister was applied to the cardiac region within four hours of the appearance of the friction. Next day the friction had entirely disappeared, the pains in the wrists were less, and on the succeeding day were entirely gone.

In both of these cases I believe that, had we been able to examine the pericardium at the time the blister was applied, we

should have found the membrane dry and injected, without any deposit whatever on its surface. The irritation caused by the application of the blister to the thoracic wall acted reflexly through the vaso-motor centre in the medulla oblongata, and induced contraction of the pericardial arteries, and a more or less complete return to the normal condition. In the case of E. B., it might be said that perhaps the friction would have disappeared even had no blister been applied; but it is improbable that in the case of J. E. it would have reappeared on a succeeding day, had its first disappearance been spontaneous, and not the effect of the blister. The cessation of pain in the joints I also attribute to contraction of the arteries in them, induced by the blister, which had thus had an effect similar to that of a hair seton in Zülzer's experiment. Several other cases of acute rheumatism which I have had under my care this autumn have convinced me of the efficacy of blisters to the joints in young persons, especially those suffering from a first attack, and in whom the vessels and tissues are probably normal; but in elderly persons who have suffered from repeated attacks, the benefit derived from blisters has not been great.

Having now considered the action of blisters as counter-irritants, let us turn for an instant to their action as irritants. One of the best means of treating a callous ulcer is to blister it. Here the irritation of the blister dilates the vessels around the ulcer, and by affording a free supply of blood, bringing fresh oxygen and fresh nutriment, the ulcer is healed just like those on the eye in Sinitzin's experiments.

The points which I have tried to show in this paper are—

1. That dilatation of blood-vessels, and a rapid circulation through them, is advantageous for the tissues, and leads to increased growth and more rapid repair. While this arterial or active congestion is beneficial, venous or passive congestion is injurious.

2. The application of an irritant induces dilatation of the vessels, and a free current of blood through them. This will help to repair any injury done to the tissues by the irritant, so that the injury, to a certain extent, brings its own remedy.

3. Arterial congestion and inflammation are entirely different

from and independent of each other, although they generally occur together.

4. Arterial congestion passes into inflammation when stasis begins to occur in the capillaries.

5. Stasis is not improbably due, as supposed by the brothers Weber, to coagulation of blood in the capillaries, the coagulation being induced by changes in the tissues composing the walls of the vessels, or immediately surrounding them.

6. Pain in an inflamed part is probably due to distension of vessels and pressure on nerves by the blood being pumped with violence through the dilated arteries against the obstruction in the capillaries.

7. Pain may be relieved by lessening tension in various ways: by position—by cold—by warmth—by blood-letting—by counter-irritants.

8. Cold probably relieves tension by contraction of the arteries going to the inflamed part, warmth by dilating the capillaries of the surrounding parts, and thus drawing away the blood from the seat of inflammation.

9. At the same time that an irritant causes dilatation of the vessels in the part to which it is applied, it causes contraction of the vessels in other parts of the body.

10. It is probable that it does not cause contraction in all parts alike, but that definite areas of skin correspond to definite sets of internal vessels.

11. The relief of pain produced by a blister in pleurisy, pneumonia, or rheumatic inflammation of a joint, is probably due to reflex contraction of the arteries in these parts.

12. Blisters are useful in lessening congestion in pericarditis, and in relieving the pain of inflamed joints in rheumatism.*

13. The benefit derived from their use in young persons, especially those suffering from a first attack, is very great. In elderly persons it is inconsiderable.

14. The beneficial action of a blister in callous ulcer is probably due to the increased supply of blood to the part, induced by its application.

* Introduced by Dr. Herbert Davies, *Lond. Hosp. Rep.*

A SIMPLE METHOD OF DEMONSTRATING THE EFFECT OF HEAT AND POISONS UPON THE HEART OF THE FROG.

(From the *Journal of Anatomy and Physiology*, vol. x, 1876.)

THE fact that heat accelerates and cold retards the pulsations of the heart, is one of such fundamental importance, both in regard to a right understanding of the quick pulse, which is one of the most prominent symptoms of fever, and to a correct knowledge of the proper treatment to apply when the heart's action is failing, that for the last year or two I have been accustomed to demonstrate it as a lecture experiment. The apparatus I use is exceedingly simple, but it answers its purpose well, and by its means the pulsations of the frog's heart can be readily shown to several hundred persons at once. I exhibited it at the meeting of the British Medical Association in London more than two years ago, and a description of it appeared in the *British Medical Journal* for August 23, 1873; but as I have reason to believe that few physiologists have seen either the instrument or its description, it may not be amiss to say a few words regarding it here. It consists of a piece of tin plate or glass 3 or 4 inches long and 2 or 3 wide, at one end of which an ordinary cork cut square is fastened with sealing-wax in such a manner that it projects half an inch or more beyond the edge of the plate. This serves as a support to a little wooden lever about 3 inches long, a quarter of an inch broad, and one-eighth of an inch thick. A pin is passed through a hole in the centre of this lever, and runs into the cork so that the lever swings freely about upon it as on a pivot. The easiest way of making a hole of the proper size, is simply to heat the pin red hot, and then to burn a hole in the lever with it. To prevent the lever from sliding along the pin, a minute piece of cardboard is put at each side of it, and oiled to prevent friction. A long fine bonnet straw or

section of one is then fastened by sealing-wax to one end of the lever, and to the other end of the straw a round piece of white paper cut to the size of a shilling or half-crown, according to convenience, is also fixed by a drop of sealing-wax. The pin, which acts as a pivot, should be just sufficiently beyond the edge of the plate to allow the lever to move freely, and the lever itself should lie flat upon the plate. Its weight too, increased as it is by the straw and paper flag, would now be too great for the heart to lift, and so it must be counterpoised. This is readily done by clasping a pair of bull-dog forceps on the other end. By altering the position of the forceps the weight of the lever can be regulated with great nicety. If the forceps are drawn back as at *c*, Fig. 158, the flag is more than counterbalanced, and does not rest on the heart at all, while the position *a* brings the centre of gravity of the forceps in front of the pivot, and increases the pressure of the lever on the heart. The isolated frog's heart is laid under the lever near the pivot

FIG. 158.—Instrument for showing the Action of Heat and Cold and of Poisons on the Frog's Heart.

and as it beats the lever oscillates upwards and downwards. If the tin plate be now laid on some pounded ice the pulsations will become slower and slower, and if the room be not too warm the heart may stand completely still in diastole. On removing the plate from the ice the pulsations of the heart become quicker. If a spirit-lamp be now held at some distance below it the heart beats quicker and quicker as the heat increases, until at last it stands still in heat tetanus. On again cooling it by the ice its pulsations recommence. At first they are quick, but they gradually become slower and slower. On again applying the spirit-lamp they become quicker, and by

raising the temperature sufficiently the heat tetanus is converted into heat rigor. Then no application of cold has the slightest effect in restoring pulsation.

Not only the effects of heat and cold, but the effect of separating the venous sinus or the auricles from the ventricle can readily be shown with this apparatus, as well as the action of various poisons. The best for the purpose of class demonstration is muscaria. A drop of saline solution containing a little of the alkaloid being placed on the heart, it ceases to beat entirely. If a drop of atropia solution be now added the beats recommence. I have seen them do so on one occasion after they had entirely ceased for four hours. When used for demonstrating the action of poisons the wooden lever should be covered with sealing-wax, so as to allow every particle of the poison to be washed off it, and thus prevent any portion from being left behind and interfering with a future experiment. By attaching a small point to the end of the straw in place of the paper flag, tracings may be taken upon smoked paper fixed on a revolving cylinder.

PHYSIOLOGICAL ACTION OF THE BARK OF *ERYTHROPHLEUM GUINENSE* (CASCA, CASSA, OR SASSY BARK).

In conjunction with WALTER PYE, M.R.C.S.

(From the *Proceedings of the Royal Society*, No. 172, 1876.)

(Abstract.)

1. It diminishes oxidation, and thus prevents fresh vegetable tissues from communicating a blue colour to tincture of guaiac.

2. It does not hinder the development of the yeast-fungus nor the germination of seeds.

Penicillium grows freely in a solution of it.

3. A watery solution of the alcoholic extract prevents the development of *Bacteria*, but one of the watery extract does not do so.

4. It does not destroy the life of *Bacteria* or Infusoria. The motion of cilia is not arrested by it.

5. It arrests amœboid movement in leucocytes.

6. It has no action on fresh muscular fibre; but muscular tissue, when kept in a solution of the alcoholic extract for some days, undergoes extensive fatty metamorphosis, but does not become putrid.

It does not alter the sensibility of muscle to electrical stimuli, nor does it diminish its lifting power.

7. It has little, if any, poisonous action on the Invertebrata.

8. It has a comparatively slight action on fishes and frogs. The symptoms produced by its administration are failure of muscular power, preceded by irregular muscular movement.

9. On birds a small dose produces violent vomiting and irregular muscular movements, with difficult respiration. These symptoms are followed by loss of muscular power and death.

10. In cats and dogs the symptoms are restlessness, nausea succeeded by violent vomiting, spasmodic jerks of the limbs during locomotion, quickened respiration, staggering gait, inability to stand, and death generally during a convulsion of an emprosthotonic character, apparently connected with an attempt to vomit. Consciousness seems to be preserved to the last.

When injected subcutaneously, although it produces violent vomiting, it never purges; division of the vagi before its administration lessens or prevents the vomiting usually observed, as well as the other symptoms of distress; and in one instance a dose which would ordinarily have been speedily fatal produced no apparent effect in an animal thus operated on.

11. When injected into the stomach of a cat it produces violent vomiting and purging. Sometimes this is followed by recovery, in other cases by loss of muscular power and death.

12. Injection of atropia does not prevent death; and although in one case it prolonged life for two hours, in other instances it seemed rather to accelerate a fatal issue.

13. It causes the heart in frogs to pulsate more slowly; the ventricle becomes irregularly contracted, leaving pouches over the surface, and finally is arrested in systole; the auricles contract for some time longer.

14. In cats the ventricle also becomes irregularly contracted before finally stopping.

15. In frogs it causes no rise of the blood-pressure in the aorta, but raises the oscillation of the mercurial column connected with the vessel to three times its previous height.

16. In cats and dogs moderate doses injected into the jugular vein first raise the blood-pressure without altering the rate of cardiac pulsation or the extent of oscillation at each beat; they then slow the heart by stimulating the roots of the vagus. The tension rises, notwithstanding the slowness of the heart's beats. An additional dose paralyses the ends of the vagus in the heart, and quickens its pulsations; the pressure rises slightly. A further dose again slows the heart by acting on its ganglionic apparatus, and the beats sometimes fall as low as three per

minute, three or four respirations occurring during each cardiac diastole. Notwithstanding the very slow action of the heart, the pressure may remain as high as 165 millimetres of mercury, a fact which indicates that the arterioles are in a state of extreme contraction. After the heart has ceased, the pressure falls very slowly. Slight pulsations of the ventricle occasionally occur when the thorax is opened.

17. Small doses do not seem to increase the excitability of the peripheral ends of the vagi to electrical stimuli; moderate and large doses paralyse these nerves.

18. After injection of casca into the veins of an animal completely narcotised by chloroform, electrical irritation of the central end of the divided vagus of one side, the other remaining intact, is followed after a short interval by marked slowing of the pulse, fall of blood-pressure and increased oscillation.

19. When injected into the veins of a cat after division of the spinal cord opposite the second cervical vertebra, the blood-pressure rises to a greater height than is attained under other conditions.

20. When in the rabbit the sympathetic has been divided in the neck on one side, subsequent injection of casca into the jugular vein produces pallor of the recently congested ear of the side on which the division had been made.

21. When locally applied to the web of a frog's foot temporary slowing of the circulation was observed, but no alteration in the diameter of the blood-vessels.

When injected beneath the skin of the back of a frog it produces no visible effect on the vessels of the web.

22. It does not appear to possess any special action on reflex excitability.

23. In moderate doses it increases the secretion of urine at the same time that it raises the blood pressure. Further doses diminish the secretion, while they raise the pressure yet more; and at the time when the pressure reaches its maximum the secretion of urine is entirely arrested. When the pressure begins to fall the secretion of urine again commences. The urine collected after the recommencement of the secretion was not albuminous.

24. When injected into a loop of intestine it does not increase the secretion, nor does it produce any distinct congestion.

25. When applied to the eye it has no action on the pupil, nor does it cause congestion of the conjunctiva or lachrymation.

26. When administered to a pregnant cat it did not produce abortion.

27. The temperature of the body is not affected by administration of the drug.

ON THE PHYSIOLOGICAL ACTION OF CASCA BARK.

In conjunction with WALTER PYE.

(Reprinted from *St. Bartholomew's Hospital Reports*, 1876, vol. xii.)

THE practice of subjecting persons suspected of crime or witchcraft to an ordeal by poison prevails very extensively along the western coast of Africa. The poison employed is not the same along the whole coast-line. In Calabar, which lies about the middle, the natives employ the bean of the *Physostigma venenosum*, or, as it is generally called, the Calabar bean. To the north of Calabar, in Sierra Leone, and to the south, in Angola, the favourite ordeal poison is not a fruit, but a bark, which bears in different districts the names of "doom," "gidu," and "sassy," "saucy," "cassa," or "casca." This bark is obtained from the *Erythrophleum Guïnense*, which, like the *Physostigma venenosum*, belongs to the natural order *Leguminosæ*. The bark is of a brownish-red colour, is in pieces about 8 inches long, 4 broad, and between $\frac{1}{4}$ and $\frac{1}{2}$ thick. When treated with water it yields a brownish-red infusion.

There are two ways in which it is employed by the natives. One is to make the suspected person fast for several hours, and then to give him a few grains of rice and some infusion of the bark. If he vomits all the grains of rice and is not purged, he is said to be innocent; but if he is purged, he is pronounced guilty The other way is to bend both ends of several boughs of trees into the ground so as to form a long archway, through which the accused walks in a stooping position after a dose of the infusion has been administered. If he is able to walk through without stumbling, he is considered to be innocent; but if he stumbles, he is said to be guilty and at once despatched. The chief effects of the poison by which the innocence or guilt of the accused are decided are thus vomiting,

purging, and loss of muscular power or co-ordination. The effects of the poison on man, as described by some missionaries, are vomiting, redness and glazing of the eyes, and loss of the power of contracting the muscles throughout the body; so that when the poison has fairly commenced its action on the system, the sufferer is incapable of standing or walking, and the head rolls heavily about the breast and shoulders. Its action on animals was tried by Santos,* who says that the decoction produced alternate dilatation and contraction of the pupils, appearance of delirium, violent retching, vomiting, symptoms of tetanus, and finally death. Professor Liebreich has also investigated its physiological action, but we have not yet seen a full account of his experiments.

A small quantity of the bark having been brought from Angola by Mr. Monteiro, who had obtained it with considerable difficulty, he kindly gave it to us, and we began a minute investigation of its physiological action, so as to ascertain not only the exact manner in which death is produced by the drug, but the mode in which the various functions are affected by it, and its possible uses in medicine.

General Action of Casca.

Beginning our experiments with the simplest forms of life, and proceeding to the more complex, we found that a watery extract of the bark did not interfere in the least with the germination of seeds; it did not hinder the growth of the yeast fungus, and ordinary mould (*Penicillium*) grows freely in it. It does not destroy full-grown bacteria nor infusoria; nor does a watery solution of the aqueous extract prevent the development of bacteria, but a watery solution of the alcoholic extract does so, a fact which seems to indicate the presence in the alcoholic extract of some principle which is absent from the aqueous extract. It has little or no action on invertebrate animals such as snails. On fishes and frogs its action, though much less than on warm-blooded animals, is nevertheless quite distinct, its administration being followed by irregular mus-

* *American Journal of Pharmacy*, April, 1849, p. 96.

cular movements and failure of muscular power. Birds are easily affected by it, a small dose producing violent vomiting and irregular muscular movements with difficult respiration. These symptoms are followed by loss of muscular power and death.

In cats and dogs it causes restlessness and nausea succeeded by violent and repeated vomiting. The respiration is very much quickened. The first symptom of any affection of the locomotor organs in cats is a peculiar jerk of the hind limbs, as if something were sticking to the feet, and the animal were trying to shake it off while walking; then the gait becomes staggering, and the animal ceases to be able to stand. Death generally occurs during a convulsion of an emprosthotonic character, apparently connected with an attempt to vomit. Consciousness seems to be preserved to the last.

The symptoms observed by us thus agree in most respects with those described by Santos, but we saw no appearance of delirium, nor any alternate contraction and dilatation of the pupil, although we looked for it carefully.

Analysis of the Symptoms produced by Casca.

Vomiting and Purging.—It has already been mentioned that while vomiting in those subjected to the ordeal by casca is regarded as a sign of innocence, purging is considered to be a proof of guilt. It is stated that the priests who prepare the infusion are able to produce either effect at will, the clear infusion being given to those whom they wish to prove innocent, while the dregs are administered to those who have offended them, or who at any rate have not propitiated them. In order to ascertain whether this was so or not we administered an infusion without the dregs to one cat, and an infusion with the dregs to another; but the result was contrary to what we expected, the one which had got the dregs recovering, while the other died. This might, however, be due to the fact that the infusion with which we operated was prepared from finely-pounded bark, which would readily yield up its active principle to water, while the infusion is probably prepared by

the priests from coarsely-pounded bark, from which water would extract the poison more slowly; and if only allowed to remain a short time in contact with the bark, the infusion would be comparatively weak, while the dregs themselves would yield up their active principle in the stomach after being swallowed, and thus have a much more powerful action. The purging is due to the local effect of the poison on the intestines, for it only occurred when the poison was given by the mouth, and was never present when the drug was administered by subcutaneous injection. Vomiting, on the contrary, occurred as constantly when the casca was injected subcutaneously as when given by the mouth. The vomiting after subcutaneous injection of the drug is probably due to its being carried with the blood to the stomach, and irritating the sensory nerves of that organ in much the same way as when introduced directly into it. The reason why we believe the vomiting to be due to irritation of the nerves of the stomach rather than to the action of the drug upon the vomiting centre in the medulla oblongata, is that when the vagi nerves were divided in the neck of one cat, a dose which would ordinarily have proved fatal produced no vomiting, nor indeed any of the usual symptoms. In other cases where vomiting occurred even after division of the vagi, it was less than usual, and it might be due to the irritation being conveyed from the stomach to the medulla by branches of the solar plexus instead of by the vagi. The purging is probably due to increased peristaltic action rather than to increased secretion, for infusion of casca introduced into a loop of intestine produced no increased secretion, as a solution of sulphate of magnesia would have done.

Muscular Weakness.—Want of power to walk properly is the second symptom regarded as a proof of guilt in those subjected to the ordeal, those who stumble before they reach the end of the archway of boughs being at once executed. In attempting to ascertain the cause of this loss of power, we worked backwards thus: The motions of the limbs are due to the contraction of muscles. The contraction of muscles is due to the stimuli they receive from motor nerves. The stimuli which pass down motor nerves to muscles proceed from nerve-centres in

the spinal cord or encephalon. Thus loss of muscular power may be due to loss of power either in the muscles themselves—in the motor nerves which supply them—or in the nerve-centres in the spinal cord or encephalon.

Action on Muscles.—This was tested by laying one gastrocnemius of a frog in a solution of casca, and the other in an indifferent liquid, such as a ·75 per cent. solution of common salt. After some time the excitability of the two muscles by electrical stimuli was compared, and also their power to lift weights. They were found to be equal. This showed that casca was not a muscular poison, for had it been so, the muscle immersed in a solution of it would have lost its excitability before the other, and its power to lift a weight would have been lessened.

Action on Motor Nerves.—In order to ascertain whether the motor nerves were paralysed or not, the artery going to one leg of a frog was ligatured and the poison injected under the skin of the back. The poison was thus carried to every part of the frog except the ligatured leg. Immediately after death the excitability of the motor nerves was tested by the application of an induced electrical current from a Du Bois Reymond's coil. It was found that the motor nerves of the leg to which the poison had been carried by the blood were not paralysed, and were quite as easily excited as those of the other leg from which the poison had been excluded by ligature of the artery. The poison, therefore, does not paralyse the motor nerves.

Action on the Spinal Cord.—Some time after the injection of casca under the skin of a frog the movements of the animal become more sluggish, are imperfectly performed; and when the toes are pinched, the foot is either moved lazily or not at all, instead of being promptly drawn up, as it normally is. The reflex activity of the cord is thus seen to be impaired, but we must not hastily conclude that this impairment is due to the direct action of the drug upon the nervous structures; for imperfect circulation of blood through the brain and spinal cord quickly deprives them of their power, and although stoppage of the circulation does not abolish the

functional power of the nerve-centres so quickly in the frog as in warm-blooded animals, it nevertheless does so after a time. In order to discover whether the casca destroyed the power of the spinal cord by acting directly upon it or not, its action upon the heart was investigated, and we found that a short time after its administration it arrested the pulsations of that organ. It seemed, therefore, quite possible that the loss of power in the spinal cord was simply due to stoppage of the heart by the poison, but of course this was only probability, as the casca might act both on the cord and the heart. We decided this point, however, by administering casca to one frog, and waiting until the heart had stopped. The instant it had done so, we arrested the circulation in a frog of a similar kind and size by a ligature around the large vessels as they arose from the heart. In these two frogs the circulation was equally arrested, but in one of them the poison had been previously carried by the blood to the spinal cord, and could still act upon it although the flow of blood was stopped. If the casca had any paralysing action upon the nervous structures of the cord itself, reflex action ought to have ceased in the poisoned frog before doing so in the ligatured frog, but this was not the case. In both frogs reflex action ceased in almost exactly the same time. The abolition of the function of the spinal cord is therefore due to stoppage of the circulation caused by the casca, and not to the action of the drug upon the cord itself. The staggering gait, inability to stand, and paralysis which we have observed in dogs and cats, we attribute, like the paralysis in frogs, to disturbance of the circulation, and not to any special action on the nerve-centres.

Action on Circulation. Action on the Heart.—The first action of casca upon the heart of the frog is to cause it to beat more slowly, then the ventricle becomes irregularly contracted, some parts of it being firmly contracted and white, while here and there other points are not contracted, and being filled with blood, look like little red pouches studding the cardiac surface. Finally, the ventricle stops altogether in a state of contraction, while the auricles continue to pulsate for some time longer. In cats also the ventricle sometimes becomes irregularly con-

tracted before finally stopping, the lower part of the ventricle in one experiment having been contracted, while the upper half was not, so that the lower half appeared to be partly pushed up into the upper in such a way as to produce a deep transverse wrinkle across the middle of the ventricle.

Action on the Vagus.—It will be seen from the description thus given that the action of casca upon the heart of the frog is almost exactly like that of digitalis, as described by Messrs. Fagge and Stevenson.* Further experiments have shown us that casca also resembles digitalis in its action upon the vagus. A moderate dose of casca injected into the jugular vein first slows the heart, a further dose greatly quickens it, and another large dose again slows it. The first slowing is due to stimulation of the vagus roots in the medulla oblongata, for when the vagi are divided so as to cut the communication between the medulla and the heart, the pulsations again become quick. The quickening which a large dose of casca produces when the vagi are uninjured is due to its paralysing the ends of these nerves in the heart, and thus destroying the communication between this organ and the medulla quite as effectually as the division of their trunks by the knife. When the nerves, as they pass down the neck, are irritated by an induced galvanic current in their normal condition, they slow the pulsations of the heart, or stop it altogether; but after the injection of casca has paralysed their ends in the heart, no irritation of their trunks has any power to slow its pulsations. The final slowing produced by a large dose of casca must be due to the action of the drug upon the ganglionic apparatus within the heart itself, as the vagus ends are already paralysed. The extreme slowness of the heart in this stage is sometimes very remarkable, as in one experiment there were only three pulsations per minute, only one occurring in the time occupied by three or four respirations.

Action on the Blood-vessels.—Casca has a most extraordinary power of contracting the blood-vessels. This is indicated by the pressure of blood within the vessels becoming high after its injection, notwithstanding the slowness of the heart's action; but it is proved most unmistakably by the fact that during the

* *Proceedings of the Royal Society*, vol. xiv, p. 270.

long diastolic pauses the pressure does not sink as it ordinarily does, but sometimes remains as high as 165 millimetres of mercury. When the arterioles are in their normal condition as regards dilatation, the blood flows readily out of the arteries into the veins, and the pressure rapidly falls in the arterial system during the cardiac diastole. When the arterioles are much contracted, however, as after the administration of casca, the flow of the blood out of the arterial into the venous system is impeded, the arteries remain full, and the tension of the blood within them high.

Digitalis also contracts the arterioles and causes the fall of pressure during the cardiac diastole to be slow. The mode in which casca and digitalis produce contraction of the blood-vessels, however, seems to be different. Digitalis causes it by stimulating the vaso-motor centre in the medulla oblongata, and this centre acts through the vaso-motor nerves upon the vessels. These nerves pass down from the medulla, through the cervical part of the spinal cord, along the splanchnics, &c., to the vessels. Consequently, when the communication between the vaso-motor centre in the medulla oblongata and the vessels is destroyed by dividing the cervical and spinal cord, the vessels dilate, and no stimulation of the vaso-motor centre has any power to cause them to contract. The contraction usually produced by digitalis, therefore, does not occur if the cord be divided before its injection, and is removed if the cord be divided after contraction has already taken place. This is not the case with casca, however, for we found that after the spinal cord had been completely divided in a cat opposite the second cervical vertebra, the blood-pressure after the injection of casca rose higher than in any other experiment. The casca must therefore act either on the blood-vessels themselves, the vaso-motor nerves, or some vaso-motor centre not contained in the medulla.

A further proof that casca acts on peripheral vaso-motor ganglia or nerves is afforded by an experiment in which the sympathetic nerve was divided in the neck of a rabbit, so as to sever the connection between the vaso-motor centre and the vessels of the ear on one side. On the other the nerves

were left intact. After injecting a dose of casca the vessels in *both* ears became pale, and apparently there was no difference between them in the ear with the divided nerve and in the other.

We are rather inclined to the supposition that it does act on some such centre or centres—possibly ganglia—in or around the vessels themselves, because the local application of casca to a frog's foot, or its injection under the skin of the back, causes no contraction in the vessels of the web, as one would expect it to do if it acted on the vessels themselves. The arterioles begin to contract after a small dose of casca before any effect is produced on the vagus, so that the blood-pressure begins to rise before the pulse becomes slow. The contraction also seems to last after the vagus is paralysed, and even after the heart has ceased to beat, so that when the animal is dying the blood-pressure falls very slowly.

The contraction of the vessels after the injection of casca is not confined to those which are under the dominion of the vaso-motor centre in the medulla. It has been shown by Ludwig and Hafiz that while this centre can cause contraction of the vessels going to the intestines, it has little or no power over those supplying the muscles. Thus it happens that when this centre is irritated the blood-pressure does not remain high during the cardiac diastole, as one formerly supposed it would do; for although the intestinal arterioles are firmly contracted, and prevent any blood from flowing into the veins, the arteries of the muscles remain uncontracted and the blood flows rapidly through them. As the blood-pressure after the injection of casca remains so high during the cardiac diastole, the arterioles in the muscles must be contracted as well as those in the intestines. In its mode of action upon the blood-vessels casca differs from digitalis, but agrees with ergot, which seems to cause contraction by acting rather upon peripheral vaso-motor nerves or ganglia, or on the muscular wall of the blood-vessels, than on the vaso-motor centre.

Action on the Kidneys.—As the action of casca on the circulation so closely resembles that of digitalis, it seemed not improbable that it might also have a diuretic action, and we

accordingly proceeded to try whether it had or not. The manner in which we experimented was as follows. A dog was anæsthetised with chloroform, the anæsthesia being kept up during the whole operation. A cannula was placed in one ureter so that the urine dropped from the kidney as fast as it was secreted, and the rapidity of secretion could be readily ascertained. The carotid artery was connected with a kymographion and the blood-pressure measured. On then injecting a dose of casca into the jugular vein, we found that the blood-pressure rose and the urine began to be secreted more rapidly. An additional dose raised the blood-pressure still higher, but the secretion of urine began to get slower instead of quicker, and when the blood-pressure had risen to its maximum the secretion stopped altogether. After a while the blood-pressure began to fall, and the secretion again commenced. The explanation which we are inclined to give of these facts is that at first the casca, by causing contraction of the vessels generally, and raising the blood-pressure, increases the pressure in the glomeruli of the kidney, and thus causes the watery constituents of the blood to filter through them more quickly than usual. It thus increases the flow of urine. It next causes the vessels of the kidney to contract more and more, so that notwithstanding the high blood-pressure in the arterial system generally, there is little blood in the kidneys. The pressure of blood in the glomeruli is consequently low, and the secretion of urine scanty, and when the contraction of the renal artery becomes very great the secretion stops altogether. When the arterial spasm again relaxes, the secretion recommences at the same time that the blood-pressure falls. In this respect the action of casca agrees completely with that of digitalis.* It seems probable that casca will also, like digitalis, be found to have a cumulative action, should it be introduced into medicine; for the effect of any drug depends on the amount of it circulating in the blood, and this amount may be increased either by increasing the introduction of new quantities or by diminishing the excretion. It seems probable that the sudden

* Brunton and Power, "On the Diuretic Action of Digitalis." *Proceedings of the Royal Society*, 1874, No. 153. *Vide antea*, p. 410.

appearance of dangerous symptoms during the administration of digitalis is due to its stopping excretion by the kidney while the drug is still taken by the mouth. The occurrence of poisoning by digitalis would thus be completely analogous to poisoning by curare in an experiment of Herrmann's.* Curare produces paralysis of motor nerves when quickly introduced into the circulation by injection under the skin or into a vein, but does not usually prove poisonous when taken into the stomach. The reason of this is that it is excreted by the kidneys as quickly as it is absorbed from the stomach, so that there is never enough of it in the blood at any one time to be injurious. When Herrmann tied the renal vessels, however, so as to prevent excretion, curare taken into the stomach proved as certainly fatal as when injected into a vein. In digitalis-poisoning the drug itself causes contraction of the renal vessels, producing the same effect as the ligature applied to them by Herrmann in the case of curare, and the same would probably be the case with casca.

Action on Respiration.—The respiration is generally quickened by casca. This quickening appears to be due to a stimulating action of the drug upon the pulmonary branches of the vagus, as it was not observed when the vagi were divided before the casca was administered.

Action on Temperature.—Casca does not appear to have any action either in lowering or raising the temperature of a healthy animal. We have not yet tried what effect it will have in fever.

Action on the Eye.—When applied to the eye it has no action on the pupil, nor does it cause congestion of the conjunctiva or lachrymation.

Action on the Uterus.—Digitalis having been said to have a powerful action upon the uterus, an action which has been found by Dr. Dickinson to be useful in arresting menorrhagia by causing contraction of the uterus, we administered casca to a pregnant cat, but it did not produce abortion.

* *Du-Bois Reymond's und Reichert's Archiv*, 1867, p. 64.

Probable Use of Casca in Medicine.

It is evident from the description we have given above of the physiological action of casca, that it is quite different from that of Calabar bean, the other ordeal poison employed on the African coast, which has become such a useful remedy since its physiological action was first ascertained by the admirable researches of Dr. T. R. Fraser. Unlike physostigma, it has no action on the pupil, and no special action upon the spinal cord. Its action is exerted chiefly upon the stomach, circulatory apparatus and kidneys. Its action on the stomach seems to be rather a drawback than otherwise, as it would have been highly advantageous to have had a drug which would act like digitalis upon the heart without producing the sickness which sometimes obliges us to discontinue the use of the latter. As, like digitalis, it strengthens the heart while slowing its pulsations, it will be useful in mitral disease, and its diuretic action will prove serviceable in dropsy arising from this cause. At the same time its more powerful action on the vessels leads us to hope that it will be useful in advanced cases of cardiac dropsy when digitalis fails. This power of contracting the vessels also indicates that it will prove a useful hæmostatic, more powerful than either digitalis or ergot, the virtues of which it seems to combine. Mr. Monteiro having kindly promised to obtain for us a large quantity of the bark, we trust we shall find that its action in disease corresponds to the hopes we have formed.

PRELIMINARY NOTES ON THE PHYSIOLOGICAL ACTION OF NITRO-GLYCERINE.

In conjunction with E. S. TAIT.

(Reprinted from *St. Bartholomew's Hospital Reports*, 1876, vol. xii.)

From the observations and experiments on the physiological action and therapeutic employment of nitro-glycerine made by numerous authorities, amongst whom may be mentioned Hering, Pelikan, Field, Thorowgood, Brady, Demme, Albers, Onsum, Eulenburg, Werber and others, it is evident that nitro-glycerine is a powerful poison, and exerts a marked action on the nervous system when given even in exceedingly minute doses. Although many facts regarding its action have already been ascertained, it has not yet been made the subject of an elaborate investigation, and it therefore seemed to us advisable to ascertain its action more thoroughly than has yet been done. Our research is still very imperfect, but circumstances having obliged us to discontinue it for a few months, we now give the results we have already obtained, and trust to fill up the numerous deficiencies in them when we are again able to resume work together. Whilst we confine ourselves in our present paper to a statement of the results of our own experiments, we purpose in a future one to enter into the literature of the subject, and to compare the conclusions to which our experiments have led us with those of previous observers.

General Action on Frogs.—A number of experiments were made by injecting a 10 per cent. solution of nitro-glycerine in alcohol, in quantities varying from about one-tenth to four-tenths of a cubic centimetre, under the skin of the back or belly of a frog. The result was in all cases nearly the same. Immediately after the injection the animals became very restless, and the respirations became very rapid. In a minute or

two the restlessness subsided and gave place to lethargy, the frogs showing a great disinclination to move, and allowing themselves to be gently pushed along the table without jumping. The respiration still continued rapid. In about two minutes more (generally three to five minutes after the injection of the poison) the frogs gave a sudden spring, and fell into tetanic convulsions. These lasted about half a minute, and then became more or less relaxed; they soon returned, however, and continued to do so at nearly regular intervals, when the frogs were left alone, but they might also be brought on by touching the animals. When the relaxation of the muscles was imperfect, so that the legs still remained extended during the intervals, the convulsions were marked by twitchings of the toes. In some instances the mouth seemed to be the part first affected by the convulsion, as the jaws were seen to open and shut, although it is possible that this was connected with respiration rather than with the general convulsions; next the arms were affected, and lastly the legs. The arms seemed also to be more sensitive than the legs, as slight spasmodic twitches could sometimes be produced by touching or pinching the arms, when similar irritation of the legs had no effect. After continuing for some time the convulsions became gradually weaker, and the animal died.

General Action on Cats.—The only warm-blooded animals on which we have as yet experimented with nitro-glycerine are cats, and although it is probable that a general similarity exists between its action on these and on other mammalia, yet it is not unlikely that there are minor differences which can only be ascertained by farther experiments. On injecting 4 cubic centimetres of a 10 per cent. solution into the peritoneal cavity of a cat, the first symptom noticed two minutes after the injection was a stretching movement of the hind leg, as if the animal were trying to shake something off the foot. In about half an hour the cat cried as if in uneasiness or pain, and then vomited. In about half an hour more the legs seemed to fail during walking, and the animal suddenly sank down and never again rose. Vomiting again occurred once or twice, the respiration becoming exceedingly rapid (120 per minute), and the

tongue and muscles of the lower jaw worked at each inspiration, so that the tongue lolled back and forwards like that of a dog which has been running. This action we have never observed in cats, either during health or after the administration of any other poison. The nostrils also moved with the respirations, and muscular twitching was observed over the body. The cornea was now found to be insensible, and pinching called forth no action in the limbs; but when the tail was pinched, a deep inspiration took place. Slight spasms resembling hiccough now occurred, and in five minutes more the animal died, two hours and five minutes after the injection of the poison.

A large dose (10 cubic centimetres) injected in the same way almost immediately caused the respiration to become rapid (120 per minute) and the gait staggering. The animal also cried, the tongue lolled out in the manner already described, and the third eyelids were drawn half over the eyes in the same manner as we have seen them in other cats after division of the vagi. In five minutes the respirations had reached 160 per minute, and the animal lay quite quiet. In 15 minutes voluntary action was quite paralysed, and reflex almost entirely so. When either the fore or hind legs were drawn out, no attempt was made to draw them up to the body, the limbs seeming quite paralysed. On tickling the inside of the ear, however, the ear was moved; and on touching the cornea, the eyelids closed.

On applying a strong induced current 20 minutes after the injection to various parts of the body and legs, muscular twitchings were produced, but no reflex movements.

In five minutes more, respiration became slow and gasping (6 per minute); the tongue ceased to loll, and in five minutes more the animal was dead, 30 minutes after the injection.

On post-mortem examination the heart was found still pulsating, and the blood of a somewhat chocolate colour.

The principal effects produced by nitro-glycerine are thus seen to be—great acceleration of the respiration, paralysis, loss of reflex action, and apparently to a great degree of sensation, and death from stoppage of the respiration. The minor symptoms are muscular twitching and vomiting.

Action on the Nervous System.—In frogs nitro-glycerine produces, as we have already mentioned, languor, tetanus, and finally paralysis. In cats there is paralysis without any tetanus, although there may be movements of a convulsive nature—such as vomiting, spasmodic respirations like hiccough, and muscular twitches—when the poison is injected into the abdominal cavity. In another experiment we found that after the injection of 1 cubic centimetre of a 10 per cent. solution directly into the jugular vein of a cat, tetanic convulsions occurred.

In order to ascertain whether the tetanus in the frog is due to the action of the nitro-glycerine on the spinal cord, or on the nervous centres within the encephalon, the spinal cord was cut across about the middle before the poison was given. The upper part of the animal immediately became very restless, and the arms were stretched out at right angles to the body with the toes outspread. There was no alteration in the hinder part of the body and legs. The nitro-glycerine, therefore, does not cause tetanus by its direct action on the spinal cord, as otherwise spasms would have been observed in the hind legs. This result was confirmed by another experiment. A frog was decapitated, and after the spinal cord had recovered from the shock, and reflex movements were again observed in the limbs, nitro-glycerine was injected under the skin. No spasm whatever was observed. Other experiments led us to believe that the tetanus is not due to any action on the cerebral lobes, but probably to the effect of the poison on the optic lobes; but we are not yet in a position to decide this with certainty.

Action on Muscle.—In order to ascertain this, two gastrocnemii of a frog were immersed in two glasses, each containing 10 cubic centimetres of a ·75 per cent. solution of common salt. To the one glass about two drops of the solution of nitro-glycerine were added. After three hours the muscle which had been lying in the pure solution of salt contracted readily on the application of an induced current, while the one which had been lying in the salt solution with nitro-glycerine was in a state of rigor mortis. Nitro-glycerine is therefore a muscle poison, and in this particular its action agrees with that of nitrites, all of

which have been found to be muscle-poisons in an unpublished research on which one of us (Brunton) in conjunction with Mr Gresswell is at present engaged in this laboratory.

Action on Motor Nerves.—On ligaturing the vessels in one leg of a frog so as to prevent the circulation of poisoned blood in that limb, the nerve being left uninjured, we have found that when paralysis had begun to appear, the spasms which could be observed were slightly more marked in the ligatured limb. On testing the irritability of the motor nerves after death, they were found to respond much more readily to an induced current in the ligatured than in the non-ligatured leg; but as the muscles of the non-ligatured leg responded but feebly to a current directly applied to them, we are at present unable to say whether the paralysis is entirely due to the action of the poison on the muscles, or whether it affects the motor nerves as well. We may possibly be able to decide this point by making farther experiments, similar to those which we have already performed, but in winter, when the muscles preserve their irritability longer than in summer, during which our experiments were made. We also propose to try them with *Rana esculenta* instead of *Rana temporaria*, the muscles of these two species of frog having been shown by Schmiedeberg to be very differently affected by caffein, a poison having an action similar in some respects to that of nitro-glycerine.

Action on the Spinal Cord.—The loss of reflex action both in frogs and cats, in the advanced stages of poisoning, indicates that the cord is paralysed; and the persistence of reflex action in parts supplied by cranial nerves, such as the eye and ear, after it has disappeared from other parts of the body, indicates that the cord is paralysed before the ganglia at the base of the brain.

Action on the Brain.—One of the most remarkable effects of nitro-glycerine is the intense headache it produces, even in infinitesimal doses. Almost all observers agree about the fact of its producing headache, but they differ regarding the nature of the headache. According to our experience, it is not always of the same kind, being sometimes frontal, sometimes occipital, sometimes affecting one side only, and at other times

the whole head. In one of us (Brunton) it was several times accompanied by vomiting. It has been said by some that continued use of nitro-glycerine makes the person more sensitive, but in one of us (Tait) the contrary seemed to be the case, as the headache was only suffered from during the first week of the investigation. None of the poison was taken by the mouth, and, as it is non-volatile, the amount taken in by the lungs must have been infinitesimal. It is possible that, as some writers have supposed, a little of it was absorbed by the skin, but the quantity thus taken into the system must have been excessively minute.

