STUDIES ON EXPERIMENTAL RICKETS.*

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RICKETS has become so familiar in hospitals and dispensaries that in many cases no attention is paid to the disease. The spontaneous recovery of many of the patients has induced a *laissez-faire* policy in its treatment on the part of many physicians.

For the past forty years sporadic attempts have been made to reproduce rickets in laboratory animals by means of the various agents which have been suspected of causing the disease. Some investigators have tried to reproduce it by extirpation of various endocrine glands. Others have tried keeping their animals under bad hygienic conditions, or infecting them with micro-organisms. Perhaps, however, the greatest number have attempted to reproduce rickets by feeding their animals on diets which were in one way or another unsatisfactory. The lack of uniformity in their results is easily explainable in the light of our present knowledge of nutrition. It has only very recently become possible to analyze a diet with sufficient accuracy to know how and to what degree it deviates from an optimal standard. For example, an animal which is fed on starch and horse meat is, as it was thought fifteen years ago, receiving a diet which is low in calcium, but we know now that such a diet is also deficient in fat-soluble A and water-soluble B, and is relatively high in phosphates. Therefore, attempts in the past to produce rickets by the diet, although they were successful in some cases, have been fruitless as far as discovering the cause of the disease is concerned.

Fifteen years ago we were taught that the daily food must contain protein, fat, carbohydrate, and the ions Ca, Na, K, Mg, Cl, Fe, S, P, and I. The latter substances, with the exception of sulphur, which had to be taken in the form of cystin, could be utilized by the body as inorganic salts. We know today that there is a considerable variation in the nutritive value of different proteins. It is generally accepted, moreover, that there are certain other substances which must be present in the food if the organism is to maintain health, growth, and function. These are the so-called vitamins or accessory food substances—fat-soluble A, water-

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soluble B, and water-soluble C. It is generally conceded that the absence of these substances from the diet is the cause of certain syndromes which have received the name "deficiency diseases." Xerophthalmia results from a deficiency of the fat-soluble A, polyneuritis from a lack of water-soluble B, and scurvy appears as the result of insufficient intake of the water-soluble C. These are the so-called "deficiency diseases," and many investigators have been disposed to add others to the list—pellagra, mucous colitis, chronic intestinal indigestion, intestinal infantilism, and rickets. Rickets is not a deficiency disease in this restricted sense. It is a condition which results from faulty metabolism,—usually, but possibly not always,—caused by a faulty diet.

We have chosen the rat as an experimental animal because of its omnivorous habits, the ease with which a large colony may be maintained, its short span of life, and period of gestation and lactation. All of our experiments have been carefully controlled as regards hygiene, illumination, and exercise.

It is necessary to stop a moment here to discuss rickets as it occurs in children. In the first place, we must appreciate the fact that while the physical pathological manifestations of rickets are largely confined to the skeleton, the disease involves the whole organism. There can be no other interpretation of the loss of muscle tone, the profuse head sweats, the gastro-intestinal disorders, and the apathy or fretfulness of the rachitic child. The pathology of the bone I shall not discuss here, but the pathology of the blood is not so well recognized, and deserves attention. Howland and Kramer found that the calcium in the blood serum of the children averages 9-11 milligrams per hundred cc.; the phosphate of the serum averages 4-6 milligrams per hundred cc. Children with rickets as it is ordinarily seen show little if any reduction from the amount of calcium in the blood, but the phosphate, on the contrary, may be reduced as low as 1 milligram per 100 cc. Children may be seen with rickets, however, whose blood serum shows a marked reduction in the serum calcium, the serum phosphate remaining at or about the normal level. If the serum calcium of these children is below 5 milligrams per 100 cc., the rickets is complicated by manifest tetany. We say that latent tetany is present if actual manifestations of tetany are not found in a rachitic child with a low serum calcium. Healing of rickets is accompanied by the restoration, on the one hand, of the normal phosphate level; on the other, of the normal calcium content of the serum. Now, when rats are fed on diets of purified foodstuffs it is possible, when an uncharacterized organic substance which is contained in certain fats

