LECTURES

ON

THE CONNECTION BETWEEN THE CHEMICAL PROPERTIES AND THE PHYSIOLOGICAL ACTION OF ACTIVE SUBSTANCES.

Delivered before the Royal College of Physicians, Edinburgh.

BY

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LECTURE I.—(Concluded.)

Chemical Constitution and Physiological Action.—The chemical properties of substances, however, depend not only on their *composition*, but also on their *constitution*. I have already said that the chemical constitution of a substance is the mode in which its constituents are arranged or united together. The difference between composition and constitution may be explained by a reference to such substances as the compound ethers. They are formed by the action of an acid on an alcohol, and may be so decomposed as to yield again the alcohol and acid from which they were produced. Now, common alcohol (C^2H^6O) and valerianic acid ($C^5H^{10}O^2$) have together the same composition as amylic alcohol ($C^5H^{12}O$) and acetic acid ($C^2H^4O^2$) together. The combination of each of these two pairs of substances gives rise to a compound ether of identically the same composition, but differing in properties; and each of these compound ethers can be decomposed so as to yield the pair of substances from which it was produced. Thus,

The one ether obviously differs from the other in the manner in which the constituents are united together; that is to say, in its constitution.

It appears, therefore, that substances may possess physical, chemical, and physiological properties that do not depend on their special composition. This independence of composition and property is also met with among inorganic substances. Some elements form only one series of compounds—as zinc with its single oxide, chloride, and sulphate. Other elements form more than one series—as iron with its proto- and per-salts, arsenic with its arsenites and arsenates, and sulphur with its sulphides, sulphites, and sulphates; and distinct physical and chemical properties are possessed by each individual series. In the examples which I have last mentioned, the investigation of the physiological action of the compounds belonging to any special series is a matter of considerable difficulty. Where varieties of constitution exist, the compounds of the less stable varieties readily undergo decomposition, and assume that constitution which possesses the greatest stability. Thus the proto-salts of iron easily change their constitution, and become converted into per-salts; and arsenates become reduced to arsenites. That changes of constitution also occur in the body, has been rendered certain by numerous observations, and more especially by those of Rabuteau, who has shown that, when introduced into the system, bromates become changed to bromides, iodates to iodides, and sulphites and hyposulphites to sulphates: in fact, that towards these substances the organism acts as a reducing agent. Hence, there is an absence of definite knowledge regarding the action of more than one series of the compounds of the elementary bodies.

Among the organic compounds, however, a large class of substances may have their constitution modified in such a manner that a change to the original or any other form is effected only with the greatest difficulty. The substances to which I refer are the natural alkaloids. Their constitution is not fully known; but it is sufficiently known to prove it to be of the same type as that of ammonia, and to show that they resemble that substance in containing triatomic nitrogen. Thus, ammonia =

Like ammonia, also, they are converted by union with acids into salts having a different constitution—a constitution in which the nitrogen, in place of being triatomic, becomes pentatomic. For instance, in the formation of hydrochlorate of strychnia, the originally triatomic nitrogen takes up chlorine and

hydrogen, and becomes pentatomic $N \begin{Bmatrix} C^{21}H^{22}NO^2 \\ H \\ Cl \end{Bmatrix}$, united by three bonds to carbon, by one to hydrogen, and by one to chlorine;

just as the triatomic nitrogen of ammonia unites itself by two additional bonds to chlorine and hydrogen, and so becomes pentatomic in hydro-

of strychnia is not rendered permanently or stably pentatomic; it easily loses the chlorine and hydrogen which it has acquired, and returns to the triatomic state. The action of alkalies, or, in many cases, even of alkaline carbonates, is sufficient to effect this, and to set free the alkaloid. It is obvious, therefore, that the change of constitution effected by the addition of an acid does not permit us to discover the corresponding change in physiological action. But if, instead of an acid, we make use of such a substance as iodide of methyl, we find that, while the triatomic nitrogen takes up methyl (CH^3) and iodine, and becomes pentatomic (just as in the former case it took up hydrogen and chlorine), it does not lose these newly acquired atoms when treated with alkalies, but remains pentatomic even when subjected to attacks more violent than any to which it could be exposed in the system.

