THE RELATION OF LEG WEAKNESS IN GROWING CHICKS TO MAMMALIAN RICKETS.

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PLATE 2.

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The beneficial effect of known antirachitic agents—cod liver oil and ultra-violet radiation—upon the condition known as "leg weakness" in young chicks, has led to the assumption that this condition is identical with mammalian rickets. To cite only a few of the statements indicating the general belief in this identity, Hughes (1) says that, "The lesions are the same and the conditions under which it is produced are the same as those which cause rickets." Probably the most extensive work in this field has been done by Hart, Steenbock, and their coworkers. In their more recent papers they appear definitely to regard leg weakness as identical with rickets. Thus "The fact that the baby chick is very susceptible to rickets... led us to investigate," etc. (2); "We have successfully prevented and cured rickets in chickens by the administration of cod liver oil" (3); and in a popular article (4) one of the chapters is headed with the caption "Leg Weakness is Rickets." In a paper by one of us (Dunn (5)) the same view-point, based on the identity of the biological reactions, was maintained.

None of the numerous papers which have appeared during the past few years has dealt specifically with the histological changes in the bones. Thus there is at present no morphological evidence for the identity of the two conditions. It was with a view to filling this lack that we undertook a comparison of the bones of a series of young chicks in which leg weakness had been experimentally produced, with those of chicks receiving an adequate supply of the antirachitic factor.
Material and Methods.

The chicks were placed upon the experimental diet immediately after hatching. The basal diet used for the production of leg weakness was the same as that employed by Hart, Halpin, and Steenbock (6), consisting of white corn 97 parts, CaCO$_3$ 2 parts, NaCl 1 part, with pasteurized skim milk ad libitum.

The conditions under which the chicks were reared were the same as those described by Dunn (5). Pine sawdust was supplied as litter, and direct sunlight excluded.

To supply control material for normal bone structure, chicks from the same families, raised under identical conditions, were given the following complete diet:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow corn</td>
<td>70</td>
</tr>
<tr>
<td>Wheat middlings</td>
<td>20</td>
</tr>
<tr>
<td>Beef scraps</td>
<td>5</td>
</tr>
<tr>
<td>CaCO$_3$</td>
<td>4</td>
</tr>
<tr>
<td>NaCl</td>
<td>1</td>
</tr>
</tbody>
</table>

A supplement of 2 per cent cod liver oil was incorporated in this mixture and skim milk provided ad libitum.

A further group was reared from hatching on a diet of yellow corn 97, CaCO$_3$ 2, NaCl 1. The purpose of this ration was to determine what modifications of bone structure might result from the introduction of the vitamin A factor alone.

Two groups, one of 10 and one of 16 chicks, were raised on the white corn ration, with the addition in the first case of approximately 5 per cent of a 1 to 150 dilution in glycerol of the active concentrate of the non-saponifiable fraction of cod liver oil. With the second group, the same preparation was incorporated in the ration to the amount of 2 per cent of a 1 to 75 dilution. This makes a final concentration of 1 part of the concentrate in 3000 parts of white corn ration in the first experiment, and of 1 part in 3700 parts of ration in the second. The proved curative dose of this preparation for rat rickets was 0.1 cc. per day of the 1 to 75 glycerol suspension.$^1$

Histological Methods.—The bones were fixed in Müller-formol,

$^1$ We are indebted to Mr. T. F. Zucker for supplying us with this preparation, and to Mrs. Margaret Gutman Newburger for information as to the antirachitic potency of the sample used.
TABLE I.

Results of Feeding Experiments with Young Chickens.

All chicks were reared from hatching time on laboratory tables covered with washed sand and pine sawdust. Windows were closed throughout all experiments.