Action on the Heart.—When the excised heart of a frog is put into 10 cubic centimetres of a ·75 per cent. salt solution, and two drops of a 10 per cent. solution of nitro-glycerine in alcohol are added, the heart begins to beat more and more slowly, and gradually ceases altogether. A similar quantity of alcohol, added to the same amount of salt solution, had no action on a heart immersed in it. In one instance, after the addition of nitro-glycerine, we observed a slight quickening before the beats became slow.

Two cubic centimetres of a 10 per cent. solution of nitro-glycerine in alcohol injected into the jugular vein of a cat stopped the cardiac pulsations entirely in 13 seconds. One cubic centimetre in another experiment greatly quickened the pulse. The power of the vagus over the heart appears to be diminished, as irritation of its trunk had less effect upon the heart after injection than before.

Action on the Blood-pressure.—Nitroglycerine diminishes the blood-pressure considerably, but its power to do so is very much less than that of nitrite of amyl.

Action on the Blood.—The blood of animals poisoned by nitro-glycerine is of a chocolate colour, even in the arteries. When blood is shaken up with nitro-glycerine solution, it acquires a chocolate colour, though slowly. In this respect nitro-glycerine agrees with nitrites, which also cause the blood to assume that colour.

With the spectroscope at our disposal, however, we were unable to discern any difference between the spectrum of blood

from an animal poisoned with nitro-glycerine, or of normal blood shaken up with it, and normal blood, either before or after the addition of a reducing fluid. If our observation were correct, this would constitute an important difference between nitro-glycerine-blood and nitrite-blood as described by Gamgee; but the strong similarity in colour between the two kinds of blood makes us doubtful about the correctness of our spectroscopic observation, and we hope to repeat it with a better instrument as soon as opportunity allows.

Action on Oxidation.—Certain vegetable substances have the power of oxidising tincture of guaiac, and causing it to become blue. In order to ascertain whether nitro-glycerine had any power to diminish or prevent this oxidising process, a potato was pounded with water, and the liquid strained off and mixed with tincture of guaiac and a small quantity of nitro-glycerine. Instead of preventing oxidation, however, it rather seemed to quicken it, the mixture assuming a blue colour more quickly and more intensely than where no nitro-glycerine was added. In this respect also its action resembles that of nitrites as described by Binz and Pick.

From our experiments it would then appear that nitro-glycerine agrees with nitrites in not lessening the oxidation of guaiac by vegetable solutions, in causing the blood of animals poisoned by it to become of a chocolate colour, in acting as a muscular poison, and in diminishing blood-pressure. Its action in this last respect is, however, much less than that of nitrite of amyl. In a future paper we hope to give a more detailed and complete account of the action of nitro-glycerine, and of the resemblances and differences between its action and that of nitrites, as well as a discussion of its possible use in medicine.

NOTE.—The severity of the headache which nitro-glycerine induced in one of us (Brunton) was so great that it made us delay in trying it on patients, and before we had done this it was proposed by Dr. Murrell as a substitute for nitrite of amyl. W. Murrell: "Nitro-glycerine as a Remedy for Angina Pectoris," *Lancet*, 1879, i, 80, 113, 151, 225.

ON THE PHYSIOLOGICAL ACTION OF THE BARK OF *ERYTHROPHLEUM GUINENSE*, GENERALLY CALLED CASCA, CASSA, OR SASSY BARK.

In conjunction with WALTER PYE.

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SEVERAL months ago we received from Mr. Monteiro a piece of Casca bark, which he had obtained with great difficulty from a native at Bembe during his residence in Angola. This bark is used by the natives as an ordeal, persons suspected of theft, witchcraft, or other crimes being made to drink an infusion of it. If it causes vomiting only, the person is acquitted; but if it causes purging, he is considered to be guilty, and is either allowed to die of the poison or at once killed. Among some tribes a practice prevails of making the accused, after drinking the infusion, walk in a stooping posture under half a dozen low arches made by bending switches and sticking both ends into the ground. Should he fall down in passing under any of the arches, he is at once considered guilty, and, without waiting for a purgative effect to be produced, he is at once put to death.

All the natives agree in their description of the effect produced on a person poisoned by this bark. His limbs are first affected, and he loses all power over them, falls to the ground, and dies quickly, without much apparent suffering.

The same bark, or one having precisely similar effects, is used as an ordeal in Sierra Leone, under the name of "red-water bark," and in Ashantee, under the name of "doom." In both these places the test of vomiting or purging only seems to be employed, and not that of stumbling, as described by Mr. Monteiro; but according to C. A. Santos, the missionaries describe the bark as causing vomiting, glazing of the eyes, and loss of

the power of contracting the muscles throughout the body; so that, when the poison has fairly commenced its action, the sufferer is incapable of standing or walking, and the head rolls heavily about the breast and shoulders.

Appearance of the Bark.—The pieces given to us by Mr. Monteiro were from 8–12 inches long, about 4 inches broad, and $\frac{3}{8}$ of an inch thick, dark brownish-red in colour, and deeply grooved externally. Their appearance agreed exactly with the description given by C. A. Santos, in the *American Journal of Pharmacy*, April 1849, p. 96, of the bark which he terms Saucy bark, or Gidu.

Chemical Reactions.—When treated with alcohol it yields a dark brownish-red tincture, and boiling water gives an infusion of a similar colour, which deposits a pale brownish-red precipitate on cooling; but at the same time the supernatant fluid remains turbid from suspended particles, which do not subside, and which are not removed by filtration. It becomes clear when heated, but the turbidity returns on cooling. The tincture, when evaporated, leaves a resinous-looking extract, and when mixed with water gives a pale brownish-red precipitate. The watery solution of either the alcoholic or aqueous extract becomes much darker in colour after exposure to air.

An aqueous solution gives a brownish-black precipitate with ferric perchloride, indicating the presence of some form of tannin. It also gives a precipitate with tincture of galls or tannic acid, mercuric chloride, stannic chloride, gold chloride, silver nitrate, and lead acetate, either neutral or basic. If the precipitate produced by neutral lead acetate be removed by filtration, the addition of basic lead acetate to the filtrate causes very little further turbidity. Platinum chloride causes little or no precipitate.

These reactions closely agree with those given by Santos and Procter.

Santos states that, by passing the dilute tincture through animal charcoal, washing, drying, and boiling in absolute alcohol, he obtained a crystalline substance which was poisonous; but Procter failed to obtain a poisonous substance, although he got crystals which were non-poisonous.

From the small quantity of bark at our disposal, we have not attempted to isolate any active principle, as we feared our supply would not be more than sufficient for the investigation of its physiological action.

Professor Liebreich, however, has lately succeeded in separating a crystalline substance, which is exceedingly poisonous.

General Action.—Its action on the lower animals has been investigated by Santos and Liebreich. The former found that a decoction of the bark caused alternate dilatation and contraction of the pupils, appearance of delirium, violent retching, vomiting, symptoms of tetanus, and, finally, death. The crystalline principle obtained from the bark by Liebreich caused vomiting and sudden death, without previous loss of consciousness. Death is attributed by him to paralysis of the heart.

In our own experiments on dogs and cats we have observed vomiting, weakness, and death during a convulsion from the effects of the drug, whether introduced into the stomach or injected under the skin, into the peritoneal cavity, or into the veins.

General Action on Mammals.

Action on Cats.

Experiment I.—February 23.

Effects of a very Large Dose.

Four and a half c.c. of a saturated alcoholic solution of Casca* were injected into the abdominal cavity of a half-grown kitten weighing 746 grammes. At three minutes after the injection it began to walk stiffly, and a peculiar jerk occurred in the hind legs each time they were lifted. Respiration 60. At 5 minutes after injection it seemed giddy, and rolled over on trying to walk. Fæces were passed. Respirations 80, gasping. At ten minutes it was lying on its side with its mouth wide open; respirations 120. At 10 minutes 30 seconds the respirations were 160, gasping. At 11 minutes it made feeble and unsuc-

* This solution was prepared by extracting the bark with alcohol and evaporating to dryness. The solid extract thus obtained was dissolved in warm alcohol in such quantity that on cooling a deposit occurred. The solution was then filtered and the filtrate employed for experiments.

cessful attempts to vomit; the respiration became intermittent; there was an oscillating movement of the eyeballs, and the pupils were widely dilated. At 12 minutes the respiration became slower, as well as irregular. At 16 minutes it was 60, irregular and laboured. At 21 minutes the respiration appeared to be entirely diaphragmatic. At 24 minutes there were strong, ineffectual attempts at vomiting, followed by sudden stoppage of respiration, and death in a condition of emprosthotonos. The pupils at that time were widely dilated.

On opening the thorax immediately after death, the ventricles were found firmly contracted; but they recommenced to pulsate, and continued to do so for a few minutes spontaneously. They responded by a single contraction to irritation for 3½ hours after death. By this time the heart looked quite dry and glazed, and rigor mortis was well marked in the muscles. The lungs were pale.

Experiment II.—February 22.

Effects of a Moderate Dose.

Three c.c. of the same alcoholic solution were injected into the abdominal cavity of a cat weighing 2238 grammes. At 25 minutes afterwards the animal vomited; and this was repeated at 35 minutes and 41 minutes. At 41 minutes the cat seemed weak; respirations laboured, 60 per minute; pulse, 100, regular. At 55 minutes respirations 80, shallow, irregular. At 75 minutes respiration deeper and more laboured. At 85 minutes the gait was staggering, and the limbs were moved with a jerk at the end of each step; respirations 40, more regular; pulse 100, regular. Four hours after injection the animal was sleepy; when roused it walked feebly; there was no further vomiting. Its condition remained unaltered as long as it was observed; and it died between eight and twenty hours after the injection.

On post mortem examination rigor mortis was well marked. The abdomen contained some yellow serum. The stomach contained no solid food, but about 2 ounces of a greyish turbid alkaline fluid.

Experiment III.—April 28.

Seven c.c. of a similar solution to that used in Experiments I. and II. were injected beneath the skin of a moderate-sized, well-nourished cat. In 15 minutes the animal vomited for the first time, and this vomiting was repeated four times within the next hour and twenty minutes. During the rest of the day it remained quiet, without further vomiting, and with no paralysis or disturbance of muscular movements. It appeared to be quite comfortable.

On the following day it remained sitting in one position, and refused its food and milk. There was no vomiting, and no urination or defæcation. When disturbed, it would immediately return to its former position in a mechanical manner.

On the following day it passed a very small quantity of fæces; it was not observed to urinate, and, as before, it neither ate nor drank anything. It vomited once, very slightly.

From this time forwards, for a fortnight after the administration of the poison, the cat remained in this condition, neither eating nor drinking, although tempted to do so with milk and meat; and even when a live mouse was placed before it, it merely pricked up its ears, and looked eagerly at it, but did not touch it, nor did it pass urine or fæces once for the last eleven days.

It sat always in one position unless disturbed, and though it got steadily weaker, did not lose flesh in the way an animal starved would have done. The temperature on May 2nd was 38° C.

Five days after the poison was given a subcutaneous abscess formed over the right scapula and ribs. No other lesions were ascertained during life. The abscess did not form at the seat of puncture.

It died, apparently from exhaustion, fourteen days after the poison was administered.

Post-mortem Examination.

Rigor mortis well marked.

Subcutaneous tissue contained a fair amount of fat.

There was a large, sloughy, subcutaneous abscess in the situation mentioned above, and another localized collection of pus a little higher up in the skin of the neck. No other superficial abscesses were found.

The muscles were pale and rather dry. There was general congestion throughout the body of the larger venous trunks, but apparently not of the smaller ones.

Abdomen.—The omentum contained rather a large quantity of fat.

The stomach was quite empty, pale, and contracted.

The small intestine contained a small quantity of bile-stained mucus; it was otherwise empty.

The large intestine contained bile-stained mucus, and in its lower half a considerable quantity of fæces, also bile-stained. The mucous membrane appeared perfectly healthy.

The bladder contained only a few drops of high-coloured urine, but had not contracted at all firmly. It had the appearance of a bladder which has been dried when inflated, and the air then let out.

The kidneys were pale, although the renal vein was much distended.

The vagina and uterus contained a large quantity of a greenish smeary fluid, which, under the microscope, was seen to be muco-pus. The mucous membrane had here and there patches of injection on it (*vide infrà*); near the orifice of the vagina the secretion had quite the character of ordinary pus, but no abscess existed there.

The diaphragm was pale, flabby, and very transparent (*vide infrà*).

Thorax.—The lungs were congested, but otherwise natural.

The heart was very pale and flabby; all the cavities contained moderate quantities of blood.

Microscopical Examination.

Kidneys: epithelium not degenerated.

Heart: muscle-fibres very granular; in many places hardly a trace of transverse striation could be seen.

Voluntary muscles (rectus abdominis) also granular (well marked, but not quite so much as the heart).

Bladder: muscular coat not degenerated.

Intestines: muscular coat not degenerated.

Remarks on Experiments I—III.

Experiments I to III show the effects of the poison on cats when administered in three decreasing doses.

It will be seen that, during life, the most prominent symptoms of a rapidly poisonous dose were in their order of constancy:—1, vomiting; 2, respiratory difficulty; 3, abnormal muscular movements.

After death the condition of the heart and great vessels and of the lungs are most noteworthy.

Vomiting.—This was a constant symptom in all the cats we experimented on, unless they were placed under special circumstances. The vomit consisted, first, of whatever food might be contained in the stomach, and then of a white frothy mucus. On no occasion did it ever have the appearance of intestinal (fæcal) vomiting.

In Experiment I no actual vomiting occurred. In this case the stomach was found to be empty of food after death; and the absence of the symptoms in this case was doubtless due to the rapid paralysis caused by the very large dose administered.

Respiratory Difficulty.—This is a constant symptom, except when very small doses are administered.

On reference to Experiment I it will be seen that at one time the respirations rose to 160 per minute. This, however, was exceptional. From 40 to 60 respiratory movements per minute is probably the average rate after administration of a moderately poisonous dose.

Abnormal Muscular Movements.—These are of two kinds; thus, immediately after the administration of any dose, large or small, there is very generally produced a peculiar twitching of the muscles of the limbs, especially of the hind legs. This is especially seen when the animal is walking.

When large, rapidly poisonous doses are administered

symptoms of general muscular paralysis and loss of coordination are developed *pari passu* with the dyspnœa and frequency of the vomiting. The animal rolls and staggers as it walks; its head falls on the ground, and, finally, it falls over on its side and is unable to stand. Death always occurs a very few minutes after the development of these last phenomena.

Appearance of the Heart post mortem.—As a rule, post-mortem examination of the heart shows a moderately firm contraction of the ventricles, with a somewhat distended condition of the auricles. The ventricles, however, were never found to be completely emptied of blood, and on one or two occasions the heart was found to be moderately distended, the left ventricle containing well arterialised blood.

On several occasions, but here also with one or two exceptions, a remarkable vitality of the auricles was noticed (Experiment I).

The post-mortem appearances of the heart and their physiological value will be noticed more particularly in the section which treats especially of the action of that organ.

The lungs were, in all cases in which they were noticed, found to be pale, except in Experiment III (see Experiment XXXI).

One of the most noteworthy phenomena is the action of a small dose upon a cat in causing an utter refusal to take either food or drink, and that, notwithstanding this total abstinence from nourishment, the animal should live such a long time, should show considerable muscular power (being able to jump from the floor upon a chair up to the day before its death), and should have still retained so much of its subcutaneous and omental fat. Another point to be noted is the occurrence of subcutaneous abscesses, none of which were near the point where the poison had been injected.

This long continuance of life and retention of strength seem to us to indicate that the processes of tissue change had been retarded by the poison; and the granular condition of the striated muscles appears to indicate a diminution especially in the processes of oxidation.

Action on Dogs.

Experiment IV.—May 9.

The effect of the poison on dogs was investigated in the same manner as it had already been on cats in Experiments I—III. It will be seen that the results do not differ in any noteworthy point from those previously obtained.

Six c.c. of the solution were injected beneath the skin of a dog weighing 8 lbs. It vomited for the first time 20 minutes afterwards, and this vomiting continued at gradually increasing intervals of from 15 minutes to three quarters of an hour for the next 4 hours. At the end of that time the animal was very restless, and continued to be so while it was observed. On the following day its gait became staggering; and, finally, it lay flat on its belly, and died about 30 hours after the drug was administered.

General Action on Birds.

Birds are affected very readily by the poison, and the symptoms produced in them are similar to those observed in mammals. This will be seen by the results of the following experiment.

Experiment V.

A full-grown pigeon had nearly 1 c.c. of the solution injected beneath the wing. In 10 minutes a quivering motion of the wings was noticed; in a quarter of an hour its feathers were puffed out, its gait was staggering; 24 minutes after injection it began to vomit. This was repeated 4 minutes afterwards more violently, and several times subsequently. 40 minutes after the injection it was unable to stand; and from that time to its death, 1 hour and 35 minutes after injection, it lay flat on the table, occasionally attempting to vomit unsuccessfully. For the last 40 minutes its respirations were hardly visible, but it moved when roused. Violent expiratory movements came on just before the respiration finally ceased.

General Action on Fishes and Frogs.

In fishes and frogs there is but slight susceptibility to the poison, and the effects produced by it are similar in the two classes. The most obvious general systems are muscular paralysis and cessation of respiration, preceded by spasmodic movements. It will be seen later, however (Experiment XVIII), that the particular action of the drug on the heart is well shown in frogs.

Experiment VI.—February 21.

One-third of a c.c. of the solution was injected beneath the skin of a medium-sized frog. In 2 minutes slight tonic contraction of the limbs was observed; in 4 minutes it was jumping rather actively, but fell over on its back; in 12 minutes the respiratory movements had become almost imperceptible; and from this time the reflex movements of the limbs on irritation gradually got weaker and weaker, and finally ceased 33 minutes after the injection.

After death, the ventricle was found firmly contracted, the auricles and venous trunks engorged.

Experiment VII.—February 21.

Experiment VI was repeated with double the dose. The frog was slightly larger than the one first used; but reflex action ceased within a few seconds of the same time after injection. The general effects were almost the same as in Experiment VI, save that 5 minutes before reflex movements ceased there were four spasmodic inspirations.

Experiment VIII.—April 18.

The effect on fishes was tried. First, 55 c.c. of a $\frac{1}{300}$ watery solution of casca were added to 3 litres of water in which a gold-fish weighing 3 ounces was swimming. At the end of 3 hours no effect was produced on the fish. 1·3 c.c. of the alcoholic solution were then injected into the side of the fish, a little in front of the tail. In 5 minutes it began to roll from side to side; the respirations were catching. For the next 10

minutes it lay chiefly on its side, occasionally swimming about actively.

At the end of 25 minutes from the time of injection it appeared to have nearly recovered itself, and 1 c.c. more of the alcoholic solution was injected. In 3 minutes from this time it lay completely over on its side, having spasmodic twitchings of its fins; in 5 minutes the respirations again became rapid and gasping; in 10 minutes the reflex movements were very weak, but respiration and reflex action did not entirely cease before 30 minutes after the second injection.

General Action on Invertebrata.

The following experiments (Nos. IX and X) show that the drug exerts very little, if any, poisonous action on the Invertebrata.

Experiment IX.

A leech was placed in a watery solution of casca nearly as strong as could be made with cold water. At the end of $2\frac{1}{2}$ hours it seemed but little affected, but was found dead on the following morning.

Experiment X.

Nearly 5 c.c. of a concentrated alcoholic solution of casca were injected beneath the back of a common snail. The animal showed no signs of poisoning, and on the following morning appeared to be uninjured.

Action on Infusoria.

Experiment XI.

In Experiment XI we investigated its action on Infusoria by placing a drop of tank-water containing some infusorians under the microscope, and adding a drop of a $\frac{1}{300}$ solution of the watery extract of casca. At the end of 2 hours no alteration in the movements of the animalcules was observed; and it may therefore be concluded that the drug exerted little or no action on them.

The action of the drug on germination and oxidation pro-

cesses, and on different ferments and ferment organisms, was investigated in Experiments XII—XX.

On germination the casca infusion was found to exert no effect.

Experiment XII.

A few mustard seeds were placed on flannel in two saucers, and kept moist in a warm place, the one with an infusion of casca, the other with water. The seeds began to germinate at the same time in each, and no difference was observed in the growth of the shoots for three days afterwards.

Effect on the Development of Bacteria.

Experiment XIII.

This experiment, which was repeated on two other occasions, shows that a weak solution of the alcoholic extract possesses the power of hindering the formation of *Bacteria*, a property not shown by the watery extract, as is shown in Experiment XIV. This difference in the properties of the two extracts does not show itself in the general action of the drug on animals; but the power of the alcoholic extract to prevent the development of *Bacteria*, while it is without action on them after their development, is interesting, as substantiating the results of Buchholz's experiments on this subject with other drugs.*

Three pieces of fresh muscular tissue were placed in bottles on March 22nd. The first contained a watery solution of the alcoholic extract of casca, the second a $\frac{1}{200}$ solution of sulphate of quinia, and the third distilled water. On March the 29th the bottles were opened; and while the bottle containing water was very offensive, and the water was crowded with *Bacteria*, neither the quinine nor casca solutions contained any *Bacteria* at all.

The bottle containing the casca solution was again examined on May 14th, and was found, as before, quite free from *Bacteria*. Long before this a thick crust of *Penicillium* had formed on its surface.

* *Archiv f. exper. Pathologie u. Pharmakologie*, vol. iv, p. 1.

Experiment XIV.

A piece of fresh cat's liver was placed in a solution of casca of the same strength as that used in the preceding experiment; but the watery extract was used instead of the alcoholic. At the end of two days the liquid was found to be crowded with *Bacteria*.

This experiment was afterwards repeated with muscular and other tissues with the same result.

Effect on the Life of Bacteria.

The effect of the drug on the life of *Bacteria*, when developed, was tried in Experiment No. XV. For this purpose an infusion of hay was made, and found to contain many rod-shaped *Bacteria*. To a drop of this infusion a drop of a solution 1 in 20 of both the alcoholic and the watery extracts of casca was added at different times, and the movements of the Bacterians carefully watched under the microscope. They did not, however, seem in any way affected by the addition.

For the sake of comparison a solution 1 in 100 of quinia sulphate was added to the hay-infusion. The Bacterian movements were found to be instantly stopped.

Effect on Red and White Blood-corpuscles.

In Experiment XVI the action on the red and colourless blood-corpuscles of the newt was investigated. The effects produced by the addition of dilute solution of casca to the blood were cessation of amœboid movements and rounding of the white corpuscles, with an irregular shrinking of the nucleus, and general crenation of the red ones. These effects were probably due to the action of the tannic acid contained in the extract.

Effect on Ciliary Motion.

The drug appears to have no action on ciliary motion; for when (Experiment XVII) two preparations of ciliated epithelium were made, the one being placed in ·75 per cent. salt solution, and the other in a $\frac{1}{300}$ solution of casca extract, it was

found on microscopic examination that the movements of the cilia ceased in about the same time in both specimens.

Effect on Processes of Oxidation.

It, however, does appear to exercise an inhibitory action on oxidation processes generally. This point was investigated in the following manner:—

Experiment XVIII.—April 20.

Four thin slices of potato were placed in two saucers, and were just covered, the one with distilled water, the other with a $\frac{1}{300}$ watery solution of casca. When a drop or two of the tincture of guaiacum were added, either to the liquid or to the potato slices, the bluing produced was much fainter in the case of the saucer containing the casca than in that containing distilled water. The results of the experiment on organized and unorganized ferments were negative, neither the development of the yeast-plant (Experiment XIX) nor the digestion of fibrin by pepsin (Experiment XX) appearing to be in the least degree hindered by the addition of the drug.

Action on the Digestive System.

One of the most prominent symptoms of poisoning by casca is the violent vomiting which it produces; and, as has already been noticed, its occasional purgative action is used as a test of innocence or guilt. The emetic or purgative action is supposed by some to depend on the administration of a pure infusion, or of one containing the drugs in suspension, and innocence and guilt are thus supposed to be practically decided by the priests, who have it in their power to administer either one or other to the accused.

In order to test this, an infusion was given to one cat, B (Experiment XXI), and an infusion containing a quantity of powder to another. The latter, however, contrary to expectation, recovered, whereas the former died. The experiment, however, was vitiated by the fact that the infusion was made from the finely pulverized bark, the only kind we had at our

disposal at the time, and consequently contained a quantity of it in suspension, which would not have been the case if the infusion had been made from a coarsely pounded bark.

In order to ascertain whether the vomiting and purging were due to the local action of the drug on the stomach and intestines, or to its action on the nervous system after its absorption into the blood, a comparison was made between the effects of the poison when introduced into the stomach and when injected under the skin. Our experiments show that whereas vomiting was invariably produced by the casca, in whatever manner introduced into the system, purging only occurred when the poison was given by the mouth, and was never observed after subcutaneous injection. The purgative action is therefore due to the local action of the drug on the intestines.

The following is a brief account of two experiments we made in investigating the action of the drug when injected into the stomach.

Experiment XXI A.—May 10.

Ten c.c. of an infusion of the watery extract of the bark, with the dregs which were deposited when the infusion cooled, were injected into the stomach of a large cat. It appeared quite well for 40 minutes and then vomited. Within the next two hours and a half it vomited five times. A little more than five hours after the exhibition of the drug it passed some solid fæces with great forcing, and from that time recovered.

Experiment XXI B.—May 10.

Ten and a half c.c. of a cold aqueous infusion of the pounded bark, containing numerous fine particles in suspension, were injected into the stomach of a small ill-nourished cat. Vomiting came on 35 minutes afterwards, and free purging an hour and a half after the injection. During the rest of that day and on the next it was very feeble, but showed no special symptoms, and it died quietly on the morning of May 12.

Comparative Action of the Alcoholic and Watery Extracts.

The action of the alcoholic and watery extracts of casca, when administered subcutaneously to cats in large doses, is almost identical; and their activity as poisons appears to be about equal, the watery extract, if anything, being rather the more powerful.

Experiment XXII.—April 28.

Two equal quantities of the alcoholic and watery extracts were dissolved in equal volumes of alcohol and water respectively. The quantities were 3 grammes of the extracts and 4 c.c. of the fluids. These solutions were injected beneath the skin of two cats of the same size. In the case of the alcoholic extract vomiting came on 15 minutes after injection, with the other symptoms of poisoning by the drug (*i.e.*, respiratory difficulty and staggering gait). The vomiting was repeated violently, and the animal died 1 hour and 15 minutes after injection, death being preceded by general convulsions.

In the case of the watery extract vomiting did not come on for 35 minutes, but death occurred, with symptoms similar to those of the former case, in 1 hour after the injection.

In order to ascertain whether the vomiting was due to the action of the drug upon the sensory nerves in the stomach itself, after it had been conveyed to that organ by the circulation, or to its action upon the nervous centre in the medulla oblongata regulating the movements of vomiting, the vagi were cut, and the chief sensory nerves of the stomach thus divided, before administering the poison. By this procedure the retching and vomiting were either completely prevented or very greatly diminished, the dyspnœa rendering it rather difficult to decide in some cases whether some convulsive movements were due to it or were movements of retching. The vomiting is therefore chiefly, and in all probability entirely, due to the action of the drug on the sensory nerves of the stomach itself, as the retching, if indeed really present, might be due to irritation conveyed to the medulla through the splanchnics after the vagi had been divided.

Experiment XXIII.—March 6.

General Symptoms after Injection, both Vagi having been previously divided.

A cat weighing 3 lbs. was chloroformed, and the vagi divided in the neck. In 25 minutes after the operation it had recovered from the effects of the anæsthetic. Its respirations were 18 per minute. 3 c.c. of a concentrated alcoholic solution of alcoholic extract of casca were injected subcutaneously. Five minutes afterwards the cat had fallen over on its side. The respirations were still regular, 16 per minute. During the next hour, with one temporary disturbance, the animal remained quiet, still breathing quietly and slowly, with no symptoms of sickness and no dyspnœa. It remained on its side the whole time, except when roused. It then staggered a few steps, and again lay down. One hour after the first injection $2\frac{1}{2}$ c.c. more were injected. For the next quarter of an hour the animal continued to breathe easily, but appeared weaker. At the end of that time there were some very slight convulsive movements. and then respiration ceased. On beginning artificial respiration one or two gasping inspirations occurred, and then entirely ceased 1 hour and 15 minutes after the first injection. On post mortem examination the heart's cavities were found distended. They did not contract on irritation or puncture. The lungs were bright scarlet, and contained a moderate amount of blood. The liver and kidneys were congested; the stomach was pale; the brain was normal.

Experiment XXIV.—April 28.

This experiment was in most points an exact repetition of Experiment XXIII, but the results were even more striking. A well-nourished cat was chloroformed, and both vagi were divided in the neck. When it had recovered from the chloroform a solution of ·3 gramme of the alcoholic extract in 4 c.c. of alcohol was injected subcutaneously. None of the ordinary symptoms of poisoning by the drug were produced. There was no dyspnœa and no vomiting, except at one time, an hour and 15 minutes after the injection, when the animal

either coughed or vomited up a small quantity of frothy mucus. When seen the next morning it was to all appearance well, and was killed, to prevent suffering being caused by the secondary effects of section of the vagi, which were found to be completely divided.

Experiment XXV.—May 17.

This experiment was similar to Nos. XXIII and XXIV. As before, no vomiting was produced by injection of the drug after section of the vagi, but death occurred 1 hour and 10 minutes after the injection, in consequence of dyspnœa occasioned by the section of these nerves.

Action of Casca on Respiration.

Powdered casca, when inhaled, acts as a violent sternutatory. All the men employed by us in grinding or pounding the bark suffered severely from the violent and irresistible fits of sneezing which attacked them; and in one instance these were accompanied by great faintness and tendency to syncope.

When injected into the circulation casca greatly accelerates the respirations (Experiments I, II, XXXIV).

This acceleration appears to be due to stimulation of the pulmonary branches of the vagus, and not to any action of the drug upon the respiratory centre, as no acceleration is noticed when the vagi are divided before the injection of the casca (Experiments XXIII and XXIV).

Action on the Intestines.

Experiment XXVI.

In order to ascertain whether the intestinal secretion was increased by casca, a cat was chloroformed, the abdomen opened, and three loops of small intestine ligatured. Into the middle loop 2 c.c. of a concentrated solution of the watery extract of casca were injected, and 2 c.c. of water into the other two. The cat vomited about an hour afterwards. At the end of about 5 hours, the animal was killed and the body examined. The upper and

middle loops were both dry, and the mucous membrane was normal in appearance, except slight congestion at the place of ligature between the upper and middle loop. The lower loop contained several c.c. of turbid greyish fluid.

The intestinal secretion is thus seen not to be increased by the drug.

Action of Casca on Circulation.

Experiment XXVII.

Preliminary Experiments on Frog's Heart.

A watery solution of the alcoholic extract and a standard salt solution were prepared; the hearts of two frogs of about the same size were them removed, and placed for a minute or two in ·75 per cent. salt solution. When they had recovered from the shock of removal, and were beating regularly, one was placed in the casca solution, the other in the salt one. At the commencement of the experiment the heart, A, placed in salt solution, was beating at the rate of 6 per 10 seconds; the heart, B, in casca, at the rate of 7·5. Both hearts became weaker and their pulsations slower; at the end of 50 minutes the heart in casca stopped entirely, that in salt solution pulsated feebly at the rate of 3 per 10 seconds. In 15 seconds more it stopped.

In Experiment XXVIII we repeated the foregoing experiment with a much stronger casca solution. The hearts at the commencement of the experiment were beating at the rate of 4 per 10 seconds. At the end of 30 minutes the heart, B, in casca, which had previously got very slow and weak, stopped, while the standard heart, A, was still beating strongly and regularly at the rate of 4 per 10 seconds.

Experiment XXIX.—March 7.

The heart of a frog whose cerebrum had been destroyed was exposed. Pulse 72 before injection.

h. m.
11 40. Injected 2 c.c. alcoholic solution beneath skin of back.
11 50. Pulse 60; regular.

h. m.

12 2. Pulse 48

12 10. Pulse 60. Clonic convulsions.

12 15. Ventricle stopped in systole, firmly contracted in its greater part, with a pouch-like dilatation of a small portion. Auricles still contracting.

12 27. Ventricle firmly contracted. Still partial contraction of auricles. Respiration and slight convulsive movements continue.

12 50. Removed from frog-board. The ventricle is not so firmly contracted. Still respiring and occasionally convulsed.

1 0 P.M. Ventricle relaxed. Slight movements of it have recommenced. 1·4 c.c. alcohol solution again injected.

1 7. Ventricle again firmly contracted. No respiration. Still slight reflex movement.

1 30. Died with heart in same condition.

Experiment XXX.—May 10.

The heart of a frog was exposed, and a little extract of casca placed on it. Pulse 34 per minute.

It had no apparent action.

A watery solution of casca was then poured into the thorax. The pulse became slower, = 24 per minute.

The ventricle then expanded irregularly; the diastole at the base being later than that at the apex.

Then the distention became imperfect, the ventricle seeming wrinkled.

The heart then stopped in systole, having two pin-point dilated pouches on it.

These experiments show that a very weak solution of casca applied to a frog's heart, when removed from the body, slows its pulsations, while, after the application of a stronger solution, the pulsations become slow, then the systolic contraction ceases to take place instantaneously over the whole surface of the ventricle; lastly, the heart stands still in systole.

When the heart of a frog is exposed, but not removed from

the body, and a solution of casca is injected beneath the skin, the heart's action is slowed, and is eventually stopped in systole; previous to its stopping, however, pouch-like dilatations are formed; in this respect the action of casca is similar to that of digitalis and other cardiac poisons.

Experiment XXXI.—April 27.

A cat was chloroformed; a cannula placed in the left jugular vein and one in the trachea. Artificial respiration was commenced, and the thorax was opened. The heart was beating regularly, but it was difficult to count the pulsations. They were counted by one person as 90, by another as 180.

Ten c.c. of a saturated watery solution of watery extract of casca were injected into the jugular vein. No apparent effect was produced.

Seven c.c. more were injected in the course of a few minutes. Within about a minute of the last injection the ventricle no longer contracted as a whole, but became pouched, the upper half seeming to overlap the under half so as to produce a transverse fold.

A few seconds afterwards, the lungs, which had hitherto been rosy, became white, and almost immediately the motions of all cavities of the heart completely ceased. On irritation of the ventricle no movement occurred.

Both vagi were divided, but without effect on the heart.

It was noticed that the rosy colour of the lungs returned, although the heart did not again beat. No pulsations were noticed in the pulmonary vessels. The heart was perfectly firm, and seemed to be in systole; but on tying a ligature round the base so as to include the large vessels, it contracted to about one-third of its former size.

The action of casca on the mammalian heart is seen from this experiment to be similar to its action on the heart of the frog.

Experiment XXXII.

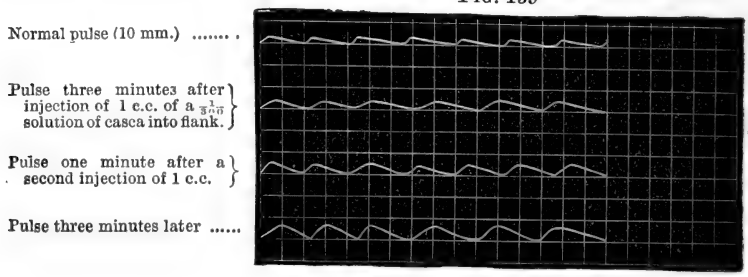
Action on Blood-pressure in the Frog.

The cerebrum of a large frog was destroyed. A cannula was then inserted into the left aorta, and was connected with a

small kymograph, the pulse-wave and oscillation being recorded on a revolving drum.

The appended curves give the oscillations of pressure in the aorta, and show that under the influence of casca the blood-pressure in the aorta rises to twice its normal height during systole, although it falls to zero during diastole.

FIG. 159



Experiment XXXIII.—March 31.

Action on the heart and blood-pressure of a large dose of casca. (For action on secretion of urine also, *vide infrà.*)

A bitch, weight 26½ lbs., was chloroformed.

A cannula was placed in the trachea.

" " left femoral vein.

" " right ureter.

" " left carotid artery.

The operation was very long, and during it the intestines became much congested.

Time.				Respirations in 10 seconds.	Amount of Urine secreted per 10 minutes.	Blood-pressure.	Oscillations.	Pulse in 10 secs.
h.	m.	s.			minims.	m.m.	m.m.	
1	54	57	Normal condition before experiments	..	5	120	10	20
			The rate of secretion of urine was estimated at two successive periods of 10 minutes each					
2	7	40	4 c.c. casca solution $\frac{1}{300}$ injected into femoral vein					
0	8	10	Showing the ordinary effect of the injection of a small					
0	10	30	quantity	..	..	140	10	20
0	17	40	Urine increased in quantity, alkaline, turbid, not albuminous	..	7	140	10	20
2	27	40	Urine still further increased	..	24	145	10	20
			Is clear; not albuminous					
2	34	30						
2	34	40	5 c.c. more injected					
2	35	40	Showing effect of further injection	..	..	160	15	20
2	47	40	Urine secreted, clear as before	..	17	160	15	20
			Clot formed. Lost about 15 c.c. of blood					
2	57	40	Urine as above	..	17	140	25	20
			With the increased dose the pulse oscillations have begun to be affected as well as the blood-pressure					
3	0	10	10 c.c. more injected					
3	0	30	Showing the immediate effect of a large dose. The systole and diastole are nearly equal; there is a very powerful action of the heart and increased blood-pressure	..	..	165	40 90	10
3	2	40	Showing the later effects of a large dose. The oscillations of the pulse are less, while the blood-pressure is greatly increased. The secretion of urine is much diminished..	..	3	200	15 20	20

Time.				Respirations in 10 seconds.	Amount of Urine secreted per 10 minutes.	Blood-pressure.	Oscillations.	Pulse in 10 secs.
h.	m.	s.			minims.	m.m.	m.m.	
3	7	40	Secretion of urine stopped	..	..	180	{ 10 / 20	16
3	17	40	Urine has again commenced to be secreted, the blood-pressure having fallen somewhat	..	5	150	30	15
3	27	40	Urine secretion again increased	..	13	110	50	12½
3	37	40	.. ..	..	9	115	30	16
3	37	50	Further injection of 15 c c.					
3	38	10	The blood-pressure is now much affected by the respiration after the injection of a large dose..	5	..	150 { 160 / 140	4	30
3	40	0	This is still more marked	5	..	170 { 190 / 150	2	40
3	42	0	The blood-pressure gradually fell, and the pulse was too feeble to write on the kymograph, while there was still a rise of blood-pressure synchronously with the respirations, which stopped at 3 h. 43 min.					

The thorax was then opened, and the heart found beating; respiratory movements recommenced on opening the thorax.

The bladder was found greatly distended; there had been micturition during the experiment, which was probably only overflow.

Remarks.

We append a diagram (p. 518) showing the coincident variations of blood-pressure and secretion of urine, which will be more fully commented on later. (*Vide* effect on urinary secretion.)

So far as the phenomena of circulation are concerned, this experiment shows that while a small dose of casca slows the pulse, an additional one greatly quickens it. This action of casca closely resembles the effect of digitalis, which first slows the pulse by stimulating the vagus-roots, and then quickens it by paralyzing the ends of the vagus in the heart. It therefore seemed probable that the cardiac ends of the vagus would be found to be paralyzed by large doses of casca.

It was possible that the primary slowing of the heart's action might be due to stimulation of the inhibitory apparatus in the heart itself, and not to the action of the drug on the vagus-roots. Two questions, therefore, were to be settled:—

1st. Is the primary slowing of the pulse due to stimulation of the vagus-roots, or to stimulation of the inhibitory apparatus in the heart?

2nd. Is the secondary acceleration of the pulse due to paralysis of the ends of the vagus in the heart?

To answer these questions the following experiments were performed (*vide antea*, p. 297):—

Experiment XXXIV.—March 21.

Action on the Heart and Arterial Pressure of a small dose of Casca.

A dog weighing 8 lb. was chloroformed, and kept under chloroform during the experiment.

A cannula was inserted into the right carotid and into the right femoral vein.

Time.			Blood-pressure.	Pulse in 10 seconds.	Oscillations.	Respirations in 10 secs.
m.	s.		mm.		mm.	
		Condition before injection ..	110	18½	10	
0	55	7 c.c. $\frac{1}{300}$ watery solution injected into femoral vein ..	125	16½	10	
1	0		130	16	10	
1	10					
1	20	Rise of blood-pressure. Commenced prolongation of diastole	155	14	10	
1	45	Systole fairly sharp, diastole very long	140	5	40	
		Commencing fall of blood-pressure				
2	5	Great fall of blood-pressure and lengthening of diastole..	65	⅓	25	
2	20	Diastole extends over 15 seconds				
		Systole extends over ½ second; does not vary with respiration				
2	40	Blood-pressure again lower. Diastole further prolonged..	45	½	30	5
3	0	Diastole 20 seconds				
		Systole ⅓ second. Diastolic curve slightly affected by respiration				
3	40	Blood-pressure recovering. Diastole shorter	50	2	25	9
3	50	Diastole 5 seconds				
		Systole ½ second				
		Respirations affect diastolic curve to extent of 3 mm.				
4	0	Blood-pressure rising	100	4	35	10
4	10	Systole and diastole nearly equal				
		Both affected by respiration to extent of 4 mm.				
4	20	Blood-pressure nearly at the height of commencement of experiments. Systole sharp	130	5	35	
4	30					
4	40	Blood-pressure higher. Diastole again prolonged ..	140	2½	60	10
4	50	Diastole 4 seconds				
		Systole ½ second				
		Respirations affect curves to extent of 10 mm.				
5	20	There was again a fall of blood-pressure with great prolongation of diastole similar to that which occurred at 2.5 to 2.20, but less marked	115	1	50	9
5	30					
6	0	Do., more marked	80	1	30	4
6	10					
6	20	Gradual fall of blood-pressure. Cessation of heart's action				
7	30					

Post mortem (immediately after death).—The heart contained blood, and contracted on puncture. The auricles contracted for 3 minutes after death.

