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REPORT

ON THE

PHYSIOLOGICAL ACTION

OF

MEDICINES.

BY

J. BLAKE, M.B., F.R.C.S., &c. &c.

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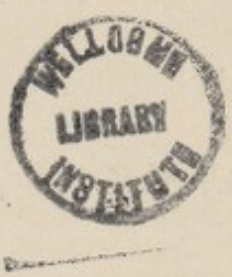

Report on the Physiological Action of Medicines. By J. Blake, *M.B., F.R.C.S. &c. &c.*

The present report is but a continuation of that which was read at the last Meeting of the Association, and which has since been published in the Transactions. The investigation of the action of medicines has been confined to the observation of the effects that follow their direct introduction into the blood, by means of injections into the arteries or veins, and in most instances the hæmadynamometer has been used, in order to ascertain more accurately the effects produced on the heart and vascular system. Although this view of the subject may appear to be of no practical utility, yet I trust that the results arrived at will justify the course that has been pursued. In my former memoirs on this subject I have endeavoured to prove that isomorphous substances, when introduced directly into the blood, exert an analogous influence on the animal economy. The experiments I am about to bring forward afford additional confirmation of the views I have already advanced, and, with the facts that have been published, will, I trust, constitute a sufficient amount of evidence to firmly establish the truth of the law in question. The experiments I have now to bring forward have been performed with the tartrate of antimony, the salts of palladium and platinum, and with the chloric, hydrochloric, bromic and iodic acids.

Tartrate of Antimony.—This substance when injected into the veins gives rise to exactly the same phænomena as would the arsenic or phosphoric acids, and which have been detailed in the last report. The quantity required to cause death was about a drachm of the salt.

Chloride of Palladium.—This salt is very poisonous, for when introduced into the veins it possesses the power of arresting the action of the heart, in smaller doses than any other substance I have experimented with. On injecting half a grain, dissolved in half an ounce of water, into the jugular of a dog, the action of the heart became rather fluttering after a few seconds, and then slower; there was no expression of pain. On injecting a grain of the salt, the action of the heart was arrested in about 12″. The respiration is often suspended for a minute or two, and then recommences, continues regularly for about a minute, and is again suspended. I have observed this to recur five times after the injection of two doses of a quarter of a grain each; the animal lay on its side without the slightest expression of pain, although perfectly sensible; there were no convulsions: after death the heart was found quite still, the blood in the left cavities of a dirty scarlet, showing that the heart had not been arrested from asphyxia; it coagulated slowly; the lungs were almost white and anæmic. On injecting a solution containing half a grain

into the arterial system, violent spasm was immediately produced: the pressure rapidly increased from 5 to 12 inches, as indicated by the hæmadynamometer*; respiration continued at intervals, and the pressure in the arterial system gradually fell, but was still at six inches four minutes and a half after all regular respiratory movements had ceased. The salts of platinum give rise to precisely similar phænomena when injected into the arteries and veins; they do not appear to be so poisonous as those of palladium, as it requires three or four grains to be injected into the vein before the action of the heart is arrested. Osmium and iridium, the other members of this isomorphous group, have not been experimented with on account of their great rarity.

I have only now to notice the phænomena that are produced by the well-known isomorphous group—iodine, chlorine and bromine. The forms under which these substances have been used are as iodic, bromic, chloric and hydrochloric acids. I shall only allude to the effects that have been observed after the introduction of the iodic acid into the veins and arteries, as the acids of chlorine and bromine give rise to effects perfectly analogous. Iodic acid and the substances that are related to it present an analogy with the salts of silver and soda in their action on the animal economy; they are however perfectly distinct in one or two particulars, in which also they closely agree amongst themselves.

