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ON

THE PATHOGENESIS OF RICKETS.*

BY

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EVIDENCE derived from experimental and clinical work on the subject of rickets has accumulated so greatly during recent years that we are now in a position to review in reasonable perspective many of the rival theories which from time to time have been advanced to explain both its etiology and its pathogenesis.

There is scarcely any element in the food which, at one time or another, from the days of Glisson (1650) downwards, has not been incriminated as the guilty factor in the causation—sometimes on the grounds of excess, sometimes on the grounds of default. Further, apart from food causes, there are few factors in the general hygienic environment—whether connected with bad housing, with confinement, with infection, with want of exercise, or with want of light—which have not been regarded by one or other authority as having an important bearing on the etiology. During the recent renaissance of interest in these sides of the subject there has been a distinct tendency for investigators to range themselves definitely either on the side of the dietetic theory or on that of the environmental explanation; but the deeper each party probes into the problem the greater are the concessions which it is compelled to make to the claims of the other, so that what appeared quite a short time ago to be a sharp line of demarcation between the two standpoints has now become an ill-defined neutral zone.

I do not think that at the present moment any impartial person who has at all followed the recent controversy would question the general truth of any of the hypotheses which have been formulated by either of the rival parties. Nobody, I believe, has any doubt that Mellanby is correct in his view that the fat-soluble "A" factor plays an important part both in the cure and prevention of the disease. Neither do I think he would quarrel with the claim made by Findlay and others that housing conditions, confinement, and want of exercise have a share in the etiology; nor with Buchholz (1904), Chick, Hume, and Mackay (1922), in their belief that ultra-violet rays have both a prophylactic and a curative influence on the rachitic changes in bone; nor with Noël Paton in his view that infection also plays a part; nor, for the matter of that, would he dispute the possibility of carbohydrate excess (Rabagliati and Hutchison), or protein deficiency (Henry), or defects of balance with respect to calcium or phosphorus, or any other of the constituents of the food being concerned in the causation of the rickety syndrome. I think it would not be overstating the case to say that at the present time most reasonable people are agreed that there is not any single cause of the disease, but there are many possible contributory factors which may exist in a great variety of combinations.

If, however, there is agreement as to the multiplicity of these remote or contributory causes, there is absolutely no unanimity of opinion as to the *causa vera* or the exact pathological process which can explain how it is that the same end-result can be reached by so many routes. Some authorities have regarded some disturbance of calcium metabolism or some faulty relationship between the phosphorus and calcium balance as the common point at which all these convergent paths meet, and many painstaking investigations have been carried out by Stheeman, Hess, McCollum, and others to estimate the exact composition of the blood in respect of these elements under normal and rickety conditions. Although there appears to be a distinct tendency for both the calcium and phosphorus content to show a noticeable diminution in cases of active rickets, and especially in the extreme phases of tetany

and other spasmophilic conditions, this result is by no means universal, and in certain cases the amount of calcium at least may be actually increased. The comparative fruitlessness of such lines of research is explicable on several grounds. In the first place, it does not follow that because the blood has a normal calcium content the whole of it, or any considerable part of it, is available either for bone building purposes or for the neutralization of acid bodies, which, according to Hamilton and Tobler, are the important functions of calcium in the metabolic processes of the body. Varying proportions of such calcium may be, so to speak, "dead," having served their purpose in the economy; little of this base may be in an ionic state and serviceable for either purpose, especially for the purpose of neutralization. In accordance with this view, whether a large or a small amount of calcium is present in the blood will depend largely on the efficiency of the excretory processes in eliminating "dead" calcium either in the urine or in the faeces, and the amount present is no index of the available supply. Further than this, there are several automatic mechanisms for maintaining the calcium content of the blood at a constant and normal level. Hence estimations of the amount of calcium present in the blood do not afford a reliable index of the amount of calcium available in the whole body, either for the purposes of bone formation or for the neutralization of acid bodies—the question of dépôts comes into consideration.