This experiment shows that the action of a small dose of casca is to raise the blood-pressure and slow the heart at first. Next, when the heart becomes very slow, the pressure falls, and finally the heart ceases to beat, and death takes place.

The cardiac pulsations remained slow from the time of the injection of the casca up till death; and although they at one time rose from 1 pulsation in 30 seconds up to 5 pulsations in 10 seconds, they never came at all near to the normal, which in this animal was 18½ pulsations in 10 seconds.

The very slow pulse here indicates that the vagus is probably stimulated by the casca; and the continuance of the blood-pressure at the height of 65 mm. during a cardiac diastole, lasting for 30 seconds, shows unmistakably that the arterioles are strongly contracted by the drug.

Action on Vagus.

Maximum Irritation.

Experiment XXXV.—March 4.

A cat, weight 4 lb., was chloroformed, and a cannula was placed in the left carotid artery and in the left femoral vein.

Time.		Blood-pressure.	Oscillations.	Pulse in 10 seconds.
m. s.		mm.	mm.	
1 0	Normal curve taken 1 minute after connexion of cannula. Oscillation at top of respiratory curve = 9, at bottom 2	80	{ 2 / 9 }	23
2 15	R. vagus ligatured and cut			
2 18	L. vagus do. do.			
	Condition after section of vagi	{ 100 / 110 }	2	40
4 40	L. vagus irritated. Coil 5°*	60	18	15
	R. vagus irritated. do.	55	12	12

* The mark ° here signifies distance in cm. between primary and secondary coils in Du Bois Reymond's induction-apparatus.

Time.		Blood-pressure.	Oscillations.	Pulse in 10 seconds.
m. s.		mm.	mm.	
8 10	Condition subsequent to irritation .. It was thus ascertained that irritation of the strength of coil 5° was almost sufficient to stop the heart's action when applied to the peripheral end of either vagus previous to injection of casca	110	1	42
8 10 } 9 12 }	3½ c.c. of casca solution injected gradually into vein			
10 0	Condition after injection	120	2	40
11 0	A clot formed			
12 0	Condition after clot was removed .. (Slight improvement of pulse)	115	4	43
12 35	Peripheral end of L. vagus irritated. Coil 5°	90	8	35
13 0	Peripheral end of R. vagus irritated. Coil 5°	95	8	35
	Condition between irritations	120	2	35
14 27	Left vagus. Coil 0°	88	5	27
	Right vagus. do.	110	0	0
	Complete stoppage of heart's action without fall of blood-pressure			
15 20	Experiment repeated with R. vagus. Coil 0°	85	5	26
17 10 } 17 44 }	Fresh injection of 4 c.c.			
18 30	Condition after injection	115	2	40
19 5	Right vagus. Coil 0°. Commencement of irritation	100	3	30
	Right vagus. Coil 0°. Latter part of irritation	118	2	36
19 30	Left vagus. Coil 0°. Commencement of irritation	104	4	30
	Left vagus. Coil 0°. Latter part of irritation	120	2	35
20 0	Left vagus. Coil 0°. Commencement of irritation	121	2	35
	Left vagus. Coil 0°. Latter part of irritation	150	2	35
20 30	Condition after irritation	120	2	40
22 0 } 22 25 }	A third injection of 2 c.c. was given			
24 25	And the central ends of the vagi exposed for irritation			
24 30	Condition before irritation	120	2	40
25 12	Central end of left vagus irritated. Coil 0° .. .. (Blood-pressure increased; pulse nearly extinguished)	130	1?	30
25 50	Condition after irritation	125	2	34
26 30	Right vagus. Coil 0° .. .. .. (Effect as before)	130	1	34

Time.		Blood-pressure.	Oscillations.	Pulse in 10 seconds.
m. s.		mm.	mm.	
27 0	Condition after irritation	120	2	36
28 16	The sciatic nerve was exposed and irritated with coil 5°	135	2	37
28 45	Condition after irritation	120	2	36

This experiment shows that when both vagi are divided the injection of a small dose of casca no longer slows the heart; and therefore the slowing usually observed after its administration is due to stimulation of the vagus-roots and not to stimulation of the inhibitory apparatus in the heart itself.

It also shows that a large dose completely paralyses the ends of the vagus in the heart, so that a strong interrupted current applied to the trunk of the nerve produces no slowing of the cardiac pulsations.

Action of a Small Dose on the Excitability of the Vagus.

As it has been stated that digitalis in small doses increases the excitability of the ends of the vagus in the heart, so that a slight irritation applied to the trunk of the nerve will cause slowing or stoppage of the heart after the administration of the drug, although previously it had no effect, it seemed advisable to ascertain whether or not a similar action was possessed by casca. The following experiment was therefore tried:—

Minimum Irritation of Vagus (peripheral end).

Experiment XXXVI.—April 6.

A cat, weight 6 lbs., was chloroformed, and kept under chloroform the whole time of the experiment.

A cannula was inserted into the right carotid artery and into the right femoral vein.

Both vagi were then cut, and the peripheral end of the right vagus attached to Von Basch's electrodes.

Operation lasted half an hour; the cat at first very feeble, afterwards recovered.

Time.		Blood-pressure.	Oscillations.	Pulse in 10 sec.
m. s.		mm.	mm.	
1 50	Condition previous to irritation, both vagi being cut	120	1-2	40
2 0	Eight vagus irritated. Coil 30°. No effect	120 / 125	1-2	42
3 20	Right vagus irritated. Coil 25°. This irritation was sufficient to slow the heart and lower blood-pressure ..	100	5	20
5 0	Condition previous to injection.. .. As the cat was stronger, the normal minimum irritability was again tried, and coil 25° was again found to be the weakest which produced any effect	155	2	44
6 0 / 6 30	1½ c.c. casca solution, as in Experiment XXXIV, injected into femoral vein			
7 0	Condition after injection..	175	2	42
7 30	Vagus irritated. Coil 30°. No effect..	175	2	40
8 0	Vagus irritated. Coil 25°. No effect..	180	2	42

From this experiment it appears that the excitability of the peripheral terminations of the vagus-nerve is not increased by casca.

Action on the Vagus-roots.

The slowness of the pulse which quickly follows the injection of casca, and which we have already shown to be due to stimulation of the vagus-roots, might be caused either (*a*) by stimulation of the central end of the vagus by increased blood-pressure in the nerve-centres, or (*b*) stimulation by the direct action of the drug itself; (*c*) it was also possible that without actually irritating the vagus-roots the casca might increase their sensibility to other stimuli, reflex or otherwise.

Effect on Minimum Excitability of the Vagus-roots.

Experiment XXXVII.—March 30.

A cat, weight 4 lbs., was chloroformed.

A cannula was inserted into the trachea.

" " left carotid.

" " left saphena vein.

The right vagus nerve was cut, and its central end placed in a Von Basch's electrode.

The left vagus remained intact. A $\frac{1}{300}$ solution of the watery extract was used.

Time.		Respirations in 10 sec.	Blood-pressure.	Oscillations.	Pulse in 10 sec.
m. s.			mm.	mm.	
0 0	Condition before experiment ..	4	105	1–2	38
1 0 } 2 20 }	The normal excitability of the central end of the right vagus was then tested; it was found that coil 10° produced slight slowing of the pulse and fall of blood-pressure, while the respirations became slower and deeper. This was the slightest irritation which produced any effect	2	100	3	30
3 30	Condition after irritation ..	2	110	1-2	34
4 0	·5 c.c. injected				
4 30	Condition after injection .. Rise of blood-pressure. No alteration of pulse. Respirations quickened and respiratory oscillations increased	3	140	1	34
5 0	Central end of right vagus irritated. Coil 15° .. .. No effect	3½	140	1	34
6 0	Central end of right vagus irritated. Coil 10° .. .. Same effect as before injection.	2¼	135	1	38
7 0	Second injection of 1½ c.c.				
8 0	Clot formed and removed				
9 0	Condition before irritation ..	3	120	2	43
9 30	Irritation with coil 10° .. The thorax remained in a state of permanent inspiration during irritation, while the effect on the heart and blood-pressure was *nil*	0	120	2	40
10 0 } 10 5 }	Irritation with coil 6° .. .. No effect on heart. Respiration as before	0	115	2	40
10 8	Condition immediately following irritation .. .. .. Slowing of pulse. Great fall of blood-pressure. Great oscillation. Systole and diastole of same length, with no pause between them	3	60	28	12
15 0 } 15 30 }	Irritation with coil 8° .. .. As before there was no effect on the blood-pressure or pulse, and there was permanent in-	0	120	2	40

Time.		Respirations in 10 sec.	Blood-pressure.	Oscillations.	Pulse in 10 sec.
m. s.	spiration during the irritation		mm.	mm.	
15 35	Condition immediately after irritation. See remarks on after effect of coil 6° ..	4	30	15	16 irreg.
16 0	Gradual cessation of after effect	2	100	7	22
16 30	After effect ceased	0½	120	2	35
17 0	Coil 8°. Irritation repeated with same results				

In this experiment, as well as in several others, the blood-pressure rose without being accompanied by a slowing of the pulse, and this indicates that the latter is not dependent on the former.

The excitability of the vagus-roots to reflex stimuli does not seem to be increased by casca, as a stimulus of the same strength applied to the central end of one vagus had a similar effect before and after the injection of the drug. We would call attention, however, to the very extraordinary effect which succeeded the application of a stronger stimulus, an effect which seems all the more extraordinary from occurring after the stimulus had ceased, and not during its application.

Irritation of the vagus-roots by the carbonic acid accumulated in the blood during the tetanic inspiration, which lasted during the irritation, at once suggests itself as a cause of the slow pulse which followed the irritation; but the fact that the pulse was not affected when the distance of the coil was 10 cm., although the thorax was tetanically expanded, seems to indicate that the slowing which followed the stronger irritation from a secondary coil at 8 or 6 cm. distance from the primary was due to reflex action, which the first irritation had been too weak to produce.

From Experiment XXXV it will be seen that after the administration of a large dose of casca, irritation of the vagi, instead of producing slowing or stoppage of the heart's action, increased the frequency of its pulsations. The acceleration

was equally great after irritation of the left, as after irritation of the right vagus. This shows that the accelerator-fibres in the vagus are not paralysed by casca, and also that accelerator-fibres, though usually, according to Boehm, contained only in the right vagus, may occasionally be present in the left.

The effect of irritating the other accelerating nerves of the heart contained in the rami cardiaci or in the sympathetic cord was not examined.

Action on Cardiac Ganglia, Effect on Pulse, &c.

Experiment XXXVIII.—June 10.

A moderate-sized cat was chloroformed, and cannulæ were placed in the carotid artery and jugular vein.

A solution of 3 c.c. of saturated alcoholic tincture added to 50 c.c. of water was used for injection into the vein.

Time.		Blood-pressure.	Oscillations.	Pulse in 10 sec.
m. s.		mm.	mm.	
0 5	Condition before injection	160	25	23
1 20	Injected 1 c.c. casca solution			
1 30	Condition shortly after injection ..	180	50	14
	Rise of blood-pressure, slowing of pulse			
2 0	Later, quickening of pulse	165	7	26
3 0	Same effect, more marked	175	5	36
4 0	Commencing slowing of pulse	170	6	30
4 30	„ „ „	140	8	30
5 0	„ „ „	150	14	24
5 5	Further injection of 1 c.c. casca			
5 40	Secondary slowing of pulse with *fall* of blood-pressure	115	25	16

From this experiment it is seen that after the primary slowing due to stimulation of the vagus-roots and the quickening due to paralysis of the vagus ends in the heart, a second slowing occurs.

This second slowing might be due either to stimulation of the inhibitory apparatus in the heart or to weakening of the cardia motor ganglia.

The latter seems improbable, from the fact that each systole during this slow period instead of being weak is exceedingly

strong, the pulsation in an artery being felt very powerfully when the finger is laid upon it, and the rise of pressure during it being very great, as shown by the oscillation of the mercurial column of the manometer.

In order to ascertain more exactly whether the inhibitory cardiac ganglia were stimulated or not the following experiment was tried:—

Experiment XXXIX.

A dog was chloroformed, and 7 c.c. of a concentrated watery solution of casca were injected into the jugular vein.

The pulse at the time of injection was 37 in ten seconds. In ten seconds after the injection it sank to 20. After the injection of 3 c.c. more the pulse rose to 37. After a further injection of 26 c.c. more in divided doses it again sank to 16.

This number was, however, uncertain, as the tracing was a very imperfect one.

The injection of 1 c.c. of liquor atropiæ, B.P., did not seem to alter the number of the pulse, but the injection of $\frac{1}{2}$ a c.c. more seemed to cause it again to become quick.

This seems to indicate that the slowing is due to an action of the casca on the inhibitory ganglia. The imperfection of the tracing renders the result somewhat uncertain; but want of time prohibited us from repeating the experiment, although we greatly desired to do so.

Experiments XL, XLI.—March 15.

The effects on the capillaries of the frog's web were microscopically observed in Experiment XL after an injection of casca under the skin of the back, in Experiment XLI when locally applied to the web.

The capillaries were observed with oc. 2 obj. 4 of Hartnack. In the first case, *i.e.*, after the drug had been injected, the results were purely negative. In the second, after application of a drop of strong casca solution to the web, the results were also indecisive. In the capillaries, and also in the larger trunks, the current was at first slowed, and in some permanent stasis occurred. When slowing only was produced, the partial arrest

was followed by reaction, which did not exceed the original rapidity of the circulation. No dilatation or contraction of the vessels was seen to accompany the original slowing.

Although the results of experiments on the frog's web gave no definite information regarding the contraction of the arterioles under the influence of casca, yet no reasonable doubt can be entertained that in mammals they do contract; for this is the only possible explanation of the exceedingly slow fall of the blood-pressure during the intervals between the beats of the heart when these have become slow, either from the action of the drug or from irritation of the vagus-trunk. (*Cf. antea*, p. 143.)

In order to ascertain whether this contraction was due to the action of the drug upon the vasomotor centre in the medulla oblongata or in the vessels themselves, the vasomotor centre in the medulla was separated from its connection with the vessels by division of the spinal cord in the neck previous to the injection of casca.

Effect on Blood-pressure after Division of Cord.

Experiment XLII.—May 17.

A large strong cat, weighing 7½ lbs., was chloroformed. A cannula was inserted into the left carotid, and another into the jugular vein. The spinal cord was then divided opposite the second cervical vertebra, and artificial respiration kept up.

Time.		Blood-pressure.	Pulse in 10 seconds.	Oscillations.
m. s.		mm.		mm.
0 0	Condition after section of cord and previous to injection of casca	80	25	5
0 3 } 0 7 }	Injected 1 c.c. watery solution of casca			
0 10	.. ..	80	25	5
0 20	.. ..	130	18	12
0 30	.. ..	140	13	20
0 40	.. ..	150	13	25
0 50	.. ..	150	18	12
1 0	.. ..	175	28	5
1 10	.. ..	190	32	4
1 20	.. ..	200	34	3

Time.		Blood-pressure.	Pulse in 10 seconds.	Oscillations.
m. s.		mm.		mm.
1 30	.. ..	210	34	3
1 40	.. ..	220	41	4
2 0	.. ..	230	44	3
2 10	Sudden alteration in character of pulse, which becomes slow. The curve flat-topped, and both systole and diastole showing numerous secondary oscillations. Blood-pressure falling ..	190	3½	40
2 20	.. ..	180	5	30
2 40	.. ..	165	6	25
3 0	Blood-pressure rapidly falling	130	6	15
3 20	Both pulse and oscillations are very irregular	100	5	?
3 40	.. ..	80		
3 50	.. ..	25		
4 0	.. ..	10		
	There was no more pulsation after this; but the blood-pressure took 1 minute 30 seconds to fall quite to zero			
	On opening the thorax the heart was found moderately contracted; electrical stimulation of the phrenic nerve caused contraction of the diaphragm			

The result of this experiment will be seen all the more clearly by the following diagram, Fig. 160, in which they have been graphically represented.

The rise of pressure in this experiment was greater than in any other in which the cord had not been divided. This seemed to us so extraordinary that we thought at first that the cord had not been properly divided; but a careful dissection made immediately after death showed us that the division was complete. A year or two ago this result would have been regarded as a proof that the drug acts on the vessels themselves; but recent researches having shown that much more importance must be attributed to vasomotor centres in the cord and in the periphery than was previously done, we cannot say whether the drug acts on these centres or on the walls of the vessels themselves. The non-contraction of the vessels of the frog's web would indicate that the action of the drug is rather on nervous centres in the cord or neighbourhood of the vessels than on the vascular walls.

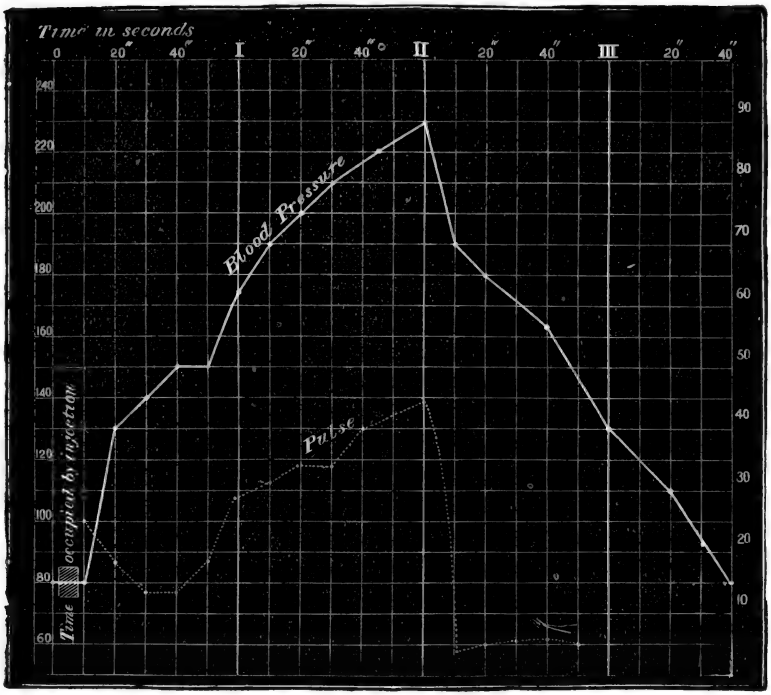


FIG. 160.

In order to exclude all centres except those in the periphery Experiment XLIII was performed.

Experiment XLIII.

The sympathetic cord was divided on the right side of the neck of a rabbit and the animal allowed to come out of the chloroform anæsthesia. The ear of the right side was deeply injected while the left ear was very moderately filled with blood. A dose of casca was then administered. The vessels of both ears became pale, those of the right ear equally so with those of the other.

VESSELS AFFECTED BY THE DRUG.

The vessels by which the blood-pressure in the body is chiefly regulated are those of the intestines, those of the skin and

muscles being very much less under the influence of the vasomotor centre in the medulla. As casca acts on the vessels without this centre, however, it was natural to suppose that other vessels than those of the intestines might be affected; and this the curves show to be the case. During the stoppage of the heart (Experiment XLII) for half a minute the pressure fell only slightly. Now Ludwig and Hafiz found that when contraction of the abdominal vessels was produced by irritation of the vasomotor centre in the medulla oblongata, complete stoppage of the heart was followed by a rapid fall in the blood-pressure, the blood finding its way out of the arterial system into the veins through the vessels of the muscles. The slow fall after the administration of casca shows that the vessels of the muscles must be contracted as well as those of the skin and intestines.

Action on Secretion of Urine.

A detailed account of our experiment on the action of the drug on the urinary secretion, together with the accompanying effects on the circulatory system, will be found in pp. 503 and 504. Underneath is a diagram showing the close dependence of the rate of secretion of urine upon the blood-pressure (Fig. 161)

Experiment XXXIII.—March 31.

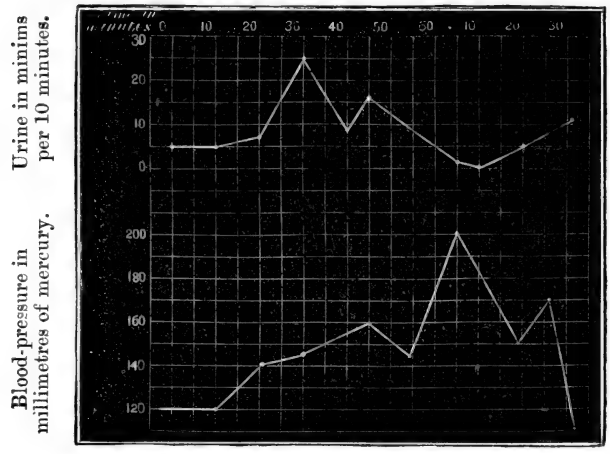


Fig. 161.

Remarks.

The results of this experiment, as regards the vascular phenomena of blood-pressure, pulse, &c., have been already fully noticed.

The action of the drug on the secretion of urine is seen to be very marked and characteristic, and the dependence of the secretion on the blood-pressure is well shown in the accompanying chart.

Thus the average rate of urine secreted before administration of casca being 5 minims in 10 minutes, an increase of 50 mm. in the blood-pressure caused by the drug brought the rate of secretion of urine up to 25 minims. When the action of the drug was further pushed there was first decrease and then total suppression of urine, the blood-pressure at the time of suppression being 200 mm. of mercury.

Subsequently as the blood-pressure fell the secretion of urine recommenced.

The physiological explanation of these successive phenomena appears to be that the primary increase of blood-pressure produces arterial fluxion to the kidney; but that if the action of the drug is pushed, the renal vessels become contracted so as to prevent the blood reaching the kidneys, notwithstanding the high pressure in the arterial system. It is worth notice that the urine collected after the secretion had recommenced did not contain albumen.

In this respect the result of this experiment differs from those obtained by Mr. Power and one of us in our experiments on the action of digitalis; it coincides, however, with those experiments in its general results. (*Cf. antea*, pp. 410 and 412.)

Action on the Pupil and Lacrymal Gland.

In order to see if the drug exerted any local action on either of these organs, we (Experiment XLV) placed some drops of strong watery solution of casca in the eye of a cat, but with purely negative results.

Action on Muscle.

Effect on Structure of Muscular Tissue.

The effect on fresh muscular tissue of immersion in casca solution was carefully watched with an oc. 3 obj. 7 of Hartnack's microscope without any change in the structure being discovered (Experiment XLVI). We then (Experiment XLVII, March 22nd) examined the "naked-eye" and microscopical changes produced in muscular tissue by prolonged immersion in a watery solution of the alcoholic extract, the effect of which solution in preventing the development of *Bacteria* has already been detailed (p. 493).

A. The solution in which the muscular tissue had been placed presented, in addition to the absence of *Bacteria*, a few noteworthy points; it preserved its original slightly resinous smell, and deposited a fine light-brown sediment, which, under the microscope, appeared as a granular structureless detritus.

B. The muscular tissue to the naked eye appeared hardly altered in consistence: the fibrous sheath was firm; there was no smell. Under obj. 7 Hartnack the fibres were seen to be very granular, in part only preserving their transverse striation; the general appearance closely resembled ordinary fatty degeneration. Some of the fibres were then soaked in ether for 24 hours; on examination after this the granulations had in great part disappeared. Many of the fibres appeared to consist merely of collapsed tubes of sarcolemma; where they were not collapsed they showed plain transverse striæ.

Six weeks later the muscle was again examined; it having remained in the same casca solution all the while, it was now reduced to the condition of a rather tough gelatinous pulp; the sheath of the muscle retained its strength. Under the microscope there was seen a mixture of granular and fibrous material, with a large quantity of oil-globules and flat crystals, and when treated with ether these were completely removed.

Effect on the Lifting-power of Muscle.

Experiment XLVIII.

The lifting-power of a frog's gastrocnemius which had been placed in a $\frac{1}{300}$ solution of casca was compared with that of a similar preparation placed in salt solution, by attaching the one muscle as quickly as possible after the other to an apparatus for estimating their lifting-power connected with a revolving drum. The irritations were made with electrodes connected with a Leclanché's battery.

The results of our first experiments appeared to show that the drug possesses a stimulating action on the lifting-power of muscle; but on repeating the experiment this result was not confirmed—the conclusion we drew from the whole series of experiments being that muscles which had been immersed in casca and salt solution respectively possessed nearly the same lifting power.

Effect on Muscle-curves.

Experiments XLIX, L.

Two frogs were injected with casca, and when they seemed dead, nerve-muscle preparations were made of the gastrocnemii. In Experiment XLIX the preparation was attached to a Fick's pendulum myograph, and a tracing taken. In Experiment L the nerve-muscle was made to trace on a revolving cylinder: the curves obtained in these experiments are evidently normal.

In Experiment LI the action on the sensibility to electrical stimuli of muscle and motor nerves was tried, also with completely negative results, by making two nerve-muscle preparations of a frog's gastrocnemii, and immersing one in casca solution, the other in salt solution. The sensibility of the two preparations was then tested by various strengths of a Du Bois Reymond's coil connected with a Leclanché's battery. The two muscles responded quite similarly.

Remarks on the Action of Casca on Muscle.

1. When applied to fresh muscular fibre no change is observed in its histological details.

2. In addition to the absence of the development of *Bacteria* which is noticed when muscular tissue is placed in a watery solution of the alcoholic extract, and which has already been remarked upon, the structural changes which the muscular tissue undergoes appear to consist in a fatty metamorphosis, which at first simulates very closely that of ordinary fatty degeneration, while the later appearances resemble those of the more complete fatty changes which go on after the death of a tissue, large oil-globules and abundant crystals of the fatty acids being everywhere found.

3. It does not diminish the lifting-power of muscle in a nerve-muscle preparation, nor when the irritation is applied to the muscle itself, and it probably does not increase it; for although apparently positive results were attained on the first occasion when the lifting-power was experimented on, these results were not borne out by further experiments.

4. The muscle-curve given by a nerve-muscle preparation taken from a frog poisoned by a large dose of casca appears to be quite a normal one.

5. It also exerts no action on the sensibility of muscle to electrical stimulation if this sensibility be tried quantitatively by estimating the weakest interrupted current which will produce a contraction.

From all these results, then, it may be concluded that while the drug produces a peculiar and characteristic change on muscular tissue immersed in it for some days, it is not a muscle-paralyzer.

Action on Motor Nerves.

If casca had any paralyzing action on the ends of motor nerves similar to that of curare, it would be found that after immersion in a solution of the drug the muscle would respond to electrical stimuli directly applied to it, but not to those applied to the nerve. In Experiment LII, however, the nerve also is seen to preserve its irritability, and therefore we may conclude that casca has no action on motor nerves.

Action on Sensory Nerves.

Effect on Reflex Excitability.

Experiment LII.—March 22.

The cerebrum of a living frog of medium size was destroyed. The circulation through the left leg was cut off by ligaturing the arterial trunks above the knee (*vide* fig. 162). The sciatic nerve was left uninjured. $\frac{1}{4}$ c.c. of the alcoholic extract was then injected beneath the skin of the back.

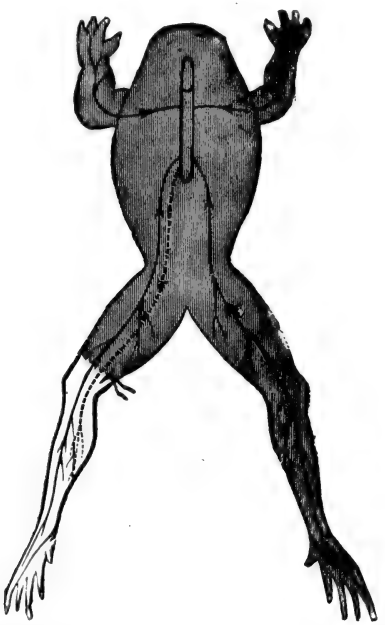


Fig. 162. The shading indicates the part to the body to which the poison was carried by the blood. The unshaded part was protected by the ligature from the action of the poison.

The reflex excitability was then tested at intervals of 5 minutes by irritating points above and below the ligature. No difference in the sensibility could be detected.

As the frog was very little affected by the injection, another $\frac{3}{4}$ c.c. was injected.

The frog became insensible to reflex irritation in 25 minutes;

during this time the irritability was tested every 5 minutes as before: the rates of increase of the insensibility appeared to be equal above and below the ligatures.

In this experiment the poison was applied to the terminations of the sensory nerves above the ligature, but not to those below it. Had it possessed any marked power of diminishing the sensibility of these nerves, a stimulus applied above the ligature would have had less effect than one applied below it; but this was not the case.

The poison therefore seems to have no action on sensory nerves, at any rate none of a paralyzing character.

Action on Reflex.

Experiment LIII.

In this experiment the action on reflex was tested by applying a very dilute solution of sulphuric acid to the leg of a frog with its cerebrum destroyed and suspended by its head. Its normal irritability was then tested. The tips of the toes only were immersed in the acid. Contraction was immediate and lasted 3 minutes (right leg). A $\frac{1}{4}$ c.c. alcoholic solution was then injected; the animal immediately hung more flaccidly. 5 minutes afterwards, on immersing the tip of the toes of the right leg, slight contraction occurred after 63 seconds. A quarter of an hour later, on immersing half the leg, contraction was immediate and lasted 5 seconds; in 10 minutes more a similar immersion produced contraction after 10 seconds, and 5 minutes afterwards after 15 seconds. 50 minutes after the injection of the drug the acid solution produced no reflex movements, and only slight ones were excited by pinching. Reflex ceased last in the eyelids 1 hour and 20 minutes after the casca had been injected.

In Experiment LIII the reflex excitability disappeared very much more quickly than it usually does.

This might be due to the action of the drug on the spinal cord itself, or to the cessation of circulation caused by the action of the drug on the heart.

In order to decide this the following experiment was made.

Experiment LIV.

The heart of a frog was exposed and casca administered. As soon as the heart had ceased to beat the heart of a second frog was ligatured at the root of the aorta so as completely to arrest the circulation. At first both frogs were able to jump readily; but gradually their movements became more sluggish, and after a jump their legs trailed out behind them and were only slowly drawn up to the body. They became less and less sensitive to pinching, and insensibility and loss of motor power occurred simultaneously in both.

The diminished power of movement and diminished reflex action observed in the frog after the administration of casca is therefore due to the arrest of the circulation caused by it, not to any action of the drug upon the nervous system.

Antagonism between Casca and Atropia and Chloral Hydrate.

The remarkable result of Experiment XXIV, in which a dose of casca, usually fatal, produced no effect in an animal with divided vagi, seemed to render it probable that such a drug as atropia, which paralyzes the ends of the vagus in the heart, might have an antagonistic action. On trying it, however, it was found that the vomiting caused by the casca was even more violent than usual; and therefore a combination of atropia with chloral hydrate was employed, the chloral being given to lessen the irritability of the vomiting centre in the medulla.

The results were not satisfactory, as will be seen from the two following experiments.

Experiment LV.—May 1, 1876.

About 11.40. Injected 4 c.c. of liquor atropiæ under skin of flank of cat A.

12^{h}. Injected 4 c.c. of a saturated alcoholic solution of alcoholic extract of casca under skin of flank of cats A and B

	A.	B.
h. m.		
12 30	.. ..	Sick and vomits. During the intervals between the fits of vomiting seems well.
12 40	Crouching, trembling, and seems about to be sick. Licks its lips. Hind eyelid much drawn up.	
12 52	Very sick; vomiting. Seems more uneasy than B.	Vomiting. Disinclined to move. When disturbed and made to walk its hind legs give a shake as if to shake off something sticking to the feet every time they are drawn up.
1 0	Very sick.	Very sick. Brings up fluid, which appears to be digested meat. Respirations 18 per minute.
1 15	Gives loud squalling cries when retching.	Seems weaker.
1 30	Seems easier; not retching.	Twitch or rather shake of hind legs is very marked.
2 35	Walking about.	Seems unable to move.
2 40	.. ..	Violent retching; crying. Convulsive extension of legs and emprosthotonos. Then two or three sighing respirations; a pause; one or two respirations at intervals; then death.
4 0	Has been vomiting at intervals. Has a violent fit of sickness and dies in the same way as B.	
	Post mortem.	
	Stomach contains a quantity of food. Heart moderately contracted. Ventricles continue to make slight pulsations, auricles not. Lungs somewhat congested. No congestion of interior of stomach.	Stomach empty, not congested. Heart moderately contracted. Lungs normal.

Experiment LVI.

Cat A. Large.	Cat B. Medium.	Cat C. Large and strong.
h. m.	h. m.	h. m.
13 3. Injected 30 minims liquor atropiæ subcutaneously.	12 45. Injected 15 grs. of chloral hydrate and 15 minims of liquor atropiæ with 5 c.c. of casca.	12 40. Injected 5 c.c. of the same casca solution.
12 20. Injected 5 c.c. saturated watery solution and suspension of casca.	12 58. Mewing.	12 49. Very restless.
12 30. Vomited.	12 59. Vomited twice.	12 52. Vomited for first time. After this it vomited frequently, but remained restless. T. 37·1°.
12 45. Vomiting has been repeated 3 or 4 times. Is lying on its side and cannot stand. R. 144. Alæ nasi working.	1 9. Vomited again.	1 30. Died rather suddenly, with violent gasping and emprosthotonic spasm.
12 52. Eyelids much drawn up. Respiration irregular.	1 14. Loud violent retching but no vomiting.	Cat C lived 50 minutes.
12 55. Gasps; seems to try but to be unable to vomit. Emprosthotonic spasms.	1 15. Involuntary extrusion of fæces and urine. Died.	
12 58. Muscular twitchings. Slow sighing respirations. Death.	Cat B lived 30 minutes.	
Cat A lived 38 minutes after injection of casca.		

In this experiment the cat which had received the casca alone lived longer than the others.

NOTE ON INDEPENDENT PULSATION OF THE PULMONARY VEINS AND VENA CAVA.

In conjunction with Sir J. FAYRER, M.D., K.C.S.I.

(From the *Proceedings of the Royal Society*, No. 172, 1876.)

In a former communication* we incidentally mentioned that in a rabbit killed by the injection of cobra poison into the jugular vein we had observed the pulmonary vein pulsating after all motion had ceased in the cavities of the heart. We have since observed the same phenomenon three or four times under conditions which show that this pulsation is not due to the action of the cobra poison with which the animal in which we first observed it had been killed. The following example will show the changes in rhythm observed in these pulsations.

A cat was chloroformed, and the vagi exposed and irritated by an interrupted current. Artificial respiration was kept up by air containing chloroform vapour, and the thorax was then opened, and a solution of atropia injected directly into the heart by means of a Wood's syringe. The vagi were again irritated, but without any effect being produced on the heart, the inhibitory apparatus in it being evidently paralysed by the atropia. A solution of glycerine extract of physostigma was now injected into the heart in a similar way. The vagi were now irritated again, and the heart stood still, the effect of the atropia having been counteracted by the physostigma. After the irritation ceased the heart again commenced to pulsate.

Artificial respiration was now discontinued, but all the cavities of the heart continued to beat for a considerable time. The ventricles then stopped, but the auricles continued to beat. It was then noticed that the pulmonary veins in the right lung,

* *Proceedings of the Royal Society*, 1874, vol. xxii, p. 125.

which was exposed to view, were pulsating. The veins, as well as both auricles, pulsated at the rate of 119 per minute, but the contractions of the veins were not synchronous with those of the auricles. Both auricles next ceased to beat, but the pulmonary veins in both lungs continued to pulsate. The ventricles now began to beat again, while the auricles remained still. The ventricles pulsated at the rate of 8 per minute, while the pulmonary veins pulsated at the rate of 46 per minute; and no motion was perceptible in any part of the auricles.

One hour and twenty minutes after the thorax had been opened, and about an hour and ten minutes after artificial respiration had been discontinued, the ventricle was still pulsating. Its rhythm was very irregular. After one beat a pause of half a minute followed, and then 37 pulsations all together. One hour and forty minutes after opening the thorax the inferior vena cava was noticed to be pulsating close to its entrance into the auricle. A contraction spread like a wave from the vena cava over the right auricle, and the appendix contracted after the auricle itself. The superior vena cava also pulsated close to the neart. The left auricle had ceased to pulsate a considerable time previously, and the ventricles had also stopped. After the auricles had pulsated for a while the ventricles again began. At one hour and fifty minutes after opening the thorax the inferior vena cava was still pulsating. In ten minutes more all movement had nearly ceased, and the observation was discontinued.

At one hour and fifty minutes after opening the thorax slight contractions of the diaphragm were noticed.

The striking points in this experiment are the contractions of the pulmonary veins and the vena cava independently of the heart, the long time during which they retained their irritability, and the continuance of their pulsations after the other parts of the heart had ceased. The pulsation of the pulmonary veins and of the ventricles at the same time, while the auricles were motionless, is also deserving of attention.

In another experiment we found the pulmonary veins pulsating in a cat killed by a blow on the head. We have also seen pulsation in animals killed in other ways; but the proportion of

cases in which we have seen it to those in which we have not seen it is very small. On looking through several modern text-books of physiology, we have failed to find any mention of the rhythmical contractile power of the pulmonary veins and vena cava; but the earlier anatomists were well acquainted with it, and Haller* states that he has seen the pulmonary veins continue to pulsate for two hours, and that others had seen the vena cava pulsate for three hours while all motion in the other cavities of the heart had already ceased. Johannes Müller† has also observed contractions of the vena cava and pulmonary veins; and in young animals the contractions of the pulmonary veins extend as far as they can be followed into the lungs.

The importance of contraction of the vena cava and pulmonary veins in preventing reflux of blood into them during the contraction of the auricle, under circumstances when any hindrance is opposed to the free flow of its contents into the ventricle, is self-evident. Indeed Haller‡ says that it was supposed to exist by Senac, although he had not seen it. Especially in cases of valvular disease of the heart is it likely to be of great service; and we think it advisable to bring again before the notice of physiologists and physicians this power of the veins, which, although so long known, appears of late years to have been overlooked.

* *Elementa Physiologia*, 1757, tom. i, pp. 410 and 399; and *Mémoires sur la Nature sensible et irritable des parties du corps animal*, 1756, tom. iv, p. 4.

† Müller's *Physiology*, translated by Baly, 2nd ed., vol. 1, p. 182.

‡ *Op. cit.*, p. 410.

ON THE SCIENCE OF EASY CHAIRS.

(Reprinted from *Nature*, October 17, 1878.)

THERE is a reason for everything, if we can only find it out, but it is sometimes very hard to discover the reasons of even the very simplest things. Every one who has travelled much, and even those who have merely looked through books of travels, must have been struck by the variety of attitudes assumed by the people of different countries. The Hindoo sits down on the ground with his knees drawn up close to his body, so that his chin will almost rest upon them; the Turk squats down cross-legged; the European sits on a chair; while the American often raises his legs to a level with his head. Nor are the postures assumed by the same people under varying circumstances less diverse. Climate or season, for example, will cause considerable alteration in the posture assumed, as was well shown by Alma Tadema, in his pictures of the four seasons exhibited in the Academy a year ago. In his representation of Summer he painted a woman leaning backwards on a ledge, with one leg loosely hanging down, while the other was drawn up so that the foot was on a level with the body. In the picture of Winter, on the other hand, we saw a figure with the legs drawn up in front of the belly. The reason for these different postures has been explained by Rosenthal. The temperature of the body, as is well known, is kept up and regulated by the circulation of the blood through it, and a great proportion of the blood contained in the whole body circulates in the vessels of the intestines. Now the intestines are only separated from the external air by the thin abdominal walls, and therefore any change of temperature in the atmosphere will readily act upon them unless they be guarded by some additional protection. The Hindoos are well aware of this, and they habitually protect the belly by means of a thick shawl or camarband, thus guarding themselves against any sudden change of temperature. This precaution is also frequently adopted by Europeans resi-

dent in hot climates, and is even retained by them after returning to England. But the function of the camarband may, to a certain extent, be fulfilled by change of posture alone. When the legs are drawn up, as in the picture of Winter already referred to, the thighs partially cover the abdomen, and taking the place of additional clothing, aid the abdominal walls in protecting the intestines and the blood they contain from the cooling influence of the external air.

