Cameron Prize Lectures

ON

THE PRESENT POSITION OF THE
VITAMIN PROBLEM.

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BY

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LECTURE II.—RICKETS AS A DEFICIENCY DISEASE.

IN this lecture I propose to consider the evidence obtained in the course of recent experimental studies, which shows that a specific dietetic deficiency plays an important part in the causation of rickets. There seems no doubt that a vitamin is involved in this deficiency or I should not now be dealing with the matter. The evidence for this claim doubtless needs closer scrutiny than was necessary in the case of certain nutritional failures dealt with in the previous lecture. For this very reason, however, I have chosen rickets as the subject of my second discourse. It is well to avoid the danger of suggesting that in such studies experimental results are always easily obtained or interpreted, especially when the reproduction of a particular disease as defined by clinicians is in question. I do not think you will deny, however, that in its final outcome the experimental study of rickets has fully justified its pursuit. Another reason for my choice of subject to-day is the desire to pay a public tribute to the work of a friend whose successful efforts to throw light upon the etiology of rickets have, I feel, lacked proper appreciation in certain quarters.

The history of the recent experimental studies of rickets and of the conflict of opinion to which they have led is in itself interesting and instructive. Honest opinions held in good faith have sharply differed. Yet the ascertained facts are now grouping themselves in such a way that both sides in the conflict may come together with flags still flying. Each side has been right, but neither side (because of the tendency to take too narrow a view) has been quite right. I would like, perhaps, just to add that I think this qualification applies especially to the side which is not my own.

There have been many views concerning the origin of rickets, but of these three only need be in your minds. One has looked upon various defects in hygiene as responsible for the disease, but from these defects faulty diet has been, on this view, expressly excluded. A second view has attached, on the other hand, a special importance to diet. It is this view, of course, in its most modern form, which involves the conception of a specific food deficiency, that I am here to support. The third view has postulated infection as a factor in the causation.

In 1908 Dr. L. Findlay published the results of experiments upon dogs which, together with his experience as a clinician, led him to conclude, alike on experimental and clinical grounds, that confinement, with consequent lack of exercise, is the main factor in causing the disease. In 1919 appeared as one of the reports of the Medical Research Council the results of an important study carried out in Glasgow by Miss M. Ferguson. This work was inspired by Professor Noël Paton, and was published with an introduction by Dr. Findlay, who had himself carried out, several years previously, a similar investigation. Miss Ferguson's study involved a careful comparison of the economic conditions in rachitic and non-rachitic families respectively. It dealt with hundreds of families of which the food budgets and housing conditions were studied with great care. The general conclusion arrived at was that inadequate air and exercise were the most potent factors in inducing the occurrence of rickets. It was held proven that diet played no essential part in the etiology of the disease. Upon these experiments and observations, supported by some others made more recently, are based the views of what is sometimes called the Glasgow school.

In direct conflict with these views were the results of Edward Mellanby's experiments, of which a preliminary

account appeared about a year after Miss Ferguson's report, though they had then been long in progress. I feel it incumbent upon me to insist strongly upon the importance of the work of my friend and former pupil, because in certain quarters at least it was received with somewhat carping criticism, still not frankly withdrawn. Moreover, not all among the more recent experimentalists, whose work took origin from Mellanby's, and has in effect confirmed it, have given him sufficient credit as a pioneer. The earlier and chief part of Mellanby's work was done at Cambridge, with support from the Medical Research Council. Although I had no hand in it, I can testify to the care with which it was done and to the patient enterprise it involved. Mellanby was blamed at the outset for making public claims before his experimental results had been fully published; but I think we should all sympathize with the dilemma of young investigators to whom priority is important but who yet suffer from a praiseworthy desire to polish their work before publishing it. There was plenty of evidence behind Mellanby's first statements. The Medical Research Council was also blamed at this time because in the first edition of the monograph, for which the Council is responsible, dealing with accessory food factors, a claim, supposed to be premature, was advanced for the importance of a dietetic deficiency in the causation of rickets. I do not think, however, that there will be anything to withdraw on the appearance of the second edition of the monograph—which is imminent—though there are many facts, derived from various lines of study, to supplement what was said in the first edition.

Mellanby's main observations were made upon puppies, and one minor criticism of his method was that in comparative experiments he did not generally use individuals from the same litter. This may appear a small point, but it is one of some interest to which I should like to devote a moment. It is known in the case of several metabolic anomalies—alkaptonuria, for example—that they are inherited on Mendelian lines. I have recently seen at Cambridge an illustration of such inheritance in the case of an anomaly which was not apparent till the metabolism was experimentally studied. I will not be more precise in my reference as the observation is not mine and is not yet published. But suppose among dogs there exists a sharp variation in susceptibility to rickets (and this would seem to be the only justification for insisting upon the use of puppies from one litter), then if by chance either relative immunity from or hypersensitivity to rickets were a recessive Mendelian character, which from what I know seems by no means impossible, segregation might have occurred in the very litter chosen for experiment. This might entirely upset experimental comparisons. Two puppies from one litter may, of course, be more alike than any two not so related. They may, on the other hand, in respect of a particular character, show exceptionally sharp contrasts. For studies in metabolism I would choose, whenever possible, dogs of the same breed and age, but I would rather select from an average population than from the same litter. This, however, is a digression.

