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ON THE ETIOLOGY OF RICKETS.

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IT is a good thing that those of us who are actively engaged in investigating the factors involved in the development and cure of rickets should leave our work periodically in order to discuss the subject from the broadest standpoint, and to hear the criticism of both clinical and laboratory colleagues. It is more specially important that this should happen at the present time, because many results of research have been published during the past year, and, both from the point of view of the investigator, of the practising medical man, and of the public health worker, it is desirable that the new facts should be appraised, and their relative value decided upon. Fortunately, the medical profession are fully alive to the importance of the problem, largely, no doubt, as the result of the investigation initiated by the Medical Research Council. The controversy that has developed from these researches has probably been useful in attracting attention to, and intensifying the general interest in rickets. Whatever disagreement there may be among investigators as to the etiology of the disease, we all recognize that the complete eradication of rickets would do away with much bone deformity, improve the physique, lower the infant mortality, and, most important of all, improve the teeth of the people of this country beyond recognition.

But while we are agreed as to the magnitude of the problem, our views as to the most important factors in the etiology of the disease are very diverse. If, indeed, we were asked to formulate plans for eradicating rickets from this country, our recommendations would be so different as to suggest chaos. Some would strongly recommend housing schemes as a panacea; some massage and electricity applied to children from birth; some more sunlight and ultra-violet rays; while there are others who think that proper feeding of children would settle the problem.

While we are still suffering from the disability of ignorance, the narrowing down of the field by recent investigations suggests that our present discussion will be fruitful; for important strides have been made on the hygienic side of the problem

since Hansemann formulated his theory of domestication, and the dietetic hypothesis of rickets has also become more definite and concise as the result of recent research.

Much of the recent work on rickets has centred round the particular dietetic hypothesis of rickets which I have put forward,[1] and as I am anxious that my views should be correctly understood and not misinterpreted in this discussion, I wish to state these briefly.

Rickets, according to my view, is a disease accompanying growth, and is due primarily to defective feeding. What is a rickets-producing diet? It is one of unbalanced nature in that it contains too little of those foodstuffs responsible for the proper calcification of bone and too much of those substances responsible for the growth of tissue, these latter substances being either neutral or antagonistic to the deposition of calcium phosphate in the growing bony matrix. Assuming that the diet contains a sufficiency of calcium and phosphorus in a form that can be absorbed from the alimentary canal, the most potent influence for procuring the calcification of bone that I have observed up to the present is something of the nature of a vitamin having a distribution and properties somewhat similar to fat-soluble A.* On the other hand, foodstuffs responsible for growth and the laying on of tissue which are indifferent or antagonistic to calcification include the cereals. Generally speaking, therefore, rickets is a disease which follows the ingestion of diets relatively poor in the antirachitic vitamin and rich in growth-promoting elements, and more particularly in cereals.

The complication which has made this hypothesis of the etiology of rickets difficult to grasp is the new conception that the various essential factors of a diet are so interdependent that many dietetic problems must be considered from the point of view of balance, and that it is no longer possible to speak of "excess" or "deficiency" of substances in an absolute way. For instance, the amount of fat-soluble vitamin which may be sufficient in one diet becomes a relative deficiency when more cereal is eaten, or the calcium in one diet may be adequate but will become inadequate if the fat (butter) be greatly increased. In general, the minimum of any substance essential for perfect health and development is a variable dependent on the other factors of the diet eaten. The new dietetics which insists on the importance of quality as well as quantity must also find a way of expressing the fact that the value of a diet depends upon the relative amounts of its essential constituents and not upon absolute amounts.

It seems necessary to mention this point of view of diet, for much of the criticism against my work has been written as if I had suggested a kind of penny-in-the-slot hypothesis of rickets: abundant fat-soluble A in the diet, no rickets; absence of this vitamin, rickets. It ought to be superfluous for me to say that I have never written of rickets as a disease of this simple

* I shall call it the fat-soluble or antirachitic vitamin throughout this paper.

etiology. I wish also to take this opportunity of saying, in view of statements made in various places that I have altered my views, that I have not written of rickets as a disease uninfluenced by exercise and general environmental conditions. I have, however, always insisted that diet was the most predominant factor, and that environment was of secondary importance. Good hygienic conditions, in so far as they lead to greater activity and greater exposure of the skin to the ultra-violet rays of the sun, will no doubt prevent a moderate diet from producing the disease. Bad hygienic conditions will have the opposite effect, but, in my experience, a good diet will prevent rickets however bad the environment may be, and a really bad diet will result in rickets under the most perfect surroundings.

