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SOME CONSIDERATIONS ON THE INFLUENCE OF COPPER AND MANGANESE ON THE THERAPEUTIC ACTIVITY OF IRON *

BY

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The last few years have seen the emergence of two fields of investigation which, though originally independent, are now beginning to unite. In the first place, modern methods of analysis have shown that in addition to the elements traditionally incorporated in the structure of protoplasm, others, principally metallic, occur with constancy in animal tissues.

This analysis at first made use of chemical methods, but as many of these elements are present only in minute traces the spectrograph has been found to have many advantages, particularly as a means of qualitative research. Using an arc spectrum, Zbinden¹ found copper, manganese, tin, silver, titanium, chromium, and zinc widely spread throughout the body. By the method invented by Ramage,² employing a flame spectrum, copper, manganese, rubidium, silver, and strontium have been found in human beings,³ while Fox and Ramage⁴ obtained similar results in invertebrates, though the range of elements found was wider and in many cases included nickel and cobalt. The advantage of the spectrograph in this type of work can be seen in the case of the eye, where the very unexpected observation was made that the choroid of cattle regularly contains barium in amounts that increase with age.⁵ It is clear that certain elements, particularly copper, manganese, zinc, and rubidium, occur with great constancy in human tissues. This is especially the case with copper, which was found in every one of 500 specimens examined by the method of Ramage; so that this element at any rate may be regarded as a universal and essential constituent of protoplasm. The first reaction to such findings is to regard these elements as contaminants rather than as substances having physiological significance. The second series of investigations referred to above has, however, begun to show that at any rate some of them have functions in the body which render them necessary to life, although they are only necessary in minute quantities. Thus in 1928 Hart, Steenbock, Waddell, and Elvehjem, showed that without the presence of an adequate amount of copper the body is unable to utilize iron to form haemoglobin.⁶ More recently Orent and McCollum⁷ and Kemmerer⁸ have found that manganese is essential to the processes of reproduction. It is in the light of these researches that I wish to advance a few

considerations as to how copper and manganese may influence the therapeutic activity of iron, a full review of the subject being beyond the scope of this paper.

COPPER IN NUTRITIONAL ANAEMIA

The experiments of Hart and his co-workers at Wisconsin showed that carefully purified inorganic iron was ineffective in the cure of the nutritional anaemia of young rats caused by the iron deficiency resulting from a whole-milk diet. When accompanied by small amounts of copper (0.025 mg. a day)⁶ this pure inorganic iron could be used as the sole source of the iron required for the cure of the anaemia, the haemoglobin being rapidly regenerated in the presence of copper. They further found that copper was unique in this property, and could not be replaced by other metals. A few workers such as Titus, Cave, and Hughes,⁹ and more recently Myers and Beard,¹⁰ while not denying that copper is the most active supplement to iron, have stated that other elements, including manganese, are also effective. Hart and his colleagues have reaffirmed their original position,¹¹ which has also been confirmed by other workers. Thus, Orten, Underhill, and Lewis,¹² using glass cages in order to prevent the rats obtaining traces of metal by gnawing the cages, found that copper was the only effective metal, and that manganese, in particular, was quite inert in the formation of haemoglobin. These experiments of Hart and his colleagues are fundamental in demonstrating that the traces of copper so consistently found in animal tissues have at any rate one definite physiological function. It is certain that others remain to be discovered. An obvious clinical application of their work lies in the nutritional anaemia of infants, which has recently been fully described by Helen Mackay.¹³ This anaemia, like that of the experimental rats, is characterized by a deficiency of haemoglobin due to iron starvation, and it is a natural inference that copper might be of similar value in this condition. Numerous observations have been reported, by Parsons,¹⁴ Josephs,¹⁵ Schiff,¹⁶ and others, and while there have been negative reports, the general trend is to show that in infants the addition of a small amount of copper to the iron preparation used does accelerate the production of haemoglobin. Here, as in so many other cases, it is difficult to transfer the comparatively simple results of controlled experimentation into the more complex field of clinical medicine. Thus it would appear from the work of Parsons on the value of yeast extracts that there is a vitamin as well as a metallic deficiency in this type of anaemia, and it has been shown¹⁷ that copper may occur as an impurity in all the preparations of iron in therapeutic use, its presence having been demonstrated in about 80 per cent. of the samples tested. There is, however, sufficient evidence to justify the use of small amounts of copper in addition to the iron needed for the treatment of these babies. Transferring the figures from the experiments on rats to the human being on a basis of weight for weight, the human baby would appear to need about 0.5 mg. copper per diem.¹⁸

