Remarks

ON

CLINICAL APPLICATIONS OF THE RECENT
WORK ON BONE DISEASE *

BY

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It would be difficult to find a subject in medicine which has yielded such a rich harvest to the investigator in recent years as that of bone disease. All branches of medical science have played their part, and have not only added greatly to knowledge of the physiology and pathology of bone, but have placed in the hands of the medical profession a number of valuable weapons for diagnosing, preventing, and curing many of the more common metabolic bone diseases. In opening this discussion my object must be to give an outline of the most important of these discoveries and their clinical applications.

Enrichment in knowledge of bone disease has depended in the main on two lines of investigation: the influence on bone structure of (1) dietetic and environmental factors; (2) the parathyroid glands. No doubt these two factors are themselves related in some way; recent work has been directed to the investigation of this association, but, up to the present, without much success. On the other hand, the increased powers of controlling bone disease which have followed the main discoveries have resulted in much activity in all branches of the subject, so that the accessory methods involved in the diagnosis and treatment of bone disease have become of greater significance and importance. Thus methods of radiography, histological technique, blood and urinary chemistry, are now more valuable as instruments of precision. In addition, the morbid pathology of the subject has been quickened by its association with the experimental method, and numerous facts, previously discovered by pathologists, have gained the interest and importance that were their due.

THE INFLUENCE OF DIETETIC AND ENVIRONMENTAL
FACTORS ON BONE

It is now known that in the normal animal the structure of bone is the outcome of a struggle between two influences—one tending to produce perfect formation and calcification with the deposition in the matrix of a compound made up largely of calcium phosphate, the other tending to prevent the adequate deposition of this compound, and thus to produce bone built up of comparatively soft, partially calcified tissue. The factors assisting perfect calcification are: (1) an adequate supply of calcium and phosphorus, (2) an adequate supply of vitamin D either in the food or as synthesized in the body by the exposure of the skin to sunlight or some other source of ultra-violet radiation. The factors preventing perfect calcification are: (1) those dietetic substances which induce growth without, at the same time, supplying a corresponding calcifying substance; (2) the foods which not only encourage growth but in some cases, at least, actively interfere with the retention of calcium salts in the body, and so prevent the deposition of calcium phosphate in the bone matrix.

What, then, are the foods which influence calcification? Those stimulating the formation of perfect bone are milk, cheese, butter, egg yolk, and the fat of meat and fish. All these contain vitamin D, and some of them—that is, milk, cheese, and egg yolk—are also rich in calcium and

phosphorus. The chief foods hindering calcification are cereals, including bread, oatmeal, maize, rice, etc. Other foods which, by stimulating growth and not exerting a corresponding influence on calcification, tend to bring about defective bone formation, include lean meat and white fish and most vegetable fats. Vegetables and fruit seem to be more or less indifferent in their action, although in some circumstances the calcium content, especially in the case of green vegetables, may aid calcification. Sometimes green vegetables may even contain a small amount of vitamin D, especially if recently exposed to sunlight. The vitamin C content of fruit and vegetables prevents scurvy, and thus defends the bones against any scorbutic influences.

From the foregoing, it is evident that the demand for the inclusion of calcifying foods in the diet is greatest (a) during growth, and (b) when cereals are the main constituents of the diet. Since a child's consumption of food is limited, the greater the amount of bread and other cereals eaten the less likely is it that sufficient milk, eggs, suet, etc., will be consumed to ensure proper bone formation. Further, cereals are the cheapest, and therefore the most greatly consumed, articles of diet. Climatic conditions in this country are such that the baneful effect of cereals cannot ordinarily be counteracted by ultra-violet radiations. Indeed, all the circumstances, climatic, dietetic, and economic, in this country appear to be conducive to defective bone formation.