I propose now to deal with some of the more salient features of recent work in the light of my experimental results on animals, and, during the past eighteen months, of clinical observations on rachitic children.

The Influence of Dietetic Factors on the Development of Rickets.

(a) *The Interaction of Fat-soluble Vitamin, Calcium, and Phosphorus.*

In my experiments on dogs no difficulty was experienced in producing rickets by diets which contained abundant calcium and phosphorus, but were relatively deficient in fat-soluble A, so long as sufficient food was eaten. On the other hand, Korenchevsky[2] has found that, whereas the absence of fat-soluble vitamin in the diet only produces true rickets in a certain number of young rats, where there is an additional deficiency of calcium rickets develops in 100 per cent. of cases. Similarly McCollum and his associates,[3] also working on rats, found that a deficiency in the diet of an element present in large quantities in cod-liver oil (I shall assume for brevity's sake it is the fat-soluble vitamin) only produces osteoporosis, but, combined with a deficiency of phosphorus or calcium, and especially the former, in the diet, allows definite rickets to develop. The point of agreement in these various researches is that the fat-soluble vitamin in the diet has a potent effect in promoting calcification of bones, and what remains to be decided is the relative importance of calcium or phosphorus deficiency in the etiology of rickets.

The necessity of having a sufficiency of calcium and phosphorus in the diet before an abundance of good bone can be formed is obvious. If either is deficient during the growth of an animal, a condition of osteoporosis must result, but, whether it will be simple or complicated with rickets, will depend on the rest of the diet. Before discussing the matter further it may be well to state that I have already supplied evidence in support of the suggestion that the balance of calcium, phosphorus, and fat-soluble vitamin in the diet is important in ways more obscure and subtle than the simple deficiency of one or more.

I have shown, for instance, that too much butter in a given diet may result in bones defectively calcified, and that the antirachitic effect of butter is best obtained when it is balanced with a sufficiency of calcium. Again, the different action of caseinogen as present in milk, and that of acid-caseinogen as prepared from milk by acid precipitation—a substance deprived of its calcium—seemed to be most easily explained by some alteration in the calcium-phosphorus ratio. I mention these facts in order to show that I have previously considered the question of calcium and phosphorus in relation to the antirachitic vitamin, and suggested that it might be of importance in some special cases. I doubt, however, whether it has the practical importance in human rickets that the recent results obtained by different investigators, working on problems of rickets in rats, have suggested.

One possible cause of the difference in the experimental results of different workers may depend on the type of animal used—for whereas later investigators have worked on rats, my experiments were made on dogs. The differences in reaction to dietetic changes found among various animals are so notorious now that this point requires no emphasis. For instance, the failure of rats to develop scurvy in spite of the absence of the antiscorbutic vitamin from the diet is well recognized. Consequently, if there should happen to be any difference in reaction to diet between rats and dogs, which cannot be explained by differences in technique, then, in so far as the results have to be extended to children, I should unreservedly support the dog experiments, because of the closer similarity between the metabolism of a human being and a dog than between a human being and a rat.

There are, however, technical variations in the experimental methods adopted, which may explain the apparent discrepancies in the results. For instance, the dietetic conditions under which the rat-feeding experiments have been carried out were more strenuous than mine, more particularly in respect to the fat-soluble vitamin eaten. In the rat experiments a point has been made to eliminate this substance from the diet, whereas in my experiments on puppies the amount of separated milk allowed was fairly high, and must have contained some of this vitamin. Since cutting out the fat-soluble vitamin from the diet of rats stops growth after a short time, and since, in my opinion, rickets is a disease of or accompanying growth, it would not be expected that the preliminary slow growth, and the ultimate marasmus associated with this defect in diet, would be accompanied by a great development of rickets. It seems to me that, if the rats' diets contained a relative rather than an absolute deficiency of fat-soluble A, the better growth that would result therefrom might be compatible with more emphatic rachitic changes of bones, and these might possibly develop as in the puppy experiments even when the calcium and phosphorus contents of the diet were not deficient in amount. Not only do the conditions of feeding in the rat experiments call forth this criticism, but, as human rickets is the problem to be solved,