Dr. Bengt Hamilton¹ has calculated that the total amount of calcium required for the purposes of internal metabolism in the infant—that is to say, for the neutralization of acid radicals—is about 0.200 gram in the twenty-four hours, and that unless this amount is afforded as income in the food or can be spared from the blood reserves the deficit must be made good by borrowing from the calcium dépôts of the body—that is, mainly from the bones themselves. Hamilton points to the interesting fact that at birth there are wide fluctuations in the amount of these reserves, and that the latter are generally stored up during the final two months of intrauterine life—an explanation which helps us to understand why premature infants are liable to develop symptoms of rickets at a very much earlier date than is usual in the case of full-term infants.

We know that in rickets, and indeed in conditions antecedent to the development of its manifest symptoms, there is always an increased output of calcium, mainly in the faeces, and to a lesser extent in the urine, and that this, in conjunction with the general depletion of the total calcium content of the body, is the most striking and constant factor in the pathology of the disease. No theory of the pathogenesis of rickets can be satisfactory which does not offer an explanation of these phenomena.

If, as Hamilton and Tobler maintain, the chief function of calcium in internal metabolism is to neutralize acid bodies, and that new bone will not receive the required quantity of this base until such vital needs have been satisfied, it seems probable that the solution to the problem will be found in discovering some common cause in all cases of rickets for an existing shortage of this base. An income of calcium which may be adequate for the neutralization of a normal production of acid bodies may be quite insufficient if the latter are produced in excess. If, therefore, among all the etiological factors of rickets we could find some common explanation of excessive acid production, or some common reason for default of calcium, we should have at least a logical basis of the pathogenesis, and we could then understand why on the same dietary one child will become rachitic and another remain in health, and also why, under similar conditions of environment, one child may develop symptoms of rickets while another may show none. I feel convinced that we can find in all cases of rickets, from whatsoever cause arising, definite reasons for explaining either an excessive acid production or a relative shortage of calcium—in other words, some definite disturbance of their normal relationships.

If the whole of the food consumed is used for physiological purposes and all its potential energy represented in the form of growth, heat production, work, or secretions, it is clear, on theoretical grounds at least, that no part of it can leave the body except in the form of completely

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oxidized and energy-free end-products—in other words, in the form of carbonic acid gas, urea, and water. In practice, however, there will always be some waste—that is, some products of incomplete combustion which will be represented in part at least by acid bodies of larger molecular size than CO_2 . Such acid bodies, unlike CO_2 , cannot be removed from the body without loss of the mineral bases which are required for their neutralization. This inevitable loss, in the case of babies, as far as calcium itself is concerned, is represented by 0.200 gram in the twenty-four hours—that is to say, if Hamilton's figures can be relied upon as accurately representing the irreducible minimum. In addition to this there will, of course, be a corresponding depletion of other mineral bases such as sodium, potassium, ammonium, iron, and magnesium. When, however, large amounts of acid are produced, correspondingly large quantities of calcium, as well as of other elements, will be requisitioned, and if they are not forthcoming in the food they must be withdrawn from the reserve dépôts.

If excess of food—that is to say, any amount over and above the existing physiological requirements—is consumed, there will be a corresponding increase in the production of acid bodies, and I propose now to explain how it is that all the known etiological factors in the production of rickets may lead to some disturbance of balance between the intake and output of energy.

The degree to which food consumed can be utilized in the body will naturally depend either on the amount of

depressed by deprivation of the essential stimuli, and the appetite still remains. The only possible alternatives to carbon dioxide production are: (1) storage, (2) non-combustion, or (3) semi-combustion of the food consumed. The limits of storage are restricted, non-combustion means albuminuria and glycosuria, while semi-combustion means the production of the intermediate products of metabolism, most of which are acid bodies which require neutralization.

It will be noted that most of the etiological factors of rickets are also depressants of metabolism, as is set out in Fig. 1.

Contrariwise most of the prophylactic and remedial measures which are employed in the treatment of rickets are also stimulants of metabolism, as shown in Fig. 2. Consequently I repeat that the obvious cause of rickets is a defective oxidation of the food consumed, with a consequent increased production of acid bodies which must be neutralized at the expense of basic elements, including calcium. It may be argued that there is not sufficient direct evidence to justify the acceptance of this very obvious theoretical line of reasoning; to this I can only reply that the most practical proof of an excessive production of acid bodies is the presence of an excess of ammonium-nitrogen in the urine; ammonium of all bases is the cheapest and most available, and one of the most characteristic features of rickets is an excess of ammonium salts in the urine, as has been shown by Dr. Amy Hodgson.² Further proof would, I am quite sure, be forthcoming if

DEPRESSANTS of METABOLISM.

