INDICATIONS FOR DIGITALIS AND QUINIDINE

When, on the other hand, there is evidence of early congestive failure, or a history of paroxysmal nocturnal dyspnoea, strict rest in bed must be enforced until such signs or symptoms have disappeared, after which cautious experiments must be made to determine how much exercise, and how long a day, can be allowed with safety. It is unnecessary for me to detail the treatment of advanced congestive failure, with oedema and ascites. I need only remind you that if auricular fibrillation is present digitalis must be given in adequate dosage; in other words, it must be pushed until signs of intolerance appear, such as nausea, vomiting, or diarrhoea, or until the ventricular rate by auscultation falls to about 70. It must be stopped at once when the rate falls below 60, and also if digitalis coupling appears. I still see patients who are suffering from auricular fibrillation with gross congestive failure being treated with such an inadequate dose as ten or even five minims of the tincture three times a day.

When dropsy persists in spite of adequate digitalization, or in the absence of fibrillation, when digitalis is not nearly so effective, the mercurial diuretics are often successful. Salyrgan is safer than novasurol, and novurit is, I think, safer and better than either; but any one of these three preparations may be successful where the others have failed.

Venesection, and, in obstinate cases of dropsy, the insertion of Southey's tubes, are not, in my experience, employed quite as often and as early as they should be.

For the relief of paroxysmal nocturnal dyspnoea no drug is comparable with morphine, which is too often withheld; not only does it relieve the distressing symptoms, but after a few good nights so obtained an astonishing improvement in the patient's general condition may be observed.

Quinidine is a drug which is used at times somewhat rashly, and in unsuitable cases. It may be helpful, therefore, to say a few words as to the indications for quinidine therapy. Quinidine is perhaps most valuable in the prophylactic treatment of auricular fibrillation. Paroxysms of fibrillation sometimes occur during the early stages of myocardial degeneration; as time goes on these paroxysms become more frequent and more prolonged, until, eventually, fibrillation becomes continuous, with a considerable resultant disability. By a daily dose of three or five grains of quinidine it is often possible to prevent such paroxysms, and to postpone for some years the advent of established fibrillation. What are the indications for quinidine therapy once fibrillation has become established? They are: a short history of fibrillation; absence of valvular disease—and especially of mitral stenosis; absence of any evidence of congestive failure; and an electrocardiograph which shows no evidence of gross myocardial change apart from the fibrillation.

In fibrillation associated with a toxic goitre also quinidine is often successful, though in most cases thyroidectomy is necessary sooner or later if normal rhythm is to be maintained. May I take this opportunity of reminding you of the importance of considering the possibility of a thyrotoxicosis when investigating a case of auricular fibrillation of obscure aetiology? It does not appear to be generally recognized that quite a small, and not at all an obvious, adenoma of the thyroid gland may cause auricular fibrillation, and may do so with very little evidence of other thyrotoxicosis; for instance, there may be no obvious proptosis, no tremor and no sweating, and the basal metabolic rate may be little, if at all, increased. Nevertheless, surgical treatment of such cases is usually followed by restoration of normal rhythm, so that I need not further emphasize the importance of early recognition of this type of case.

THE MINERAL BASIS OF LIFE*

BY

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Most medical men were brought up on the teaching that, in spite of the great variety of the elemental constituents of the inorganic world, the living body was extremely selective in its needs, and made use of only a few of these elements. For many years the occasional presence of traces of others has been reported by various workers, but their observations have attracted little interest, and it was generally thought that they were accidental contaminants. It is now recognized that the original list of the constituents of protoplasm (C, H, O, N, S, P, Na, Ca, K, Mg, Cl, I, Fe) must be widely extended. In the first place, new methods of research, both chemical and physical, have shown that many other elements, particularly metallic ones, are commonly present in animals and plants. Secondly, there are certain observations which tend to show that in the course of evolution nature has been making experiments in the attempt to find the most suitable metal for certain functions, particularly for use in the respiratory pigments.

The most important evidence that the original list is too exclusive, however, is the successful demonstration by the Wisconsin school, led by Hart, Steenbock, and Elvehjem, of the essential role of copper in the formation of haemoglobin. Their work, which has now become classical, indicates that the presence of copper can no longer be regarded as accidental—the metal, though present only in "traces," has a definite function in which it cannot be replaced by any other element. It is this work in particular, and also the demonstration of the necessity of certain other elements for plant life, that has stimulated a search for those that may be found to occur in living tissues, and for the functions that they may perform. It may be said at once that the former line of work is much the easier, and that in consequence our knowledge of it is in a more advanced state. The pioneer work of Bertrand in Paris, and of Ramage in Norwich, has contributed greatly to our knowledge. The discovery of the actual function in cell metabolism of the mineral constituents presents a problem that does not often yield readily to frontal attack, and depends on the general advance of biochemical knowledge. This may be seen in the case of magnesium, where the recent investigations on the processes of fermentation and of muscular contraction have shown that this element possesses a specific action on the phosphatase enzymes. A review of the mineral basis of life must therefore at the present time largely concern itself with a review of the various elements which have been found to occur with any constancy in living tissues.

