PHARMACOLOGY AND THERAPEUTICS;

OR,

MEDICINE PAST AND PRESENT.

Pharmacology and Therapeutics;

OR,

Medicine Past and Present.

THE GOULSTONIAN LECTURES DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS IN 1877.

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TO

J. BURDON SANDERSON, M.D., F.R.S.,

FOR HIS SERVICES IN PROMOTING

THE STUDY OF PATHOLOGY AND THERAPEUTICS

IN THIS COUNTRY,

AND IN GRATEFUL RECOLLECTION OF MANY KINDNESSES,

THIS WORK

Is Dedicated

BY

THE AUTHOR.

PREFACE.

THIS work consists of the Goulstonian Lectures delivered before the Royal College of Physicians in the Spring of 1877. For the convenience of the reader the lectures have been divided into a number of chapters, and some slight additions have been made to them.

The object of the lectures was to show how the progress of therapeutics is aided by an exact knowledge of the action of drugs obtained by experiments. So great has been the advance in the study of the physiological action of drugs, that a new name, pharmacology, has been given to it, and so rapidly does this advance continue that it is hard, even for one who has been well trained in the subject, to keep pace with it, and it is difficult for those who have studied medicine a good many years ago to understand the methods employed in it and its practical bearings. In the larger works on therapeutics and pharmacology it is generally assumed that the reader is acquainted with the plan of investigating the action of drugs, and the results of experiment only are given. It not unfrequently happens that, even if the reader understands the result of experiments on the physiological action of drugs, he is unable to perceive how they bear on therapeutics, because he is unacquainted with the pathological observations which are equally necessary with those of a pharmacological nature for rational therapeutics, and in order to supply such an introduction to the study of rational therapeutics these lectures were written.

In order to give a better idea of the present position and mode of progress of therapeutics, it seemed advisable to present the reader with a short historical *résumé* of the various methods by which the study of medicine has been pursued in the past. It is only by a clear conception of the errors into which our predecessors have fallen that we are likely to avoid them, and to estimate at their proper value the various branches of medical science and the bearing of each upon medical practice.

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PROGRESS OF MEDICINE.

CHAPTER I.

MEDICINE PAST AND PRESENT.

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IN the course of these Lectures I purpose to consider pharmacology and its relations to therapeutics;

or, in other words, the relations between the action of drugs on the healthy body and their uses in the cure of disease. In dealing with this subject, I shall divide it into four sections:

1. The reason why therapeutics has made such slow progress in the past, as shown by the history of medicine.

2. The methods by which it is at present advancing.

3. Some of the most important results obtained by the use of these methods.

4. The prospects of therapeutics in the future.

Although few persons possessing any knowledge of the history of medicine will deny that therapeutics has made some progress during the last thousand years, yet it is impossible to read the writings of the ancients without feeling that if some of the old Egyptian physicians, not to mention such men as Hippocrates and Galen, were to arise from their graves and commence practice, we should have but little cause to sneer at their treatment, although we have the advantage of possessing the medical knowledge accumulated during the two or three thousand years which have elapsed since they flourished.

For those old Egyptians seem to have been acquainted with the use of emetics, enemata, and purgatives, those potent agents which are, perhaps, more used and more useful than any others in our own armamentarium. They paid attention to the diet of their patients. For the cure of dropsies, they used squills and iron.[1]

An ancient Greek, in addition to employing drastics,[2] squill, broom,[3] and balsams,[4] would have tapped the abdomen when the distension became great, and would have taken every precaution to prevent syncope from the operation.[5]

These are the very methods of the modern physician; and, although he might give digitalis and blue pill along with the squills, and suggest

[1] Pauw, *Recherches Philosophiques sur les Egyptiens et les Chinois.* Berlin, 1773; tom. i. p. 134.

[2] *Paulus Ægineta*, by Adams, Sydenham Society, p. 570.

[3] *Op. cit.*, p. 575.

[4] *Op. cit.*, p. 571. Compare H. Thompson, *Lancet*, Nov. 29th, 1869, p. 742.

[5] Hippocrates, *Aphorisms*, Lect. vi. § 27. Syd. Soc. Ed., p. 756. *Paulus Ægineta.* Syd. Soc. Ed., vol. i. p. 572, *et seq.*

nitrous ether and juniper, yet his reasons for this would be the same as those of the Egyptian or Greek—viz., that he had seen the remedies prescribed do good before, and expected them to prove beneficial again. As to the *modus operandi* of these remedies, or the reason why they should succeed in one case and fail in another, the ancient and the modern would be almost equally in the dark; for medicine with both would be an art, not a science.

If we turn to other branches of knowledge—astronomy, chemistry, or physics—the case is widely different. Not that the ancients were entirely ignorant of these subjects—far from it.

The Egyptians had a fair knowledge of chemistry as an art, for they made glass mosaics such as Venetian manufacturers have only of recent years been able to fabricate.[1] They produced imitations of precious stones such as moderns can hardly surpass.[2] They mixed metals into a bronze almost equal in toughness

[1] Wilkinson's *Popular Account of the Ancient Egyptians*. London, 1854, vol. ii. p. 61.

[2] Wilkinson, *op. cit.*, p. 63.

and elasticity to steel.[1] They used metallic oxides so as to give their porcelain most beautiful colours. They knew how to fashion patterns in cloth by the use of acids, in much the same way as our own Manchester manufacturers.[2]

Their technical knowledge was deep and varied. Modern skill has striven in vain to equal or surpass many of their achievements. But here their triumphs end; for in modern times — we may say in the preceding century—science has taught us that wonderful affinity in nature which enables us almost to rival nature in the beauty and perfection of our work; to discern the relationships of the elements; to pull a compound to pieces; to tear down and build up; to create the most complex products of vegetable life — dyes of brilliant and enduring lustre,[3] and poisons of deadly power.[4]

[1] Wilkinson, *op. cit.*, p. 159. [2] Wilkinson, *op. cit.*, p. 66.

[3] Graebe and Liebermann, *Jahresber. für Chemie für* 1869, pp. 494 and 1160.

[4] Conia made synthetically by Hugo Schiff, *Bericht der Deutsch. Chem. Gesellsch.*, December 26th, 1870, p. 946; and Muscarin by Schmiedeberg and Harnack, *Centralblatt für die Med. Wiss.*, 1875, p. 598.

The same is the case with astronomy and physics. Thales might predict eclipses,[1] and Hipparchos could calculate them with accuracy; but they had no conception of the laws which regulate the movements of the heavenly bodies—laws which enable us to calculate the position of the planets at any given moment for centuries backwards or forwards, to determine their masses, to measure their distances from the sun, to ascertain the rate at which they roll along their orbits, and foretell the existence of unseen bodies which disturb the regularity of their motions.

Archimedes was acquainted with the reflection of the solar ray, and may have used his knowledge to destroy the ships of an enemy;[2] but he was utterly ignorant of those wonderful properties of light which have enabled us within the last few years to accomplish the apparent impossibility of analysing the composition of the sun and

[1] Herodotus, i. 74, Whewell's *History of the Inductive Sciences.* 3rd ed. vol. i. p. 134.

[2] Buffon, "Introduction à l'Histoire des Minéraux," Œuvres, tom. v. p. 301. Paris, an. vii.

stars, millions of miles removed from us, almost as readily as that of a meteorite which has fallen to the earth;[1] to ascertain that an apparently motionless star is receding from us with enormous rapidity;[2] and to affirm that a great conflagration is going on in another star with as much confidence as that a chimney has caught fire in a neighbouring street.[3]

While the ancients had a knowledge of isolated facts, we know them in their relations. This difference is as great as the difference between our knowledge of one man from a casual meeting in the street, and of another from a thorough acquaintance with his early training, his circumstances, his associations, his life-long conduct. You can tell what the former will do in circumstances in which, to your knowledge, he has already been; you can foretell what the latter will do under conditions in which he has

[1] Kirchoff, Lockyer, Jansen, Huggins. *Vide* Roscoe's *Spectrum Analysis*.

[2] Huggins, *Proceed. of Roy. Soc.*, May 14th, 1868, p. 385.

[3] Huggins and Miller, *Proceed. of Roy. Soc.*, 1866, p. 149.

never been. Your knowledge of the former is **empirical**; of the latter, **scientific**. You can tell that your casual acquaintance will salute you in passing, or that he will leave town by his daily train, because you know that he has done these things regularly for weeks, months, or years back; but you do not know whether he would prove a true man or a knave if you were to intrust him with an important commission. In the case of your life-long acquaintance, on the other hand, you could predict the result of such a trial, although you had never made it; and from your knowledge of him you could make certain that, according to his character and circumstances, he would wilfully break his pledge, like the faithless friend of the unfortunate Essex; or would, like Regulus,[1] fulfil his engagements, though torture and death should be the result.

It is such an intimate acquaintance as this with the properties of light that enables us to predict that, under certain conditions, one beam

[1] Appian, lib. viii., *De Punices Rebus*, § iv.

will extinguish another, so that, contrary to all our usual experience, two lights make a dark; and to understand the reason of our partial failure if we produce mere dimness instead of complete darkness in our endeavours to demonstrate the fact experimentally.

An intimate knowledge of the chemical nature and relations of bodies enables us not merely to say that certain substances—for example, members of the alcohol series—may exist, but to foretell their properties, and, by using certain processes, to make them, although they had previously never been known, and probably had never even existed in a separate state.

Unfortunately, we do not know medicine as we do chemistry and physics. We have medical sciences; for physiology, pathology, and pharmacology, are justly beginning to lay claim to the title; but medicine itself—the recognition and cure of disease—is still an art, and not a science.

The truth of this becomes evident if we consider the case of ague, the disease of all others in which the power of medicine, both as regards prophylaxis and treatment, is most marked. We know that if a man pass through certain districts, and more especially if he sleep in them, he is likely to be attacked with a fit of shivering, which, after lasting some time, will be succeeded by a burning fever and then by profuse sweating, after which he will feel comparatively well until the next day, when another shivering fit will come on at the same hour, and run the same course as the first. We know that, by warning the man against the dangerous locality, or by making him adopt certain precautions, take cinchona alkaloids, if he cannot avoid the place, we may be able to prevent the disease; by administering one large dose of quinine before a paroxysm we may stop its approach, and by continuing the remedy we may prevent its recurrence altogether. But we are ignorant of the nature of malaria, as we term the cause of these paroxysms, whatever it may be. We do not know how it acts upon the bodily mechanism, so as to cause them. We have no notion of the manner in which quinine counteracts the malarial effects, or why quinine should sometimes fail and arsenic prove efficacious.[1] We foretell the occurrence of an ague-fit after exposure in a certain locality and its prevention by quinine, in the same way that an astronomer of ancient Babylon could predict the recurrence of an eclipse.[2] He saw that one was followed after a certain interval by another; and we have observed that exposure is followed by ague, and the administration of quinine by the diminution or absence of the paroxysm. Having seen the same sequence of phenomena before, he reasoned that it would come again, even as we reason now. But he had no idea of the cause of the eclipses. He did

[1] The recent researches of Lanzi and Terrigi render it highly probable that malaria is of a vegetable nature; but this cannot yet be considered as perfectly proven. Lanzi was able to produce a zooglœa-like vegetation by cultivation of the pigment granules found in the livers of persons who had suffered from malaria. These granules he considers to be identical with the granules found in withered algæ; and Terrigi found them in animals which had breathed for some time the air from a swamp.—*Centralblatt d. Med. Wiss.*, 1875, p. 713.

[2] Whewell's *History of the Inductive Sciences*, 3rd ed. London, 1857, vol. i. p. 121.

not know what was going on in the eighteen years' interval between them, nor could he account for any irregularity in their occurrence. We may say that the immediate cause of the ague-fit is probably intense irritation of the vaso-motor centre in the medulla oblongata, but we have no idea of the nature of the irritant, and we cannot even guess why the irritation should occur at regular intervals. We do not know the changes in the nervous system and tissues which occur during the intermissions, and we are utterly at a loss to explain why a man should come from a malarious district in India and die in England of jungle-fever, although he had never had it while abroad, and it is never seen in residents at home. We have no such accurate and comprehensive knowledge of the relations between the organism, malaria, and quinine as astronomers have at the present day of the relations between this globe of ours, its attendant satellite, and the solar and stellar systems, a knowledge which enables them to fix, years before, the precise spot on the earth's surface at which an eclipse may be seen, although totally invisible for thousands of miles around their home, and to make preparations for observing it accordingly.

If we inquire why medicine is so far behind astronomy, we shall find two reasons. The first is, that medicine is much more complicated and difficult than astronomy. For, instead of depending on mathematics and physics, it rests upon pathology and pharmacology, which in their turn depend upon physiology, while physiology depends on chemistry and physics. Some one has compared the advance of the sciences to a game at leap-frog, one jumping over the backs of the others. There is much truth in the comparison. Physics helps chemistry, chemistry, helps physics, and both help physiology. Indeed, it is only through them that physiology can advance; for, without chemistry, the processes of respiration and digestion would be incomprehensible, and without physics a knowledge of the properties of the nervous system would be unattainable. Until chemistry and physics had made a certain amount of progress, physiology was obliged to stand still, and consequently pathology, pharmacology, and therapeutics could not advance.

The second reason for the slow progress of medicine is, that during many centuries it has been studied by wrong methods. In reading its history, I have found it by no means easy to understand the various phases through which it has passed, for I could not enter into a manner of thought so different from our own as that of Paracelsus until I remembered a trifling incident which occurred when I was a child. As others may have had the same difficulties as myself, and as this incident may help them as it has helped me, I shall not scruple to relate it.

One day, when playing with a box, I "made believe" that the lock was out of order; and again "making believe" that I could mend it by the proceeding, I picked off a piece of the ivory with which the box was inlaid, and drove it into the keyhole, thus ruining the lock and seriously injuring the box.

Every one here, I may even say every one in the world, has had some similar experience, for the habit of "making believe" is universal, and some of the oldest relics of nations past and gone are children's toys.[1] The little boy "makes believe" that a walking-stick is a horse, and feeds it with hay and corn. The little girl "makes believe" that her doll is good, and she pets it; naughty, and she punishes it; or sick, and she nurses it. As these children grow up, they throw aside their rocking-horses and dolls, but they do not altogether throw aside their practice of "making believe."

In early ages it did, and amongst rude peoples

[1] When at Larnica in Cyprus, several years ago, I saw some relics obtained from excavations made in the neighbourhood. Underneath an old Greek town, and about fourteen feet below its level the explorers came to the ruins of a Phœnician town. As the Greek town had been destroyed about the Christian era, and the depth at which the Phœnician ruins lay below it showed that it had been demolished many years before the Greek town, we are probably within the mark in estimating the age of the Phœnician relics at three thousand years. Amongst the most interesting objects discovered was a wooden horse, the plaything of some Phœnician boy. Wooden dolls, found in Egyptian tombs, are also figured by Sir J. Gardener Wilkinson, *Popular Account of the Ancient Egyptians*. London, 1854, vol. i. p. 196.

it still does, remain as a lifelong habit. Nor is it entirely destroyed, although it is of course lessened, by an advanced civilisation. We daily see around us illustrations of the proverb that the wish is father to the thought, the person who wishes "making believe" that facts correspond to his desire. It is evident, therefore, that this practice of "making believe" is not a mere childish folly, unworthy of a moment's consideration, but the outcome of a deeply-rooted tendency of the human mind, and therefore deserving of most serious attention.

Its nature is evident enough, for a few moments' thought will suffice to show that, in "making believe," we form a conception in our own mind, and proceed to act upon it, as if it were true, when there may be not the slightest accordance between it and things as they really are.

Indeed, the name we give to the power is sufficiently descriptive—imagination; *i.e.*, the forming of images, or, as the Germans term it *Einbildung* the painting of pictures in our brains, which may be perfectly unlike the real things they are intended to represent. We probably have all heard of the story of the camel, the parts played by the different nationalities varying according to the country in which it is told. An Englishman, a Frenchman, and a German were asked to describe and figure a camel. The Englishman went to Egypt, where he could see it in its home. The Frenchman went to the Jardin des Plantes, where he could see it without trouble. The German went to his study and evolved it out of his "moral consciousness."[1]

We laugh at the idea of the ludicrous discrepancies there would be between the picture of the camel drawn by the student from his imagination and the actual portrait of the animal, and yet every day we make a similar blunder. We form mental pictures of persons, of scenery, of occurrences, but how rarely do these coincide with the reality? How seldom does any celebrated person, for example, resemble the ideal of the imagination. Even after we have

[1] The term "moral consciousness" in this connection is evidently absurd, but I give the story as I got it.

seen him, our mental portrait is still an ideal, for we picture him to ourselves either with qualities which he does not possess, or without qualities which he does possess. It is only by frequent intercourse, by repeatedly comparing our ideal with the reality, that we come to know the truth.

In medicine, we find the same thing. Two physicians stand by the bedside of a patient who has a high temperature, rising at night and falling in the morning, a doubtful spot or two on the skin, tenderness over the abdomen, slight diarrhœa, moist râles in the chest, and a very indefinite and unsatisfactory history. One says the patient is suffering from typhoid fever with bronchitis, and immediately pictures to himself ulcers in the intestines and congestion of the bronchi. Both of these, he thinks, may get well, and he looks for the recovery of the patient. The other says "tuberculosis," and pictures to himself the lungs studded throughout with white nodules, and the serous membranes strewed over with pearly granules. Instead of recovery, he looks for exacerbation of the symptoms, and predicts a fatal issue to the illness. The pictures which each physician paints to himself may be equally vivid, each may be equally positive in his assertion that his picture alone represents the reality, but only one can represent the truth, only one picture can agree with the conditions actually present in the patient's body, only one statement can be true, the other picture is a mere figment of the physician's imagination, not corresponding to any objective reality, and the statement corresponding to it is false.

The late Dr. Hughes Bennett, in his clinical teaching, used to insist strongly on the difference between ideas and facts. A student would be called to auscultate a patient, and was then asked by the professor what he had heard. "I think I heard a murmur," he would say. "Think," said Bennett, "I don't want to hear what you think; I want facts; there either is, or there is not, a murmur; and I want to know which." Of course it is impossible for any one to communicate to another anything more than his idea, but he may take much trouble to make it coincide with facts; and the importance of insisting upon this in teaching, as Dr Bennett did, cannot be overestimated.

It is the agreement or non-agreement of the idea in the physician's mind with objective facts that makes his diagnosis right or wrong, and his treatment a success or failure.

It is the practice of acting as if the creations of the physician's imagination were realities, without ascertaining whether they were so or not, that has proved so fatal to the progress of medicine; and it is only through the diligent comparison of ideas with facts by observation and experiment that we can hope for its advance.

CHAPTER II.

PROGRESS OF MEDICINE IN THE PAST.

History of Medicine—Modes of Medical Study and Practice devisible into Three Classes—First Error in Medicine, Imaginary Gods and Spirits—Childish Notions regarding a Box—Similar Ideas of rude Peoples regarding Medicine—Medicine in the Friendly Islands—in Tahiti—in Madagascar—in ancient Greece—in Alexandria—Influence of Jewish and Persian Ideas on Greek Medicine—Ideas of the early Christian Fathers—of the Middle Ages—Prevalence of similar Ideas up to a late Period—Magical Relations and Powers—Planetary Influence—Sympathy—Prevalence of similar Notions at the present Day—Paracelsus—Notions regarding Magnetism—Van Helmont—Magnetic power of Body—Supposed Power of the Will—Mesmer—Hahnemann—Homœopathy—Recognition of the Principle by Hippocrates—Vagaries of Hahnemann—Second Error in Medicine, False Notions regarding the Body, Disease, and Powers of Remedies — Childish Fancies — Historical Parallels — Mosaic Cosmogony—Three Sources of Life—Fluids, Solids, Spirit—Corresponding Division of Medical Ideas — Humoral and Chemical Pathology — Solidist Pathology — Pneumatic and Vitalist Pathology—Pathology of Hippocrates—Bile as a Cause of Disease—Dogmatic School—Plato—Erasistratus—Athenæus—Pneumatic School — Asclepiades — Themison — Pneumatic School—Influence of ancient Ideas at Present—Eclectic School—Galen—Origin of the Practice of Bleeding in Spring.

As the practice followed by physicians depends upon the ideas existing in their minds regarding the nature of disease and the qualities and powers of remedies it will be more or less correct according as these ideas correspond more or less closely with objective facts. The ideas which are prevalent at any time or place determine the mode of treatment, and we may divide the history of medicine according to the nature of these ideas and the mode in which they were obtained.[1]

We may thus divide the modes of studying and practising medicine into three classes.

1. Where the disease has been attributed to unseen powers, gods, or spirits, and means have been sought to influence them ;

2. Where disease has been attributed to some disturbance of the mechanism of the body, but where the physician's ideas regarding that mechanism as well as regarding the action of his curative measures upon it, have been erroneous ;

3. Where disease has been attributed to some disturbance in the mechanism of the

[1] For an excellent account of the development of medical theory and practice, vide *Hauptemomente in des geschichtlichen Entwickelung der Medicinischen Therapie*, von Dr. Julius Patersen, 8vo., 1877, Kopenhagen, Höst und John.

body, and where the physician's ideas regarding that mechanism, as well as the action of his curative measures upon it, have been rendered more or less correct by means of experiment.

In the two first of these classes medicine has dealt with ideas only and has thus fallen into error, in the last it deals with facts and thus has advanced.

I have already dwelt much upon the practice of "making believe," and have preferred this childish expression to the usual term of imagination, because childhood's follies present us with an exaggerated picture of our own, and enable us clearly to see things to which we might otherwise have been blind. For this reason I shall ask you again to turn to the trivial incident which I have already mentioned, and consider what a child finding a box locked is likely to do. He may believe that some spirit, good or evil, prevents him from opening the lid, may consider his failure as a punishment for breaking his mother's china vase, and endeavour to appease the spirit by weeping over the fragments; he may try to propitiate it by burning his sister's best doll as a peace-offering, or may attempt to drive it away by putting snuff into the key-hole. Or, without believing in a spirit, he may fancy the lid held down by some occult indefinite power—bewitched, in fact—and may pull hairs out of the cat's tail to remove the enchantment. If we replace the words child, open, and lid, by physician, cure, and patient, we shall have a tolerably fair example of medicine in one of its phases.

The first error into which medicine has fallen is that of attributing disease to imaginary gods or spirits.

Perhaps no better illustration can be given of this form of "making believe" than that which I now quote from the book of Isaiah.[1] Speaking of an idolater the prophet says: "He planteth an ash, and the rain doth nourish it. Then shall it be for a man to burn: for he will take thereof, and warm himself; yea, he kindleth it,

[1] Isaiah xliv. 14, *et seq.*

and baketh bread; yea, he maketh a god, and worshippeth it; he maketh it a graven image, and falleth down thereto. He burneth part thereof in the fire; with part thereof he eateth flesh; he roasteth roast, and is satisfied: yea he warmeth himself, and saith, Aha, I am warm, I have seen the fire: and the residue thereof he maketh a god, even his graven image: he falleth down unto it, and worshippeth it, and prayeth unto it, and saith, Deliver me; for thou art my god. And none considereth in his heart, neither is there knowledge nor understanding to say, I have burned part of it in the fire; yea, also I have baked bread upon the coals thereof; I have roasted flesh, and eaten it: and shall I make the residue thereof an abomination? shall I fall down to the stock of a tree?" Should such a devotee as this be stricken by plague, pestilence, or famine, he will believe it due to the wrath of his block of wood, and will offer gifts to appease it; or he may attribute his calamity to the anger of a lump of stone, and call upon his block of wood for deliverance.