the diets used are abnormal in ways not commonly met with in the feeding of children. It is unlikely that human diets, except under rare conditions, should be so deprived of fat-soluble vitamin as are the synthetic diets of Sherman and Pappenheimer,[4] and Korenchevsky,[2] in their rickets experiments on rats. If this did happen, much more keratomalacia would be found among children. It has been argued by some that the fat-soluble vitamin cannot be an important element in rickets because, under experimental dietetic conditions which result in keratomalacia owing to the absence of this vitamin from the diet, rickets does not necessarily develop. This criticism seems to me to miss the point of my work, for, whereas keratomalacia appears to result from a simple defect of diet—namely, the absence of the fat-soluble vitamin—rickets is more complicated in that, so far as the bone is concerned, it is the outcome of a race between growth of bone and calcification of that bone. The antirachitic vitamin reacts with calcium and phosphorus on the diet, and thereby controls the actual calcification process, but there are other factors involved in the development of rickets, such as the amount of cereal eaten, and these additional factors make the two diseases of malnutrition under discussion largely independent, although one and the same dietetic factor plays an important part in the etiology of each disease. Keratomalacia is a rare disease because it is only seldom that the diet is practically devoid of fat-soluble vitamin, but, on the other hand, a relative deficiency of this substance in many articles used in the feeding of children is common, and rickets is widespread.

Further, it is unlikely from a consideration of diets which produce rickets in children that the calcium and phosphorus deficiencies are of prime importance. This remark applies more particularly to the question of phosphorus, the importance of which is being so stressed in many recent publications. Although children develop rickets when the calcium content of the diet is adequate, it is true, nevertheless, as I have pointed out elsewhere, that a diet deficient in fat-soluble A is likely to be deficient also in calcium, for these substances are often closely associated in their distribution in natural foodstuffs. For instance, milk, egg yolk, and green vegetables are rich sources of each, whereas flour, rice and maize, pulses, potatoes, sugar, and jam are almost devoid of both. When, however, we consider the phosphorus content of various foodstuffs and their relation to rickets, there is no evidence that phosphorus deficiency is a problem of practical importance, although the observations of Sherman and Pappenheimer[4] and Shipley, Park, McCollum, and Simmonds[8] on this point may be of great scientific interest. It has been said that a combined deficiency of phosphorus and at-soluble vitamin in the diet produces more typical rickets than that produced by a deficiency of calcium and fat-soluble A. I am unable to pronounce any opinion on this point, but I have little doubt that some specific relation exists between the antirachitic vitamin and phosphorus. In 1918 I failed to obtain

any evidence that this vitamin had the direct influence on the formation of calcium carbonate in eggshells that it exerts on the combination of calcium and phosphate in bone. Parenthetically, I wish to allude here to the experiments of Pappenheimer, McCann, and Zucker,[5] made to test the efficacy of the fat-soluble vitamin in preventing rickets and in promoting the deposition of calcium phosphate in bone. They failed to show that the vitamin exerted such influence, but as they first took the precaution to remove most of the phosphorus from the diet their experiments will probably not be accepted as crucial.

I find it impossible to interpret my own experiments in terms of much of the recent American research on rickets in rats, where the standard rickets-producing diet is deficient in both the fat-soluble vitamin and phosphorus.[4] It is true that meat has some antirachitic action, and this may be related to its high phosphorus content, but its effect in any case is small. Again, separated milk powder when given in large quantities, with the cereal element of the diet low, has an antirachitic action. This may be related to its high phosphorus content. As mentioned above, however, there is undoubtedly some fat-soluble vitamin left in separated milk, and its action on calcification becomes apparent when large quantities are ingested. When, however, the rickets-producing effect of the cereals is considered, it is manifest that phosphorus is of secondary consideration, because oatmeal, which has the strongest effect in inducing rickets of all the cereals so far examined, has also the highest phosphorus content, the P_2O_5 in oatmeal, flour, and rice being of the order 1.25 per cent., 0.25 per cent., and 0.2 per cent., respectively.