I have alluded to the type of the natural alkaloids being that of ammonia, but certain varieties of constitution are met with, to which I would now draw your attention. In ammonia, the nitrogen is united to three equivalents of hydrogen. Now, one or two or three of these equivalents may be replaced by one or more radicals, and in this way we have amine, imine, and nitrile bases. Thus, one equivalent of hydrogen is replaced by CH^3 in the amine base, methylamia, $N \begin{Bmatrix} (CH^3) \\ H \end{Bmatrix}$; two equivalents by the diatomic radical (C^8H^{14}), in the imine base, normal conia, $N \begin{Bmatrix} (C^8H^{14}) \\ H \end{Bmatrix}$; and three equivalents, by the same diatomic radical, and by CH^3 , in the nitrile base, methyl-conia, $N \begin{Bmatrix} (C^8H^{14}) \\ CH^3 \end{Bmatrix}$, or, to take another example of a nitrile base, by one equivalent of the triatomic radical ($C^{21}H^{22}NO^2$), in strychnia, $N \begin{Bmatrix} C^{21}H^{22}NO^2 \end{Bmatrix}$.

These various bases are distinguished from the bases derived from them in which nitrogen is stably pentatomic (called ammonium bases) by certain chemical characters common to them all. Their salts, for instance, are decomposed by caustic potash, so that the base is set free, and water and a salt of potassium formed; and a similar effect is produced by moist oxide of silver. The salts of the ammonium bases, however, are not acted upon by caustic potash, and, when treated with moist oxide of silver, a hydrated oxide of the ammonium base (in which nitrogen remains pentatomic) is formed, and the acid unites with the silver.

The powerful decomposition action which caustic potash is able to exert does not, therefore, change the chemical constitution of these ammonium bases. It, indeed, has no effect upon their salts; and even when these salts are treated with moist oxide of silver the characteristic pentatomicity of their nitrogen is retained. In the living body, they cannot possibly be subjected to the influence of such powerfully decomposing agents; and hence, by studying their action, and comparing it with that of the nitrile or other base from which they are derived, the relationship between physiological action and a certain form of chemical constitution may be discovered.

It was owing to this consideration that Dr. Crum Brown and I resolved to examine the action of a number of the ammonium bases derived from the vegetable alkaloids. Our experiments were made with the methyl, and, in a few instances, the ethyl, derivatives of strychnia, brucia, thebaia, codeia, morphia, nicotia, atropia, and conia, and more especially with their iodides and sulphates.

The results that we obtained may, perhaps, be best illustrated by describing, with a little detail, several of our experiments with iodide and sulphate of methyl-strychnium.

It is well known that strychnia acts on the living economy in a distinctly defined and characteristic manner, and that it is one of the most active of poisons. When administered subcutaneously, doses varying from one-twentieth to one-fiftieth of a grain produced in rabbits the most violent tetanic convulsions, and in a few minutes killed the animal. Few poisons have been more carefully studied, and it is now almost undoubtedly established that the phenomena produced by strychnia are due to a localisation of its action on the spinal cord.

The effects of iodide of methyl-strychnium were first examined by subcutaneous injection. It was administered as a fine powder suspended in warm distilled water, in which menstruum it is but sparingly soluble, though more so than in water at the ordinary temperature. In this way, by a series of progressively increasing doses, it was found