is insufficiently supplied, to induce rachitic changes in the skeleton in either one of two ways. The diet may be low in phosphorus but high in calcium, or may contain an approximately normal amount of phosphorus and be low in calcium. In other words, there is a level on either side of a normal calcium-phosphate balance at which an abnormal calcium-phosphate ratio of the diet may result in rachitic changes in the bones. In the rat, then, there are two sorts of rickets, one of which results from a diet, *caeteris paribus,* low in phosphorus; one which follows the administration of a diet, *caeteris paribus,* low in calcium. It would seem as if the same thing might be true of children. Normal growth of bone depends on the maintenance of a normal ratio between the two ions,—not on the absolute amount of either in the food. The fact that a perfectly normal bone may be produced on diets which are low either in calcium or phosphorus, providing that the level of the other ion is proportionately depressed, shows that the rachitic lesion is really dependent on the ratio of calcium to phosphorus. There is an optimal level, however, for both ions, and when the balance in the diet is maintained at this point the optimal growth of the animal is assured, provided all other factors of a complete diet are sufficiently supplied. Below this point the salt content of the food may become to some extent a limiting factor as far as growth is concerned.

The optimal amount of calcium which the diet can furnish for growth, maintenance, and function in the rat has been shown to be 641 milligrams per 100 grams of ration, all other factors of the diet being satisfactory. The amount of phosphate has not been so well worked out, but it is about 493.6 milligrams per 100 grams of food. A diet containing 832 milligrams of calcium and 305 milligrams of phosphate produces a lesion which exactly corresponds to the severest form of rickets seen in children. Such an animal will have 10 milligrams of serum calcium per 100 cc., which is the same that a normal rat would show. The blood phosphate for a rachitic animal of this, the low phosphate, type, will be 2.5–3 milligrams per 100 cc.; that of a normal rat will be 8 milligrams per 100 cc. If now an animal is fed on a diet in which the calcium is reduced to 52 milligrams per 100 grams of ration, the phosphorus remaining at 364 milligrams, a lesion also results which presents all the essential characteristics of rickets. The blood of such an animal will contain ca. 4.5 milligrams of calcium and 8–9 milligrams of phosphorus.

The rôle of the fats in rickets. In May of 1921 we published an article which showed that a deficiency of fat-soluble A does not produce rickets, providing the required salt balance is maintained in the food. This has

been since confirmed by numerous investigators. A deficiency in this vitamin is followed by a cessation of growth and a condition of osteoporosis develops. There is, however, a substance present in cod-liver oil, and to some extent in butter fat, which enables an animal to compensate for a faulty calcium-phosphate ratio in the food. This substance is not the same as fat-soluble A. This uncharacterized organic substance is present, according to Zucker, in the unsaponifiable fraction of cod-liver oil. It is present in butter fat and coconut oil, as well as in cod-liver oil, but to a much less extent. Thirty per cent. of butter fat is not the equivalent of 2 per cent. of the diet in cod-liver oil, which will prevent the development of rickets on a rickets-producing diet, and in five days will usually cause visible signs of healing to appear in the bones of a rachitic rat. It will cause healing of the low calcium, as well as of low phosphate rickets. In the low phosphate form of rickets the administration of 2 per cent. of cod liver oil for fifteen days causes the phosphate in the serum to rise from 3 milligrams to 5 milligrams per 100 cc. Howland and Kramer, who have made the studies of the blood which I have quoted, have shown that exactly analogous changes occur in the blood of children under analogous conditions.