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>No. of chicks</th>
<th>Basic diet.</th>
<th>Supplement.</th>
<th>No. of chicks with leg weakness</th>
<th>Age at appearance of leg weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>N 10</td>
<td>13</td>
<td>White corn.*</td>
<td>None.</td>
<td>8†</td>
<td>16-24</td>
</tr>
<tr>
<td>N 15</td>
<td>6</td>
<td>&quot; &quot; &quot; *</td>
<td>&quot;</td>
<td>6</td>
<td>19-37</td>
</tr>
<tr>
<td>N 13</td>
<td>10</td>
<td>&quot; &quot; *</td>
<td>5 per cent D.†</td>
<td>5§</td>
<td>17-25</td>
</tr>
<tr>
<td>N 18</td>
<td>16</td>
<td>&quot; &quot; *</td>
<td>4 &quot; &quot; &quot; **</td>
<td>13‖</td>
<td>24-31</td>
</tr>
<tr>
<td>N 12</td>
<td>17</td>
<td>Yellow corn.¶</td>
<td>2 &quot; &quot;</td>
<td>None to 2 mos.</td>
<td></td>
</tr>
<tr>
<td>N 17</td>
<td>15</td>
<td>&quot; &quot; ¶</td>
<td>C.L.O.**</td>
<td>&quot; 2 &quot;</td>
<td></td>
</tr>
<tr>
<td>N 14</td>
<td>11</td>
<td>&quot; &quot; ¶</td>
<td>C.L.O.**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N 16</td>
<td>12</td>
<td>Normal ration.¶† †</td>
<td>2 per cent C.L.O.</td>
<td>None to 3 mos.</td>
<td></td>
</tr>
</tbody>
</table>

* The white corn diet consisted of ground white corn, 97, CaCO₃, 2, NaCl, 1, with pasteurized skim milk as drink, ad libitum.
† Five chicks died from pneumonia or chilling at 1 week of age.
‡ D designates the active antirachitic non-saponifiable fraction of cod liver oil used in a 1:150 suspension in glycerol; thoroughly incorporated in the ration.
§ Three chicks died from undetermined causes at 10 to 13 days of age; two had not developed leg weakness at 1 month of age.
‖ One died at 9 days; two died at 24 days without previous symptoms of leg weakness.
¶ The yellow corn diet consisted of ground yellow corn, 97, CaCO₃, 2, NaCl, 1, with pasteurized skim milk as drink, ad libitum.
** Freshly opened cod liver oil-Harris, thoroughly incorporated in the ration.
† † Two chicks killed for study before leg weakness appeared.
† † † Our normal ration consisted of:

Yellow corn ................................................. 70
Wheat middlings .......................................... 20
Beef scrap ................................................... 5
CaCO₃ ....................................................... 4
NaCl ........................................................ 1

supplemented by a scratch feed of 2 parts of cracked corn and 1 part of cracked whole wheat.
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partially decalcified in Müller's fluid, and stained with hema-
toxylin-eosin and with silver nitrate-safranin. The upper ex-
tremity of the tibia was taken for routine study.

EXPERIMENTAL RESULTS.

Since this paper is primarily concerned with the bone changes
associated with leg weakness, the summary given in Table I will
suffice to show the results of the experiments as regards the onset
of leg weakness, and the protective value of the various additions
used.

Radiographic Examinations.

Radiographs of normal and leg weakness bones were taken
after fixation, but before decalcification. The radiographic
findings varied somewhat in individual birds. The appearance
which seemed most typical of the leg weakness bones is illustrated
in Fig. 1. The head of the tibia is traversed by a dense shadow,
corresponding to the zone of calcified cartilage. Below this is a
definitely rarefied zone which does not appear in the normal control
of the same age, and which, as becomes evident from the histo-
logical comparison, is due to the loss of the primary spongiosa.
There is no swelling or deformity of the end of the bone, and the
cupping, so characteristic of the rachitic metaphysis, is conspicu-
ously lacking.

Histological Examination.

It may be stated at the outset that in none of the 30 chicks
(including normal controls) studied were there present lesions
which could be regarded as rachitic. Certain very definite and
striking alterations, however, were found, the interpretation of
which will be discussed later. It is unnecessary to give in detail
descriptions of the individual chicks, since with slight variations
the appearances were identical in all essentials. The following
may be taken to exemplify the series:

Chick 9764.—Hatched Jan. 31, 1925. Fed a diet of white corn 97, CaCO₃,
2, NaCl 1, skim milk ad libitum. Developed typical leg weakness and was
killed on the 18th day.

