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Is there more than one kind of rickets?¹

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I. CLINICAL OBSERVATIONS SUGGESTING THE EXISTENCE OF MORE THAN ONE KIND OF RICKETS.

For at least two years our attention has been attracted to the possibility that there might be more than one kind of rickets. We were led to think of this possibility as the result of the consideration of certain peculiar manifestations of the disease and associations with other diseases. The facts are as follows: Rickets occurs with great frequency in premature children, even when breast fed. It seems to affect the head more than the extremities or ribs. In a group of cases of rickets the disease shows an especial tendency to involve the shafts of the long bones declaring itself clinically by the occurrence of multiple fractures from trivial causes. There is a curious association between rickets and certain forms of secondary anemia (the so-called alimentary anemias and

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the anemias of the von Jaksch type). The rachitic involvement of the head in the children suffering from the combined conditions appears to be out of all proportion to the involvement of the extremities. Rickets is associated with the most severe forms of chronic interstitial nephritis or developmental defects of the kidney in which there is the most extreme degree of disturbance in renal function. Curiously, tetany sometimes occurs with rickets and sometimes not. Since the conception that there might be more than one kind of rickets was supported solely by clinical observations of at most a suggestive character, we did not feel at liberty to express it as a definite hypothesis. Recently, however, our experiments have yielded results which indicate that there may be two distinct forms of the disease.

II. THE EXPERIMENTAL EVIDENCE.

In previous publications¹ we have described certain defective diets which, when fed to the young rat, produced marked disturbances in the growth and calcification of the skeleton. The diets in question were all insufficiently supplied with a factor or factors present in cod liver oil. They differed from each other considerably, however, in the composition of their mineral fraction, chiefly, however, as regards the calcium and phosphorus. They may be divided into two groups according to the relative amounts of those two elements present. In one group, the phosphorus was at a low level but the calcium at or above the optimal level; in the other group, on the other hand, the calcium was at an extremely low level but the phosphorus was not far from the optimal.

When the diets of the first group (the phosphorus being deficient and the calcium-phosphate ratio high) were fed to young rats living under ordinary laboratory conditions (room light), there developed a diseased condition of the skeleton which was identical in all essential particulars with that seen in the rickets

¹ McCollum, E. V., Simmonds, Nina, Parsons, H. T., Shipley, P. G., and Park, E. A. *Jour. Biol. Chem.*, 1921, xlv, 333.

Shipley, P. G., Park, E. A., McCollum, E. V., and Simmonds, Nina. *The Johns Hopkins Bulletin*, 1921, xxxii, 160.

McCollum, E. V., Simmonds, Nina, Shipley, P. G., and Park, E. A. *Amer. Jour. of Hygiene*, 1921, i, 492.

McCollum, E. V., Simmonds, Nina, Shipley, P. G., and Park, E. A. *Jour. Biol. Chem.*, 1921, xlvii, 507.

of human beings. The costo-chondral junctions were greatly enlarged; in some animals the thoracic wall was sunken at the sites of the costo-chondral junctions and the shafts of the ribs were fractured. The long bones of the extremities were enlarged at the ends; they could be cut and broken easily. Between shaft and cartilage lay a yellowish zone two to three mm. deep, the rachitic metaphysis. The proliferative cartilage extended in irregular prolongations toward the shaft. Calcium deposition in the cartilage was entirely lacking or extremely defective. The intermediate zone between cartilage and shaft presented the picture typical of the metaphysis in the bones of rachitic children. It was composed of cartilage in all stages of metaplasia or degeneration into a material indistinguishable from the osteoid, trabeculae consisting of osteoid, blood vessels bordered by marrow elements, scattered, irregular deposits of calcified material incased in osteoid, and connective tissue. All were intermingled in a disorderly manner. The trabeculae of the shaft were surrounded by broad investments of osteoid.

When the diets of the second group (the calcium being deficient, the phosphorus at a level not far from the optimal and the calcium-phosphate ratio low) were fed to rats kept under ordinary laboratory conditions (room light), there developed a diseased condition of the skeleton which also bore marked resemblances to the lesions found in the rickets of human beings. The gross deformities caused by the second group of diets were as great or greater than those caused by the first group and corresponded exactly to the deformities found in rachitic children. The thorax was even more deformed than in the rats fed the diets of the first group; it was flattened from side to side and marked at the sides by deep grooves following the costo-chondral junctions; the angular deformities produced by the costal cartilages and the shafts projected into its interior; the costo-chondral junctions were enlarged and greatly distorted; fractures in the shafts of the ribs were especially numerous. The lower ends of radius and ulna were enlarged as were also the ends of all the long bones of the extremities. The bones were extremely soft and weak. Between the cartilage and the shaft was a white intermediate zone one to three mm. deep. Microscopic examination showed that the cartilage was entirely

free from calcium or nearly free from it and was invaded in an irregular manner by the vascular elements of the shaft. In consequence the cartilage extended toward the shaft in irregular prolongations. The cells of the cartilage in proximity to the shaft showed evidences of degeneration and metaplasia. The intermediate zone was composed of cartilage in a more or less degenerated state, osteoid trabeculæ, blood vessels surrounded by marrow elements, a few deposits of calcium for the most part situated near the periphery and connective tissue. The trabeculæ of the shaft were bordered by rather broad zones of osteoid. A loosely arranged fibrous tissue invested many of the trabeculæ. In those places in which it filled in the spaces between them, it gave rise to histological pictures which closely resembled those presented by the fibrous marrow in the rickets of human beings.