1. *The Halogens*

The presence of chlorine in the body is well known, and its importance needs no stressing. The importance of iodine as a constituent of the thyroid secretion is also well known, but recent work indicates that the role of this element is not confined to its participation in the structure of thyroxine, and that it has other unsuspected activities. Iodine is a constant constituent of the blood in an amount that is generally agreed to be of the order of 12 γ per 100 c.cm. (1 γ = 1/1,000 mg.), the total amount in the blood being, therefore, less than one milligram.¹ The amount is raised in hyperthyroidism and lowered in hypothyroidism, and indeed the level of the blood iodine reflects the functional state of the

* Presidential address delivered to the Staffordshire Branch of the British Medical Association, October, 1933.

thyroid in the same way that the blood sugar reflects that of the islet tissue, or the blood calcium that of the parathyroids. An interesting recent discovery has shown that while all parts of the brain contain iodine, the greatest amount is found in the region of the tuber cinereum, which contains twice as much as the cerebrum and three times as much as the cerebellum.² This fact gains in significance when it is remembered that the tuber lies just above the pituitary, and that in this region is undoubtedly concentrated the control of many of the metabolic processes which are affected by the pituitary. Iodine would therefore appear to be concerned in the control of metabolism through the diencephalon as well as through the thyroid.

The presence of bromine in the normal body has not been recognized for so long, but there appears to be no doubt that bromine must be classed with iodine and chlorine as an element which is constantly present. In one investigation it was found in the blood in each of 150 cases—in an amount from 0.8 mg. to 1 mg. per 100 c.cm.³ A very curious feature, originally described by Zondek and Bier³ and since confirmed by the original authors and by three separate groups of workers,^{4 5 6 7} is that the blood bromine is lowered to half its normal figure in cases of manic-depressive psychosis, and only returns to normal values with an improvement in the clinical condition. The blood bromine also appears to vary with menstruation. In the tissues, bromine is found in greatest amount in the pituitary gland, especially in the anterior lobe, where it occurs in a concentration seven to ten times greater than in any other organ. It shows an extraordinary variation with age; after 45 the amount begins to fall, and in persons who reach the age of 75 the bromine is either present in the merest traces or is not detectable at all.⁸ These facts are intriguing, and strongly suggest that bromine plays an important part in the body economy. It is curious that bromine should be so concentrated in the pituitary, while iodine is concentrated in the tubular region just above. Bromine also appears to be a normal constituent of plants, the amount varying between 0.17 mg. and 2 mg. per 100 grams of dry matter.

In the case of fluorine, the remaining member of the halogen series, the picture is different, for there is no decisive evidence that it is a normal constituent of either the animal or plant kingdom, although it has been found on many occasions, and is said to occur in blood and milk.⁹ While it is still an open question as to whether fluorine has any physiological function, there can be no question as to its pathological importance, especially with regard to the teeth. In rats, feeding with fluorine produces a characteristic overgrowth of the upper incisors, accompanied by a defective development of the enamel, leading to a mottled appearance.¹⁰ This is of great practical importance, for in Algeria it has been shown that a widespread illness known as "darmous," which affects animals as well as man, and which is characterized by a general cachexia in addition to dental dystrophy, is due to the high fluorine content of the water supply, which is derived from beds containing "natural phosphate."¹¹ The mottled appearance of the teeth is caused by white chalky patches, which are areas of defective enamel formation. In Iowa an outbreak of mottled teeth in children occurred for the first time in the locality following the use of water from new deep wells, the previous water supply having been from shallow wells.¹² In a recent study of English children a similar condition of the teeth occurring in children from Maldon, Essex, was also found to be associated with a high fluorine content of the water supply.¹³ It would appear that the limit of fluorine which can be regarded as safe is not more than 1.5 parts per million.

2. Boron

It is generally agreed that boron is universally present in the plant kingdom, and that it is essential to normal plant growth.¹⁴ The optimum concentration for plant growth is of the order of 1 part per million. Its effects appear to vary in different species, but in leguminous plants, such as the broad bean, the presence of these minute quantities of boron are essential for the proper formation of the root nodules. In the absence of boron the structure of the nodule becomes defective, and the nitrogen-producing bacteria lose their symbiotic habits and become parasitic, invading the host.* Nitrogen assimilation is consequently much below normal. It also plays a part in calcium metabolism, since in the absence of boron the broad bean cannot assimilate calcium. There is no certain knowledge of either its presence or function in the animal kingdom, though Bertrand and Agulhon claim to have demonstrated it in blood,¹⁵ and it has also been demonstrated in human milk.²⁷