Section through upper extremity of tibia.

The zone of proliferating cartilage and the zone of provisional calcifica-
tions are greatly increased in depth, with numerous blunt prolongations
extending downward towards the diaphysis. The columnar arrangement of the cartilage cells is only partially preserved. There are numerous large penetrating vessels, anastomosing with those of the epiphyseal cartilage. These are surrounded by loose fibrous tissue. The epiphyseal cartilage contains no ossification center, and is wholly uncalcified.

Calcification of the cartilage in the zone of provisional calcification is quite uniform and complete in the distal portion.

The primary spongiosa is almost absent; there is a notable lack of osteogenetic tissue about the calcified cartilage cells. Such small fragments of bone trabeculae as remain are very thin and irregular in their disposition and, for the most part, completely separated from the cartilage. Some of the trabecular remnants are apparently in process of resorption, staining as indistinct pinkish purple clumps. There are fairly numerous multinucleated osteoclasts lying against these resorbing bone spicules. Occasionally they are surrounded by a row of flattened cells, but well formed osteoblasts are conspicuously lacking. There is no osteoid visible.

The cortex of the bone is likewise much rarefied, and especially in the region of the epiphysis, where it is composed of irregular trabeculae and in places completely interrupted. Differentiated osteoblasts are not to be found, and bone formation is evidently in abeyance. The bone corpuscles are small and angular. An osteoid margin is nowhere to be seen. The periosteum is not thickened.

The marrow is the seat of striking and interesting changes. It is everywhere altered into a myxomatous tissue composed of polyhedral connective tissue cells, with branching processes, embedded in a pale mucoid bluish-staining ground substance. No fat cells are seen. There is great reduction in the blood-forming elements, which are represented only by sparsely distributed islands composed chiefly of eosinophil polymorphonuclears and myelocytes. The blood sinuses are not prominent; some appear collapsed.

The foregoing lesions (Fig. 2) present a striking contrast to those encountered in mammalian rickets, either of spontaneous or experimental origin. The epiphyseal cartilage is increased in width, and the columnar alignment is more or less disturbed, but there is no defect in calcium deposition. As can be seen in radiographs, and in sections stained with silver nitrate, the cartilage is traversed by a broad band of calcium; in rachitic bone, the calcium is characteristically absent in the zone of provisional calcification, and the failure of the cartilage to calcify is a fundamental feature of the rachitic state.

In the subchondral zone, there are equally striking contrasts. In the chicks, there was in every case a marked impoverishment of the spongy trabeculae. Small fragments, undergoing resorption
and often surrounded by giant cells, marked the site of the original trabeculae. No new bone was being formed about the cartilage. This complete arrest of endochondral ossification was most striking. In rachitic bone, the subchondral region is occupied by broad, irregular trabeculae, composed largely of osteoid, and surrounded by distinct and presumably active osteoblasts. Multinucleate cells are rare.

**TABLE II.**

*Comparative Histological Lesions in Leg Weakness of Chicks, and in Experimental Low Phosphorous Rickets.*

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Leg weakness. Chicks</th>
<th>Experimental rickets. Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage...</td>
<td>Moderately widened.</td>
<td>Very greatly widened.</td>
</tr>
<tr>
<td>Calcification of cartilage...</td>
<td>Present. Occasionally small areas of defective calcification.</td>
<td>Absent.</td>
</tr>
<tr>
<td>Spongiosa...</td>
<td>Absent or reduced to small fragments undergoing resorption.</td>
<td>Broad trabeculae, composed largely of osteoid.</td>
</tr>
<tr>
<td>Osteoblasts...</td>
<td>Indistinct or absent. No osteogenesis.</td>
<td>Large, conspicuous. Osteogenesis active.</td>
</tr>
<tr>
<td>Osteoclasts...</td>
<td>Numerous.</td>
<td>Rare or absent.</td>
</tr>
<tr>
<td>Cortex...</td>
<td>Thin. No osteoid margin.</td>
<td>Calcified portion often thinned, but there are large endosteal and periosteal osteoid thickenings.</td>
</tr>
<tr>
<td>Osteoid...</td>
<td>Practically absent.</td>
<td>Great excess.</td>
</tr>
<tr>
<td>Marrow...</td>
<td>Fibroid or myxomatous transformation.</td>
<td>Little marrow in metaphyseal region because of osteoid excess. Diaphyseal marrow not much altered.</td>
</tr>
</tbody>
</table>

An excess of osteoid tissue, perhaps the most significant and distinctive feature of rachitic bone, was never present in the chick preparations. Indeed, the amount of osteoid seemed diminished in comparison with that normally found in the healthy growing control of the same age.