(*b*) *The Effect of Cereals.*

Whereas the fat-soluble vitamin working in conjunction with calcium and phosphorus ensures the calcification of bone, other elements in the diet have an influence in promoting the laying down of new bony basis without at the same time ensuring its calcification. Whether they actually inhibit calcification or are simply indifferent to this change is not certain, but in either case they have a definite rickets-producing effect as opposed to the calcifying or antirachitic action of the vitamin substances discussed. The worst offenders are the cereal and carbohydrate elements of the diet. This action of food was suggested by Cheadle[6] and has been long discussed by clinicians, but, as far as I know, the fact has never been proved until recently, and there was no experimental evidence in support of it.

I have shown that, when puppies eat diets which are complete except for a deficiency of fat-soluble vitamin, the severity of the rickets produced depends on the amount of cereal eaten if all other conditions are constant. If, for instance, a puppy A eats $2x$ bread as compared with B eating x bread, then, all other conditions being constant, A will develop worse rickets than B. I thought at the time, and I attempted to prove, that the carbohydrate moiety of the cereal was the essential element responsible for the action. These latter experiments were not very successful because of the difficulty in getting young puppies

to eat diets deficient in fat-soluble A and rich in pure carbohydrate such as starch, cane-sugar, or glucose. Nevertheless, the results obtained suggested that the carbohydrate in itself played some part in the production of rachitic symptoms. In view of my more recent experiments, however, it is difficult to believe that the rickets-producing effect of cereals is wholly due to their carbohydrate content, and I am at present engaged in finding the new factors involved. The most prominent fact brought out in the cereal experiments is that oatmeal has a greater rickets-producing effect under the conditions of these experiments than equal weights of flour, especially white flour, or rice. Since the amount of carbohydrate in oatmeal, wheaten flour, and rice is respectively of the order 65 per cent., 7.35 per cent., and 77 per cent.—that is to say, there is less carbohydrate in oatmeal than in the other cereals—it is manifest that the greater rickets-producing effect of oatmeal as compared with the other cereals cannot be due to its carbohydrate moiety.

In some way the effect of cereals is no doubt related to their property of producing growth, both in the sense of producing longer and bigger bones and an actual increase in weight. This action of cereal is best illustrated by contrasting its effect on the metabolism with that of fat. Adding more cereal to a diet already adequate causes young animals to increase more rapidly in weight, to develop a deposit of fat which is undoubtedly formed from carbohydrate, and to become more lethargic. Under the same conditions the addition of fat makes no difference to the rate of increase in body weight, for it neither increases the laying down of tissue nor is it deposited subcutaneously as dépôt fat. It is burnt up and increases the metabolism. These opposite effects of cereal and fat on the metabolism of young animals are most striking and have probably not received the attention they deserve.

Cereals, then, increase the laying down of fat and tissues generally, including the bones, and thereby make a greater demand on the calcification processes, so that any tendency to lag behind in this respect is increased by allowing the child or animal to eat a larger quantity of cereal. Increasing the bread, therefore, in a diet slightly rickets-producing only emphasizes the disease and causes the development of larger quantities of cartilage and osteoid tissue in the bones. This explanation, however, is not a complete one, for it does not satisfactorily explain the differences between oatmeal, white flour, and rice. In some series of experiments there was no obvious difference between the rates of growth or in the rates of putting on weight when oatmeal, white flour, and rice were the only variables, yet the rickets produced by oatmeal was much greater than that produced by equal quantities of the other cereals. Undoubtedly some other factor in oatmeal is at work which either prevents endochondral calcification or increases the formation of tissue at this point, thereby producing a relative lag in calcification at the ends of the bones. It does not appear to be the carbohydrate moiety, and as I pointed out in a previous Section the larger amounts of calcium and phosphorus in oatmeal discredit

any explanation which centres round deficiency of these substances. Further experiments will have to be carried out before a definite pronouncement can be made on this point.