Another influence which enables the organism to compensate for unfavorable calcium-phosphate ratios is light—from the sun or the mercury vapor lamp. Huldschinsky was able to demonstrate healing in the bones of rachitic children after radiation with the mercury vapor lamp, and we have found that radiation with sunlight, the mercury vapor lamp, or the Fe-Cr, or Cd arcs, prevents the development of rickets in rats although they are maintained on diets which would cause rickets to develop without fail without the influence of radiation. Such radiation will induce healing in rachitic animals without change in the diet, and causes much the same changes to occur in the salts of the blood serum which follow cod-liver oil therapy. Radiated animals which have been treated with the light of the Cd arc under the same conditions as those which obtained in treating others with the Fe-Cr arc and the mercury vapor lamp, show more advanced healing than the other groups. Filtering the light through window glass removes the protective rays. These facts would make it seem as though the beneficial rays were of the shorter lengths of ultraviolet. From these facts it will be seen that consideration of natural illumination must in the future modify the dietary of miners, convicts, and those who from necessity or ignorance are deprived of light. Individuals who are exposed to full daylight can get on normally with the diet which in the absence of radiation would be

extremely defective. Light, though it protects against and cures rickets, has no demonstrable influence on the appearance of xerophthalmia.

The last consideration which modifies the results of a rickets-producing diet is starvation. Starvation will precipitate in three days an extraordinary degree of healing in a rachitic animal and this healing is accompanied by a marked rise in the blood phosphate. It might be supposed that this might be the result of the restoration of a normal calcium-phosphate balance when the body is left to draw its supplies of these ions from its own tissues. This is, however, not the case. The phosphate of the blood rises from the rachitic level of 3, to 12 mgs. per 100 cc., which is double the amount of the normal blood phosphate. This may be the result of tissue destruction and the release of phosphate from disintegrated muscle tissue.

To sum up, (1) rickets is a disease of metabolism usually due to faulty food. 2. It may be produced in rats by certain diets containing an improper balance between calcium and phosphorus, when an uncharacterized substance associated with certain fats is absent or deficiently supplied. 3. There are two sorts of rickets in rats, one a low calcium type, produced by diets relatively low in calcium, but containing an approximately normal amount of phosphorus, other things being equal, and second, a low phosphate type, produced by diets deficient in phosphorus, with a normal or high calcium content. 4. Some uncharacterized organic substance, which is present in abundance in cod-liver oil, enables the organism to compensate for a defective calcium-phosphate ratio in the food. 5. Exposure to sunlight or to the rays of the mercury vapor quartz lamp will do the same thing. 6. Either of these factors will induce healing in the bones of rachitic animals. 7. Starvation also will induce healing.

These investigations so far leave a great many questions still unsettled. Some of them we are in a position to answer; others await further study.

DISCUSSION OF DR. SHIPLEY'S PAPER.

DR. R. B. OSGOOD, Boston: The paper this morning by our distinguished guest, Dr. Jansen, and this most interesting and extremely stimulating paper by Dr. Shipley started so many thoughts that I hardly know where to begin to comment on the work. This work that Dr. Shipley has brought out gives us some of the causes of this disturbance and shows us how treatment should be administered. As he says, the work has just begun. Starting with the

theory that there is a nutritional deficiency either in quantity or in the proper ratio of calcium intake, we must at once think of other diseases besides rickets, the etiology of which these investigations may partially solve. Possibly we still do not know whether there is such a disease as that called adolescent rickets. Dr. Freiberg says positively there is. His experiments seem to show that adolescent rickets is amenable to the same kind of treatment —I think he said cod liver oil—to which this experimental rickets is amenable. Then we have osteomalacia, a deficiency disease or a hunger disease, as the Germans suggest. This seems to be very common as a result of the war. Then we do not know how far we shall go toward solving the problem of osteitis fibrosa cystica or how far toward solving osteitis deformans or perhaps even Dr. Barrie's hemorrhagic osteomyelitis. There are suggested many problems which we shall ask Dr. Shipley to investigate in the next hundred years in connection with rickets.

I do not know how many of you have seen the book written by Mr. McCann. He recites the history of a ship's crew who all came down with what was called beriberi. A diet rich in vitamins was administered and all these so-called beriberi cases got well.

Dr. Jansen's paper is most stimulating as representing an almost philosophical approach to the problem of etiology of rickets and the bearing of heredity.