Its Mode of Action

The usual explanation of this action of copper has been that it is a catalytic one. Josephs¹⁹ has recently published some very important work which carries our knowledge a stage further, and which should be borne in mind when copper is employed as a therapeutic adjunct to iron in children. He fed a series of rats on: (1) milk alone, (2) milk plus 0.5 mg. iron per diem, and (3) milk plus 0.5 mg. iron plus 0.1 mg. copper per diem. The rats were killed at various ages, during and after the nursing period, and the total amount of iron in the whole body was found by chemical analysis. The haemoglobin percentage

* Paper read in the Section of Pharmacology and Therapeutics at the Centenary Meeting of the British Medical Association, London, 1932.

being known, the total haemoglobin was calculated from a formula correlating weight and blood volume. On the assumption that haemoglobin contains 0.34 per cent. of iron²⁰ the percentage of the total iron of the body present as haemoglobin could then be calculated.

The results are of great interest. It was found that in Groups (2) and (3) the retention of iron averaged about 10 per cent. of the intake, and that copper had no influence on the degree of retention of iron. The effect of copper was to increase the proportion of retained iron found as haemoglobin, so that rats fed on copper plus iron had smaller amounts of iron in the tissues than had rats fed on iron alone. Indeed, these rats fed on iron and copper together had, within the limits of experimental error, the same amount of tissue iron as had those fed on milk alone, indicating that under the influence of copper 100 per cent. of the retained iron was being used for the formation of haemoglobin. The tissue iron consists of two moieties—(a) the functional iron, which is essential to life and is mostly located in the nucleus in organic combination, and (b) a reserve store of iron, which is chiefly found in the liver. In rats fed on milk alone there is from birth a steady drop in the total tissue iron of the body (as the reserve store provided during foetal life is used up), until a steady level is reached, representing the functional iron necessary for the life of the tissues. Since the store is depleted, not only by the call for iron for haemoglobin but also for the growing tissues, there is a progressive diminution in the amount available for the formation of haemoglobin, resulting in the development of anaemia. When this mechanism is exhausted the level of functional iron in the tissues is maintained at the expense of growth.

Practical Applications

It is to be noted that the rats receiving copper plus iron resembled those on a milk diet alone in that there was no reserve store of iron, since all the iron retained from the food was utilized for the formation of haemoglobin. It is therefore probably advisable when giving copper to give larger doses of iron than would otherwise be given, so as to ensure that there is an adequate supply of iron for the two purposes of growth and haemoglobin formation. Mackay's work has shown that there is a correlation in infants between rate of growth and haemoglobin level—the faster the rate of growth the lower the haemoglobin level—owing, of course, to the demands of the new tissue for nuclear iron. It is a noteworthy fact that young growing tissues appear invariably to have a higher copper content than older tissues (for example, teeth from the first dentition of a child gave distinctly stronger copper lines on spectrographic examination than did adult teeth,³ and Bodansky, by chemical examination, found foetal brain to be richer in copper than was adult brain²⁴).

The results of our general spectrographic survey of human tissues led Ramage and myself to suspect that copper plays an important part in the phenomena of growth, and, if this is the case, the giving of copper to an infant may cause a stimulation of the demand for iron for purposes of growth and haemoglobin formation. If insufficient iron is being given, this may lead to a relative shortage. It is probably largely a question of the relative dosage of the two metals, of which little is known, since it is difficult to transfer the experimental figures in animals to human material. At any rate, it is conceivable that some such explanation as this may underlie the failure of some clinicians to obtain results with copper, and it is at any rate advisable, when giving copper to an infant, to make sure that adequate doses of iron are given in addition. In fact, this work provides a further argument in favour of the

modern method of employing iron in larger doses than formerly, since at least 80 per cent. of the iron preparations used themselves contain copper as an impurity.

STORAGE OF COPPER IN FOETUS AND INFANT

The fundamental importance of copper in the animal economy is shown by the fact that at birth the infant is provided with a large reserve of it in the liver. An extensive series of human livers has been investigated spectrographically, from this point of view, in conjunction with H. Ramage and W. Sheldon. By their courtesy I am able now to refer to this material, which is being prepared for publication.