Mellanby, as I have said, has worked on a large scale, and must by now have employed in experiments nearly 500 dogs. His general plan of work was on the following lines. Having established a standard diet which could be relied upon to produce rickets in puppies—an end that could be attained without much difficulty—he replaced one constituent of this diet by other material and observed the effect in respect of the development of rickets. In particular he exchanged one form of fat for another, and found that, while one fat might have little or no preventive power, another might prove strongly prophylactic. He found, further, that the fats most potent in this respect were those which on other evidence were known to contain the highest proportion of vitamin A. As I can testify, Mellanby arrived at this result without bias of any kind. It was originally unexpected by himself. I ought to mention that for the diagnosis of rickets he employed, apart from the general appearance of the animal, x-ray photography, histological examination, and also estimations of calcium in the bones.

Mellanby found that cod-liver oil was particularly potent in the prevention and cure of the experimental rickets. If

one set out to deal adequately with the question of cod-liver oil therapy in rickets much would have to be said. I will content myself with mentioning such facts as bear directly on the vitamin question. Since the work of Hess and Unger on negro children, and that of Mellanby on dogs, further and conclusive evidence has been gathered to prove that cod-liver oil is a prophylactic against rickets. Its influence in this respect is indeed most remarkable. It was the confirmed belief of many physicians, especially of the French school, and this long before the experimental era which we are considering, that cod-liver oil could also cure the disease, and at the moment I think almost everybody believes that its curative power is considerable. The question arises, however, as to what is the active agent in the oil. Mellanby's evidence seemed to show that it might be vitamin A, though he himself did not dogmatize on this point. Certain it is that if the curative factor be not vitamin A its distribution in fats and other materials is closely similar to that of the said vitamin, and when the latter is concentrated by fractionation of cod-liver oil the antirachitic factor is found in the same fraction (Zucker, Johnson, and Barnett). Nevertheless, as you are to hear, it is now likely that the two are not identical. It will be convenient, therefore, if for the moment I speak simply of fat-soluble vitamins.

In the years 1920-21 several observers, too numerous to quote, reported failures to obtain definite experimental rickets in animals as the result of simple deprivation of the vitamin or vitamins associated with fats. They did obtain, however, osteoporosis of the bones, indicating that in the absence of such vitamin or vitamins the body cannot deal normally with its mineral supply. There was nothing surprising in the failure to produce true rickets under these conditions. As Mellanby pointed out long ago (having to recognize the circumstance as a factor in his own experiments), typical rickets, showing the classical changes in the ossifying cartilages, is essentially a disease of growth. If the animal does not grow the typical histological changes are not developed. Now the vitamin A, because of some influence exerted in the body much more general than any effect upon ossification, is essential to growth: hence a somewhat remarkable impasse for the experimentalist. There are suggestions that a fat-soluble vitamin prevents rickets, but when the point is tested in what should be the clearest type of experiment—that is, one in which the diet is made wholly free from any such factor—the circumstance just mentioned intrudes. There is no growth, and therefore no rickets. It would seem as if either the presence or absence of a vitamin prevents rickets! This is not the paradox it seems. In the first place it is, as you will admit, quite an artificial though clinically convenient custom to treat a disease like rickets as an entity. If, however, we do this and give the disease a name, clinicians are perhaps justified in insisting that certain accepted criteria, empirically chosen, must all be present when we claim to have established the disease experimentally. Now in order that faulty diets should establish typical rickets in this sense it is necessary that there should be a certain quantitative balance among the factors concerned. No one has recognized this more clearly than Mellanby. It is, indeed, a point upon which he more than any other has insisted, though it is emphasized by much recent work. But since we are considering vitamins and their general influence on the body the significant thing is that in the absence of some such factor the mineral metabolism as well as other aspects of metabolism is abnormal. This is seen in the diminished deposition of calcium in the bones even when the classical picture of rickets is absent. It is noteworthy, moreover, that bone changes due exclusively to the absence from the food of vitamin-containing fats may after all, in certain animals, upon diets suitably balanced, assume the typical appearances of rickets.