When injected into the veins, iodic acid evidently exerts an influence on the passage of the blood through the lungs: immediately after the injection of a solution containing 10 grains of the acid into the veins, the pressure in the arteries becomes lowered. In a short time we have most unequivocal proofs of its action on the lungs, by the escape of a quantity of frothy fluid from the air-passages, which soon causes the death of the animal by asphyxia. If the dose be larger (25 grains of iodic acid for instance), the passage of the blood through the lungs becomes at once arrested, and the animal rapidly dies from congestion of the venous system. After death the lungs are found congested and red, serous effusion having taken place in their tissue as well as in the air-passages. The heart generally contains a medium quantity of dark blood, which coagulates firmly. If the thorax is opened immediately after death, the ventricles are found beating rhythmically, although the auricles have lost all trace of irritability,—a fact which forms a curious exception to the general rule, and which has only been observed in connection with this class of substances. When injected into the arteries, the phænomena produced by iodic acid are very extraordinary. The first effect that followed the introduction of six grains of the acid into the artery was an immediate diminution of the pressure in the arterial system: in the instance alluded to, it fell in the course of a few seconds from six to eight inches down to two, the heart's action being very slow; the animal cried, respiration became suspended, and in about a minute it lay to all appearance quite dead; after another minute however the pressure in the arterial system suddenly increased to nine inches, the heart beating quite regularly, although the animal still lay as if dead; the pressure gradually diminished, and at four minutes after the injection, and three minutes after every external sign of life had ceased, it had again sunk to five inches. A most curious phænomenon now presented itself, viz. a sudden rise of full three inches, in the pressure of the blood in the arterial system. This increase in the pressure was followed by two respiratory movements, and by slight motion in the legs and tail. After this the

* The pressure in the arterial system is given in inches of mercury, as ascertained by the hæmadynamometer.

pressure gradually sunk, and the heart stopped seven minutes after the injection. The chloric and bromic acids give rise when injected into the arteries to phænomena exactly analogous to those just described: with hydrochloric acid the action of the heart does not continue so long after respiration has ceased, nor has the augmentation in the pressure after the cessation of respiratory movements been observed with this substance; this might possibly be owing to its not containing oxygen.

Having now brought forward the facts which have been ascertained since my last report, in support of the analogous action of isomorphous substances on animals, I propose to take a general review of the whole of the evidence we are now in possession of relating to this law, and also of those facts which appear to militate against it; merely premising, that, in the present imperfect state of our knowledge as regards the isomorphous relations of bodies, it is not to be expected that a first attempt to arrive at any generalization founded on these properties should not present many anomalies and apparent contradictions, which it will require further investigations to clear up, or which may lead to important modifications in the expression of the law itself. The evidence in favour of the law is derived from the following facts:—first, the similarity of action of the following isomorphous substances belonging to the magnesian class; viz. magnesia, lime, manganese, iron, cobalt, nickel, zinc, cadmium, copper and bismuth,—substances which present striking differences in their ordinary chemical affinities, but which agree in being isomorphous, and also in producing analogous phænomena on animals when introduced directly into the blood. The salts also of another well-marked isomorphous group, viz. lead, strontia and baryta, closely agree in their actions on the animal system. Palladium and platinum, in the effects they produce when introduced directly into the blood, lend their support to this law. Phosphorus, antimony and arsenic, a strictly isomorphous group, give rise to analogous reactions on the animal economy. The chlorine group also fully bears out the law, at least as regards iodine, bromine and chlorine, for fluorine has not been experimented with. The salts of soda and silver also agree in the effects they produce, although presenting a more striking contrast in many of their chemical properties than is to be found in any other class. On the other hand, potash and ammonia, two substances between which well-marked isomorphous relations exist, differ to a certain extent in the phænomena they give rise to when introduced into the blood. It is possible that the compound nature of the radical of ammonia, differing so completely as it does from the other inorganic radicals, may introduce certain modifications in its relation to organized compounds. The only other fact that my investigations have made me acquainted with, which appears to oppose itself to this law, is, the analogy that exists to a certain extent between the salts of lead and the chlorine group and silver. As regards the more marked phænomena produced by the salts of lead, they are such as its connection with strontian and baryta would lead us to suppose; but in one respect, viz. in their action on the lungs, they resemble the salts of silver. As regards this anomaly I would merely observe, that galena and sulphuret of silver are found under the same form.