It would appear that copper and iron are the only metals stored as reserve material in the liver during foetal life (it should be mentioned that zinc is very difficult of detection by the flame spectrum used, and no opinion is offered with regard to this metal). The values rise steadily during foetal life and reach their peak at birth, when figures as high as 0.06 per cent. (dry) for copper and 0.4 per cent. (dry) for iron may be obtained, which represent more than ten times as much as is found in adult life. After birth these figures drop steadily until the stable value is reached, at the age of 12 to 18 months, which then persists throughout life. A curious feature is that once this level has been reached the amount of individual fluctuation from the average figure is nothing like as much as is found between birth and the attainment of the adult level, due to the fact that though there is in every case a store of copper and iron provided to tide the child over the nursing period, the amount of this initial store is subject to a very wide degree of variation. This is probably an important point, since owing to the small amount of these metals in milk the infant depends on this store to prevent the development of a nutritional anaemia. It is to be presumed that a child with a poor initial reserve runs a much greater risk of developing anaemia, and if the suggestion already made is true—that copper may be an essential factor in growth—the growth of such a child may be retarded. The reserve store is, of course, acquired from the mother, and it is possible that by ensuring that she receives an ample supply of these metals in her diet during pregnancy the incidence of anaemia in infants might be lessened.

Effect of Milk Diet

It is of some interest to compare the amounts of copper and iron that an infant receives in the milk during the nursing period with that provided as a reserve store at birth. In our series, the liver at birth contained an average of about 7 mg. of copper and 50 mg. of iron. Human milk contains about 0.25 mg. of copper¹⁸ and 2 mg. of iron per litre. On this basis a breast-fed infant receives during the first nine months of life somewhere about 50 mg. of copper and 600 mg. of iron. At first sight this would suggest that the foetal store is of much less importance than the amount provided in the milk. It is, however, not known how much of this supply can be absorbed and retained. It is certain that there is a steady loss of copper from the body even in foetal life. Foetal bile and foetal gall-bladders contain considerable amounts of this metal, and that this probably represents a path of excretion is shown by the fact that meconium contains copper in recognizable amounts. On the basis of Josephs's observation that about 10 per cent. of the iron is retained, this would make the useful contribution from the milk about 40 mg. of iron and 5 mg. of copper, an amount closely similar to that provided in the liver at birth. The importance of the amount found in milk receives an added confirmation from a teleological point of view in that human milk is richer in both copper and

iron than cow's milk—evidently an adaptation to the longer period during which the infant is entirely dependent on milk alone. The same mechanism is apparently at work in the guinea-pig, which has practically no reserve store, since this animal supplements its nursing diet almost from birth. It is worth pointing out that the copper content of milk cannot be increased by feeding the mother with copper. This has been shown by Elvehjem²¹ in the case of cow's milk, and it also applies to manganese.²² Elvehjem has also found that the percentage of copper in the egg cannot be increased by feeding copper to the hen. We know, however, nothing of the reverse. Whether a maternal diet that is deficient in copper leads to a milk that is also low in its copper content or whether this figure is maintained at the expense of the maternal organism is unknown, but it is obviously a point that requires further work. It would appear, however, that the infant depends on both sources for its supply of copper—the reserve store in the liver and that provided by the milk—and the causes of deficiency in each of these need further investigation.

It is impossible as yet to say whether the anaemia of adults characterized by a haemoglobin deficiency is connected with a shortage of copper in the body as well as of iron. No post-mortem material from which a direct knowledge of the copper content would be obtained has been available, and the estimation of the therapeutic value of copper as a supplement to the large doses of iron employed in its treatment is rendered exceedingly difficult both by the great variations in the extent to which copper occurs as an impurity in the therapeutic preparations of iron, and by the considerable amounts of copper taken in with the food.