Thus it is that in cold weather, when the quantity of covering in bed is insufficient, persons naturally draw up their legs towards the abdomen, so as to retain as much heat as possible before going to sleep. In hot weather, on the contrary, they wish to expose the abdomen as much as possible to the cooling influence of the atmosphere. The posture depicted by Alma Tadema is the most efficient for this purpose. It no doubt answers the purpose to lie down flat on one's back, but in this position the abdominal walls are more or less tight, whereas, when one of the legs is drawn up as in the painting just alluded to, the walls are relaxed, and the intestines not being subject to any pressure, the blood in them will circulate more rapidly, and the cooling process be carried on more effectually. In this attitude also the thighs are completely separated, and loss of heat allowed from their whole surface.

Varying conditions of fatigue also alter the postures which people assume. When slightly tired one is content to sit down in an ordinary chair in the position of the letter N with the middle limb horizontal. As we get more and more fatigued we usually assume positions in which the limbs of the N become more and more oblique, the trunk leaning backwards and the legs extending forwards. If we lie down in bed on our back the legs will probably become straight, but if we rest upon our side they will be more or less bent. The straightness of the legs in the supine position is simply due to their weight, which is then supported at every point by the bed, but when we lie on our sides the genuflexion of the legs is most agreeable, because not only are the muscles more perfectly relaxed, but, as the late Professor Goodsir pointed out, the bones which form the knee-joint are slightly removed one from another, and thus the joint

itself, as well as the muscles, passes into a state of rest. Some of the bamboo easy chairs manufactured in India allow us to obtain the advantages of both positions. These chairs are made in the form of a somewhat irregular straggling W, and in them one can lie on one's back with every part of the body thoroughly supported, and the knees bent in the same way as they would be if one lay upon one's side.

Thus simple inaction, the relaxation of muscles, and the laxity of joints, are some of the factors necessary for complete rest, and an easy chair, to be perfect, must secure them all.

But it is possible for an easy chair to secure all these and yet be imperfect. We have just said that usually, as the fatigue becomes greater and greater, the tendency is to assume the position of the N with the limbs at a more or less obtuse angle, but when sitting in an ordinary chair we find relief from raising the feet by means a foot-stool, although this tends to make the angles of the N more acute instead of more obtuse. Still more relief, however, do we obtain when the legs are raised up on a level with the body by being placed upon another chair, or by being rested on the Indian bamboo seat already described. If, in addition to this, the legs are gently shampooed upwards, the sensation is perfectly delightful, and the feelings of fatigue are greatly lessened. To understand how this can be, it is necessary for us to have some idea as to the cause of fatigue. Any muscular exertion can be performed for a considerable time by a man in average health, without the least feeling of fatigue, but by and by the muscles become weary, and do not respond to the will of their owner so rapidly as before; and if the exertion be too great, or be continued for too long a time, they will ultimately entirely refuse to perform their functions. The muscle, like a steam-engine, derives the energy which it expends in mechanical work from the combustion going on within it, and this combustion, in both cases, would come to a standstill if its waste products or ashes were not removed. It is these waste products of the muscle which, accumulating within it, cause fatigue, and ultimately paralyse it. This has been very neatly shown by Kronecker, who caused a frog's muscle, separated from the body, to contract until it

entirely ceased to respond to a stimulus. He then washed out the waste products from it by means of a little salt and water, and found that its contractile power again returned, just as the power of the steam-engine would be increased by raking the ashes which were blocking up the furnace and putting out the fire. These waste products are partly removed from the muscles by the blood which flows through them, and are carried by the veins into the general circulation. There they undergo more complete combustion, and tend to keep up the temperature of the body. At the same time, however, according to Preyer, they lessen the activity of the nervous system, producing a tendency to sleep, and in this way he would, at least to some extent, explain the agreeable drowsiness which comes on after muscular exertion. It would seem, however, that the circulation of the blood is insufficient to remove all the waste products from the muscles, for we find that they are supplied with a special apparatus for this purpose. Each muscle is generally ensheathed in a thin membrane, or fascia, and besides these we have thicker fasciæ ensheathing whole limbs. These fasciæ act as a pumping apparatus, by which the products of waste may be removed from the muscles which they invest. They consist of two layers, with spaces between. When the muscle is at rest these layers separate, and the spaces become filled with fluid derived from the muscle, and when the muscle contracts it presses the two layers of its investing sheath together, and drives out the fluid contained between them. This passes onwards into the lymphatics, where a series of valves prevent its return, and allow it only to move onwards, till at last it is emptied into the general circulation.

In strong and healthy people the veins and lymphatics together are quite able to take up all the fluid which the arteries have supplied to the muscles, and thus prevent any accumulation from taking place either in them or in the cellular tissue adjoining them, or at least prevent any such accumulation as might become evident to the eye. In delicate, weakly persons, or in those who suffer from certain diseases of the vascular system, this is not the case; and after standing or walking for a long time the legs become swollen, so that the

boots feel tight, and sometimes even a distinct impression may be remarked at that part of the ankle which was uncovered by the boot. In such persons we can actually see the swelling disappear after the feet have been kept rested for some time on a level with the body, and it may be removed more quickly still by gently and steadily rubbing the limbs in one direction from below upwards. It is almost certain that what we thus see in weakly persons occurs to a slighter extent in all, and that even in the most healthy person after a long walk a slight accumulation of fluid, laden with the products of muscular waste, occurs both in the muscles themselves, and in the cellular tissue around them, even although we cannot detect it by simple inspection. So long as the limbs of such a person hang down, the force of gravity retards the return both of blood through the veins and of lymph through the fasciæ and lymphatics, and thus hinders the muscles from getting rid of those waste products which caused the fatigue. When the legs are raised, this hindrance is at once removed, both blood and lymph return more readily from the muscles, carrying with them those substances which had been formed by the muscles of the limbs during the exertions which they had undergone when carrying the body about. So long as these substances remained where they had been formed, they might cause in the muscles of the legs an undue amount of fatigue, although when distributed over the body generally, they may produce only a pleasing languor. When the legs are long, the obstruction to the return of blood and lymph is of course greater than when they are short, and this return will take place more readily when the legs are raised above the body than when they are only on a level with it. This may be one of the reasons why some of our long-legged American cousins are so fond of raising their feet to a level with their heads, or even higher, although it is very probable that there are reasons still more powerful, which we may discuss at a future time.

It has already been mentioned that the lymph is propelled along the interstices of the fasciæ into the lymphatic vessels by the intermittent pressure which the muscle exerts upon them from within, and it seems natural to suppose that the flow

may also be aided by a pressure from without, in the form of shampooing. Even when the hand is rubbed backwards and forwards upon the leg it will relieve fatigue, but the relief is greater when the leg is firmly grasped and the hand moved gently upwards so as to drive onwards as much as possible any fluid which may have accumulated in the limb, and the grasp being then relaxed, the same process should be repeated.

But while the lymph is thus most readily removed by the pumping action of intermittent pressure either of the hand without or of the muscles alternately contracting and relaxing within, it seems to us probable that this process may also be aided by steady, constant pressure from without. No doubt it is impossible for such a steady pressure to take the place of the regular pumping action produced by the alternate contraction and relaxation of the muscles when in action, yet it will have a somewhat similar action, though to a very much less extent. For at each beat of the heart, as Mosso shows, the entire limb is distended by the blood driven into the vessels, and during the pauses between the beats it again becomes smaller. Each pulse, therefore, by distending the whole limb and each individual muscle, will press out a little of the fluid contained in the fasciæ in the same way as the contractions of the muscles themselves, and it seems to us probable that it is the aid which is afforded to this process by the gentle pressure exerted on the outside of the legs by a seat which supports them along their whole extent, that renders such a seat so peculiarly restful and agreeable. For an easy chair to be perfect, therefore, it ought not only to provide for complete relaxation of the muscles, for flexion and consequent laxity of the joints, but also for the easy return of blood and lymph not merely by the posture of the limbs themselves, but by equable support and pressure against as great a surface of the limbs as possible.

Such are the theoretical demands, and it is interesting to notice how they are all fulfilled by the afore-mentioned chair in the shape of a straggling **W**, which the languor consequent upon a relaxing climate has taught the natives of India to make, and which is known all over the world.

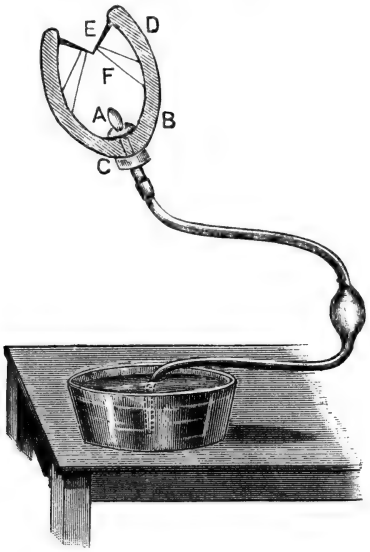
ON A SIMPLE INSTRUMENT FOR EXAMINING THE COMPETENCY OF THE TRICUSPID AND MITRAL VALVES.

(Reprinted from *St. Bartholomew's Hospital Reports*, vol. xiv, 1878.)

It has often seemed to me that the present method of examining the tricuspid and mitral valves of the heart in a post-mortem examination is not so satisfactory as that which we use for the aortic and pulmonary valves. In examining the latter, we pour water into the aorta and pulmonary artery, and actually see whether the valves are competent or not; but in the case of the tricuspid and mitral valves we determined their competency either by simple inspection, or at most by pouring a little water into the ventricular cavities, and observing the appearance of the valves as they float upwards upon it. It has occurred to me that a simple instrument, such as has been used for experiments on the cardiac sounds, might be useful for ascertaining the competency of these valves under such conditions of pressure as they are subjected to during life. Such an instrument may be very readily made from the nozzle (A) of an ordinary india-rubber enema syringe. This consists of an ivory tube, about $2\frac{1}{2}$ inches long, with a horizontal shield about half an inch from one end. The longer end of the nozzle is pushed through the auriculo-ventricular orifice, and onwards through the ventricle (B), until it projects on the outside of the ventricular wall close to the apex. It is then pulled through, and a thick india-rubber ring (C) is pushed over it, so that the wall of the ventricle is compressed between the ring outside and the ivory shield of the nozzle inside. The nozzle is then connected by a piece of india-rubber tubing either with a tap or with an enema syringe. If water be now made to pass into the ventricle through the nozzle, the valves (D) float upwards, and become firmly opposed. The aorta and pulmonary artery are now firmly held with the finger and thumb, so as to prevent the water from flowing out at the ventricle

through them, and the pressure inside the ventricle may be raised to any necessary degree. If the heart be healthy, no water will escape until the pressure becomes excessive, and then a small jet may be seen to issue from between the valves. By connecting the tube leading from the water supply to the heart with a mercurial manometer, the pressure at which the valves become incompetent may be at once ascertained. The ventricle may be

FIG. 163.*



then cut open, the nozzle removed, and the valves inspected in the usual way. I do not claim the idea as an entirely new one. The instrument has doubtless been used in various forms many times before, but the form in which I employ it is exceedingly cheap; and the time required for its application is very short, a couple of minutes sufficing to ascertain the competency of both valves, and it does not in the least injure the heart if it be wished to preserve it as a specimen afterwards. It may therefore, I think, be more widely employed than any other instrument of the sort, and may thus lead to the discovery of very interesting results.

* This figure was not in the original paper.

ON PULSATION* IN THE JUGULAR AND OTHER VEINS.

(From the *Medical Press and Circular*, July 2nd, 1879.)

PULSATION in the jugular veins is usually regarded as a sign of tricuspid regurgitation, and therefore of grave import. When I thus speak of pulsation in these veins, I of course exclude the apparent pulsation produced by the motion communicated to them by the pulsation of the carotids, and refer only to pulsatile movements in the veins themselves. Several writers have noticed that pulsations in the jugular veins may occur without any cardiac lesion. Some have attributed these to contraction of the right auricle, while others have supposed them to be caused by the aorta pressing the blood out of the intrathoracic veins into the jugulars during its distension by the cardiac systole. Some observations which I have made upon jugular pulsation have shown me that it is sometimes due to the distension of the aorta acting in a somewhat different way from that described by Friedrich. I cannot believe that the phenomena I have observed have previously been unnoticed, and I feel quite sure that they must have been already described by older authors, although I have been unable to find an account of them in more recent works. These phenomena consist in apparent pulsation in the left jugular alone, while it is absent from the right. In the first case of this sort which I saw, the apparent pulsation was very marked in the left jugular. On comparing it with the right, I noticed that it also appeared to be much fuller; and when I compressed it just above the clavicle, in order to ascertain whether I could thus stop the pulsation, it filled up very rapidly, and became much distended. This showed that the peripheral vessels by which it was supplied were much dilated, and that blood was flowing very rapidly into it. On compressing the right jugular

* This should rather be termed pseudo-pulsation.

in a similar manner, it also became very much distended. On relaxing the pressure, it quickly emptied, and when I alternately increased and diminished the pressure, the alternate filling and emptying produced an appearance of pulsation. If it was compressed with the finger simultaneously with each beat of the pulse, an exact imitation of the pulsation observed in the left jugular was produced. It therefore appeared to me that the pulsation in the left jugular was simply due to alternate compression and relaxation of the innominate vein by the aorta during its dilatation and contraction at each beat of the heart. Since my attention has been attracted to this unilateral jugular pulsation, I have observed several cases of it. These have all been females, and all have been more or less anæmic. The following cases may serve as examples:—

Rosana R., æt. 22, cartridge maker, in following her occupation, stands in a close room. About twelve months ago she began to get very pale. She had no fright, but during the course of the last year she has had much worry. The patient is markedly chlorotic; menstruation is regular, but scanty; the bowels are constipated; tongue clean; appetite rather poor. There is an anæmic murmur over the pulmonary cartilage; the cardiac sounds are otherwise healthy. There is apparent pulsation in the left jugular vein, none in the right. When either jugular is compressed, it fills very rapidly. On compressing the right jugular with the finger at each beat of the pulse, apparent pulsation is produced in it. On first beginning to auscultate, the pulsation in the left jugular was very distinct. The heart's action was somewhat excited. As the agitation of the patient subsided, the pulsation in the left jugular diminished, and finally disappeared. It did not return when the patient walked across the room, but she could only be induced to do so slowly.

Elizabeth G., æt. 19, is also very pale. For nearly nine months she has had a slight cough, and has been losing flesh. Her appetite is very poor; the bowels are regular; she has not menstruated for the last three months. Percussion sounds are normal. There is a slight click at the end of inspiration over the right infraclavicular region. The breath sounds are otherwise

normal. There is a systolic bruit over the pulmonary cartilage; the heart's sounds are otherwise normal. Pulse, 150, when the patient is standing. The left jugular vein pulsates visibly, but only during expiration. During inspiration the vein empties completely. There is no pulsation in the right jugular, and that in the left is stopped by pressure above the clavicle. It may be imitated in the right jugular by pressure with the finger. There is no distinct venous hum.

Margaret B. came to the hospital complaining of weakness and nervousness. While in attendance, she began to suffer from vomiting, and, a week or ten days after the vomiting commenced, she spat a little blood. Her nose also bled frequently about seven in the evening. There was no abnormal pulmonary, or cardiac sound. On one occasion, a curious persistent contraction of the jugular vein was noticed at the place where her collar had pressed upon it.*

In the case of Rosana R., the pressure exerted by the aorta on the left innominate vein was insufficient to produce the pulsation when the circulation was quiet, but it did so when it was excited by emotion. In that of Elizabeth G., it was insufficient to produce it when the thorax was dilated and the sternum raised by inspiration, but did so when the thorax had collapsed and the sternum had fallen during expiration. In all of them the peripheral vessels were dilated, so that the vein filled very rapidly during compression, and but for this no appearance of pulsation would have been produced. These few observations may serve to direct attention to a cause of jugular pulsation which, so far as I can find, is not generally recognised.

There is another venous pulsation which is also omitted from modern text-books, although it is to be found in the older writers. This, however, is not a simulated, but a real, pulsation, occurring in the pulmonary veins, and in the vena cava. Some time ago, Sir Joseph Fayrer and I found† that occasionally the pulmonary veins and the vena cava in rabbits might be seen to pulsate rhythmically for a considerable time after the auricles and ventricles had become perfectly still. In one

* Compare *antea* "Local contraction of arteries," p. 178.

† *Cf.* p. 528.

animal, all the cavities of the heart continued to beat for a considerable time after the thorax had been opened. The ventricles then stopped, but the auricles continued to pulsate, as well as the pulmonary veins. The veins and auricles both pulsated at the rate of 119 per minute, but the contractions were not synchronous. The auricles then ceased to beat, but pulsation continued in the pulmonary veins, and the ventricles again commenced, although the auricles remained perfectly quiet. The pulsation of the ventricles was at the rate of 8 per minute; while in the pulmonary veins it was at the rate of 46 per minute. Both the superior and inferior vena cava in the same animal were found to be pulsating an hour and forty minutes after the thorax had been opened. From the inferior cava contraction spread like a wave over the right auricle, the ventricle being quiet. But after the auricle had contracted two or three times, the ventricle again commenced to pulsate. These rhythmical contractions of the pulmonary veins, and of the vena cava, occur in animals killed in various ways. Sir Joseph Fayrer and I observed them in animals killed by a blow on the head, by the action of cobra poison, and by the combined use of chloroform, atropia, and physostigma. They do not occur frequently, and the conditions under which they take place are at present unknown, and we are unable to say whether they occur in man at all. But it has been shown by observations on decapitated criminals that the inferior vena cava, as well as the hepatic, portal, and several of the subpleural pulmonary veins, besides others, are strongly contractile. It seems, therefore, not improbable that such contractions may occasionally occur in the human subject. In one case, as I have already said, Sir Joseph Fayrer and I noticed that the contraction of the pulmonary veins was not synchronous with that of the auricles. The ventricles, at this particular time, were not pulsating, but, had they been doing so, their contractions must needs have been synchronous with those of the pulmonary veins. Supposing that in a case of mitral regurgitation a similar rhythmical contraction should occur in the pulmonary veins, a most powerful obstacle would be opposed to the backward flow of the blood, and the force of the current,

driven by the powerful left ventricle into the lungs, would be broken, and the injurious effects it would otherwise produce be greatly diminished. A similar action may be exerted by the vena cava in cases of tricuspid regurgitation.

We have already noticed the persistent contraction which occurred in the left jugular vein in Margaret B., at the point where it had been compressed by the collar. This constriction is an indication of one of the properties possessed by veins which is little regarded in considering the mechanism of the circulation—viz., that of contractility. This property they possess to a very great extent, and it is especially remarked in the smaller veins. In these, the walls sometimes approach each other so closely as to completely obstruct the lumen, and altogether prevent the flow of blood through the vein. In them, too, rhythmical pulsations may frequently be noticed. The importance of venous contractility in reference to the maintenance of the circulation in health and in disease is very great. It is obvious that, if venous radicals contract, they may oppose a resistance to the flow of blood in the capillaries, and by thus increasing the pressure within them may cause more fluid to exude from them into the tissues; while, on the other hand, a rhythmical contraction may forward the onward progress of the blood in the normal condition, and may prevent some of the injurious effects which are usually noticed in tricuspid regurgitation. Everyone who has studied cases of chronic bronchitis must have been struck with the variety of forms in which the obstruction to the circulation manifests itself in them. In one we find considerable œdema, but no albuminuria; in another, great dyspnœa, with signs of pulmonary œdema, although the legs may be very slightly, or not at all, swollen. In the same case you may see the legs begin to swell, and the pulmonary œdema and dyspnœa at the same time diminish. Such an occurrence I have observed in a patient suffering from chronic bronchitis, and who was apparently at death's door from an acute exacerbation of the disease. This patient was obliged to sit upright in bed, gasping for breath; the lips were purple, and all over the lungs there was loud sibilus, and rhonchus, with occasionally coarse mucous râles

and fine crepitation at the bases of both lungs posteriorly. Notwithstanding the interference with the circulation, there was but very slight œdema of the legs. After the administration of an emetic, followed by ipecacuanha and squill, the patient was greatly relieved, but the œdema of the legs increased temporarily. The increase did not, however, last long, and the patient, from the moment of the administration of the emetic, steadily recovered.

The action of drugs upon the veins has hitherto received very little attention, and therefore we are unable at present to bring together pharmacological experiment and clinical observation so as to give us any efficient aid in treatment. But it is probable that before very long we may have some definite knowledge of the action of drugs on the veins, which may help us in many cases where now we are sadly at a loss in the treatment of those diseases in which venous engorgement plays a prominent part.

ON THE PATHOLOGY OF NIGHT-SWEATING IN PHTHISIS, AND THE MODE OF ACTION OF STRYCHNIA AND OTHER REMEDIES IN IT.

(Reprinted from *St. Bartholomew's Hospital Reports*, vol. xv, p. 119.)

After the night-sweats which occur in phthisis the patients are very exhausted, and not unfrequently feel a certain soreness of the limbs similar to that which occurs in healthy persons after great exertion. The exhaustion produced by the sweating is sometimes attributed to the actual loss of material from the body in the perspiration, but this can hardly be the case, as the amount of nutritive matter contained in the sweat is very small, and we notice that the perspiration which occurs in healthy persons after exertion does not cause any feeling of weakness. It occurred to me, therefore, that instead of the sweating being the cause of the exhaustion in phthisis, the exhaustion and the sweat were both consequences of one common cause. In order to discover what this cause may be, it may be well to proceed to track, as it were, the process of sweating backwards, until we find some condition that may account both for it and for the weakness. Now, the production of sweat is due to the functional activity of the secreting cells in the sweat glands, which remove from the blood a quantity of water and salts, and pour it out upon the surface of the skin. For the functional activity of these cells two things are requisite: the one is a supply of blood to them which will provide them with the fluid necessary to form the sweat; the second is the nervous stimulus imparted to them by the secreting nerves, which excites them to functional activity. It is only recently that the importance of these nerves as a factor in the secretion of sweat has been fully recognised, although various circumstances seemed to point to the fact that sweat was not dependent merely upon a full supply of blood to the sweat glands. In the perspiration which follows active

physical exercise, we no doubt find that the skin is suffused with blood, and the sweat glands are therefore richly supplied with it. But in fever we not unfrequently find that the skin is even more suffused with blood, as is shown by its redness, so that the glands may have an abundant supply, and yet, notwithstanding this, the skin, instead of being covered with sweat, is perfectly dry. This shows, then, that a free supply of blood alone is insufficient to induce perspiration. On the other hand, we find that perspiration may occur freely when the supply of blood is exceedingly scanty. In persons stricken with sudden fear, or in those at the point of death, we find that the skin is pallid or livid, the surface cold, indicating that the supply of blood to it is very scanty, and yet at this very moment it may be bedewed with heavy drops of perspiration. This fact shows that perspiration may occur with a scanty supply of blood. The facts are exactly analogous to what we find in the secretion of saliva by the submaxillary gland. In this gland, irritation of the chorda tympani nerve causes dilatation of the vessels of the gland, a copious supply of blood to it and a free secretion of saliva. Irritation of the sympathetic nerve also causes secretion of saliva, but instead of the vessels being widely dilated and the circulation in the gland rapid and free, the vessels are contracted and the circulation is very slow. We find, also, that there is a similarity between the secretion of saliva and the secretion of sweat, not only in the nervous conditions under which they may occur, but in the way in which they are affected by various drugs. The effect of atropine, for example, upon the submaxillary gland is to paralyse the ends of the secreting nerves in the glandular structure, and the consequence of this is, that when the chorda tympani is irritated after the administration of a dose of atropia, the vessels of the gland dilate as usual, blood flows freely through it, but, the secreting nerves having been paralysed, the secreting cells take up nothing from the blood, and not a drop of saliva flows from the duct. When, on the contrary, calabar bean is administered, the effect is strikingly different, for its action is not to paralyse, but to stimulate the secreting nerves. In consequence of this, the secreting cells begin actively to take fluid from the blood and to

pour it out through the duct of the gland in the form of saliva. But this process does not last long, for the bean has a second action. Its stimulating power is not confined to the secreting nerves of the gland, but extends also to the vaso-motor nerves which regulate the calibre of the blood-vessels which supply it. These vaso-motor nerves, being stimulated by the drug, cause the vessels to contract to such an extent as to cut off the supply of blood from the glands almost entirely. The secreting cells are thus deprived of the material from which the saliva ought to be formed, and thus, notwithstanding the functional activity which they are exerting under the stimulus of the secreting nerves, the formation of saliva very shortly comes to an end. In persons who are poisoned with belladonna it has been observed that the vessels of the skin were much dilated, so that the skin itself was covered with a scarlet flush, notwithstanding which the surface was dry. This dryness was not confined to the skin, but extended to the mouth, and it was caused both in the mouth and on the skin by the paralysis of the secreting nerves of the salivary and sweat glands produced by the drug. Calabar bean, on the contrary, causes a certain amount of salivation and cold sweats; and other drugs, such as pilocarpine, which does not, like calabar bean, limit its own action upon the secreting cells of the salivary glands by lessening their blood supply, causes very profuse salivation as well as profuse sweating. Now the action of pilocarpine is exerted upon the terminations of the secreting nerves in the salivary and sweat glands, and does not seem to be dependent upon any action on the nerve centres. But although pilocarpine may stimulate the sweat glands by acting upon the ends of the secreting nerves within them, it is probable that, in ordinary circumstances, the secretion is regulated, not by the conditions of the terminal filaments of the secretory nerves, but by the nerve centres acting on the glands through those nerves. The nerve centres for the secretion of sweat lie partly in the spinal cord and partly in the medulla oblongata. In this respect they resemble two other important nerve centres, viz., the centre for respiration, or respiratory centre, and the vaso-motor centre—the respiratory centre, by which the respiratory muscles are inner-

vated and the respiratory movements kept up, and the vaso-motor centre, from which stimuli constantly proceeding to the vessels keep them in a state of chronic contraction.

Both these centres were formerly supposed to be situated in the medulla oblongata alone, because when the medulla was separated from the cord by a transverse cut at the level of the occiput, respiration ceased, and the tonic contraction of the vessels in the body at once ceased, and they became dilated.

It was first shown by Schiff, however, that if part of the medulla were destroyed, so as to cause the respiratory movements completely to cease, the death of the animal, which would usually occur under such conditions, might be prevented by the continuous use of artificial respiration for many hours. By this process time was allowed for the remaining portion of the medulla to learn, as it were, how to perform the function of the part which had been destroyed, as well as its own, so that after artificial respiration had gone on for several hours, the animal began to make feeble attempts to breathe, and these became stronger and stronger, until at last respiration was again established. It was thus shown that when a part of the respiratory centre in the medulla was destroyed, the remainder might become sufficiently powerful to perform the functions of the whole; but the experiments of Prokop Rokitanski* have shown that, instead of being limited to the medulla oblongata, as was formerly supposed, the respiratory centre actually extends for some distance down the spinal cord. When the medulla is completely separated from the cord by a transverse cut of the level of the occiput, respiratory movements usually cease, and do not recommence. But if strychnia be injected into the circulation immediately after the cord has been divided, the respiratory movements again commence. It is evident that these movements in this case do not depend upon the action of the medulla at all, as they did in the experiments of Schiff, for here the whole of the medulla has been cut off from any connection with the respiratory muscles, and the respiratory movements must therefore depend upon stimuli proceeding to the respiratory muscles, not from the medulla oblongata, but from the

* *Vide antea*, p. 323.

spinal cord. It is clear, then, from these experiments, that the respiratory centre is not confined to the medulla oblongata, but extends to the spinal cord. Usually, however, the spinal part of it is too weak to keep up the respiratory movements alone without the aid of the medullary part, and can only do so when it is stimulated to excessive action by means of strychnia. This conclusion is also borne out by the fact that when strychnia is given to an animal before the division of the cord at the occiput, the respiratory movements do not entirely cease at the moment of division, as they usually do. And what is true of the respiratory centre holds also for the vaso-motor centre. When the cord is divided at the occiput, the vessels being no longer under the influence of the vaso-motor centre, usually dilate. But here also, after the injection of the strychnia, the vaso-motor power is restored, and the vessels again contract to a greater or less extent. It is evident, then, that the vaso-motor centre, like the respiratory, extends a certain distance down the cord, and that it also, like the respiratory centre, is stimulated to increased action by strychnia.

Closely associated with these two centres appear to be the sweat centres. It was first observed by Goltz that irritation of the sciatic nerve would produce sweating in a limb, and it was shown by Kendall and Luchsinger that this sweat was independent of any alteration in the vascular supply, for it occurred in animals poisoned with curare, where all the vessels going to the limb had been tied; and it even occurred in an amputated leg for a quarter of an hour after its severance from the body. The nerve centres by which the sweat nerves are usually excited were localised by Luchsinger in the spinal cord, but Nawrocki, who repeated his experiments, came to the conclusion that the sweat centre was situated, not in the spinal cord, but in the medulla oblongata, because he found that division of the spinal cord high up arrested the secretion of sweat. The reason of this discrepancy between the conclusions of Luchsinger and Nawrocki probably is that the sweat centre, like the respiratory and vaso-motor centres, is not confined either to the medulla or to the cord, but extends through both. It is probable that, like the respiratory and vaso-motor centres, a great portion of the sweat

centre is situated in the medulla, and in Nawrocki's experiments, when the influence of this part was destroyed by section of the cord, the perspiration ceased, just as respiration and vascular tone are also destroyed under ordinary circumstances. It is probable, however, that in Luchsinger's experiments the spinal portion of the vaso-motor centres was sufficiently powerful to excite perspiration, even after the separation from the medulla. These centres were found by Luchsinger to be excited, and perspiration produced by increased temperature of the blood, by increased carbonic acid in the blood, and also by nicotine which had been introduced into the circulation. Increased temperature, as we well know, causes sweating, usually accompanied with dilatation of the vessels of the skin, as when we are exposed to a hot sun or get warm from exertion. Tobacco, on the other hand, causes sweating with diminished supply of blood to the skin, the countenance becoming exceedingly pale at the same time that a cold sweat breaks out, as most young smokers find out by sad experience. The effect of increased carbonic acid in the blood is visible in the cold sweats which bedew the brows of dying persons. I have watched the process, and have observed that it was just as the finger-nails, the lobes of the ears, and the lips began to get livid that the sweat drops began to appear on the forehead. It was a consideration of this fact which led me to suspect that the sweats of phthisis might be due to accumulation of carbonic acid in the blood stimulating the sweat centres. Nor would it do this only, for any imperfect aeration of the blood would lead to imperfect oxidation of the products of tissue waste in the body, and their consequent accumulation would produce the same soreness and lassitude which come on from the accumulation through overproduction by excessive muscular exertion. But it may be said, How is it that carbonic acid comes to accumulate in the blood in this way? In a healthy person no such accumulation takes place, because, although carbonic acid in the blood acts as a stimulus to the sweat centres, the vaso-motor centres, and the respiratory centres, yet the latter are more susceptible than the two former, so that whenever a slight increase of the amount of carbonic acid in the blood occurs, the respiratory

centre is stimulated, the respiratory muscles are thrown into increased action, and the blood being more aerated, the amount of carbonic acid in it is once again reduced to the normal. But supposing the respiratory centre is weakened in any way so as to become less sensitive to the stimulus of carbonic acid in the blood than the other two centres, this will no longer be the case, and then we shall find cold perspirations occur. This is the condition which I believe to be present in phthisis. The constant stimulation of the respiratory centre by the irritation in the lungs, and the violent respiratory efforts which occur in coughing, so exhaust the irritability of this centre, especially during sleep, that it no longer responds in the normal manner to the stimulus of carbonic acid in the blood. The blood may thus become more and more venous, until the carbonic acid in it excites the sweat centres, and possibly also the vaso-motor centres, before the respiratory centre begins to respond.

This, then, I believe to be the pathology of night-sweating in phthisis. The respiratory centre becomes exhausted by the reflex irritation from the lung, so that it no longer responds so readily as it ought to the stimulus directly applied to it by carbonic acid in the blood circulating through the medulla and through the spinal cord. In consequence of this the blood becomes more or less venous, and to this venosity, and the consequent imperfect tissue change, and not, as was formerly supposed, to the actual loss of fluid or sweat in the sleep, are the nervous and muscular exhaustion and prostration observed in night-sweats to be attributed. If this pathology were correct, it occurred to me that night-sweating might be prevented by administering some remedy which would increase the excitability of the respiratory centre. Now such a remedy exists in strychnia, as has been shown by Rokitanski's experiment. If, then, a dose of strychnia or nux vomica were administered at bedtime, the excitability of the respiratory centre ought to be so much stimulated that any excess of carbonic acid would excite it to increased action, and thus the accumulation of carbonic acid in the blood would be prevented, and the sweat, which I have supposed to be the consequence of such accumulation, would be arrested.

was increased to twenty drops, and after this there was no sweating.

But it is evident that if strychnia increases the excitability of the respiratory centre to stimuli applied directly to it, such as the carbonic acid present in the blood, it is likely also to increase its susceptibility to reflex irritation, such as that caused by tubercle in the lungs, and thus it might be that it would tend to increase the cough in case of phthisis. This, indeed, it appears, in some instances, to do. I have tried here to remedy this by a combination of strychnia with opium, and this appears partially to succeed. Where, however, strychnia does not appear to suit, atropia may answer perfectly. Now, atropia, no doubt, acts upon peripheral terminations of the secretory nerves in the sweat glands, and thus it will altogether prevent sweating. But this is not the whole action of atropia. It has been noticed by Ringer that the beneficial action of atropia continues for a very considerable time after its administration. It seems difficult to believe that this is merely due to its action upon the sweat nerves, for it is probable that the greater part of the atropia has been excreted from the body before the beneficial action which it produced has come to an end.

It seems not improbable, therefore, that the benefit derived from the employment of this drug in the night-sweating of phthisis is not due merely to its action upon the peripheral terminations of the sweat nerves, for, as has been shown by Von Bezold, it has a marked action in stimulating the respiratory centre. At the same time it lessens the irritability of the sensory nerves in the lung, and is thus likely to diminish the exhaustion of the respiratory centre, which the reflex irritation produced by the tubercle would otherwise occasion. It is to this stimulation of the respiratory centre, as much as to the paralysing action on the respiratory nerves, that I should be inclined to attribute the benefit to be derived from atropia or from hyoscyamus, which acts almost in the same way as atropia, and is so frequently given, along with oxide of zinc, in sweating of this sort. In Dover's powder we have a combination having an action somewhat resembling that of atropia in certain respects, though differing from it very markedly in others. In

health, Dover's powder is a powerful sudorific, but it frequently arrests, in the most satisfactory manner, as Dr. Murrell has shown, the night-sweating of phthisis.*

This seems at first sight extraordinary, and yet it is quite natural if the view which I have advanced regarding the pathology of night-sweating in phthisis be correct. For the opium, by lessening the irritation from cough, will tend to prevent the exhaustion of the respiratory centre. At the same time ipecacuanha is a powerful stimulant to this centre, and thus we have in Dover's powder two of the actions that we have already observed in atropia, viz., a power of diminishing irritation from the lungs, with a power of increasing the activity of the respiratory centre. Unlike atropia, it does not paralyse the peripheral terminations of the secretory nerves in the sweat glands. Picrotoxine, also, has been found to be useful in night-sweating. It also is a powerful stimulant to the respiratory centre (Büchheim, Arzneimittellehre, 3te Aufl.), and probably it is by its stimulating action upon this centre that it arrests sweating. But while it is probable that the night-sweats of phthisis chiefly depend upon exhaustion of the respiratory centre, and are to be arrested by stimulation of this centre, we must bear in mind that this may not be the only cause of such sweats. They may occur through stimulation of the sweating centres by increased temperature as well as by increased amount of carbonic acid in the circulating blood. In such circumstances quinine will probably be the best remedy, as Dr. Murrell has pointed out (*op. cit.*).

One of the great difficulties which we have to contend with in medicine is that of choosing the best drug in each particular case. Much may no doubt be done by very long experience, but it is hard, even for an old physician, and almost impossible for a young one. The only way in which this difficulty can be surmounted is by our obtaining an accurate knowledge of the pathology of disease, and of the mode of action of the remedies which we employ. In the night-sweats of phthisis atropia is probably the most powerful remedy which we possess, and we can well see how it should be so, for it combines the power of

* *Practitioner*, vol. xxiii, p. 195, September, 1879.

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lessening irritability of the sensory nerves in the lung, of stimulating the respiratory centre, and of paralysing the ends of the secreting nerves in the sweat glands. But it possesses other actions which may render its employment inadvisable. It may so influence the salivary glands as to arrest their secretion, and cause very great discomfort to the patient by the dryness of the mouth thus occasioned. In such cases we may use Dover's powder, but if this, again, should interfere with digestion, we may resort to strychnia or nux vomica. The cases in which strychnia seems to be specially indicated are those in which the cough is not so violent as to be very distressing, and where the general debility and weakness of the circulation and digestion are prominent symptoms. It not unfrequently has happened, probably owing in some measure to the difficulty of obtaining correct statements from hospital patients, who are so readily influenced by any bias of the physician, that a remedy has had in the hands of its proposer a success which has not been observed by those who have tried it subsequently. It may be so with strychnia also as a remedy in night-sweating, but if this should not be the case, and it proved in the experience of others to have the same marked power of arresting the night-sweats of phthisis which it has had in the trials I have made of it, it will be interesting as being another remedy whose therapeutical use has been arrived at by a knowledge of its physiological action, and of the pathology of disease discovered by experiments upon animals.

ON THE EXPLANATION OF STANNIUS'S EXPERIMENT AND ON THE ACTION OF STRYCHNIA ON THE HEART.

In conjunction with THEODORE CASH, M.D.

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THE remarkable experiment to which Stannius has given his name consists in applying a ligature around the venous sinus of the frog's heart, just at the point where it joins the auricles. The consequence of this is, that the auricles and ventricles at once cease to beat, and remain in a state of quiescence, lasting for a time varying from a few minutes to half an hour or more, while the venous sinus still continues to pulsate uninterruptedly. A similar result is produced when, instead of applying a ligature round the sinus, the sinus itself is separated from the auricles by an incision. If, however, instead of suddenly removing the whole of the venous sinus from the remainder of the heart, it is gradually removed, the instant stoppage of the auricle and ventricle does not take place. If the ventricle be now separated from the auricle, while the two are remaining in a state of complete quiescence, the ventricle again commences to pulsate, while the auricle remains perfectly still. Two explanations of these phenomena have been given. The one is that the section or ligature of the heart at the junction of the venous sinus and the auricles excites the inhibitory apparatus in the auricles to such an extent as to prevent both them and the ventricle from moving. This explanation, however, seems to be disproved by the fact that the same result is obtained after the heart has been previously poisoned by atropia, which completely paralyses its inhibitory apparatus, and it would therefore appear that the still-stand of the heart in this experiment cannot be due to excitement of the inhibitory apparatus. The second explanation is, that the motor ganglia of the heart are unequally

distributed in the ventricle and auricle, the greater number being in the venous sinus and ventricle, and the fewest in the auricle.

When the sinus, then, is separated from the remainder of the heart, the motor power in the auricles and ventricle is insufficient to make them pulsate, although the ventricular ganglia are sufficient, when separated from the auricle, to set the ventricle in motion. This explanation is opposed to the fact that if the venous sinus be gradually, instead of suddenly, separated from the auricle, they will still continue to pulsate. Notwithstanding this objection, however, it seems to us that this explanation, although very probably it does not represent the whole truth, is to a considerable extent true, and the cessation of the auricular and ventricular movements, after the removal of the venous sinus, is really due, in a great measure at least, to want of motor power. It occurred to us that if this were so, we ought to be able, by stimulation of the motor ganglia, to reinduce the cardiac pulsations after they had ceased from ligature of the venous sinus. It is well known that if a single galvanic shock be applied to the ventricle when in this state of diastolic quiescence, the ventricle will contract once at each application of the stimulus, but the single pulsation is not succeeded by a succession of rhythmical beats. As warmth has a very powerful effect in increasing the cardiac activity, it seemed probable that the application of warmth to the heart, when in the condition of still-stand thus described, might so far stimulate its motor ganglia as to allow it to resume its rhythmical pulsations. We therefore induced complete still-stand in the frog's heart by applying the ligature in the usual way. On then warming the heart, either by directing upon it a current of air heated by passing it through a hot glass tube, or by bringing into its neighbourhood a heated copper wire, we found that the rhythmical pulsations again commenced, and continued for two or three minutes after the time that warmth was applied.

The cessation of the movements of the heart, after the removal of the venous sinus, seemed to us analogous to the cessation of respiratory movements and of vaso-motor tone after the influence of the medulla oblongata has been removed by

division of the spinal cord at the occiput. It has been found by Prokop Rokitansky that the movements do not cease completely after division of the cord, when the animal has been previously poisoned by strychnia, and that both vaso-motor reflex and respiratory movements can be reinduced in such animals by strychnia administered after the cord has been divided, *cf. antea*, p. 323. It occurred to us that possibly a similar phenomenon might be observed in the heart. We therefore administered strychnia to a frog, and as soon as the spasm occurred, the animal was killed and a ligature placed round the heart. No cessation of movement, however, was observed. When a frog was first killed, however, and still-stand of the heart was induced by application of a ligature, a solution of strychnia placed on the outside of the heart did not reinduce rhythmical pulsations, but when the solution was injected by a fine pipette into the interior of the ventricle, rhythmical pulsations again commenced. This rhythm, however, was independent of that which the venous sinus still continued to pursue. After maintaining this for some minutes, it again stopped, and the auricle was seen to contract after the ventricle. The aorta was now cut, and the ventricle again contracted, but the auricles remained quiescent. On stimulating the ventricle, it now went on beating regularly.

