THE THERAPEUTICAL ACTION OF IRON.

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THE action of iron from a physiological and therapeutical standpoint is of such interest that no apology is needed for devoting some attention to the results of the more recent investigations on the subject, and the theories to which they have given rise. It is freely acknowledged by most authorities that our information regarding the absorption of iron and its *modus operandi* in disease is in an extremely unsatisfactory condition, considering how largely it is used. This feeling has given rise to many researches, most of which, it must be confessed, have not tended to dispel the darkness which envelopes the subject. Among them, however, the investigations of Professor Bunge of Basel stand out as remarkable not only for their brilliance and originality, but also for the light which they throw on many points which have hitherto puzzled clinicians and pharmacologists.

It is chiefly of Professor Bunge's researches that I propose to give a short account in this article; and while the question of the absorption of iron can by no means be considered as entirely settled by them, yet it must be generally admitted that a great step has been made in the right direction.

Iron takes a peculiar position among the heavy metals in relation to the animal organism. It is an essential element of our body, where by far the greater part of it is concentrated in the red blood corpuscles, but at the same time it is present in small amount in all our tissues and secretions. Bodily tear and wear causes its constant excretion, and hence it of necessity must constitute a part of our daily nourishment. Its ingestion is necessary not only for the preservation of health and strength, but for mere existence.

In nature and in the blood it seems to subserve very much the same function. On the earth's surface iron plays the part of a carrier of oxygen. Here it exists in the form of ferrous and ferric oxides. The former is a strong base, and combines with all acids to form neutral salts, while the latter is a feeble base, and particularly is not capable of holding carbonic acid in combination. When ferrous silicate becomes decomposed by the carbonic acid of the air to form ferrous carbonate, (a process which goes on continuously in nature), the latter becomes dissolved in CO_2 —containing water, and is thereby diffused all through the earth. But so soon as it comes in contact with atmospheric air, it is oxidised to ferric oxide, the carbonic acid being set free and returning again to the atmosphere. The ferric oxide, however, by contact with organic matter in the earth is reduced to ferrous oxide, thus giving up its oxygen and acting as an oxidiser. The ferrous oxide again combines with carbonic acid and repeats the same cycle time after time. The carbon oxidised in the soil by the reduction of ferric oxide is returned to the atmosphere as carbonic acid, in which form it is assimilated by plants and formed into complex organic bodies. These ultimately in one form or another reach the earth's surface, where they decay, and

where their carbon is again oxidised by ferric oxide. In this way we are indebted to iron for keeping oxygen and carbon constantly in circulation in nature.

In our organism iron in the form of hæmoglobin and oxyhæmoglobin plays the same part as the ferrous and ferric oxides on the earth's surface. By means of this compound oxygen is carried to the tissues, and carbon in the form of carbonic acid returned to the atmosphere.

Hæmoglobin is contained in the red blood corpuscles solely, and is a complex molecule the constitution of which has not yet been determined. It forms the red colouring matter of the blood, and contains by far the greater part of all the iron in our body. It consists of hæmatin ($C_{32}H_{32}N_4O_4Fe$) *plus* a complex molecule of albumen. In the blood of certain cephalopods iron is replaced by copper.

The amount of iron in the blood of an average sized man is reckoned at about 3 grms., most of it forming part of the hæmoglobin. Hæmoglobin is not present in the dietary of herbivora, and only in very small quantity (which is broken up in the alimentary canal) in that of carnivora, hence it must be formed synthetically in the body from the iron and albumen of the food.

The ordinary dietary of animals contains a much larger quantity of iron than is requisite to compensate for the waste of hæmoglobin, so much so that a large amount of iron is excreted daily by the bowel unused.

This brings us to the question of the excretion of iron from the body, and here we must carefully distinguish between the results following on different methods of administration. (1) If a soluble iron salt which does not coagulate albumen be injected into the circulation directly, we get marked symptoms of metallic poisoning—depression of the muscular and nervous systems, cardiac weakness, renal inflammation, and other effects—while the iron is excreted mainly by the walls of the intestine and by the kidneys. Given in this way, therefore, iron is extremely poisonous even in small amount. (2) If iron be taken in our food or by the mouth, no symptoms of poisoning ensue even with a very large dose, and it is this method of administration in which we are chiefly interested.