that as much as twelve grains could be given to a rabbit, weighing three pounds, without any effect whatever. Fifteen grains, however, produced serious symptoms, though followed by recovery; and death was caused by the administration of twenty grains. In none of our experiments, not even in the fatal cases, were the symptoms those of strychnia-poisoning; no starts nor spasms occurred, nor did stimulation give evidence of the slightest increase of reflex activity. In fact, a condition exactly the reverse of that produced by strychnia was caused by iodide of methyl-strychnium. In place of violent spasmodic convulsions and muscular rigidity, the appearances were those of paralysis with a perfectly flaccid condition of all the muscles. The limbs of the animal first yielded; its head gradually sank until it rested on the floor; by-and-by, it lay in a perfectly relaxed condition; and when death occurred, it was due to stoppage of the respiratory movements. In the necropsies, further evidence was obtained to distinguish the effects of iodide of methyl-strychnium from those of strychnia. The heart was found acting with nearly its normal rapidity; the spinal motor nerves were either paralysed, or nearly so; and, in place of the early or almost immediate occurrence of rigor mortis that follows the action of strychnia, the muscles continued flaccid, contractile, and alkaline for many hours.

The effects of internal administration were examined by passing a gum-elastic catheter down the oesophagus of a rabbit, and so injecting iodide of methyl-strychnium, suspended and dissolved in warm distilled water. It is unnecessary to give any description of these experiments, as no effect was produced by this method of administration, although as much as thirty grains was given at one time; and it was inconvenient, as well as unnecessary, to give larger doses. It is well known that to produce symptoms with a poison in a rabbit, a much larger quantity is required when the poison is administered by the stomach than when it is injected subcutaneously. The contrast between the activity of iodide of methyl-strychnium and strychnia itself was, however, well shown in the rabbit to which thirty grains of the former had been given without any effect; for one-tenth of a grain of strychnia, also administered by the stomach, quickly produced violent tetanic convulsions, and in a few minutes killed the animal.

As the sulphate of methyl-strychnium is a very soluble salt, we anticipated that it would act with much greater activity than the iodide, and our experiments confirmed this anticipation. One grain dissolved in water and injected under the skin of a rabbit caused its death in eighteen minutes. Half a grain, however, produced no marked effect. When eight-tenths of a grain were similarly administered, symptoms of a most serious character were produced, but death did not result. Some days afterwards, one-twentieth of a grain of strychnia, dissolved in very dilute sulphuric acid, was administered to this rabbit by subcutaneous injection; and it produced symptoms of strychnia action, followed by death fifteen minutes after the injection. Eight-tenths of a grain of sulphate of methyl-strychnium contain about six-tenths of a grain of strychnia: the effect of converting this nitrile base into an ammonium base by adding to it sulphate of methyl had been, therefore, to reduce its poisonous activity at least twelve times.

The symptoms that are produced by sulphate of methyl-strychnium are the same as those produced by the corresponding iodide. The very short account I have given of the symptoms and *post mortem* appearances that occur after the administration of iodide of methyl-strychnium is sufficient to suggest a close resemblance between its action and that of curara (*wourali*)—a resemblance, indeed, which had previously been pointed out by Professor Schroff, of Vienna. Both substances undoubtedly produce a condition of general paralysis, but the special characteristic of curara-poisoning is that this paralysis results from an impairment or destruction of the function of the peripheral terminations of the motor nerves. It is impossible to demonstrate such an action without undertaking experiments of a special character. Dr. Brown and I accordingly extended our research for the purpose of studying the exact causation of this paralysis. Among other experiments, we made the following. The sciatic artery and veins were tied above the knee of a frog, and a small dose of sulphate of methyl-strychnium, dissolved in water, was injected under the skin at the back. Eight minutes afterwards, the frog was lying in a perfectly flaccid state; and, in ten minutes, irritation of any portion of the skin produced energetic movements of the tied limb below the point of ligature, but nowhere else. The sciatic nerve of the untied limb was now exposed, and on stimulating it with a weak, interrupted, galvanic current, movement occurred in the tied limb only; not the slightest movement occurred in any part to which the poison had access. At the same time, the muscles were everywhere active, and freely contracted when directly stimulated. The sciatic nerve was then exposed in the tied limb, above the points of ligature, and on stimulating it energetic movements occurred below the knee of that limb,

and there only. The heart at this time was acting at the rate of 50 per minute.