3. Silicon

The pathological activity of silica, especially in regard to the industrial importance of its inhalation as silica dust, is well known. In minute quantities this element is a constant constituent of the plant kingdom, particularly in the stems of cereals. It is concerned with the metabolism of phosphorus. The amount of phosphoric acid taken up by the plant is proportional to the amount of water-soluble silicate in the soil.¹⁴ It is said to be of constant occurrence in human blood,¹⁶ averaging 16 mg. of SiO₂ per 100 c.cm., and a combination of silica and carbohydrate has been demonstrated in gelatin, ox blood, and human urine.¹⁷ The most striking evidence of the widespread occurrence of silica in human tissues is the spectrographic demonstration of its presence in the aqueous humour of the eye.¹⁸ It is quite impossible to say whether it has a function, but its presence is not unexpected, in view of its constancy in plants and therefore in food. The silica content of bread varies up to 3.2 mg. per 100 grams (dry), being greater in whole-meal bread than in fine milled bread.¹⁹

4. Alkali Metals (Na, K, Li, Rb, Cs).

The distribution of the alkali metals is peculiar. Sodium and potassium are, of course, essential to life and of universal occurrence. The remaining elements show great variation. Lithium is sometimes found in human²⁰ and in invertebrate tissues,²¹ but only spasmodically. It is constantly present, however, in marine animals, and in plankton it usually reaches a considerable concentration. So far as land animals are concerned, it appears likely that the metal is taken up by the tissues when present, but there is nothing to suggest that it has any definite function. Caesium offers a sharp contrast in that it is almost universally absent from animal tissues, although feeding experiments show quite definitely that it is readily absorbed. Caesium is a constituent of sea-water, and has been detected in plant ash²² and in oyster shells.

Rubidium is of much more frequent occurrence. It occurs in plants,²³ and appears to be especially important in the fungi,²⁴ some of which contain quite remarkable amounts, reaching at times 0.2 per cent. (dry), which compares with an average figure for human beings of about 0.003 per cent. It is also of widespread occurrence in the animal world. In invertebrates the analysis of English snails and earthworms showed considerable differences with regard to locality, since rubidium was present in specimens from Liverpool and Marlborough, and absent from specimens obtained in Cambridge and London.²¹

* It is not known whether this finding has any application to the problems of medical bacteriology.

This suggests that the element resembles lithium in being absorbed by protoplasm in proportion to its availability. In human beings, on the other hand, rubidium is found much more frequently. We found that it was almost invariably present in adult human tissues,²⁰ while in an examination of 111 foetal and infant livers the metal was present in every instance but one.²⁵ A curious feature was that the amount of rubidium was much greater than the average in those dying from congenital pyloric stenosis. Rubidium is present in human milk,^{26 27} which suggests that it may be of physiological importance. The amount in the liver rises slightly during the nursing period, and this, together with its height in pyloric stenosis, suggests that it may be of importance in growth, possibly of the muscles. This suggestion derives some support from one particular fact—namely, that in wheat, barley, and oats—and ratio Rb : K is always higher in the growing point than in other parts of the straw.

5. Alkaline Earths (Be, Ca, Ba, Sr, Mg)

Of these metals, calcium and magnesium are well known as constant and essential constituents of protoplasm. Magnesium occupies a position of particular importance in the plant world owing to the fact that it enters into the composition of chlorophyll. Recent work has confirmed the importance of magnesium. Krause, Orent, and McCollum²⁸ found that animals deprived of magnesium died in a short time, showing marked vasodilatation and tetany. Cramer²⁹ discovered the very intriguing fact that rats fed on a diet deficient in magnesium developed clear evidence of renal damage. Beryllium does not appear to have been described in living tissues, but it is important in that it is capable of producing a severe rickets when fed to animals. Strontium occurs spasmodically in both animals and plants. We found it in the tissues of a ten-weeks human foetus, so that it is able to pass the placenta,²⁰ and it has also been found in the human eye.¹⁸ Snails appear to have a predilection for strontium when it is available,²¹ but show the same type of variation with locality that is found with rubidium. All the evidence goes to suggest that strontium is readily taken up by tissues when it is available, but the irregular character of its distribution does not suggest that it has any definite function. Barium is found much less frequently than strontium, occurring only spasmodically and in minute traces. The solitary exception to this is in the eyes of cattle, which regularly contain barium in the choroid, in amounts which increase with age. Concurrently with this increase in barium there is a decrease in the amount of copper and certain other elements in the choroid. This observation was confirmed for cattle coming from Wolverhampton and Norwich, but it does not occur in any other animal that we have been able to investigate.³⁰ The significance of this observation is entirely obscure.