Iron may always be found in the urine and in the fæces. In the urine there is *never* more than a mere trace, probably in the form of a complex organic compound, while the fæces invariably contain a large quantity, almost, if not quite entirely as sulphide. Here the great difficulty meets us that the metal is a normal constituent of our food and of our secretions, and hence it has been found impossible to decide how much of it is simply unabsorbed iron, and how much of it is excreted iron. To determine this, Bidder and Schmidt made observations on starving dogs, where of course there is no ingestion of iron. In the urine they found daily 0·0014–0·0017 grm. Fe, in the fæces 6–10 times more. In the bile of man and other animals Bunge found only unweighable traces of iron, while Hamburger got a similar result even after adding sulphate of iron to the diet. Of all the excretions, the gastric juice was found to contain most iron, but Bunge is of opinion that in the starving dog the fæces-iron is derived from the epithelium of the alimentary canal, a tissue which when dried contains no less than 0·46% Fe, a larger quantity than hæmoglobin does.

Iron, then, is excreted in small amount by the kidneys, the quantity being unchanged during ordinary diet, ordinary diet *plus* iron, and starvation. The fæces always contain a considerable quantity, depending entirely on the amount taken *per os*. The secretions poured into the alimentary canal contain mere traces of iron.

We must now consider the question of the absorption of the ordinary iron preparations used in medicine. With regard to these, Bunge is of opinion that it is by no means proved that they are ever absorbed, but, on the contrary, thinks it most probable that they never leave the alimentary canal.

He bases this opinion on the results of excretion experiments (as given above) made by himself and by Hamburger, in which the administration of iron did not increase the amount excreted in the urine, or only did so by 2 mgrm., a quantity from which no reliable conclusions can be drawn as it is well within the limits of error. Besides this, Bunge lays great stress on the fact that manganese is never absorbed from the bowel; manganese, as is well known, being closely allied to iron in every way and not being an ordinary constituent of the body, is capable of detection even in the minutest trace.

If Bunge has not been able to prove it, he has certainly shown it to be extremely probable that iron preparations such as we use in medicine do not become absorbed from the alimentary canal.

Objections which may be brought against his arguments are:—(1) That the quantities of iron required to make up for hæmoglobin waste are so small, that they fall within the limits of chemical error and cannot be investigated; and (2) the non-increase of excretion of iron by the kidneys after administration *per os* is not definite proof of non-absorption into the blood, as iron may be excreted in some other unknown way. These objections hold theoretically quite well, but they want proof.

What becomes, then, of our medicinal preparations of iron after reaching the stomach. The general teaching, I believe, is, that they are converted into the protochloride or an albuminate, are absorbed as such into the blood, and are again excreted almost *in toto* by the liver, ultimately mingling with the fæces and forming the sulphide of iron found there.

Bunge, however, states that all the iron *salts* (inorganic, organic, and albuminates) become in the stomach either ferrous or ferric chloride. In the intestine the sodium carbonate (which is always present) turns the ferric chloride into ferric oxide, which remains dissolved in the organic matters of the alimentary canal. On the other hand, the ferrous chloride is transformed into ferrous carbonate, which also remains dissolved in the carbonic acid and organic matters. Both are finally converted into sulphide by the alkaline sulphides formed during digestion, and are so excreted in the fæces.

In the choice of an iron preparation, therefore, to treat disease we should be guided not by considerations of supposed easy absorbability, but rather by the state of the stomach and bowels. On account of their very different local actions which I need not enlarge on, it is by no means a matter of indifference which iron preparation is administered, but so far as absorption is concerned it is so.

Now if the foregoing arguments be correct, we are driven to the conclusion that our food must contain other iron combinations which

are not broken up in the alimentary canal, which are absorbed, and which yield the material to form hæmoglobin.

To discover the nature of this immediate precursor of hæmoglobin in our food, Bunge has investigated the iron combinations found in yolk of egg and in milk. From both, hæmoglobin is built up—in one case to form the red blood corpuscles of the chick, in the other of the young mammal. In both cases no other nourishment is taken, and hence yolk of egg and milk must contain iron in an absorbable form. If we can determine what this form is in one instance, we can thereafter readily investigate it in all kinds of food. Now Bunge has succeeded in isolating the iron-containing body of yolk of egg, and has shown that it is not of the nature of a salt, but a combination of the nature of hæmoglobin itself, the corollary being that all the iron of our food exists in a similar condition. The iron is in the nuclein of the yolk, the body having the following percentage composition: C 42·11; H 6·08; N 14·73; S 0·55; P 5·19; Fe 0·29; O 31·05. This body has been named Hæmatogen, and from it undoubtedly the hæmoglobin of the bird's blood is built up, as the yolk contains no other iron compound.