The pioneer work of Mellanby upon dogs was followed a good deal later by that of Korenchevsky upon rats. This author found that, providing the deficiency were made sufficiently severe—for instance, when the mothers as well as the offspring were deprived of the specific factor—the young developed a condition in all respects similar to rickets. I wish I could devote more time to

Korenchevsky's interesting work, which should be studied by all who wish to appraise properly the available evidence concerning the point at issue. Goldblatt has extended the work and has shown that in the case of young rats which, by suitable feeding of the mother, are made to start life with an abnormally small store of the fat-soluble organic factor, grading the amount of that factor in their diet results in a corresponding grading in the amount of calcium deposited in the bones.

I have already pointed out that Mellanby has never asserted that the antirachitic factor present in certain fats is identical with the vitamin A, but only that its distribution is similar. In 1922 the results of some observations were published by McCollum and his colleagues which go to show that the vitamin necessary for the maintenance of growth and the prevention of keratomalacia is distinct from that which controls the proper deposition of calcium. The former is vitamin A; the latter, though it certainly comes under the only available definition of a vitamin, being a food constituent potent in minute amounts, we may with Edwards Park call the antirachitic "X." The proof of this distinction was obtained by oxidizing cod-liver oil by means of a current of air. This, as I myself showed a few years ago, results in the destruction of vitamin A. The American authors found, however, that after such treatment the oil, though it always fails to support growth, is still potent as a prophylactic against rickets. The antirachitic substance is less easily oxidizable than the growth vitamin. When we learn further how to destroy the former while leaving the latter intact no one will need to face the experimental difficulties earlier discussed.

Whatever may prove to be the actual nature of the mechanism whereby an organic factor in food promotes the deposition of lime salts in the body—for in some sense the specific substance under discussion most certainly exerts such an influence—it is clear that for proper calcification there must be in the food a sufficiency of lime itself. Moreover, since in the bones lime is present as phosphate, there must also be for proper bone formation a sufficient supply of phosphoric acid. A great deal of experimental work, old and new, has been done to elucidate the effect of reducing the supply of these constituents to below the minimum, or below the optimum. An actual deficiency of the kind can scarcely occur in practice however. The results do not concern us except in so far as variations in these inorganic constituents elucidate the influence of the vitamin factor. Interesting work, however, has been done by the school of McCollum which has such a bearing. It has been shown, for instance, that rickets occurs on a diet which is adequate in respect of lime, but, while deficient in phosphoric acid, is also deficient in the antirachitic vitamin. Further, a diet adequate in respect of phosphoric acid, but deficient in lime and the organic factor, will produce rickets. This work has also established in an interesting way the necessity, for the prevention of rickets, of a proper proportion between the calcium and the phosphorus in the food. What is of chief importance to the present discussion, however, is the evidence brought forward that a sufficiency of the vitamin is able, within limits, to correct a deficiency of calcium or of phosphates in the diet or a faulty balance of these two. If the deficiency in the inorganic constituents is large the amount of the organic factor required to ensure normal growth of the bones is found to be much in excess of that needed when calcium and phosphorus are supplied at the optimum. In the latter case a supply even of butter (which has but a low content of the antirachitic factor) will prevent symptoms; while in the former case cod-liver oil may prove necessary. Goldblatt, indeed, has found that with an adequate (though less than optimal) calcium supply butter in reasonable amount will secure normal calcification of the bones as fully as an optional quantity of cod-liver oil.

If anyone will survey and fairly appraise the literature of the last three years dealing with rickets as induced experimentally in animals, I do not think he can fail to admit that it strengthens Mellanby's original claim

that deficiency in an organic dietary factor closely associated with (but not necessarily identical with) the vitamin A plays an important part in the causation of rickets.

The further evidence which I would now like you especially to consider comes from the study not of animals but of children. Before dealing with this truly conclusive evidence I must, however, make brief reference to the remarkable studies which have demonstrated that radiant energy directly influences the processes of calcification in the body.

It is remarkable how long information with regard to the effect of light upon rickets has been in the literature without receiving general notice. As far back as 1890 Palm called attention to the fact that sunlight is very potent in preventing or curing the disease. Later, in 1912, Raczyński showed that sunlight has a remarkable effect in promoting mineralization of the tissues generally. In 1919 Huldshinsky showed that precisely the same result can be got by the use of the radiations from a mercury-vapour quartz lamp, and demonstrated the actual healing of rachitic lesions in children under the influence of these radiations. Hess of New York has with his co-workers confirmed and extended these observations. They have, moreover, been extended to experiments on animals. McCollum and his colleagues have shown that in the case of rats the antirachitic effect of light is similar to that of cod-liver oil in correcting dietetic deficiencies. If, for instance, the diet lacks vitamin "X" exposure to sunlight, or to the mercury lamp radiations, will prevent the occurrence of rickets. On the other hand, as Hess, and later, Goldblatt and Soames, have shown, if the diet is satisfactory, and contains a sufficiency of the vitamin, rickets never develops, even when the animals are kept in the dark. It would seem, indeed, as though certain radiations and the influence of vitamin may each act vicariously for the other in regulating the mineral metabolism of the body. This is a truly remarkable relation. When we understand it we shall possibly know much more than we know now about the functions of vitamins. Now since a proper supply of sunlight is certainly a factor in hygiene, and a vitamin is no less a factor in diet, I think I was right in suggesting earlier in this lecture that the facts as now known should form a basis for an honourable peace between the two opposing schools of thought then mentioned.