Fibrosis of the marrow in the region of the epiphysis occurs in the more severe forms of human rickets, but is not pronounced
in the experimental rat rickets produced by low phosphorous diets. The majority of chicks with leg weakness showed a striking fibromyxomatous transformation of the marrow, with depletion of the blood-forming cells. This was especially marked in the subchondral area, but in some preparations a strip of fibrous marrow extended along the inner surface of the cortex for a considerable distance.

The periosteum was unaltered, and the marked thickening which is so striking a feature of rachitic bone, did not occur.

In Table II the skeletal changes in the two conditions are compared in tabular form.

The substitution of yellow corn for white not only delayed the onset of the symptoms of leg weakness but produced a definite improvement in the bone structure. This is illustrated in the following protocol.

*Chick 9823.*—Fed on diet of yellow corn 97, CaCO₃ 2, NaCl 1. Killed on 21st day, having shown no symptoms of leg weakness.

The zone of provisional calcification in the upper extremity of the tibia is broad and deep, and well calcified in its distal portion. The spongiosa is composed of numerous well calcified narrow trabeculae, with a distinct, but not broad, osteoid margin, and conspicuous cuboidal osteoblasts. The cellular marrow extends to the cartilage, and the myxomatous change seen on the white corn diet is absent. The cortex is relatively stout. The central cartilage of the diaphysis is completely resorbed.

There is practically no difference therefore at this age from the normal bone structure exhibited by birds on a complete diet. It would seem that the administration of the vitamin A as contained in the yellow corn has brought about more active osteogenesis in the young growing bone.

As shown in Table I, the administration of an actively antirachitic substance in the form of a concentrate of the non-saponifiable fraction of cod liver oil, was not efficacious in preventing the onset of leg weakness in chickens on a white corn diet. Thus of ten chicks in this group, four died of other causes before the age of incidence of leg weakness, but the remaining six acquired the typical symptoms at the usual time. The following protocol brings out the fact that addition of this active antirachitic substance failed entirely to bring about an improvement in the histological bone structure.
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Chick 9880.—Placed on white corn ration Mar. 30, with the addition of 5 per cent of a 1:150 dilution of the active concentrate. Symptoms appeared on the 15th day and the chick died with typical leg weakness on the 21st day.

Section through upper extremity of tibia.

There is increased depth and irregularity in the growing cartilage, accompanied by massive, though unevenly distributed, deposition of calcium. There is little evidence of active bone growth at the epiphyseal junction. The blunt calcified cartilage processes lie exposed and no bone trabeculae are being formed about them. There is no penetration of blood vessels, nor erosion of the cartilage cells. The marrow in the vicinity of the cartilage and further down the shaft is much depleted of blood-forming elements, and shows the same fibromyxomatous structure as in Chick 9764, and other birds on the white corn diet without additions. The cortex is well calcified without visible osteoid margin. Osteoblasts are indistinct.

The picture presented is thus virtually the same as that on the white corn ration without antirachitic substance, and one may conclude that the addition of an active antirachitic agent alone, as contrasted with the addition of whole cod liver oil, brings about no improvement in the bone structure. There is, in other words, no stimulating effect upon the osteogenetic function of the marrow.

DISCUSSION.