Variations in Blood Copper

Before leaving the subject of copper there is one curious feature that is worth mentioning. Since copper is an essential factor in the formation of haemoglobin, one would expect that cases of anaemia characterized by deficiency in haemoglobin might show a deficient amount of copper in the blood. (Copper occurs in the blood both in the red cells and in the serum. This has been found by all workers, though there is disagreement as to which has the greater amount.) Although there has been as yet no work directed to this subject, there are a number of isolated observations in the literature which appear to show that the reverse is actually the case, and that many instances of anaemia show a definite increase in the copper content of the blood. Thus Gorter, Grendel, and Weyers¹⁸ found that in the nutritional anaemia of children the copper content of the serum averaged 2.1 mg. per litre as against 1.4 mg. per litre for "convalescents." Warburg and Krebs²³ found in birds that three to four days after severe bleeding the copper content of the serum might be raised fourfold or fivefold. In a series of twenty-eight bloods, Sheldon and Ramage³ found that the strongest copper lines of all were given by a case of very severe anaemia of pregnancy, while the next strongest were given by a case of severe haemorrhage of puberty in a girl. (The copper lines were also very strong in a case of carcinoma.) In a case of pernicious anaemia, on the other hand, the copper lines were only just visible. It is hard to say what these findings may mean, and in any case they need confirmation on an extended scale. It may be that all the available reserves of copper are being mobilized to cope with the demand for new haemoglobin or that the figure is high because the copper, though mobilized, cannot be utilized by the body owing to the absence of a further factor, such as some vitamin lack. The observation serves at any rate to show how wide are the gaps in our knowledge of the physiological action of copper.

MANGANESE: DISTRIBUTION AND FUNCTIONS

Manganese occurs in many of the organs, but is chiefly concentrated in the liver, kidneys, pancreas, and suprarenals. The liver has the greatest and most constant supply, and the amount found averages about 0.0008 per cent. of the dry weight. It also occurs in blood, and we found it spectrographically in fourteen out of twenty-eight specimens examined.³ It was invariably found in the serum and never in the red cells, though Zbinden¹ reports it as occurring in the latter. As the arc spectrum employed by him is more sensitive than the flame spectrum, this presumably means that at any rate its concentration is very much greater in the serum. No particular variations were found in the bloods of patients with various diseases, nor did the amounts appear to be affected by the presence of an anaemia. Unlike copper, the amount of which in the blood is slightly increased during pregnancy, manganese was unaffected.

A further marked contrast between the behaviour of copper and manganese is provided by the study of the liver of the newborn. A preliminary survey of our unpublished results shows clearly that there is no reserve store of manganese provided during foetal life to tide the infant over the nursing period. The manganese content of the liver rises during foetal life and reaches its maximum during the last three months, but this maximum is the normal adult level of about 0.0008 per cent. of the dry tissue, and once this has been attained it apparently remains at this figure throughout life. Nature therefore makes no effort to give the newborn a special supply of manganese, and this fact is, I think, very strongly in favour of the view of Hart that the functions of manganese are not concerned in the formation of haemoglobin.

Another point of view is provided by the extremely careful work of Orent and McCollum.⁷ Using a spectrographic control as to the purity of the food, they fed rats on a diet deficient in manganese. (Incidentally it may be pointed out that this is the only satisfactory means of arriving at a knowledge of the functions played by these "trace" elements. Merely to feed animals on the element in question leads nowhere, as minute quantities only are required by the body, and amounts added in excess of this throw no light on its essential function.) Orent and McCollum found that manganese was essential to the life of the animal, and that deprivation of the metal led in time to death. The lack of manganese caused a failure of function of some of the endocrine organs, the male rats evincing atrophy of the testis and the female rats a lack of normal readiness to suckle their young, features which the authors explain by the assumption that manganese is essential for the production of internal secretion by the anterior pituitary. Kemmerer, Elvehjem, and Hart⁸ also found that there was a close relation between lack of manganese and the reproductive processes, as mice failed to ovulate normally in the absence of this metal. It is to be noted that Orent and McCollum in their experiments were able to confirm the work of Hart that manganese plays no part in the utilization of iron to form haemoglobin.

Thus, while there is abundant evidence that copper is an essential factor in the formation of haemoglobin—sufficient, indeed, to justify the giving of small amounts as a supplement to the iron used in the treatment of anaemia—the weight of the available evidence is heavily against the view that manganese has a similar function. It may be mentioned that in any case all the preparations of iron in common use contain manganese as an impurity,¹⁷ and it sometimes occurs in quite large amounts—exceeding 0.02 per cent. Manganese is probably essential to the proper function of the endocrine organs, particularly

those concerned directly with reproduction. The elucidation of the physiological part played by these and other metals found constantly in minute traces in the body offers a promising field of work.

