LECTURES

ON

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

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BY

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LECTURE I.

MR. PRESIDENT AND GENTLEMEN,—In addressing those who possess some familiarity with the subject I have the honour to bring before you, it is scarcely necessary to make the statement that a connection exists between the chemical properties and the physiological action of substances. The slightest effort of memory, or, at most, a glance at a table of elementary substances or list of chemical compounds, is sufficient to convince any one of the truth of this statement. For, among the numerous elementary substances or chemical compounds whose action has been investigated, it is difficult, if not impossible, to find two that possess exactly the same physiological action—that produce the same train of symptoms, and modify the functions of the same histological elements in the same way and with the same activity. Now, as one elementary substance is distinguished from every other elementary substance by the possession of certain distinctive chemical properties, and as one compound substance is likewise distinguished from all other compound substances by the possession of certain special chemical properties, it is obviously suggested that a relationship exists between the chemical properties and the physiological action of active substances.

Substances resembling each other in chemical properties possess actions that resemble each other.—No doubt, analogies, often of a close and striking description, occur between the physiological actions of different substances; but these analogies tend to bring more distinctly into view the relationship referred to, by shewing that similar physiological effects are often produced by substances which resemble each other in many of their chemical properties. For instance, the various salts of potash in a remarkable manner paralyse the heart's action, those of ammonia accelerate the circulation and produce spasms and general convulsions; and, indeed, the general truth of the proposition, enunciated by Dr. Blake in 1839—to which, however, there are several exceptions—that the salts of the same base have analogous actions, is now universally recognised. To the industry of this observer we are also indebted for another general proposition of great interest which bears upon this relationship. Several chemical substances possess the property of crystallising in the same form, and of replacing each other in crystalline compounds without alteration of the characteristic geometrical figure; in other words, they possess the property of isomorphism. The physiological action of a large number of inorganic substances belonging to different isomorphous groups has been examined by Dr. Blake. The symptoms that were observed have led him to believe that, with a few exceptions, a striking analogy exists between the isomorphous relations and the physiological action of the substances examined, an analogy to which he has given expression by the statement that "isomorphous substances produce similar effects."

Substances which resemble each other in certain of their chemical properties, possess similar degrees of poisonous activity.—Not only is there evidence to show that substances which resemble each other in their chemical properties may possess physiological actions of a similar kind, but a correspondence may likewise be traced between certain of the chemical properties and the physiological activity, or poisonousness, of substances. The combining or atomic weight of elementary bodies forms an important character by which they may be distinguished from each other, and Dr. Rabuteau has published an extensive and valuable series of experiments, which he had undertaken for the purpose of determining whether any relationship exists between the atomic weight and physiological activity of elementary bodies. As a result of this investigation, he has found that *the metals are more active physiologically according as their atomic weights are more elevated.* For example, in reference to sodium, potassium, and thallium: sodium, with an atomic weight of 23, is almost inert; potassium, with an atomic weight of 39, is active in moderate doses; and thallium, with an atomic weight of 204, is a

dangerous poison, nearly as poisonous, indeed, as lead, whose atomic weight is 207. On comparing magnesium, zinc, and cadmium, it is seen that magnesium, with an atomic weight of 24, is scarcely more active than sodium (23), for the salts of the former are prescribed in about the same doses as those of the latter; while zinc, with an atomic weight of 65, is a dangerous substance, although much less so than cadmium, whose atomic weight is 112. In reference to the metalloids, Dr. Rabuteau has found that those which are *diatomic*, as oxygen, sulphur, selenium, and tellurium, conform to the same law as the metals. The monatomic metalloids, however, are governed by a law which is the reverse of this; a fact which had previously been pointed out by Bouchardat and Stuart Cooper, who observed that chlorine (35.5) is more active than bromine (80), and the latter more so than iodine (127).

By changing the chemical properties of a substance, we may modify the physiological action.—These various facts show that resemblances between the chemical properties of substances may be accompanied with certain similarities in their physiological action and activity. The support that is thus given to the theory of a relationship between chemical property and physiological effect, is greatly strengthened when we find that the physiological action of substances may be modified by changing their chemical properties. Among the many examples that might be brought forward in illustration of such change, one of the most remarkable is that afforded by amygdalin. This neutral principle is derived from bitter almonds, and it is a substance that is devoid of physiological activity. There occurs along with it in the bitter almond, another principle, emulsin, which also is a substance that possesses no physiological activity. A large dose either of amygdalin or of emulsin alone may be injected into the circulation of an animal without any effect whatever being produced. When, however, the two substances are together injected, even at points far removed from each other, physiological effects are produced with great activity, and death occurs. The originally inert amygdalin has become a powerful poison, and this change is the result of a modification in its chemical properties—a modification which you will easily recognise by comparing the odour of the moistened amygdalin with that of the mixture of amygdalin, emulsin, and water, which I now place before you, and which may be represented by the equation:—