From the anatomical point of view, it is plain that the bone lesions found in the leg weakness of young growing chicks, at least with the experimental diets used, are not those of rickets. The essential feature of the rachitic state is the failure of calcium deposition, both in the growing cartilage and in the new formed osteoid tissue. In the bones of leg weakness chicks, with the diets used, the central change seems rather to be a failure of osteogenesis, with continuing and possibly exaggerated resorption of previously formed bone. Were it not for the absence of hemorrhage, the lesions would far more closely resemble the effects of scurvy than of rickets. Indeed, the resemblance is sufficiently striking to bring up anew the question as to whether the absence of antiscorbutic vitamin may not be a factor in determining the character of the lesions. The literature contains a number of positive statements bearing upon this point. Thus Hart, Halpin, and Steenbock (7) state that the administration of orange juice has no beneficial effect in the prevention or cure of leg weakness. Emmett
and Peacock (8) found no growth stimulation upon the addition of tomato juice, and conclude that vitamin C is not essential. Mitchell, Kendall, and Card (9) have made similar observations. Plimmer and Rosedale (10), Sugiura and Benedict (11), Shorten and Ray (12), and Carrick and Hauge (13), are all agreed that chickens do not require the antiscorbutic vitamin, and the last authors have shown that, as in the case of the rat, the antiscorbutic substance is contained in abundance in the liver even when the animal is maintained for a long period on a vitamin C-deficient diet.

It is thus generally held that birds are insensitive to lack of antiscorbutic vitamin, and possibly have the power of synthesizing it. So far as we are aware, detailed histological studies of the bones of chicks on diets deficient only in vitamin C have not been published. We have, however, examined sections of bones of chicks receiving the preventive addition of cod liver oil, and since this agent which does not contain the antiscorbutic factor effectually overcomes the failure of osteogenesis and the accompanying marrow fibrosis, there can be little reason for regarding these changes as scorbutic.

We are thus dealing with a condition which is pathologically distinct from rickets, but which in its biological reactions shows undoubtedly close relationship to this disease. However, the biological resemblance, though intimate, is not complete. Thus the concentrate of the non-saponifiable fraction of cod liver oil (Zucker), which is actively antirachitic in rats, failed to protect against leg weakness (Table I).

It might be thought that the bone changes in leg weakness are merely the effect of failure of growth. Fasting, and indeed faulty nutrition from any cause in young animals, is accompanied by arrest of bone formation. In a number of the chicks examined growth during the experimental period up to the time that symptoms developed as judged from the weight curves, was virtually normal.2 The lesions, therefore, cannot be attributed to inanition, nor can it be maintained that the rachitic lesions are masked by the malnutrition. While it is in general true that the severity of

2 Unpublished data indicate that the growth of chicks which develop leg weakness does not differ significantly from the growth of chicks which do not develop leg weakness, until the onset of this condition.
rachitic lesions is greatest in animals showing rapid growth and that fasting tends to induce healing, most intense rachitic lesions may and frequently do develop in experimental animals though the weight curve remains stationary.

Because of the addition of skim milk to the basal ration, the phosphorus content of the chick diets is considerably higher than in the low phosphorus diets used for the experimental production of rickets in rats. We have calculated that the average daily phosphorus intake of chicks on the white corn-skim milk ration is about 33 mg. during the first 3 weeks. On the Sherman-Pappenheimer low phosphorus rickets-producing diet, the average daily intake of phosphorus is probably 12 mg. or less. While these figures have no claim to accuracy, and do not take into account the availability of different forms of phosphorus, or actual absorption, they do indicate that the leg weakness ration is relatively higher in phosphorus than one of the standard rickets-producing diets.

We have tested the same diet which produced leg weakness in chicks (namely, white corn 97, CaCO₃ 2, NaCl 1, skim milk ad libitum) upon a small series of rats. Direct sunlight was excluded. Growth from the 3rd to the 7th week was normal and histological examination of the ribs in three rats showed no rachitic changes. The skim milk was then withdrawn from the diet, and the three remaining rats examined after a further period of 3 weeks. All showed grossly and microscopically pronounced and typical rachitic lesions. Thus it is seen that leg weakness diet is antirachitic with milk supplement; rachitic without milk.

It is quite possible that under the conditions of the experiments, the phosphorus assimilation was sufficient to cover the calcification of the inactively growing skeleton, though not adequate for optimal bone growth. A similar condition obtains when to Diet 84 (Sherman and Pappenheimer (14)) are added 75 mg. per cent of phosphorus, which amount suffices to protect against the development of rachitic lesions, but is undoubtedly below the amount necessary for normal bone growth. Whether it will be possible by further reduction of the phosphorus intake to produce true rachitic lesions in the bones of young chicks remains to be demonstrated.