The nuclein-albuminous iron compound is not decomposed by hydrochloric acid and alcohol, nor is it split up by gastric digestion. It is, however, soluble in alkaline solutions. It therefore passes through the stomach without being decomposed, and being in a state of solution may be readily absorbed from the bowel. From alkaline solutions, however, ammonium sulphide slowly but completely precipitates the iron. The iron in this case is therefore much more firmly combined than it is in albuminate of iron, but less firmly than in hæmatin, from which it cannot be separated by ordinary reagents. Similar iron compounds are present in milk and in vegetables.

What bearing has this on our views regarding the action of iron in chlorosis? There are at present two chief theories regarding the action of iron in this disease. According to some authorities, typical chlorosis is the result of long-continued insufficient absorption of food, and is ushered in by loss of appetite and dyspepsia. The excretion of iron goes on, and not being supplied from the food, there ensues a deficit. The iron which we give makes up for this deficit, and if we give an excess, more is absorbed, and thereby an impetus given to the formation of red blood corpuscles from leucocytes.

The other view is that iron acts as a stimulus to the circulation in the alimentary tract, and hence result better assimilation and better nutrition. They consider that in the daily food there is iron enough and to spare without giving more, but that the more which is given acts as a tonic and causes satisfactory absorption.

Bunge's views, however, are different from either of these. He says that three facts require to be considered :—

1. Iron increases hæmoglobin formation in chlorosis.
2. Iron salts are not absorbed.
3. Our food contains only organic compounds of iron.

He holds that in chlorosis there is great poverty of gastric juice, with attendant dyspepsia and formation of alkaline sulphides. These alkaline sulphides, as shown above, are capable of decomposing the absorbable albuminous iron compounds, and thereby render them,

like ordinary iron salts, incapable of absorption. Hence the deficiency of hæmoglobin.

Now when ordinary iron preparations are given the alkaline sulphides attack these, thereby leaving the others free to be absorbed. In favour of this view is the fact that such enormous doses of iron require to be given to cure a case of chlorosis—small doses being of no value. In two or three days more iron may be given than is present in the whole body. Secondly, good hygienic measures and attention to diet frequently cure chlorosis without iron.

Thirdly, in a healthy subject continued administration of iron does not raise the red corpuscles and hæmoglobin above the normal standard.

In all forms of anæmia which have their origin outside the alimentary canal iron must therefore be powerless.

Bunge's explanation of the action of iron in chlorosis has no bearing, of course, on its ætiology, which has been stated by Virchow to depend on a deficiency of the arterial system. One symptom of this deficiency, however, is a form of dyspepsia which interferes with the assimilation of iron, secondary to which we have all the clinical symptoms of anæmia. Iron, given in large doses by the mouth, counteracts the effects of the dyspepsia, and thus cures the most distressing symptoms of the disease. The vascular deficiency, however, it can never remedy.

PLANTAR NEUROTOMY.

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I HAVE thought that a few practical remarks on the operation of plantar neurotomy, with some statistics which I am able to give, might be of interest to the veterinary profession; the more so as I am in the fortunate position of being able to trace the horses operated upon for some time afterwards, when they have been put to work, which is not, as a rule, easily done in ordinary practice. Besides, the operation is not looked upon with much favour in country districts; and should the veterinary surgeon happen, unfortunately, to be unsuccessful in his first one or two cases, he gets disheartened, and generally advises his client to sell, rather than try again.

With regard to the operation itself, it is too well known to require more than a few remarks from me. I never use chloroform, although I do not doubt it would be of great benefit to the horse in obviating the pain at the moment the nerve is divided. I dispense with it because its application would take up much time; and seeing that I generally operate on two or three cases the same afternoon, it would be necessary to have a casting place for each horse. In my experience, if the horse has been prepared for casting, *i.e.* has had a short allowance of food the previous day and none on the day of operation, I generally find that when he gets back into his box his head goes into the manger, and he seems quite comfortable.

The time occupied for each horse, casting and operating on both fore legs, never exceeds three-quarters of an hour.