Another example of a similar kind, which may be here adduced, has been made known within recent times by the chemical researches of Matthiessen and Wright, and the physiological observations of Drs. Gee and Pierce, and others. The two chemists whom I have here named, in the course of their elaborate researches on the opium-alkaloids, found that when morphia was acted upon by hydrochloric acid at a high temperature its chemical properties are modified, and its composition changed so that one equivalent of water is separated from it. The action of morphia thus modified has been examined, and it has been ascertained to possess a physiological action very different from that of morphia itself. In place of producing hypnosis, this changed morphia—to which the name of apo-morphia has been given—acts as a powerful emetic substance, so powerful, indeed, that in man emesis occurs within a very few minutes after the one-thirteenth part of a grain, or even a smaller dose, has been subcutaneously injected.

The general law, that the physiological action of a substance may be modified by changing its chemical properties, is, indeed, one whose truth is widely recognised in medical science. On it has been founded the application of chemical antidotes for poisons; that is to say, of substances that modify the physiological effects of substances by changing their chemical properties. The chemical properties of arsenious acid are changed by hydrated sesquioxide of iron or of magnesia, those of tartar emetic by tannin or albumen, those of lead by sulphate of magnesia, those of prussic acid or soluble cyanides by proto and persalts of iron, those of oxalic acid by carbonate of lime, and those of morphia, strychnia, and various other alkaloids by tannin or iodine; and as a result of this change the physiological properties of these substances are modified.

To the recognition of this law, likewise, therapeutics has become indebted for the introduction of a remedy which everyone must admit has proved of the greatest value in the treatment of disease. Although chloral was discovered more than thirty years ago, it was not until 1869 that Liebreich ascertained its important physiological action. The belief that a certain change in its chemical properties would enable it to produce a well defined physiological action, induced Liebreich to investigate the action of this substance. I need hardly say that the chemical change anticipated was the decomposition of the chloral, after its introduction into the circulation, by the alkaline salts present in the blood. This decomposition may readily be seen by adding, as I now do, some caustic alkali to a tolerably strong solution of chloral hydrate; the

result being the precipitation of minute globules of chloroform and the simultaneous formation of formiate of the base that is added :—

The physiological action of an active substance may be accompanied with obvious chemical reactions between it and certain of the constituents of vital structures.—The principle which I am now endeavouring to illustrate, namely, that a connection exists between the chemical properties and the physiological action of active substances, receives a further and obvious support from several well-known facts, which show that the physiological action of active substances may be accompanied with distinct chemical reactions between them and certain of the vital structures. Thus, in producing its violent corrosive action, sulphuric acid withdraws the element of water from the tissues, liberates the carbon of their ternary hydrocarbons, and separates from them their basic constituents. The analogous corrosive effects of nitric acid are accompanied with the oxidation of tissue-elements, and combinations with electro-positive substances, and with the formation of xanthoproteic acid—by the last of which reactions the characteristic orange staining of the skin and fibrous tissues is caused. It is needless to point out how the local effects of the caustic alkalis are also accompanied with well-defined chemical changes in the vital structures on which they act.

One of the most striking examples of a definite change of chemical property accompanying the physiological action of a substance is that afforded by carbonic oxide. You are aware that this gas is largely present in the fumes of burning charcoal, and that it acts as a violent poison. Its special effects have formed the subject of a well-known investigation by Claude Bernard—an investigation that marks an era in the history of pharmacology. This distinguished physiologist discovered that carbonic oxide renders the blood of a marvellously florid colour, that it thrusts out oxygen from that fluid, and that its action is in some way related to the latter effect. More recent investigations, especially those of Lothar Meyer and Hoppe Seyler, have confirmed Claude Bernard's results, and also shown that carbonic oxide forms a definite chemical union with the hæmoglobin of the blood. The resulting compound is one of great stability; so much so, that carbonic-oxide-hæmoglobin resists the action of powerful reducing agents. The connection of these results with the action of this substance is easily seen. The physiological action is the direct result of the change in the chemical properties of hæmoglobin—a change which has, among other effects, that of preventing those chemical interchanges between it and the oxygen of the air on which life depends. The relation of the great stability of the combination between carbonic oxide and hæmoglobin to certain of its physiological effects is also apparent, for the serious symptoms which are produced by the most minute quantity can be recovered from but slowly. They can, however, be recovered from; and again we find that a chemical explanation may be adduced for this physiological change, as it has been recently discovered that, under the prolonged influence of oxygen, the carbonic oxide is at last liberated from its combination with the hæmoglobin.

There is some reason for supposing that somewhat similar chemical effects are produced during the action of prussic acid; and it has been shown by the careful and elaborate observations of Dr. Gamgee that nitrites conduct themselves towards hæmoglobin in an analogous manner to carbonic oxide—a fact which may explain certain of the phenomena produced by nitrite of amyl.