From these experiments it would appear that the still-stand induced by ligature of the venous sinus has a deficiency of motor power in the auricle and ventricle, and that when we increase the excitability of the ganglia in these parts by warmth or by strychnia, the pulsations recommence. The following seems to us the best explanation of the phenomena observed. The motor ganglia of the heart, we think, are in all probability called into action by reflex stimulation. This reflex stimulation may originate in impressions conveyed to them by afferent nerves from the internal or external surface of the heart, or by impressions conveyed to them by the afferent nerves from the other cavities of the heart. We think, also, that although they respond to the stimuli conveyed reflexly from the internal or external surfaces of that part of the heart in which they are contained—as shown, for example, in contraction of the ventricle on stimulation by a needle or an electrical current—they

are, nevertheless, most readily thrown into rhythmical action by the impressions conveyed to them from the other cavities. In a normal condition of the heart, the venous sinus is the first cavity to contract; next comes the auricle, and next the ventricle; and a stimulus of contraction probably proceeds from one to the other along a channel furnished by the nervous filaments which connect them. When the channel is suddenly interrupted, as by ligature or division of the venous sinus, the motor stimuli proceeding from the venous sinus to the auricle and ventricle can no longer pass to them, and the reflex impulses proceeding to their ganglia from the external and internal surfaces of these cavities are insufficient to call them into action. The auricles and ventricles, therefore, remain in a state of quiescence for a longer or shorter period; this quiescence, however, is not completely permanent. After a while the ganglia seem to become adapted to the new conditions. Their sensibility, too, increases, and the stimuli proceeding to them from the surface of the heart are sufficient to call them into action. When the venous sinus is gradually removed from the auricles and ventricle, instead of being suddenly detached, time is afforded for this adaptation to take place before the removal has been completely effected, and thus the rhythm is not disturbed, as it is when the division is suddenly made or the ligature suddenly applied. In these respects the cardiac nervous system is analogous to the vaso-motor and respiratory systems. The ordinary channels through which the vaso-motor and respiratory centres and spinal cord are called into action are the fibres which proceed to them from the medulla oblongata. If these channels are suddenly interrupted by section of the spinal cord at the occiput, those parts of the vaso-motor and respiratory centres contained in the spinal cord cease to act. The same is the case when a large portion, but not the whole, of the respiratory centre in the medulla is destroyed, as by division of one-half of the medulla. When a large portion of this respiratory centre is thus destroyed, the animal at once ceases to breathe, and remains in this condition for many hours. If left to itself, death would of course take place; but if artificial respiration be maintained

for a long time, by and by faint respiratory movements occur, which very soon cease if the animal be left to itself. But Schiff has found that if artificial respiration be still kept up, these movements become stronger and stronger, until at length spontaneous respiration is sufficiently re-established to save life.

In Rokitansky's experiment, the ordinary channels for the passage of stimuli from the medulla oblongata to the respiratory and vaso-motor centres in the cord were at once destroyed; but the application of strychnia before or after the section had so greatly increased the activity of the centres in the spinal cord that they were able to take up their functions at once, instead of after a lapse of time, as in Schiff's experiment. It seems to us, then, that the function performed by the venous sinus in regard to the rhythmical movements of the frog's heart is to a certain extent analogous to the functions of the medulla oblongata in regard to respiration and vascular tension, and that the action of heat and of strychnia upon the systems is very similar indeed. The very marked action as a cardiac stimulant which strychnia is shown by the experiment to possess, is one the practical importance of which it is hardly necessary to point out. We would merely remark, that in cases of general debility and lack of tone, especially when occurring in consequence of overwork, there is, perhaps, no tonic in the pharmacopœia to be compared to strychnia; and widely known though its utility may be, it is not nearly so commonly employed as it deserves, especially at this season of the year (July), when both medical men and their patients are suffering from the consequences of prolonged overwork and mental strain. Small doses of strychnia or nux vomica restore both mental and physical power, and give a sense of well-being in a manner in which, so far as our experience goes, nothing else will.

ON THE ACTIONS AND USE OF CERTAIN REMEDIES EMPLOYED IN BRONCHITIS AND PHTHISIS.*

* Read before the Medical Society of London, December 19th, 1880.

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In both bronchitis and phthisis the first symptoms that attract notice are cough and expectoration, and the first remedies that claim our attention are the so-called sedatives and expectorants. Cough consists in deep inspiration, closure of the glottis, and violent expiratory effort, by which the glottis is forcibly opened by the compressed air, which carries with it, in its exit, mucus or other matters which may have lodged in the lungs or respiratory passages. The nervous centre for this act lies in the medulla oblongata. It is bilateral, and situated on each side of the central raphe. It is excited into action reflexly by irritation of the respiratory branches of the vagus distributed to the glosso-epiglottidean folds, to the whole interior of the larynx, to the trachea, especially at its bifurcation, and to the bronchi, and the substance of the lung itself, as well as the pleura when it is inflamed. Irritation of the internal auditory meatus at the point to which the auricular branch of the vagus is distributed also causes coughing, and so also may irritation of the liver and of the spleen. As coughing is a reflex act, excited by irritation applied to a sensory nerve, and reacting through a nerve centre upon the respiratory muscles, it is obvious that it may be lessened, either by removing the source of irritation or by diminishing the excitability of the nervous mechanism through which it acts. Both methods are employed in medicine. One of the commonest is that of lessening irritation by the use of glutinous and saccharine substances. These have in themselves little or no action upon the nervous mechanism. They do not pass down to the bronchi, or lung substance, so that they can have no direct effect upon the mucous membrane there, nor

have they, so far as we know, any effect upon them after they have been absorbed into the blood; and yet one of the commonest observations is that glutinous and saccharine substances have a very great power to allay cough when applied to the back of the throat, even in cases where we know that inflammation and consequent irritation exist in the respiratory passages below the glottis, at a point which the mucilaginous substances cannot reach. The probable explanation of this action of such substances as marsh-mallow lozenges, jujubes, consisting of gum and sugar and Spanish liquorice, is that the irritation which occasions the cough exists at the root of the tongue and around the fauces, as well as in the trachea, bronchi, or lungs, the combined irritation rendering the cough worse than either the one or the other alone would do; and, therefore, if we soothe the tongue and fauces we relieve the cough, even though the irritation in the bronchial tubes or lung may remain as before. The power of such substances as those mentioned to relieve cough depends, no doubt, to a great extent either on their covering the inflamed and irritable surface directly with a mucilaginous coat, and thus protecting it from the action of the air or from irritation by other substances passing over it, or by exciting an increased flow of saliva or mucus, which has a similar effect. At the same time, we cannot deny the possibility of their having other actions, though with these we are at present unacquainted. The use of the mucilaginous substances containing opium or other sedatives, which we know under the name of "linctus," is a more complicated one. In them we have the soothing action of the mucilaginous compound, combined with the local sedative action of morphia, chloroform, or hydrocyanic acid upon the inflamed or irritable mucous surfaces at the root of the tongue and back of the throat, and this renders even their local action more powerful than that of a mucilaginous substance alone. Such drugs as opium, hydrocyanic acid, and chloroform have a certain amount of local action upon the peripheral ends of sensory nerves, and lessen their sensibility to impressions. When they are applied to the ends of the nerves only for a very short time, as they are when we swallow these drugs in a liquid form, their local action is comparatively slight. It is much

greater when they are taken in a mucilaginous vehicle, which, adhering to the irritated mucous membrane over which it passes, keeps the sedatives in contact with it for a longer time, and thus allows them to exert a more powerful action. But the sedatives which we give to relieve cough are not unfrequently administered in the form of solution, and then, though their local action must be comparatively slight, they still lessen a troublesome cough. Their action here is a different one from that which we have just discussed, but it is possessed by the sedative whether given in the form of linctus or of solution. In either way it is swallowed by the patient, absorbed from the stomach and intestines into the circulation, and carried by the blood to the medulla oblongata, and also to the inflamed mucous membranes, in which the blood circulates freely, just as well as in other parts of the body, although here its action is likely to be very much less than if it were applied for a length of time directly, as in the shape of the linctus; but, as we have mentioned, the linctus can only be applied to the back of the tongue and throat, and the source of irritation of the afferent nerves may be in the bronchi or in the lung itself. Here, no doubt, a linctus cannot penetrate, but we may to a certain extent act locally upon the nerves by the use of spray and inhalation. Some of these, such as the vapour of conium and the vapour of hydrocyanic acid, are intended to lessen the irritability of the sensory nerves in the respiratory passages, and thus lessen cough. Others, such as the spray of ipe acuanha, and inhalation of essential oils and terebinthinous substances, have probably a different action, and do not lessen the irritability of the sensory nerves in the respiratory passages, but alter the nutrition of the mucous membrane in such a way as to diminish the irritation which the abnormal condition of the membrane exerts upon the nerves. When the irritation is situated in the larynx, as in cases of laryngeal phthisis, one of the best means of relieving it is by applying the sedatives locally, whether by means of a brush, or, what is perhaps still better, by blowing it, in the form of a powder, directly upon the irritated surface. A useful application in laryngeal phthisis consists of a mixture of morphia and starch, in the proportion

of about one-sixth of a grain of morphia to two grains of starch. This mixture is introduced into a glass tube, of a proper shape, and is blown down the throat at the instant that the patient takes a deep inspiration. The powder is thus distributed over the interior of the larynx, and exerts its local sedative influence upon the irritated surface, as well as a general sedative effect upon the central nervous system after its absorption.

This brings us to the second mode in which sedatives relieve cough. After their absorption into the blood, in whatever manner they may have been applied, they are carried to the medulla, and there lessen the excitability of the nerve centre through which the reflex act of coughing is produced. In large doses their sedative effect may be so great as to endanger life, and the caution is given in every text-book, and by every teacher, that respiratory sedatives such as opium should be carefully administered to persons suffering from bronchitis with profuse expectoration, lest the irritability of the medulla should be so far diminished that it will no longer respond even to a powerful stimulus from the lungs, and the secretion may consequently go on accumulating until when the patient awakes the respiratory passages are so clogged with mucus that no effort which he can make is sufficient to clear them, and he dies of suffocation. By administering them in smaller quantities, however, the effect of respiratory sedatives may be graduated so as to diminish cough without any risk of causing death, and their effect would be exceedingly beneficial if they acted only upon the respiratory centre. Unluckily, however, this is not the case, and the most powerful of all—viz., opium—not only influences the respiration, but the digestion. It diminishes the cough, but sometimes, also, it diminishes the appetite, and may interfere with the proper action of the bowels. When this is the case, we are obliged carefully to steer between two dangers: (1) the injurious effects of the cough itself, and (2) the injurious effect of disturbed digestion. If we leave the cough alone, it exhausts the patient, for the muscular exertion involved in a violent fit of coughing is very considerable indeed, and the muscular effort exerted by a patient with a bad cough during

the twenty-four hours is really more than equivalent to that of many a man in a day's work. Nor is this all. Anyone who watches the face of a patient during a violent fit of coughing will see the skin become flushed, and then dusky; the veins in the forehead and in the jugulars swell up, and become so tense that they seem as if about to burst; so that there is both venous engorgement and interference with the respiration. But what we see in the face takes place elsewhere. The same tension which we see in the jugulars is also present in the right side of the heart, in the vena cava, and in the portal system; for the portal vein has no valves, and the increased tension is transmitted backwards to the veins of the stomach, spleen, and intestines. By-and-by this all begins to tell upon the heart and upon the digestive system as well as, to some extent, upon the kidneys. The stomach becomes congested, and we have loss of appetite, nausea, and vomiting. The patient, too, is kept awake, and we have nervous exhaustion, or loss of sleep, added to the weariness caused by the muscular exertion, and to the depression occasioned by digestive disturbance. These are what we have to fear: on the one hand, continuous coughing; on the other, we must avoid the digestive disturbance produced by our sedatives; and the duty of the physician is, so far as possible, to relieve the cough without disturbing the digestion. Numerous combinations have been devised, and are found to be, empirically, of very great service. If we take one of them and attempt to analyse it, we shall find that its components are such as to diminish the excitability of the respiratory centre, and at the same time to lessen the injurious effect of the sedatives upon the stomach. Such a one is the following mixture:—Solution of hydrochloride of morphia and dilute hydrocyanic acid, of each eighteen minims; spirit of chloroform and dilute nitric acid, of each one fluid drachm; glycerine, three fluid drachms; infusion of cascarilla or infusion of quassia, two fluid ounces; a sixth part to be taken three or four times a day.

In this mixture, which in its essence was much used by the late Dr. Warburton Begbie of Edinburgh, to relieve the cough in phthisis, we find the sedatives morphia, hydrocyanic acid,

and chloroform to lessen the excitability of the respiratory centre; we find glycerine, which will tend to retain the sedatives for a longer time in contact with the back of the throat, and will also act to some extent as a nutrient. We have combined with these nitric acid and infusion of cascarilla or of quassia, which have so-called tonic (?) action upon the stomach. In what this effect precisely consists we cannot at present say, but we may imagine that it will in some way partially counteract the effects of the congestion which the cough produces, and at the same time we know that they have the power of exciting appetite, and they will thus in a great measure counterbalance the injurious effects of the morphia upon digestion. Nor is this all. The nitric acid, as I shall shortly have to mention, has a very definite effect indeed upon the secretion in the lungs themselves; and this brings us to the consideration of another part of our subject—viz., the effect of drugs upon the secretion and nutrition of the lungs, by which they tend to restore the healthy condition of the bronchial and pulmonary tissues, and thus diminish coughing.

First of all, then, we must consider those drugs which lessen congestion. If a person, hastily eating or drinking, gets a crumb of bread or a drop of fluid down the larynx, or into the wrong throat, as it is termed, he suddenly begins to cough violently, and the cough continues until the source of irritation has been removed. If the irritation has been violent he may give a few coughs after the crumb has been coughed up, although the primary source of irritation—namely, the crumb—has disappeared; but the congestion which it occasions still remains for a short time, and acts as an irritant. If a person suffering from disease of the mitral valve makes any sudden exertion he is very likely to bring on a cough, which, however, quickly subsides after a short rest. The cough here is not due to inflammation of the mucous membrane, but simply to congestion, and when the congestion disappears the irritation goes with it. In cases where we have inflammation of the respiratory vessels actually present, as in persons suffering from bronchitis, the congested condition of the membrane is a source of considerable irritation, and we frequently notice that such

persons, on going out into the cold air, may cease to cough, but again begin to cough violently when they return from the cold air into the warm room. The reason of this is that the cold air has acted upon the congested vessels of the respiratory passages in a somewhat similar way to what it does upon the vessels of the face; it causes them to contract, and the congestion being thus diminished the cough is lessened. When the patient goes into the warm room the face, which may have been pale while he was exposed to cold, flushes up with the heat, the vessels of the respiratory passages also become engorged, and the increased congestion causes irritation, bringing on the cough. In other cases, again, we notice that, just as the face becomes pale when exposed to cold, it shortly afterwards becomes flushed, although the application to cold continues. A person suffering from bronchitis, on going into a cold room, will begin to cough violently, the cold here increasing instead of diminishing congestion.

The pulmonary capillaries have great contractile power. Ten years ago I made some experiments, which I have not yet published, on the subject (*cf. antea*, p. 334). I found that on the application of cold to the lung of a frog, when placed under the microscope, the capillaries would contract to two-thirds of their former diameter. We have, however, very few observations on the action of drugs upon the pulmonary circulation, the difficulties in the operative procedure being very considerable. I have observed that muscarin appears to have a power of contracting the pulmonary vessels, and that this effect is abolished by atropia. I am unaware, at present, of any other observations on the action of drugs upon the pulmonary circulation. Circumstances have prevented me from studying the recent researches on this subject in the way I should have wished while drawing up this paper. From its power of contracting the vessels in other parts of the body, we should expect that digitalis would have a similar action upon the lungs; and we find, in looking over Beasley's "Book of Prescriptions," that digitalis has been used in pulmonary affections—as, for example, in the following draught, employed by Sir A. Crichton in acute phthisis: lemon-

juice, half an ounce; carbonate of potash, to saturation; decoction of sarsaparilla, ten drachms; tincture of digitalis, ten to thirty minims; acacia mucilage, ten drachms: to be taken every sixth hour. In such a prescription as this we have the tincture of digitalis, which will, in all probability, by contracting the vessels, diminish the pulmonary congestion and lessen cough. It is combined with carbonate of potash, and the effect of potash upon the lungs is very marked indeed. For my knowledge of its action I am indebted to Dr. Andrew Clarke. Its action is perhaps best noticed in a patient suffering from consolidation and softening of a limited portion of one lung. When such a patient is in ordinary health, one may observe, on stethoscopic examination, crepitant râles, limited to one spot. When he catches cold, one may hear, in addition to those, dry râles extending for some distance around the irritated spot, and the cough at the same time becomes more frequent and troublesome, while there is very little, if any, expectoration. If potash be now given alone, or, still better, in combination with a vegetable acid, the dry râles subside, and are replaced by moist ones, which in the course of a day or two, as the potash is continued, alter in character, giving one the impression of their being caused by less viscid fluid. At the same time the expectoration becomes more copious, and the cough less frequent and less troublesome. Now is the time to alter the treatment, and for the potash to substitute nitric acid. If this be given too soon the cough, which had begun to get easier, will again become drier and harder, but if it be administered at the proper moment the cough becomes still less troublesome, the expectoration diminishes, and the moist râles disappear from the neighbourhood of the consolidated part of the lung, although they may still remain, as before, in that part itself. Potash, then, has a very marked effect in rendering the pulmonary secretion more fluid and abundant, while nitric acid has an opposite effect. As in many cases we wish to diminish the secretion rather than increase it, it is nitric acid rather than alkalies which we employ for long periods in the treatment of phthisis, as we have already seen in the modified formula of Dr. Begbie's phthisis mixture.

One of the most powerful expectorants is simply a little warm food in the stomach, and in cases of chronic bronchitis, in which the patients complain of violent coughing immediately after rising, one of the best expectorants is a glass of warm milk, either with or without a little rum, and a biscuit or a piece of bread about a quarter of an hour before they get up. A little warm beef tea will have a similar effect. After taking this for a short time they generally tell you that the sputum comes away much more easily than before, and they are not so much exhausted by it. But perhaps the remedy, *par excellence*, not only in cases of phthisis, but in chronic bronchitis, is cod-liver oil. Persons suffering from long-standing chronic bronchitis will often come to a hospital to beg for cod-liver oil, saying that it eases their cough far more than any cough mixture. Other oils or fats have not this power to the same extent as cod-liver oil. We cannot say positively what the reason of this may be, but I think there is no doubt about the fact. My own belief is that cod-liver oil is more easily assimilated than other oils, and not only so, but more easily transformed into tissues themselves. Whether it owes this property to its admixture with biliary substances, or to its chemical composition, we cannot say. In his book on "Fat and Blood, and how to make them," Dr. Weir Mitchell quotes a remark made by an old nurse, that "some fats are fast, and some fats are fleeting, but cod-liver oil fat is soon wasted." By this she meant that there were differences in the kinds of fat accumulated under the subcutaneous tissues of men, just as there are differences in subcutaneous fats which accumulate in horses. The horse fed on grass soon gets thin by hard work, while fat laid on when the horse is feeding on hay and corn is much more permanent. Persons fattened on cod-liver oil soon lose the fatness again, and this, I think, points to the power of ready transformation which the oil possesses. Supposing that it does possess this power, we can readily see how very advantageous it will be. In chronic bronchitis, and in catarrh and pneumonia, we have a rapid cell-growth, but want of development. The cells lining the respiratory cavities are produced in great numbers, but they do not grow as they ought to do. They

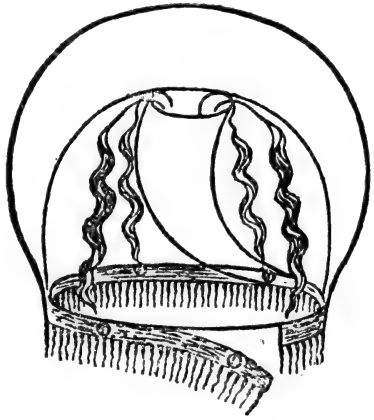
remain, more or less, lymphoid cells, instead of developing into proper epithelium. They so rapidly form, and are thrown off so quickly, that they have not time to get proper nutriment, and if they are to grow properly we must supply them, not with an ordinary kind of nutriment, but with one which is much more rapidly absorbed, and is capable of much more rapid transformation in the cell itself than the usual one. This power is, I believe, possessed by cod-liver oil, and to its quality of nourishing the rapidly-formed cells in the lungs in cases of bronchitis and catarrhal pneumonia I believe its great curative power is owing.

The next subject we will consider is the action of some drugs in the vomiting associated with cough. The action of vomiting, like that of coughing, is reflex; the nervous centre for it is also in the medulla oblongata, closely associated with the respiratory centre, and it is excited by various afferent nerves, the chief of them being the branches of the vagus distributed to the stomach. When congestion of the stomach is present, these become irritated, and we get loss of appetite, nausea, and vomiting. Like coughing, vomiting may be prevented by the removal of the irritant. For example, where the irritant is indigestible food, the vomiting ceases after the ejection of the offending substances. When the irritation depends on inflammation of the walls of the stomach, it may be soothed by sedatives having a local action upon the nerves, such as ice and hydrocyanic acid, or by drugs having the power of lessening the irritability of the nerve centre of the medulla, such as opium. In the chronic vomiting of phthisis, all these drugs may be employed, but there is one other which has been useful in this affection, and which probably has no effect either upon the nerve centre or the nerve ends. This is alum. Its mode of action probably is that by its astringent power it contracts the vessels of the stomach, and thus lessens the congestion and consequent irritation produced by the continued coughing in the manner already described.

NOTE REGARDING THE EFFECT OF ELECTRICAL STIMULATION OF THE FROG'S HEART, ETC.

THIS research was the outcome of the observations made by Romanes in 1876 and 1877 upon Medusæ. He found in these animals that the rhythmical movements of the bell are kept up by a ring of ganglia round its margin. When a strip of contractile tissue containing the ganglia is cut away from the bell for a certain distance but left attached at one end, stimuli can pass along the strip in two ways, either as contraction in the contractile tissue of the strip or along the nerves. The nervous

FIG. 164.



conduction may either pass along in front of the contraction when this is present, or may pass along without any contraction at all occurring in the strip, and only become manifest by movements in the tentacles which fringe the strip and are more sensitive than the strip itself.

It was in order to find out whether the cardiac contraction

which begins in the venous sinus or auricle passes along to the ventricle through the contractile tissue of the heart, or through its nerves, or through both, that the following experiments were undertaken.

But the research was not so easy as that upon Medusæ, for the bell of the medusa shows by its contraction, or the tentacles on a strip by their motion when the stimulus has reached them, whilst in the heart there is a refractory period during which the application of a stimulus produces no contraction.

This rendered the research a very long and tedious one, requiring an immense number of experiments, so that although the results of a number of them were communicated to the Royal Society in 1881, the full research was not published till 1883.

After the publication of our first notice, an admirable paper by Gaskell appeared on the transmission of stimuli in the frog's heart, but his method of working was different from ours, as he employed compression of the contractile tissue as a means of regulating the passage of stimuli along it.

The results of our experiments appear to show that stimuli in the heart may pass from one part to another along nervous channels as well as along contractile tissue.

In regard to this, I may note especially that stimulation of the auricle causes contraction both of the auricle and ventricle, but the ventricular contraction follows the auricular one in a way that seems to indicate that the stimulus has been propagated through the muscular substance. On the other hand, stimulation of the venous sinus sometimes produces a simultaneous contraction of the auricle and ventricle, which appears to indicate that the stimulus has been conveyed along nervous channels to the auricle and ventricle, and not along the muscular substance from the sinus to the auricle and then to the ventricle.

ON THE EFFECT OF ELECTRICAL STIMULATION OF THE FROG'S HEART, AND ITS MODIFICATION BY COLD, HEAT, AND THE ACTION OF DRUGS.

In conjunction with THEODORE CASH, M.D.

(Reprinted from the *Proceedings of the Royal Society*, vol. xxxii, No. 214, 1881.)

Received May 16, 1881. Read June 16, 1881.

FROM the results of the recorded experiments conducted on the frog's heart in its normal position and still exercising its circulatory function, we have found—

I. That electrical stimulation by a single induced shock has either an obvious effect on the contraction and rhythm of the organ, or no such effect is apparent.

II. That the effect is modified by—

(a.) *The Time of the Cardiac Cycle in which Stimulation Falls.*—Thus Marey has already shown that a so-called refractory period is demonstrable under certain conditions.* Well-marked variations in latency when the stimulation is potent to induce a systolic contraction are to be recognised.

(b.) *The Strength of the Stimulation Applied.*—Refractory periods possible under minimal stimulation can no longer be demonstrated under maximal, whilst a disturbance of the relationship of auricular and ventricular contractions may be induced.

(c.) *The Area of the Heart to which Stimulation is Applied.*—A refractory period demonstrable under stimulation of the ventricle may cease to occur when the sinus venosus is the seat of irritation.

* The conditions of this refractory period, or "period of diminished excitability," have been very fully investigated by Dr. Burdon Sanderson and Mr. Page. *Proc. Roy. Soc.*, vol. xxx, p. 373.

(d.) *The Action of Heat, Cold, and Drugs.*—Thus cold prolongs the systole, the refractory period, and the latency of an induced contraction; whilst strychnia, leaving the curve of systole unaltered, lengthens the refractory period to a marked degree.

ON THE EFFECT OF ELECTRICAL STIMULATION OF THE FROG'S HEART, AND ITS MODIFICATION BY HEAT, COLD, AND THE ACTION OF DRUGS.

In conjunction with THEODORE CASH, M.D.

(Reprinted from the *Proceedings of the Royal Society*, vol. xxxv, p. 455, No. 227, 1883.)

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In the following research we have examined the effect of electrical stimuli applied to the different cavities of a frog's heart, and the modifications of their effect by heat, cold, and the action of strychnia. The effect of electrical stimuli upon the ventricle, and the alterations occasioned in it by the application of heat, have already been studied by Professor Marey. The time relations of excitation in the frog's heart have also been very exactly determined by Dr. Burdon Sanderson and Mr. Page. But it seemed desirable to extend the scope of the research, and instead of confining ourselves like previous observers to the effect of stimulation applied to the ventricle alone, to observe also the effect of stimulation of the ventricle, auricle, and venous sinus, both on the ventricular and the auricular contractions. This we did with the hope that from such series of observations we might be able to arrive at some conclusions regarding the transmission of stimuli from one part of the heart to the other in the ordinary course of the circulation. Professor Marey found that when an electrical stimulus was applied to the ventricle of a pulsating frog's heart the effect differed according to the condition of contraction or relaxation in which the ventricle was at the time the stimulus was applied. During the first part of the contraction of the ventricle, from the commencement of the contraction until nearly its maximum, stimulation had no apparent effect at all, and this period Marey terms the "refractory period." Following this phase is a second

one, to which we have given in the following paper the term of the "sensitive phase," lasting from the maximum of systole to its end. The refractory period varies in duration according to the intensity of the stimulus, and the conditions under which the heart is operated upon. The feebler the stimulus, the longer is the refractory period. When the stimulus is very slight the refractory period may persist during the whole ventricular systole; as the stimulus is increased, the refractory period becomes shorter, and finally, when it is very strong, disappears altogether.

Heat applied to the heart shortens the refractory period or abolishes it altogether. Cold has an opposite effect, and lengthens the refractory period. The contractions caused by artificial stimulation do not much alter the cardiac rhythm, for the accelerated beat is followed by a longer pause than usual which compensates for the diminished interval between the two first beats. Sometimes no ventricular contraction is induced, and then instead of acceleration there is apparent inhibition, the application of the stimulus being followed simply by a longer diastolic pause than usual.

Marey's observations were confined entirely to the movements of the ventricle, but we have extended ours to the movement of the auricle as well. We employed two levers: one resting upon the ventricle, and the other upon the auricle, which recorded movements upon a revolving cylinder covered with smoked paper.

It is unnecessary to enter here into a fuller description of the apparatus, which is given elsewhere.*

By the method employed we are able to study the effects of maximal and minimal stimulation applied to the ventricle, auricle, and venous sinus upon the movements both of auricle and ventricle.

By minimal stimulation we understand the smallest shock that produces any visible effect that in any way modifies the course of contraction or the rhythm of the organ; and by maximal stimulation we mean the electrical irritation of such a strength that its intensification produces no visible increase in its effect.

* Cash, *Journal of Physiology*, vol. iv, No. 2.

The apparatus for stimulation consisted of a bicromate battery with two zinc (3½ inches by 2 inches) and three carbon plates, the size of these being 8 inches by 2 inches. This was connected with a coil, and a key was interposed by which the primary circuit could be made and broken at pleasure. The moments of opening and closing the circuit were registered upon the same revolving cylinder as that upon which the cardiac pulsations were noted, by means of an electro-magnet, the marker of which was placed immediately under the pens of the cardiac levers. In all the tracings the upper curved line shows the ventricular contractions, the lower curved line the auricular contractions, and the broken straight line the moment of excitation. The descent of the line indicates the opening, the ascent the closing of the current.

In the secondary circuit were placed the electrodes for stimulating the various parts of the frog's heart, and this circuit also could be broken or changed at pleasure by means of an interposed double key.

The heart was stimulated by a single induction shock. In minimal stimulation only the breaking shock was effective, in maximal stimulation both making and breaking shocks. The apparatus, which is described in a separate note, admitted of the venous sinus, auricle, or ventricle being stimulated at will.

When recording the effects of stimulation of the venous sinus we speak only of changes in rhythm of auricle and ventricle.

We shall examine *seriatim* the results of irritation of each of these. The temperature of the room in which the experiments were conducted was 67° to 70° F. The frog employed was, on all occasions, the *Rana temporaria.*

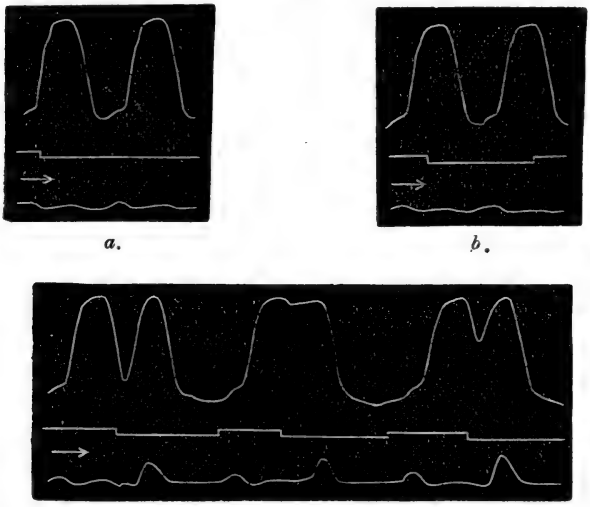
Stimulation of the Ventricle—Minimal.

On stimulating the ventricle with a single induction shock of minimal potency we find—

(1) That between the commencement of the ventricular systole up to or nearly up to its maximum there is a refractory period (Fig. 165, *a* and *b*) during which stimulation applied to the ventricle has no effect whatever on that beat of the heart, or the one succeeding it, nor is the auricle in anywise affected.

(2) That after the refractory period has elapsed stimulation causes a reduplication of the beat (Fig. 165, *c*).

FIG. 165.



a. *b*.

c.

Stimulation of Ventricle (minimal).

a and *b*, stimulation in different phases of refractory period.
c, stimulation after refractory period has passed, showing different forms of reduplication.

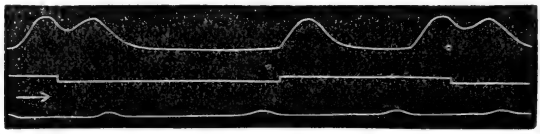
(3) The latency of this reduplicated beat becomes distinctly shorter as the systole passes into the diastole. Thus supposing the value of a single cardiac systole to be 1″·3, stimulation falling just at the maximum of a beat will cause a reduplicated beat with a latency of 0·33. When the stimulation occurs half way down the curve of relaxation, the latency is 0·18 or 0·2, and when applied at the instant before the abscissæ would have been reached the latency is only 0·13.

(4) Where acceleration or reduplication occurs, the subsequent diastolic pause is prolonged, so that the time occupied by the two beats, the interval between them longer or shorter, and the subsequent pause, is nearly equal to the time which would be occupied by two normal beats with their associated diastolic pauses (Fig. 165, *c*).

(5) The ventricular reduplication is often associated with a reduplication of the auricular beat, but in no case has the latter its commencement before the former. It is usually, in fact, distinctly later (Fig. 166, *a*).

It is to be noted that, *minimal stimulation* applied to the *ventricle* during its refractory period produces *no* effect on the *auricle.*

FIG. 166.

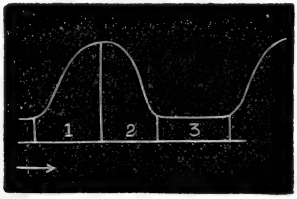


a.

Stimulation of Ventricle (minimal). Tracing shows long pause after reduplication. The two opening stimulations occur after maximum of systole has passed.

FIG. 167.—Time-Writer, marking seconds. Applicable to all tracings in the paper, except those in the Appendices.

We may divide each ventricular cycle into three parts, the first reaching from the commencement of systole nearly up to its maximum, the second from nearly the maximum of the systole to its end, and the third embracing the whole diastolic period from the end of one systole to the beginning of another (*vide* diagram A) except when the stimulation falls immediately



A.

FIG. 168.—Diagram A shows the division of the ventricular cycle into three parts.—1. Refractory period. 2. Sensitive period. 3. Accelerative period.

after the end of the refractory period. In all these points our results agree with those already obtained by Marey.*

Stimulation applied to the ventricle during the first period has no effect whatever either in accelerating the occurrence of the second beat, or altering the length of the subsequent pauses. This constitutes the refractory period.

Stimulation applied during the second period causes reduplication of the systole, the next systole succeeding with a constantly diminishing latency up to the end of the period. When the stimulation is applied in this period, the two systoles being more or less united, there is no distinct pause between them, but the diastolic pause succeeding the second occupies very nearly the interval of time corresponding to two normal diastolic pauses. In this second period the heart is more sensitive to the action of minimal stimuli than in the first period. In the third period, that of acceleration, stimulus applied to the ventricle hastens the advent of the succeeding systole, and the latent period is very short, being nearly equal throughout its whole extent to the latency at the end of the second period. The sensibility of the heart to stimuli is scarcely so great in this period as in the second.

The length of the diastolic pause succeeding the accelerated systole is longer than normal, the increase in length being nearly equal to the amount of acceleration.

Stimulation of the Ventricle—Maximal.

When stimuli of maximal potency are applied to the ventricle between the maximum auricular systole and the commencement of ventricular systole, the ventricular systole immediately following the stimulus is rarely slightly higher than normal, and the diastolic pause succeeding it is excessively long—so long, indeed, as to be nearly, if not quite, equal to the time which would, as a rule, be occupied by two diastoles, so that the time occupied by the systole and diastole after stimulation applied at this period of the heart's cycle, is equal to the time usually occupied by one systole and two diastolic pauses.

* *Op. cit.*, p. 72.

In most cases this systole was apparently no higher than normal, and consequently we cannot with plausibility regard it as a case of superposition of two systoles.

In some cases the time within which this pause may be produced is strictly limited to the point indicated; in others, however, it may extend some little distance towards the maximum of systole, though it never reaches this. In other words, it may encroach upon the refractory period which we have mentioned when speaking of minimal stimuli, although it never extends through the whole of it.

This phase may occasionally, though rarely, be absent. Its place is then taken by reduplication, or very rarely by insensibility to stimulation, as in the refractory period.

Reduplication with maximal stimuli occurs during all times of the cycle, except at the very commencement of the systole.

A very considerable latency is to be observed in cases where stimulation falls early in the systole. The latency, when this is the position of the shock, is usually 0·5′ or even more, and occasionally where stimulation is coincident with the earliest possible attempt at systole, nearly the whole beat may lapse before reduplication.

The latency is greatest when the stimulus is applied at the commencement of the ventricular systole (with the exception of its very beginning), and it gradually decreases towards the end of systole, at which time it is at a minimum. During the diastole the latency seems to remain constantly the same as at the end of systole. The later in the phase of ventricular activity the reduplicated systole commences the more perfect is it.

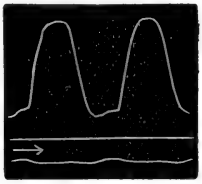
In all the points already mentioned our results agree with those of Marey.

Stimulation of the ventricle falling before or at the maximum of ventricular systole, *i.e.*, during the refractory period of a minimal stimulation, frequently causes a reduplication of the auricular systole which holds the same relation to the induced ventricular beat that the auricular contraction normally holds to the ventricular.

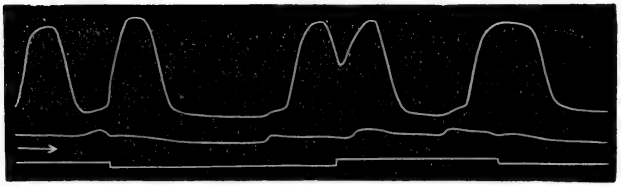
Stimulation falling after the maximum of ventricular systole

may cause an induced auricular contraction, but this is nearly synchronous with, or even subsequent to, the induced ventricular contraction (Fig. 170, *a* and *b*, and Fig. 169, *c*).

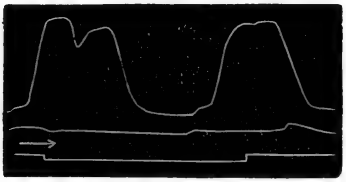
FIG. 169.



a.



b.

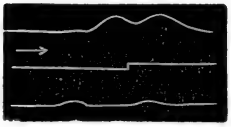


c.

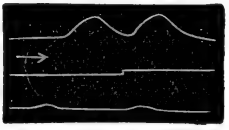
Stimulation of Ventricle (maximal).

a, normal tracing; *b*, effect of maximal stimulation. In *b* inhibition is seen.

FIG. 170.



a.



b.

Stimulation of Ventricle (maximal).

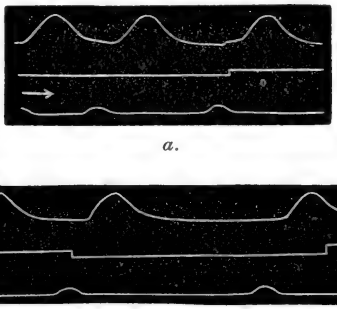
Sometimes reduplication of the ventricular beat may occur without reduplication of the auricular (Fig. 169, *c*).

These results may be possibly due, in part at least, to direct stimulation of the auricle itself by the strong current used to stimulate the ventricle.

Stimulation of the Auricle—Minimal.

When minimal stimuli are applied to the auricle, there is occasionally a refractory period, extending from the beginning to the maximum of auricular systole. When the stimulus is applied at the maximum of auricular systole, or just after it, it sometimes produces an omission, or, as we may term it, an apparent inhibition of the next auricular and ventricular systoles (Fig. 171, *b*). Stimulation falling after this point and occasionally on it, will cause a reduplication of auricular and ventricular contractions to occur which may have a latency of as much as 1·25 seconds.

FIG. 171.



a.

b.

Stimulation of Auricle (minimal).

No secondary contraction can usually be produced in the ventricle till an induced auricular contraction has occurred; and as the auricular latency is considerable, the ventricular latency is also very long. Thus, should the stimulus producing contraction fall at the commencement of ventricular systole, the auricle may have a latency of one second and the ventricle of 1·4 seconds.

The sensibility of the auricle to minimal stimulation may generally be divided into three phases:—

1stly. Stimulation may fall at such a stage of auricular activity that it does not cause an instantaneous response, but allows the auricle to pass through its diastole before it causes reduplication.

2ndly. It falls at such a time that the auricle responds instantaneously.

3rdly. About or shortly after the period of auricular maximum stimulation may cause inhibition of the auricular and the ventricular sequential beat.

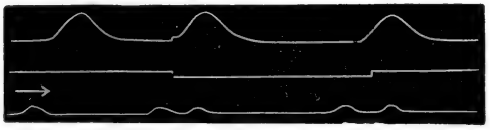
Stimulation at any period during the diastole of the auricle until the abscissa is reached, causes a reduplication. The latency of this reduplicated beat is shorter the further the diastole is advanced. It is followed by an induced ventricular beat in ordinary rhythm.

Stimulation during complete auricular diastole and before systole commences causes a contraction with very short latency, succeeded by an induced ventricular contraction. But it is to be noted that occasionally stimulation at this period causes a normal auricular contraction with an appreciable latency, and followed by a ventricular contraction.