FIG. 1.

food itself or on the physiological demand for its utilization—in other words, on the relationship of the intake and the output. Whether, therefore, any particular diet is excessive or not cannot be decided by arbitrary codes or diet tables. If the body is an efficient working machine, and the output of energy in the form of heat or work is correspondingly high, a liberal diet may not be physiologically excessive, whereas with a defective machine and a small output even a very exiguous diet may be relatively excessive. The efficiency of the machine itself will depend on a great variety of antecedent conditions—its innate qualities, and the uses to which it has already been subjected; hence we can well understand why hereditary, ante-natal, and previous environmental conditions play a part in the existing output of energy, in the fate of the child, and in the etiology of rickets. Without any change in the machine itself the actual output of energy will in large measure depend on the circumstances under which it is working—that is to say, on the environment and on the stimuli for activity which the latter affords. In the case of the child such stimuli are not exclusively physical; many of them are of a psychological character, and hence we can understand how it is that such influences as joy, pleasure, play, sunshine, opportunities for exercise, and exposure to fresh air can be etiological factors in rickets. In this connexion I would especially direct attention to the influence of cool air in stimulating metabolism. Dr. Leonard Hill has proved that the output of carbon dioxide, which is an index of metabolism, may be doubled by exposing the child to the open air.

Although under such conditions appetite is increased and more food consumed, it may well be asked what happens to the food when the metabolic processes are

STIMULI of METABOLISM.

FIG. 2.

the degree of depletion of the alkaline reserves of the blood were to be consistently estimated in cases of active rickets. Clinically there is abundant evidence of such depletion, especially in the crises which complicate severe cases of the disease. Theoretically the alkaline treatment of rickets, by affording substitutes for calcium as neutralizing bases for acid products, ought to be most efficacious; and so in my experience it is, but to be effective it must be continuously employed as long as acid bodies are formed in excess. Such treatment by calcium spacers if spasmodic or intermittent will fail.

Since calcium is not readily excreted by the kidneys but mainly by the bowel, we must search the faeces for evidence of this base in combination with acid bodies, and here again we find the expected result, for calcium soaps present in excess are a striking feature of the rickety and pre-rickety condition. Such soaps may be, and probably are, excretions from the blood, and represent the defective oxidation of fats rather than the surplus of fat which has never been absorbed and passed through the processes of internal metabolism.

It is not always easy to understand why all the known factors of rickets impair the efficiency of the body as a working machine and thus limit the output of work. Some of the dietetic causes may owe their results to the withholding of certain elements necessary for the performance of certain special functions. For instance, iodine starvation may depress the metabolic processes by depriving the thyroid gland of the particular element which is necessary for the elaboration of its specific secretion. On these grounds we can understand how it is that certain authorities have regarded rickets as the result of thyroid defects; and even in the light of more recent knowledge there

seems to be no reason for excluding in exceptional cases the thyroid from all participation in the disease. For the thyroid secretion is the great stimulator of the metabolic processes.

If these views on the pathogenesis of rickets are well founded, it seems illogical to expect that there can be one cure for the condition; each case, in accordance with its own particular etiology, must be treated on specific lines. It would be unreasonable, for instance, to expect good results from treating a case of rickets due to carbohydrate excess on the same basis as one due to a chronic infection or vitamin starvation. The specific treatment of rickets lies in the specific treatment of the contributory factors, although the symptomatic treatment of the resulting mineral depletion certainly lies in the adequate supply of available calcium salts, and in alkali therapy.

I have drawn up a schematic diagram (Fig. 3) to show the common etiological factors of rickets in such a way that their contributions to the common end-result may be easily visualized. These various factors are arranged in

FIG. 3.

groups. Like a vast watershed they afford their respective contributions of acid products to the common reservoir—the blood—which is indicated in the centre of the figure.