In the Friendly Islands,[1] for example, the natives believed that when a chief was sick he might appease the Deity by strangling his relations and thus recover from his disease. In Tahiti,[2] the priests pronounced certain words over the sick man, and tied cocoa-nut leaves to his fingers and toes. "In Madagascar,[3] when any person is sick, the nearest relations apply to the *ombiasse* or priest, who goes by night to the *amounoque* or sepulchre of the father, or, if the father be still living, of the grandfather of the afflicted person; then making a hole in the monument, he places a kind of cap upon the aperture, and begins his incantations with many grimaces, invoking the spirit of the deceased to take pity on the person disordered, and restore his helpless progeny to health and vigour. If the patient recover the *ombiasse* receives great applause and is loaded with presents; but if he die, the *ombiasse* imputes it to the evil demons, or to fate (for the Madagaserians are

[1] Cooke's *Universal Geography*, vol. i. p. 90.
[2] Cooke, *op. cit.*, p. 35. [3] Cooke, *op. cit.*, p. 814.

great predestinarians), but never to any fault in himself or his incantations."

In ancient Greece the medical art was almost entirely exercised by the priesthood, and especially by the priest of Æsculapius, to whose temple patients were brought in order to be cured. The remedies consisted partly in prayers and offerings, and partly in remedies applied to the body, and intended to act upon it.[1] As time rolled on, the secrets of the priests became known to the laity, and their practical traditions became modified by the speculations of the philosophers.

Alexandria, as it rose to eminence amongst the schools of learning, attracted the Greek philosophers and physicians who there met with the sages of the East, and learned from them the wild fancies of the Jewish Kabbalah.[2] While some rejected these new doctrines, and strove by eager examination of nature to advance their art, others

[1] *Works of Hippocrates*, Sydenham Soc. edition, vol. i. p. 6; Sprengel, *Histoire pragmatique de la Médicine*, traduit par Geiger, tom. i. sec. iii. p. 43.

[2] Ennemoser, *History of Magic*, translated by Howitt, Bohn's ed. vol. i. p. 443.

gave themselves fully up to the influence of fancy, and developed a complete system in which the Deity, good spirits, and evil spirits, all played a part. Good spirits were coerced by prayers, evil ones by oaths (contracts) and offerings. The latter could be exorcised by means of certain magical words, and these were written up above the doors to prevent disease from entering.

The early Christian fathers, Origen, Tertullian, and others, adopted this doctrine;[1] it became the creed of the Church, and, during the dark period of the middle ages, the influence of evil spirits or of undefined powers, included under the terms witchcraft and magic, were generally regarded as a common cause of disease. Amulets, relics, prayers to saints,[2] and visits to holy places were the chief means of cure employed by the monks in whose hands medicine almost entirely lay, and the Church pursued with unrelenting severity all those who were so unfortunate as to incur the suspicion of witchcraft. Luther ascribed most

[1] Sprengel, *op. cit.*, tom. ii. sect. v. § 100, p. 171

[2] Sprengel, *op. cit.*, sect. v. tom. ii., § 98 p. 161, *et seq.*

diseases to the direct agency of the devil; according to Robert Fludd, the exponent and apologist of the Rosicrucians, they were consequences of sin, and caused by four fallen angels. The celebrated Hoffmann attributed nervous diseases to diabolical agency, and it is little more than half a century ago that Windischmann, professor in Bonn, declared that a physician ignorant of exorcism lacked one of the most powerful agents of his art.

Besides the direct influence of demons, various undefined sympathies, relations, and powers were supposed to exist between man and the stars, lower animals, plants, and metals. A man's fortune in life depended on the star under which he was born. The result of an undertaking could be foretold from the position of the planets. It was most important that medicines should be prepared and administered exactly at the time of particular planetary conjunction. By making an image in wax, repeating certain incantations, and performing certain ceremonies, it was supposed that one might establish such a relation between the image and a person whom he hated, that on pricking it with pins his enemy would be racked with pains in every part of the body, and would fall dead when it was pierced through and through. A sympathy was also supposed to exist between a wound and the sword, or other weapon with which it had been inflicted; so that by applying a salve to the sword, and carefully leaving the wound alone, it would heal. But if an enemy became possessed of the weapon, he could so treat the weapon as to cause the wounded man to suffer intolerable pain. A similar belief is not quite extinct even yet, for many persons still think that if a dog go mad after it has bitten a man he runs a risk of getting hydrophobia, and they therefore kill it to avert the danger. It is not much more than a year ago that a man in the Midland counties killed a poor woman by whom he thought himself bewitched. Nay, more, we daily use in our prescriptions a sign which, although now intended for recipe, was formerly the sign of the planet Jupiter, the cross in its tail bearing witness to its origin.[1]

[1] Paris's *Pharmacologia*, 8th ed. p. 13.

The doctrine of relations received a new impetus from Paracelsus, who in particular gave prominence to the imaginary virtues of magnets, and applied them to the body as a means of cure. He supposed that the body itself also possessed a kind of magnetic power by which the sick could infect the healthy. His follower, Van Helmont, also believed in a magnetic power of the body capable of such external action, that he himself was often able by his mere presence to cure the sick and to impart peculiar virtues to medicines by his will.

These ideas were adopted by various authors, but received their full development at the hands of Mesmer and Hahnemann. The former, by the application of magnets, afterwards by passes of the hands, and, latterly, by mere contact through a rod, was able to produce many extraordinary effects upon his patients, which he attributed to magnetism, but which we now ascribe simply to suggestion. The latter propounded the doctrine that diseases may be cured by small doses of those drugs which, in the healthy man, produce symptoms similar to those of his disease.

This principle, *similia similibus curantur*, is recognised by Hippocrates, who remarks that under certain circumstances purgatives will bind the bowels, astringents will loosen them, and substances which cause cough and strangury will also cure them.[1] But the Father of Medicine also admitted the other doctrine, *contraria contrariis curantur*, and Hahnemann not merely rejected this, but launched out into the wildest vagaries. He was not content with making his doses so small as to obviate the slightest risk of producing symptoms like those they were intended to cure, but reduced them to an infinitesimal amount; imagining, however, that what he lost in quantity he gained in quality by imparting to the drugs through repeated trituration a mysterious potency which Van Helmont had fancied he could do by the simple exercise of his will.

The second error into which medicine has

[1] *Works of Hippocrates*, Sydenham Society's edition, p. 77.

fallen is that, while diseases have been rightly attributed to alterations in the body, it has been supposed to have a composition and remedial measures to possess powers which were purely imaginary and utterly different from the reality.

Returning, again, to our illustration of the child and the box, we may compare the medical doctrines which come under this head to the child acknowledging that it is the lock which keeps the box shut, but fancying it to be composed of butter, iron, and quicksilver, or of little brass thimbles, and believing that the lock will not open because the butter and quicksilver have become wrongly mixed, or the thimbles have been turned upside down.[1] In the various attempts it makes to remedy this condition, it may happen to introduce a key, and thus gain its object; but if it fail, it may be led to drive a piece of ivory into the keyhole, and will thus attribute the unsuccessful, not to say disastrous, result to its not having used tortoiseshell instead. It may

[1] Compare Plato, *Timæus*, Sprengel, tom. i. p. 371, iv. 10.

happen to succeed, but its chances are very small, for there are endless possibilities of error.

In the history of medicine we find that similar methods have in some rare instances been successful, but generally have led to utter failure. Let us shortly run over some examples, beginning with the ancient Greeks, who are said by some to have derived their first philosophical notions from the Phœnicians, and possibly, through them, from the Jews.

In the Mosaic cosmogony, we read of the earth, of the waters, and of the Spirit of God which moved upon the face of the waters.[1] From the earth and from the waters, all vegetable and animal life were evolved by the Spirit;[2] and we find a similar triad in the Greek writings, although Stanley may be wrong, and Thales may not have derived his ideas from either Jews or Phœnicians.

Corresponding to these three sources of life,

[1] Genesis chap. i.

[2] Stanley, *History of Philosophy*, p. 5. Stanley cites Numenius, quoted by Porphyry, *De Antro Nympharum*, cap. x., ed. mdcclxv., *Traject. ad Rhenum*, p. 98; but the passage hardly supports his view.

we find three lines of thought, running down almost to the present day. In one, the liquids; in another, the solids, are regarded as of most importance to life and health; and, in the third, both solids and liquids sink into comparative insignificance before the formative power or spirit which acts upon them.

Alterations in the fluids of the body were regarded as the causes of disease in the humoral pathology, with which, in later times, the chemical pathology became closely connected.

Alterations in the solids took the place of the liquids in the solidist and mechanical schools; and changes in the formative principle, under the various names of nature, pneuma, vital spirit, Archæus, vis medicatrix, &c., were regarded as the essential of disease by the pneumatic school and vitalists.

In the writings of Hippocrates we find the humoral pathology well illustrated, and accompanied by the germ at least of the vitalistic pathology, although Hippocrates seems only to have received them from his predecessors, to have himself been but little influenced by theory, and to have practised chiefly by the light of experience.[1] Adopting the idea of Empedocles, that there were four elements—fire, air, earth, and water; he considers that there are four corresponding qualities—heat, cold, dryness, and moisture; and four corresponding juices or humours—blood, phlegm, yellow bile, and black bile.[2] The heart is the seat of the blood, the brain of the phlegm, the liver of the yellow, and the spleen of the black bile. Besides these, there is a principle pervading and modifying them all, which he calls nature, and which he regards as the healer of diseases.[3] So long as the juices remain in their proper places, and are in due proportion to one another, there is a condition of health; but when they become disproportioned to one another, or leave their proper places, disease is the result. It is curious that the bile, which even in the present day has more sins laid to its

[1] Sprengel, *op. cit.*, sect. iv. § 14, tom. i. p. 381.
[2] Sprengel, *op. cit.*, sect. iii. § 70, tom. i. p. 328.
[3] Works of Hippocrates, Sydenham Soc. ed., p. 17.

charge than any other secretion of the body, was the first to be accused of causing disease. According to Anaxagoras, it left its proper place, and, passing into the lungs, pleura, and blood-vessels, gave rise to all acute maladies.[1]

The successors of Hippocrates gave less heed than he to the teachings of experience, and allowed themselves to be carried away by theories.[2] Some confined their attention to the fluids as the chief cause of disease, and, teaching their speculations for facts, founded the dogmatic school. Others regarded the formative principle as the most important agent, and from them issued the pneumatic school. This principle or spirit was considered to be something apart from matter, but underlying it, and determining its form and condition. The successors of Hippocrates regarded this principle, which they termed pneuma, as the motor power of the body and identical with the soul.[3] Plato supposed it to

[1] Sprengel, *op. cit.*, vol. i. sect. iii. p. 33.
[2] Sprengel, *op. cit.*, sect. iv. § 5, tom. i. p. 361.
[3] Wunderlich, *Geschichte der Medecin*, p. 16.

come from the air, and assigned certain ways by which it could get to the heart. Erasistratus divided this spirit into two: the psychical soul, spiritus animalis, and the vital soul, spiritus vitalis.[1] To these, Athenæus, the founder of the so-called pneumatic school, added a third: the physical spirit; and alterations in them he considered to be the causes of disease.[2] These terms are still in daily use; though few of us suspect, when we say that some one is full of or has an excess of animal spirits, that we are using an expression more than fifteen centuries old.

Alterations in the solids of the body were little regarded as causes of disease until the time of Asclepiades, three hundred years after Hippocrates.[3] Following Democritus and Epicurus, he regarded the world as composed of atoms of different sizes, which never came quite close together, but left between them pores of various widths in which finer atoms played freely about,

[1] Sprengel, *op. cit.*, sect. iv. § 72, tom. i. p. 484.
[2] Wunderlich, *Geschichte der Medicin*, p. 30.
[3] Sprengel, *op. cit.*, sect. v. § 10, tom. ii. p. 14.

and in the free and unembarrassed movements of which the condition of health consisted. Disease was due either to stoppage of the atoms or variations in size of the pores. Themison simplified this doctrine by disregarding the atoms and teaching that diseases depended either on relaxation or contraction of the pores.[1] The simplicity of this doctrine gained it ready acceptance, and led to a method of cure equally simple, the adherents of which formed the methodic school. Diseases depending on contraction of the pores were to be cured by relaxants, and those depending on relaxation by astringents.

This doctrine also has survived to our own day, and I have heard Turkish baths regarded as beneficial, and purgatives as rendering one liable to catch cold, because they opened the pores; the person who employed the phrase seeming to be quite unaware that he was talking not so much of anatomical facts as of the fanciful doctrines of two Greek philosophers promulgated before the Christian era.

[1] Sprengel, *op. cit.*, sect. v. § 16, tom. ii. p. 23.

Although some physicians held almost exclusively to the doctrines of one school or another, yet the great mass had their opinions influenced by all the schools together, even when they professed to adhere to one. Many of them openly selected from each school what they considered best in it, and, uniting the practices of all, founded another school: that of the eclectics.[1]

The opinions of the methodic school were rejected by Galen, but, nevertheless, seem to have affected his pathology. This was, however, chiefly based on the humoral system, and partly on the vitalistic. Like Hippocrates, he attributed many diseases to the four juices of the body, and, like him, used emetics, laxatives, and revulsives to remove the offending humours or change the direction of their current.[2] These revulsives were intended to draw out the offending humours from the body, or at least away from the part of the body into which it was supposed to have wandered and to be doing harm. Purga-

[1] Sprengel, *op. cit.*, sect. v. § 55 and 63, tom. ii. pp. 85 and 99.

[2] Sprengel, *op. cit.*, sect. v. § 83, tom. ii. p. 136.

tives were used for this purpose; but the most powerful revulsive was venesection, the blood being regarded as a more usual cause of disease than the other juices. In spring, its quantity was supposed by Galen to be increased; and it is in all probability to his ideas that we may trace the custom, which prevailed in some parts of this country until a few years ago, of all adults indiscriminately submitting to the loss of several ounces of blood every spring, often by the hands of the farrier or barber.

CHAPTER III.

PROGRESS OF MEDICINE IN THE PAST (*continued.*)

Long continuance of Galen's Authority—Beneficial effect of the Turkish Invasion—Scepticism—Search for Truth—Appeal to Nature — Paracelsus — His modification of Greek Notions — Elements—Vital Spirit—Mode of Strengthening it—Chemical and spiritual Element in his Writings—Development of these by Van Helmont — Archæus — Ferments — Stahl—Anima — Sylvius de la Boe—Fermentation—Acids and Alkalis—Alteratives—Willis—Influence of Nervous System—Mechanical School —Borelli—Opening the Pores—Baglivi—Boerhaave—Haller—Irritability—Hoffman—Spasm and Atony—Brown—Sthenia and Asthenia—Rasori—Stimulus and Contrastimulus—Broussais—Bleeding—Fatal Effects of False Doctrines—Importance of the practice of "making believe"—Its influence on Medicine —still continues—Vagueness of present Notions regarding some Medicines—We begin to Localize and Define—Reign of Law —in Physics—in Medicine—Exactness of chemical Reactions—Apparent inexactitude of medicinal Action—Reason of this Difference—Comparison between present Ideas and those of the Middle Ages—Cause and Effect—Invariableness of Law—Each Law has its own Penalty—Illustrations—Facts independent of Fancies—Necessity of conforming to Facts.

GALEN was the last founder of a system of medicine before the fall of the Roman empire,[1] and his doctrines and practice, modified by the mysticism and magic of the Middle Ages, were

[1] Wunderlich, *Geschichte der Medecin*, p. 37.

regarded as of almost Divine authority until about the time of the Reformation.

At the end of the fifteenth century, the Turks conferred an inestimable benefit on Europe by taking Constantinople and driving the Greeks to take refuge among the Western races.[1] One result of this was that the banished Greeks brought with them the original Greek versions of those ancient medical writings, so much reverenced by the Westerns, although known to them only through corrupted Latin versions. On comparing these translations, previously so venerated, with the originals, many discrepancies were discovered ; and men were thus led to doubt the correctness of the statements made in either the originals or the copies, and to appeal to nature to settle the dispute.

The most noted opponent of the Galenical doctrines was Paracelsus, who, in the course of a wandering life, had consorted with alchemists, miners and metal-workers, fortune-tellers, wise women, and all sorts of curious characters, and had learned from them such secrets as they

[1] Wunderlich, *op. cit.*, p. 62.

possessed. In his writings, we seem to meet again the doctrines of the early Greeks, modified by the influence of his strange associates. In place of the fire, air, earth, and water, with the underlying formative principle or nature of Hippocrates, Paracelsus puts sulphur, salts, and mercury with a vital spirit which governs them. Sulphur seems to correspond to the fire and air, salts to the earth, and mercury (which dissolves and renders fluid) to the water. This vital spirit pervaded the whole body, but had a special action in every part: heart, liver, brain, lungs, and kidneys. When it was cut off from any part, that part died; and whenever it was weak, it required to be strengthened. His manner of strengthening it in the heart was very sensible, and likely to prove both useful and agreeable to his patients; for he first made an essence of crocus with pure spirit, and then administered one drop of this in good wine to old persons and to those who were melancholic or suffering from low spirits.[1]

[1] *Drey herrliche Schrifften Herryn Doctors Theophrasti von Hohenheim von Krafft der ausseren Gliedern.* Das dritte Buch, das andere Capitel. Basel, Samuel Apiario, 1572.

In his writings, we find both a chemical and spiritual element; and these formed the points of departure for two schools, just as the humoral and spiritual elements in the pathology of Hippocrates formed the points of departure of the dogmatic and pneumatic schools of the ancients.

Both the chemical and spiritual notions of Paracelsus were developed by his follower Van Helmont, who converted his spiritus vitæ into a mortal spirit, which he named Archæus, and which built up the body out of other materials. Instead of pervading the whole body, like the spiritus vitæ, the Archæus had his seat in the stomach, and ruled over a number of smaller Archæi, which he sent to different parts of the body to do his bidding. He was of a very uncertain temper, sometimes angry, sometimes depressed, and sometimes heedless. Paracelsus regarded fermentation, or, as he termed it, putrefaction, as an essential element in the generation of new beings, as well as in the digestion of food.[1] According to Van

[1] *Metamorphosis, Doctoris Theophrasti von Hohenheim der Zerstörten guten künsten unnd artzney restauratoris gewaltigs unnd nutzlichs schreiben*, 1572. *Von naturlichen Duyen*. Das Erste Buche.

Helmont, it was by means of a ferment that Archæus built up the body out of other materials; and epilepsy and mania were caused by his sending acid ferments out of the stomach into other parts, without thinking what he was doing. It is the Archæus, rather than the ferment, which plays the chief part in Van Helmont's pathology; and it is this spiritual side of it which is chiefly developed in the doctrines of Stahl, in whose writings the *spiritus vitæ* and the *Archæus* are replaced by the *anima* or soul, which he regards as the essential part of a man, the body being merely the organ through which it acts. The soul builds up the body, causes its different parts to act in harmony, and keeps it alive by preventing the putrefraction from taking place to which the body is constantly liable, and which occurs when ever the soul leaves it.

The chemical element in the pathology of Van Helmont was much more generally accepted than the spiritual. One of its greatest followers was Sylvius de la Boë, according to whom fermentation is the basis of life and of all its functions.

The chief products of this fermentation are acids and alkalies. Diseases are produced by the predominance of one of these over the other; and are to be treated by neutralising the faulty humour with acids or alkalies, according to the requirements of the case, by expelling it by evacuants, especially diaphoretics, and by correcting the morbid process of fermentation by means of alteratives. This theory of fermentation found a strong supporter in Willis, who introduced the notion that it was influenced by the nervous system—a notion which seems to express the real meaning of Stahl, who lived long afterwards but had not Willis's clear insight. The chemical system was displaced for a time by others; but recent researches show that many of the processes of life are really carried on by means of ferments, and that, if our present knowledge do not yet justify us in saying that life is fermentation, yet such a statement would contain much truth.

The system which, for a while, cast the chemical into the background was the mechanical one which was founded by Asclepiades and

Themison, but, having been rejected by Galen, had few or no adherents during the Middle Ages. It was again revived in another form by Borelli, who discarded the atoms but retained the pores, and attributed disease to stoppage of the openings of the nerves in the skin and glands by a glutinous matter, so that the nervous juices were retained. In consequence of this, they underwent fermentation, irritated the nerves and heart, and caused fever. Alterations in the solids of the body were also regarded as causes of disease, and his treatment consisted in opening the pores by diaphoretics and strengthening the solids by quinine. Baglivi paid little attention to the juices, and regarded diseases as depending only on relaxation and tension of the solids. The celebrated Dutch physician Boerhaave combined the humoral and solidist pathology, and regarded changes in the circulation, produced by alterations in the solids, as the causes of disease.

The mechanical notions regarding rigidity and relaxation of the fibres became modified by Haller's demonstration of the irritability and inherent contractile power of muscular fibre, apart from the nervous system, but influenced by it; and Hoffman, consequently, divided diseases into those due to spasm and those due to atony.

A great advance was made by Brown, who recognised the vital functions as the result of reaction against stimuli, and divided diseases into sthenic and asthenic, according as the reaction was defective or excessive. His doctrines were adopted and somewhat modified by Rasori, who replaced the terms sthenic and asthenic by diathesis de stimulo and diathesis de contra-stimulo. These were not to be recognised entirely by symptoms, but by the reaction of the body to certain drugs, and especially to venesection. If venesection did good, the disease belonged to the diathesis de stimulo; if not, to the other. The excessive or defective reaction, which Brown regarded as a character of the whole body, was limited by Broussais to parts, and stimulants were considered by him to have a different action according as they were applied to the part affected or another. In the first case, they were stimulants;

in the second, revulsives. Brown regarded the asthenic as the common type of disease; but Rasori and Broussais took the other side, and contra-stimulants (such as large doses of tartar-emetic and bleeding) were their favourite remedies—remedies so destructive that it has been computed that Brown's doctrines have, through the hands of his followers, directly or indirectly, cost more lives than the French Revolution.

From this short account of the history of medical doctrines and precepts, it will be seen why, at the outset of my lecture, I dwelt upon the child's pastime of "making believe," as in some senses an illustration of medical science in the ancient and the mediæval times—why, in fact, an illustration so simple and trivial might apply to the whole practice of medicine, even to a period as recent as the earlier decades of the eighteenth century. The simplicity of the child's speculations about the construction of a lock may show us the true nature of some of those precepts of Galen, which, for centuries, were regarded with blind obedience, and as an authority almost Divine on questions of medical practice. Even yet, we are not free from an influence, which is worthy of respect and inquiry only because it takes us back to those earlier times, of poetry and fable. We may still occasionally hear, from members of our own profession, that such a remedy "will cleanse the blood," that another will "open the pores," forgetting that they are repeating the long-discarded theories of Hippocrates and Themison. We all of us speak of laxatives and astringents, of sedatives, and tonics, and alteratives, without knowing always what we mean. If we were summoned to explain the exact tissue, or organ, or process we proposed to alter by our alteratives, or the exact cell or fibre we proposed to strengthen by our tonics, we might be sorely puzzled for a true answer.