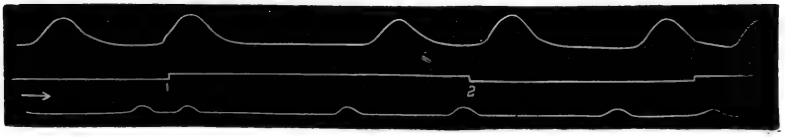
Stimulation of the Auricle—Maximal.

Maximal stimulation of the auricle almost always produces some effect both on the ventricular and auricular beat; this effect is usually one of stimulation, but it may be of apparent inhibition.

FIG. 172.



a.



b.

Stimulation of Auricle (maximal).

Maximal stimulation usually induces a ventricular beat whenever it is applied (Fig. 172, *a*), excepting when it falls just after the summit of the auricular contraction.

Stimulation at this point may cause no auricular contraction, but on the contrary may induce omission of the subsequent auricular and ventricular beat (Fig. 172, *b* 2).

When an auricular beat has been induced by stimulation, it is followed in the ordinary way by a beat of the ventricle, excepting when the stimulus is applied to the auricle just at the commencement of the ventricular systole. In this case an auricular beat may be induced, which instead of being followed by a corresponding ventricular one, is followed, on the contrary, by an omission of the ventricular beat (Fig. 172, *a* 1).

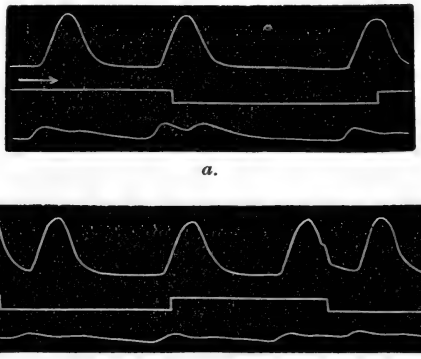
At this point the latent period may be looked upon as indefinitely long, as stimulation produces no contraction at all.

The more closely after this point stimulation is applied the longer is the ventricular latency.

Stimulation of Venous Sinus—Minimal.

The venous sinus appears to be more sensitive to stimulation than either auricle or ventricle, so that stimuli applied to it produce an effect, although they are much slighter than the minimal stimuli of either auricle or ventricle.

FIG. 173.



a.

b.

Stimulation of Venous Sinus (minimal). In neither *a* nor *b* is the closing shock effective.

Stimulation of the venous sinus by a minimal shock is usually potent to produce some effect or other at every stage of ventricular activity (Fig. 173, *b*).

Stimulation at the instant of commencement of ventricular systole usually causes omission of the following sequential beat of both auricle and ventricle.

This period may occasionally be slightly prolonged into systole.

Stimulation of the sinus at all other periods of ventricular activity causes a reduplication of the systole. This induced ventricular systole is preceded by an induced auricular systole, and therefore has the prolonged latency before referred to.

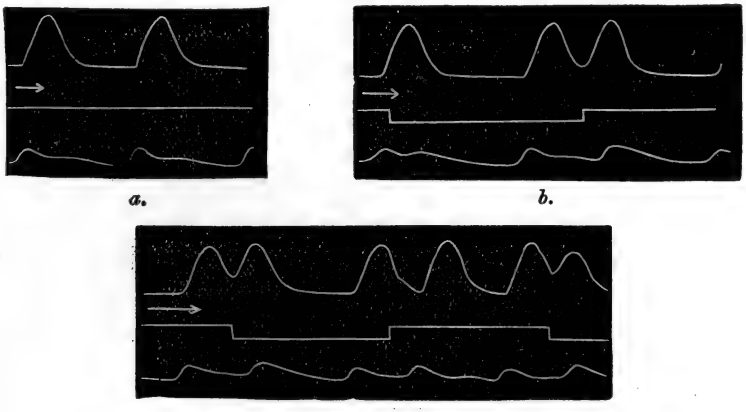
Stimulation falling at the commencement of ventricular systole may cause auricular reduplication with ventricular omission (Fig. 171, *a*).

In consequence of the long latency, we find all ventricular curves separated by a distinct interval from (their) reduplications.

Stimulation of Venous Sinus—Maximal.

The period during which stimulation causes ventricular omission is well marked, and in some cases extends into the

FIG. 174.



a. *b.* *c.*

Stimulation of Venous Sinus (maximal). *a*, normal rhythm; *b* and *c*, stimulations all effective.

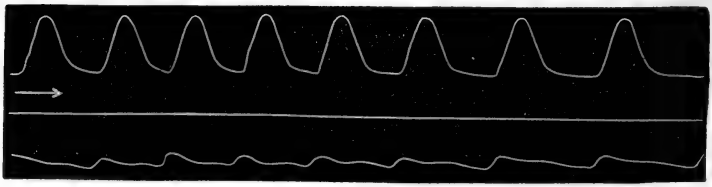
ventricular systole as it advances towards its maximum, though the effect is never produced at the maximum.

This omission of the ventricular beat is most usually associated with a reduplication of the auricular beat, the second auricular contraction occurring within that ventricular systole at the commencement of which the shock was communicated (Fig. 174, *b*).

Reduplication occurs in all phases except at the period when stimulation causes omission. The latent period of this reduplication is usually short, as in the case of a ventricle stimulated directly, inasmuch as the induced auricular contraction does not precede the induced ventricular, except when stimulation falls before the maximum of ventricular systole, in which case there is usually a regular sequence of auricular and ventricular contraction (Fig. 174, *c*).

Usually after the maximum of ventricular systole stimulation causes a reduplicated beat with short latency, inside of which curve falls that of the induced auricular contraction; however, genuine sequential reduplication of auricle and ventricle with long latency is not uncommon. Not unfrequently, after repeated stimulation of the sinus, the heart assumes a new rhythm, which may be twice as rapid as it was originally, and though omission of the alternate beat may still be produced by stimulation at the time already indicated, the organ returns again to its accelerated pace. In time, if stimulation be withheld, the rhythm returns again to the normal. The auricle shares in the ventricular excitement (Fig. 175).

FIG. 175.



Rhythm which has been changed by repeated stimulation of Sinus returning to normal.

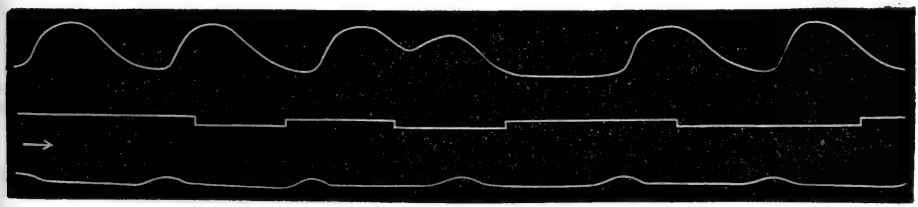
The Effect of Cold on the Frog's Heart.

In these experiments the animal was placed upon a wire gauze grating, and covered with a small bell-jar. Underneath the grating and around the bell-jar was placed ice, so as to surround the frog, which was kept in this position for an hour or longer. When its movements had become slow and torpid it was killed, without loss of blood, and placed on the cardiograph, already described, the temperature in the vicinity being kept low by means of blocks of ice placed on the metal bars supporting the animal. The apparatus was employed in the same manner as in our observations on the effect of electrical stimuli on the normal heart, and the same order was observed in recording the results.

Effects of Electrical Stimulation of the Ventricle—Minimal Stimuli.

The contraction of the chilled frog's heart, as is well known, lasts for longer time than in the ordinary condition. When minimal stimuli are applied to the ventricle (Fig. 176) it is found that there is a distinct refractory period, extending from the beginning of systole up to the last third of the summit of the curve in the accompanying tracing, and persisting past the maximum of systole.

Fig. 176.



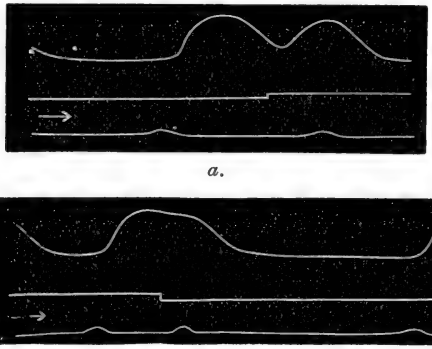
Stimulation of the Ventricle (minimal). Opening stimulation only effective

It is, therefore, always longer than in the normal heart. After the refractory period has passed, stimulation causes reduplication of the ventricular beat. The later on in the diastole that the stimulus falls the shorter is the latency.

Ventricular Stimulation—Maximal.

Stimulation sometimes causes omission when applied at the very commencement of systole. All stimulation thereafter applied causes a reduplication of the ventricular systole, with a latency that becomes shorter the later the stimulation is applied. If auricular reduplication occurs it is always sequential to ventricular (Fig. 177, *a*). Stimulation at the maximum of systole may cause a blending with the reduplicated beat closely resembling one prolonged systole (Fig. 177, *b*). The induced beat is most perfect when stimulation falls, just as the abscissa is reached. Stimulation before the maximum of systole has longer latency than stimulation at the maximum.

FIG. 177.



a.

b.

Stimulation of the Ventricle (maximal).

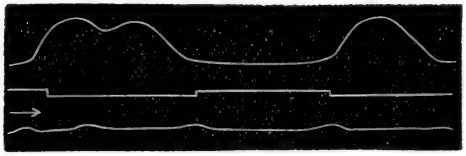
Auricular Stimulation—Minimal.

A refractory period is obviously present, but it is not of so great length as in the case of ventricular stimulation. It may be said to extend usually through the maximum of auricular systole (Fig. 178), and even up to near the maximum of ventricular systole; occasionally it exists only just at its commencement.

As regards the reduplication, we find that as in the case of the normal heart, a long latency prevails, because an induced

auricular systole must occur before the ventricle contracts again. But if the stimulation fall just at the time when the

FIG. 178.



Stimulation of Auricle (minimal).

abscissa is reached, or rather before this point, a ventricular contraction may exceptionally be produced with a short latency, and the auricular induced contraction succeeds it.

Auricular Stimulation—Maximal.

The same features are to be observed as in the last section, except that there is no refractory period (Fig. 179).

Stimulation in all phases of the ventricular cycle usually causes a reduplicated auricular and ventricular beat. Should the stimulation fall before the ventricular maximum is attained, the auricular reduplication precedes the ventricular in the ordinary way, but should the stimulation fall after the ventricular maximum, the auricular reduplication is exceptionally synchronous with, or subsequent to, the ventricular; usually however, the induced ventricular beat precedes in ordinary rhythm the induced ventricular.

Stimulation of the Venous Sinus—Minimal.

A refractory period may be present on minimal stimulation, nearly up to the maximum of ventricular systole. Thereafter reduplication results. A strictly minimal stimulation may originate a reduplication at any period of the beat having a long latency, that is to say, the ventricular reduplication is preceded by the auricular induced contraction (Fig. 180). Thus stimulation applied just before the ventricular relaxation is completed, instead of having an instantaneous ventricular and auricular

response resulting from stimulation of auricle or ventricle, has a long latency, wherein the auricle reduplicates. The further

Fig. 179. Stimulation of Auricle (maximal).

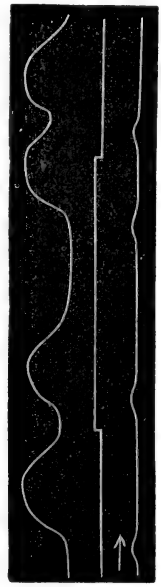


Fig. 181. Stimulation of Venous Sinus (maximal).

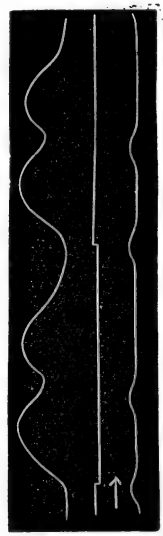


Fig. 180. Stimulation of Venous Sinus (minimal).

Fig. 183. Stimulation of Ventricle (maximal).

Fig. 182. Stimulation of Ventricle (minimal). Auricular tracing omitted.

on in the systole the stimulation is applied, the shorter is the latent period, and the more perfect the reduplicated contraction.

Stimulation of the Venous Sinus—Maximal.

Omission may be caused by stimulation applied at the commencement of systole, or reduplication may occur in all phases (Fig. 181).

Reduplication has the longest latency at the commencement of systole, and there is true auricular precedence up to or beyond the maximum in this phase. In the decline of systole, after the maximum is passed, and the abscissa has been nearly reached, there is occasionally reduplication with short latency, the auricular and ventricular contraction being synchronous.

ACTION OF HEAT ON THE HEART.

In this series of experiments the pithed frog in which the brain and spinal cord had been destroyed, was laid upon a metal plate, the temperature of which was gradually raised by means of a flame beneath it.

Ventricular Stimulation—Minimal.

The refractory phase is generally wanting in the ventricular systole, but it may be present in exceptional cases, not unfrequently in the same tracing in which stimulation most generally produces reduplication (Fig. 182).

It may be noted that irregularity of response to stimulation is one of the characteristics of the heated condition. Stimulation usually causes reduplication. Should stimulation fall at the commencement of ventricular systole, no effect is produced till the whole cycle of the systole has been passed through, when reduplication by a very perfect systole occurs. Latencies diminish in proportion as the stimulation occurs later in the systole of the heart. Reduplication occurring in response to stimulation falling at the maximum is often demonstrated by a beat originating when the relaxation after systole is completed, and therefore distinct from the original beat: this is due to the fact that the curve of the heated heart is much shorter in

duration, and therefore the reduplication falls outside the systole during which stimulation occurs, the latency being actually shorter, however, than in the unheated heart.

Ventricular Stimulation—Maximal Stimuli.

When stimuli of maximal intensity are applied to the ventricle of the heated heart, we notice (Fig. 183) :—

(1) That there is no refractory period; (2) Stimuli at the commencement of the ventricular systole may cause omission of the succeeding beat; (3) Reduplication occurs at all phases, and has the same characteristics as in minimal stimulation; (4) Latencies follow the same rule as in minimal stimulation; (5) The reduplicated beat is most perfect when stimulation falls—

I. At the very commencement of systole.
II. At its termination.

The value of any beat and its reduplication, with the time intervening and of the succeeding pause, was about equal to two normal cardiac cycles. Occasionally a double reduplication, or a series of contractions, resulted from a single stimulation.

Auricular Stimulation—Minimal Stimuli.

There is apparently no refractory period. All stimuli cause reduplication, and in all cases induced auricular systole precedes an induced ventricular systole. This occurs even in advanced auricular diastole, when occasionally in the normal heart a simultaneous auricular and ventricular systole results.

Auricular Stimulation—Maximal Stimuli.

There is no refractory period. Stimulation just after the auricular maximum has been passed frequently causes an apparent omission of the following beat.

Stimulation before the maximum of the ventricular systole causes an induced ventricular beat preceded by an auricular contraction.

After the maximum, stimulation usually has the same effect,

but occasionally causes an instantaneous reduplication of both auricular and ventricular beats.

A reduplicated ventricular beat is of the character already described.

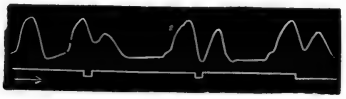
Stimulation of the Venous Sinus—Minimal Stimuli.

The venous sinus in its general absence of a refractory phase shows a resemblance to the ventricle, but it may manifest the same exception in exhibiting it.

When this occasional refractory period is present it may exist during active systole, and up to its maximum. It is exceptionally present in cases which as a rule show no refractory period.

Stimulation falling before the maximum of systole (Fig. 184, a ventricular tracing alone given) causes a reduplication which

FIG. 184.



Stimulation of Venous Sinus (minimal).

is preceded by an auricular contraction, whilst stimulation falling immediately after maximum of systole causes reduplication, which may be preceded by an auricular pulsation, or may occasion an induced systole, auricle and ventricle contracting at the same time.

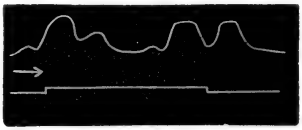
The most perfect reduplicated beat occurs when stimulation falls at the end of systole.

Venous Sinus—Maximal Stimulation.

Occasionally a stimulation of maximum strength falling at the commencement of the ventricular systole causes an apparent omission of the following pulsation; but this result is not so frequent as in the case of the normal heart. Usually a distinct reduplication occurs at whatever time in the cycle stimulation falls (Fig. 185).

The reduplication is at all times, except in the last stage of systole, preceded by an auricular contraction.

FIG. 185.



Stimulation of Venous Sinus (maximal).

The auricular induced contraction appears to follow stimulation more rapidly than in the case of the normal heart. Therefore the induced ventricular contraction (Fig. 185, ventricular tracing alone given) which follows the auricular has a shorter latency than is normally the case. The heating process having been carried so far that a rapid cardiac rhythm with imperfect systole has resulted, it is often found that there is an indifference to stimulation in the so-called refractory period, or even in all phases of the cardiac cycle alternating with the usual sensibility.

ON THE EFFECT OF STRYCHNIA UPON THE FROG'S HEART.

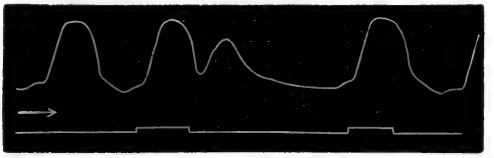
The apparatus used in this series of experiments was identical with that employed in the investigation of stimuli applied to the frog's heart. The frog was killed by the brain being destroyed, and a small dose of strychnia was then introduced into the dorsal lymph sac. As soon as the effect of the drug upon the spinal cord was evidenced by distinct spasm, the heart was rapidly exposed, placed on the cardiograph, and stimulation applied. The same order will be observed as in the description of the experiments on the normal heart.

Stimulation of the Ventricle—Minimal.

On applying a minimal stimulus to the strychnia heart (Fig. 186) we were struck, in the first instance, by the extreme length of the refractory period. Stimulation has usually no effect, not only when applied before the maximum of the systole as in the

normal heart, but also in the maximum, and often far into relaxation. After the phase has passed the stage of reduplica-

FIG. 186.



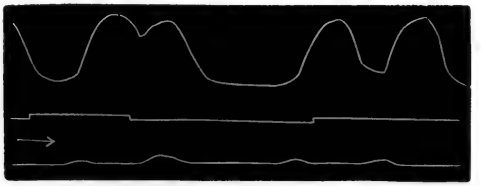
Stimulation of Ventricle (submaximal).

tion ensues. Reduplication is very complete; its latency becomes diminished as diastole advances. The reduplicated ventricular beat is succeeded by an auricular pulsation. After the customary pause, the heart resumes its wonted rhythm. It is rarely that stimulation falling at the commencement of ventricular systole causes inhibition. If the auricle is unstimulated and its rhythm is unaltered, there is short latency for the ventricular reduplication. If the auricle is stimulated and contracts before the ventricle, there is long latency, but the latter is rarely seen when a refractory phase is present.

Ventricular Stimulation—Maximal Stimuli.

In this case no refractory period exists. An inhibitory period exists occasionally, but with this exception, all stimulations produce reduplication (Fig. 187). Should stimulation fall at the

FIG. 187.



Stimulation of Ventricle (maximal).

commencement of systole, the latency is long, nearly equal to the length of the beat; and the reduplication is very complete.

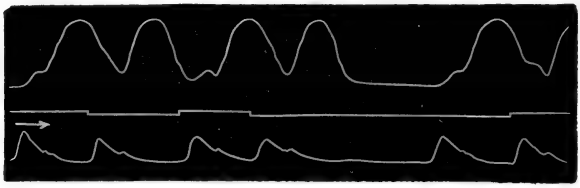
Stimulation at the maximum of systole has a latency of about

two-fifths of a second, and thereafter during the subsidence of the ventricle, the period of latency rapidly diminishes. The most perfect beat of reduplication is produced by stimulation at the commencement of systole, or after relaxation of the ventricle.

Stimulation of the Auricle—Minimal.

It is but rarely that we see a refractory period whilst applying minimal stimuli to the auricle. Usually, stimulation at all times causes a reduplicated beat, the auricular reduplication preceding that of the ventricle in the usual rhythm. On stimulation, an auricular systole is produced, and not until this movement has reached the usual point does the ventricle commence its systole (Fig. 188).

FIG. 188.



Stimulation of Auricle (minimal).

Stimulation of the Auricle—Maximal.

There is no refractory period. Occasionally the stimulus falling at the very commencement of the ventricular systole will cause inhibition or coincidence of the following beat, or it may cause a reduplication with a latency of about one second (Fig 189).

FIG. 189.

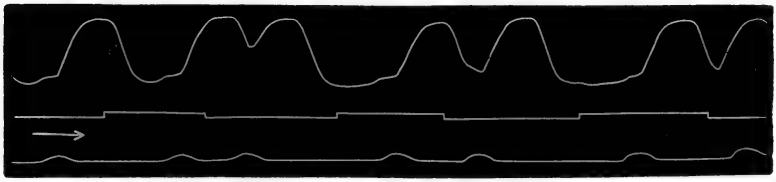
Stimulation of Auricle (maximal).

The latencies are invariably long when the auricle is so stimulated that its induced beat is a normal one and precedes the induced ventricular systole in its normal rhythm.

Stimulation of the Venous Sinus—Minimal Stimuli.

With minimal stimulation of the venous sinus there is no refractory period except occasionally for an instant at the maximum auricular systole. Reduplication occurs at all phases of the ventricular systole. Length of latency depends upon whether the stimulation induces an auricular contraction or not. If the auricular systole follows the stimulus, then the ventricular latency must be long (Fig. 190).

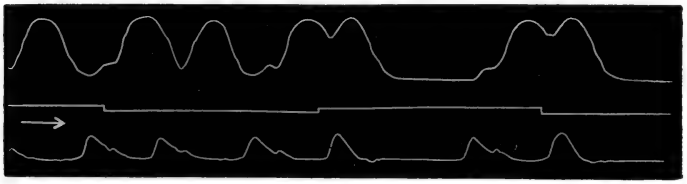
FIG. 190.



Stimulation of Venous Sinus (minimal).

It is longer if stimulation falls at the commencement of ventricular systole, because at that phase, until the auricle has contracted, no ventricular reduplication occurs. Occasionally, though rarely, and that after the maximum of ventricular contraction, auricular reduplication follows, or is synchronous with the ventricular systole, and then latency is invariably short. Reduplication with prolonged latency, probably from auricular reduplication, is well seen in the appended tracing (Fig. 191).

FIG. 191



Stimulation of Venous Sinus (minimal).

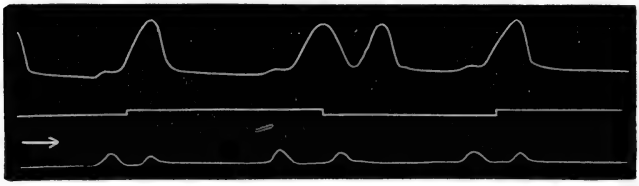
The stimulation at the end of relaxation in one case causes reduplication of the auricle, coinciding with that of the ventricle.

The tracing illustrates the rule that when the sinus is stimulated no refractory period is observed as regards the ventricular reduplication.

Venous Sinus—Maximal Stimulation.

There is no insensitive period as far as regards the ventricle. During all phases of the systole stimulation causes a reduplication of the ventricular beat (Fig. 192). Inhibition of the ventricular systole has not been found in many of the hearts examined, though it occasionally occurs.

FIG. 192.



Stimulation of Venous Sinus (maximal).

Should the exciting shock fall at such a time as to cause an instantaneous auricular systole, we find this systole is nearly synchronous with that of the ventricle, and that the latter has a short latency, but should the shock fall so that the auricle responds by a genuine contraction, the ventricular reduplication follows with a long latency.

Inhibition of the ventricular with reduplication of the auricular beat may result occasionally from stimulation of the venous sinus.

Appendix A. COOLED HEART.

The construction of a simple piece of apparatus has enabled us to obtain curves much more striking than those which appeared in the foregoing paper, as they represent a far greater variation of temperature.

Instead of the gutta-percha support for the heart already described, a hollow copper pan of similar shape was employed. It was provided with influx and efflux tubes, and insulated below by a plate of ivory in which ran also the electrodes destined for the stimulation of the sinus. This was connected with the usual support passing over the body. Upon minimal stimulation of the ventricle itself the succession of auricular and ventricular contraction is illustrated in the charts A 1—4 (Fig. 193) here inserted. It is seen that the action of cold modifies considerably the relation between the ventricular contraction and the succeeding auricular beat. In A_2 we find a reduplicated ventricular beat succeeded by a normal auricular contraction.

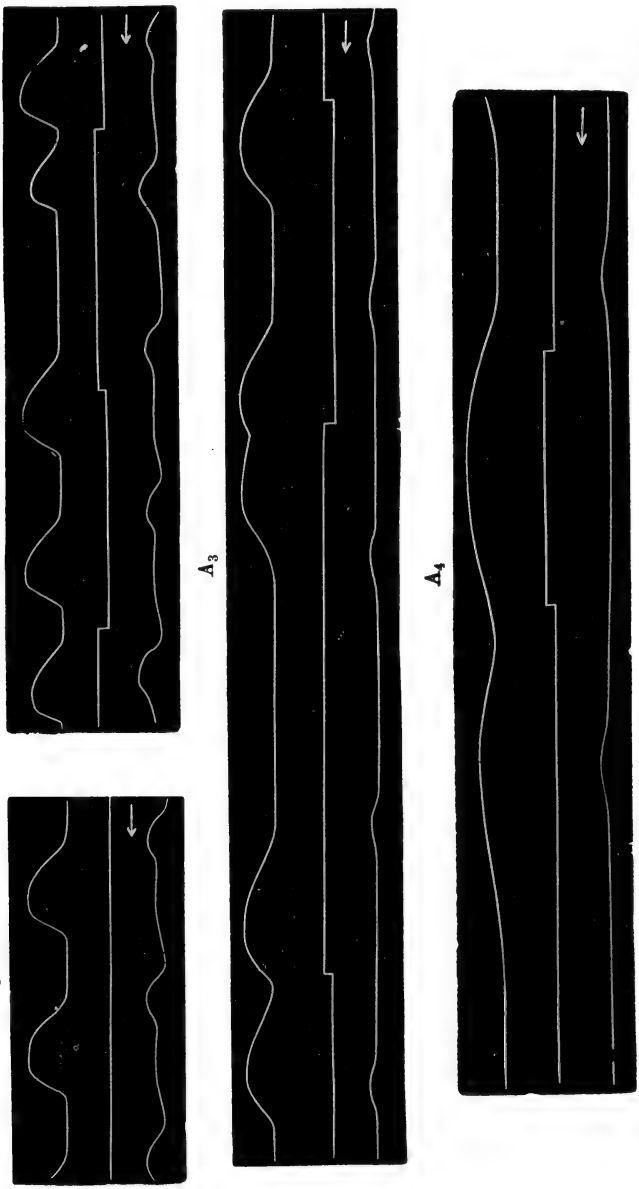
In A_3 cooled through about 2°·5 C., the ventricle responds to the same stimulation, and the way does not pass upward to the auricle; and in A_4, in which the contraction and relaxation of the heart had become very slow from a further reduction of 2°, we find the auricular rhythm is regular in spite of ventricular reduplication. There is in A_1 and A_2 an indication of aortic expansion; it is to be noticed that after the reduplication in A_2 this is omitted.

Auricular Stimulation.

Many additional experiments upon cooled hearts have tended to show that it is very rarely that stimulation of considerable strength calls forth a ventricular beat, preceding or coexistent with the auricular. Usually at all phases of stimulation which cause a reduplication of the auricular beat, the ventricular succeeds in normal relationship (B 1 and 2 Fig. 194). There is an exception to this, however, which is frequently demonstrated; this is that whilst the auricular beat is reduplicated the ventricular is not, but is succeeded by a long diastolic pause (B_3), after which the auricle takes up its old rhythm. Still more rarely stimulation just before commencement of ventricular systole causes omission of both succeeding auricular and ventricular beats (B_4).

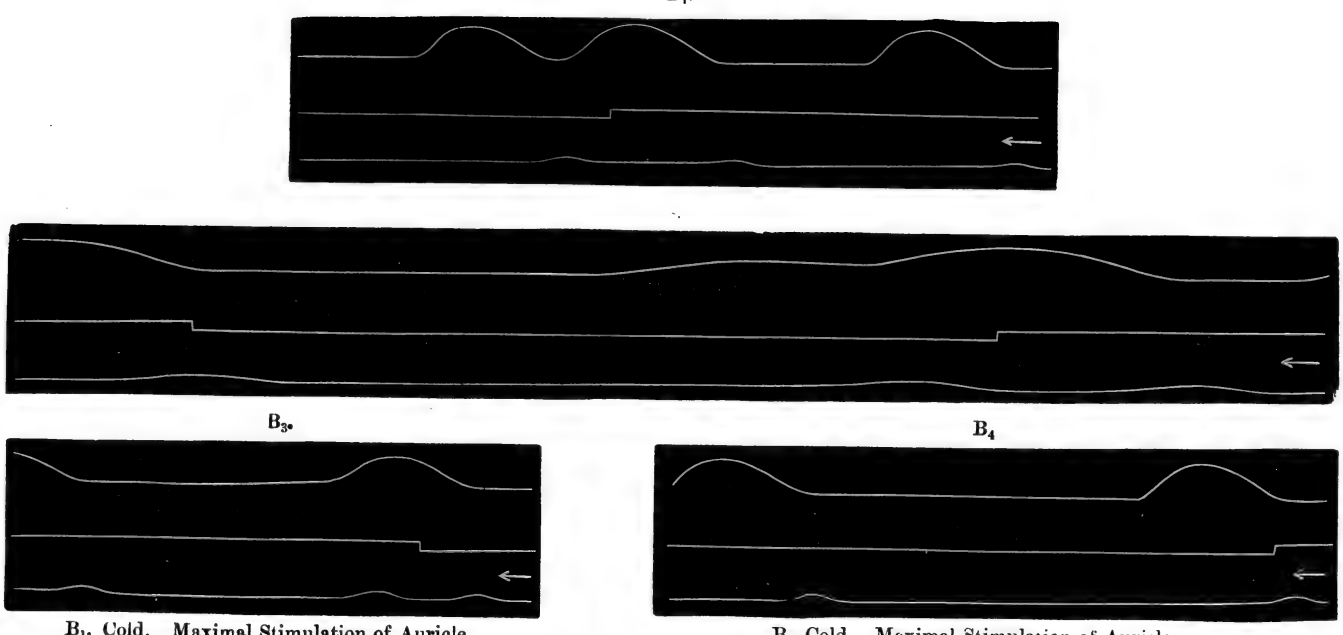
The latency of reduplication varies considerably in minimal stimulation of the auricle, but this variation is not so much owing to loss of time in the auricular as in the ventricular

Fig. 193.



A_1. Normal Heart tracing.
A_2. Stimulation of Ventricle of the normal Heart.
A_3. Stimulation of Ventricle of Heart cooled through 2°·5 C.
A_4. Stimulation of Ventricle of Heart cooled through 4° C.

FIG. 194.

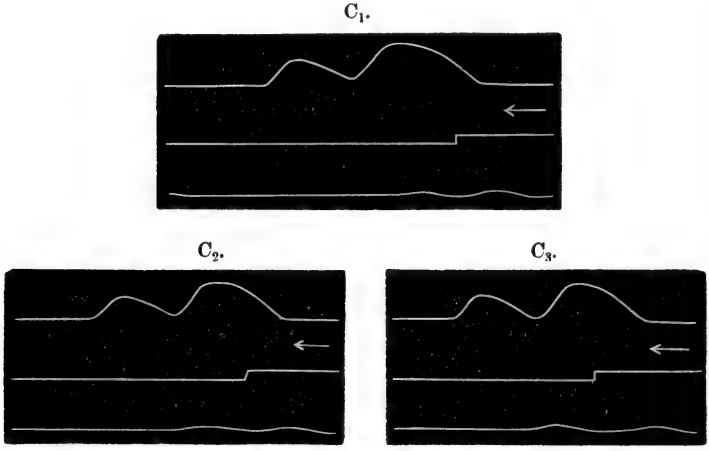


B_1. Cold. Maximal Stimulation of Auricle.
B_2. Considerable cold. Maximal Stimulation of Auricle.

B_3 Cold. Maximal Stimulation of Auricle.
B_4 Cold. Maximal Stimulation of Auricle.

reduplication. Thus in C_1 (Fig. 195) stimulation at the end of auricular relaxation, ventricular latency is 1″·2, in C_2 stimulation halfway to ventricular maximum latency is 1″, and in C_3, when stimulation, is at ventricular maximum, the latency is for the ventricle only 6″.

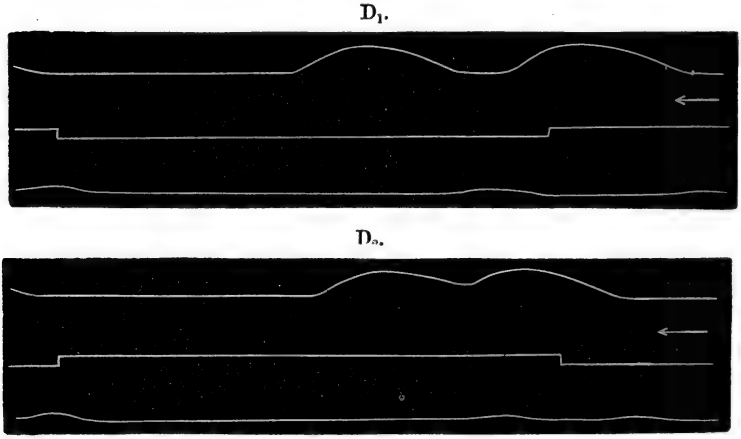
FIG. 195.



C_1 to C_3. Levers as in **A.** Auricular Stimulation (minimal) of Cooled Heart.

On the other hand, more powerful stimulation of the auricle causes reduplications of the ventricle, which are at all times of

FIG. 196.



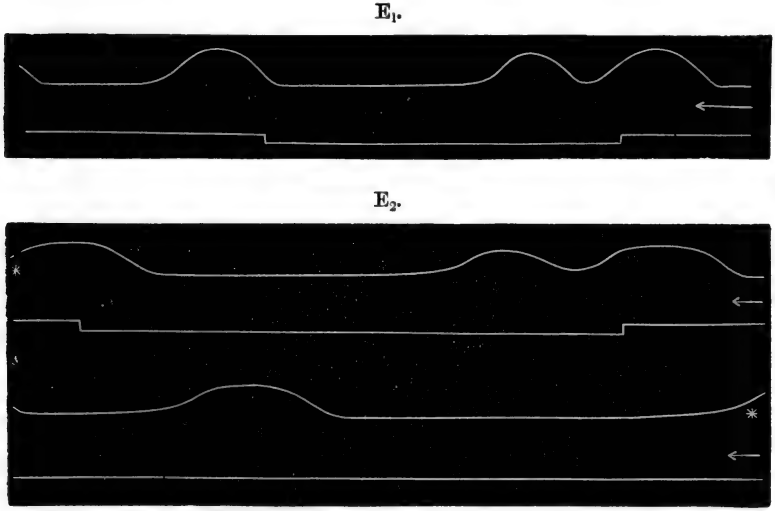
D_1 to D_2. Levers as in A. Auricular Stimulation (maximal) of Cooled Heart.

equal or of very slightly differing values. Thus in a heart much cooled (D 1 and 2 Fig. 196) we have towards the commencement of ventricular systole and towards the end of relaxation a latency for the induced ventricular beat of 1″·2.

Venous Sinus.

In the heart which has been moderately or slightly cooled, 4—6° C., the occurrence of ventricular reduplication without a precedent auricular reduplication is very rare, even when strong stimulation is employed. The refractory period occasionally observed may disappear after a few stimulations have been given, or it may persist. Furthermore, on cooling a heart which has at a certain temperature, E_1 (Fig. 197), shown a refractory period, we may find this converted into a period during which stimulation causes an omission of the following beat, E_2.

FIG. 197.



E_1 to E_2. Levers as in A, but no auricular tracing given. Stimulation of Venous Sinus. E_1, before cooling; E_2, after cooling.

The duration of the diastolic pause is markedly influenced by temperature, whereas it appears to be but slightly affected by variation in the instant of stimulation by which it is produced.

In (Fig. 198) G_1 water of melted ice had passed through the support for two minutes.

G_2 water had passed 5′.
G_3 „ „ 10′.
G_4 „ „ 20′.

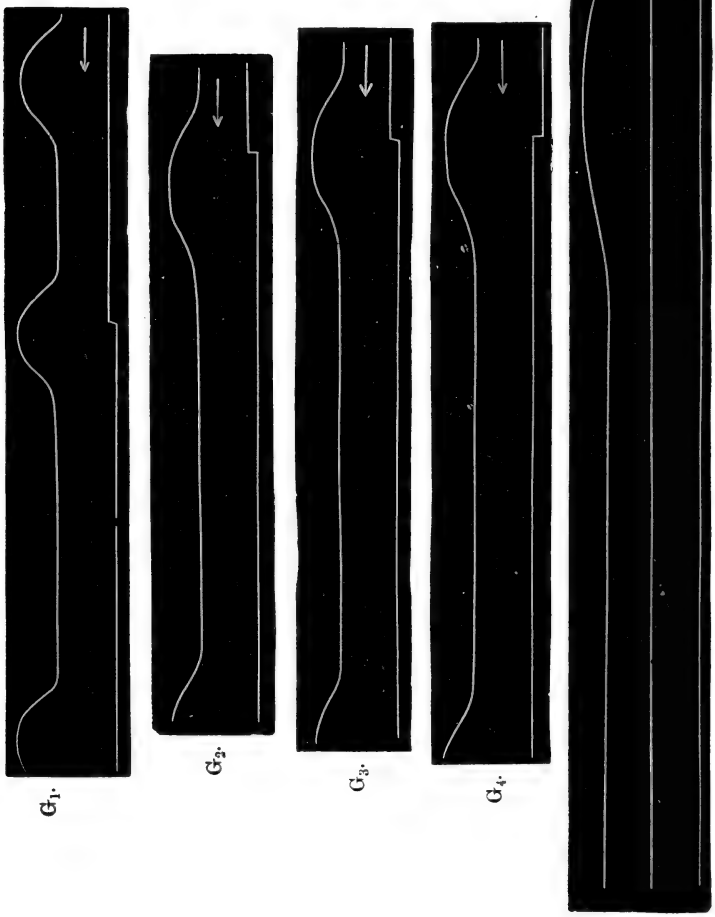


FIG. 198.

Levers as in E. Stimulation of Venous Sinus. G_1 to G_5, gradual cooling of Heart.

G_1	Duration of contraction		1″·4	Length of pause from stimulation	...	4″·2
G_2	„	„	... 1″·9	„	„	5″·6
G_3	„	„	... 2″·2	„	„	6″·0
G_4	„	„	... 2″·4	„	„	6″·2

G_5 was obtained from a heart cooled for a considerable time, and shows a remarkable prolongation of the systole and diastolic pause.

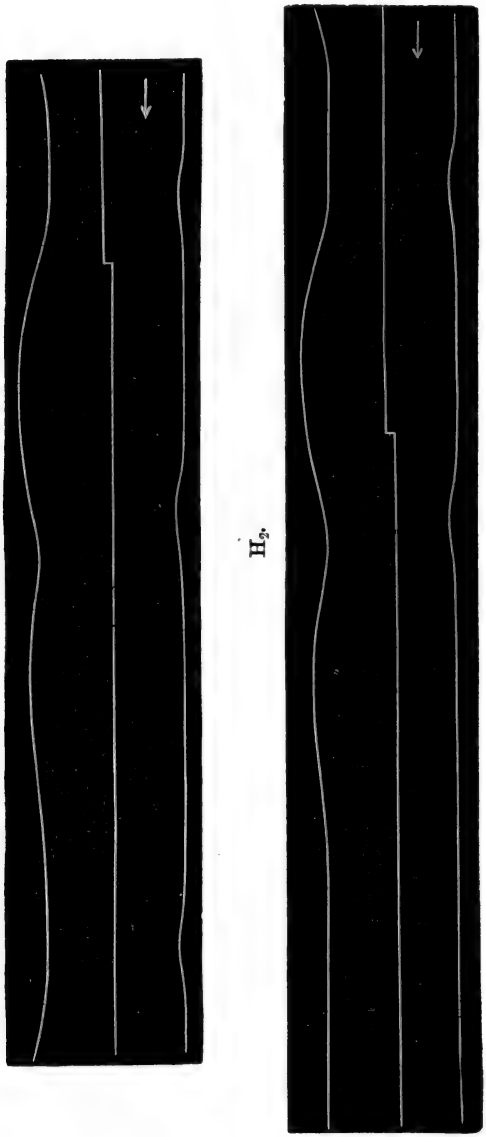
G_5	Duration of current	4″·4	Length of pause from stimulation	...	10″

It will be seen in all these cases that there is a certain relationship between the length of the contraction and of the pause.

The reduplication of the ventricular beat varies in regard to the time of stimulation under minimal stimulation. Thus in H (Fig. 199) when stimulation falls near the commencement of systole, auricular reduplication occurs in 1″·8 and ventricular reduplication in 3″·2. But in the same heart a stimulation during a period of relaxation yielded an instantaneous auricular response, the ventricular reduplication occurring 1″·3 after stimulation.