BONE DISEASES DUE TO DEFECTIVE FEEDING

Rickets, Late Rickets, and Osteomalacia.—When the dietetic conditions in infancy and childhood are unbalanced, as just indicated, rickets follows, and if such conditions prevail in adolescence "late" rickets may ensue. Even in the adult, when all growth has ceased, bone is not in a static condition, but is constantly being absorbed and re-formed. Thus a poor calcifying diet in the adult, extending over a long period, may result in osteomalacia, especially when there are increased calls on the mineral constituents of bone as in pregnancy. Associated with, or independently of, these pathological states, osteoporosis may arise. With advancing age, partly because of the relatively small rate of growth and partly because of some unknown factor which ensures greater stability to the bony skeleton, gross bone deformity of dietetic origin becomes rarer, so that whereas rickets and its associated deformities in early childhood are extremely common in this country, late rickets and osteomalacia are rare. Even active rickets is uncommon after the age of 4. Only in extreme poverty and in countries where the diet is greatly restricted and is almost entirely composed of cereals, as in China and India, is osteomalacia common. Rickets is still one of the greatest social evils of this country, in spite of the fact that its aetiology and methods of prevention are known. It is probably true that in London there has been a great diminution in the number of gross rachitic defects in the young during recent years, but in the industrial towns of the Midlands and North the disease is still rampant. A rickets clinic has in recent years been established in Sheffield, and there are never fewer than 500 children attending for treatment.

Defective bone formation is, however, much more widespread than is indicated by gross bone deformity, and it is probable that a very large proportion of infants and children in this country have at some time passed through a period of defective bone calcification short of florid rickets. This point has been emphasized by medical men interested in public health.¹ Other evidence showing the great prevalence of milder forms of the disease is that of Schmorl,² who from 1901 to 1908 examined by histological methods the bones of 386 children in Dresden

* Read in opening a discussion in the Section of Medicine at the Centenary Meeting of the British Medical Association, London, 1932.

between the ages of 2 months and 4 years, and found 345 (89.4 per cent.) with rachitic changes. In 201 (58.3 per cent.) the disease was active, in 80 (23.2 per cent.) healing, and in 64 (18.5 per cent.) healed. These figures cannot be taken as typical of the average population of children, but they do indicate a serious state of affairs, at least among hospital children, in a country where the dietetic conditions are not greatly different from those in our own. Only 41 (10.6 per cent.) were free from signs of rickets, and in some of these the disease had probably healed.

The structure of a tooth reveals the history of the processes of calcification during the whole period of development; unlike the bones, the tooth, once formed, remains practically unchanged. M. Mellanby³ found, on examining the histological structure of large numbers of deciduous teeth, that about 80 per cent. were imperfectly developed. Examination of the mouths of about 1,300 L.C.C. school children under 6 years of age revealed that only 1.3 per cent. had perfectly formed sets of teeth.¹

Prevention of Rickets.—A fundamental method is to increase the consumption of milk, and especially to procure breast-feeding by properly fed mothers. Although it is probably true that the need for a large intake of vitamin D is less when the diet is wholly milk than when it is mixed, it must be remembered that the younger the child the greater is the tendency to rickets, and that many samples of both cow's and human milk do not contain sufficient vitamin D to ensure perfect bone formation in early life, even when milk is the only food ingested. For this reason supplementary dietary additions of substances rich in vitamin D are advisable for all infants and children, as well as for the nursing mother. Cod-liver oil is a specific against rickets as well as a curative agent of great potency. Only small quantities are necessary as a prophylactic, from one to three teaspoonfuls daily being ample, the small quantity being given from birth. The need for cod-liver oil is, of course, greater when the milk consumption is small and the cereal intake large. Apart from its vitamin D content, cod-liver oil is rich in at least two other dietary factors which are often deficient in the ordinary diet—namely, vitamin A and iodine. It is easily taken by infants and young children if administered by a reasonably sensible mother or nurse.