But these old notions are gradually disappearing. The vagueness of the former times gives place to a sure and scientific grasp of our calling and its duties. We begin to localize and determine the parts upon which our remedies are to act. We approach to a clear idea of what we wish medicine to do. But we are still in the earliest stages of what, I trust, will soon be one of the ripest and most advanced, as it is one of the most beneficent, domains of modern science. Our ideas are often hazy and indefinite. We give medicine at random, with no defined idea of what it should do, and trusting to chance for a good result. When a remedy fails in its work, we can give no reason for the failure. We do not even seek out a reason, but content ourselves with saying, "Oh, it did not act as it usually does."

We forget that there must be some reason for this; that there are reasons for failure as well as for success. This law pervades the universe, and we cannot escape it in the dominion of medicine. If a stone do not fall to the ground, it is because gravity is prevented from drawing it to the earth. We seek out the cause, we remove the agent that arrests the operation of a law of nature, and down the stone must fall. We know that it will fall with a certain velocity; that it will exert a certain force. We know that this velocity will not vary the millionth part of a second, that this force will not lose the minutest fraction of a foot-pound, unless some other force interferes and interrupts it.

Now, why should a law, which is so manifest to all the world, which is seen in the wonderful scenery of the earth, and whose powers we can gauge with an accuracy so minute and unerring, why should the law which governs the falling of a stone be better known to science than the laws which govern us in dealing with life and growth, sickness and health? It is in endeavouring to answer this question that we may hope to bring medical science into as advanced a position as other sciences. An ounce of sulphate of magnesia, dissolved in half a pint of water, will precipitate a solution of baryta, and will give us a definite quantity of the sulphate of baryta. This result we can count upon with infallible certainty. Given as a purgative, and we cannot be sure of its action, although its power should be as certain and definite in the human frame as in the test-tube. The reason that we cannot be sure of its action as a remedy is because of differences in the conditions under which it is acting. It is our business to find out these conditions, so that, when we meet them again, we may know how to meet them. For there is an invariable relation between cause and effect, as invariable as the relation between an unchecked falling stone and the earth.

We are, as I have said, just learning in medicine the paramount importance of tracing effects to their true cause. We may laugh at the credulity of the Middle Ages, when the way to cure a sword-wound was to apply a salve to the sword; when the only reason for the pestilence was the eccentric advent of some wandering fiery comet. But it is only with our own day that we improve upon the knowledge of our fathers; that, disdaining witchcraft, and spells, and delusions, and charms, and fables, we begin to see that the laws under which our bodies live are as immutable as the laws which govern Jupiter and the Pleiades; that, when we break them, we must suffer the penalty; that every infraction has its penalty.

We learn that there is no such thing as an effect without a cause; we learn too that the penalty for breaking one law will not attend the violation of another. It would be absurd to say that, if a child killed a fly, it would have a pain in the stomach; and yet the time has been when such a statement would have been logical according to the accepted logic of medicine. The child may kill a fly—the child may have a pain in the stomach; but the pain does not result from the deed. The deed may lead to the pain in this, that the child may have to go dinnerless as a punishment for cruelty, and may gorge itself with green apples to supply nature's needs. But the penalty would be for eating unripe fruit, not for killing flies. In the same way, an unrighteous community given to cheating, lying, and profane speech may be visited by an epidemic. But the epidemic would come, not as the penalty for broken scriptural commandments, but as the penalty for broken sanitary laws, the penalty for impure water, imperfect drainage, or communication with an infected district. The violation of scriptural laws may lead to buildings being scamped, to imperfect drains, and a polluted water-supply. But simple repentance for these sins will not stop the epidemic until the sanitary laws are observed. The laws of nature admit of no exception and no excuse. The rain falls alike on the just and the unjust. If a viaduct break and a train be thrown into a river or a valley, the good and the bad alike suffer. Good and bad alike suffer, because, whatever respect they may have shown to moral laws, in this case they have offended the law of gravity—a law which exacts their lives or their limbs as its penalty. If a man swallow poison, the poison will do its work, whether the act of taking was a conscious or an unconscious act. This knowledge has enabled us to avert danger from ourselves and from those who, like children, would, in their ignorance, swallow the bright and tempting berry merely because it was pleasing to the eye, unconscious of the deadly principles lurking in its core. It is only within a short time that we have learned that men may become dull, listless, unable to command their faculties, because of the poisonous fumes from a fireplace, or a stove, or the impalpable powder that floats from the arsenical paper decorating the walls. We know that the green tracery which scatters garlands and vines over our modern walls may be as death-dealing, because of this unseen arsenical presence, as the fumes of carbonic acid gas. We know that a whole district may fall under the terrible scourge of typhoid fever because the water-supply has found some contamination. We know that dinner guests may be affected by scarlet fever because of ices composed of milk which contained the virus of that disease.[1]

The laws of nature are independent of our fancies. We must conform to them, or suffer the penalty of disobedience and neglect. Ignorance will not prevent disease. A physician's fancies as to the cause of a disease, or the nature of a remedy, will not check it. It is only by knowing as a truth, by patient study and investigation, the exact causes of disease, that we can avoid it.

[1] Buchanan, Mr. Simon's *Public Health Report* for 1875.

It is only by knowing these causes, the value of the remedies which will affect them, and the conditions of the human frame under which these remedies can have their full influence, that we can effect a cure. How this is to be done is the subject to which I propose to address myself in the next lecture.

CHAPTER IV.

RATIONAL AND SCIENTIFIC STUDY OF MEDICINE.

Difference in the action of the child and of the grown-up man—Illustration from the different attempts to open lock—Comparisons between the actions of a child and empirical methods of studying medicine—Comparison between the action of a grown-up man and the rational study of medicine—Sketch of the empiric and dogmatic schools—Theorising without data the cause of the decline of the latter—Revival of the former by Sydenham—Necessity for its continuance until pathology and pharmacology are sufficiently advanced to allow of the formation of a scientific system—Historical sketch of the progress of anatomy—Athothis—Praxagorus—Herophilus — Erasistratus—Study of anatomy forbidden by the Romans—Comparison with physiological study in modern times—Galen—Mondini—Vesalius — Progress of minute anatomy under Malpighi—Bichat—Schwann—Historical sketch of Physiology—Galen—Discovery of the circulation—Harvey and Cæsalpinus—Harvey's use of experiment—Demonstration of the circulation as a fact, and not merely an idea—Historical sketch of pathology — Nature of the study—Pathological anatomy—Morgagni—Bichat—Rokitansky—Virchow—Pathology proper—John Hunter, the founder of true pathology or the study of disease in the living body—Magendie—Claude Bernard—Brown-Sequard—Gaspard.

IN my former lecture, I considered the reasons why the progress of therapeutics has been so slow; and I tried to show that one of the chief obstacles to its advance had been the habit of mind which induced physicians to act like children at play, and to mistake the products of their imagination for realities.

This habit led them into two errors. In one they attributed disease to occult powers: in the other, to disturbances of the body of an entirely imaginary nature.

I now purpose to consider the methods by which therapeutical knowledge is being at present advanced, and this leads us at the same time to the third method of studying medicine. **This method consists in comparing the ideas of the physician with objective facts.**

In my previous lecture, I insisted upon the folly of mistaking fancies for facts, and upon the necessity of accepting the latter and not dallying with the former. I illustrated my meaning by the trivial incident of a child attempting to open a lock. I shall again ask you to turn with me to this illustration, and to try to imagine a person following the plan which we are now about to discuss. On doing so, however, we at once recognise that this method differs from the two former in being no longer that of a child, but that of a grown-up man.

There are two ways in which the person might attempt the lock : either he may take a succession of keys, one after the other, until he finds the one which fits, and thus may, and very possibly will, succeed ; but he will require numerous trials and may be finally baffled.

The second plan may be the slower at first, but is in the end the surer of the two. He takes as many locks as he can find, separates the different parts from each other, and examines their positions until he thoroughly knows the anatomy of the lock. He then studies the action of the parts, at first singly, then two by two, and lastly all together, until he discovers the working of the whole. He then tries the action of the key, first upon each part, and then upon the entire lock, adjusting it as he finds necessary, until at last he is able to open any lock, however complicated, even though he be previously unacquainted with its construction.

Comparing this example with what we find in the history of medicine, we recognise that the first method corresponds to the so-called empirical method in medicine, and the second to its rational or scientific study.

The first method was the earliest. It was that by which the priests of Æsculapius treated those who were brought to the temple of their god. Numerous histories of their different patients having been gradually collected, Hippocrates, the greatest of the Asclepiades, was able to compile an admirable empirical system.[1] His successors, however, as we have seen, departed from these rules,[2] and, launching out into mere hypothesis, founded the dogmatic school of medicine.

The study of anatomy under Herophilus and Erasistratus showed that the absurd notions of this school were utterly incompatible with the real construction of the human body. Many of the physicians of Alexandria, under the leading of

[1] Work of Hippocrates, Sydenham Society edition.

[2] Sprengel, *Histoire Pragmatique de la Médecine.* Paris, 1869, tom. i. p. 361.

Philinus and Serapion, consequently discarded theories altogether,[1] and based their practice solely upon a consideration of the symptoms of disease and of those produced by the administration of drugs.

It was impossible for any man to learn how to treat diseases simply from his own experience. Careful records of cases were, therefore, kept; and a physician of this school was expected to treat a patient by comparing the symptoms not only with those of a similar case he might have already seen, but with those recorded by others, and learning from their experience as well as his own the remedies most likely to prove beneficial.

The commerce of Alexandria brought medicines and poisons from all parts of the known world, and, by trying these, the empirics obtained many remedies of great value. But it would seem that men cannot be satisfied without a theory of some sort to guide their practice; they will not be content slowly and painfully to feel their way. They will have a light of some kind to show them

[1] Sprengel, *loc. cit.* p. 528.

where they are going and enable them to step forth freely; and they will rather have a false light than none at all.

Thus the empirics began to attribute to various substances qualities which they did not possess, but which they desired them to have; and they administered such remedies as the brains of a camel, the dung of a crocodile, the heart of a hare, and the testicles of a boar. By the use of such measures, their practice became at length as absurd as that of the pneumatic or dogmatic schools; and, as they disdained any theoretical knowledge, their ignorance and folly caused the name of empiric to become a term of opprobrium. So it continued even to our own day. Their method of practice was long cast aside; but at length it was again taken up by an English physician well termed the modern Hippocrates, who revived the practice of his great predecessor and gave to English medicine a practical tendency which it has ever since retained.

In spite of theories, English practice from the time of Sydenham has been regulated more by the teaching of experience than by the doctrines of the schools. For this reason, English physicians are justly trusted. They may sometimes be behind those of other countries in their theoretical knowledge, but in skilful and successful treatment of their patients they are second to none. So long as we lack a sufficient basis of facts experimentally ascertained in pathology and pharmacology, on which to found a rational system of therapeutics, we must be guided by clinical experience and practise empirically. Only as our knowledge slowly extends will we be able to cast aside empiric rules and confidently trust to the aid of science. Very slow indeed has been the progress of the medical sciences; for, although it is now forty-five centuries since the Egyptian Athothis[1] is said to have written the first book on anatomy, it is little more than as many years since pharmacology, the youngest of the medical sciences, began to be systematically studied.

If we turn again to the illustration we have

[1] Or rather his successor Usaphaïs (Egyptian Aesepti). Baedeker's *Handbook to Lower Egypt*, p. 86.

already so frequently employed, of the child and the lock, we will readily see that the study of the various parts of the lock in our illustration corresponds to anatomy, of their use and actions to physiology, of the derangements to which they are liable to pathology, and of the actions of the keys by which they may be affected to pharmacology.

Before therapeutics can become a science, the physician must know the action of his drugs, just as the locksmith does that of his keys, and since pharmacology is still so young, it is little wonder that medicine is yet only an art.

Let us now glance briefly at the history of the various branches of medical science, and see the way in which the ideas of its students were one by one corrected, when erroneous, by reference to fact. Amongst the early Greeks, there were several who studied the anatomy of animals; but it does not appear that human anatomy received any attention until the scholars of Praxagoras of Cos, coming to Alexandria, founded a new school.[1] Transplanted to this new soil, the old school

[1] Sprengel, *op. cit.* tom. i. p. 462.

seems to have found free scope for its development. Numerous were the discoveries made by its heads, Herophilus and Erasistratus ; and their works upon anatomy remained, indeed, the only worthy guide to the subject for ages together; for, although some of their scholars followed in their footsteps, yet the prejudices of the people soon put a stop to their pursuits. It seemed to them natural and right that slaves should be crucified ; that Christians should be covered with pitch and burned alive like torches ; that thousands should be made to slaughter one another, or should be devoured by wild beasts in the amphitheatres ; but the idea that a single dead body should be profaned by the dissecting scalpel was too horrible to be contemplated. Consequently, the refined, the cultivated, the compassionate, the sensitive Romans put a stop to the infamous study of anatomy, and then went with a clear conscience to enjoy the sight of a gladiatorial combat or the writhings of a Christian in the jaws of a tiger. History repeats itself : then it was anatomy which suffered ; to-day it is physiology.

The prejudices of his countrymen prevented Galen from studying human anatomy for himself; and he was thus obliged to trust to the discoveries of his predecessors, and to supplement them so far as he could by dissections of animals. His writings remained as the text-book of anatomy for nearly thirteen centuries. In 1315, Mondini again commenced the dissection of human bodies, and found that the descriptions contained in these writings were not always correct; yet the authority of Galen remained paramount for more than two centuries afterwards, until, indeed, Vesalius dared boldly to dispute it, with the result of drawing down upon himself the anger of the Church, and dying during a pilgrimage which he was compelled to undertake to avoid persecution and expiate his supposed crimes.

From this time onwards, the forms and relations of the different organs of the body were carefully studied, until little remained to be learned. A second impulse was, however, given by the application of the microscope under Malpighi; and another new era was inaugurated by Bichat's division of the body, not into organs merely, but into tissues. Another step not less important than that made by Bichat was taken by one still alive; for it was in 1838 that Professor Schwann applied to the animal body the discoveries of his colleague Professor Schleiden, and recognised the cell as the ultimate constituent of animal tissues.

A knowledge of the construction of the body was naturally followed by an inquiry into the functions of its various organs. The conclusions, however, which were drawn from appearances found in a dead body were frequently erroneous, and could only be corrected by comparison with the conditions existing in the living animal. Thus Erasistratus, misled by the empty condition of the arteries after death, concluded that during life they served for the transmission of air throughout the body. This opinion, when examined by Galen experimentally, was found to be wrong; for, wherever cut during life, blood issued, not air. Galen was on the brink of making the discovery of the circulation, and one would have thought that his immediate successors could hardly have avoided it; but, unfortunately, the plan which he followed of subjecting theory to the test of experiment seems to have been forsaken by them, and it was reserved for our countryman Harvey to discover and demonstrate this great truth.

Harvey employed the same method as Galen, and, like him, obtained great results. Before Harvey, Cæsalpinus seems to have arrived at a correct idea of the course taken by the blood. Harvey himself was led to form his ideas regarding it from the position of the valves in the veins, and might possibly have been able to describe it exactly without making a single experiment. Had he done so, Cæsalpinus and he would have stood nearly on the same level. Both would have given utterance to opinions, correct indeed, but unsupported by a sufficient array of facts to establish their truth. Thus they would have remained opinions only, liable to acceptance or rejection at the fancy of each succeeding student.

But Harvey did not stop here; he submitted his opinion to the test of experiment;[1] he saw that everything that his theory assured him ought to exist did exist; and then, strong in consciousness of truth, gave to the world, in an unpretending treatise of seventy-two pages, the results of his cogitations, now no longer mere opinions, but attested as facts by his experiments.

As physiology is intimately connected with pharmacology, and we shall be obliged to consider them together at a later period, we shall not pursue its history further at present, but pass on to pathology.

Just as the structure and functions of the healthy body are studied under two divisions—anatomy and physiology—so do its structures and functions in disease fall under the heads of pathological anatomy and pathology proper. Pathological anatomy shows what structural changes the disease produces; pathology proper informs us of the processes by which these changes are produced.

[1] *Exercitatio Anatomica* "De motu Cordis et sanguinis in animalibus." Francofurti, mdcxxviii. pp. 20 and 47.

Although the study of pathological anatomy was first pursued by Beneviani, it received its first essential impulse from Morgagni. The discoveries of Bichat inaugurated in it a new era, just as they had done in normal anatomy. The development of disease, so far as it could be traced from the alterations it had produced in the structures of the body at different stages of its progress, was examined by Rokitansky; and to Virchow we owe the recognition of the cell as a pathological unit.

Pathology proper—the study of disease in the living body—may be said to have begun with John Hunter. It was taken up and greatly developed by Magendie and his scholars, amongst whom may be specially mentioned Claude Bernard and Brown-Séquard; nor must Gaspard be forgotten, who, in the endeavour to produce typhus, injected putrid matter into the veins of a living animal. He failed, indeed, to obtain the result he expected and desired; but he discovered what was still more important—the effect of septic poisons.

CHAPTER V.

HISTORY AND METHODS OF PHARMACOLOGY.

Modern pharmacological research originated by Magendie—His plan of working—First example—Investigation of the action of upas (strychnia)—General effects when swallowed—Ideas of Magendie regarding the causation of these effects—His method of testing the truth of these ideas—Absorption of the poison—Difference between its absorption from mucous and serous surfaces—Does the poison act through the circulation?—Does it cause convulsions by acting on the brain or on the spinal cord?—Does it really act upon the cord?—Immediate application by Magendie of his pharmacological research to therapeutic purposes—Fouquier—Strychnia the first new remedy added to medicine by systematic pharmacological experiment—Second example of research—The investigation of curare by Claude Bernard—General action of curare—Brodie's discovery regarding mode of death and means of preventing fatal effects—Localization of its effects by Bernard—Exclusion of action on the muscles as cause of paralysis—Exclusion of action on the nerve trunks—Localization to ends of motor nerves—Action on the rest of the nervous system—How ascertained—Action of curare on the spinal cord and sensory nerves—Von Bezold—Schiff—Curare fatal when absorbed from a wound—Innocuous when absorbed from the stomach—Explanation of this—Elimination of poison—Bernard's experiments—Hermann's—Comparative action of drugs given on a full and empty stomach.

THE study of pharmacology, or the investigation of the action of drugs upon the body apart from their use in disease, appears to have had its origin in men's desire to discover poisons by which the lives of their enemies might be destroyed, or antidotes whereby their own might be saved. The general action of many drugs has long been known, and some of the most graphic descriptions ever given of them are those of Nicander of Colophon; but the analysis of their mode of action, like the study of microscopic anatomy, is of very recent origin. After localizing the seats of disease more exactly than had ever been done before, Bichat began to feel how vague and unsatisfactory were the notions then prevalent regarding the action of drugs, and how necessary it was to localize this action.

His early death prevented him from attempting the task; but it was taken up by his scholar Magendie, who not only laid the foundation-stone of modern pharmacology, but left behind him works which may still serve as a model for investigators.

The plan he pursued was exceedingly simple. It consisted, first, in preventing the drug which he wished to examine from reaching the particular part of the body on which it was supposed to act, and observing whether its action was abolished by this procedure; secondly, in applying the drug to that part of the body only, and noting whether it still exerted the same action as when applied to the whole body. The first poison with which he experimented was the upas, which was afterwards discovered to owe its activity to the presence of strychnia. The symptoms produced by this poison led him to think that it acted on the spinal cord. This supposition he tested by allowing the upas to act as far as possible on the rest of the body, but not on the cord. He then found that the symptoms were absent so long as the poison did not reach the cord, but that they appeared as soon as it did so. He next tested his supposition by applying the poison to the cord alone. When this was done the symptoms came on at once, although all other parts of the body were free from the poison. The demonstration was thus complete that the symptoms produced by the upas were due to its action on the spinal cord, and on it alone.

The method of experiment employed by Magendie in this research is so important that we will now consider it more in detail.

He first introduced a little of the upas under the skin of the thigh of a dog, and found that for the first three minutes no symptoms at all were produced. Then succeeded general *malaise*. The animal took shelter in a corner of the laboratory; and almost immediately afterwards convulsive contraction of all the muscles of the body occurred, the fore-feet quitting the ground for a moment on account of the sudden extension of the spine.

This contraction was only momentary, and almost immediately afterwards ceased; the animal remained calm for several seconds, and was then seized with a second convulsion, more marked and prolonged than the first. These convulsions succeeded each other at short intervals, gradually becoming more severe. The respiration was hurried, the pulse quick; and it was observed that, each time the animal was touched, a convulsion immediately followed. Finally, death occurred at an interval increasing with the age and strength of the animal.

These symptoms suggested to Magendie the following explanation of the action of the poison. It was, he thought, absorbed from the wound into the blood, by which it was carried to the heart, and thence to all the organs of the body. On arriving at the spinal cord, it acted upon it as a violent excitant, producing the same symptoms as mechanical irritation or the application of electricity.

But, just as Harvey was not to be satisfied with the mere probability suggested by the position of the valves in the veins, so Magendie was not content until he had tested his theory by experiment. The first question to be settled was *whether the poison were absorbed or not.*

To test this supposition, he applied the upas first to the serous membranes, the peritoneum and pleura, from which, as he had learned by previous experience, absorption takes place with extreme rapidity. The result showed that his supposition was correct. The symptoms appeared almost immediately after the injection of the poison into the pleura, and within twenty seconds after it had been injected into the peritoneum. In order to ascertain whether absorption took from mucous as well as from serous surfaces, he isolated a loop of small intestine by means of two ligatures, and injected a little of the poison into the part between them. In six minutes, symptoms of poisoning appeared, showing that absorption had occurred; but they were less intense than when the poison was applied to a serous surface.

Further experiments showed that absorption took place from the large intestine, from the bladder, and from the vagina; but that it was comparatively feeble and slow. When introduced into the stomach along with food, upas invariably caused death; but the symptoms did not appear until half an hour after it had been taken. This delay might have been due either to absorption from the stomach having taken place very slowly or not at all; so that the drug had passed on to the small intestine, and thence been absorbed into the blood. To determine this point, he isolated the stomach by ligatures applied to its cardiac and pyloric orifices, and then injected a little of the poison into its cavity.

Under such conditions, symptoms of poisoning were only observed after the lapse of an hour. This showed that, while absorption from the stomach did occur, it was much slower than from the small intestine.

The second question was, *Does the poison act through the circulation?* If so, reasoned Magendie, the first symptoms of the action of the poison will come on more slowly when it has far to travel to the spinal cord from the point of introduction; and *vice versâ.* On testing this by experiment, he found that, when the poison was injected into the jugular vein, tetanus occurred almost instantaneously, and death took place in less than three minutes, for the upas had only to pass through the pulmonary circulation and heart to the arteries of the cord.