Gentlemen, these various illustrative examples are, I think, sufficient to convince you that there are good reasons for supposing that resemblances between the chemical properties of substances may be accompanied with certain similarities in their physiological action and activity; that the physiological action of many substances may be modified by changing their chemical properties; and that the physiological action of a substance may be accompanied with distinct chemical reactions between it and certain of the vital structures. It is on these generalisations, and the facts by which they are supported, that the belief in a connection between the chemical properties and the physiological action of active substances has in all probability been originated.

Various attempts have been made to determine on what special chemical properties the physiological action of substances depend; and I have had occasion to refer to several of these attempts, of which those of Blake and Rabuteau are undoubtedly the most important. It is also worthy of mention, that Dr. Broadbent of London has advanced the opinion, supported by many ingenious arguments, that the physiological action of a substance is related to a property which he terms *chemical tension*, and defines as the amount of energy developed by any possible rearrangement of the constituents of the substance; while Dr. Benjamin Richardson has shown that, in a series of bodies belonging to the same chemical type, the character of the

symptoms somewhat depends on the volatility and solubility of the various members of the series. It is not necessary to occupy your time by discussing these theories. Whatever germ of truth they may contain, their value in indicating a connection between the chemical properties and the physiological action of active substances is a comparatively limited one. I prefer, therefore, to pass without further delay to the consideration of some other investigations which bear upon this subject.

Before doing so, it is necessary to inquire on what the chemical properties of substances are dependent. It is quite obvious that these properties depend on the chemical *composition* and *constitution* of substances; the latter term implying the mode of arrangement of their constituents, or the way in which these constituents are united together.

Chemical Composition and Physiological Action.—There are numerous indications of a relation between the chemical composition of a substance and its physiological action. Thus, as I have already mentioned, the salts of the same base have generally a common action—a law that is departed from when the base is united to an acid which itself has a distinct action. Similarly, the compounds of the same acids with physiologically indifferent bases produce the same effects. When, however, we consider more fully the relationship between composition and physiological action, we fail to discover the cause of the peculiar action of substances in the presence and proportion of particular elements. Many substances having identically the same composition—termed by chemists isomeric—possess very different physiological actions. This, for instance, is the case with the isomeric series represented by oil of turpentine, oil of lemons, oil of juniper, etc., all of which have the composition $C^{10}H^{16}$; and with that represented by nitrite of ethyl and glycol, both of which have the composition $C^2H^5NO^2$. Kakodylic acid likewise very well illustrates the insufficiency of composition alone as an explanation of physiological action; for, although it is a soluble substance, and contains more than 54 per cent. of metallic arsenic, it may be administered in large quantities without producing any effect whatever. And, finally, the action of the organic alkaloids is obviously opposed to this explanation—an opposition which becomes apparent when we consider that aconitia paralyses the spinal cord, and also the inhibitory cardiac ganglia; while strychnia increases the activity of the reflex apparatus in the cord, and stimulates rather than paralyses the cardiac vagi nerves, although both substances are alike composed of carbon, hydrogen, nitrogen, and oxygen.

[To be continued.]

A CASE OF EVULSION OF THE IRIS.

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On the 26th May, 1872, a railway pointsman, named Samuel Tew, aged 42, met with the following accident. He was pulling at a piece of wood, the opposite end of which was held down by a weight, when a portion of it, about a foot in length, suddenly broke off and flew up, striking him in the right eye with the splintered end. Feeling that he was severely injured, and suffering great pain, he came directly to my house, about a quarter of a mile from where the accident happened. On examination, I found a wound in the outer and lower edge of the cornea. The anterior chamber had some blood in it, and chemosis was setting in, but at the time nothing more was made out, owing to the pain any examination produced. I at once applied atropine, and employed antiphlogistic treatment.

When all inflammation had subsided, and the corneal wound had healed, the iris was found to be completely torn away, a piece of the size of about two pins' heads only remaining at the corner of the wound. There was for a long time great intolerance of light ; which, however, has gradually subsided, and the patient is now able to bear any moderate amount of light. At the present time the lens is perfectly clear. If anything the eye is slightly contracted. On closing the other eye he can see, but cannot discern distinctly.

When tested with Jäger's types he could read nothing, but looking through a circular hole, one-sixteenth of an inch in diameter, in a piece of dark paper, he could read Jäger No. 19. With a test spectacle (No. 9) covered with the same piece of paper, he could read No. 16. When the hole in the paper was enlarged to the eighth of an inch he could not distinguish anything; and with neither aperture did any other spectacles suit him.

There are on record some cases of congenital absence of the iris, but such cases as the one just related of complete evulsion of the iris without other damage to the lens or sight, and with perfect restoration to the eyeball, are, I think, sufficiently rare to justify me in thinking this a case worthy of being recorded.