No cereals or cereal concoction ought to be given to an infant for the first eight or nine months, and even after this only in small amounts for the first two years. Cereals form far too great a part of the diet at all ages, and might well be replaced to a large extent by milk, eggs, cheese, vegetables, and fruit throughout life. The high cost of milk makes a sufficiency almost unprocurable by a large section of the population; large-scale reduction of rickets by increased consumption of milk is therefore unlikely under present economic conditions. Nor will butter act as a substitute for milk, since in the presence of cereals the antirachitic action of butter is small. Bread-and-butter is not greatly superior to bread alone, although other factors, such as a high calorie value and vitamin A, are important attributes of butter. Butter can, however, be made much more strongly antirachitic by giving it with additional calcium; thus butter with 10 per cent. calcium phosphate or carbonate has a powerful antirachitic action.⁴ If some means could be found of making butter so that it retained the calcium of the milk a great advance in the improvement of bone formation would follow. In the case of poor people, where milk consumption is low and consumption of cereals is high, an effort should be made to increase the calcium intake. In the Sheffield Rickets Clinic, under the guidance of Dr. C. Lee Pattison, calcium phosphate (bone ash) is given to rachitic children (about 2 grams daily) as well as cod-liver oil.

There is little glory attached either to the diagnosis or to the cure of rickets, and possibly for this reason the medical profession shows comparatively little interest in this scourge. Only when the public conscience is aroused will its prevention and its elimination from our midst follow. It is doubtful whether this conscience will be sufficiently stirred either by the sight of enlarged epiphyses, delayed closing of fontanelles, or even bent legs, but if every woman and man grasped the fact that perfectly formed teeth could be ensured by the same simple means of feeding the young, a great advance in the prevention of rickets might naturally follow. Also every woman ought to be made to realize the troubles of childbirth that are in store for those females who have been allowed to develop rickets in childhood.

Late Rickets and Osteomalacia.—Both these conditions can be cured by the treatment specific for rickets. Thus cod-liver oil or some other source of vitamin D such as irradiated ergosterol is curative, especially when the diet is improved in its mineral salt content. Since it is much more difficult to produce defectively calcified bones in the adult than in the infant and young child, it is doubtful whether a simple vitamin D deficiency is the cause of these conditions. There is little doubt that the calcium intake is also very deficient, so that the bones lose their stores of this substance. The demands of the foetus and infant for calcium, phosphorus, and vitamin D, via the placenta and the mammary gland, no doubt account for the increased incidence of osteomalacia in child-bearing women. Hunger osteomalacia may be common in those living under famine conditions.

The fact that osteomalacia is most often found in countries where there is abundant sunlight is a curious commentary on modern discoveries concerning the effect of ultra-violet rays on bone calcification, and indicates the preponderating influence of diet. If osteomalacia in Indian women were confined to those living in purdah, this could be well understood, but according to Wilson⁵ women when working on the land and exposed to much sunlight also develop this disease. The diet of these women consists almost entirely of cereals. There are some who think that osteomalacia in an incipient form is more common in England than is generally recognized. It may well be so, and in women complaining of back and thigh pain, especially if associated with bone defect, the possibility of osteomalacia ought to be considered. It is certain that a woman in pregnancy ought to be so fed that the demands of the developing embryo should not make it necessary for the maternal organism to sacrifice its own chemical stores, whether these be calcium, phosphorus, iron, iodine, vitamin A or vitamin D, or any other substances essential for health. Many of the ills associated with pregnancy could be thus avoided. I have seen in this country two cases of osteomalacia in childless women produced by restriction of diet (on medical advice) because of dyspepsia. In osteomalacia the serum calcium is usually low (5 to 7 mg. per 100 c.cm.) and rises rapidly on the administration of vitamin D and calcium (Maxwell⁶). Tetany is a common accompaniment of osteomalacia, but responds to the dietetic treatment of the disease.

Before leaving the subject of diet and calcification three further practical points may be mentioned.

The Use of Standardized Vitamin D.—Since there is now an international unit of activity of vitamin D, all preparations which claim to contain this substance ought to be standardized, and the medical profession should take advantage of this fact. An ordinary sample of cod-liver oil contains about 100 units per c.cm., but good samples may contain up to 250 units per c.cm. Since the isolation of vitamin D in the form known as

calciferol, preparations of intense activity are procurable, but it is probably not desirable to use those of greater strength than 3,000 units per c.cm. for ordinary purposes.