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DIPHTHERIA IN THE DUNEDIN HOSPITAL, 1921-31

A STATISTICAL AND CLINICAL STUDY

BY

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In recent years there has been a disconcerting recrudescence of diphtheria in many parts of the world. Twenty-two out of twenty-eight European countries record this experience. Coincidentally with increased morbidity several countries, notably Germany and Russia, have experienced a great increase in case mortality. This seems to be due to a more toxic form of disease, which is proving intractable to the usual doses of antitoxin, and which is attended by severe cardiac and nervous complications.

In New Zealand since 1912, and particularly since 1921, diphtheria incidence has steadily declined. Thus in 1921 notifications were 2,611 (21 per 10,000 of mean population) and deaths 107 (0.87 per 10,000), whereas in 1930 notifications were 1,440 (10 per 10,000) and deaths 58 (0.41 per 10,000). There was no evidence of undue toxicity until 1929, when a few cases of the new type occurred in the Dunedin Hospital. The occurrence of more cases of the kind in 1930-1 has given occasion for this report, and to illustrate it we have to review the incidence of diphtheria in the Otago Hospital District and in the Dunedin Hospital.

MORBIDITY DATA

For the period 1921-31 inclusive the total number of cases notified in Otago was 1,319, the population in 1921 being 137,062 and the estimated population in 1931 152,600. Of these cases 847 (64.2 per cent.) were admitted to the Dunedin Hospital. (In Otago, and in New Zealand generally, practically 100 per cent. of notified

cases are admitted to hospital.) The annual numbers and rates are shown below.

TABLE I.—Number of cases of diphtheria notified in the Otago Health District during the period 1921-31, rate per 10,000 of population, and number admitted to the Dunedin Hospital.

Year	Cases of Diphtheria Notified in Otago	Rate per 10,000 of Mean Population	Cases of Diphtheria Admitted to Dunedin Hospital	Percentage of Total Admissions
1921	356	25.60	225	8.33
1922	149	11.02	135	5.08
1923	70	5.05	55	2.04
1924	190	13.40	168	5.55
1925	147	10.50	84	2.03
1926	211	14.90	68	1.67
1927	29	2.05	15	0.38
1928	15	1.02	4	0.09
1929	12	0.81	4	0.09
1930	43	2.90	32	0.75
1931	97	6.50	57	1.33
Total ...	1,319	—	847	2.11

This table shows that the greatest incidence was in the years 1921, 1922, and 1924, and that a notable fall occurred in the years 1927, 1928, and 1929. During the period 1921-4 Schick testing and active immunization was carried out in Otago, and some 1,250 children were immunized. The work was done by students in the Preventive Medicine Class at the University of Otago, with the consent and close co-operation of the Health Department. We venture to assume that the 1927-9 decline in incidence was in part due to this work, and support is lent to this assumption by experience at a school known as the North-East Valley School. This school was fully immunized in 1927; a small outbreak occurred there in 1930, but the disease was confined to children who were below the school age in 1927. The unfortunate Bundaberg disaster of January, 1928, in which twelve out of twenty-one children inoculated for diphtheria died, led to the temporary suspension of diphtheria immunization in Otago.

AGE INCIDENCE

Table II shows that the largest number of cases in our series occurs in the 5-15 age period, but that 34 per cent. of the total cases occurred in the age group 15 and over.

TABLE II.—Age distribution of diphtheria cases in the Dunedin Hospital and deaths for the five years 1927-31.

Age Period in Years	Total Cases	Total Deaths	Age Period in Years	Total Cases	Total Deaths	Age Period in Years	Total Cases	Total Deaths
0-1	1	0	5-6	5	0	15-20	14	0
1-2	0	0	6-7	6	1	20-25	10	0
2-3	5	2	7-8	5	0	Over 25	14	0
3-4	8	2	8-9	7	0			
4-5	6	3	9-10	9	0			
			10-15	21	2	Total ...	38	0
Total ...	20	7	Total ...	53	3	All ages	111	10

It is usually stated that diphtheria occurs chiefly in children under 15 years of age, and that the maximum frequency is reached between the second and fifth year. In a recent study by Goodall, Greenwood, and Russell