The pathological condition induced in the bones by the diets of the second group did not, however, exactly correspond at all points to that usually found in the human subjects of the disease. The cartilage was invaded and its columnar arrangement was disrupted to a less extent than is commonly the case in the rickets of human beings. The metaphysis was composed in larger part by osteoid trabeculæ. Though these osteoid trabeculæ were free from calcium deposition, they, nevertheless, retained a certain semblance of orderly arrangement. The osteoid zones about the trabeculæ were not so broad as in the rats on the diets of the first group, though they were quite as broad as the osteoid borders in the bones of rachitic children. Cells evidently derived from the fixed tissues with large basophilic granulations were numerous in the immediate vicinity of the trabeculæ. Resorptive activity was exceedingly marked. In the fundamental respects, however, in particular, degeneration and metaplastic changes in the cartilage, defective calcification of the cartilage and trabeculæ and the consequent osteoid production, the irregular invasion of the cartilage and the production of a rachitic intermediary zone, the pathological conditions produced by the faulty diets of the second group corresponded to the rickets of human beings. While one of the diets in question, diet 2638, did not give constant results, in some animals it produced a pathological condition corresponding to that found in human rickets even in its minor details.

III. DISCUSSION.

Our experiments make it clear that in the rat, when deprived of certain active light rays and an unidentified factor contained in cod liver oil, a pathological condition corresponding in all fundamental respects to the rickets of the human being can be produced through the diet in two ways; it can be produced (1) by diminishing the phosphorus in the diet and supplying calcium in excess of the optimal or at the optimal concentration, or (2) by reducing the calcium but maintaining the phosphorus at a concentration somewhere near the optimal. In the former case the calcium-phosphate ratio in the diet is large, in the latter case it is small. We have not the slightest doubt that in the human being similarly deprived of active light and the unidentified factor it would be possible to produce true rickets through a manipulation of the calcium and phosphorus of the diet in the two ways mentioned. As the result of our experiments we are led to believe, therefore, that there are two main forms of rickets, one characterized by a normal or nearly normal blood calcium and a low phosphorus, the calcium-phosphate ratio being high, the other by a normal or nearly normal blood phosphorus but a low calcium, the calcium-phosphate ratio being low. Between the two forms there are probably innumerable intermediary forms marked by calcium-phosphate ratios which are less effective in preventing calcium-phosphate deposition. Diets with these intermediary ratios manifest themselves pathologically as rickets in various stages of healing or of healing and relapse or as slight disturbances of calcification of the skeleton which have more or less remote resemblance to rickets.

At one time we were under the impression that tetany sharply marked off one form from the other, *i.e.*, that the two main divisions of rickets were ordinary rickets and the rickets of tetany. The investigations of Howland and Kramer¹ have shown, however, that tetany *in a latent* form, at least, may be associated with the low phosphorus form of the disease. Though tetany may occur with the low phosphorus form, however, it is probably regularly associated with the low calcium form and may be regarded as a

¹ Howland, John, and Kramer, Benjamin. *Amer. Jour. of Dis. of Child.*, 1921, xxii, 105.

symptom of the latter. The low calcium form of rickets is, generally speaking, the rickets of tetany. Tetany may of course occur independently of rickets. If tetany persists long enough, however, evidence of defective calcification of the skeleton would almost certainly develop.

On theoretical grounds entirely, we think it possible that the rickets which develops in the youthful subjects of the severe functional derangements of the kidney may belong to the low calcium form of the disease; in other words, that the rickets in these patients may be truly endogenous in origin depending primarily on the inability of the kidney to excrete phosphorus. If this view proves to be correct "renal dwarfism"¹ is in reality renal rickets and ought so to be called and regarded.

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Variations in aliquot fractions of gastric contents.

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Aliquot fractions obtained by the Rehfuß method of fractional gastric analysis do not accurately represent the total gastric contents, as indicated by the results of the following experiments on subjects showing no clinical evidence of gastric disease:

1. Instead of the usual periodic aspiration, the total gastric contents were removed after three quarters of an hour by withdrawing 10 c.c. fractions in rapid succession. A wide variation was found in the acidity of these fractions, indicating that the total gastric contents are not a homogeneous mixture and that a single 10 c.c. sample is not a valid aliquot. This was more noticeable in subjects having a high rather than low gastric acidity.

2. (a) By inserting *three* Rehfuß tubes in one individual and aspirating the fractions simultaneously at fifteen minute intervals, it was found that there was considerable variation of acidity in different parts of the stomach at the same moment. X-ray pictures established the relative position of the tubes.

¹ Barber, Hugh. *Quart. Jour. of Med.*, 1921, xiv, No. 55.