Factors of Hygiene and their Influence on Rickets.

The two factors of hygiene that influence rickets, evidence of whose action rests on a definite experimental basis, are exercise and sunlight. The evidence that infection is of any importance in this respect seems to me too meagre at present to warrant discussion.

I have dealt elsewhere[1] with the exercise hypothesis and Findlay's claim[13] that it is the most important factor in the etiology of rickets, and will only state here that, in my opinion, the exercise taken by a child at the ordinary period of rickets development consists of small movements; also that this general activity depends almost entirely on its diet and not on its environment. Diet not only, therefore, has its direct action on the tissues of the body—including, from our particular point of view, the bones—but, by controlling the activity, has an indirect effect.

The second factor of hygiene—namely, sunlight—has quite recently come into great prominence as the result of experimental work, and demands closer consideration. The recognition of the antirachitic action of sunlight has been gradual and is the outcome of Huldschinsky's[7] observations of the curative effect on rickets exerted by the ultra-violet rays emitted by the mercury-vapour quartz lamp. Later, he supplemented the ultra-violet ray treatment of rachitic children with sunlight, whereas Riedel[8] treated cases of rickets by sunlight supplemented with ultra-violet rays on sunless days. Hess and Unger[9] then showed that sunlight alone is capable of bringing about curative changes in rickety bones. There is now but little doubt that it is the ultra-violet rays of sunlight which are the effective agents. Many publications have appeared recently on this subject, and the action of sunlight in stimulating calcification processes in bone is generally accepted.

This effect on calcification of bones is of great interest, but of even greater importance is the recognition that sunlight has a much wider influence, especially in the case of animals on defective diets, for in these cases it is capable of stimulating their appetite and increasing the rate of growth and activity. Even cases of latent tetany (Sachs[10]) and definite tetany (Huldschinsky[11]) have been cured by ultra-violet rays. It is evident, therefore, that the ultra-violet rays promote some chemical change in the body which results in profound modification of many activities. Since these rays have very little penetrating power it is probable that their action is on the skin, and that some powerful chemical substance is thereby liberated. Hess[12] has pointed ut that the antirachitic effect of the ultra-violet rays is smaller in the case of black rats as compared with white rats. Certainly in the case of puppies with dark hair the effect of sunlight in preventing the development of rickets, when placed on rickets-producing diets, is, in

my experience, negligible. It is interesting that sunlight, when it strikes the skin, produces changes in the bones and general condition of rachitic children and animals in some ways comparable to the effect produced by giving cod-liver oil, and it seems possible that the fat-soluble vitamin is the substance liberated into the circulation by the action of the ultra-violet rays on the skin. If this is the case then sunlight and ultra-violet rays ought to have other specific effects, such as (1) the cure of xerophthalmia, when the diets remain devoid of this vitamin, and (2) resumption of growth in young rats when growth has ceased owing to lack of this substance in the diet. Should these results be produced by exposure of the skin to ultra-violet rays, no doubt will remain as to the chemical substance set free into the circulation.

The scientific importance of these facts is obviously great, for they appear to open up a new field in physiology, but, in evaluating their importance in the prophylaxis and curative treatment of rickets in children, we must not be carried away by the interest of the subject. It will be agreed that, if the sunlight has to pass through clothing, its effect on the skin will be greatly diminished, if not destroyed, and even in its passage through window glass its ultra-violet rays are lost. Then, again, it is customary for a mother in this country to prevent sunlight falling directly on the only uncovered part of an infant out of doors—namely, its face. All things considered, the amount of direct sunlight falling on to the skin of a child in its first year of life, a time when it is most susceptible to rickets, must be very little. I am inclined to think that in this country at least the part played by sunlight in preventing rickets is small. If it be answered that rickets is rife in this country for the reason that children are not exposed to sunlight, then, I ask, are the excellent teeth and absence of rickets in the Eskimo in his natural surroundings due to exposure of the skin to the sun during infancy ? In tropical countries, where less clothing is worn and more sunshine is obtained, the ultra-violet rays undoubtedly hold a place of greater significance, although even here nature tends to diminish such influence by depositing pigment in the skin.