This experiment was frequently repeated—on several occasions the iodide having been substituted for the sulphate—and the same general results were obtained. The evidence that was thus acquired in favour of an action on the peripheral terminations of the motor nerves, was strengthened by a modification of the experiment.

The right gastrocnemius muscle of a frog was carefully dissected from its connections; excepting that its origin and insertion, and the nerves entering it, were uninjured, and that all its blood-vessels were ligatured. A small dose of sulphate of methyl-strychnium, in solution, was then injected under the skin of the back; twenty minutes afterwards, the animal being in a perfectly motionless and flaccid condition, the two sciatic nerves were exposed. Galvanism of the left produced no movement of the left limb, while galvanism of the right produced energetic movements of the right limb, which were seen to be due solely to contractions of the right gastrocnemius muscle, the other muscles remaining motionless. At the same time, direct stimulation caused contractions as freely in the poisoned muscles as in the non-poisoned right gastrocnemius.

In experiments where iodide of methyl-strychnium was substituted for sulphate, the results were the same. The methyl derivatives of strychnia, therefore, produce paralysis and death, by destroying the function of the peripheral terminations of the spinal motor nerves. Accordingly, their mode of action is identical with that of curara. This result is an extremely curious and interesting one. It is difficult to imagine a more decided modification in the action of any substance than is produced by the change of chemical constitution resulting from the addition of iodide or sulphate of methyl to strychnia. The striking characteristic of the action of strychnia is the great and uncontrollable activity of the muscular system; that of curara, of iodide and sulphate of methyl-strychnium, and, as we also found, of other similarly modified alkaloids, is the flaccid and motionless condition caused by the impossibility of exciting muscular action through the nervous system. So opposite are their effects, that many physiologists look upon curara as a powerful counter-agent to strychnia, while physicians have employed it in the treatment of strychnia-poisoning and of tetanus. It is certainly remarkable that so thorough a change of physiological action should be produced by this simple change of chemical condition.

The other vegetable alkaloids examined, all possess, though in varying degrees, the same peculiar spinal-stimulant action as strychnia. Brucia and thebaia exert this action with great energy; codeia and morphia with somewhat less power; and nicotia, atropia, and methylconia, in a still slighter degree, though quite obviously. The result of the combination of each of them with a salt of methyl is, as in the case of strychnia, to change their chemical constitution from that of nitrile bases with triatomic nitrogen, to stable ammonium bases with pentatomic nitrogen; and the change of physiological action following this change of chemical constitution having been found to consist of a removal of spinal-stimulant action, and addition of paralysing action restricted to the terminations of the motor nerves, it is unnecessary to give any further details of the results of our experiments. The important general fact which they indicate is, that a change of chemical constitution, even when it is of a simple kind, may produce a very essential change in physiological action; and, although they are perhaps as yet insufficient to warrant any positive assertion, they render it extremely probable that all the stable ammonium bases have a curara-like action. Every such compound that has as yet been examined has been found to possess this action. To the list of those which I have mentioned may be added chloride of oxethyl-strychnium—recently studied by Dr. Vaillant—and iodide of tetra-ethyl-phosphonium—which has formed the subject of a careful investigation by Dr. Vulpian—both salts of ammonium bases, and both found to possess a powerful action on the terminations of the motor nerves.

I am anxious, however, to guard against conveying the impression that the compounds of pentad nitrogen act simply as nerve-paralysers: their action is not necessarily restricted to these structures. In several cases it is, no doubt, so restricted; and notable examples of this are found in the salts of methyl-strychnium, methyl-brucium, and methyl-thebaium, whose nitrile bases have probably no other decided action than a spinal-stimulant one. In those cases, however, in which the salts of ammonium bases are derived from alkaloids that produce complicated effects, a restriction of action to the terminations of the motor nerves does not occur. The original actions of the alkaloid, excepting the spinal-stimulant one, are retained by the salts of its ammonium base; and thus the salts of methyl-atropium not only act like curara, but they likewise paralyse the cardiac inhibitory fibres of the vagi and dilate the pupils, while the salts of dimethyl-conium retain the paralysing action on the vagi that is possessed by conia itself.