Hypervitaminosis D.—The danger of this condition, due to the administration of potent preparations of vitamin D, is small if the infant or child also has plenty of milk. There is, however, a real danger of producing hypervitaminosis, with calcification of the kidney vessels and tubules, if concentrated preparations are given to marasmic infants and children not taking a reasonable amount of milk and other food. In my experience, even 1,500 international units of vitamin D daily in the form of irradiated ergosterol bring about curative changes at the epiphyses of rachitic children when the diet is not in itself curative and the children are not exposed to direct sunlight. This dosage produces a relatively slow rate of healing; 3,000 units is a more effective dose, and I should regard 5,000 units as the maximum required for a cure. To cure rickets under ordinary dietetic conditions 20 c.cm. or 6 drachms of cod-liver oil containing (on an average) 2,000 to 3,000 units of vitamin D are sufficient. These figures are given as a general guide for avoiding hypervitaminosis, but it is always desirable to see that the diet itself is good when vitamin D is given in large doses. In marasmic children it is probably better and safer to give cod-liver oil in small doses at first and to increase them gradually rather than to give irradiated ergosterol.

Osteotomy.—With improved control of rickets and its resulting bone deformities, the need for osteotomy should almost have disappeared. So long as a child is growing, a good diet rich in vitamin D, calcium, and phosphorus will, if continued, correct most gross bone deformities of the limbs; treatment for a year or more is generally necessary in such cases. Whether pelvic deformity in childhood also recovers under these conditions I am unable to say, but it is a subject which merits investigation. Osteotomy to correct bone deformity due to rickets should only be performed when growth is ceasing or has ceased, and the operation ought to be followed by a diet of high calcifying qualities.

GENERALIZED OSTEITIS FIBROSA CYSTICA (VON RECKLINGHAUSEN'S DISEASE)

The Parathyroid and Bone Structure.—If the problem of rickets is generally regarded with indifference, especially from the prophylactic aspect, which matters most, there is certainly no indifference to the problems of bone

defects associated with parathyroid abnormality. The diagnosis and treatment of hyperparathyroidism is a matter of great interest at the present moment. The subject has been ably reviewed recently by Dr. Donald Hunter,⁷ who is with us to-day; it is therefore unnecessary for me to say much. Our present knowledge is based on work directed from all angles of medical research. This includes the observations of the morbid anatomists—von Recklinghausen,⁸ Askanazy,⁹ Erdheim,¹⁰ Schmorl,¹¹ and Dawson and Struthers¹²; the experimental work of MacCallum and Voegtlin,¹³ Collip,¹⁴ and Jaffe and Bodansky¹⁵; and the clinical experiences of Mandl,¹⁶ Aub and his colleagues,¹⁷ and Hunter.⁷ Many other names could justly be added to this list.

The diagnosis of generalized osteitis fibrosa cystica calls for complete laboratory equipment, and involves radiography, blood chemistry, and, when possible, a chemical balance sheet of calcium and phosphorus intake and output. The rarefaction of the bones, sometimes with osteoclastomata and cysts, which may or may not expand the bone itself, the high serum calcium (over 10 mg. per 100 c.cm.), the low plasma phosphorus (below 3 or 4 mg. per 100 c.cm.), the high blood phosphatase, the large loss of calcium via the urine, even when on a low calcium diet—all these points must be considered in the diagnosis. I have attempted to draw up a table giving in brief the main points which differentiate generalized osteitis fibrosa cystica from such conditions as osteitis deformans (Paget's disease), osteomalacia, and healed rickets with deformity.