If it should happen, as seems possible, that the chemical hormone liberated by the sunlight is the antirachitic vitamin about which much of my experimental work on rickets has centred, then it only serves to emphasize the importance of diet in the etiology of this disease. For, although we cannot control sunlight, we can control the diet and we can see that it not only contains an adequate amount of this substance, but that it is so balanced with other factors that full use is made of it in the metabolism of the child.

I suggest that the following statements will cover most of the conditions where diet and sunlight interact:

(1) That when a child is well fed the presence or absence of sunlight makes no difference to its health in so far as rickets is concerned.

(2) That in the case of a child fed on a mediocre, borderline diet, exposure of the skin to sunlight will probably prevent rickets.

(3) That in the case of badly fed children—that is, when diets contain much cereal and a deficiency of fat-soluble vitamin and calcium—sunlight will not prevent rickets, but may ameliorate the symptoms to some extent.

It will be seen that, as in the case of exercise, so in regard to this other condition of hygiene—namely, sunlight—I consider it to be of secondary importance to diet in the etiology of rickets.

Diet and Rachitic Children.

A typical diet that I give to children with severe rickets is as follows:

Milk, 1 to 1½ pints.
Beef dripping, 1 to 2 oz. with bread.
Meat, 1 to 2 oz.—usually raw scraped and mixed with potatoes.
One egg.
Milk pudding.
One orange.

This diet alone will bring about rapid improvement, but the process of healing is hastened by the administration of cod-liver oil, 1 to 4 drachms t.d.s. In a recent publication Findlay [14] states that cod-liver oil produces very little clinical improvement, although definite evidence of healing, as seen by radiograph, can be observed. He further states that the administration of cod-liver oil and phosphorus does not produce healing of bones any more speedily than that produced by massage and electricity, which, he says, takes two or three months before any change in ossification of the bone can be noticed. I have had no experience of massage and electricity as a treatment for rickets, but there is no difficulty in producing great improvement in calcification of bones by the above diet, especially if cod-liver oil be added, during the course of one month. More noticeable, however, is the improvement in the general condition of these children apart from the calcification of bone. The most lethargic and miserable of infants, even in the later old-standing cases when a marasmic and semi-paralytic condition has developed, become bright and active. So active, indeed, do they become, when treated in the above-described way, that in many cases their cots have to be netted. Children, in fact, react to diet in the same way as do puppies, and the influence of diet on muscular movement is so prominent that I am surprised no observations of this type have been made by the Glasgow workers. However small a kennel, and however unhygienic its surroundings, with no access to sunlight and no special precautions as to cleaning, a properly fed puppy will remain very active and free from rickets. It is equally easy, by improper feeding, to make other puppies listless and lethargic, with but little desire to run about even when placed in open fields. By improper feeding I do not mean starvation, for these animals are usually fat and look well nourished. It is

also a matter of common experience that diets of high cereal content more particularly produce fat, lethargic, and contented children, whose small movements and general activity are subnormal, although the other environmental factors may be good. Nothing is more dramatic than the change in behaviour produced in rickety babies when the diet is altered to the type previously described. Clinical improvement and increased calcification and growth of bone are synchronous, and both are obvious within a few weeks of giving the good diet.

It is true that cases of rickets in children occasionally appear where it is difficult to account for the disease on the basis of the facts as I have described them. Investigation often shows that these cases are associated with some exceptional condition —such, for instance, as premature birth, or twins, or, in some cases, the children may have just recovered from a severe infection. But these cases only indicate that we have still much to learn of the factors which control the growth and calcification of bone. In my experience, all rachitic children react favourably to a good diet such as I have described.

There is one point about this dietetic treatment of rickets that may give trouble—namely, the fat dyspepsia that cod-liver oil may produce in some cases, more especially if the other fat in the diet is kept high. Some children in the early stages of treatment can only tolerate a moderate amount of fat, and are made ill by 2 ounces of beef dripping and 6 or more drachms of cod-liver oil per diem. If this happens, all recovery processes cease, and the sickness and other symptoms may be severe. It is well in these cases to cut down all the fat in the diet, and, starting with smaller quantities, to increase it step by step.

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