In extending, however, the study of radiation from rickets to the more fundamental phenomenon of growth itself, Miss Margaret Hume has discovered facts which show that light may, after all, not act vicariously for the vitamin nor (as has been suggested) bring about a photosynthesis of that factor in the body. Rather does it render more mobile the residual stores of the vitamin already in the tissues. When the vitamin is absent from the food exposure to suitable radiations will maintain growth for a period, but not, it should be noted, indefinitely. Miss Hume concludes from her work that (in relation with growth at least) light can neither create nor be substituted for the vitamin; it appears to act as an economizer or activator of the stores so that a deficiency in the supply is less readily felt. When, however, the stores are exhausted the animal fails.

The briefest reference only can be made to another and most fascinating aspect of this subject. In quite another connexion it had been shown by Kestner that exposure to air previously irradiated may have the same effect upon an animal as direct exposure to the radiation itself. Acting upon a hint from Professor Hans Meyer, Miss Hume determined to test whether this would prove to be the case in connexion with her own studies. She found that as a matter of fact rats fed upon a diet deficient in vitamin A, when kept in glass jars containing air which had been exposed to the mercury-vapour quartz lamp for ten minutes every second day, showed definite prolongation of normal growth when compared with control animals not so treated. Miss Hume's work was mainly done in Vienna as part of the enterprise to which I would now direct your special attention.

Most of you will doubtless realize that I allude to the studies carried out in Professor Pirquet's clinic by Drs. Chick, Dalyell, and Mackey, Miss Henderson Smith and Miss Hume. These five women workers went to Vienna under the combined auspices of the Medical Research Council and the Lister Institute. They submitted themselves to three years' exile in order that studies might be made where material was abundant and conditions ideal. The conditions were indeed ideal, and all who read the Medical Research Council's report which deals with the enterprise will admit that the final results were proportionally clear and unequivocal. The intention underlying the enterprise was to study the effect upon the prevention and cure of rickets in children of diets poor or rich respectively in those fats which contain vitamins. The organization of Pirquet's clinic was such as to convert this comparison into an experiment perfectly controlled. It was an experiment wholly justified because the control diet, relatively deficient in the vitamin, was one which all the infants would have received but for the arrival of the British workers. It was a diet, too, of which the details had been carefully worked out by Professor Pirquet himself, than whom there is no higher authority on such matters. Before the observations under review were made he fully believed in its efficiency, the belief being based in the main upon its adequacy in respect of calories. The experiment gained greatly in accuracy because advantage was taken of the remarkable organization for the quantitative feeding of children which Professor Pirquet has established, and because all factors of faulty hygiene could be completely eliminated. The accommodation available permitted observations to be made upon sixty infants at any one time. The methods used for diagnosis must, I think, satisfy the most critical. Fortunately the work of the latest year was done with full knowledge of what had been discovered elsewhere concerning the influence of sunlight and irradiation. This factor was therefore controlled and separately studied. I cannot, unhappily, stop to put the details of the results before you. It seems enough to quote from the statement with which Professor Pirquet has prefaced the Medical Research Council's report.

"When Dr. Chick and her colleagues on behalf of the Medical Research Council and the Lister Institute began their work in my Klinik in 1919," he writes, "I had little expectation that it would lead to results of much practical value. At that time I was of the opinion that a vitamin deficiency in our ordinary diet was a very exceptional occurrence, as, for example, in case of infantile scurvy (Möller-Barlow disease). With regard to the etiology of rickets I held the view that it was an infectious disease, widely prevalent in this part of Europe, producing severe symptoms only in case of those children who possessed special susceptibility as the result of an inherited tendency, of a faulty diet, or of defective general hygiene. I imagined rickets to be a disease comparable to some extent with tuberculosis."

Professor Pirquet was indeed a critic not easily convinced, but later in his preface he states:

"The crucial experiment was thus successfully made. The British workers succeeded with the accuracy of a laboratory experiment, in a city where rickets is extremely prevalent, in maintaining a large number of artificially-fed babies free from the disease, and further, in the same wards, were invariably successful in healing children admitted with rickets already developed."

"With this the chain of evidence appears to me to be complete that animal experiments upon rickets are applicable to man, that rickets is a disease of nutrition, and that deficiency of fat-soluble vitamins in diet is an essential cause of the disease."

Thus is Edward Mellanby's pioneer work confirmed and his conclusions justified.

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