In the case of maximal stimulation, the usual result is an instantaneous auricular systole succeeded by a ventricular. The latter, therefore, has a latency equal to the auricular beat: this is seen in I_1, I_2 (Fig. 200), in both of which the latency is about 0·7″; but in I_3 we have, on the other hand, no auricular reduplication for 1″·1. In both this instance and H_1 stimulation occurred at the commencement of ventricular systole

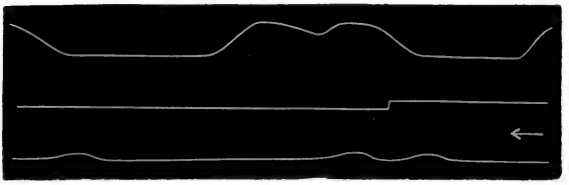
FIG. 199.



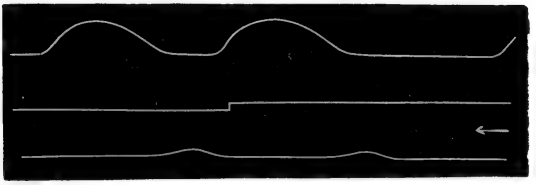
H_1 to H_2. Levers as in A. Stimulation of Venous Sinus (minimal

FIG. 200.

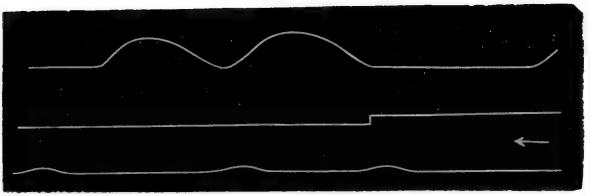
I_1.



I_2.



I_3.



I_1 to I_3. Levers as in A. Stimulation of Venous Sinus (maximal).

FIG. 201.

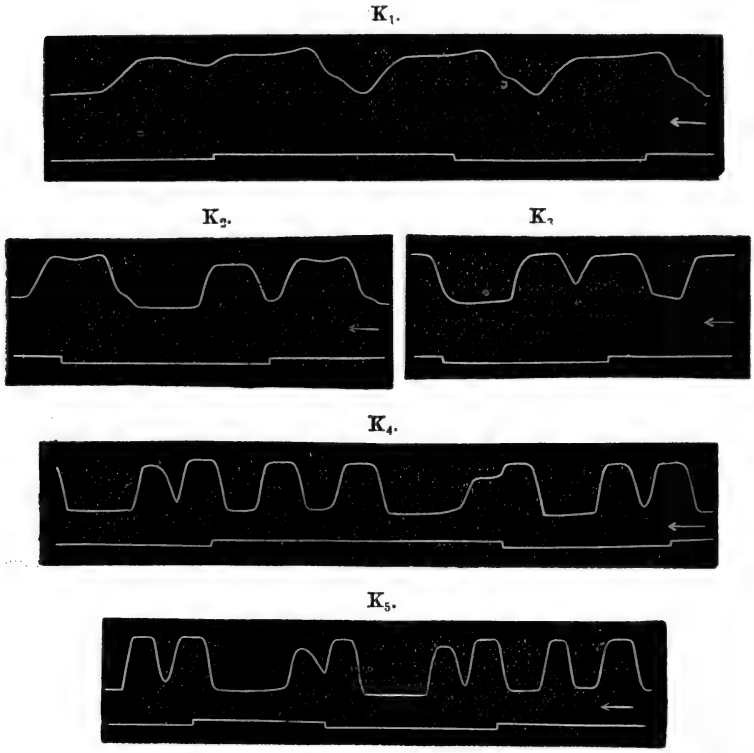
Time tracing. Electro-magnet recording seconds. Applicable to all tracings in Appendix A.

Appendix B. HEATED HEART.

In some cases, heating a frog's heart through 4°·5 C. may fail to obliterate entirely the period of resistance to stimulation. Heat, however, in the same experiment may be shown to shorten the refractory period much, and to limit it to the very commencement of ventricular systole (in stimulation applied to the ventricle). The series of tracings given were taken from a large specimen of *Rana esculenta*, which had been kept at a low

temperature for a considerable time before the experiment. The tracing obtained at room temperature (K_1 Fig. 202) is therefore that of a cold heart, and the refractory period extends up to the commencement of relaxation after systole. After hot water had been run through the support for 5′, and the temperature raised about 2° C., we find diastole increased and systole much shortened; at the same time there is a refractory period as extensive as in the cold heart, that is to say, extending to the commencement of relaxation K_2.

FIG. 202.



Stimulation of Ventricle (maximal stimulation).

K_1. Heart at room temperature, frog long kept in cold room.
K_2. Temperature raised 2° C.
K_3. Taken 10′ later than K_2, during which time temperature was raised 1° C
K_4. Temperature raised again 1° C.
K_5. Temperature raised 1° C., making about 5° C. altogether above K_1.

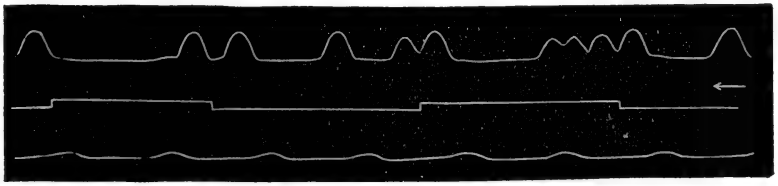
FIG. 203.

Drum of more rapid rotation used in tracings given in Appendix B. The electro-magnet marks seconds.

In K_3 after heat had been applied 10′, and the temperature raised another degree, stimulation at an earlier phase produces reduplication. Heated still further, K_4, there is reduplication at systolic maximum, and at K_5 everywhere except at the very commencement of systole. After heating through about 5° we still have a refractory period, whilst the curve has been reduced from 1″·4 to 0·4″. In many cases, however, the same amount of heat may obliterate the refractory period completely. The heart which yielded these curves passed into rigor without showing the abolition. In the heated heart, of which the ventricle is stimulated, we may find that the auricle does not in any way participate in the ventricular excitement, but continues to beat in its usual rhythm. Thus when the heated heart yields a series of contractions in answer to a single stimulation—a result not unfrequently obtained—the auricle does not reduplicate, but may give its systole in due place, whilst the ventricular contractions are still occurring. Not only is this indifference to ventricular action observed on the part of the auricle, but the counterpart may be occasionally seen in the ventricle, failing to follow the normal systole of the auricle L (Fig. 204). This is in part due to the fact that the auricle has only shared imperfectly in the heating.

FIG. 204.

L.

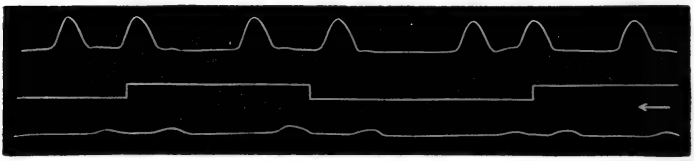


Stimulation of Ventricle (maximal). Heart heated about 7° C. Time as in K.

There is thus a disturbance of both muscle-wave and nervous impulse produced by the heating to which the auricles and ventricle have been exposed. This failure on the part of the ventricle occurs only after there has been a reduplication of its beat, and does not often occur, so far as we have seen, when stimulation, applied to the auricle itself (M Fig. 205), originates

FIG. 205.

M.



Stimulation of Auricle (maximal). Heart heated about 6° C.

a systole there, for then the ventricle follows in due course; we should therefore regard the exhaustion of the ventricle after its unusual activity as the cause of its quiescence after the normal auricular beat. Should stimulation be applied to the auricle during ventricular diastole, a reduplicated auricular beat succeeded by a ventricular at once occurs. In all phases this natural sequence is maintained, though sometimes at the end of its systole the auricular reduplication may be 0·5″. Whilst a long pause follows this reduplication, it is very rarely that a stimulation of the auricle produces omission of the succeeding auricular and ventricular reduplication.

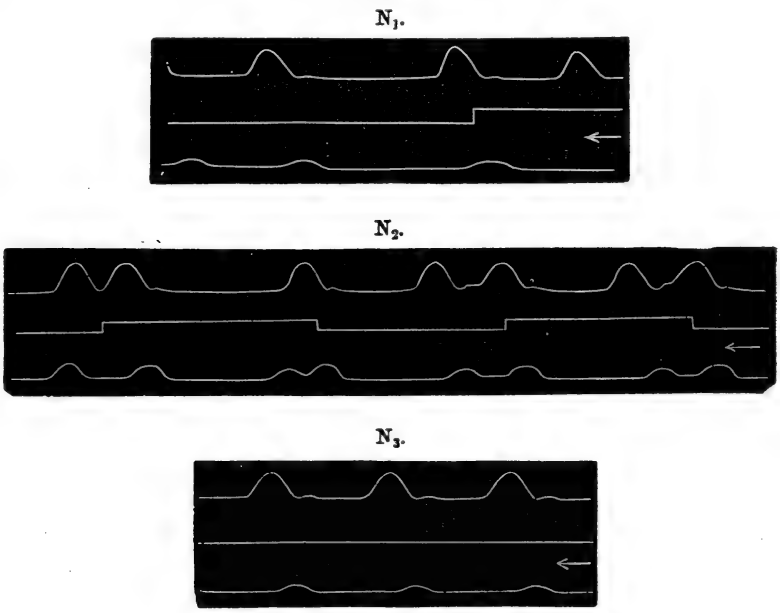
In stimulating the venous sinus, however, omission of the following ventricular beat is frequently produced when the shock falls at the commencement of ventricular systole (N_1 Fig. 206), but we may find that there is an impulse propagated to the auricle, for this may reduplicate whilst the ventricle remains quiescent (N_2).

A little later, and up to the maximum of systole, the auricular reduplication is succeeded by a ventricular (N_2), and after the maximum, and during the diastole of the ventricle, the induced auricular beat may occur synchronously with the ventricular, or it may precede it in regular course.

Both of the charts N_1 and N_2 (Fig. 206) are taken from a

heart warmed through about 5° C., and N_3 gives a tracing of the same, in which stimulation does not occur.

FIG. 206.



Stimulation of Venous Sinus (maximal).

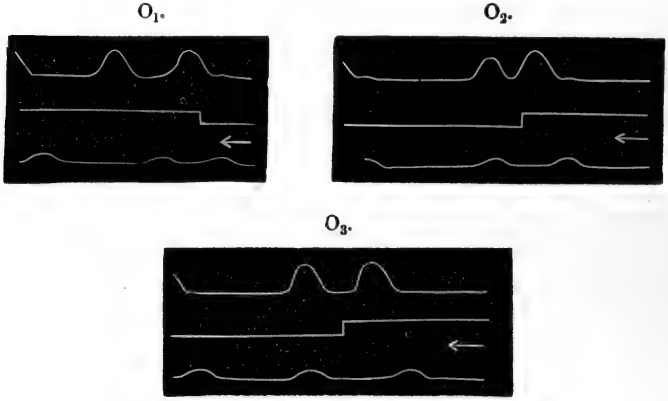
In the stronger tendency to cause omission of a ventricular beat, as well as in the frequent occurrence of an auricular contraction coincident with or succeeding the ventricular, when stimulation fails after ventricular maximum or in diastole, we see a marked contrast in the reaction of the venous sinus and the auricle to stimulation.

From the charts O_1, O_2, O_3 (Fig. 207) we see that the latency of the auricular beat varies. Thus stimulation occurring just at the end of auricular relaxation (O_1) causes an instantaneous reduplication, whilst during diastole proper it has a reduplication, with a latency of 0·2″. In the former case auricular induced systole precedes the ventricular, in the latter they occur at the same moment (O_2, O_3).

Contrast this result with the stimulation of the auricle itself,

in which reduplication occurs at once on stimulation, and ventricular reduplication succeeds or occurs occasionally (stimulation at the end of auricular relaxation) in 0·5″, followed by ventricle.

FIG. 207.



Stimulation of Venous Sinus (maximal).

Appendix C. ACTION OF STRYCHNIA ON THE FROG'S HEART.

In order to test the correctness of the conclusion that strychnia lengthens the refractory period, we placed frogs in which the medulla and cord only existed on the cardiograph. The effects of stimulation were then observed, and subsequently a small dose of strychnia was injected into the dorsal lymph sac; as soon as the resulting spasm was well developed, stimulation was again applied, the strength of stimulation and the position of the electrodes remaining constant.

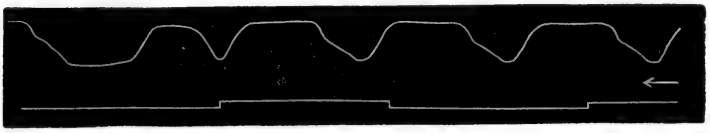
Thus in Fig. 208 P_2, a frog's heart, in which active circulation was present, showed a refractory period through about one-half of the maximal maintenance of systole. In 3′, after the injection of a small dose of strychnia into the dorsal lymph sac, distinct spasm was present, and in 5′ Fig. P_1 was taken, which showed that the refractory period had become prolonged, until relaxation of the ventricle had commenced.

It may happen that stronger stimulation before the maximum of systole is reached, causes an auricular beat, which precedes

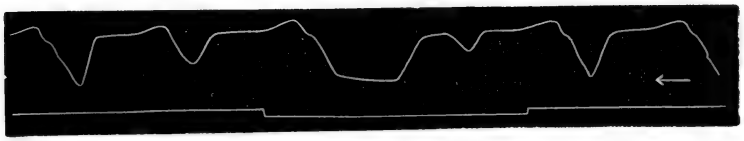
in normal rhythm the induced ventricular contraction. This is observed when the electrodes are placed near the base of the

FIG. 208.

P_1.



P_2.



Stimulation of Ventricle.

1. Before injection of strychnia. 2. After injection of strychnia.

FIG. 209.

Time-marker, recording seconds. All tracings in Appendix C taken at this speed, except S and T.

ventricle, or when stimulation is passed through the same portion of the heart from the float to an electrode placed beneath the heart upon the supporting shelf. After the maximum of systole, however, the auricular contraction succeeds the induced ventricular. Both these facts are demonstrated in Fig. 210 Q, in which this occasional increased auricular excitability is shown.

Auricular Stimulation.

Occasionally maximal stimulation applied to the auricle produces at all times an auricular contraction succeeded by a ventricular; more usually, however, this relationship exists only up to the maximum of systole (ventricular), and thereafter the induced auricular beat succeeds the ventricular.

Should stimulation cause an instantaneous auricular systole, then the ventricular reduplication has a latency of *nearly* equal value at all times at which it may occur, but should there be, as in Fig. 211 R_1, a considerable auricular latency (about 1″) then the ventricular latency is liable to great variations.

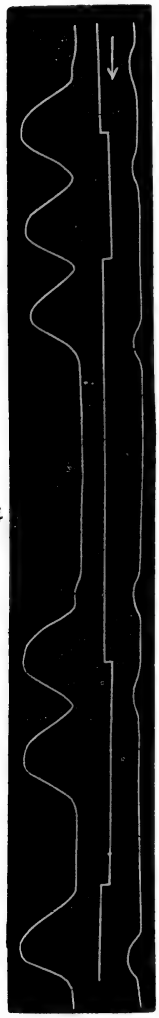
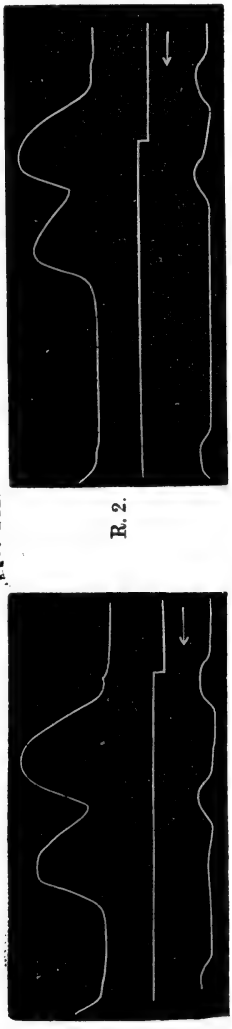


FIG. 210.
Q.
Stimulation of Ventricle (maximal).



R. 2.
R. 1.
R. 3.

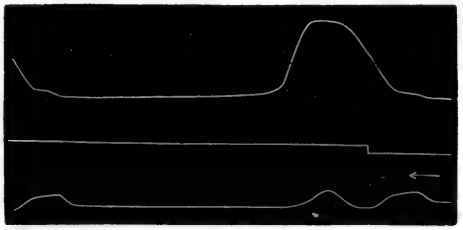
FIG. 211.
Stimulation of Auricle (maximal). 1, 2, 3, varying times of stimulation.

At the maximum of auricular systole, Fig. 211 R_2, we have an immediate auricular response, and a ventricular latency of 0·4″; and in Fig. 211 (R_3) there is an almost instantaneous ventricular systole, with an auricular latency of about 15″. The diastolic pause is the longer the later stimulation falls. In Fig. 211 R_1 it is 0·9″; in Fig. 211 R_2 it is 1″·9; in Fig. 211 R_3 it is 2″·3.

Stimulation falling just after maximum of auricular systole, and at the commencement of ventricular systole, may cause in addition to the results enumerated, omission of the succeeding auricular and ventricular contractions, or reduplication of the auricular, but omission of the succeeding ventricular (Fig. 212 S).

FIG. 212.

S.



Stimulation of Auricle (maximal). Levers as in Fig. Q.

Thus the induced auricular contraction in this instance, instead of passing a motor impulse downwards to the ventricle, appears not only to check the reduplication, but greatly to prolong the diastole.

It is easily recognised from the auricular tracing that the induced contraction is one of the unfilled cavities (Fig. 212 S), but though little or no blood passes into the ventricle, a positive effect upon the latter is still produced.

Venous Sinus.

As regards the relationship of the auricular reduplication to the time of stimulation, we find the latency of the auricle occasionally varying in length, but usually it has very nearly equal values, except when the shock, falling during ventricular relaxation, calls forth a simultaneous auricular and ventricular

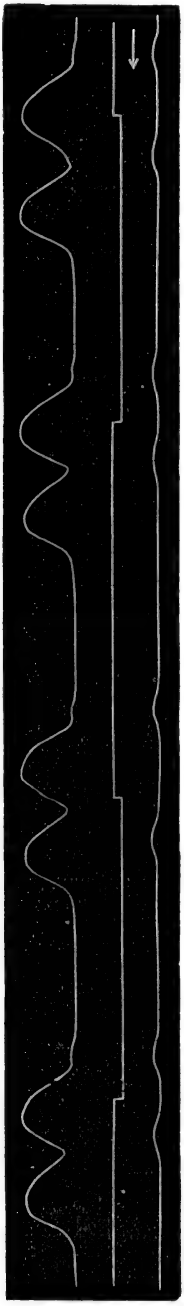


Fig. 213.

T.

Stimulation of Venous Sinus (maximal).

contraction, and in this case latency is reduced. It is to be noted that this induced auricular contraction does not cause another induced ventricular systole: its further effects seem to be lost or dissipated.

At two points in chart T (Fig. 213), ventricular systole being advanced half-way and 0·6 of the way to its maximum, the auricular latency is equal, and when at the end of ventricular relaxation the auricle contracts at the same time as the ventricle, the latency is still about the same. The time lost, therefore, in this case is in ventricular reduplication: either the impulse from the auricle is transmitted at different speeds at different times, or it meets at different times with variation in the excitability of the ventricle. The later in the systole the stimulation falls the less is the resistance to the transmission of the impulse or the greater the excitability of the ventricle.

The whole subject of the rhythmical contraction of the frog's heart and its stimulation and inhibition is a very complex and difficult one. The points upon which our present research seems to us to throw some light are the nature and mode of transmission of the stimuli which one cavity transmits to another in the ordinary process of rhythmical contraction. Marey's researches have shown that in the ventricle itself

there is a time when stimulation applied to it has no apparent action; this time is, however, in many cases of very short duration and limited to the commencement of ventricular systole. At the commencement of ventricular systole stimulation without provoking contraction causes often a positive effect, namely, a greatly prolonged diastolic pause, which we have been inclined to regard as due to omission of a ventricular contraction.

It seemed of interest to ascertain whether a similar condition occurred in the other cavities of the frog's heart. We find that in the auricular stimulation about or shortly after the period of maximum contraction of the auricle may cause inhibition of the next auricular beat.

We have not yet succeeded in registering the contractions of the venous sinus with sufficient accuracy to enable us positively to determine the occurrence of a similar refractory period in the venous sinus itself, but the results we have obtained lead us to hope that we shall soon be able to do so.

Another interesting consideration is, whether the stimulus which each cavity of the heart transmits to the succeeding one, consists in the propagation of an actual muscular wave, or in the propagation of an impulse along the nerves. The observations of Gaskell have given very great importance to the muscular wave occurring in each cavity of the heart of cold-blooded animals as a stimulus to the contraction of the next succeeding cavity. Our observations appear to us to show that while this is an important factor, it is not the only one in the transmission of stimuli. We have observed that stimulation of the auricle rarely or never causes contraction of the ventricle unless the auricle also contracts. When stimulation of the auricle causes both itself and the ventricle to contract, the auricular contraction precedes the ventricular one in such a way that we might be justified in regarding the ventricular contraction as due to the propagation of the contractile wave from the auricle to the ventricle. It would also appear that a contractile wave may be propagated backwards, for on stimulation of the ventricle we have observed the contraction of the ventricle produced by stimulation has been succeeded by an auricular contraction such as might be supposed to be due

to propagation of the contractile wave back from the ventricle to the auricle. While these observations appear to show that the propagation of the contractile wave from one cavity of the heart to another is of importance in keeping up the rhythmical sequence, we consider that stimuli are also propagated from one chamber of the heart to another through nervous channels:—thus we find that irritation of the venous sinus will sometimes produce simultaneous contractions of the auricle and ventricle instead of the ventricular beat succeeding the auricular in the usual way. This we think is hardly consistent with the hypothesis that a stimulus consists of the propagation of a muscular wave only from the auricle to the ventricle.

As additional evidence we may notice the occurrence of an auricular beat followed by absence or inhibition of a ventricular beat as the result of stimulation of the auricle, or venous sinus. Moreover, we have noticed in the heated heart the occurrence of groups of regular beats in the ventricle in consequence of a single stimulation applied to it, while the auricle has continued to beat with its ordinary unaltered rhythm undisturbed by the ventricular excitement.

It is not however our purpose to do more in this paper than state the results we have hitherto obtained, and we shall therefore reserve for a future communication the consideration of this and some other questions of importance closely allied to it.

Another question is the nature of the inhibitory influence exerted by one cavity of the heart upon another. Marey had shown that stimulation of the ventricle during a great part of the refractory period exercises an inhibitory instead of a motor action upon the ventricle itself. It might be supposed then that a stimulus of either kind, whether proceeding from the auricle in the form of a contractile wave, or a nervous impulse, might produce inhibition of the ventricle, provided the stimulus reached it during that part of the refractory period in which stimulation usually causes inhibition. From our observations it seems that the inhibition of the ventricle which may follow stimulation of the auricle is not due to the muscular wave propagated from the auricle and striking the ventricle during the

refractory period. In Fig. 172, p. 585, we notice that the auricular contraction succeeded by ventricular inhibition occurs after the refractory period of the ventricle has passed; we must, therefore, look upon the inhibition as due to the propagation of a nervous impulse from one cavity to another. In the auricle we find that stimulation may produce inhibition of the auricular and ventricular beats, or of the ventricular beats alone. We may, therefore, suppose that the stimulus applied to the auricle acts upon two different nervous mechanisms; seeing that it is enabled to inhibit the ventricular beats without affecting the auricular ones, we are unable to say precisely what the effect of a single stimulus applied to the venous sinus is upon the sinus itself, but here we note that the same result will follow stimulation of the sinus, as of the auricle, viz., inhibition of the ventricular without inhibition of the auricular beat, or inhibition of both together.

As has been already pointed out by Professor Marey, the refractory period is increased when the heart is artificially cooled. We have also found that there is a prolongation of the time during which stimulation causes an inhibition or omission of the following systole.

It is very seldom that stimulation of the auricles or of the venous sinus causes a ventricular contraction without auricular systole preceding it in the ordinary rhythm. In this respect the action of the heart offers a contrast to the normal. Though the muscular wave started in the auricle is usually succeeded by a ventricular contraction, it may occasionally be succeeded by a ventricular inhibition, or auricular stimulation may be followed by inhibition of both auricle and ventricle.

The propagation of the wave in an upward direction, viz., from ventricle to auricle, is not so regular as in the normal heart, the time elapsing, when it does occur between the ventricular and auricular systole, bearing a relationship to the degree of cold produced. Whilst the ventricle is reduplicating in response to direct stimulation, the auricle may maintain its regular rhythm. Stimulation of the venous sinus almost invariably gives an auricular contraction at all times preceding the ventricular. It has been already shown that in the case of

the normal heart stimulation in advanced diastole frequently causes a spontaneous auricular and ventricular contraction, or a ventricular beat preceding the auricular.

In the heated heart we have noticed, in addition to the excessive diminution or abolition of the refractory period in the ventricle already observed by Marey, that usually the refractory period in the auricle entirely disappears. A single stimulation of the ventricle sometimes gives rise to a series of contractions with incomplete relaxation intervening. After this has occurred, or after a simple reduplication has been caused, it often happens that the auricular beat occurring in normal sequence is not followed by ventricular, which seems to show a temporary state of exhaustion of the ventricle. In the heated heart the duration of a systole is so short that two beats immediately succeeding one another may be perfectly distinct, while, in the normal heart, the second one would have fallen within the time of the systole of the first, so that it could only have appeared, if it were possible at all, as an increase either of the height or length of the first systole. Inhibition occurs in the heated heart as well as in the normal, which is most frequently observed upon stimulation of the venous sinus, and it is frequently at this time associated with a reduplicated auricular contraction. The effect of strychnia is to prolong the refractory period of the ventricle. Stimulation of the ventricle is frequently succeeded by contraction of the auricle. There is an increased tendency for stimulation of the ventricle to induce a beat of the auricle preceding the ventricular systole. There is less tendency for the stimulation of the venous sinus or auricle to induce a beat of the ventricle succeeded by one of the auricle; and, indeed, this only occurs when the stimulus falls just at the end of the ventricular systole, *i.e.*, when the ventricle itself is most sensitive. These facts seem to indicate that the nervous channels are more active in transmitting stimuli, both downwards from the venous sinus to the auricle and ventricle, and from the ventricle back to the auricle.

In its effect upon the refractory period, and in the tendency it produces to maintain the regular rhythm, the action of strychnia agrees with that of cold, as shown in the present series of

experiments; but, as we have already shown in a former paper,* its effect in causing the ventricle when arrested by a ligature applied around the junction of the venous sinus with the auricles to recommence pulsation resembles that of heat.

There are many other points on which we think that a fuller consideration of our experiments will throw light, but to take them up at present would involve too lengthy a discussion of doubtful points in the physiology of the frog's heart, and so we must reserve them for a future time.

* *St. Bartholomew's Hosp. Reports*, vol. xvi, p. 229.

THE VALVULAR ACTION OF THE LARYNX.

In conjunction with THEODORE CASH, M.D.

(Reprinted from the *Journal of Anatomy and Physiology*, vol. xvii, 1882–1883.)

CLOSURE of the glottis plays a most important part in all expulsive acts, such as coughing, sneezing, vomiting, or defæcation or in those muscular actions where it is necessary to have the thorax fixed, in order to enable the muscles attached to it to act with greater advantage or greater precision. On looking at the human larynx, it not unfrequently happens that the mere act of introducing the mirror into the fauces excites movements of retching. The appearance which the larynx then presents, is that of a somewhat circular or slightly elliptical opening completely filled by three bulging segments, strongly reminding one of the appearance of the aortic valves, as seen from below in an injected aorta. On consulting several text-books on physiology we find that the mode of closure of the glottis is treated in a very cursory way. In the wonderfully complete physiology of Haller we can find no definite information, nor is there any in Todd's *Cyclopædia of Anatomy and Physiology*. In Müller's *Physiology*, translated by Dr. Baly, 2nd edition,* we find the statement that in holding the breath the air tubes are cut off from the mouth and nostrils by approximating the posterior palatine arches, and pressing the root of the tongue against the palate. In Carpenter's *Physiology*, 9th edition, and in Foster's *Physiology*, 3rd edition, we have also failed to find a definite account of the mechanism of the closure of the glottis. In Czermak's *Treatise on the Laryngoscope*,† he states that during closure of the glottis he has observed that—

"(1) The arytenoid cartilages intimately meet at their internal surfaces and processes, and they bring the edges of the vocal cords in contact; (2) the superior vocal cords approach

* Vol. i, p. 360.

† New Sydenham Society publications, vol. xi, 1861.

the inferior vocal cords, so as to obliterate the ventricles of Morgagni, at the same time they also meet in the median line; (3) the epiglottis being lowered, and its cushion becoming more prominent still, it presses against the closed glottis; the contact takes place from before backwards. These three-fold occurrences in the hermetic closure of the larynx explain the resistance which the glottis successfully opposes to the pressure of the air, without a development of much force during the effort."

Czermak also gives an accurate picture of the appearance of the glottis when completely closed during effort, though a still better one is given by Grützner in Hermann's *Handb. ch der Phys.* (Band 1, Theil 2, page 59). In Grützner's picture (Fig. 214)

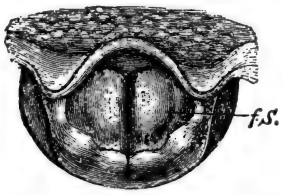


FIG. 214.—Glottis closed by the approximation of the false vocal cords (*f. s.*) after Grützner.

the rounded and bulging nature of the protuberances formed by the false vocal cords is very evident, and suggestive of inflation from below. Grützner, however, only remarks that the false vocal cords, or ventricular bands, are often approximated, and the cushion of the epiglottis depressed upon them, whereby a very firm closure is produced. In an inaugural thesis presented to the Edinburgh University by Dr. Wyllie in 1865, the author discussed the mode of closure of the glottis very fully, and illustrated it by very numerous experiments. These showed very clearly, indeed, what an important part is played in the closure of the glottis during expiration by the false vocal cords, and that, indeed, it is chiefly if not entire y through them that the closure is usually accomplished. These experiments were published in the *Edinburgh Medical Journal*, September, 1866, but as they are not referred to in many standard text-books,* it

* We must except Turner's *Introduction to Human Anatomy*, in which these experiments are referred to.

would appear that they have not received the attention they deserve. Wyllie points out that Czermak was probably deceived in regard to the second factor in the closure of the glottis.

Czermak thought that the superior vocal cords approach the inferior, so as to obliterate the ventricles of Morgagni, at the same time that they also meet in the median line.

As Wyllie points out, and as reference to the accompanying Fig. 215 will show, it is impossible to say anything with certainty regarding the condition of the entrance to the ventricles of

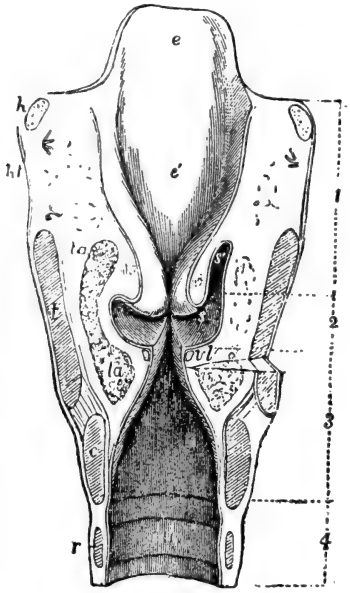


FIG. 215.—Anterior half of a transverse vertical section through the larynx near its middle. (From Allen Thomson in *Quain's Anatomy*.) 1, Upper division of the laryngeal cavity; 2, central portion; 3, lower division continued into 4, part of the trachea; *e*, the free part of the epiglottis; *e'*, its cushion; *h*, the divided great cornua of the hyoid bone; *ht*, thyro-hyoid membrane; *t*, cut surface of the divided thyroid cartilage; *c*, that of the cricoid cartilage; *r*, first ring of the trachea; *ta*, thyro-arytenoid muscle; *vl*, thyro-arytenoid ligament in the true vocal cord covered by mucous membrane at the rima glottidis; *s*, the ventricle, above this the superior or false cords; *s'* the sacculus or pouch opened on the right side.

Morgagni when the glottis is closed, inasmuch as these are simply oblong orifices in the lateral walls of the larynx, and the false vocal cords completely hide them from view when they are approximated. Wyllie points out that an anatomical misconception prevails regarding the nature of the vocal cords, many considering them as the free edges of membranes which are flattened above and below. They are, however, really wedge-shaped projections from the sides of the larynx, the apex of the wedge being directed downwards and attached to the laryngeal wall, its upper flat surface forming the floor of the ventricle of Morgagni, and its projecting edge forming the true vocal cord.

Their shape is as badly adapted as we can possibly imagine for retaining air in the thorax, though very well adapted for preventing air from entering it. Wyllie's experiments showed that by no adjustment could the true vocal cords completely prevent the exit of air, but that when they were simply approximated, not even being pressed together, they completely prevented its entrance. With the false vocal cords the case was just the reverse; they present no obstacle whatever to the entrance of air, but when they are approximated they completely obstruct its exit from the lungs, and the air getting behind them into the ventricles of Morgagni, inflates them, and thus the greater the pressure behind them is, the more perfect is their apposition.

Our own investigations completely confirm those of Dr. Wyllie. He extends his experiments to the production of voice, we have restricted ourselves to the simple mechanism of the closure of the larynx during effort; but instead of confining our observations to the human larynx, we have made comparative observations on the larynges of some animals.

Before entering into those in detail, it may be advisable to say a few words regarding the comparative anatomy of the larynx.

A good anatomical classification of laryngeal variations is the following, proposed by Milne-Edwards*:—

* Milne-Edwards, *Leçons sur la Physiologie et l'anatomie comparée de l'homme et des Animaux.*

I. The aglottic type, in which the laryngeal cavity is not separated into two spaces by well-marked vocal cords.

II. The simple glottic type, in which there are well-marked vocal cords, but in which no false cords nor ventricles are present.

III. The composite type, in which the upper or anterior portion of the larynx is furnished with a second pair of cords—commonly termed false or superior cords—and which are separated from the true cords by a distinct ventricle.

IV. The cavernous type, in which the cavity of the larynx is in communication with a sinus possessing accessory pouches, of which the mouths are situated in the ventricles of the larynx, or in other parts of this organ.

In following this classification, the animals whose larynges determine their serial position will be mentioned indiscriminately, and peculiarities of the glottis briefly expressed, whilst reference to the author who is responsible for the statement will be made in a footnote.

Class I.—In the *pisciform mammals*, where the larynx has *not* the function of a vocal instrument, but only that of insuring continuity of respiratory work during deglutition, and maintaining free communication between the trachea and nasal cavities. This form of organisation is found in the Cetaceans.

The Dugong has no ventricle.

In the Dolphin* the glottis opens into the posterior nares, and has a pyramidal form. It is patent only at its summit, and leaves at either side a passage for food. The pyramidal elevation is formed by the arytenoids and the epiglottis. Probably in these, and in the Cetaceans generally, there is *no* voice, as no true means for its production are present.

Marsupialia.—In the Kangaroo† there is no false cord, no ventricle, and only the faintest indication of true cords. The arytenoids are capable of considerable elevation, and permit the passage of air through a large gap between their inner surfaces.

The Kangaroo has a cavernous sinus.

It is probable that the Kangaroo is mute.

The fœtal Hippopotamus has no cords but a simple longi-

* Cuvier, p. 797. † Milne-Edwards, p. 442.

tudinal elevation, formed by the anterior extremity of the arytenoid*.

Class II is a very large one, and embraces mammals from very widely differing orders.

The Hedgehog† belongs also to this class.

In the Elephant‡ the arytenoids do not touch by their inner surfaces, and the true cords are placed obliquely. The false cords are indicated in position by a faint projection of the mucous membrane, and the ventricles are only formed by an excavation of the upper surfaces of the true cords. At the anterior commissure there is a transverse fold.

In the Ruminants§ the arytenoids have, besides their articular facette, a superior angle which is curved forwards, and an inferior to which the vocal cords are attached.

The *inferior* margin of these cords is obtuse and continuous with the rest of the internal lining membrane, the *superior* margin is more or less free and trenchant—it is much more so in the Deer than in the Gazelles, and it is very indistinct in the case of the Cow and Sheep. The internal fauces of the arytenoids touch, and air could only pass between the anterior margins and the epiglottis. This passage is more or less narrow according to the species. There is no superior ligament and no ventricle properly so called, neither does any cuneiform cartilage exist.

Sometimes, as in the *Antilope gutturosa*,‖ the thyroid is bulged outwards in the neighbourhood of the attachments of the vocal cords.

In Hares and Rabbits (*Lepus timidus* et *cuniculus*) there is an intermediary form, as the false cords are wanting, but the ventricle exists. In the *Lepus timidus*, however, Wolff denies the existence of a ventricle.¶

In the Rein-Deer** there is a large subepiglottal sac, but this is not found in the Deer.

The Sloth (*Bradypus tridactylus*) has a peculiar form of vocal

* Cuvier, p. 791.
† Milne-Edwards, p. 442.
‡ *Op. cit.*, p. 442.
§ Cuvier, p. 795.
‖ Cuvier, p. 795.
¶ Wolff, *Dissertatio Anatomica*, p. 19.
** Milne-Edwards, p. 442.

cord. The true cord recurves at its free margin in such a manner that with its fellow it could exert a valvular action which would seem to be sufficient to prevent the exit of air, and in the expiratory movement it vibrates with the impulse of the passing air. Cuvier* has shown that there is neither ventricle nor false cord to be found in the glottis of the *Bradypus*.

Class III.—Man and the greater part of Ungulate mammals are to be referred to this class, though others have the cavernous glottis which is embraced in the fourth and final division.

Here the vocal cords are not only well developed and possess a free border more or less fine, while each is capable of advancing to meet its fellow of the opposite side in the median line, but there exists above the true cords a second pair of analogous folds, less adapted to phonation, and between these projections one recognises a fossa, bilocular but not communicating with a sac or cavern. This structure is found in the Carnivora for the greater part, but this group has many variations amongst its members. In the Dog† (*Canis domesticus*) the larynx is very large. The true cords are well developed and broad. They are capable of being bulged to a considerable extent when air distends the ventricles, which are very deep, and ascend a considerable distance along the inner surface of the thyroid. The false cords are neither strong nor prominent. Wolff‡ testifies to the strength of the cords of this animal, and mentions that the ventricle is deeper at its extremities than in its middle part. *Canis lupus.*§—The ventricles of Morgagni are large and deep. In the different species of the Genus *Felis* the false cords are very prominent and well detached from the walls of the larynx. They are attached directly to the arytenoids, and at their point of juncture, under the epiglottis, they form a small vault-like attachment. In the Lion‖ the true cords are neither so free nor their borders so trenchant as in the Dog; they are, in fact, thick, and but slightly prominent. The superior part of the larynx is dilated. There is no

* *Ibid.*, p. 790.
† Milne-Edwards, p. 445.
‡ Wolff, *Dissertatio Anatomica*, p. 10.
§ *Op. cit.*, p. 10.
‖ Milne-Edwards, p. 445.

ventricle according to Wolff.* In the Cat (*Felis catus*) the larynx is small, and guarded by a long upper and pointed epiglottis. Anteriorly, the false cords are widely separated; they are in structure very fine, instead of being thick as in the Lion; the true cords touch at their anterior extremities. There are no cartilages of Santorini.†

In the Tiger the arytenoids are much raised.

In the Hyæna‡ (*Hyæna striata*) the superior ligaments are scarcely visible, and there is but a faintly-marked ventricle.

Plantigrada.—In the Bear§ both pairs of cords are so arranged as to raise themselves nearly to the same level by their free edges, and to direct towards the epiglottis the slit which forms the entrance to the ventricles.

Cuvier‖ says:—The posterior ligaments or true cords, which are thick but very distinct, and which are attached to the arytenoids, rise between the two anterior ligaments, which are attached to the cuneiforms in such a manner that the four ligaments are upon the same level, and that the ventricles of the glottis are simply two deep slits, open no longer towards the laryngeal cavity but facing the epiglottis. They bend inwards very little between the epiglottis and the thyroid. The ligaments—or rather the external anterior—are little separated from the epiglottis.

Wolff¶ also adopts the terms external and internal for the ligaments of the larynx as being topographically correct. He mentions that, whilst the external are inserted into the cuneiform cartilages, the internal are attached to the arytenoids. All four are inserted into the root of the epiglottis. (His examination was made upon a specimen of *Ursus arctos*).

The ventricle of the *Ursus meles* he found large and very deep.

The *Erinaceus Europæus*** has only small superior cords, though the ventricles are deep and sacculated.

* *Dissertatio Anatomica*, p. 9.
† Wolff, *Dissertatio Anatomica*, p. 8.
‡ *Op. cit.*, p. 9.
§ Milne-Edwards, p. 446.
‖ *Anat. Comp.*, Tom. viii, p. 787.
¶ *Dissertatio Anatomica*, p. 12.
** *Op. cit.*, p. 15.