The investigations of Hess (15) and of Casparis, Shipley, and Kramer (16) have shown that egg yolk possesses antirachitic
properties comparable to those of cod liver oil. Bethke and Kennard (17) were able to raise chicks indoors to maturity by the addition of 15 per cent egg yolk in place of cod liver oil, and Collier also found that young chicks may be successfully reared without exposure to direct sunlight or administration of cod liver oil when hard boiled eggs are added to the ration. The Wisconsin Experiment Station (4) has also reported that a ration of white corn, middlings, and skim milk may be made adequate for normal growth by the addition of one egg per day to the ration for 30 chicks.

It seems established, therefore, that egg yolk is not only antirachitic, but also protects against leg weakness. The question thus arises whether the absence of rachitic lesions in chicks may not be due to the storage of yolk or its active component in the tissues during the experimental period. That there is no permanent storage of the substance which prevents leg weakness is shown by the fact that this condition frequently appears in the 3rd week, and occasionally as early as the 17th day. This, however, gives no evidence as to the possible storage of an antirachitic substance, and the question must be left open until typical rickets has been experimentally produced in chicks.

CONCLUSIONS.

1. Radiographic and histologic study of a series of bones of young growing chicks with experimentally produced leg weakness showed no rachitic changes.
2. The bone lesions found were arrest of osteogenesis, osteoporosis, and fibromyxomatous transformation of the marrow.
3. Administration of the active antirachitic concentrate of the non-saponifiable fraction of cod liver oil did not prevent the onset of leg weakness, nor modify the character of the bone lesions.
4. The addition of whole cod liver oil prevented leg weakness, and brought about normal bone structure.
5. The diet which produced typical leg weakness in chickens was fed to young rats for 4 weeks but did not produce rachitic changes in their bones.

Addendum.—While this manuscript was in press there appeared an article by Hart, Steenbock, and Lepkovsky (19) in which the use of a white
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corn ration for testing the antirachitic potency of stored cod liver oil is criticized on the ground that the results are complicated by vitamin A deficiency. Experiments are reported in which the basal ration is composed of yellow corn 97, calcium carbonate 2, and sodium chloride 1, with skin milk ad libitum. This diet is said to produce a distinctly rachitic condition, recognized by the shambling gait, ruffled feathers, low ash content of the alcohol-extracted bones, and microscopically, by the wide uncalcified area of proliferating cartilage.

The microscopic examination was carried out on bones decalcified for 7 to 10 days in 10 per cent nitric acid.

We should like to make the following criticism. (1) A diminished ash content in itself does not establish rickets, but is found in simple osteoporosis; (2) acid decalcification makes the microscopic recognition of calcium unreliable; (3) Fig. 1 showing wide rachitic proliferating cartilage is made from a section which does not pass longitudinally through the shaft of the bone, and the widening of the cartilage shown in the picture may be due to the fact that the joint cartilage has been cut tangentially; (4) excess of osteoid, the most characteristic histological feature of rachitic bone, is not mentioned, nor does Fig. 1 suggest its presence.

It does not seem to the writers that the diagnosis of rickets is warranted from the data presented. In our experience (see protocol of Chick 9823) a yellow corn diet identical with that used by Hart, Steenbock, and Lepkovsky did not produce rickets.

BIBLIOGRAPHY.

A. M. Pappenheimer and L. C. Dunn


EXPLANATION OF PLATE 2.

Fig. 1. Radiographs of bones of normal and leg weakness chickens.
   a. Chick 9799, killed at 15 days, normal.
   b. Chick 9860, died with leg weakness at 21 days.

Fig. 2. Photomicrographs of bones of normal and leg weakness chicks
   (stained with silver nitrate-safranin).
   a. Chick 9772, normal, killed at 15 days. Normal tibia.
   b. Chick 9768, died with leg weakness at 24 days. Tibia showing normal
      calcification of cartilage, absence of spongiosa, rarefaction of cortex.
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