6. Copper

Copper is so universally present in both animal and plant kingdoms that it may be accepted as an element necessary to life. No extensive investigations of tissues making use of modern methods have failed to demonstrate the presence of copper. In plants it occurs in all parts, but is found in greater concentration in leaves and fruit than in the roots, and it is especially concentrated in the fruit. (This is true also of most of the heavy metals which occur in plants; as they pass up the stem from the root they appear finally to be concentrated in the fruit.)²⁴ In animals the greatest amounts of copper are found in the liver, though it is present in all tissues. It occurs in greater concentration in the blood plasma than in the cells, and the greater part of the serum

copper appears to be in combination with the proteins. The level of the serum copper is normally about 80 to 90 γ per 100 c.cm. It is raised in certain types of anaemia, in pregnancy, and probably in malignant disease,³¹ though much more work is necessary on these points. It is a curious fact that the alterations in the mineral content of the blood tend to be of a similar nature in both pregnancy and carcinoma.

Of the many functions undoubtedly exercised by copper in the body, only one is known with any certainty—its essential role in the formation of haemoglobin. This has been conclusively proved by Hart and his co-workers at Wisconsin in the case of the chicken, pig, rat, and mouse, and their work has also made it clear that no other metal can replace copper in this particular function.³² There is no rigid experimental proof that the same is true of man, but the collateral evidence leaves little doubt that this is the case. The most important evidence is the fact that the human infant is provided with a store of copper in the liver, which is mainly laid down during the last months of foetal life. This store is rapidly used up during the nursing period, and the very close similarity in this respect of the curves for copper and iron strongly suggests that they are both being used for similar purposes. This initial store appears to be true of all animals the young of which depend for a time on a milk diet alone, though it is not the case with animals, such as the guinea-pig, in which a milk diet is supplemented by other food from birth. It should be pointed out that although the copper content of human milk is low it is higher than cow's milk, and that all milk appears to have the power of abstracting copper from metal containers. Thus there is a significant rise in the copper content of cow's milk which has been submitted to pasteurization in contact with copper.³³ The participation of copper in the formation of haemoglobin is, however, not the whole story, for one generally finds that copper is richer in young growing tissues than in adult ones—thus we found a distinct difference between the copper content of teeth of the first and second dentitions.²⁰ This suggests that copper may be directly concerned in the processes of growth. In this connexion it is interesting to note that in carcinoma cells the amount of copper is usually low although the blood copper may be high. There can be little doubt that this element has many important functions, and the demonstration of a copper-porphyrin compound in cells³⁴ suggests that, like iron, it may be concerned in the processes of intracellular oxidation. The pigment of the tail-feather of the touraco is due to the presence of a copper-porphyrin compound.

It has also been suggested that copper acts in the body in relation with the vitamin B complex.³⁵ The available evidence suggests that in vertebrates, at any rate, iron and copper have closely related physiological functions. Copper appears to play a more predominant part in invertebrates. It is a well-known fact that in certain arthropods and molluscs the respiratory pigment of the blood (haemocyanin) contains copper in place of iron. One of the highest copper values in the whole of the animal kingdom is found in the wall of the ink-sac of the octopus,³⁶ where the enormous figure of 914 mg. per kilogram of dry tissue may be found. The ink itself contains only minimal traces of copper, being of melanin nature, and this extraordinary finding suggests that copper may have unsuspected points of contact with the metabolism of the melanins.

From a pathological point of view, copper is of chief interest in relation to cirrhosis of the liver, and to haemochromatosis. A well-known explanation of haemochromatosis is that advanced by Mallory,³⁷ who thought

that the disease was the result of chronic copper poisoning. Although for many reasons this theory is untenable, the fact remains that in haemochromatosis the tissues, especially the liver, do appear to have a higher copper content than normal.³⁸ High copper values are also common in ordinary cirrhosis of the liver (the figures may equal those found before birth); they are, as far as I know, the only conditions in which these high copper figures are found. It would be tempting to conclude that in each case the copper is playing an operative part in the production of the disease, especially in view of the successful experimental production of cirrhosis by the use of heavy metals, but the available evidence strongly suggests that in both instances the high copper content is a secondary phenomenon. The most important evidence lies in the fact that these high values are not universal, and there is clear evidence that cirrhosis can develop with normal copper values. In one example of congenital cirrhosis of the liver which we were fortunate enough to obtain for examination,²⁵ the copper values were very much less than the normal for that age.