The Coati* has a somewhat similar arrangement to the Bear, but the Badger† has ligaments of the usual position, the anterior with a sharp margin, the posterior, however, being obtuse. The ventricle is open and leads into a sac. The sound which this animal emits is probably produced by the friction or impaction which the air suffers against the posterior border of the anterior cords and its division into these diverticula.

The Civet‡ has a glottis like that of the Cat.

It results from the structure of the larynx in the genus of the cat tribe, that it is chiefly the anterior ligaments which must perform the functions of vocal cords. Their union towards the epiglottis forming a little vault against which the air must strike with force, favours this view.§

Movements of the false cords only become apparent in great expiration and inspiration. In phonation they do not advance in the manner of a platform above the true cords, but they depress and apply themselves on the basal portion of these so as almost entirely to efface the entry of the ventricle of the larynx, and to limit the vibrations of the true cords to a certain length.‖ As the voice rises, these membranous folds cover progressively from without inwards the vocal cords.¶

Pinnigrada.—The Seal** has an obtuse vocal cord which is but slightly free. The anterior ligament blends with the base of the epiglottis. The ventricle is superficial.

The Marmot has a very sharp margin of the anterior ligament, more so, in fact, than that of the posterior.††

Class IV may be regarded as containing animals which would belong to the third class, had they not some "cavernous" character superadded, and also animals of a less perfect type.

The Llama has false and true cords, a ventricle, and a common larynx, and therefore with the Camel (*Camelus bactrianus*) forms an exception to the usual Ruminant type. (The latter animal has a trachea 3 feet in length, but very narrow; its larynx is small and its voice proportionately weak.)‡‡

* Cuvier, p. 788.
† *Ibid.*
‡ *Ibid.*
§ *Ibid.*, p. 787.
‖ Milne-Edwards, p. 512.
¶ *Ibid.*, p. 525.
** *Ibid.*, p. 788.
†† Cuvier, p. 789.
‡‡ *Dissertatio Anatomica*, p. 23.

In Solipedes* the vocal cords are narrow and situated deeply. There are no false cords, and no ventricle properly speaking, but a hole pierced in the lateral wall above the true cords conducts into a large oblong sinus, hidden between the wall and the thyroid, and covered, to a great extent, by the thyro-arytenoid muscles, which should be able to compress it.

This opening is large in the Horse,† but the cavity is not very deep. There‡ is also in this animal a triangular membrane situated in the angle of the thyroid. This easily vibrates as it rests upon the moving cords beneath it. The commencement of the "hinny" is due to repeated shocks of expired air upon this membrane.

In the Ass§ two sacs are situated above the attachment of the cords. A tendinous membrane is also present. There is a great deepening of the thyroid.

Cuvier‖ considers the larynx of the Mule more allied to that of the mare, and speaks of Herrissant's observations as inaccurate, and as regards the triangular membrane of the horse's and ass's larynx, exaggerated.

The Rhinoceros¶ has well-marked vocal cords and deep ventricles, before each of which is a nearly vertical opening, and it is at the bottom of this excavation that the anterior ligaments are attached.

In the Pig** the true cords are free and sharp. The superior ligament is large and its margin rounded. The ventricle is shallow, and from this opens an oblong sinus which rises up between the mucous membrane and the thyroid, and is the size of the end of the little finger. . . . . (It is to be observed that in many animals of this class, *i.e.*, quick runners,†† the two cartilages are arranged in such a manner as not to coaptate completely, and so allow a space to remain free between them

* Cuvier, p. 793.
† *Ibid.*, p. 793.
‡ Herrissant, *Récherches sur les Organs de la Voix*, p. 282.
§ *Op. cit.*, p. 285.
‖ Cuvier, p. 793.
¶ *Op. cit.*, p. 791.
** *Op. cit.*, p. 791.
†† Milne-Edwards, p. 455.

when they are touching by their summits. It results from this, that by the approximation of the true cords the glottis is not closed, and that there remains always a passage for the air behind the membranous part. Mr. Mandl thinks that this is peculiar to the species which run rapidly.)

In the Howling Ape* (*Mycetes*) the hyoid is enormously developed in the form of a bell to lodge the air sacs peculiar to this animal. There are also air sacs in the pharynx.

In *Simia sabœa*† at the root of the epiglottis, and above the ligaments, there is a transverse opening which leads to a membranous sac situated between the thyroid cartilage and the hyoid bone. In the walls of the sac the fibres are partly tendinous and partly muscular.

In *Simia parnisco*‡ there is a sac between the cricoid and trachea. The trachea has continuous rings in some Simians.

If the view that the function of the false cords or ventricular bands is to close the glottis during effort, and thus to fix the thorax, we should expect them to be very strongly developed in those animals whose habits render such fixation likely to be serviceable; on the other hand, we should expect them to be absent in those animals where fixation of the thorax would be of little or no service; and this seems to be actually the case.

In animals whose motions are chiefly those of running, we find the ventricular bands absent, or slightly developed. But in animals where the anterior extremities are used for striking, hugging, or climbing, the vocal cords are strongly developed. We might at first expect also, that in cases where the anterior extremities were employed for the purpose of prehension, we would also find the ventricular bands developed. But this is not always the case.

When engaged in any very delicate work where the least oscillation of the hand might be injurious, we often hold our breath, but for ordinary prehensile actions we do not close the glottis, unless considerable effort is required at the same time. In marsupials such as the kangaroo, the anterior extremities

* *Op. cit.*, p. 448. † *Ibid.*, p. 1.

‡ Wolff, p. 1.

are used for holding food and conveying it to the mouth. We might therefore expect that the false vocal cords would be strongly developed. But the fore limbs are small and weak, and very slight muscular effort is employed in the movements just mentioned. The fact that in these animals the ventricular bands are absent, is, therefore, very much what might have been expected. In the solipedes they are also absent. In the pig they are rounded; and there is a shallow ventricle in the hedgehog. They are present, but small, in the llama, and in the camel they are fairly well marked. In the dog the true cords are well developed and broad; the ventricular bands are not strong or prominent, but the ventricle of Morgagni is deep. In the wolf the ventricle is also deep and large. In the lion and tiger the ventricular bands are prominent and well detached from the walls of the larynx. In the cat they are not large; and they are very fine instead of being thick as in the lion. In the three-toed sloth they are well developed. In the bear, in which the closure of the glottis would require to be specially strong, from its habit of climbing trees and destroying its enemies by hugging, the arrangement of the ventricular bands is very remarkable; the vocal cords are capable of being raised until they and the ventricular bands are nearly at the same level, and the opening between them is directed towards the epiglottis from which the false cords are but little separated. During the closure of the glottis the cushion of the epiglottis will, therefore, to a considerable extent, be directed against the opening of the ventricles, and the glottis will, we should think, be closed with very great firmness.

We have, however, not seen any specimen of the larynx of the bear, and these considerations are drawn only from the description which we have read.

In the howling monkey the ventricular bands are well developed.

Our own experiments were made upon the fresh larynx of the sheep, of the dog, of the cat, of the ape, and of man.

The experiments were made by fixing a T-cannula in the trachea below the larynx. The lower arm was connected with a bellows, and the side branch with a water or mercurial

manometer; the arytenoid cartilages and the vocal cords were then approximated, as well as the ventricular bands when these were present. The strength of current which these structures could resist in various positions, and during inspiration and expiration, was estimated by the height at which the water or mercury stood in the manometer. A curved needle was passed through the bases of the arytenoids which were then coaptated by means of a figure-of-eight ligature. In some experiments in which the larynx possessed cords of such dimensions as to admit of it, needles were passed through the thyroid cartilage, one on either side of the middle line, and just external to the anterior attachment of the false cords, and the points were pushed backwards inside the edge of the false cord towards the arytenoid cartilage. In this way, approximation of the cords could be easily produced by movement (separation) of the eye end of the needle. In smaller larynges, however, approximation was assisted by seizing the coaptated edges of the cords with a pair of fine pointed curved forceps. Lateral pressure was exercised by means of a weighted scale pan which was connected with a movable concave surface of wood placed externally over the line of attachment of the cord to the wall of the larynx.

This was aided or substituted by manual pressure, and manipulation was also resorted to in pushing the base of the tongue with the epiglottis backwards over the larynx.

In the sheep the ventricular bands are absent. The following figures represent the result of these experiments:—

	Resistance.	
	In millimetres of mercury.	In inches of water.
Experiment 1	4	2
„ 2	5	2·5
„ 3	8	4·25
Average about	5·5	3

On blowing upwards through the glottis, the true vocal cords being closed (no false cords).

On sucking air downwards through the glottis, the resistance

rose to heights varying from 54 to 140 mm. of mercury, or from about 28 to 72½ inches of water.

In the cat the resistance to the exit of air from the larynx presented by the true vocal cords alone is very small, generally about 6 mm. of mercury.

When their approximation is aided by a lateral pressure of 100 grammes, a resistance of 16 mm. of mercury may be reached.

The ventricular bands in the cat are thin and easily coaptated, but they are not calculated to resist much pressure unless they are supported: such support is afforded by the epiglottis, if it is slightly pressed backwards, and the gentle lateral pressure is made so as to coaptate the cords.

If firm pressure is applied in this way the resistance presented to the exit of air by the ventricular bands is very considerable, and they may not yield even under pressure of from 24 to 40 mm. of mercury. To reach the latter figure, however, considerable support from the base of the epiglottis and from the lateral aspects of the larynx is required. When the true cords are approximated, as well as the ventricular bands in the cat, the epiglottis being at the same time slightly depressed and gentle lateral pressure exerted, they easily resist a pressure of 30 mm. of mercury, or more.

The resistance to the ingress of air afforded by the true cords alone, in the cat is very considerable; when a lateral pressure of 20 grammes is exerted so as to bring them together they easily resist a suction power of 50 or 60 mm. of mercury, and when the lateral pressure is increased they will resist considerably greater suction than this.

The ventricular bands when ordinarily approximated will not resist more than 2 or 3 mm. of mercury.

In such experiments as these there is not a little difficulty in approximating the vocal cords so as to imitate their closure during life. The lateral pressure exerted, the position of the epiglottis in regard to the cords, the freshness of the larynx. and many other circumstances modify the results obtained to a very considerable extent. By way of example we may mention that in eight measurements of the resistance offered by the

approximation of true and false cords in the cat, at the same time, variations from 30 to 60 mm. were registered. The former figure is, however, the more exact, though, if there be a slight increase of lateral pressure, and the epiglottis be pushed gently backwards over the glottis, a pressure of 40 and 60 mm. may be obtained.

The following figures in mm. of mercury may be taken as representative of the results:—

Blowing.			Suction.		
True and False	True alone.	False alone.	True and False.	True alone.	False alone.
30–50	4–10	24–40	60–120	60–120	2–10

It appears from these figures that closure of the superior cords did not increase the powerful resistance afforded by the inferior to the ingress of air as represented by suction. A quick, powerful suction (*i.e.*, inspiration) movement closes the true cords, but this does not affect the false cords in the same manner, nor does the negative pressure in the trachea extend to them. The larynx again tends to pass downwards, and the "telescoping" due on the one hand to the elevation of the larynx, and on the other to the pressing backwards of the root of the tongue and of the epiglottis with its supporting pad, which occurs in efforts to vomit, is here entirely absent.

We could, however, imagine that the ventricle becoming distended in expiration after narrowing of the larynx by muscular action and approximation of the false cords, the inferior might themselves be closed by the pressure from above, and that thus a slight measure of support might be afforded.

The false cords in the dog are inconspicuous and weak in comparison with the broad well-developed true cords.

They offer almost no resistance to the ingress of air: 4 mm. of mercury being the utmost, and this amount is only reached when sticky mucus on the bands adds to the resistance.

The true cords, either alone or with the false cords, resist the ingress of air with a force of 80 to 180 mm. of mercury.

The true cords alone offer a resistance of only about 9 mm. to the exit of air.

The ventricular bands alone offer 18·5 mm., and this may be increased to 60 mm. if the glosso-epiglottidean sulcus be thoroughly distended; and the true and false together, 21 mm.

The relatively high pressure of the true and false cords together was accompanied by a bulging upwards of the glosso-epiglottidean sulcus. It is possible that the inflation of the ventricle tends also to push the true cords together, and that thus they aid, to a slight extent, in closing the glottis during expiration.

The larynges examined were those of small dogs.

In the ape, when the ventricular bands alone are approximated, inflation of the ventricles is well marked at the bases of the bands. It is distinctly seen in this animal that powerful expulsion of air, and especially sudden expulsion, tends to close the ventricular bands, and this strongly confirms the views already expressed in regard to the function of these structures.

A sudden inspiratory effort when both true and false cords, or when the true cords alone, are approximated, is seen to cause the lateral fossæ to sink considerably downwards, and the resistance to the ingress of air which they afford is very great: being equal to 75 mm. of mercury and more.

When the ventricular bands alone are approximated, their power of resistance is very small, unless they are firmly coaptated, when they present considerable resistance to the ingress of air. But it is very improbable that in the living larynx they can be pressed together in this way; and their functions, therefore, are evidently very different from that of the true cords, in which the simple occurrence of a rapid inspiratory movement, when the true cords are approximated, effectually closes the glottis.

Old World Ape (Small Specimen).

Pressure.			Suction.		
True closed and False.	True closed.	False closed.	True closed and False.	True closed.	False closed.
30 mm.	2–5 m.	24 m.	70–140	70–140	2–4

Only two specimens of the human larynx were examined.

The ventricular bands alone afforded a resistance of 30·0 mm. when gentle lateral pressure was employed. Whilst blowing air from below, a slight telescoping, by pressing the base of the tongue and the epiglottis backwards, being permitted, a bulging upwards of the hyoid fossa and the root of the ventricle underneath the attachment of the ventricular bands could be distinctly seen. When firm lateral pressure was associated with this movement a much higher pressure was resisted. The ventricular bands alone, when not forcibly held together, presented no resistance whatever to inspiration—in fact, they separated even when the true cords were in contact, and resisting a powerful suction.

The true cords alone resist the ingress of air quite as much as when the ventricular bands also are approximated. The resistance is very great, and sometimes reaches 140 mm. of mercury, and even more—in fact, suction of greater power than we could employ failed to separate them, but rather tended to increase their resistance.

Closure of the glottis is so important a factor in the act of vomiting, that we must now consider how far the development of the false vocal cords in different classes of animals is associated with the easy and perfect performance of the act.

We find that in *Ruminants* generally true vomiting is either difficult or impossible. The same is the case with the *Solipedes* and the *Rodentia*, while in the cat and dog it is performed most effectually. There is no doubt, in the act of vomiting, another factor than that of simple increase in intra-thoracic, or, more accurately, intra-tracheal pressure, for however greatly this pressure be increased, as in coughing, defæcation, or parturition, vomiting does not occur unless the cardiac extremity of the œsophagus be dilated. One explanation of the difficulty with which vomiting occurs in horses, for example, is that the œsophagus passes a considerable way below the pillars of the diaphragm, and that thus the fibres which radiate from it on to the stomach tend to exert rather a longitudinal than a lateral action, and to pull the œsophagus down, or the stomach up, rather than to dilate the orifice. This explanation may, to a considerable extent, be correct, but we think that the other

factor, viz., the want of true vocal cords, and the consequent difficulty of greatly increasing the intra-thoracic pressure, is also a factor which ought not to be entirely disregarded. We have made some experiments on the intra-thoracic pressure in vomiting; these were performed by narcotizing an animal with ether, passing the arms of a T-shaped cannula upwards and

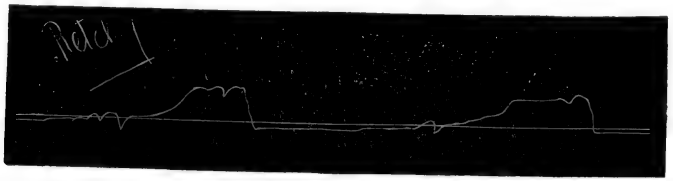


FIG. 216.—CHART A.—Retching movements of cat, showing sustained intra-tracheal pressure of 12·5 mm. mercury.

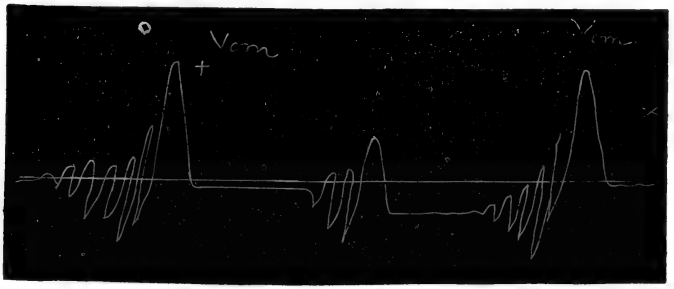


FIG. 217.—CHART B.—Vomiting movements of same, showing resistance to intra-tracheal pressure yielding at *x* to 31 mm. mercury.

downwards into the trachea, the cross-limb of which was connected with a manometer. Sulphate of zinc was then injected into the stomach, and the action of the anæsthetic was diminished to the same point as in surgical operations where vomiting occurs before the return of consciousness. The results will be seen from the portions of the curves which were obtained and which we here append.

The middle curve was merely of retching.

The secondary waves arise from mercurial oscillation.

By the same kind of experiment it was proved that vomiting was still possible when the projecting arm of the T-cannula was unconnected with the manometer, and left open, but in this case vomiting occurred with much greater difficulty than when

the resistance of the mercurial column was brought to bear in closing the trachea, and thus permitting the cords to resist the pressure favourable to this action.

Conclusions.

Our experiments completely confirm those of Dr. Wyllie. The ingress of air into the glottis is prevented by approximation of the true vocal cords, but these have very little power to prevent its egress. The false cords or ventricular bands, on the contrary, have very little power to prevent the ingress of air into the lungs; but when the edges are brought together they act as valves and offer great resistance to the egress of air: they are, therefore, to be regarded as the chief factors in the closure of the glottis during exertion.

Although our data are insufficient to enable us to speak with certainty, so far as they go, they appear to show that, in such animals as do not require to have the thorax fixed, ventricular bands are rudimentary or absent: that in those animals where fixation of the thorax is advantageous for giving greater precision or force to the movements of the anterior limbs in striking, climbing, or hugging, the ventricular bands are well developed. This condition is seen in the cat, lion, sloth, bear, ape, and man.

Though the power of any species of animal to vomit is not entirely dependent on the presence of the false cords, yet, when present, their action in closing the glottis is an important factor in the act of vomiting.

See, for description of larynges referred to, the following authors, from the works of some of whom we have translated largely:—

Milne-Edwards, *Leçons sur la Physiologie et l'Anatomie Comparée de l'Homme et des Animaux*, xii, pp. 422 *et seq.*
Cuvier, *Anatomie Comparée*, viii, pp. 772 *et seq.*
Wolff, *Dissertatio Anatomica de Organo Vocis Mammalium.*
Herrisant, *Récherches sur les Organs de la Voix.*
Cyclopædia of Anat. and Phys., vol. iv, pt. ii., "Voice."
Turner, "*Balænoptera Sibbaldii*," *Trans. Roy. Soc. Ed.*, xxvi.
Watson & Young, "Anatomy of Northern Beluga," *Trans. Roy. Soc. Ed.*, vol. xxix.

APPENDIX.

EXPERIMENTAL INVESTIGATION OF THE ACTION OF MEDICINES.

V.—RESPIRATION.

(Reprinted from the *British Medical Journal*, January 2, 1875.)

[This Lecture ought to have followed on at the end of Lecture IV on p. 322, but it was accidentally omitted and the omission was not discovered until the whole of this book had been printed off, and it was consequently impossible to insert the Lecture in its proper place.]

Respiration in Unicellular Organisms; in the Cells composing higher Organisms. —Distinction between Respiration in an Amœba and a Fixed Cell.—Internal Respiration.—External Respiration.—Internal Respiration may be diminished or arrested by Diminution or Arrest of the Circulation generally or locally.—Pathology of Fatty Degeneration, by lessening or destroying the power of Hæmoglobin to act as an Oxygen-carrier. (*a*) Action of Carbonic Oxide; (*b*) Action of Nitrites; Action of Phosphorus.—Examination of the effect of Drugs on Hæmoglobin.—Colour.—Spectrum—Reducing Agents. —Absorption of Oxygen.—Action of Carbonic Oxide.—Ozonising Power of Blood.—Formation of Acid in Blood.—External Respiration.—Respiratory Movements.—Respiratory Nervous Centre; Excitants to this Centre.—Venosity of Blood.—Dyspnœa.—Apnœa: two opposite meanings of this term.—Effect of temperature on this Centre.—Effect of Drugs: Tartar Emetic, Chloral, Opium.

THERE is a great deal of truth in the oft-repeated comparison between an animal body and a steam-engine. In both, the motion which is their characteristic function is kept up by combustion, and for combustion there is necessary a free supply of fuel and a free supply of oxygen. Simple organisms, such as the amœba, which consists of a single cell or minute mass of protoplasm only, derive their oxygen, as well as their nutriment, from the fluid in which they swim, and the individual cells which compose the tissues of the higher animals are nourished in much the same way. As Bernard strikingly puts it, "we do not live in air" any more than a number of amœbæ swimming about in a glass of water live

in air. The cells of which our bodies are composed live, like the amœbæ, in a fluid—the intercellular fluid or lymph in which they are bathed; and our skin may be compared to the glass in which the amœbæ and the water in which they swim are contained. There is, however, a very great difference between the amœba and the cells composing the bodies of the higher animals, for it can swim about freely, whereas they are for the most part fixed. The amœba can thus obtain fresh supplies of nutriment and oxygen by moving through the water in which it lives, while in higher organisms the fluid moves over the cells. This fluid, or lymph, is the liquor sanguinis, which passes out of the capillaries and supplies all the tissues with nutriment and oxygen, at the same time that it removes from the system carbonic acid and the products of tissue-waste.

The interchange of oxygen and carbonic acid between the tissues and the blood is termed *internal respiration.*

But this interchange would soon remove all the oxygen from the blood and load it with carbonic acid, unless it had some means of absorbing oxygen and giving off carbonic acid to the atmosphere. This is effected in the lungs, and the interchange of gases between the blood and external air is termed *external respiration.*

The blood, therefore, acts as an oxygen-carrier between the lungs and the tissues. A certain amount of the oxygen taken up by the blood is simply dissolved in it; but the amount of this is not sufficient to supply the wants of the tissues, and the greater part of the oxygen which they require is carried to them by means of the hæmoglobin, or colouring matter of the blood. This substance forms a loose compound with oxygen in the lungs, and gives it off to the tissues when it reaches the capillaries, and on again passing through the lungs it takes up a fresh supply. The carbonic acid which is formed in the tissues by their oxidation is taken up by the blood in the capillaries and given off in the lungs; but it seems to be carried from the tissues to the lungs, not by the hæmoglobin, but by some one or other of the salts in the blood. Both internal and external respiration are essential for the

maintenance of life, and it may be destroyed by putting a stop to either one or other of them.

1. Internal respiration may be completely stopped by preventing supplies of fresh blood from reaching the tissues. The stoppage may be general or local. General stoppage of internal respiration is produced by arresting the circulation in the whole body, by stopping the action of the heart, or obstructing the flow of blood through the large vascular trunks which are connected with it. Internal respiration may be arrested locally in any part of the body by compressing or tying either its arteries or veins. Thus, if the arteries going to the head be tied, so that no fresh blood can reach it, or the veins coming from it be ligatured, so that the deoxygenated blood cannot leave it, the blood which is present in the capillaries of the brain loses all its oxygen and becomes charged with carbonic acid. The nervous centres are thus effectually suffocated, although the lungs may be working vigorously, and the blood in the rest of the body may be richly arterialised. That the loss of function which follows stoppage of circulation in a part is due to the want of the oxygen carried to it by the blood, rather than to the want of nutriment, is well shown by the experiment of Kronecker, who found that contractility could be restored to the excised gastrocnemius muscle of a frog, after exhaustion by repeated contractions, by passing through its vessels a solution of permanganate of potash, which supplied oxygen to the interior of the muscle, but conveyed to it no nutrient matter.

When the circulation is diminished but not completely arrested, as, for example, by weakening the heart, or by contracting without obliterating the lumen of the blood-vessels, or when the oxidising power of the blood is impaired, internal respiration will be diminished, but not stopped.

The tissues, or at any rate the albuminous tissues, in all probability do not undergo combustion directly, *i.e.*, the albumen does not combine at once with oxygen. It is first split up by the action of a ferment into (1) nitrogenous substances, which, after being oxidised, form urea, and (2) non-nitrogenous substances, such as fat, and probably also glycogen. When

internal respiration is imperfect, the nitrogenous substances may not be oxidised, and appear in the urine instead of being converted into urea. The non-nitrogenous substances may also continue unoxidised, and, instead of being converted into carbonic acid, remain in the tissues as fat, giving rise to fatty infiltration or fatty degeneration. This is seen in the heart when the size of the coronary arteries is diminished by atheroma. The supply of blood being insufficient to keep up perfect combustion in the muscular fibres, the non-nitrogenous products of decomposition accumulate and cause the heart to become fatty.

When there is little hæmoglobin in the blood, as in anæmia, internal respiration is diminished, and there may frequently be noticed a tendency to the deposit of fat in anæmic girls. The peasantry in some parts of Germany are acquainted with this fact, and bleed their cows so as to induce an artificial anæmia whenever they wish to fatten them.

2. Internal respiration may be arrested by the action of substances which deprive hæmoglobin of its power to take up and give off oxygen easily, and thus render it useless as an oxygen-carrier. *a.* Certain gases—for example, carbonic oxide and nitric oxide—do this by driving out the oxygen from its combination with hæmoglobin, and forming compounds with it themselves. These compounds resemble those with oxygen, but are more stable, and are not decomposed during the passage of the blood through the capillaries, nor by the action of reducing agents added to the blood, as oxyhæmoglobin is. *b.* The oxygen-carrying power of hæmoglobin has been shown by Dr. Arthur Gamgee to be also destroyed by nitrites, but in a different way. Instead of driving out the oxygen from its combination with hæmoglobin, the nitrites combine with the oxyhæmoglobin, and as it were lock up the oxygen in it, so that the oxygen no longer separates from the hæmoglobin when the compound is placed in a vacuum, nor can it be driven out by the action of carbonic oxide. At the same time, the blood which has been acted on by nitrites is deprived of its power of absorbing any more oxygen. But, although the nitrites lock up the oxygen in oxyhæmoglobin so firmly that

it cannot be driven out by carbonic oxide, they do not prevent its removal by reducing agents. These first break up the nitrite compound, and then deoxidise the hæmoglobin; and when this is next exposed to air, it takes up oxygen in the normal way. On this account, the action of nitrites in impeding or arresting internal respiration is only transitory; for, when the blood on which they have acted once becomes deoxidised during its passage through the capillaries, it is restored to its normal condition. The action of carbonic oxide, on the contrary, is permanent, the blood with which it has combined remaining unaltered during its circulation either through the body or the lungs; and, if the greatest part of the hæmoglobin have been acted upon, life can only be saved by the transfusion of fresh blood into the vessels, although, in slighter cases, a fatal issue may be averted by the dilig nt use of artificial respiration. Internal respiration is also diminished by phosphorus; and the fatty degeneration produced by this substance has been shown by Voit and Bauer to be partly due to this action. It is not due to this alone, however, for the phosphorus has a double action: 1. It causes the albuminous tissues to split up more rapidly; 2. It lessens the combustion of the products of decomposition. The increased rapidity of albuminous decomposition causes more urea to appear in the urine; and, if the nitrogenous compounds be not sufficiently oxidised, leucin and tyrosine may appear instead of urea. Fat is also formed from albumen more rapidly, as well as more slowly oxidised, than in the normal condition.

In order to ascertain whether the hæmoglobin of the blood has been altered by the action of a drug: 1. If it be poisonous, examine the blood from the arteries and veins of an animal which has been poisoned by it, and note whether its colour is normal in both sets of vessels or not. 2. Dilute a portion of this blood with water, examine it with the spectroscope, and see what spectrum it presents. Shake it with air, and observe if the bands of oxyhæmoglobin alone are present, and if they are of their normal intensity and in their normal place. Take another portion of the diluted blood and add to it a deoxidis-

ing solution, such as sulphide of ammonium or Stokes's fluid,* and see if the spectrum of reduced hæmoglobin appears. 3. Take two portions of normal blood, or of a solution of hæmoglobin, and add to one of them the drug to be tested, or pass it through, if it be a gas. Note, as before, whether any change is produced in the colour or spectrum, or in its behaviour to oxygen or reducing agents. 4. Take two equal portions of diluted blood or solution of hæmoglobin in small test-tubes, shake them with air till they are thoroughly oxygenated, and add to one of them the drug to be tested. Then add to each an equal quantity of deoxidising solution. Let the test-tubes be full, and cork them so as to exclude the solutions from contact with air. Note the length of time which elapses before the spectrum of oxyhæmoglobin disappears and is replaced by that of reduced hæmoglobin in each. 5. Take two equal portions of normal blood, and act on one of them with the drug. Bring them into contact with equal portions of oxygen or air, and let them remain so for some time. Then ascertain how much oxygen has been absorbed and how much carbonic acid has been evolved by each, by seeing whether any alteration has taken place in the volume of the gas, and by analysing it in order to determine its composition. 6. Act on a portion of normal blood with the drug; arterialise it completely, and then determine the amount of each gas which it contains by extracting them by means of warmth and a vacuum, and analysing the mixture thus obtained. 7. Oxygenate a portion of blood thoroughly, act on it by the drug, and then ascertain whether the oxygen can be driven out by carbonic oxide. To describe the methods of gas-analysis would occupy more space than can be devoted to it here; and I must, therefore, refer to Bunsen's or Frankland's text-books on the subject, or to Sanderson's *Handbook for the Physiological Laboratory;* for an excellent example of the mode of ascertaining the action of a drug on the blood, to Dr. Gamgee's paper on the Action of Nitrites in the

* Stokes's fluid consists of a solution of protosulphate of iron, to which is added a sufficient quantity of tartaric acid to prevent precipitation, and then as much ammonia as will render it decidedly alkaline.

Philosophical Transactions of the Royal Society for 1858, pp. 589–625; and to Dr. Harley's paper on the Action of Alkaloids, etc., in the *Transactions* for 1864, p. 687.

The object of adding the drug to the blood before arterialising, as in 6, and after arterialising, as in 7, is to discover whether it prevents the blood from taking up oxygen in the former experiment, or of giving it off in the latter. Normal blood has the power to produce ozone, or to withdraw it from substances which contain it, and transfer it to others which are easily oxidised. Arterial respiration may be modified, and the process of oxidation diminished, by the action of certain substances which deprive blood of this power. The usual test for ozone is fresh tincture of guaiac (1 part guaiac to 6 of alcohol), which is oxidised by it with extreme rapidity. It shows the progress of the oxidising process with great distinctness by the blue colour which it assumes. A few drops of tincture of guaiac are put upon a piece of porous paper, allowed to become almost quite dry, and a drop of blood or solution of hæmoglobin is then placed on it. In a few minutes, the drop becomes surrounded by a blue ring from the formation of ozone and the oxidation of the guaiac in its neighbourhood. The formation of ozone is independent of the oxygen contained in the hæmoglobin; and carbonic-oxide-hæmoglobin will produce it as well as oxyhæmoglobin, provided air be present. When the hæmoglobin itself contains oxygen in the form of oxyhæmoglobin, the presence of air is not necessary to the reaction. The oxidation of guaiac by means of blood alone is, however, not nearly so easily observed as when another substance containing ozone is added to it, such as peroxide of hydrogen or oil of turpentine which has been kept for some time. The hæmoglobin takes the ozone from these substances, and yields it up again to the guaiac.

The method adopted by Binz, in order to test the influence of drugs on this ozonising power of hæmoglobin, is to take a mixture of tincture of guaiac with a few drops of ozonised oil of turpentine, and divide it into two parts. A few drops of a solution of the drug to be tested is added to one of them, and a few drops of solution of hæmoglobin then dropped into

both. If the drug increase the oxidising power of the hæmoglobin, the solution containing it will become blue more quickly than the other, but more slowly if the oxidising power be diminished.

Another process more simple than that of analysing the gases of the blood has been used by him and his scholars Zuntz and Schultz, in their observations on the effect of drugs on oxidation in the blood. This process is based on the fact, noticed by Zuntz, that, immediately after blood has been drawn from the body, an acid begins to form in it, so that its normal alkalinity goes on decreasing. The formation of acid is most abundant during the first few minutes after the blood has been drawn, and before coagulation has taken place, so that Zuntz considers it a vital phenomenon; but it continues, though in a less degree, till putrefaction commences. They take the rapidity with which acid is formed as an index of the rapidity with which oxidation takes place in the blood; and, when they find that the addition of a drug to the blood has diminished the formation of acid in it, they consider that the drug has diminished oxidation in the same proportion. The following method is the one which they employ:—Three equal portions of the same blood, of fifty cubic *centimetres* each, are measured out. The alkalinity of the first portion is then determined at once. To a second portion, the drug to be tested is added. The solution of the drug must be neutral; or, if it be acid, the amount of its acidity must be determined and allowed for in the final calculations. To the third portion, nothing is added. The second and third portions are then kept for one or two hours at a temperature of about 40° C. They are then allowed to cool, and the alkalinity of both portions is determined. If acid have been formed in either of these portions during this time, the alkalinity will of course be less than that of the first portion, and the amount of acid formed is estimated by the diminution which the alkalinity has undergone. The alkalinity is ascertained by noting what quantity of a standard solution of phosphoric acid must be added to the blood before it begins to give a red colour to blue litmus paper. But, if phosphoric acid were used alone,

the red colouring matter of the blood would be apt to stain the litmus paper, and it would be almost impossible to say when the reddening was due to it, and when to free acid. In order to prevent this, a quantity of chloride of sodium is added to the acid. The salt prevents the corpuscles from being dissolved, and the hæmoglobin from disturbing the reaction. The acid and salt are gradually added to the blood, and the reaction tested from time to time by putting a drop of the blood on a piece of fine satin paper coloured with litmus. The paper should be first moistened with a tolerably strong salt solution, the drop of blood allowed to remain on it for a few seconds, and then wiped off with blotting paper. The point of saturation is held by Schulte, who has also employed this process, to be reached whenever the blue litmus paper becomes distinctly reddened, even though the red colour should disappear again immediately. This transient reddening is due to carbonic acid; and Schulte prefers it to the first permanent reddening, because it can be more easily observed. This does not give the absolute amount of alkalinity; but all that is wanted is the comparative alkalinity of the three portions, and this is got accurately enough if they be all treated in the same manner as regards temperature, shaking, etc. In this way, Zuntz, Scharrenbreich, and Schulte, find that quinine lessens oxidation in the blood, and Binz finds that it does the same in a solution of hæmoglobin.

External respiration, or the interchange of gases between the blood and the atmosphere, takes place whenever they come into sufficiently close relation with one another, as they do in the capillaries of the skin, intestinal canal, or lungs. In the frog, respiration is carried on by the skin to such an extent, that it can live for a considerable time after the lungs have been excised; but in mammalia respiration is carried on almost entirely by these organs, and any interference with their function quickly puts an end to the life of the animal. In order that the blood which circulates through the body may get rid of its carbonic acid and take up oxygen sufficient for the wants of the tissues, fresh portions of it must constantly be brought into contact with the air, and therefore

it must constantly circulate through the pulmonary capillaries. But the air in the lungs would soon become saturated with carbonic acid and deprived of its oxygen by the blood which comes into contact with it, and all farther diffusion would be arrested, unless it also were constantly renewed. This is effected by the respiratory movements. These consist in the alternate enlargement and diminution of the thoracic cavity, after the fashion of a pair of bellows, by the motion of its walls and of the diaphragm. These movements are kept up in a rhythmical manner by a nervous centre, situated in the medulla oblongata and upper part of the spinal cord, which sends off periodic motor impulses to the diaphragm and inspiratory muscles. When the breathing is quiet, expiration is usually a passive act performed by the elasticity of the lungs and ribs, and by the weight of the thoracic walls. But when it becomes excited, active expiratory muscles are brought into action, and they receive their motor impulses from the respiratory centre alternately with those of inspiration. It is probable, though not certain, that the respiratory centre is not a mere reflex apparatus, which simply transmits impressions which it receives from sensory nerves to motor ones; for its activity continues, although its connections with sensory nerves be almost entirely destroyed. The periodic impulses which it imparts to the motor nerves of the respiratory muscles are not due to its being periodically excited by impressions from afferent nerves, but to its being constantly excited by the venosity of the blood circulating in it; while some resistance within itself prevents the excitation from being constantly transmitted to motor nerves, and only allows it to be so at periodical intervals.

The venosity of the blood consists in the absence of oxygen and the presence of carbonic acid, and it is not certain whether or not both of these act as excitants to the respiratory centre; but it seems not improbable that the presence of carbonic acid is the excitant, while the amount of oxygen simply alters the excitability of the centre. According to this view, when there is much oxygen in the blood, the excitability of the centre will be slight, and little affected by any irritant applied

to it, whether this be carbonic acid or anything else. When the amount of oxygen in the blood is small, the centre will be very excitable and easily affected by any irritant. In venous blood, there is both little oxygen and much carbonic acid, so the centre is both rendered more sensitive, and is more strongly excited by the acid. The more venous the blood, the greater is the excitation of the respiratory centre, and the more active the respiratory movements. When other interfering circumstances are excluded, it would appear that greater excitement of the respiratory centre causes the respirations to become quicker, and, at the same time, deeper. This excited respiration is termed dyspnœa, and it occurs when the blood becomes venous in the respiratory centre. As the venosity increases, the ordinary muscles of respiration are no longer employed alone, but the expiratory and accessory muscles are called into play; and, lastly, all the muscles of the body are affected by clonic convulsive movements, called asphyxial convulsions.

When the blood which circulates in the respiratory centre is not at all venous but is perfectly arterialised, as it is when artificial respiration is vigorously performed, the centre is both rendered less sensitive, and the irritant, viz., the carbonic acid, is at the same time diminished or removed, the centre is not excited at all, and respiratory movements cease.

This condition, in which no desire for respiration is felt, and respiratory movements cease, is termed "apnœa" by German writers, and it must be carefully distinguished from the "apnœa" of English authors, which is simply extremely great dyspnœa; so great, that the blood is hardly aërated at all.

The activity of the respiratory movements and the amount of air respired in a given time, depend on the degree of excitement of the respiratory centre. As we have just seen, this excitement depends on two factors: 1. The excitability of the centre; and 2. The amount of irritation applied to it. In general, the venosity of the blood determines both factors, and it is not the venosity of the blood in the general circulation which does this, but only of that blood which courses through the vessels of the medulla. This was shown by

Hering,* who passed a stream of arterialised blood through the vessels of the head while venous blood was circulating in those of the body. The respiratory movements then ceased exactly in the same way as if the whole blood in the body had been perfectly oxygenated. When he reversed these conditions, and passed arterialised blood through the body and venous blood through the head, asphyxial convulsions took place. This shows that the degree of activity of the respiratory centre in the medulla oblongata depends on the greater or less venosity of the blood circulating through it, and not on an irritating action exerted by venous blood on the ends of afferent nerves in the lungs, or other viscera.

The excitability of the respiratory centre may be greatly modified: 1. By the temperature of blood in it; 2. By the action of drugs upon it. When the blood becomes warmer, the excitability of the respiratory centre is greatly increased; the movements of respiration become much more vigorous, and it is no longer possible, by the most active artificial respiration, to produce a state of apnœa. Certain drugs, as tartar emetic, or apomorphia, when injected into the veins also prevent the production of apnœa, but whether they do so by increasing the excitability of the centre, or by acting as irritants to it, is uncertain.

Other drugs, such as chloral, greatly diminish the excitability of the respiratory centre, so that the respirations

* The request of a correspondent for a reference to Hering's experiments has, fortunately, directed my attention to a mistake of some importance in this lecture. I stated that Hering found that respiratory movements ceased when arterialised blood was passed through the head and venous blood through the body; while, on the contrary, asphyxial convulsions took place when venous blood was passed through the head and arterial blood through the body. I ought to have said that movements occurred in the blood-vessels such as would have taken place had the same sort of blood which circulated through the brain been passing also through the body. The experiments, however, were made on curarised animals, so that respiratory movements were impossible. Hering had previously ascertained that the arterial movements were synchronous with the respiratory movements, and might, indeed, be regarded as caused by impulses proceeding from the respiratory centre. They might thus serve as indications of the condition of the centre, where respiratory movements had been paralysed by curara. This paper is to be found in the *Wiener Acad. Sitzungsber., Math.-naturw. Classe*, vol. lx, abth. 2, pp. 829—856.

become fewer, notwithstanding the increase of carbonic acid in the blood to which their diminution gives rise, and if the dose be large they may stop altogether. Apnœa may also be produced by means of artificial respiration with great ease after their administration, and it may last so long, that one is sometimes inclined to think that the animal is not going to breathe again at all.

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