In considering how these various facts bear upon the connection between chemical constitution and physiological action, it is no doubt essential to remember that a change of composition as well as of constitution has been produced by the conversion of the nitrile into the ammonium bases. In the substances examined by Dr. Brown and myself, the composition of the original alkaloids was changed by adding to them a salt of methyl. Are, then, the subsequent changes of physiological effects produced by the action of the added salt of methyl? This hypothesis is so improbable as scarcely to deserve consideration. It is opposed by the experiments made with iodide of tetra-ethyl-phosphonium, to which I have already alluded; for this, also, is the salt of an ammonium base, which, however, differs greatly in composition from any of the substances examined by Dr. Brown and myself, although it exerts the same physiological action. It is opposed, also, by the results of experiments with conia and its derivatives; for the hydrochlorate of the nitrile base (methyl-conia), formed by the addition of hydrochlorate of methyl to the imine base (normal conia), exerts, notwithstanding this addition of methyl, a more marked spinal-stimulant action than normal conia, into whose composition methyl does not enter; while the salts of the ammonium base di-methyl-conium have a prominent curara action, and no spinal-stimulant action whatever. Besides, the action of iodide of methyl itself does not give the least support to this idea—for its effects are those of a powerfully irritating substance, and its action, even when induced by subcutaneous injection, results in inflammation of the bronchial mucous membrane and coma, and not in paralysis of motor nerves.

It might also be asked, if the processes by which these ammonium bases are prepared do not so profoundly modify the chemical nature of the alkaloids from which they are derived, that no actual relationship exists between the new substances and their original sources; that, for example, sulphate of methyl-strychnium, though derived from strychnia, is in no special manner related to sulphate of strychnia—the elements of the latter substance having been so disarranged in its conversion into the former, that the strychnia has been altogether destroyed. It is, I think, a sufficient answer to this conjecture to point out that the ordinary colour reactions of the alkaloids are retained by their methyl derivatives.

Gentlemen, the various facts which, in a somewhat discursive manner, I have now brought before you, confirm the opinion that chemical composition bears some relation to the physiological action of active substances, and they also prove that this relationship is to an important extent due to the arrangement of the atoms in the substance. They appear, likewise, to point to the conclusion that physiological action is often, if not always, the result of a chemical reaction between the foreign body and certain of the constituents of the vital structures whose action is modified by it. The results of investigation with such substances as carbonic oxide, show, indeed, that physiological action may be chiefly the result of chemical reactions. The effects of other substances have not been connected with chemical action in so direct a manner, but this is to a great extent explainable by the difficulties attending the demonstration of a connection of this kind. Although experimental research, in many cases, has discovered the exact histological elements which are acted upon, the chemical characters of these elements have not yet been sufficiently ascertained. We have no means of determining their normal conditions with the delicacy that is required, and we are, therefore, unable to investigate the chemical reactions that almost certainly accompany modifications of their normal physiological condition during the operation of active substances. Thus, although we know that the normal physiological condition of the terminations of motor nerves are modified by the salts of the ammonium bases derived from strychnia, brucia, thebaia, etc., and that this modification is produced by substances that have definite chemical properties, we cannot discover what chemical change is produced so long as we are ignorant of the special chemical properties possessed by these structures. The trustworthy observations of Kühne have shown that a recognisable change occurs in the physical characters of the nerve terminations—a change which renders their outlines more distinct; but we are unable to connect this change with any definite chemical reaction. In the course of time, reactions of a more delicate kind than any we yet possess will, no doubt, be discovered, not only for these structures, but likewise for each of the special structures on which the physiological action of active substances is localised. Physiological investigation has shown that one substance may chiefly exert its influence upon the cardiac inhibitory ganglia, another on the nerve-fibres intermediate between these ganglia and the ends of the vagi nerves, and another on these endings themselves. How are these localisations of action to be explained? There must undoubtedly be a difference between the chemical properties of each of the structures influenced. The discovery of the spectroscopic characters of hæmo-