When injected into the femoral artery (at D Fig. 1), the distance to be travelled before reaching the cord would be greatly increased, for the poison must first pass through the artery itself, through the capillaries, and along the vena cava, traversing the whole distance marked D A B in Fig. 1, before it reached the point where it entered the circulation when it was injected into the jugular. Under these conditions, the action should be slow,

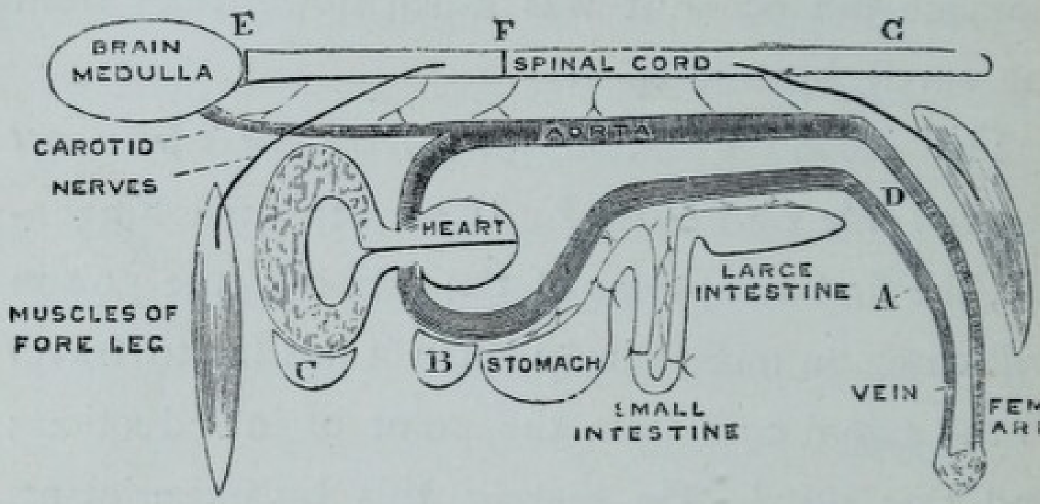


FIG. 1.—Diagram illustrating method of investigating the mode of action of upas (strychnia). A, femoral vein ; B, peritoneum ; C, pleura ; D, femoral vein ; E, F, G, spinal cord, to which small arteries are seen passing from the aorta.

and experiment showed this to be actually the case, for no symptoms appeared until seven minutes after the injection. Although these experiments of Magendie's appear to prove completely that the upas poison acts through the circulation, a number of persons nevertheless considered that the symptoms were produced through the nervous system by means of so-called sympathy. In order to remove their doubts, Magendie narcotised a dog by means of opium, and then divided all the structures of one leg with the exception of the artery and vein. Into this almost isolated limb he then introduced a little of the poison. This was followed by the usual symptoms almost exactly as if the limb had been intact. By pressing upon the vein which passed from the limb to the body when the symptoms of tetanus appeared, he was able to arrest their further development, and by releasing the vessel and allowing circulation to have free course, the symptoms reappeared. Lest by any chance the poison might have acted through nerves or lymphatics contained in the walls of the artery and vein, he divided these structures also, connecting the severed ends by means of quills, through which circulation then took place. When the poison was applied to the severed limb connected with the body only by these quills, the same succession of phenomena occurred as when the limb was uninjured. The possibility of the action being due to sympathy between the nervous system and the point of application of the poison was thus completely excluded, and the operation of the poison through the circulation triumphantly demonstrated. The fact, however, that by arresting the circulation after the symptoms of poisoning had occurred, taken in connection with the diminished violence of the symptoms when the poison was absorbed from the stomach instead of being applied to a wound or injected directly into the circulation, became the point of departure for another investigation. This, however, as we shall see by and by, was not made by Magendie himself, but by Claude Bernard (p. 93).

The next question was, *whether the convulsions were caused by the action of the drug on the brain or the cord.* To ascertain its action upon the brain, a little of the solution was injected into the carotid artery. The effects produced were the same as those of any irritating liquid. The intellectual faculties disappeared, the head was laid between the paws, and the animal rolled over and over like a ball. These effects passed off as the circulating blood removed a quantity of the drug from the brain, and were succeeded by the ordinary tetanic convulsions when sufficient time had elapsed for it to reach the spinal cord.

The question, *whether it really acted upon the cord*, still remained to be put to a crucial test. If its effects were really due to its action upon the spinal cord, they ought to cease upon the destruction of that part of the nervous system, and to occur when the drug was applied to it alone.

The cord was, therefore, destroyed by running a piece of whalebone down the vertebral canal at the moment of injection. When this was done, no tetanus occurred. In another experiment, Magendie waited until tetanic spasms had been induced by the upas, and then destroyed the spinal cord by slowly pushing the whalebone down the vertebral canal. As the whalebone advanced, the tetanus disappeared, first in the fore-legs, when the dorsal part of the cord was destroyed, and then in the hind-legs, when the whalebone had reached the lumbar vertebræ.

In another experiment, an animal was narcotised by means of opium, and the spinal canal laid freely open. The upas was then directly placed on a part of the spinal cord. Tetanus immediately occurred in that part of the body, and in that part only, to which the nerves arising from this portion of the cord were distributed. When the poison was successively applied to other parts of the cord, the convulsions spread to the corresponding regions of the body.

Having thus clearly demonstrated the *modus operandi* of the poison, his next thought was to turn this discovery to practical use. I here quote the passage in which he suggests the therapeutical employment of the first fruits of modern pharmacological research.

"Medicine would, perhaps, derive great advantage from the knowledge of a substance whose property is to act especially on the spinal cord, for we know that many very severe diseases have their seat in this part of the nervous system; but upas does not occur in commerce, and, even though experience should show it to be a precious medicine, how is to be procured?"

This question Magendie himself answered by investigating the physiological action of a substance obtained from the same natural order of plants as that from which the upas was derived. This was *nux vomica*, which is found abundantly in commerce. The extract obtained from it was shown by experiment to have an action almost exactly like that of upas. While seeking an opportunity to apply this in practice, his intention was forestalled by M. Fouquier, who was induced, probably by the publication of Magendie's research, to use nux vomica in cases of paralysis. His success was great, and the results he obtained were shortly afterwards confirmed by Magendie himself, who had used the drug as he originally intended, before becoming aware of Fouquier's experiments. To pharmacological research, therefore, we owe one of the most valuable remedies we possess.

The second example that we shall take of pharmacological research is the investigation of the curare poison by Magendie's pupil, Claude Bernard.

This poison, under the various names of curare, woorara, wourali, urari, ticunas, &c., is used by the natives of Demerara and the valley of the Amazon to poison their arrows. An animal, wounded by one of these arrows, soon lags behind the rest of the herd, becomes powerless, quietly dies without any sign of suffering, and appears indeed to go quietly to sleep.

After the animal is apparently dead, however, the heart can be felt beating vigorously for a considerable time, and if an artery be cut across, the blood jets forcibly from it. This shows that death does not occur from failure of the circulation; and it occurred to Sir Benjamin Brodie, so long ago as 1812, that, if he could only keep up the respiration artificially until the poison was eliminated, the animal would be saved. Although he was unsuccessful in his first attempts, a little perseverance enabled him to overcome all obstacles, and his endeavours were rewarded by perfect success.[1] Brodie thus proved that curare caused death by paralysing the respiration; but he did not discover how this paralysis was produced;

[1] *Phil. Trans.* 1812, pp. 205–227.

nor was it until 1844 that the researches of Bernard solved the problem.

Paralysis may depend either on the muscles which, by their contraction, effect movements, on the motor nerves which excite these muscles to action, or on the nervous centres from which the stimuli to these motor nerves usually proceed.

Working backwards, Bernard found that curare did not produce paralysis by acting on the muscles, for, on stimulating them by a galvanic current in a frog killed by this poison, he observed that they contracted as readily and strongly, and continued to do so for as long a time after the death of the animal, as when it had been killed by decapitation. But when he applied the current to the nerves the result was very different. Then the muscles to which the nerves were distributed contracted readily in the decapitated frog, but did not contract at all in the one poisoned by curare. The motor nerves were thus proved to have lost their power, and the abolition of their function might be fairly regarded as the cause of the paralysis and death produced by the poison.

Was this loss due to the action of the curare on the nerve-trunks, or on their terminations within the muscles? This question Bernard settled by steeping a nerve and a muscle for a short time in a solution of the poison and then stimulating them by a galvanic current. When the trunk of the nerve ~~animal~~ alone had been exposed to the action of the curare, its irritability and power over the muscle remained apparently unimpaired; but when the muscle had been soaked in the solution, so that the poison reached the ends of the nerves within it, the power of the nerve to cause such action was perfectly destroyed.

The action of the poison was thus localised to the ends of the motor nerves, and the abolition of their functions might be fairly regarded as the cause of the paralysis and death produced by the poison.

But it was also possible that other parts of the nervous system might be affected in a similar way; and, to ascertain whether this was so or not, Bernard adopted a most ingenious method of experiment. It was evident that the paralysis of the motor nerves, which the curare produced, would completely destroy the usual means of communication between the nerve-centres and the muscles, and thus prevent the brain or spinal cord from setting the muscles into action. These centres might, therefore, still retain their functions unimpaired, although they had no power to manifest them.

In order to give them an opportunity of doing this, it was necessary to exclude one limb from the action of the poison, in order that, by retaining its power to move, it might act as an index to what was going on in the nerve-centres. Bernard accordingly tied the artery and vein in the leg of a frog, close to the knee, and then introduced some curare under the skin of the back. The poison was soon carried by the blood to every part of the body, excepting that from which the circulation had been cut off by the ligature.

In the accompanying figure, the poisoned parts are shaded, while the unpoisoned part is unshaded.

When the whole frog was poisoned, Bernard observed that pinching the skin produced no movement in any part of the body; but he now found that, while no movement took place in the poisoned part, pinching the skin on any part of the body

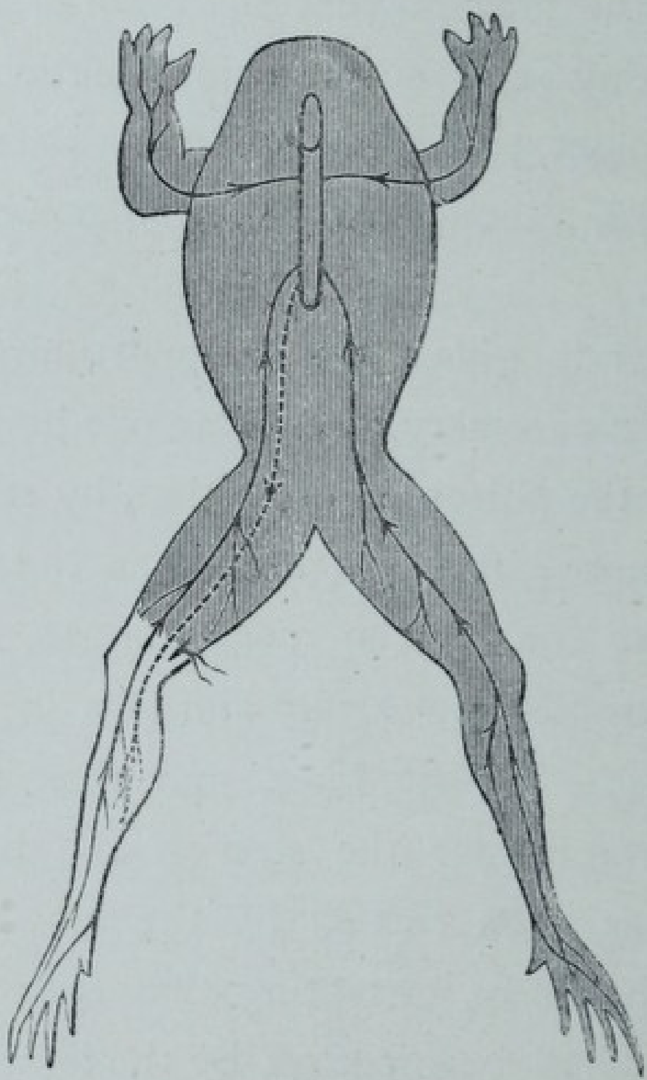


FIG. 2.

was followed by movements of the non-poisoned leg. It was then clear that the sensory nerves and spinal cord retained their functions, and that the want of movement in the poisoned parts of the body was due only to the paralysis of the motor nerves, which prevented the spinal cord from setting the muscles in these parts into action.

When, for example, the skin of the poisoned leg (which in the diagram is the shaded right one) was pinched, the irritation was transmitted up the sensory nerves, in the direction of the arrows, towards the spinal cord, and reflected by it down the motor nerves of the other limb to the muscles both above and below the knee. But it was only below the knee, in the part protected from the poison, that they responded to the stimulus.

As he had previously determined that the contractility of the muscles was not affected by the poison, this experiment seemed to prove that the action of the poison was limited to the peripheral ends of the motor nerves. For the sensory nerves, the spinal cord, and the trunks of the motor nerves above the knee had all been exposed to the action of the poison, and yet they still continued to do their work.

Thus it appeared that the fault must lie with the terminations of the motor-nerves within the muscles, and with them only.

But it often happens that the discovery of some prominent fact throws others into the shade for a while, and it is only after some time that its importance, at first overlooked, begins to be recognised.

Thus it was with curare. Its action seemed at first to have been so strictly limited to the motor nerves, by Bernard's experiments, that any slight indication to the contrary would have been passed over without attention. But, after some time, Von Bezold noticed that reflex action ceased before the nerves had completely lost their power over the muscles; and Schiff observed[1] that, when the circulation in a frog was arrested at the knee, a pinch below the ligatured point caused movement, while it had no effect on the poisoned skin of the thigh.

Bezold's observation showed that the spinal cord was affected by the poison, and Schiff's, which I have myself repeated and confirmed, shows that

[1] Schiff and Lange, *Lo Sperimentale An.* xxii.

the sensory nerves have their conducting power destroyed by curare, but that they are less affected and after a longer interval, than the motor nerves.

Magendie noticed, in his experiment with the upas, that the symptoms not only came on more slowly, but were less violent, when the poison was introduced into the intestines, than when applied to a wound, and that when they might be controlled by arresting the return of blood from the point of introduction.[1]

A similar observation was made by Bernard, who found in his experiments with curare, that, although invariably poisonous when introduced into a wound or injected directly into the circulation, it apparently did not act at all when taken into the stomach, unless the dose was very large. At first, Bernard imagined that this might be due to the destruction of the poison by the juices of the stomach. Mixing it, however, with gastric juice, he found that its activity remained unimpaired. Another reason then suggested itself, viz., that while absorption was taking place

[1] *Vide* p. 82.

from the stomach, excretion of the poison might occur by the kidneys. If these were to go on *pari passu*, the amount of poison present in the blood at one time would be too small to produce its characteristic effects. This hypothesis he at once tested by extirpating the kidneys of a frog, and thus entirely checking excretion through those organs. When curare was then administered by the stomach, poisoning took place more slowly, but quite as surely, as when it was applied to an open wound. The same result was arrived at independently by Ludimar Hermann, who was unaware of Bernard's researches. In his experiments, he used warm-blooded animals, and tied the renal artery, instead of extirpating the kidneys. These researches enable us to understand how it is that drugs exert a more rapid action when introduced into the empty stomach than when given along with a full meal, and why a dose of morphia, injected under the skin, should not only act more quickly, but more powerfully, than the same quantity given by the mouth or by the rectum.

CHAPTER VI.

PHARMACOLOGICAL METHODS.

Third example of pharmacological research, erythrophleum (casca) —Its source—Employment as an ordeal poison—Action as a purgative—As an emetic—As a diuretic—As paralysing motion —Determination of its mode of action—On the intestines—On the stomach—On muscular power—Stumbling noticed in cases of poisoning—Elimination of muscles and motor nerves as cause of weakness—Localization of its action on the spinal cord—Direct action or indirect action?—Elimination of direct action—Demonstration of the dependence of paralysis on weakened circulation—Mode of action of casca on the circulation—Action on frog's heart—On the vagus—On the cardiac ganglia—Action on the blood-pressure—Contraction of the arterioles not due to effect on the vaso-motor centre—Action on the muscular walls of arterioles or nerves within them—Action of the drug on the secretion of urine—In small doses—In large doses—Probable cumulative action of the drug.

As a third example of pharmacological investigation, I shall take casca bark, which I have lately been examining with Mr. Pye, and I choose this because it illustrates various methods of examining the action of a drug on the different organs of the body. The methods we employed were not new. I could have found a better investigation of the action of a poison upon the heart and circulation in Von Bezold's admirable work on *Atropia*, of action upon muscles in his examination of veratria, of action upon the stomach in Giannuzzi's investigation of tartar-emetic, and of action upon the kidneys in Ustimovitch's research on urea and potash. But in none of these works should I have found all the methods combined. I have selected this drug, moreover, because I believe it to be deserving of attention and likely to prove of great use in practical medicine.

This bark is used as an ordeal poison along the greater part of the coast line of Western Africa, with the exception of Old Calabar. In different districts it bears the names of "doom," "gidu," "sassy," "saucy," "cassa," and "casca." It is obtained from the Erythrophleum Guinense, which, like the calabar-bean, belongs to the natural order Leguminosæ.

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. If he be purged, he is pronounced guilty.

The other way is to bend several boughs of trees, and stick both ends 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 be able to walk through without stumbling, he is considered to be innocent. If he stumble, 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 is decided, are thus: vomiting, purging, and loss of muscular power or co-ordination. (*Vide* Appendix.)

Some of this bark having been brought from Angola by Mr. Monteiro, I made a few experiments on its action, the results of which he published in his work. These experiments showed that the poison acted upon the heart in much the same way as digitalis; but other engagements prevented me from making at the time an exhaustive investigation.[1]

[1] *Angola and the River Congo*, by I. Monteiro, p. 61. London: Macmillian, 1875.

The experiments of others have shown that vomiting and purging may be due either to local action of an irritant substance upon the mucous membrane of the stomach and intestine, or to its effect upon those parts of the nervous system which regulate the secretion and movements of these organs.

In order to ascertain in what manner the casca produced these effects upon the intestinal canal, a quantity of infusion was administered to an animal. Vomiting and purging both took place, just as in the case of the persons subjected to the "ordeal." When the infusion was injected under the skin, or into a serous cavity, equally violent vomiting occurred, but there was no purging.

It was, therefore, clear that the purging was due to the local action of the poison upon the intestine, but that the vomiting was caused through the medium of the circulation.

The poison, however, is conveyed by the blood to the stomach itself, as well as to the central nervous system. Its effects might, therefore, be produced by irritation of the walls of the stomach, as well as by means of its action on the nervous centres.

The connection between the stomach and the nervous centre is kept up chiefly, if not entirely, through the vagi and the splanchnics. If these nerves were divided, a poison, which acted by irritation of the stomach, ought no longer to be capable of producing its usual effect. The vagi were, therefore, divided before the injection of the poison, and then we often found that vomiting or retching either did not occur, or was much less violent than usual.

The purging might be due either to increased secretion or increased peristaltic action. If it had been caused by the former, a quantity of the drug, introduced into an empty loop of intestine, isolated from the rest by two ligatures, ought to have caused a secretion of fluid, as Moreau has shown to result from other purgatives, such as sulphate of magnesia.

This, however, was not the case; and we therefore concluded that the purgative action was due to increased peristaltis of the bowel.

The following diagram shows the method of experiment :—

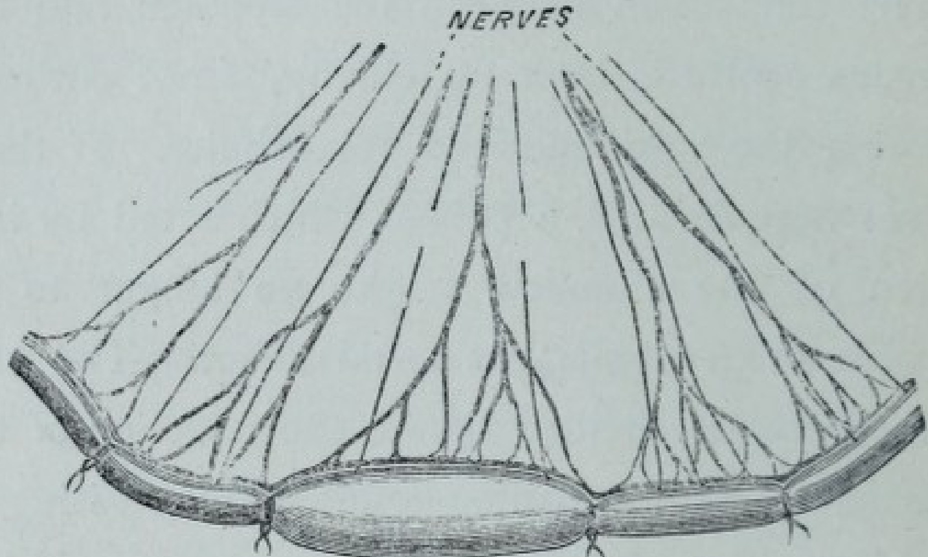


Fig. 3.—Intestine, with mesentery attached. Three loops are isolated by ligatures, and into the middle one the drug to be investigated is injected, and the effect ascertained after four or five hours.

The second symptom, regarded as a proof of guilt in those subjected to the "ordeal," is want of power to walk properly. 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 excluded the muscles and motor nerves, as we found that neither of them lost their irritability when the poison was applied to them in the same manner as curare in Bernard's experiments.

The spinal cord was the next point of the nervous system to which we directed our attention. We noticed that, some time after an injection of casca under the skin of a frog, the movements of the animal became sluggish and were imperfectly performed. When the toes were pinched, the foot either moved lazily or not at all, instead of being promptly drawn up.

The reflex activity of the cord was thus seen to be impaired. It would not be wise, however, to conclude hastily that this impairment was due to the effect of the drug upon the nervous tissue itself; for imperfect circulation through the brain and spinal cord quickly deprives these organs of their power.

Although arrest of the circulation does not abolish the functions of nervous centres so quickly in the frog as in warm-blooded animals, it nevertheless does so after a time. The effect of the casca upon the cord might, therefore, be due to its action, not upon the nervous tissues, but upon the circulation.

On examining the heart of the frog after the drug had begun to act, it was found that its pulsations had ceased. It seemed, therefore, quite possible that loss of power in the spinal cord was due to an arrest of the circulation; but, of course, this was only a hypothesis, as the casca might act both on the heart and the cord itself.

To decide this point we administered casca to one frog, and waited until the heart had stopped. The instant it had done so, we arrested the circulation in another frog of a similar size, by a ligature drawn round the large vessels close to the heart.

The circulation was thus arrested equally and simultaneously in both animals. In one of them the poison had been previously carried by the blood to the spinal cord, and could still act upon it, although circulation had stopped.

If the casca had any paralysing action upon the nervous substance of the cord, reflex action ought to cease in the poisoned frog first. But this was not the case. In both animals reflex action ceased almost exactly at the same moment.

The diminution of power in the spinal cord seemed, consequently, to result from the action of the drug on the circulation. We therefore arrived at the conclusion that alterations in the heart's pulsations were the cause of the staggering gait and want of muscular power exhibited by the victims of the "ordeal."

The action of the drug upon the heart and circulation was the subject of our next inquiry. After its administration to a frog the first effect observed is that the heart beats more slowly. Then the ventricle contracts irregularly, some parts of it being firmly contracted and white, while others remain partially dilated and filled with blood, so as to present the appearance of little red pouches studding the surface of the organ. Finally, the ventricle stops altogether in systole, while the auricles continue to pulsate for some time.

This condition is almost like that produced by digitalis. Further experiments have shown us that casca also resembles this drug in its action upon the cardiac nerves. When a moderate dose of casca is injected into the jugular-vein, the pulse becomes slow. A further dose makes it quick; and another large dose again renders it slow.

