EXPERIMENTAL CRETINISM

I. A RACHITIC-LIKE DISTURBANCE IN EXTREME HYPOTHYROIDISM

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Findly (1908) and Mellanby (1919) clearly demonstrated that rickets occurred in young animals fed on a diet containing an insufficient amount of certain substances now known as the "antirachitic vitamine." As a result of this, the British Medical Research Committee announced that rickets is a deficiency disease due to a lack in the diet of an anti-rachitic factor. For literature up to 1923, covering the etiology of rickets with special reference to dietary deficiencies, the curative values of cod liver oil and of ultraviolet radiation and the importance of the salt composition of the diet in this disease, the reader is referred to the excellent reviews of Korenchevsky (1921) and of Park (1923).

Inasmuch as the present report deals entirely with disturbances in the growth and calcification of the bones of young rabbits, due to causes other than dietary factors, brief mention should be made of the literature on the etiology of rickets dealing with the problem from other aspects than dietary deficiencies. Park and McClure (1919) reviewed the literature on the effects of thymus extirpation on young animals and report results of their own findings on 24 out of 75 thymectomized puppies; 19 control dogs from four different litters were used. These authors present photomicrographs of the long bones and ribs of their experimental animals and conclude that no signs of rickets appear at the junction of the cartilage and shaft, and that extirpation of the thymus does not influence growth or development but the possibility of a retardation in development or a delayed closure in the epiphysis cannot be absolutely excluded. Park and McClure did not make chemical analyses of the calcium and phosphorus content of the blood.

Relative to the influence of the pancreas on the production of rickets, Park and McClure (1919) state that "Pawlow observed pathological conditions of the skeleton in the nature of osteomalacia after various kinds of operations in the pancreas region and after the production of intestinal

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fistulae, and Fisher and Looser, after operations on the bile ducts.” Betke (1915) removed both carotid bodies and describes changes in growth and the production of rickets resulting from his experiments. Korenchevsky (1922) reviews the literature on the influence of parathyroidectomy on the skeleton of animals normally nourished and on rickets and osteomalacia produced by deficient diets. Korenchevsky shows that the histological pictures through the costochondral junctions of his three rats parathyroidectomized and receiving a normal diet did not differ essentially from those of the control animals. One of these showed a very slight amount of increase in the endothelial osteoid tissue and a slight osteoporosis and narrowing of the proliferating cartilage which was completely impregnated with calcium.

An undersized condition has been described in children and young adults, which is accompanied by a severe form of chronic interstitial nephritis or developmental defects of the kidneys. These subjects had rachitic deformities. This syndrome has been called renal dwarfism.

Hofmeister (1894), (1896), (1897-1898) successfully thyroidectomized young rabbits and noticed a retardation in the growth of the long bones as determined by actual measurements of the tibia and ulna, and a delay in the disappearance of the epiphysis. Hofmeister gave the name of chondrodystrophia thyreoprevia to this condition and declared it to be identical to chondrodystrophia foetalis. He also states that histological section through the epiphysis presents the same picture as the so-called fetal rickets. This author also cites a clinical case of Kocher dating back to 1883, where post-mortem findings reveal a disturbance in the development of the epiphysis of a girl aged 20 and thyroidectomized at 11 years.

If we except the experiments of Park and McClure on the thymus and of Korenchevsky on the parathyroids we find that in most instances no consideration has been taken of dietary or hygienic influences on the production of rickets, where this condition is said to occur as the result of some glandular or operative disturbance. In most instances the reports were published before the importance of the diet and environmental conditions had been experimentally demonstrated. With these factors well known, the present investigation was planned to determine whether or not thyroidectomy in the very young rabbit living on a diet adequate in every respect for normal rabbits, would result in disturbances in the developing skeleton other than a diminution in growth.

**Experimental.** Young rabbits between 2 and 3 weeks after birth were thyroidectomized according to the method outlined by Hofmeister (1894) and described in detail by Tatum (1913) and by Basinger (1916); one or two rabbits from each litter were not thyroidectomized; these served as controls and received exactly the same diet and were subjected to the same environmental conditions as their thyroidectomized litter mates.
In most instances control and cretin occupied the same cage. The dietary consisted of unrolled oats, an abundance of high grade alfalfa leaf, carrots, and a small amount of yellow corn, with water ad libitum. The rabbits were housed in a moderately well-lighted laboratory, but (with some exceptions which will be explained later) were not exposed to the unfiltered rays of the sun.