globin has greatly extended our knowledge of the action of such substances as carbonic oxide, by placing at our disposal a means of defining the chemical reactions that take place between it and the blood. In giving expression to the anticipation that similarly delicate tests of chemical reaction will yet be discovered for each of the special histological elements of the body, I do not think that we err by being too sanguine. Were such means of investigation at our disposal, it may safely be predicted that knowledge would be acquired of as perfect a kind as is indicated in the following quaint sentence, written by Locke: "Did we know the mechanical affections of the particles of rhubarb, hemlock, opium, and a man, as a watchmaker does those of a watch, whereby it performs its operations; and of a file, which, by rubbing on them, will alter the figure of any of the wheels, we should be able to tell beforehand that rhubarb will purge, hemlock kill, and opium make a man sleep." It is encouraging to find that even now we know of certain "affections of the particles" of active substances which enable us to tell beforehand that, wherever these affections occur, well defined and characteristic physiological effects will be produced.

CLINICAL LECTURES

ON

MENTAL AND CEREBRAL DISEASES.

By J. CRICHTON BROWNE, M.D., F.R.S.E.,

Medical Director, West Riding Asylum; Lecturer on Mental Diseases to the Leeds School of Medicine; etc.

III.—SIMPLE MELANCHOLIA.

GENTLEMEN,—You will recollect that, at your last visit to the wards, I called your special attention to the case of Jane S., as being, in many respects, a typical example of a form of mental derangement about which I should have to speak to you to-day. You will remember that this woman was an inmate of Ward 25, to which she was admitted on the 31st of May last, just a fortnight ago, being returned as twenty-eight years of age, single, and a domestic servant, from Bradford. The history of the case, which I read to you, was as follows. Jane S. is a native of Scotland, but has been resident in Yorkshire for five years. Her mother's brother was once insane and an inmate of an asylum; but, with that exception, no member of her family has ever suffered from mental or nervous disease. The patient herself has had no serious illness nor cranial injury, and has always been of sober habits. On the 1st of May last, she gave birth to an illegitimate child. Her fall from virtue had preyed much upon her mind during her pregnancy; and the depression of spirits thus occasioned deepened considerably at the time of her confinement, when she was in poor lodgings and could not command liberal nourishment or careful nursing, and passed into morbid despondency three days after delivery, when the unexpected announcement of her father's death reached her. She at once formed the idea that her father (who was a very aged man, and really died in the course of nature) had been killed by the shame of her misfortune. She sank into a state of inconsolable grief, wept incessantly, was sleepless, and twice attempted to put an end to her existence and sorrow by jumping through the window. After this she refused all food, complained of insupportable misery and weakness, and repeatedly threatened suicide; so that, for her own protection, she was sent to this asylum. After reading this history, as you will recollect, I introduced you to the patient—a thin, pale, careworn-looking woman, whom you found seated in the day-room, with her head bowed down, and her hands crossed upon her lap, in an attitude of listless dejection. Her features were fixed in an expression of mental suffering, the angles of the mouth being drawn down, and the corrugators of the upper eyebrows being firmly contracted. When I spoke to her, she answered slowly and with evident reluctance, turning away from me, as if shrinking from observation and seeking solitude. In reply to my repeated questions, however, she told me that she was quite wretched, and tired of life, and that she had nothing to look forward to but death. She added that she had killed her father by her conduct, and had no affection for her child, so that she did not care if she never saw it again. Her answers must have satisfied you that she was perfectly intelligent—she at once apprehended the meaning of all that was said to her; that her memory was good—she accurately recalled all the facts of her past history which had been communicated to you; and that no delusion existed in her mind—she repudiated several delusive beliefs which I suggested to her. The nearest approach to a delusional state of mind which she