7. Manganese

Manganese is widely spread through both animal and plant kingdoms, and there is abundant evidence that this element is essential for life. The presence of manganese in plants is said to have been discovered by Scheele as far back as 1785. It has been proved to be necessary for the growth of plants,¹⁴ and it seems to bear some relation to the formation of chlorophyll, for it is found in leaves in amounts proportional to their greenness.³⁹ Generally speaking, it is far more abundant in those parts in which active chemical changes occur—such as roots and leaves and especially in the reproductive organs—than in the passive parts such as the stem. This has recently been confirmed for Australian plants in a very careful study by Bishop.⁴⁰ Manganese resembles boron in that, though essential for growth, too high a concentration leads to toxic changes; and a very curious feature described by Bishop is that calcium has the power of protecting the plant from this toxic action. In animal tissues manganese is widely spread, but occurs in greatest quantity in the liver and pancreas, while in some individuals we have found the suprarenals to contain large amounts. Different species show a considerable variation in the manganese content of their tissues. Herbivorous animals such as the guinea-pig usually have high values, while in comparison man has low values.²⁰

Manganese is found in the blood, and so far as our limited observations go²⁰ it occurs in the serum but not in the cells. It is widely spread in invertebrates, but, as with other metals, the amount tends to show considerable variation with locality. Thus snails from some regions possess enormous amounts.²¹ In human beings there is no pre-natal store of the metal, and the values, beyond showing a slight drop during the nursing period, tend to follow a remarkably constant course throughout life. This suggests that manganese has no particular functions during development, but against this there is the very remarkable fact that meconium contains a quite remarkable amount of manganese,⁴¹ and there is no doubt that the human foetus is normally provided by the mother with an excess of this metal. In view of the general tendency to ascribe to manganese a function as a stimulant of oxidative processes, it is tempting to associate the marked temporary provision of this metal for the foetus with the relative oxygen deficiency of foetal blood, due to the fact that the placenta is not as good a filter as the lungs.

A series of feeding experiments on animals conducted by Orent and McCollum⁴² have indicated that manganese

is in some way essential to the reproductive processes. Briefly, an absence of sufficient manganese in the diet leads to: (1) an atrophy of the testes in the male, and (2) in the female to a peculiar alteration of the maternal instinct so that she fails to suckle her young. In vertebrate animals manganese has apparently no function in the formation of haemoglobin, though in invertebrates a remarkable fact which should not escape notice is that the Lamellibranch *Pinna squamosa* contains a respiratory pigment very similar in constitution to haemocyanin, except that it has manganese in place of copper. This appears to be a solitary experiment on the part of nature to produce a respiratory pigment having manganese as its metallic basis.⁴³

8. Cobalt and Nickel

These metals are only rarely found in tissues, and certainly do not possess the universal importance of copper and manganese. There is no satisfactory proof of the presence of cobalt in vertebrate tissues, but it is occasionally found in invertebrates, and, curiously enough, this is generally the case in species which also have a predilection for nickel. Nickel is a more widely distributed element than cobalt. In human beings it is said to be concentrated chiefly in the pancreas,⁴⁴ though this awaits confirmation. It is found in some plants, especially the tropical spices, to a considerable extent.²⁴ In invertebrates it has an irregular distribution in polychaetes and molluscs—usually in association with cobalt. A fact which illustrates the extraordinary selectivity exercised by some organisms for these metals is that, of two species, *Haliotis* has a high nickel content (0.004 per cent.) without cobalt, while *Archidoris tuberculata* contains cobalt (0.003 per cent.) but no nickel.²¹ Although nothing is known of any natural function of either of these metals, cobalt in mammals has the power of producing a true red-cell polycythaemia—a fact which may have therapeutic applications.

9. Aluminium

It may be accepted that aluminium is present as a constant constituent of plant and animal tissues, but this is not surprising in view of the wide distribution of this element in soils. On an average human diet the intake of aluminium is somewhere about 12 mg. per diem, of which about half at least comes from the food and not from cooking utensils.⁴⁵ We have no knowledge of whether it is an "essential" element for the tissues, or whether it is merely taken up passively. In any case, in the amounts absorbed from an ordinary diet it appears that it does no harm, and that there need be no fear of toxic effects from the use of aluminium cooking vessels.

10. Zinc

Zinc is found universally in tissues, and must be regarded as essential to life. It occurs in blood in an amount of from 1.5 mg. to 2.5 mg. per 100 c.cm., and is, in contrast to copper and manganese, mainly present in the cells.⁴⁶ It occurs in human milk, and in the milk of the cow and ewe, in amounts of 2 to 3 mg. per litre. In all these cases the amount is highest at birth, with a sharp drop to a steady level after ten to fifteen days.⁴⁷ In the tissues it occurs in greatest amount in the genital organs and in the thyroid, and in the case of the liver recent work suggests that there is a pre-natal store of zinc as well as of copper and iron⁴⁸—the birth value being of the order of 114.3 mg. per 100 grams (dry) as against 32.4 mg. per 100 grams (dry) in the adult. This, if confirmed, must be regarded as proof of the necessity of the metal for life. Recent work has shown that zinc appears to be essential for normal reproduction in the rat, though it does not appear to be essential for growth.⁴⁹