It is important also to note that *localized* osteitis fibrosa is not necessarily associated with the above-described blood and urinary changes (Hunter⁷), nor with hyperplasia of the parathyroid. It was probably for this reason that Schmorl¹⁸ only found four cases of parathyroid enlargement in twenty-five patients suffering from osteitis fibrosa. Nor are all cases of parathyroid hypertrophy associated with osteitis fibrosa, for in forty-seven such cases Hoffheinz¹⁹ found only twenty-seven suffering from bone abnormality, including seventeen cases of osteitis fibrosa, eight cases of osteomalacia, and two cases of rickets.

The removal of the enlarged or adenomatous parathyroid in generalized osteitis fibrosa, whether surgically or by x-ray therapy, as recently practised by Merritt,²⁰ has dramatic results, the most important immediate changes being the reduction or disappearance of the disabling pain and weakness and the diminution of the blood and urinary calcium. There is some difference of opinion

Some Indications for Differential Diagnosis of Some Bone Diseases in the Adult

	Radiographic Examination	Blood Examination			Urinary Examination	Time of Onset
		Calcium in Serum	Phosphorus in Plasma	Phosphatase		
Generalized osteitis fibrosa cystica	Involves many bones. Multiple cystic areas with little sclerosis. Cysts and osteoclastomata may extend along axes or may expand corticals. Diminished density of bone shadows	High, usually above 13 mg. per 100 c.cm.	Low, usually below 3 mg. per 100 c.cm.	High	Calcium and phosphorus several times as high as normal, even on low calcium diet	Early adult life and later—20 up to 55
Local osteitis fibrosa	Often only one bone affected. Spacing out of lamellae to form cystic areas	Normal	Normal	Normal	Calcium and phosphorus excretion normal	Chiefly in adolescence
Osteitis deformans	Bones thickened. May affect only one bone, but usually extends to others. Skull may be thickened and woolly. Pelvis often first affected. Bone structure eventually lost, and acquires more or less uniform density	Normal	Normal	High	Calcium and phosphorus excretion normal	Later life—45 to 65
Osteomalacia	General rarefaction of bones and structure to some extent lost. Shafts of long bones reduced in girth, and cortex diminished. "Drumstick" appearance of long bones. Coxa vara, increased convexity of sacrum, sclerosis, and triradiate pelvis	Low (5 to 8 mg. per 100 c.cm.), but rises on giving vitamin D and calcium	Usually low (2 to 4 mg. per 100 c.cm.)	High, but diminishes on giving vitamin D and calcium	Usually high calcium excretion	Often associated with pregnancy or history of famine conditions
Healed rickets with deformity	Bones deformed, but otherwise normal	Normal	Normal	Normal	Calcium and phosphorus excretion normal	History of deformity in childhood or adolescence

as to the bony changes following operation, but it must be remembered that often the bones may have to be completely rebuilt, and therefore only a slow reversion to normal structure can be expected in severe cases. Tetany commonly follows operative removal of the hyperplastic parathyroid, but this condition can be controlled by parathyroid extract. This sequel is difficult to understand, especially as removal of the gland, although reducing the serum calcium, still leaves it near the normal figure. It is interesting to note that Johnson²¹ has recently described tetany in puppies following the cessation of administration of parathyroid extract which had been given to produce the bone changes characteristic of generalized osteitis fibrosa. This seems comparable to the tetany following removal of the gland in osteitis fibrosa, and ought to assist in affording a solution to this problem.

There is still much to be learnt about this condition—the cause of the parathyroid hyperplasia often of only one gland, the reason why a more general hypertrophy of the parathyroid glands is associated sometimes also with other defective conditions (for example, osteomalacia and rickets), the origin of the pain which is so disabling, and of which such complaint is made by patients, the action of parathyroid hormone on the blood and on the bones, and especially its relation to osteoclastic activity, and, finally, the reason why the tendency to tetany following operation diminishes after the first few days. Clinical investigations and results of experimental work on animals have made it absolutely clear that parathyroid enlargement and hyperactivity is the primary cause of generalized osteitis fibrosa, but a subject has been opened up which calls for the combined efforts of physiologists, pathologists, and, indeed, of all whose object it is to add to the understanding of biological problems of practical interest.