The evidence we present was obtained entirely from the operated animals which actually suffered from marked thyroid deficiency during the growing period as determined from a comparison of the growth curves of the operated animals and the normal litter mates. An apparently complete thyroidectomy very frequently results in little or no thyroid deficiency due, presumably, to accessory thyroids or to hyperplasia of a few thyroid cells which remained after the operation. The growth curve of such animals during the first three months after operation approximates the curve of a normal rabbit. Such animals were discarded from the experiment. Occasionally an animal shows marked thyroid deficiency during the first three months after operation but later grows fairly well, due
perhaps to more effective functioning of accessory glands or hypertrophied thyroid tissue. These animals also show marked disturbance in bone development which results in permanent deformities (see fig. 1, D).

From the spring of 1923 up to the present time (June 6, 1927) 404 rabbits out of a much larger number of thyroidectomized animals have shown marked thyroid deficiency and were chosen for the study of rickets in experimental cretinism.

The gross findings of these animals which indicate a disturbance in the development of the skeleton consist chiefly in marked dwarfing of growth, flatfooted posture, bowing of the forelegs, lateral displacement of the clavicles, bulging of the occipital and parietal bones and marked kyphosis. In addition to this the animals early (4 to 8 weeks after operation) developed a pronounced potbelly and later (3 to 4 months after operation) the coat became shaggy and the skin covered with scales as described for cretin condition in rabbits (Hofmeister, Tatum, Bassinger).

Roentgenograms of the fore legs of a cretin five weeks after operation, and its control litter mate are shown in figure 3, A and B. In the cretin the following deviations from the normal are seen: The distal ends of the radius and ulna clearly show the increased width of the epiphyses, the translucent metaphysis, the narrow zone of calcification at the epiphyseal end of the bones and the lessened density of the shaft of the long bones. Figure 3, C and D, shows roentgenograms of cretin and control 5 months later. Here the distinct bending of the long bones of the cretins' front legs is apparent, also the still open epiphysis.

Histological examinations of longitudinal sections through the epiphyseal ends of the long bones (fig. 2, B) give evidence of excessive multiplication of cartilage cells as denoted by the enlarged zone of proliferation. Near the metaphysis the cells are larger and the columnar arrangement less clearly defined. This proliferating zone is incompletely or entirely devoid of calcium. An abundance of osteoid tissue separated by wide medullary spaces, and a diminution or absence of normal bone trabeculae are apparent in the metaphysis.

Blood examination. Chemical analysis of the blood (table 1) shows that the acid soluble phosphorus is markedly below normal, whereas the calcium content is normal. Occasionally the calcium is very slightly below that of the normal litter mate but usually falling within the lower limits of normal variation. Preliminary reports have been made on the marked anemia and the increase in cholesterol of the blood which is found in this condition (Kunde, 1926).

DISCUSSION OF RESULTS. Our experiments demonstrate that when rabbits are thyroidectomized between 2 and 3 weeks after birth and suffer marked thyroid deficiency as indicated by the growth curve, a pathological condition develops which corresponds in all fundamental respects to rickets
in human beings. This is not due to a deficiency in the anti-rachitic
vitamines of the dietary inasmuch as the unoperated litter mate living in
the same cage and sharing the dietary of the operated animal shows no
disturbance in the skeletal development. Moreover, the dietary consists
of an abundance of high grade alfalfa leaf, unrolled oats, a small amount
of yellow corn, carrots and water ad libitum. McCollum et al. (1917)
showed that a dietary consisting of 40 per cent alfalfa leaf and 60 per cent
rolled oats was sufficient for normal growth and the rearing of young, and
later Steenbock and Gross (1920) demonstrated that where 15 per cent
of the rations of the white rat consisted of alfalfa, the requirements for
the fat and water soluble vitamines were satisfied, i.e., normal growth and
reproduction followed. These same authors (1919) also found that where
15 per cent of the dietary consisted of carrots, normal growth and the rear-
ing of young occurred. In our rabbits the disturbance of the bone
development is not due to a deficiency in the dietary but to an inability
to properly utilize the essential substances present in the food in great
abundance. The marked lowering of the metabolic rate in very young
growing rabbits due to thyroidectomy soon develops into a general meta-
bolic disturbance with a syndrome of signs comparable to a severe dis-
turbance in nutrition brought about by feeding diets insufficient in certain
essential factors.