Such is the evidence with which my researches have furnished me, in support of the law of the analogous action of isomorphous substances on organized beings, and I think it sufficient to justify us in admitting that the molecular reactions that take place between the elements of living bodies and inorganic substances are to a great extent independent of chemical affinity, but are connected with those properties of matter which are expressed by its isomorphous relations. It is evident that this law must lead to important

modifications in the investigation of physiological phænomena : in considering the action of unorganized substances on organized beings, it is clear that our attention must not be so exclusively directed to the chemical properties of these substances: it must not be as alkalies or acids or salts that their action on organized beings must be investigated, but as regards their isomorphous relations, or those properties of matter which are evidently connected with the form it assumes, and which have recently been elucidated by the researches of Kopff. But whilst this law would tend to remove the investigation of physiological phænomena from the domain of pure chemistry, it is far from leading us to conclude that the reactions that take place amongst materials of which organized beings are composed are essentially of a different character from those which we observe amongst the simpler forms of matter. The difference between the more simple combinations of the elements with one another and those they form with the more complicated compounds of carbon, hydrogen, oxygen and nitrogen that exist in the living body, seems to be, that in the former instance they combine under the influence of chemical affinity, whilst in the latter it would appear to be a physical polarity that influences the formation of the compound : it is the former power that gives rise to the union of sulphuric acid and soda, whilst the latter causes the compound to assume a definite crystalline form. It would appear, in fact, as if the force of chemical affinity was more or less neutralized in living beings, and that their elements are held together by other forces than those which prevail amongst unorganized compounds. In the present early stage of these researches, I would not attempt to generalize this law beyond that class of facts to which it has been proved experimentally to apply ; it may admit of a far more extended application, embracing in its expression not merely the combinations of the compound elements of organized beings, but also the combinations of carbon, hydrogen, nitrogen and oxygen, of which these elements consist. In the present imperfect state of our knowledge, it would be hazardous to offer an opinion on the nature of the compounds that are formed under the influence of this law, when inorganic substances are introduced into the blood ; it remains even to be proved if the phænomena they give rise to are owing to the formation of any definite compounds between them and the elements of the blood and tissues. In the absence of all direct proof on this point, I would offer one or two considerations which would tend to indicate that the probability is in favour of the formation of definite compounds between the inorganic element and the blood and tissues.

The researches of Mulder on the composition of albumen and fibrine prove, that the presence or absence of certain elements in very small proportions may essentially alter the properties of the protein compounds. The whole of the fibrine, for instance, in the blood of a small animal does not contain more than two grains of sulphur, which however appears to form as essential an element in its composition as it does in sulphuric acid ; if therefore we introduce into the blood any substance which should deprive the fibrine of its sulphur, either by combining with the sulphur itself, or by replacing it in the protein compound, we should immediately have a fluid circulating over the body which would not contain any fibrine, and which might be totally unfitted for carrying on the vital phænomena; two or three grains of baryta for instance, supposing it capable of producing such a reaction, would suffice to defibrinize the whole of the blood. Another consideration that would favour the supposition that isomorphous substances form certain definite analogous compounds with the blood and tissues, is, that we generally find that the different substances belonging to the same isomorphous group give rise to certain physical changes in the blood which are readily

recognizable ; thus the whole of the magnesian family agree in depriving the blood in a greater or less degree of its property of coagulation ; the same remarks will appiy to most of the other groups. It is highly probable that these physical changes are owing to the formation of certain definite compounds between the elements of the blood and the substances mixed with it. A careful analysis of the organs on which different classes of substances appear more particularly to act, would probably elucidate this point.

Before concluding, I would offer a remark on the relative poisoning powers of the substances that have been experimented with. The salts of palladium, platinum and baryta are those which prove fatal in the smallest doses ; and it is a curious fact, that, under an isomorphous point of view, these three substances are those which have the least analogy with the elements that enter into the formation of the animal solids and fluids ; on the other hand, arsenic, which might have been supposed to be rapidly fatal, is so inert when introduced into the blood that it will not speedily produce death, unless indeed it is injected in quantities sufficient to directly coagulate the blood. It remains for future experiments to determine if this is owing to its being isomorphous to one of the elements of the fluids and solids, the phosphorous.