The work of Dr. Percy Howe of Boston has interested me greatly in relation to the possible infectious etiology. He has considered pyorrhoea as a deficiency disease rather than an infection. He has carried out some experimental work in which he has fed guinea-pigs a certain diet, following which they have exhibited various bone and joint disturbances which seem to resemble the changes we have associated exclusively with the infectious type. Then by simply changing the diet, the pigs become perfectly free from these joint symptoms.

All this subject is, of course, too wide for anybody to discuss. I wish to thank Prof. Jansen and Dr. Shipley most heartily for their papers.

DR. FRANK E. PECKHAM, Providence, R. I.: This paper is very important to the orthopaedic man. Children are being brought in increasing numbers for orthopaedic conditions which seem to be directly due to faulty metabolism. Probably it is the calcium salts which are at fault, as Dr. Shipley has brought out. In treating these cases, that certainly should be taken into account. For instance, it was only within a few days that a slightly knock-kneed and flat-footed little fellow, dragging one leg, was brought into my office. The physician who referred him to me had first referred him to a neurologist. It was simply a case where the calcium metabolism was at fault. There was the knock-knee, flat-foot, and dragging leg. The treatment of this may be mechanical to a certain degree, but it should be largely a dietetic treatment.

This study which Dr. Shipley has applied to rickets is also applicable to other deficiency diseases. There are lots of these children and they seem to be increasing in numbers, so it is brought to one's attention that something is radically wrong with the nutrition. I do not know who is to blame for it, but that element has to be taken into account. Another very important thing is that in these children the resistance to disease is lowered. I may be wrong about the statistics, but as I understand it there are about a half million children under ten years dying every year in our country because they have not the resistance to put up against the diseases which attack them. Now this lessened resistance in young life is due to some factor, and the points brought

to our attention by Dr. Shipley are of great importance. I want to thank Dr. Shipley personally.

DR. PAUL SHIPLEY, Baltimore (closing the discussion): It may be that I have perhaps unintentionally overstated the dietary side of disease in childhood. In considering diet in relation to disease I should like to say that we have to remember that, as Dr. Jansen said to you a few minutes ago, there are many other agents which aid in the production of illness which apparently is caused and remedied by changing the diet of the child. Col. McCarrison in India has shown—and the point should be emphasized—that faulty nutrition may, by lowering the resistance of the organism to invading bacteria or to other factors of which we at present know nothing, contribute to many diseases which we are accustomed to consider of parasitic origin. It would, however, be a grave error to insist that, because the manifestations of these conditions appear coincidentally with the administration of a bad diet and are alleviated or cured by a good one, the conditions are the result of a bad diet alone. It is time that a warning should be uttered against the rising tendency to attribute disease after disease to nutritional faults. "Avitaminosis" is becoming a fad and is forming a base for the operations of quacks, nostrum venders, and misguided enthusiasts. Dr. Osgood has just now mentioned Riggs's disease as a pathology which has origin in an unfortunate dietary. While pyorrhea certainly follows the ingestion of faulty food, the diet is probably not the sole factor in the production of the disease. The resistance of the tissues, the local and general resistance, is lowered by the faulty diet, and the body is no longer able to take care of the invading organisms, which under normal circumstances it would cope with quite effectively. These organisms are allowed to carry on their work of destruction and produce an apparently inflammatory disease which in many cases is, however, remedied by restoring the diet to the optimal level and so enabling the body to realign its forces against the invading organism. There are probably other factors as well as bacteria which are allowed to work out their harm when the resistance of the organism is impaired by faulty diet. I am quite certain that the whole story of scurvy is not yet told. I am equally certain that we are not as well informed concerning beriberi as we might be. It is equally possible that there are other factors besides nutritional ones operating to produce rickets. All one can say now of rickets is that diets which are faulty in certain respects when fed to animals, are followed by the appearance of the disease. This has held through three years of careful experimental work, but as I mentioned at the beginning, we cannot tell whether these diets behave as chemical reagents, whether they act indirectly on the body as a whole, or whether they lower the resistance of the organism to some morbific agent of which at present we have no conception.

I want to thank the gentlemen who discussed this paper and the members of the American Orthopedic Association in my own name and in the name of those who have collaborated with me.