11. Silver

This element has a very curious distribution. In plants it occurs in some species, but the evidence does not suggest that it is universal. It has, however, a stimulating effect on the growth of watercress, and in the tobacco plant the addition of silver inhibits root growth but causes a precocious development of the nicotine-secreting hairs.⁵⁰ In fungi it sometimes occurs in remarkable amounts—up to 0.2 per cent. (dry)—and it is a curious fact that in every specimen of edible fungus so far examined Ramage has found silver. This applies not only to English specimens, but also to South African.²⁴ In human tissues Zbinden found it in blood and in all the organs he examined.⁴⁴ Using a less delicate method, Ramage and I have found it in every investigation in about 30 per cent. of the specimens. We are in agreement with Zbinden that the thyroid gland is especially rich in silver, and the same appears to be true of the tonsil.²⁰

12. Arsenic

There is a growing body of evidence that minute traces of arsenic are of widespread occurrence in tissues, and that the element is of physiological importance. In human blood it occurs in an average amount of 63.8 γ per 100 c.cm.⁵¹ A very interesting feature is that during menstruation the figure rises by 50 per cent. to an average of 92.5 γ , and in pregnancy it rises to a maximum during the fifth and sixth months, reaching a figure of 220 γ . Similar values are apparently also found in carcinoma.

13. Cadmium

This metal, which is closely related chemically to zinc, was never described in living tissues until it was found spectroscopically in 1931 by Fox and Ramage.²¹ The extraordinary feature is that apparently it occurs in one species only, the common scallop (*Pecten maximus*), but in every specimen of that species, obtained from four different localities, cadmium was present in the tissues. This suggests that, as with vanadium, nature has made an experiment with cadmium which has not been carried further.

14. Lead

Lead occurs in the tissues to a much greater extent than is usually believed. Its ubiquity is shown by the fact that it was found in the human eye on spectroscopic examination.¹⁸ Lead is a normal constituent of sea-water and has been recorded as present in crustacea and molluscs.⁵² There is nothing to indicate whether in the minute amounts constantly found it is of physiological importance or not.

15. Tin

In human beings minute amounts of tin have been described in the brain, spleen, and thyroid.⁴⁴ In oxen, horses, and sheep the tin content varied from 0.5 mg. per kilo (dry) in the stomach to 4 mg. per kilo in the pancreas.⁵³ The muscle of the tongue gave 12 to 16 mg. per kilo, while the mucous membrane of the tongue gave 18 to 26 mg. per kilo. These extraordinarily high figures for the tongue, and especially for its mucous membrane, suggest that this region of the body may have unsuspected functions.

16. Vanadium

Vanadium occurs regularly in the blood in certain ascidians, where it forms 5 to 10 per cent. of the respiratory pigment.⁴³

This list of elements found in tissues is not intended to be complete—thus, titanium has been described in human tissues and human milk,²⁷ uranium in the chicken's egg, molybdenum in apples, etc.—but is intended as a

justification of the thesis advanced at the beginning, that the normal metabolism of the body is based on a much wider chemical foundation than was originally thought to be the case. The determination of which elements are of functional importance and which are accidental in their presence must await further work, though it seems clear that copper, manganese, and zinc are of universal importance. The fact that gold is a constituent of sea-water, but is not found in marine organisms, suggests that the other rare elements owe their presence at any rate to a selective absorption. It is unlikely that the whole of life makes use of the same elements, since nature appears undoubtedly to have made experiments which have subsequently been abandoned—this is the best explanation of the species rigidity of the occurrence of vanadium and cadmium. It would not be adequate to leave the matter here, and a few further general remarks seem to be worth making, though it is clear that we are merely on the threshold of a branch of knowledge, the very existence of which is only a recent discovery. The following are points of view which appear to be matters of legitimate speculation.

INTERRELATIONSHIPS BETWEEN MINERALS

It is already clear that the mineral constituents of the body are not independent entities, and that in various ways their physiological activities are interrelated in the directions of either antagonism or synergism.

Antagonism.—The most obvious instance of a biological antagonism can be seen in the mutual relations of calcium and magnesium, for which there is abundant evidence that need not be detailed here.

Synergism.—This is a field which will undoubtedly play an important part in the dietetics of the future. The most striking instance is provided by the mutual relations of calcium, iron, and copper. It has been known for some time that in some way calcium conserves iron in metabolism. In our examination of infant livers²⁵ we obtained a remarkable degree of correlation between the two metals, which is indicated in the figure. The mean

(Reproduced by permission of the Royal Society.)

curve was obtained by plotting the average percentages of calcium found for each percentage of iron. It will be seen that the two tend to increase together. If lines are drawn parallel to this mean line at a distance representing a variation of ± 0.04 per cent., it is found that 81 per cent. of the cases fall within these limits. It was further found that the average birth value of iron (0.3 per cent.) was never obtained when the amount of calcium was below a certain limiting figure (0.08 per cent. dry).