The blood is also included in this metabolic disturbance. After several
weeks of induced cretinism a severe anemia develops (Kunde, 1926). The
details of this will be reported later. It is quite possible that the rickets
which develop in the animals is secondary to this anemia. This rachitic
condition readily responds to thyroid medication, as can be seen by in-
creased calcium deposition in the zone of provisional calcification of the
epiphyses after desiccated thyroid has been given to these rabbits daily
for a short period of time (fig. 2, C). This supports the theory of Lanz
(1894) who suggested the use of thyroid in rickets, but does not agree with

Fig. 2. Photomicrographs of longitudinal sections through the epiphysis of the
distal end of the femur of 3 littermates 13 weeks old, living on the same dietary and
under identical conditions of light. A = normal unoperated rabbit; note the narrow,
uniformly arranged columns of the epiphysial disk of cartilage which is completely
calcified, the proliferating layer being only 1 to 3 cells deep and the beginning of the
diaphysis containing the normal amount of bony trabecula. B = the littermate
thyroidectomized between 2 and 3 weeks after birth; note the marked increase in the
width of the epiphysial disk of cartilage, the absence of calcium in the wide prolifer-
ating zone of cartilage and the irregular arrangement of the uncalcified cartilage.
The metaphysis contains an overproduction of osteoid tissue. C = Thyroidecto-
tomized rabbit 4 weeks after daily doses of thyroid had been given; note the com-
plete calcification of the proliferating zone of cartilage and the calcium deposits
in the metaphysis. Magnification \( \times 52 \) (hematoxylin and eosin). bt. = bony
trabecula; e. car. = epiphysial disk of cartilage; e. cav. = epiphysial cavity;
ost. = osteoid tissue.
Fig. 2
the results of Knoeppelmacher (1895) and of Heubner (1896) who report no effect of thyroid medication. Clinically, it has been shown that many children with marked secondary anemia develop rickets. The deformities in this type of rickets differ slightly from those ordinarily seen, in that

![Fig. 3](http://ajplegacy.physiology.org/)

**Fig. 3.** *A and B are roentgenograms of littermates. A = normal animal; B = cretin 7 weeks old thyroidectomized 2 weeks after birth. Note the difference in the width of the epiphysis, E, of the normal and cretin animals, also the calcium deposits, c, at the beginning of the normal shaft, whereas in the cretin the metaphysis, M, shows very little calcium. C and D are roentgenograms taken 5 months later. Note the bending of the radius and ulna of the cretin, D, and the straight lines of the normal animal, C.*

the enlargements of the ends of the extremities and at the costochondral junctions are not so marked as in rickets due to dietary deficiencies. These moderate enlargements describe the condition in our experimental animals.

The low acid soluble phosphorus in the blood, and the normal or very
slightly below normal calcium content of the blood of our cretin rabbits corresponds to the reports of Kramer and Howland (1921); these authors made chemical analyses of the concentration of the calcium, phosphorus and magnesium in the sera of rachitic children and found that, excluding frank tetany, the calcium content of 12 cases out of 25 fell within normal limits and with the remaining 13 cases the calcium decrease was not significant. But the acid soluble phosphorus of the sera was markedly below normal. Our experiments show that the type of rickets which occurs in cretin rabbits living on an adequate diet is characterized by a low acid soluble phosphorus of the serum. Shipley et al. (1922) showed that this type of rickets (normal calcium and low phosphorus in the serum) could be produced in rats by diminishing the phosphorus and supplying the optimal amount or an excess of calcium in the diet, provided the diets contained an insufficient amount of the substance found in cod liver oil, or if the rats were deprived of certain active light rays.

**TABLE 1**

*Showing variations in the blood calcium and in the acid soluble phosphorus of the serum of normal and of cretin rabbits*

<table>
<thead>
<tr>
<th>CONDITION OF ANIMAL</th>
<th>NUMBER OF ANIMALS USED</th>
<th>PHOSPHORUS ACID SOLUBLE PER 100 CC. SERUM</th>
<th>CALCIUM PER 100 CC. SERUM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Highest</td>
<td>Lowest</td>
</tr>
<tr>
<td>Normal...............</td>
<td>4</td>
<td>5.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Cretin..............</td>
<td>9</td>
<td>3.7</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Our rabbits were housed in a moderately well lighted laboratory but not exposed to the unfiltered rays of the sun. Under these conditions no un-operated rabbit ever showed signs of rickets, showing that under normal conditions this environmental factor did not contribute to the production of the disease. Recent experiments seem to indicate that the type of rickets which occurs in cretin rabbits (not of dietary origin and not responding to a normal diet) is improved by certain active light rays. The evidence in this respect is not sufficient at present to justify definite conclusions.

The investigations of disturbances in skeletal development were all made during the phase when the rabbits were still growing though growth was markedly delayed. After growth ceases in certain absolute cretins, which rarely live more than 10 to 12 weeks after operation, the epiphysis becomes narrow and the picture of active rickets can no longer be clearly demonstrated.
SUMMARY

Cretin rabbits (thyroidectomized between 2 and 3 weeks after birth) develop a condition of disturbance in skeletal development which fundamentally simulates clinical rickets. This is not due to a dietary deficiency. This rickets-like condition is accompanied by severe anemia.

This ricket-like condition is characterized by a normal or slightly below normal concentration of the blood calcium and a low acid soluble phosphorus of the serum.

BIBLIOGRAPHY

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