Slow pulsation of the heart indicates that its regulating nerves are in a state of abnormal excitation. This regulating or inhibitory nervous apparatus is partly situated in the heart itself, and partly in the medulla oblongata, and these two are connected by means of the vagi nerves.

The medullary or central is more sensitive to the action of many drugs than the cardiac or peripheral portion, and was, therefore, likely to be the one first affected by the poison. If this were so, division of the vagi, through which it acted upon the heart, would remove the slowness of the pulse occasioned by the action of the casca.

Experiment confirmed the truth of this. The effect produced by section of the vagi was an immediate quickening of the pulse. The same condition was brought about, as I have already mentioned, by the injection of an additional dose of casca when the vagi were left untouched. This effect rendered it probable that the additional dose paralysed the ends of the vagi in the heart.

When an electric current is applied to the vagus, it usually causes immediate stoppage of the heart's pulsations. If, however, this irritation be applied after the casca has quickened the heart, no effect is produced by the galvanism. This clearly shows that the usual power of the nerve over the heart has been completely abolished.

Since, then, a moderate dose of casca destroys the power of the vagus, through which slowness of the pulse is usually produced, and, nevertheless, the injection of a further dose still slows the heart's pulsations, this slowness must, we think, necessarily be due to an action of the drug upon the ganglionic structures or muscular fibre of the heart itself.

We have hitherto considered its action upon the heart alone; but, on the injection of a small dose, an effect upon the circulation becomes manifest before any change whatever can be noticed in the pulse. This effect is a rise in the blood-pressure.

This rise continues after the pulse has become slow, and it does not fall during the intervals between each cardiac systole.

This satisfactorily demonstrates that the arterioles through which the blood flows from the arteries into the veins have become contracted, for the blood-pressure would otherwise fall much during the intervals. The next question is, How is this contraction induced? It may be that the drug acts upon the muscular walls of the arterioles themselves, upon the nerves which stimulate these walls to contraction, or upon vaso-motor centres situated either in the spinal cord or the medulla oblongata.

The chief vaso-motor centre is situated in the medulla; and usually, when its connection with the arterial system is destroyed by cutting across the cord at the occiput, the arterioles dilate and the blood-pressure falls.

If any drug should raise the blood-pressure by acting upon this centre in the medulla, its effect will be prevented by dividing the cord in this way before its administration. On dividing the cord and injecting casca, we found that the blood-pressure rose higher than in any other experiment.

The drug, therefore, does not produce contraction of the arterioles by its action upon the general vaso-motor centre in the medulla, but by acting either upon the arterioles themselves or upon vaso-motor nerves or ganglia not contained in the medulla.

In order to ascertain, if possible, whether these centres were contained in the spinal cord, or were in the neighbourhood of the vessels themselves, we divided the sympathetic in the neck of a rabbit, and thus cut off the vessels of the ear from their connection with any nervous centre excepting such ganglionic cells as might lie in the immediate neighbourhood.

We then injected a dose of casca, which caused the vessels in both ears to become equally pale. Had the contraction depended upon excitation of a vaso-motor centre in the spinal cord, it would have affected the ear whose nerves had been left entire to a greater extent than the one in which the vaso-motor nerves had been divided. We thus localize the excitation to muscular fibres or nerves in the arterial walls.

As the action of casca resembles in many points that of digitalis, it seemed not improbable that it would exert a similar action upon the kidneys also. A dog was, therefore, anæsthetised by chloroform, and a cannula placed in one ureter, so that the urine could be collected as it flowed from the kidney, and the rate of secretion exactly discovered.

The experiments of Ludwig and Max Hermann had already shown that this rate depends upon the pressure within the renal glomeruli ; and it was to be expected that, as the pressure rose after the injection of casca, the rate of secretion would be increased.

On trying the experiment our expectations were realised, for a single dose both raised the blood-pressure and quickened secretion. Another dose raised the blood-pressure still higher; but the secretion of urine, instead of becoming quicker, began to slacken ; and, when the blood-pressure had risen to its maximum, it stopped altogether.

But when, after a while, the blood-pressure began to fall, the secretion again commenced. This indicated that the casca had exerted its contracting power to a greater extent upon the arteries of the kidney than upon those of the body generally; so that, notwithstanding the rise of pressure in the arterial system, the contraction of the renal arteries had almost entirely cut off the supply of blood to that organ. As the effect of the drug passed off, the renal arteries relaxed again allowing the blood free access to the kidneys.

In this respect, the action of casca agrees exactly with that of digitalis.[1] It seems likely that, like digitalis, casca will possess a cumulative action; for if, during the course of its administration, it should arrest excretion by the kidneys while it is still being absorbed from the stomach, poisoning will occur, just as in Hermann's experiment with curare.

[1] *Vide* Brunton and Power "On the Diuretic Action of Digitalis," *Proc. Roy. Soc.* No. 153, 1874.

CHAPTER VII.

PATHOLOGY.

Application of Pharmacology to Clinical Medicine—Connection between Pharmacology and Semiology by Pathology—Meaning of Pathology—Example—Explanation of Symptoms in Mitral Disease—Of Duskiness—Remedy for this—Œdema—Cause of it—Experiments of Lower—Ranvier—Demonstration that Œdema depends on Vaso-motor Paralysis as well as Vascular Obstruction—Effect of Vaso-motor Stimulation in causing Absorption—Goltz's Experiment—Use of Digitalis and Erythrophleum in Œdema—Pathology of Aortic Disease—Injurious Action of Digitalis—Utility in later stages where Mitral Incompetence is superadded.

In casca, then, we possess a drug which strengthens and slows the heart, contracts the arterioles, and increases the urine.

Having gained this knowledge, how are we practically to apply it? What connection is there between our acquaintance with the parts of the body on which the drug acts and the symptoms of any disease with which we meet at the bedside?

The connecting link between these two, pharmacology and symptomatology, is pathology. This traces back the symptoms of disease to alterations in the structure and functions of the different organs, just as we have seen pharmacological experiment in the hands of Magendie trace back the symptoms produced by strychnia to the spinal cord.

Only too often are we called upon to see cases where, on the least exertion, the heart begins to palpitate ; the breathing becomes difficult ; and, as the disease progresses, suffocation threatens. The patient sits upright in bed ; the face becomes dusky, the lips livid ; the feet swell ; and death ends the scene.

To what organic changes are these symptoms due ? and how are these changes to be remedied ? Harvey's discovery and Malpighi's demonstration of the capillaries have made it easy and natural to connect the rosy hue of health and the flush of exertion with full vessels and active circulation, and to attribute the pallor of death to absence of blood.

It is to the blood, then, that the skin chiefly owes its hue ; and duskiness of the skin indicates darkness of the blood. But the experiments of Lower have shown that darkness of the blood is caused by deficient respiration, and is removed by exposure to air. We therefore trace the dusky skin to deficient aeration ; but we cannot yet say whether the air has been prevented from reaching the blood, or the blood from reaching the air.

Here the discoveries of Auenbrugger, Laennec, Corvisart, Hope, Williams, Corrigan, and many others, come to our aid. We percuss the chest and listen to its sounds. We find, let us suppose, no hyper-resonance, and hear no rattling in the bronchial tubes. We thus learn that the air is not prevented by mucus from filling the lungs, nor is the area of contact with the blood lessened by emphysema.

The lungs, then, are not in fault, and we pass on to examine the heart. On percussion, we find the organ enlarged ; on palpation, we perceive the apex displaced to the left ; and on auscultation, we hear the sharp "lubb" of the first cardiac sound replaced by a whiff like that of a bellows. From this, we know that the valve which ought to prevent the backward flow of blood from the left ventricle during its systole is inefficient; and that, like one sliding back at each step while walking on a slippery road, the heart must beat with abnormal power to carry on the circulation. No wonder, then, if it palpitates at the slightest unusual call upon its efforts.

But more than this: each pulsation not merely fails of its proper effect in forwarding, but positively retards the circulation; for each systole sends a jet of blood back into the auricle and obstructs the flow in the pulmonary veins. The blood cannot pass through the lungs with sufficient rapidity; aeration is, therefore, deficient. Thus we learn why the respiration is laboured, the skin dusky, and the lips livid.

How, then, is this to be remedied? First of all, it would be an advantage to make the heart beat more slowly; for, when it pulsates rapidly, there is no time for the pulmonary veins to become well emptied between each systole. By lengthening the interval between them, the ventricle has time to become better filled, and sends a fuller current into the wide aorta, and a proportionately small amount back into the pulmonary veins through the narrow chink in the mitral valves.

But, if this were all, why should not a drug like aconite serve our purpose, for it slows the heart? The reason is that it also weakens it; and, in the conditions which we have just been considering, one of the most important factors is weakness of the right ventricle; for it is in the pulmonary circulation that the resistance lies, and one of our most important tasks is to strengthen the propulsive power of the right ventricle, as well as to remove obstruction in front.

This end we gain by employing digitalis or casca, which increase the strength at the same time that they diminish the rapidity of the cardiac contractions.

The next symptom is the œdema. This depends upon accumulation of fluid in the cellular tissue, and may be due either to too much being poured out from the blood-vessels, or to too little being re-absorbed.

It was attributed by. Lower, in 1680, to diminished absorption by the veins ; his idea being based upon some experiments in which he tied the vena cava, with the effect of producing great œdema of the lower extremities. His opinions were confirmed by the observations of Bouillaud, who noticed a similar condition in patients suffering from thrombosis of the iliac veins. His experiments, however, were repeated by Valsalva, Hewson, and several others, with a different result ; and it was not until Ranvier, in 1870, again investigated the question, that the cause of the discrepancy between these observations was ascertained.

On tying the vena cava in the abdomen of a dog, Ranvier found that œdema did not come on unless the nerve of the limb was divided at the same time. But when the sciatic was cut on one side the arteries dilated, the leg became warm and œdema came on, while no swelling was perceptible on the opposite limb, although the venous circulation was equally obstructed in both.

The reason of this appears to be that, so long as the arteries were not unnaturally dilated, the lymphatic system sufficed to absorb the fluid poured out for the nutrition of the tissues, so that no excess accumulated in them.

Whenever section of the vaso-motor nerves allowed the arteries to become dilated, more fluid was poured out than the lymphatics could absorb; and, the veins being prevented from removing the excess as they would have done under ordinary circumstances, it remained in the tissues, producing œdema.

That this effect was due to paralysis of the vaso-motor, and not of the motor nerves of the limb, was shown by Ranvier in another experiment. He divided the roots of the sciatic nerve in the spinal canal before they had been joined by the communicating branches from the great sympathetic.

He thus cut the motor without injuring the vaso-motor nerves, and rendered the leg completely powerless, without altering the vessels. In this case, no œdema occurred, although the vena cava had been tied as in the former experiment.

We see, then, that contraction of the arterioles may prevent œdema, even although venous obstruction exists; and we are warranted in

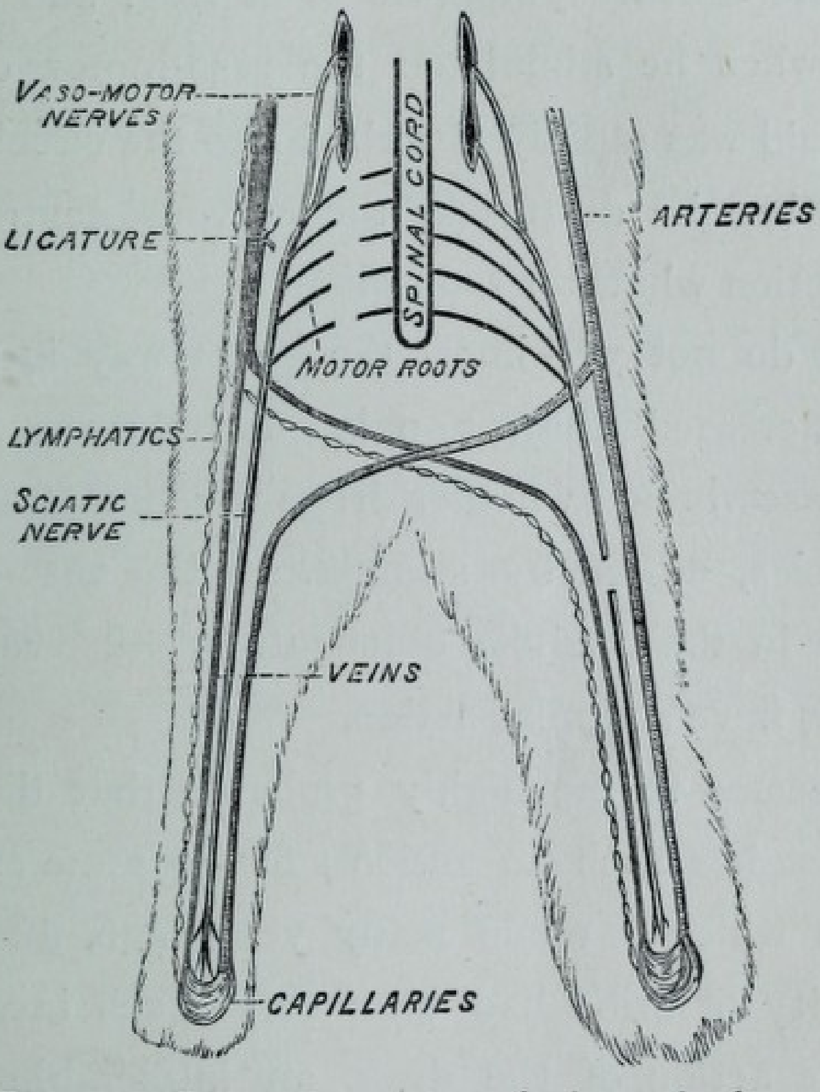


FIG. 4.—Diagram to illustrate the pathology of œdema. On the one side the sciatic nerve has been cut, and the limb rendered both powerless and œdematous; on the other side the motor roots alone have been divided, and the limb, though powerless, is not œdematous.

supposing that it will diminish the œdema after it has already come on.

But more than this: stimulation of the vaso-motor centre increases absorption. This was shown by Goltz, who injected a quantity of fluid into the dorsal lymph-sac of a frog, and found that, when he stimulated the vaso-motor centre, this fluid was rapidly absorbed into the circulation. But when he destroyed the nervous centres, no absorption whatever took place.

We do not yet know the exact way in which this increased absorption is effected; nor has it been ascertained whether drugs which contract the arterioles, either by stimulating the vaso-motor centre in the medulla oblongata or other vascular nerves, have a similar action.

It seems to me highly probable that digitalis at least has such an action; for, in some experiments which I made many years ago, after the quantity of urine had been very much increased by the action of the drug, an intolerable thirst came on, which I was obliged to satisfy by drinking a quantity of water greatly in excess of the allowance to which I had restricted myself every day for the preceding six months.

By the use, then, of a drug like casca, which contracts the vessels, we will almost certainly lessen œdema by diminishing the flow of blood through the arterioles. At the same time, in all probability, we will increase absorption, both by a direct action upon the circulation and tissues and by the secondary effect proceeding from the augmented urinary discharge.

Digitalis has hitherto been our great resort in mitral disease, but I think it probable that in casca we possess a drug more powerful still; at least, its effect upon the arterioles appears to be greater than that of digitalis, and it is quite possible that it may succeed in those cases of advanced mitral disease where digitalis fails.

From these examples, it will be evident that the use of experiment to the student of medical science is the same as that of a solar observation to the mariner. An unwise sailor may trust to his "dead-reckoning," and thus make shipwreck; but the wise navigator will not be content with calculating his position from his rate of sailing and the direction of his course. He knows that irregular winds and unseen currents may falsify his calculations, and he will use every opportunity of correcting them by actual observation of his latitude and longitude. Day by day, he rectifies any error into which he may have fallen, and thus he can proceed with confidence, knowing he can never be far astray. When, on the other hand, no such a correction is made, each erroneous calculation forms a false starting-point for the succeeding one, and the error daily grows.

Thus it was that the ancients, founding a great speculation on a small fact, and building one fancy on another, landed themselves in utter confusion. Erasistratus found the arteries empty after death; he therefore concluded that they contained air during life, and then went on to fancy that when blood got into them it troubled the spirit they contained, and caused fever or inflammation.

Harvey found valves in the veins, and therefore thought it probable that the blood circulated, instead of oscillating backwards and forwards; and the tetanic spasms caused by upas led Magendie to believe that it acted on the spinal cord. But neither was content with mere probability ; each walked as on a quaking bog, and tested each step before taking it. If their interpretation of the facts was a correct one, they should be able to predict, and by actual experiment they could ascertain whether their predictions accorded with facts, and thus determine the truth or falsehood of their beliefs.

If the blood circulated, pressure on the veins must make them empty above and full below the point of constriction. If upas acted on the spinal cord, its action must cease when the cord was destroyed. In each case the experiment was tried—the expected result followed, and thus the thoughts of Harvey and Magendie passed from the region of speculation and belief into that of ascertained fact. Every step thus gained affords sure foothold for another, and thus science daily grows.

Already the experimental method has done much for medicine, and in my next lecture I purpose to consider the chief gains we have obtained by its use.

CHAPTER VIII.

THERAPEUTICS.

Pathology of Aortic Disease—Casca and Digitalis do not fulfil indications in ordinary cases, but do so in later stages where Mitral Incompetence is superadded—Gastric Irritation a cause of irregular Cardiac Action—Scientific treatment of this condition—Bromide of Potassium—Opium—Chloral—Double action of Atropia on Vagus—on sensory Nerves of the Heart—Use in Irritable Heart—The Vaso-motor Centre a Regulator of Blood-pressure by its action on Arterioles—General Contraction of Arterioles a cause of Angina Pectoris—Method of reasoning—Object of Bleeding—Use of Nitrite of Amyl in Angina—in localised Spasm of Arterioles, in Migraine—in Epilepsy—Bromide of Potassium in Epilepsy—in Uterine Diarrhœa—Anæmia and Sleep—Digitalis indicated in vascular flaccidity—Chloral in Cardiac over-action and excessive vascular tension—Chorea—Use of Hemlock (conia and methyl-conia).

Having now described some examples of the method by which medicine is at present advancing, I purpose to enumerate some of the gains to therapeutics already obtained by the employment of this method.

These are fourfold in their character. We have new remedies. We are taught how to use our old remedies. We learn what to do. We learn what to avoid.

For example, we discover that the action of casca on the heart and vessels indicates it as an useful remedy in defective circulation. At the same time, we are cautioned that the drug may disturb the digestion and cause an unpleasant surprise if carelessly given.

Again, if casca is to be beneficial in one form of heart disease, why not in another? If it is to do good in mitral, why not in aortic, incompetence?

To answer these questions, let us consider the pathology of the disease. During the cardiac diastole in the normal condition the left ventricle usually receives only the blood which pours into it from the auricle.

When the aortic valves are incompetent the ventricle receives in addition the blood which flows back from the aorta. It thus becomes filled to a much greater extent than usual. The quantity of blood, therefore, which is propelled by it into the arterial system by each systole is very large, so that the arteries become tense.

During the diastole the blood which ought to be retained in the aorta by the sigmoid valves is allowed to flow backwards into the ventricle; so that the arterial system may be compared to a vessel open at both ends—viz., at the capillaries and at the heart—instead of at one end only, as in health. It thus becomes much emptier during the heart's pause than it should be.

The condition, indeed, is comparable to that of a man from whose artery a jet is allowed to flow between every pulsation, only that in the disease the blood flows back into the heart instead of out of the body.

The variations in tension of the arteries in their full and empty condition are thus very much greater than in the normal condition. We get the full and bounding pulse first recognised by Corrigan as characteristic of the valvular lesion we are now considering.

We all know how difficult it is to break a cord by steady strain, and how easy by a sudden jerk.

The arteries in aortic regurgitation are subjected to a greater strain than usual by the great variations in tension which occur.

Supposing, then, that we were to increase the force of the heart by such drugs as digitalis and casca, we would increase the strain upon the arteries. But, besides the increase in the force of the heart, these remedies would make it pulsate more slowly, and more time would thus be allowed for the blood to flow into it both from the auricles and from the aorta.

The ventricle would thus become fuller than usual; a greater volume of blood would be poured into the arteries at each beat; and the tension would be increased by the size of the wave, as well as by the rapidity of its propulsion.

But the increased length of the diastole would also allow the arterial system to become emptier both from the onward current through the capillaries and the backward flow into the heart. The variations in tension and the consequent danger of rupture would thus be still further increased.

Another danger is that at each pulsation of the heart the tension would become very great, but at each pause very low—so low, indeed, that the current through the capillary system might cease entirely, especially in those parts of the body such as the brain, where it is counteracted to the greatest extent by the force of gravity. Syncope would, therefore, be likely to ensue, and might pass into death if the cardiac diastole were much prolonged.

We see, therefore, that the use of digitalis in such circumstances would be highly injurious. But if the ventricle, subjected to the constant strain by the blood flowing into it under pressure from the aorta even during its period of rest, should begin at last to yield and dilate, so that the bicuspid valves are no longer competent to close the enlarged mitral orifice, the regurgitating blood will obstruct the circulation through the pulmonary vessels, the strain will be transmitted back to the right ventricle, and we will have all those symptoms of obstructed respiration, œdema, &c., which we have already considered.

The danger now is, not of death by syncope, but death from suffocation. The condition now approximates to that which we have already considered under the head of mitral disease, when casca or digitalis proves most beneficial.

The recognition of digitalis as a cardiac stimulant is one of the great advantages which we have derived from experiment; for, although clinical experience seemed to show its utility in cases of cardiac debility, yet, until its power to strengthen the cardiac pulsations was actually shown by experiment, many practitioners were afraid to employ it even in those cases in which it would have been most serviceable.

But it is not only in the treatment of organic diseases of the heart that we have gained much from scientific pathology and pharmacology. One of the greatest obstacles to the successful employment of any general empiric rule, such as *contraria contrariis curantur*, or *similia similibus curantur*, is, that symptoms do not always arise from disease of the organ apparently most closely related to the disordered function.

Thus we have seen that, although the laboured respiration may be the most urgent symptom in mitral disease, the heart, and not the lungs, is at fault. In the same way we sometimes may have the heart palpitating and the pulse irregular or intermittent, when the disorder is really in the stomach.

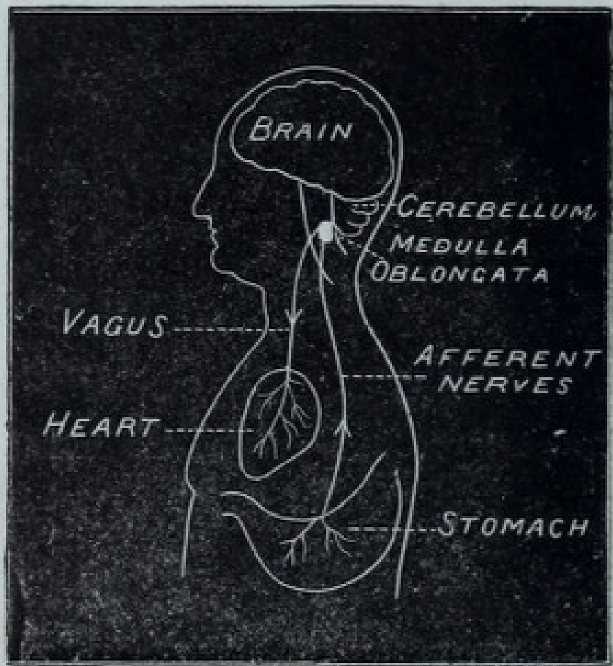


FIG. 5.