Similar, but less marked, relations were found to exist between iron and copper, and consequently between calcium and copper. It was noteworthy that the limiting calcium figure for the average copper figure at birth was the same as for iron. There is clearly a close relation between these three metals which cannot be without significance for further nutritional studies. This mutual

relation has clinical significance, for it is stated by Davidson⁵⁴ that "a normal blood level can be maintained on a diet rich in calcium and moderate in iron, but that anaemia will occur on the same iron intake if the calcium is reduced." In plants the influence of boron on calcium assimilation and of silicon on phosphorus assimilation provide examples of similar close mutual relations. In a satisfactory diet a proper balance between the various mineral ingredients is probably a feature the importance of which comes next to that of the actual presence of the minerals concerned. It is hardly realized yet how much the balance of the "trace" elements may be altered in our diet by the widespread use of various chemical fertilizers and insecticides, but there can be little doubt that with advance in knowledge this will need investigation.

MINERAL DEFICIENCY

In view of the great advances which have followed the discovery that many human beings are living on a diet deficient in vitamins, it is natural to ask whether there is any evidence of a similar deficiency with regard to minerals. It is well known that in some districts there is a shortage of iodine, to which endemic goitre is attributed. In general, however, it may be said that the clearest evidence of deficiency is found in the case of iron, the effects of which are probably accentuated by a parallel shortage of calcium. This is especially the case with the women and the children of the working classes. The famous investigation of Helen Mackay showed that a large number of London children were deficient in iron,⁵⁵ and the same was found for the working women of Aberdeen by Davidson.⁵⁴ In this district there are no similar observations, but we have found that meconium, while rich in other metals, has practically no iron,⁴¹ indicating that at any rate the average mother here is unable to provide the foetus with an excess of iron. It might be assumed that this is due to the total absorption of iron by the foetus for storage in the liver; but copper, which is also stored, appears in the meconium in considerable amounts. There is no doubt that the usual diet of the poorer classes in this country is deficient in iron, and that the burden of this falls mainly on women and infants. It must be remembered that calculation of the iron intake based on analysis of uncooked material is very unsatisfactory. In the case of broccoli, for example, 50 per cent. of the iron is lost by boiling for twenty minutes⁵⁶—a particularly important fact since vegetables form one of the chief sources of iron in the food.

The case with regard to copper and manganese is not so clear. There are several lines of evidence which suggest that it is rare for there to be a deficiency of these metals in human beings. The average intake of copper in Aberdeen was found to be about 3 mg. per day,⁵⁴ which is certainly enough to meet all requirements. This is probably the explanation of the fact that there has never been any satisfactory evidence of the medicinal use of copper having the same effect in nutritional anaemia as it undoubtedly has in experimental animals, in spite of occasional individual successes. The fact that meconium from this district was found to contain strong copper lines on spectrographic examination indicates that the mother is usually able to supply the foetus with all the copper it needs. Although there is nothing to suggest any common deficiency of copper in human diets, this does not occur with animals. In Florida a nutritional anaemia of cattle has been shown to be due to a deficiency of copper in the vegetation.⁵⁷ The amounts of the other metals, such as manganese and zinc, which are necessary are so small that there does not appear to be either any evidence or any likelihood of deficiency.

ISOTOPES

The extraordinary selectivity displayed by living organisms with regard to the elements employed in their make-up leads one to ask whether this same selectivity extends to the isotopes of the elements. For some time I had wondered whether the explanation of the colossal doses of iron now employed in the treatment of anaemia and of some spinal cord degenerations might not find their explanation in the fact that possibly only one of the two isotopes of iron could be employed in the synthesis of haemoglobin or had a therapeutic effect on the nervous system. A selectivity on the part of life, not only as regards the elements but also as regards their isotopes, is so highly speculative⁵⁸ that but for the fact that it now has some experimental basis I would not mention it.

Hydrogen consists of two isotopes, of mass respectively (omitting decimals) 1 and 2, which are usually written as H^1 and H^2 .⁵⁸ These are present in ordinary hydrogen in a relative abundance ratio of roughly $H^1:H^2$ as 6,500:1, though the exact figures are not settled. Recent physical research has succeeded in effecting an almost complete separation between these isotopes, and it has thus been possible to make "heavy" water, in which all the hydrogen consists of the heavy H^2 isotope—although the amount that can be made is, of course, very small. Such water differs from ordinary water in several physical properties. It has a higher freezing point ($3.8^\circ C.$) and boiling point ($101.42^\circ C.$), but the startling fact is that such "heavy" water is incapable of supporting life. Tobacco seeds failed to grow in it, while controls in ordinary water grew normally. In water in which half the hydrogen consisted of the heavier isotope, development took place, but only at about half the speed of controls in ordinary water. Thus of the two kinds of atom of which ordinary hydrogen is composed, one appears to be inimical to life. Seeing that oxygen and carbon have also at least two isotopes each, the complexity of the organic chemistry of the future stuns the imagination. The future applications of this method of research to the mineral constituents of the body may yield very surprising results.