OSTEITIS DEFORMANS (PAGET'S DISEASE)

Ignorance of the aetiology of osteitis deformans is at present probably the greatest hiatus in our knowledge of bone defect. This disease, in my experience, is much more common than generalized osteitis fibrosa, and the history of its discovery by Paget²² makes a special call on English investigation. The morbid anatomy of osteitis deformans, especially in its early stages, is so similar to that of osteitis fibrosa that it might be supposed that here also hyperparathyroidism plays a part, but there is no evidence that such is the case. This disease more usually attacks older people than does osteitis fibrosa; it is more chronic in nature, and the absorption of bone and its new formation keep pace better than in osteitis fibrosa, where rarefaction predominates. Undoubtedly there is some aetiological factor in common between osteitis fibrosa and osteitis deformans, but it has not yet been identified.

It has been my practice for some years to treat this disease by giving a highly calcifying diet, including much milk and egg yolk together with cod-liver oil. Although absorption of bone in osteitis deformans is active, the tendency to recalcification and laying down of new bone is still great. The encouragement of this recalcification by diet seems to me, therefore, to be the right line of treatment while we are ignorant of the aetiology of the disease. In one case where the only bone affected is the femur shaft, this form of treatment has continued for six years. There has been no spread of the disease to other bones during this time, and although the femur shaft has remained defective in structure and calcification, the patient has continued at work throughout. Unfortunately osteitis deformans generally attacks poor people, who find it difficult to procure the right type of feeding for long periods.

The calcium and phosphorus content of the blood is within normal limits in this disease, but the blood phosphatase is high (Kay,²³ Roberts²⁴). In this connexion it may be well to point to the advantage of using the shorter method of estimating the blood phosphatase as described by Roberts²⁴ or that of Jenner and Kay²⁵ more recently published.

RENAL RICKETS

The Kidneys and Bone Structure.—Renal rickets can probably be classed with osteitis fibrosa as being due, not to diet, but to some derangement of the functional activity of an organ (in this case the kidney) and as having no direct relation to ordinary infantile rickets. The presence of Dr. Barber and Dr. Parsons to-day makes it unnecessary for me to dwell on this subject, the main interest of which lies in the facts that the rachitic changes in the bones are associated with sclerotic kidneys and that the bones do not respond to treatment with vitamin D and a high calcifying diet. On the basis of the first principle in all research—namely, to treasure the exceptions—it would appear that greater knowledge of this interesting condition is imperative, for it would probably throw much light on the action of vitamin D and other factors influencing bone calcification. Parsons²⁶ has laid special stress on the importance of the inability of the kidneys to excrete phosphorus in renal rickets, an aspect of the subject which is of great interest. There are some clinical indications that the kidneys and parathyroid glands are closely related in their actions; experimental evidence on this point has recently been given by Cowell in a communication to the Physiological Society (unpublished). The relation of the kidneys to calcium metabolism seems to be a promising line of investigation.

CONCLUSIONS

I have now dealt briefly with the more commonly recognized bone diseases whose origin is dependent on metabolic disorders. Coeliac rickets and osteoporosis associated with hyperthyroidism have not received the attention they deserve. Bone infections such as osteomyelitis and tuberculosis have not been considered, nor has any attention been given to bone tumours, although the relation of the osteoclastomata of osteitis fibrosa to some of the benign giant-celled bone tumours well merits consideration (Dawson and Struthers¹²).

As the result of animal and clinical investigations made in recent years: (1) rickets, late rickets, osteomalacia, and bone changes associated with scurvy can now be prevented and cured; (2) generalized osteitis fibrosa cystica can be cured or, at least, its progress can be stopped and great improvement in the general condition brought about; (3) most important of all—perfect formation of bones (and their allied organs, the teeth) can be produced in infants by proper feeding.

Nothing is yet known as to the cause of osteitis deformans (Paget's disease) although its progress can possibly be retarded by treatment. Renal rickets, fragilitas ossium (except its hereditary factor), and achondroplasia still remain enigmas.

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

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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.