But physical diagnosis enables us to ascertain the absence of organic lesion, and experimental pathology has shown us the mechanism by which gastric disturbance produces cardiac irregularity. The irritation from the stomach is transmitted up the afferent nerves to the medulla oblongata, and down the vagus to the heart, interfering with its pulsations.

It is evident, then, that, instead of meddling with the heart, the proper treatment is to remove the irritation of the stomach; but, if we cannot immediately do this, we may prevent its effect upon the heart in two ways. As the action is reflex, we may lessen or destroy it by diminishing the activity of the centre through which it occurs. Since it is produced through the vagi, we may stop it by destroying their power.

So far as I know, no experiments have been made on the influence of drugs over this particular form of reflex action; and we must, therefore, use one which we know to lessen reflex action generally, such as bromide of potassium, opium, or chloral, without being able at once to select the best.

But we do know that, if the long intermissions should threaten danger, we can avert it by a free use of atropia; for this alkaloid completely paralyses the ends of the vagus in the heart, and no amount of stimulation to the nerve, either direct or reflex, can then stop the pulse.

Nor is this the only action of this drug. It has another of considerable importance, for it paralyses the sensory nerves of the heart, and is thus useful in cases where the organ is irritable or hyperæsthetic.

But in order that the action of atropia, and of some other drugs of which we have yet to speak, may be fully understood, it may be well to say a few words regarding the nervous mechanism which regulates the mutual relations of the heart and blood-vessels. For the healthy performance of the functions of every organ in the body a proper supply of arterial blood is requisite, and this supply depends upon the maintenance of a proper pressure within the arteries, just as the supply of water to a city depends upon the pressure in the main pipes. It is only so long as the blood is in the arteries that it is available for the use of an organ; so soon as it gets into the veins it is of no more use for the nutrition of the organs than if it were in a vessel outside the body, and is only again available for the nutrition of the tissues when it has been pumped out of the veins into the arteries by the heart. The pressure of blood in the arterial system, or blood-pressure, as it is usually termed, is therefore of great importance, because upon it depends the rate at which arterial blood circulates, and therefore the amount of nutriment received by the various organs in the body. This pressure depends upon two factors; firstly, the rate at which blood is pumped by the heart into the aorta, and secondly, the rate at which it flows out through the arterioles and capillaries into the veins. The veins act as a large reservoir; they are able to contain, when fully dilated, the whole of the blood present in the body, but normally, like the arteries, they are kept more or less in a state of partial contraction by the vaso-motor nerves. The nervous centre which regulates the relations between the heart and vessels is situated in the medulla oblongata, from which proceed nerves which cause the heart to beat more quickly or more slowly, and the arteries and veins to contract or dilate according to the requirements of the body and of its parts. The pulsations of the heart probably depend upon ganglia contained in its substance, for the organ will continue to pulsate for a long time after it has been removed from the body. But if the heart were to pulsate in the living body irrespective of the other organs, the consequences might be serious. If its beats became too rapid and strong, the pressure in the arteries might rise so high as to burst them, and produce apoplexy, and if they became too slow or weak, the muscles would receive an insufficient supply of blood, and the individual would be unfit for any exertion. To prevent either of these consequences we have two sets of nerves, besides others which we will not at present consider, as it would complicate the question too much. The first nerve is the vagus, which proceeds from the medulla oblongata to the heart, and when in action, has the power of rendering the cardiac pulsations slower and feebler, so that its action upon the heart may be compared to that of the reins upon a horse. If by any means the pressure of blood in the arterial system is increased, the pressure is felt in the arteries of the medulla as well as elsewhere, and this stimulates the roots of the vagus nerve, and consequently renders the beats of the heart slower and weaker. In consequence of this less blood is pumped by it into the aorta, and the pressure in the arterial system falls. The stimulus is thus again removed from the vagus roots, the heart beats more quickly, and the pressure again rises. The vagi nerves may thus be said to play the same part in the animal economy, that the governor balls do in the steam-engine, for through them the cardiac pulsations are kept constant, like the motion of the fly-wheel by the governor balls. So long as the vagi are healthy, increased blood-pressure renders the heart slow, but, if we cut the vagi across, we find that increased pressure in the arteries produces an exactly opposite effect to what it did before, and renders the cardiac pulsations stronger and sometimes quicker. The reason of this appears to be that increased pressure stimulates the cardiac ganglia, and here again it is easy to see how useful this stimulation will be. We know from experiment that during active muscular exertion the pressure of blood in the arteries rises enormously, and thus, through the rise of pressure, muscular exertion itself stimulates the heart to increased efforts to maintain the circulation, and supply the muscles with the additional nutriment they require for exertion. At the same time the vagus, which has its roots in the brain, prevents the pressure from rising so high as to endanger the nerve centres by rupture of a vessel within them.

In persons who are obliged to make numerous and violent muscular efforts, the heart seems to become hyperæsthetic, and the least strain is sufficient to produce violent palpitation. Now Schiff[1] has found that belladonna has the power of paralysing the sensibility of the heart to the pressure of blood within it, so that in doses little more than sufficient to dilate the pupil it reduces the sensibility so much that the blood-pressure may be increased to three times its normal amount without producing any effect upon the pulse.

Belladonna is, therefore, theoretically indicated

[1] Schiff, *La Nazione*, 1872, No. 235.

in irritable heart; and I have been informed that at Netley Hospital it has practically been found very efficacious. I have myself prescribed it with great advantage in such cases; but, while successful when given shortly after the first appearance of the symptoms, it failed to benefit at a more advanced stage of the disease.

Besides the mechanism which we have already considered in the vagus, there seems to be another nervous apparatus for regulating the blood-pressure. This acts, not upon the heart, by which the blood is forced into the arteries, but upon the arterioles or capillaries, through which it flows out of the arteries into the veins.

The veins form a great reservoir, large enough, when dilated completely, to hold all the blood in the body, as they indeed do after death. But during life both they and the arteries are kept in a state of semi-contraction, or tone, as it is termed, by means of the vaso-motor nerves. The vaso-motor fibres, which proceed to both arteries and veins, probably arise from minute ganglia situated in and around the coats or sheaths of the vessels.

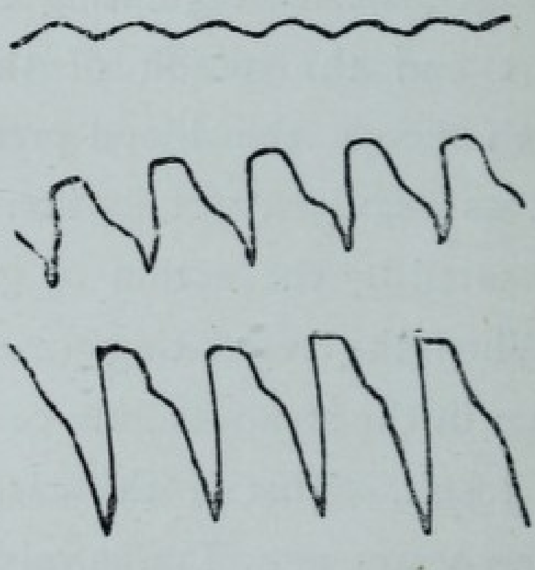
These ganglia probably have the power of regulating the contraction of those parts of the vessel close to which they are placed; but just as a sergeant who has under his orders ten or a dozen men has himself to obey the orders of his captain, and the captain, again, those of his general, so these ganglia which control these vessels are themselves controlled by higher vaso-motor centres, the chief of which is situated in the medulla oblongata. It was formerly supposed that this centre was limited to the medulla, but it has now been found to extend a considerable distance down the cord. This centre can be reflexly excited by stimulation of various afferent or sensory nerves. Through the branches of the fifth nerve especially it can be stimulated with great ease, and irritation of this nerve will, by exciting the vaso-motor centre to action, greatly raise the pressure of blood throughout the whole body. In syncope, therefore, when the vessels are relaxed and the blood-pressure is low, we hold before the patient's nose strong ammonia or acetic acid, and by thus reflexly raising the blood-pressure we quicken the circulation through the brain, and again restore the patient to consciousness. Where this method is insufficient we may have recourse to the stimulation of other sensory nerves by applying mustard plasters to the limbs or chest, or even by flagellation.

Usually, when the spinal cord has been divided just below the medulla oblongata, no irritation of a sensory nerve has any power to raise the blood-pressure, for that part of the vaso-motor centre which is situated in the spinal cord, and which, therefore, unlike that in the medulla oblongata, has not had its connection with the vessels destroyed by section, is too weak to have much action upon them ; but if strychnia be now injected into the circulation, the activity of the spinal portion of the vaso-motor centre becomes greatly increased, and stimulation of a sensory nerve will then act in a similar way as in the animal before the separation of the medulla. We can thus readily see how strychnia may prove such a useful tonic to the vessels in cases of anæmia and debility.

Now in the case of the vaso-motor centre, just as in the case of the heart itself, we have a nervous arrangement to regulate its action in accordance with the wants of the body. When a sensory nerve is irritated, dilatation of the vessels of that part ensues, accompanied by contraction of the vessels throughout the rest of the body. In consequence of this, as we may see in the eye any day when a grain of sand happens to get under the eyelid, a quantity of blood rushes to the injured part to supply nutriment and repair the damage, just as streams of ants at once swarm around the injured part of an ant-hill. But whenever the action of the vaso-motor centre is too violent, and the pressure in the vessels becomes too high, we not only find that the heart becomes slower, but it would appear that the pressure within the heart re-acts on the vaso-motor centre itself. From the heart, nerves, which in the rabbit and horse are called the depressor nerves, pass up to the medulla oblongata, and whenever they are stimulated they depress the action of the vaso-motor centre in the medulla, allow the arterioles to dilate, especially in the skin and in the intestines, and thus cause the blood-pressure to fall. It is probable that increased pressure within the heart is the stimulus which usually throws those nerves into action, and, by thus dilating the arterioles, lessens the resistance which the heart has to overcome, and thus prevents it from being over-strained. We thus see that there is an arrangement for regulating both the beats of the heart and the action of the vaso-motor centre, which keeps the blood-pressure pretty regular, just as regularity of motion in the steam-engine is insured by the action of governor balls.

When the regulating mechanism is disturbed, either in the steam-engine or circulation, danger is the result. This is the case in angina pectoris. Some years ago, I was placed in exceptionally favourable circumstances for studying this disease. I was able to watch a patient at every hour of the day and night, and to observe every phase of the attack.

By the aid of Marey's sphygmograph, I discovered that, during the paroxysm, the blood-pressure rose and the pulse became quick. I might have imagined that the rise in pressure was due to the quickness of the heart's pulsations; but the experiments of Marey and Chauveau enabled me to say, from the form of the tracing, what I could not have discovered by the finger, that the arterioles were excessively contracted.



Pain Severe.

Pain relieved for a few minutes by inhalation of nitrite of amyl.

Pain completely removed by inhalation.

FIG. 6.—These three tracings were taken in the course of a few minutes, and the sphygmograph remained during the whole time upon the patient's wrist.

This is shown clearly by the accompanying tracings, from which it will be seen that during the attack, the pressure in the artery, instead of rising much during the cardiac systole, and falling during the diastole, only underwent a slight oscillation at each beat of the heart. It will be observed, also, that slight though this oscillation is, the ascent is very slow, as well as the descent, a form of tracing which clearly indicates that the resistance to the cardiac action was great, and the systole consequently slowly performed, as well as that the vessels were firmly contracted, and allowed little blood to pass out through them during the diastole. It will be observed, also, that the nervous mechanism which regulates the circulation is here in a state of profound disturbance. Instead of the high tension during the spasm causing the heart to beat slowly, as it ought to have done, we find that its pulsations are much more rapid than normal, the high arterial tension having acted upon it in the same way that it usually would upon an animal whose vagus nerves had been divided. The reduction of pressure, too, has a different effect upon the pulse from that which it usually produces. Ordinarily, a lessened arterial pressure quickens the pulse-rate, and when nitrite of amyl is inhaled by a healthy person the pulse quickens as the vessels dilate, and the pressure falls under the influence of the drug. In angina the reverse is the case, and, as the vessels dilate and the pressure falls, the heart beats more slowly, instead of more quickly.

As the pressure rose, during the attack of angina, severe pain came on in the heart, and when the pressure fell the pain disappeared. It was, therefore, natural to look upon the pressure as the cause of the pain, and my opinion was confirmed by the effects of bleeding; for this lowers the pressure, and each bleeding prevented an attack.

The pathology of the disease thus seemed clear, and the next question was how to treat it. The remedy wanted was one which would dilate the vessels, and this the researches of Richardson and Gamgee supplied. Nitrite of amyl they had shown to possess the very power which I desired, and thus their experiments on the pharmacology of the drug and my observations on the pathology of the disease, united, led to successful therapeutics.

I administered the remedy, and the pain disappeared. In the hands of others it has usually produced similar results; but sometimes it has failed. The failure has been used as an argument to prove that angina does not always depend on excessive blood-pressure.

This may be the case, but the proof is insufficient; for in some patients the nitrite ceases to act after it has been kept a few days, while the newly made drug always affords relief. If such cases are treated with old nitrite only, they will be recorded as failures.

Whether the loss of activity is due to conversion of the nitrite into nitrate, or to decomposition or evaporation of some nitrous compound present in the newly formed nitrite, but still more active and unstable than it, must be determined by future research.

While angina seems to depend on spasmodic contraction of the vessels generally, local spasm may cause pain or disturbance of function.

Du Bois Reymond's observations of the contracted condition of the arteries in migraine, led me to use the nitrite in headache, and sometimes with success. On the hypothesis that epilepsy depends on spasm of the cerebral vessels, I administered it during the fits of epilepsy, but without result.

By giving it before the fit comes on, Dr. Crichton Browne has been more fortunate, and has succeeded in averting the paroxysm.

But in this disease the remedy *par excellence* is bromide of potassium, for the extended use of which we are much indebted to the late Dr. Begbie. How it acts in epilepsy we do not as yet know; but experiment has shown that it lessens reflex action generally, and we thus have a general rule to guide us in its use.

It is not an astringent in the usual sense of the term, yet it may sometimes check diarrhœa. In a patient where the looseness of the bowels seemed to depend upon reflex irritation from the uterus, the general rule I have just mentioned led Dr. Ferrier to use it, and his success was complete.

Various researches have shown that the substance of the nerve-centres may be affected by drugs independently of the circulation, but the experiments of Durham have shown that sleep is connected with anæmia of the brain.

The difficulty which the congested condition of this organ, after poisoning by opium, was supposed to present on Durham's theory, has been explained by the experiments of Hammond. He finds that in the sleep produced by a small dose of opium, the brain is anæmic, but, as the sleep passes into coma after a large dose, the anæmia gives place to venous congestion, slow circulation to stagnation. Knowing, then, the connection between anæmia and sleep, active circulation and mental activity, we are able to choose our remedies accordingly.

If the patient constantly fall asleep when standing or sitting, and cannot sleep when lying down, we know that the vessels are probably flaccid and allow the blood to gravitate to the lowest point, away from the head in the upright, and to it in the recumbent posture.

In such cases, we know that digitalis will probably be useful by giving contractile power to the vessels, and chloral injurious by weakening them.

But when the tight arteries and powerful heart seem to be driving the blood rapidly through the brain, then we have recourse to chloral, for its weakening action on the heart and vessels will now aid its action on the nervous tissue.

Nor is it only on the nerve-centres that we are able to act. As Bernard showed, we can influence peripheral nerves also by our drugs. It is impossible to look at the jerking limbs and irregular movements of chorea, without wishing that we could load every muscle with lead, and still its useless and disturbing movements.

Sleep will do this and opium will produce sleep, but we cannot keep the patient constantly in a state of insensibility; we wish to leave their activity to the mental powers, and only to quiet the muscles.

This we might do by curare, but we have another remedy, which seems still more suitable; for conia acts on the motor-nerves in the same way as curare, and methyl conia lessens the functions of the spinal cord.

Ordinary hemlock contains both, and thus the succus conii, by deadening the motor-nerves and enfeebling the cord, should render movement more difficult and wearisome, the very result which we desire to produce. We should thus be able to ameliorate the symptoms, even though we may not touch the real source of the disease.

CHAPTER IX.

RESPIRATION.

Object of respiration—Internal and external respiration—Dependence of respiratory movements on the respiratory nerve-centre—Action of carbonic acid upon this centre—Effect of anæmia—Effect of the administration of iron—Causes of cough—Action of carbonate of ammonia and atropia—Of hyoscyamus.

LEAVING the circulation, let us now turn to the function of respiration. It was known to the ancients that animals could not live without breathing, but they supposed that the chief use of respiration was to cool the blood. This notion prevailed until it was put to an experimental test by Boyle, who found that an animal died when confined in a limited space, although the air was kept constantly cool by means of ice. He therefore supposed that the air became poisoned by some injurious substance which was given out to it by the blood, and in this opinion he was followed by Hales and Haller. Hales, however, also imagined that one of the chief uses of respiration was the mechanical effect of the thoracic movements which assisted the circulation of the blood. When they stopped the circulation was supposed to be arrested. This notion again was disproved by Hook, who kept up a continuous stream of air through the lungs by blowing in through the trachea, and allowing it to have egress through an opening in the lower part of the lungs and the chest wall. Lower observed that when the thorax was opened and respiration kept up artificially, the blood became brighter in its passage through the lungs. He also showed that blood shaken with air became bright, and thus imagined that the blood took something from the air, and this was said by Mayow to be nitro-ethereal spirit, and asserted by him to be the same substance which was used up in combustion. The something which Boyle imagined that the air gives out, was shown by Black to be carbonic acid. The something which Lower and Mayow supposed it to take in was shown by Priestley to be oxygen. But it was Lavoisier who first satisfactorily correlated the different facts, and established the complete theory of the respiration.

The objection was soon brought that if, as he imagined, combustion took place in the lungs, the heat would be sufficiently great to destroy those organs, and to meet this objection Crawford supposed that the specific heat of arterial was greater than that of venous blood. Legrange supposed that oxygen was absorbed in the lungs, entered into a loose combination with the blood, imparting to it a scarlet colour, that during the course of the circulation a more intimate union took place between oxygen and carbon, and carbonic acid was formed which was afterwards given out during passage of the blood through the pulmonary vessels. Legrange's theory has been confirmed by the experiments of Davy, Magnus, and Ferney, and the substance in the blood with which the oxygen combines has been shown by Hoppe-Seyler to be hæmoglobin, the colouring matter of the red corpuscles. As the blood passes through the lungs, it gives off carbonic acid, and the hæmoglobin takes up the oxygen and carries it with it to the tissues where it is required. The exchange between the blood and the air is *external* respiration. But Spallanzani found that snails and reptiles, when confined in an atmosphere of hydrogen, still give off carbonic acid, and that pieces of muscle cut out from the body will use up oxygen. This was the first indication of respiration in the tissues themselves. Spallanzani's observations were nearly forgotten, but similar ones made by G. Liebig called attention to the subject which Spallanzani had first studied, and the researches of Ludwig and his pupils, of Pettenkofer, Voit and others, have in a great measure cleared up the obscurity in which it was involved. They have shown that as the arterial blood circulates through the tissues, it gives off oxygen to them, and picks up carbonic acid. But the relation between the quantity of oxygen taken up and carbonic acid given out by the tissues is by no means constant. They seem to have the power of storing up oxygen within themselves, and using it as required, but the supply requires to be renewed, otherwise they suffer from asphyxia. The interchanges of gases between the blood and the tissues is *internal* respiration. The internal and external respiration are kept in relation to each other by means of the respiratory centre in the medulla oblongata. From this, nerves proceed to respiratory muscles, and effect the respiratory movements. When the blood circulating in the medulla itself is highly arterialised, the respiratory centre is little stimulated, and respiratory movements are diminished. When the blood circulating through it is, on the contrary, highly venous, it is much stimulated, and the respiratory movements become increased. Therefore the blood circulating through the lungs again becomes oxygenated, and when it reaches the respiratory centre in the course of circulation, the irritation being diminished, the respirations again become less. The activity of the respiratory centre depends rather on the condition of the blood flowing through it than upon the condition of the lungs, although it may be and is influenced reflexly by sensory nerves proceeding to it from those organs.

By tying all the vessels proceeding to the brain, dyspnœa and asphyxial convulsions may be produced, although there be no impediment either to the flow of blood through the pulmonary vessels, or to the ready entrance of air into the lungs. For the arterial blood is prevented by the ligature from reaching the medulla, and the small quantity of oxygen contained in the blood which is stagnating the vessels is soon exhausted. Supposing that instead of ligaturing the vessel entirely we were to allow only a very small stream to pass through it, this might, under ordinary circumstances, supply a sufficient amount of oxygen to the medulla, but should any unusual exertion be required this would prove insufficient, and dyspnœa would be the result. If we lessen the power of the blood to take up oxygen, it amounts to the same thing as reducing its quantity. In anæmia, the hæmoglobin of the blood is diminished, it has less power to take up oxygen, and we therefore find that persons suffering from this disease become breathless after very slight exertions, just as we would expect them to do if the supply of blood to the respiratory centre were diminished by means of a ligature. Dyspnœa depending upon this cause is to be removed by increasing the quantity of hæmoglobin, and this we are able to do by the administration of iron. Under the influence of this remedy the blood corpuscles become more numerous, the hæmoglobin they contain is increased, and persons who before were unable to speak after running up a few steps are rendered capable of making considerable efforts without the least shortness of breath. It is evident that if we were to remove the ligature from the vessels of the medulla and place it on the pulmonary artery, we would produce a somewhat similar effect, for we would diminish the supply of oxygen to the medulla in both cases, only the diminution would be local when the ligature was applied to the carotids and vertebrals, and it would extend to the whole body when the ligature was applied to the pulmonary artery. The same effect as that of a ligature is produced by narrowing of the mitral or pulmonary orifices, or by incompetence of their valves. In those diseases, therefore, we find the same symptoms as we would expect from partial ligature of the vessels of the medulla, viz., dyspnœa upon any exertion. When arising from such a cause, the dyspnœa is to be treated by such drugs as, like digitalis, will aid circulation of blood through the lungs.

We have already seen how cardiac disease may prevent the blood from sufficiently getting to the air, but obstructions to the respiratory passages may also prevent air from getting to the blood. The former condition requires remedies which act upon the heart, the latter those which will affect the lungs.

In bronchitis the air-tubes are clogged with mucus, which interferes with the passage of air through them, and by its constant irritation causes troublesome cough.

Cough being a reflex act, we can diminish it, like other acts of the same sort, by drugs, which, like opium, will act on the reflex centres. But in old and debilitated persons, this centre, though irritable, lacks power, and the expulsive expiratory efforts require increase rather than diminution.

Clinical experience has shown us the value of carbonate of ammonia in such cases; but it is pharmacological experiment which informs us that ammonia stimulates the respiratory centre, and thus gives us a reason for our treatment.

Atropia combines two qualities likely to make it useful in the cough of debility. It stimulates the respiratory centre, but at the same time it lessens the irritability of the sensory nerves of the lung, and will thus, while increasing respiratory efforts, diminish the sensibility of the lung to irritation.