Studies on the mineral basis of life are only in their very early infancy. They are of extreme interest in that the evidence so far collected tends to show that many of the elements resemble the vitamins in being necessary only in minute amounts. It is clear that, as Bertrand has said, the body cannot be regarded as a democracy, but rather as an oligarchy, in which a large amount of passive elements are ordered and governed by minute amounts of active ones, and the biological investigation of these very active elements cannot but be fruitful.

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CARCINOMA OF THE MAXILLA AND ETHMOID

A SURVEY OF THE NOTES OF FIFTY CASES

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Carcinoma of the maxilla is fortunately comparatively rare, and statistics show that it accounts for about 1 to 2 per cent. of all malignant tumours.¹ This paper is limited to a survey of fifty cases of carcinoma of the maxilla and the ethmoid seen during the past twelve years. All other tumours of the maxilla have been excluded. These cases can be divided into two definite groups.

TWO GROUPS OF CASES

The first, or lower, group consists of nine cases of squamous epithelioma arising in the alveolus or hard palate in the region of the molar teeth. The growth extends into the cheek sulcus, or may begin there, and quickly involves the cheek. Sooner or later it bursts through into the antrum and, taking the line of least resistance, fills the antrum with a soft, vascular, necrotic tumour. This squamous epithelioma may commence as the usual typical ulcer, or the growth may be deep-seated and of the burrowing kind, and when it appears on the surface it has already infiltrated the cheek and

antrum. The section of this deep-seated tumour was called an adenocarcinoma.

The second, or upper, group comprises forty-one cases in which the growth arose in the upper part of the nose. At the time of operation it is so extensive and necrotic that it is almost impossible to say where it originally started. There was definite evidence in fifteen of these cases to show that it originated in the floor of the orbit around the infra-orbital canal. In ten patients it began in the ethmoid and spread to the floor of the orbit. In the remaining sixteen the origin of the growth was doubtful. However, in all these it filled the antrum, being attached to the orbital periosteum and having spread into the ethmoid, even to the anterior fossa of the skull and to the other nasal sinuses.

The sections have been described as those of squamous carcinoma, adenocarcinoma, columnar-celled carcinoma, pleomorphic carcinoma. One or two were first called sarcoma, and then changed to squamous carcinoma. There were two endotheliomata arising from the middle turbinal. The sections sometimes revealed variation in the same tumour. The adenocarcinomata were those which arose near the infra-orbital canal. Though pathologists agree that these growths are undoubtedly carcinomata, there is considerable diversity in the nomenclature adopted for the type. Pathologists vary as to the Christian name, so to speak, which they give to a particular carcinoma. As would be expected, French pathologists have a different nomenclature from the British, and between most countries this variation exists. However, to the surgeon and to the clinician the pathology was the same—a rapidly growing malignant epithelial tumour, more malignant than the lower group commencing in the alveolus. The two endotheliomata were definitely less malignant than the true carcinomata. It may be possible to apply Broders's classification of malignancy to these carcinomata. It would be of greater importance to know which types are more radio-sensitive than others.

The first, or lower, group were more commonly seen at a dental hospital or in a general surgical clinic. The second, or upper, group came to the nose and throat clinic or were sent to that clinic from an ophthalmic hospital, so that the difference in the numbers of the two groups is relatively of no importance. There were twenty-seven males and twenty-three females; the ages were from 45 to 70. The younger the patient the more malignant the growth. The patients' surroundings and occupations showed a very wide variation, and the cause of the tumour was as unknown as that of cancer. There was no history of previous disease, and no suppuration of the nose, and there was nothing which could be called precancerous.

SIGNS AND SYMPTOMS

Early diagnosis is of the utmost importance. This should not be difficult in the first, or lower, group of cases; but in spite of this nearly all these came too late for successful extirpation. There was the typical epitheliomatous ulcer, or the deformity of the alveolus and palate with painful or loose teeth. It was rarely necessary to remove a piece for section before operation. If a piece is removed the wound should be sealed by the diathermy button to prevent sepsis or a flare. The early diagnosis of the upper, or second, group of cases is well-nigh impossible, because cancer in itself does not produce any specific symptoms or signs, and it is only when the cancer cells form a tumour that a series of mechanical results appear. Furthermore, the development of these is slow and insidious, particularly in a hidden cavity like the nose, and a patient often only consults a doctor when such symptoms are well marked—frequently too late for successful removal. The general signs, such as blood changes, were of no practical value in the diagnosis.