The clinical picture of any given case of rickets must be just as composite as the etiological factors which are responsible for its production. The symptoms and the general clinical picture of a case which is due to vitamin starvation, or calcium inanition, will be quite different from a case due to carbohydrate excess or a chronic infection, although they may have certain symptoms in common—namely, those which are due to the resulting acidosis.

Since almost every variety of malnutrition, either acting alone or in combination with others, can lead to one and the same end-result, we can easily understand why there has been so much confusion between the symptoms proper to the rickets condition and those due to the contributory causes—a confusion which is really one between cause and effect.

In conclusion, I would once again repeat that the essential basis, or the *causa vera*, of rickets is most probably a relative excess of acid bodies produced in the system by a disproportion between the intake and the output of energy—a condition which results either from an innate inefficiency of the body machine itself, or from defects in the environment, the latter being regarded as including the quantity and the quality of the food as well as the character of the stimuli afforded by the hygienic surroundings.

REFERENCES.

- ¹ *Acta Paediatrica*, vol. ii, fols. 1 and 2. ² *Lancet*, 1921, ii, p. 945.

NEPHROPTOSIS: ITS CAUSATION, SYMPTOMS, AND RADICAL CURE.

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ABOUT thirty years ago Dr. Suckling of Birmingham was led to the conclusion that, as many cases complaining of nervous dyspepsia, neurasthenia, and depression had also movable kidney, there might be in these associations more than a casual relationship. His further investigations convinced him that the renal displacement and the nervous disturbances stood in the relation of cause and effect. When my attention was first drawn to Dr. Suckling's work, published in 1907, I had already seen and treated many cases in the usual way. In consequence of the striking results disclosed in his work, I decided to operate on all suitable cases.

CAUSATION.

Movable kidney may be classed under two heads: (1) accidental; (2) constitutional or congenital. Cases of the first class are usually due to accident or injury of a crushing nature, and are easily diagnosed by the history and acute symptoms. The second class comprises the vast majority of all cases, varying from the least increase of the normal mobility to the complete dislocation of the organ from its anatomical site.

To account for the fact that many more women than men suffer from nephroptosis various explanations have been advanced—such as frequent pregnancy, loss of flesh, loss of intra-abdominal pressure, chronic constipation, chronic cough, etc.; but these causes do not account for more than a small percentage of the cases I have seen. I am convinced that there is something in the anatomical formation of women which is the primary physical origin of the condition. I suggest that there is a congenital or family defect of shape of the renal pouch, which predisposes to an easy descent of the organ, and that there is some inherent weakness in the suspensory tissues which disposes them to stretch easily. Can we deny the hereditary influence, in tone of tissue, while admitting it in type of outline of body, in temperament, and in nervous responses? I am strongly disposed to consider the larger proportion of cases as directly due to some transmitted congenital defect. In support of this I would cite the instance of a father with double nephroptosis and two daughters with a similar condition; another of a mother and two daughters; and at least twenty cases of sisters. Suckling states that he has often found movable kidney in children, and that he is inclined to the view that it is hereditary and congenital. Billington and Pardhy confirm this observation.

Volkow and Dilitzin state that the paravertebral niches in which the kidneys rest are shallower and more open below in women than in men. This observation is supported by Morris, who examined one hundred men and found movable kidney in two only, and in a series of operations by him for this condition ninety-six were upon women and only two upon men.

In addition to the congenital tendency and anatomical defect in the formation of the renal pouch, there are contributory causes, of which the most important are nutrition and occupation. A large proportion of my cases in the Samaritan Hospital have been operatives from half-time age. Inquiries from doctors in large practices in other manufacturing towns confirm my view that the too early employment of girls in occupations causing long standing and weight carrying is an important causative factor. Another contributory cause which has been suggested is repeated pregnancy, but I believe it to be a negligible factor, for over 50 per cent. of my cases were unmarried or non-parous, and I have examined many mothers of large families and found no displacement. Loss of intra-abdominal pressure may, in some cases, aggravate the condition, but is never its cause. Other alleged causes are tumours of the kidney and calculi, but I do not attach much importance to them. Were nephroptosis the result of accident, physical strain, etc., we