Hyoscyamus has an action almost the same as that of atropia, and often proves a valuable remedy in chronic bronchitis. But here the question of dose comes in, and although experiment assures us that certain drugs have certain actions, we may not get the result we desire when we administer them in disease, because we give too small doses, either from ignorance, timidity, or from the action of the drug upon other organs of the body preventing its being pushed to a sufficient extent.

Regarding the action of drugs upon the bronchial secretion, we have no experimental knowledge. We know that something to eat and a drink of warm fluid before rising generally lessen the troublesome morning cough of chronic bronchitis better than any expectorant; but still experience shows that tartar emetic, ipecacuanha, and iodide of potassium will also diminish the tenacity of mucus, and aid expectoration, while balsams will lessen the profuse secretion in bronchorrhœa.

But how these drugs act on the bronchial glands we do not know, and it is a comfort to turn from our unsatisfactory acquaintance with the action of expectorants to the action of remedies on digestion.

For here we are acquainted with the chemical processes which go on and the agents which originate them. We have a good knowledge of the mechanism of secretion in the various glands of the alimentary canal, and in the case of the stomach we have the great satisfaction of being able to see what our drugs are doing inside the body by means of gastric fistulæ established experimentally in animals and sometimes occurring accidentally in man.

It is cheering, too, for the physician who has been giving cough-mixtures without success until he has nearly lost all confidence in medicine, to have his faith re-established by a sight of the wonderful relief given by rhubarb and soda in flatulent dyspepsia.

Hope rises in our breasts when we compare the wild fancies of our predecessors with our own certain knowledge, and we look forward to a bright future for medicine.

Mayow, for example, thought that digestion was performed by the vital spirits which came down from the head to the stomach, did their work, and then returned to the head again. Thus he explained the drowsiness which comes on after eating, and the digestive disturbance which deep thought and anxiety occasion.

For the vital spirits could not be in two places at once; when they were digesting the food in the stomach they left the head, and so caused drowsiness; when they were busily engaged with cogitations or passions in the head they neglected their work in the stomach, and the food remained undigested.

It would be impossible to bottle up such intangible beings as Mayow's vital spirits and make them do their work in a water-bath or oven, but we can do this with ptyalin or pepsin ; it would be difficult to localise the paths by which the spirits ran backwards and forwards, but we know the vessels by which the blood flows to the stomach and brain, and we are beginning to learn the exact nerves which cause it to flow to the one rather than the other.

CHAPTER X.

DIGESTION.

Modern knowledge of the process—Our facts compared with Mayow's theories—Food in the mouth, stomach, duodenum, &c. —Ferments contained in all the secretions of the digestive tract —Condition of ferment and gland substance—Digestive ferments—Zymogen—Secretion of digestive juices dependent on nervous action and blood-supply—Secretory nerves—Vasodilating nerves—Secretion in the salivary gland—Reflex salivation—Action of opium—Action of atropia—Digestion in the stomach—Alexis Saint Martin—Experiments upon animals—Effect of stimuli on the stomach—Effect of acids on the secretion of the stomach—Effect of sapid food—Action of alkalies —Why given before meals—Probable action of smoking.

EXPERIMENT has taught us that the food begins to be digested in the mouth, and its starchy constituents are even then partially converted into sugar. In the stomach it meets with the gastric juice, which converts the albuminous matters partly into syntonin and partly into peptones.

In the duodenum it is mixed with the bile, which emulsionises the fats, and with the pancreatic juice which combines the properties of all the three others, digesting the starch, albumen, and fats. Lastly, the intestinal juice probably finishes the solution of albumen and starch, as well as converts cane into grape sugar. In each secretion we find its ferment: ptyalin in the saliva, pepsin in the gastric, and trypsin in the pancreatic juice.

But these ferments do not exist ready-formed in the glands. They are stored up in the form of a mother-substance or zymogen in the secreting cells, and when these are called into activity by the nerves of the gland, the zymogen yields up the free ferment ready for its work.

But something more is required than the nervous impulse, or, as Mayow would probably have called it, the vital spirit. Unless the glands have a free supply of blood to yield them oxygen and nutriment they cannot secrete much, however strong the nervous stimulus may be.

The secretory nerves of a gland are, therefore, accompanied by other filaments, which cause the vessels of the gland to dilate, so that a copious stream of blood pours through them, making the veins pulsate and jet like arteries.

But, though these nerves may often run together, yet their functions are quite distinct. Stimulation of the secretory nerves alone will only cause the gland to yield a few drops of juice and then cease, if the vaso-dilator nerves do not quicken the blood-stream at the same time; and

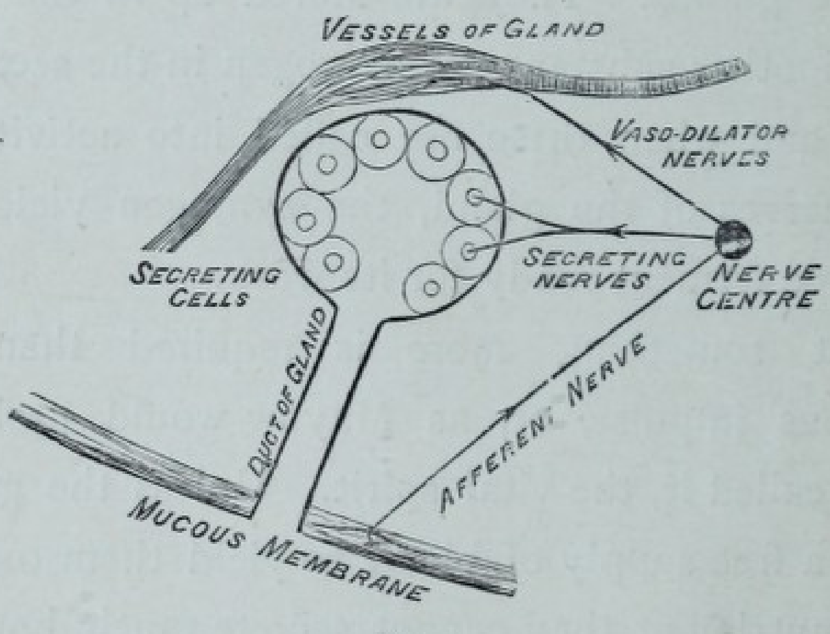


Fig. 7.

no action of the vaso-dilator nerves, no rapidity of the circulation, however great, will produce a single drop unless the secretory nerves act also.

Usually, they are both excited simultaneously, and in the following manner. A stimulus applied to the mucous membrane lining a part of the alimentary canal, mouth, stomach, duodenum, or ileum, is conveyed by afferent nerves to a nervous centre.

Thence the stimulus is reflected down efferent nerves, as in the adjoining diagram, both to the cells and vessels of the glands connected with the part to which it was applied, and the secretion is poured out. Each gland seems to have its own favourite stimulus—for the salivary glands acids and sapid substances, for the stomach alkalies, for the liver acids applied to its duct, for the pancreas food in the stomach and duodenum, and for the intestine the presence of food in it.

When savoury substances or acids are taken into the mouth, the stimulus they apply is conveyed up to the fifth nerve to the encephalon, and is thence reflected down the seventh to the vessels and secreting cells of the salivary glands. When the secretion is insufficient, it can be increased by applying a stronger stimulus to the mouth, and it is in this way that pellitory and such other sialagogues act.

But sometimes there may be a strong and permanent stimulus in the mouth, such as the loose teeth or sore gums produced by the action of mercury, or a stimulus in the stomach, such as acidity or gas, which causes salivation excessive

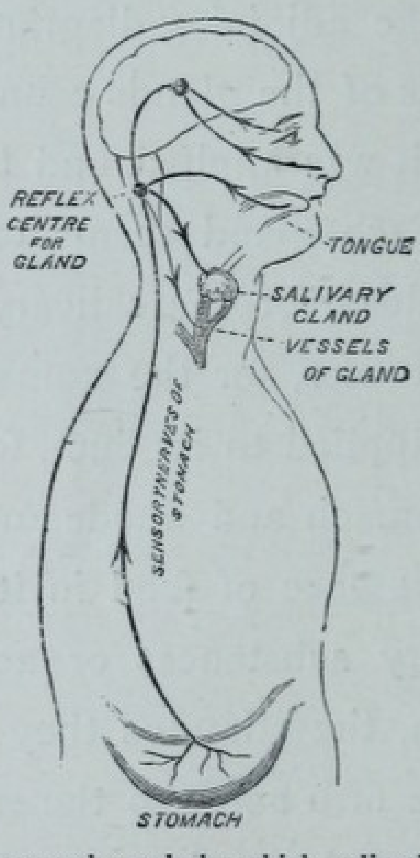


FIG. 8.—Diagram of nervous channels by which salivation may be excited—by sight, smell, or thought of savoury food,—by taste—by acidity or irritation of the stomach.

in quantity, and not merely useless, but annoying to the patient.

This may be checked by opium, which acts on the nerve-centre, lessening its irritability; so that the strong stimulus only excites the same reflex action that a weak one would do under normal conditions, and the excessive flow is arrested. But supposing the opium fails or cannot be given in sufficient doses to produce the desired result, without affecting other organs in an undesirable manner, is there any other drug which we can use?

It is not very long since we would have been obliged to reply in the negative; but pharmacological research, besides explaining the *modus operandi* of opium, has given us another remedy more powerful still. This is atropia, which Heidenhain[1] found to paralyse the ends of the secreting nerves in the submaxillary gland, so that no irritation would excite the slightest flow of saliva. At the same time, it leaves the vascular nerves unaffected, and, on the application of the stimulus, the vessels dilate as usual.

The paralysis may be removed by Calabar bean, and secretion again will occur. The bean alone has a curious effect, for it excites the secreting nerves, but at the same causes contraction of the

[1] Pflüger's *Archiv.* v. p. 40.

vessels. The gland, therefore, begins to secrete, but soon stops from want of blood.

The profuse flow of saliva occasioned by smoking is known to every one, and examination of the action of nicotine shows that this is just what we might expect; for the drug has a double action on the gland, and does not merely stimulate the sensory nerves of the mouth as pellitory would do, but stimulates the ends of the secreting nerves within the gland itself.

In larger doses it paralyses these nerves and arrests the secretion, but as the poison is quickly excreted, the stoppage only continues for a short time. Thus we can understand how moderate smoking may increase the flow of saliva, and excessive indulgence in it may cause temporary dryness of the mouth, especially if the tobacco be strong.

A great part of our knowledge regarding secretion in the stomach has been obtained from the observations made by Dr. Beaumont, through a fistulous opening accidentally made by a charge of duck-shot in the stomach of a Canadian voyageur.

But this information would have been very imperfect had it not been supplemented and extended by observations on the stomachs of animals through circular openings, made by a much less tedious and painful process.

From both classes of observation, we learn that the healthy stomach during fasting has a pale colour and velvety appearance, and is covered with a thin coating of transparent mucus.[1]

When a moderate stimulus is applied, such as gentle friction with a glass rod, the introduction of food, or a weak alkaline liquid, it begins to secrete, the gastric juice oozes out from the follicles, and collects in drops on the surface of the mucous membrane. At the same time the circulation is increased, as in the salivary gland, and the colour becomes rosy. The stimulus has been conveyed by afferent nerves to nerve-centres, and then through efferent nerves to the vessels and cells, as indicated by the letters A, B, C, D in the diagram (Fig. 9, p. 168).

[1] Bernard, *Archives Générales de Médecine*, tome *Supplementaire* " *l'année* 1846, p. 5.

But if the stimulus be stronger—if, for example, the stomach be violently rubbed with a rod introduced through a fistulous opening, the rosy colour at once disappears, the vessels contract, the mem-

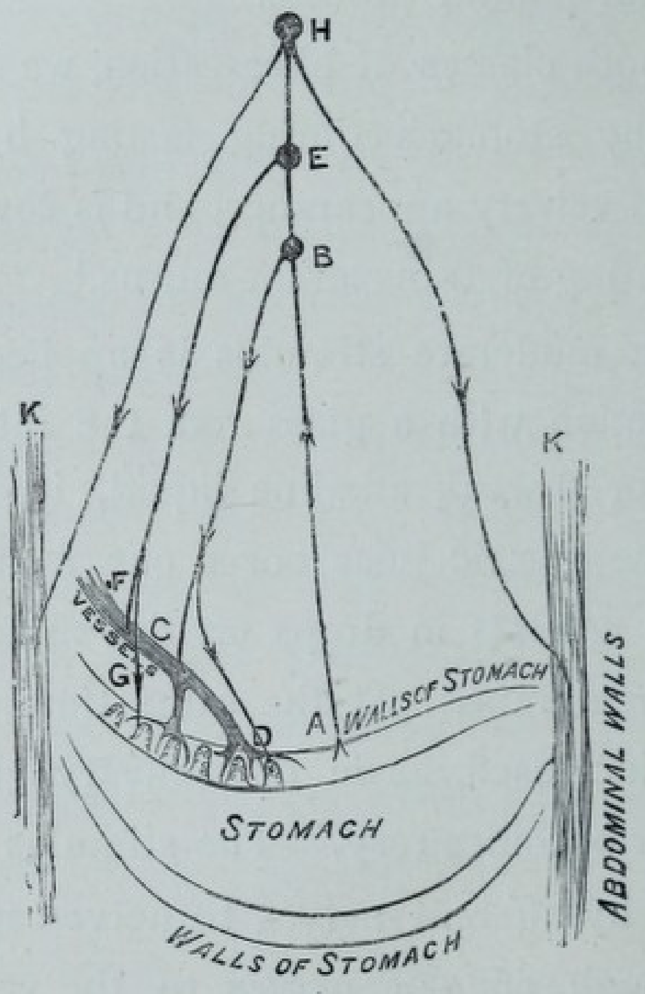


FIG. 9.

brane becomes pale, and secretion of gastric juice stops, a flow of mucus is produced, and nausea comes on.

The stimulus has now awakened a different nervous mechanism (A, E, F, G, in the diagram), and the results are different. If the irritation be still increased, the muscles of the abdominal wall are called into action, and vomiting occurs (A, H, K, K). Pain arising from injury to other parts of the body than the stomach has a similar effect in arresting digestion, and often causes vomiting.[1]

Weak alkaline solutions, such as saliva, are amongst the most powerful stimulants to the gastric secretion, while acids diminish it.[2]

Thus vinegar will lessen the quantity of juice, and will thus interfere with digestion. If constantly employed for some time, it will not only reduce *embonpoint*, but lead to fatal emaciation.[3]

Increase in the quantity of saliva will act as an increased stimulus to gastric secretion, and, where digestion is slow, well-cooked and sapid food will aid the process by making the mouth water. But the sapid food must not be bolted, it must be

[1] Bernard, *op. cit.* p. 5.

[2] Bernard, *op. cit.* p. 6.

[3] *Blondlot*, quoted by Bernard, p. 6.

turned slowly about in the mouth and well masticated, so that time may be allowed for the stimulus given by the agreeable taste and prolonged mastication to have full effect.

The effect of dilute alkalies upon the stomach is a good example of the errors into which one may be led by a purely chemical view of digestion.[1] Mialhe, regarding the stomach merely as a test-tube, recommended that when a person was taking metallic iron as a medicine, he should abstain from drinking lest he should dilute the gastric juice, and should take especial care to avoid alkalies, which would neutralise its normal acidity, and prevent its dissolving the iron.

The same reasoning may be, and has been, applied to the ordinary process of digestion; for pepsin will not act except in acid solutions, and one might imagine that fluids at meal times, and especially alkalies, such as soda-water, would prove very injurious. But Bernard's experiments show that, although a weak alkali will saturate a little of the acid contained in the gastric juice, yet it

[1] Quoted by Bernard, *op. cit.* p. 205.

will so stimulate secretion that very quickly it will become completely neutralised, leaving a large excess of acid fluid ready to digest any albuminous food that may be presented to it.

Thus it is that weak alkalies, such as bicarbonate of soda, given before meals, are so useful in the treatment of atonic dyspepsia. When the food is taken into the stomach, the organ only responds slowly to the stimulus ; too little gastric juice is secreted ; the food lies heavy at the epigastrium ; and, decomposition of an abnormal kind occurring, gas is formed, and eructations annoy the patient.

But when a small quantity of alkali is given shortly before the meal, it stimulates secretion ; a quantity of gastric juice is poured forth before the food is actually swallowed, and is ready to attack it so soon as it reaches the stomach ; the food is quickly digested, and the unpleasant symptoms disappear.

If given with or immediately after a meal, the alkali may have a similar action, but will not be so effectual, for the stomach will already contain some gastric juice secreted under the stimulus of the food. This will immediately neutralise part of the alkali, so that little or none may remain to stimulate the stomach.

It is possible that a pipe of tobacco, smoked after dinner, may act by stimulating a flow of saliva, and thus acting upon the stomach; but it is not impossible that it may have an action upon the gastric follicles similar to that which it exerts upon the salivary glands. That it has some action upon the stomach is rendered probable by its power to allay hunger when no food can be obtained.

CHAPTER XI.

DIGESTION (*continued*).

Cause of hunger—Anorexia from gastric irritability—Craving appetite—Anorexia from deficient sensibility—Treatment of these conditions—Of sluggish reaction of stomach—Strychnia—Treatment of extreme gastric debility—Pepsin—Vomiting a reflex act—Treatment by removal of irritant—By prevention of reflex—Digestion in intestines—Action of nitrohydrochloric acid—Stimulants of the biliary secretion—Action of blue pill—Experiments of Lussana, Schiff, and Heidenhain—Antagonistic action of the several digestive ferments—Object of ditto—Formation of sugar—Action of enzymes—Effect of drugs on formation of sugar.

THE question, What is the cause of hunger? is one which cannot be regarded as definitely answered. It is, no doubt, immediately dependent on some condition of the nervous centres in the cranium, and may be present when the blood circulating in these centres is impoverished, although the stomach be full, as in children suffering from tabes mesenterica; yet the stomach is the part in which it is apparently felt, and it may be produced by local conditions of the stomach which do not affect the nutrition. For the stomach has little power to discriminate sensations; and the bitterness which quassia or quinine causes in the mouth, and the heat caused by mustard or cayenne, are both felt by the stomach as appetite;[1] and so is the slight irritation caused by small doses of tartar emetic or arsenic, which on this account are said to act as gastric tonics. The usual appetite felt by the healthy stomach after a short period of abstinence seems to depend upon slight irritation of the nerves in the stomach, caused by some condition either of the gastric follicles or blood-vessels. Increased irritation causes violent appetite, and such an appetite may be induced by the stimulus of a bitter taken before meals or an irritable condition of the stomach itself This craving appetite may be observed in some forms of dyspepsia, and not unfrequently precedes a so-called bilious attack with vomiting. When the irritation is increased still farther, the appetite, as shown by Bernard's experiments and by Beaumont's

[1] Buchheim, *Arzneimittellehre*, 3rd Ed. p. 31.

observations,[1] disappears and is succeeded by nausea or even by vomiting. From these observations we learn how to treat anorexia due to different conditions of the stomach. When the stomach is languid and lacks its normal sensibility, there will be want of appetite, because the condition of its walls does not afford sufficient stimulus to its nerves. But, when this is supplemented by the additional stimulus of food, appetite is felt. Thus such persons have no appetite before a repast, but, after they begin to eat, acquire a relish for their food and make an excellent meal. When the appetite is due, on the other hand, to excessive irritability of the stomach, the persons feel beforehand as if they could eat a great deal, but; as soon as they have swallowed a morsel or two, the additional stimulus of the food acts like the excessive friction of the rod in Bernard's experiments, appetite disappears, and nausea or even vomiting succeeds. The treatment is evident from the pathology. If the anorexia be due to deficient sensibility, we

[1] *Vide* Beaumont, *Physiology of Digestion*, 2nd edit. Burlington, 1847, p. 251.

must give an extra stimulus, such as bitters before meals, or a little more spice and seasoning with the food. Many a time I have been disappointed with the result, when I have ordered quinine or quassia before meals as an appetiser, without considering the pathology of the particular case I was treating, it being one, not of deficient sensibility, but of excessive irritation. The proper treatment was to soothe the mucous membrane instead of stimulating; and on adopting this, and giving bismuth and magnesia instead of bitters, the appetite returned. Sometimes one meets with persons who complain that, after a full meal, they feel as empty as if they had not had anything to eat. Normally, hunger is appeased by eating, probably because the condition of the gastric walls, which causes appetite, whatever it may be, is relieved by secretion; but, in the cases I have just mentioned, the food does not produce its ordinary effect. The reason which suggests itself to explain this is, that the stomach does not react so readily as it ought. We have no experiments, so far as I know, to show what drug will affect the reflex action of the gastric nerves; but we know that strychnia increases other reflex actions, and why not this? Strychnia appeared theoretically to be the most likely remedy for such cases; and, on trying it experimentally, I found it successful. Theoretically, also, it ought to be useful in those cases of atonic dyspepsia in which we give alkaline solutions; and its utility in such cases is practically well known.

But if the stomach be too debilitated, from old age or from exhaustion by disease, to respond to such stimuli as bitters, alkalies, or alcohol, even when aided by strychnia, what is to be done? The organ is then a passive vessel, and as such we must treat it. It possesses a temperature of 99 deg. Fahr.; and we know that, under such circumstances, weak hydrochloric acid with pepsin will actively digest meat mixed with it in a glass vessel. By putting pepsin and acid into the stomach, we supply the gastric juice which it cannot secrete; and the products of digestion, by strengthening the body, will gradually enable the stomach to do its own work and dispense with extrinsic aid.

Bernard's experiment shows us that great irritation of the stomach will cause vomiting; and we know, from other researches, that it is because the irritation is transmitted by sensory nerves, and especially by the vagus, up to a centre in the encephalon[1] and probably in the medulla oblongata, whence it is reflected to the muscles of the abdominal walls. It is by irritation of the nerves in the stomach that vomiting is usually occasioned; but it may also be produced by irritation of other nerves, such as those of the intestine[2] or ovaries.[3] It is a reflex act, and is to be arrested either by removing the irritant or diminishing the sensibility of the nerve-centre through which it acts. If the irritant be undigested food or acrid fluids in the stomach, a little mustard and water will remove it; if it be an inflamed condition of the stomach itself, we must use bismuth and hydrocyanic acid to soothe it and deaden the sensibility of the nerves within it; but if it be an irritant which cannot be removed, like a calculus

[1] Gianuzzi, *Centralblatt für die Med. Wiss.*, 1865, pp. 1 and 129.

[2] Schiff, Moleschott's *Untersuchungen*, Bd. x. p. 390.

[3] Cyon, Pflüger's *Archiv*, Bd. viii. p. 351.

in the gall-duct or a fœtus in the uterus, we must

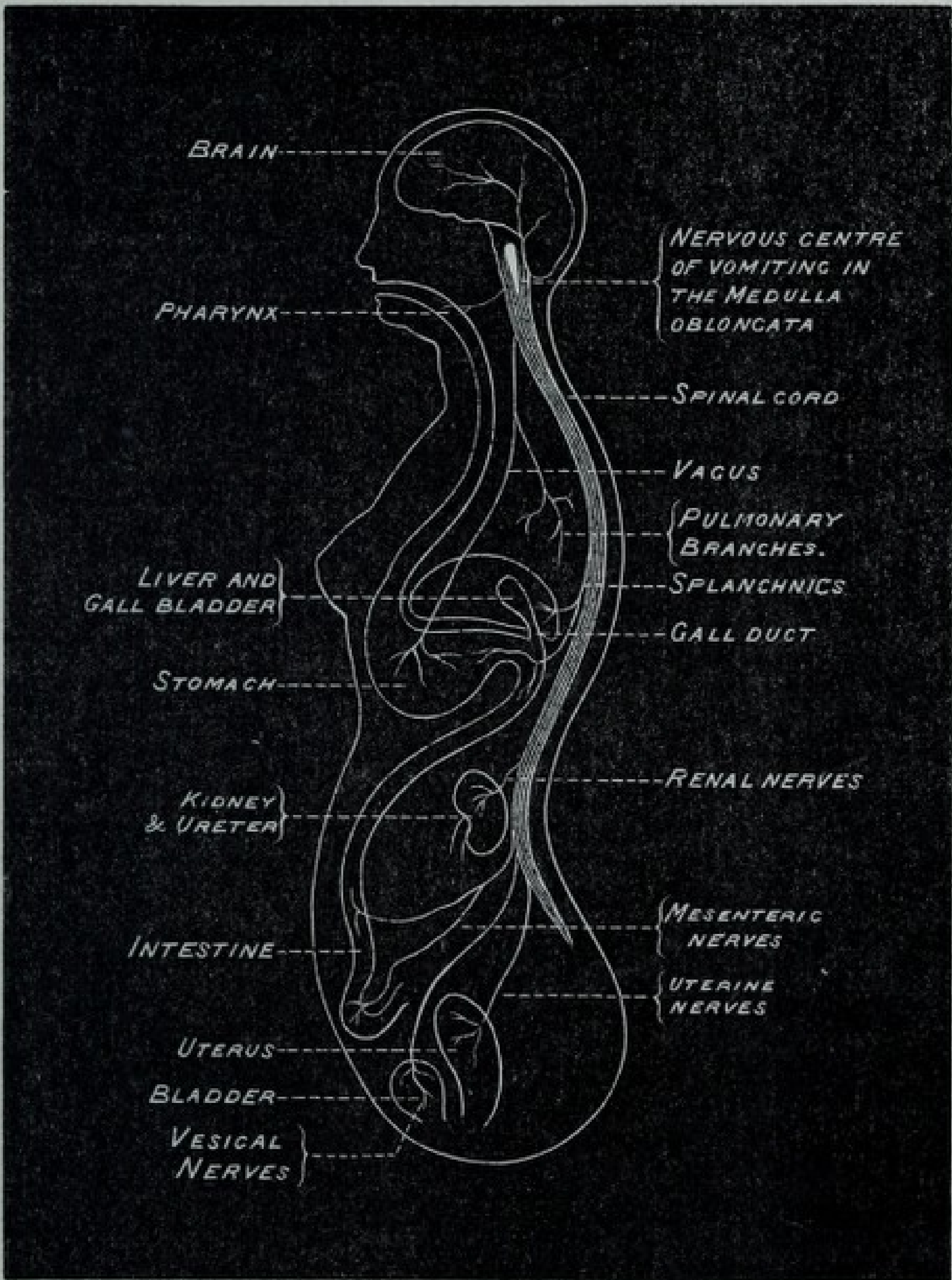


FIG. 10.—Diagram of nerves through which the vomiting centre can be reflexly excited.

employ opium or bromide of potassium to act on the nervous centre within the cranium and prevent it from transmitting any reflex impulses.

In the intestine we can no longer watch so readily as in the stomach what our drugs are doing, but still experiments are teaching us something about their action there. They have shown that acids applied to the mouth of the bile-duct stimulate the discharge of bile from the gall-bladder, so that the acid chyme from the stomach causes a flow of bile as it passes along the duodenum ; but we do not yet know whether the utility of nitro-hydrochloric acid in bilious disorders is due in any measure to its increasing the stimulus afforded by the chyme. Rutherford has shown that podophyllin, rhubarb, aloes, and colchicum increase the secretion of bile ; but he, as well as the Edinburgh Committee, of which he formed a member, found that calomel does not. The benefit which follows a dose of calomel or blue pill in biliousness is so marked that the discrepancy between clinical observation and the results of experiment led many to believe that the latter were worthless and misleading. But facts never contradict one another, although they may run counter to our opinions. The apparent contradiction in this case may be explained by the farther experiments of

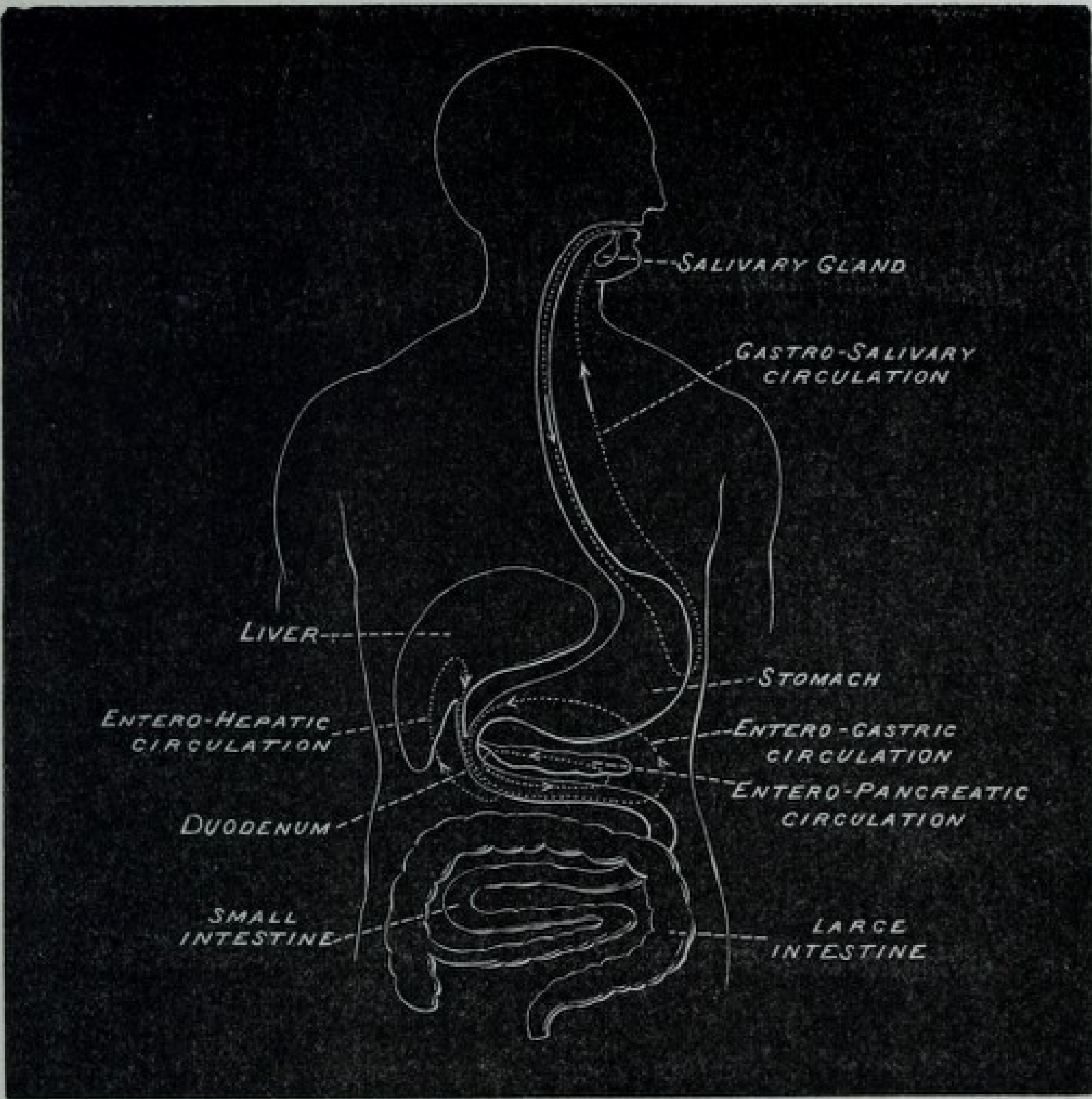


FIG. 11.

Lussana, Schiff, and Heidenhain. These physiologists have found that the liver does not only form new bile, it again secretes old bile which has been absorbed from the intestine. Thus all purgatives which sweep out old bile and food from the intestine (and thus prevent its absorption) lessen the quantity circulating in the blood, whether they increase the activity of the liver or not. The power of any purgative to clear away bile in this manner will depend on the part of the intestine on which it acts. If it hurry on the contents of the duodenum before they have time to be absorbed, it will clear away the bile ; but, if it act only on the large intestine, it will have comparatively little effect. We still want experiments on the part of the intestine affected by different purgatives; but it is probable that it is to an action on the duodenum that calomel owes the cholagogue properties which sulphate of magnesia wants.

The digestion of food in the intestinal canal is, we know, carried on by ferments, which decompose and prepare it for absorption. It would appear that each ferment must do its own work, but must not overdo it; for there seems to be a provision for stopping the action of each after it has acted for a while. The ptyalin will not act in an acid fluid; and gastric juice lessens, if it does not destroy, its activity. Pepsin is precipitated by bile, and is rendered inert by the pancreatic juice, so that its digestive power is destroyed when the food reaches the duodenum. It has not yet been ascertained whether the action of the pancreatic juice is altered by the intestinal juice, but it will not act except in an alkaline fluid; and thus, if the chyme be very acid, pancreatic digestion will be retarded. The various processes of digestion depend upon one another; and, if one be disturbed, the whole will suffer more or less with it. Hence the satisfaction with which we hail such experiments as those of Bernard and Rutherford on the action of our remedies, and the interest with which we look for farther information regarding the digestive process to Brücke and Kühne, who have already taught us so much regarding it.

CHAPTER XII.

ACTION OF FERMENTS OR ENZYMES IN FORMING TISSUES.

Effect of alkaloids and salts on this action—Relation between fermentation and muscular contraction—Power of the nervous system to regulate fermentation—Effect of drugs on fermentation in the body—Salicylic acid—Pathology of fatty degeneration — Relation of oxidation and arterial supply to fatty degeneration—Fatty heart—Effect of heat—Treatment of fatty degeneration—Iron—Alkalies—Effect of higher temperature on tissue change—Treatment of pyrexia—Quinine—Salicylic acid—Aconite—Cold baths—Cold water no new remedy—Indication for its use—How to avoid its dangers—Indication for atropia—The future of experimental pathology and pharmacology—Rapidity of new discoveries—Glimpses of therapeutic laws—Artificial formation of medicinal alkaloids—Conclusion.

BUT it is not in the intestine only that ferments, or, as they are better called, enzymes, play a part. After the food has been absorbed and actually forms a part of the liver in the form of glycogen, it is still subject to their influence, and they convert it partly into sugar. Here, too, our drugs seem to influence these enzymes, and bicarbonate of soda will lessen their activity and retard the formation of sugar.

Some ferments seem to possess the power of building up compounds, instead of breaking them down, and it appears to be the action of one ferment which causes fibrinogen and fibrinoplastin to unite to form fibrin, while the action of another, such as pepsin, would decompose fibrin into other substances.

Facts all seem to point to ferments or enzymes as the agents by which the tissues are built up and again pulled down in that constant change which continues during life, and the action of drugs upon these enzymes is becoming one of the most interesting questions in pharmacology.

Their action can be increased or diminished by the action of alkaloids, such as morphia and veratria, and by various salts, such as nitrates, sulphates, and chlorides. But the results differ with the dose as well as with the ferment and the salt used. The same salt in different quantities may at one time quicken and at another retard the action of the ferment.

A muscle cut out of the body becomes acid through the action of a ferment it contains. The same muscle in the body becomes acid in a similar way when it contracts. The processes of fermentation and of contraction are thus seen to be closely connected, and the question naturally suggests itself, Does the nerve directly act on the muscular substance, or does it act on it through a ferment which it liberates from zymogen in the muscle in much the same way as it does in the cells of a gland? Is it possible, too, for the nerves to liberate this ferment and decompose the muscles without causing them to contract?

These questions are of great practical interest, because one product of muscular decomposition is lactic acid, and this acid is generally regarded as an important agent in the production of rheumatic fever, that disease which so frequently leaves behind it the organic diseases of the heart, the treatment of which we have already considered.

It is possible that rheumatic fever is not caused by acid in the blood and secretions, but that the acid and the disease are consequences of one common cause, which may have its seat in the nervous system.

But, however this may be, can we arrest the decomposition in the muscles? can we stop the formation of acid by any drug? It would appear that, to some extent, we can; for salicylic acid or its soda-salt not only reduces the temperature in rheumatic fever, but lessens the urea, showing that lessened decomposition of albuminous tissues is taking place.

This useful drug we owe entirely to pharmacological research, and, although it is not all we desire, yet the beneficial power it does possess encourages us to hope that we will ere long discover some other remedy which shall satisfy our wants.

We now know that decomposition of the tissues composing the body, whether it be effected by the agency of ferments or not, goes on independently of oxidation, and that it may be increased while oxidation is diminished. According to Voit, albuminous substances, such as those which compose the muscles, liver, and kidneys, do not undergo combustion by direct union with the oxygen supplied to them by the blood, but split up so as to yield urea and fat.

The fat should usually undergo farther combustion into carbonic acid and water; but, if the supply of oxygen be lessened or the decomposition be quickened, combustion becomes insufficient and the fat accumulates in the tissues as fatty infiltration and fatty degeneration.

Thus it is that, when a limb is disused and the supply of oxygenated blood to it consequently lessened, fatty degeneration of the muscles takes place. When the coronary arteries can no longer meet the increased calls of a hypertrophied heart for arterial blood, or when they become abnormally contracted, fatty degeneration of the cardiac wall sets in.

When the power of the blood to convey oxygen is lessened by diminution of its red corpuscles the consequent want of oxidation leads to the accumulation of fat frequently noticed in anæmia, and a tendency to obesity frequently appears after severe hæmorrhage.

The pathology of fatty degeneration indicates its treatment. The supply of arterial blood to the organ must be increased, if possible, and its power to carry oxygen is to be augmented by the use of iron, so as to favour combustion.

But, at the same time, we must try to restrain the decomposition of the tissues within proper limits. Alkalies have the power to check decomposition of one sort, as in diabetes, but we do not yet know their action upon other changes in the tissues, nor are we able to say that their utility in obesity is due to their possession of a power to diminish tissue-metamorphosis.

But there is one way of influencing tissue-change which I must not forget. By simply keeping an animal in a hot chamber for a little while, the tissues decompose more rapidly, and the evidence of their waste is to be found in the urine as increased urea. Quicker decomposition is followed by increased combustion, and the temperature of the body rises.

Now begins a vicious circle; for the higher temperature itself quickens tissue-change and the fire supplies itself with fuel. The heat, too, stimulates the cardiac ganglia, quickens the heart, dilates the vessels, and accelerates the circulation. Acting on the respiratory centre, it quickens the respiration, increases the supply of oxygen to the body, and thus fans the flame.

But, quick as the respiration may be, rapid as is the circulation of arterial blood, it is, as Wickham Legg has shown, insufficient in many instances to keep pace with the decomposition of the albuminous tissues, the products of waste accumulate, and we find them in the fatty heart of fever patients and in the livers of Strasburg geese.

Now we clearly see that, whatever may have led to increased tissue-decomposition and combustion in the first instance, the high temperature itself is a cause of mischief, and must be reduced.

We no longer regard it as a conflict of vital spirits with which we cannot intermeddle, nor as an angry struggle of the vital powers with some foe from without, to be encouraged by keeping up a roasting fire in the sick-room, carefully closing every cranny through which fresh air might enter, swathing the patient in folds of flannel, and giving him nothing but warm drinks, in spite of his earnest entreaties for a drop of cold water to cool his parched tongue.

Instead of this, we regard it as a chemical process going on too quickly, and we try to retard it by securing cool pure air through careful ventilation, while we refresh the patient with washes to his fevered skin and cool drinks to quench his raging thirst.

We endeavour to lessen the inward fire which is consuming him by quinine, eucalyptus, or salicylic acid, and to slow his feverish pulse by aconite. But when these means fail and the temperature persistently rising will assuredly cause death, we know that we can bring it down by the free use of cold water.

This is no new remedy, for by its use Musa saved the life of Augustus. But it is not one to be ignorantly or rashly used; for, while it cured the emperor, it killed his nephew. Even now, in spite of the numerous instances in which life has been undoubtedly preserved by it, many scruple to use it on account of the dangers which they apprehend from it.

Experimental pathology and pharmacology have not given us the remedy, but they have taught us how to use it, what are its dangers, and how they are to be avoided. They are death from failure of the heart, and death from failure of the respiration.

The researches of Panum, Cyon, and others, have shown us that the heart is stimulated to increased action by warmth, but that a sudden fall in the temperature to which it is exposed may act upon its inhibitory ganglia, and suddenly arrest its pulsations.

The respiratory centre also is stimulated by warmth to increased action. But while a high temperature quickens the heart and makes it beat more powerfully, it also exhausts it more rapidly. Supposing, then, that both the heart and the respiratory centre should be weakened by continuance of fever, we can readily see that the withdrawal of the stimulus supplied to them by the high temperature may cause them to act so feebly as to endanger life, as well as that a sudden fall in the temperature may cause instant death by stopping the heart through its inhibitory ganglia.

A knowledge of the dangers teaches us how to avoid them, and the lessons of experiment coincide with those of clinical observation. The temperature in such cases must not be brought down too quickly; it must not be brought down too low, and stimulants must be administered to prevent the action of the heart and respiratory centre from flagging.

While experimental pathology and pharmacology have done so much for us already, will they not do more? They have taught us how to use such remedies as cold affusion, which were known before, and they have put new ones, like salicylic acid, into our hands. But collapse still sometimes occurs after a cold bath, and salicylic acid does not always prevent the temperature from rising.

Will this always be so? I think we may confidently answer, No. We will yet discover remedies to prevent the collapse, and to keep the

[1] The remedy indicated in cases of imminent danger would be the subcutaneous injection of atropia, which paralyses the inhibitory nerves of the heart while it stimulates the respiratory centre.

temperature within its proper limits. Every day is enriching medical science with some new discovery, diseases are being traced more precisely to their origin, the action of remedies is being more exactly defined and localised. Order is beginning to appear amongst the crowd of new acquisitions to our knowledge, and isolated facts begin to range themselves under general laws. Pharmacology is allying itself to chemistry, and the rigid laws of the latter are beginning to extend to the former.

We no longer attribute the power of drugs to an inherent energy, and say, with Molière, that opium causes sleep because it possesses a *vis dormitiva*. We are beginning to look upon the sleep as only one link in a chain, the beginning of which is a chemical affinity between opium and certain molecules in the nervous system. We observe that drugs having different chemical affinities differ in their effects on the body, while those belonging to the same chemical groups are nearly allied in their action. By altering the chemical composition of our drugs, we can alter the place of their action and change the nature of their effect. We can counteract the effects of one drug by another, and prevent death from a poisonous dose.

We are learning the conditions which cause our drugs to affect one part of the organism rather than another, so that we hope ere long to foretell from the chemical constitution of any substance the organ it will attack and the functional changes it will effect.

At the same time, pathology is teaching us the parts we must act upon, and the nature of the influence we must exert, in order to prevent or arrest the processes of disease. Thus we may hope to predict that a body having a certain chemical constitution will prove an efficient remedy in a particular disease.

Hitherto we have been obliged to trust to the substances we procure from plants for our most powerful agents; and, even if we were to know the constitution of the particular remedy we required, it might be impossible to procure it.

But now one alkaloid has been made, another and another have rapidly followed it. We can change the constitution and action of these in the same way as we alter those derived from the vegetable kingdom. It is, therefore, highly probable that we shall be able to produce artificially the substances which will act on the body in any way we desire.

Nor may the time be so very far distant. When the oldest licentiates of this College now living were studying their profession, the discoveries of Lavoisier were novelties; digestion was still regarded as a process of solution; the functions of sensory and motor nerves were unknown, and the doctrine of reflex action was still far in the future. The distinction between the tissues had just been made, and the importance of the cell had not been recognised. Pathology had hardly begun, and scientific pharmacology did not exist.

When we think of all this and compare it with our present knowledge, we are astonished. If we compare our practice, as at the beginning of these lectures, with that of the Egyptians and Greeks, we are discouraged; but if we glance at the advances made during a single lifetime, we cry, Slow has been the advance of medicine, because she went astray; now the path she follows is right, swift is her progress, and glorious will be her future.

APPENDIX.

Since these lectures were written I have received through the kindness of Mr. Frederick Macmillan an account of the use of an ordeal bark in which the occurrence of diuresis or stoppage of the urinary secretion is used as an indication of the guilt or innocence of the prisoner. In our experiments on casca, Mr. Pye and I found that an infusion of this bark in large doses caused stoppage of the urinary secretion, whereas in moderate doses it caused diuresis, and this seems to render it very probable that the root described under the name of imbando is really that of the *Erythrophleum guinense.* The district in which this ordeal by diarœsis is employed coincides very nearly with that from which Mr. Monteiro obtained the cassy bark.

The account is contained in "The Strange Adventures of Andrew Battel, of Leigh in Essex, sent by the Portuguese Prisoner to Angola, who lived there and in the adjoining Regions near Eighteen Years," which appears in *Pinkerton's Voyages and Travels* (1814), vol. xvi., page 317. It is difficult to find the names of the places as he spells them in a modern map, but so far as I can understand, the usage described by Battel was among a people called by him *Matimbas*, who lived in Loango north of the river Zaire. It is in the chapter of his narrative entitled, "Of the Provinces of Bongo, Calongo, Mayombo, Manikesocke, Matimbas; of the Ape-Monster Pongo, their Hunting, Idolatries, and divers other Observations," and the passage (page 534) runs as follows: —

"When any man is suspected for an offence, he is carried before the king, or before Mani Bomma, who is a judge under the king, and if he denies matters not to be proved except by their oath, then this suspected person swears thus:—They have a kind of root which they call Imbando; this root is very strong, and is scraped into water. The virtue of this root is, that if they put too much into the water, the person that drinketh it cannot avoid urine: and so it strikes up into the brain, as if he was drunk, and he falls down as if he was dead. And those that fall are counted guilty, and are punished.

"In this country none on any account dieth, but they kill another for him: for they believe they die not their own natural death, but that some other has bewitched them to death. And all those are brought in by the friends of the dead whom they suspect; so that there many times come five hundred men and women to take the drink, made of the foresaid root Imbando. They are brought all to the high-street or market-place, and there the master of the Imbandos is with his water, and gives every one a cup of water by one measure;

and they are commanded to walk in a certain place till they make water, and then they are free. But he that cannot urine presently falls down, and all the people, great and small, fall upon him with their knives, and beat and cut him to pieces. But I think the witch that gives the water is partial, and gives to him whose death is desired the strongest water, but no man of the bystanders can perceive it. This is done in the town of Longo, almost every week throughout the year."

Whether *Imbando* is the same thing as *Casca*, or whether the two ordeals, though similar in character, are conducted by means of different materials, can hardly be decided with certainty only from the accounts of the symptoms produced. It seems probable, not merely from the action of the *Imbando* on the urinary organs, but also from its causing those who had drunk it to fall as in one of the forms of ordeal with *Casca*. In any case Battel's Imbando is interesting from its likeness to Monteiro's *Casca*. Battel's voyage began in 1589.

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