A STUDY OF BARLOW'S DISEASE EXPERIMENTALLY PRODUCED IN FETAL AND NEW-BORN GUINEA PIGS.*

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Plate 38.

The relation between the organisms of the mother and offspring during the period of pregnancy has been the subject of thorough investigation. In both clinical and experimental pathology a number of studies, through a varied series of influences on the maternal organism, throws light upon the secondary influences on the fetal body. The agents employed to produce disease have usually been chemical, physical, or parasitic in character, but investigations as to the influence of dietetic changes upon pregnancy are limited in number. I may mention here particularly the dietetic experiments with strontium made by Lehnerdt[1] on pregnant rabbits. He succeeded in producing in young fetuses a disease of the osseous system, which exhibited macroscopically numerous fractures and infractions of the long tubular bones, and microscopically an increase in the osseous tissue, with extensive new formation of osteoid tissue and greatly impeded reabsorption.

In the present paper I wish to describe certain experiments made upon guinea pigs during pregnancy. The constant character of the frequently fatal disease that was produced in guinea pigs within a period varying from ten to twenty-eight days by a diet consisting exclusively of oats and water in Holst and Frölich's experiments[2] coincided closely both macroscopically and microscopically with Barlow's disease in man.[3] This, therefore, seemed to give an

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[1] Lehnerdt, F., *Beitr. z. path. Anat. u. z. allg. Path.*, 1909, xlvi, 468; 1910, xlvii, 215.

[2] Holst, A., and Frölich, F., *Ztschr. f. Hyg. u. Infectionskrankh.*, 1912, lxxii, 1.

[3] Ingier, A., *Frankfurter Ztschr. f. Path.*, 1913, xiv, 1.

opportunity of studying the possible changes in the osseous system of the fetus produced by a scorbutic diet, and also of obtaining some insight into the biological relation existing between mother and offspring. These studies might lead to conclusions with regard to the relation of the various constitutional osseous diseases of unknown etiology that occur spontaneously in man, the principal symptoms of which are dystrophy of the bone-forming elements.

The following diseases will be considered: osteogenesis imperfecta (congenital osteopsathyrosis), rachitis, and osteomalacia.

Before describing my experiments I wish particularly to emphasize the fact that the diet was tried on mature animals and on quite young ones, and also at various stages of pregnancy. The investigations showed that the stage of embryonic development as well as the resisting power of the pregnant animals is of importance, since in the experiments mainly older animals and those during the latter half of the period of pregnancy gave birth to living and apparently mature offspring, whereas experiments performed on young animals and those in the earlier stages of pregnancy invariably resulted in premature birth or in the birth of a dead fetus.

Thirty-three of my experiments were successful. They may be divided into three groups. Group I comprises the fetuses that were born early, prematurely or by miscarriage, within ten days after the beginning of the new diet. The second group comprises fetuses that were born prematurely or fetuses in an advanced stage of development between the tenth and twenty-fifth days. Group III comprises the young ones that were apparently fully developed and living, born within twenty-three days after the beginning of the experiment, which survived and were given a scorbutic diet; *i. e.,* milk from scorbutic mothers and later on oats and water.

The first group contains the litters of twelve animals. The fetuses had been alive for five to ten days after the experiment began. The litters consisted mainly of two, in some few cases of three or four animals. The young were either still-born or were found as dead fetuses in the uterus of the dead mother.

It appears that animals are more sensitive to changes in diet during pregnancy than at other times, since a comparatively large percentage of the mothers died in the early stages of the experiment.

All the fetuses showed a low stage of development. The weight varied from seventeen to fifty-five grams (the latter occurring once only), and the average was between twenty and thirty grams.

Macroscopically the bones presented nothing remarkable. Microscopic examination revealed no changes in the skeletons even of the longest living fetuses, with the exception of hemorrhage and thrombosis in the marrow.[4]

The second group comprises the litters of seventeen animals that had been fed during pregnancy on a scorbutic diet for twelve to twenty-five days. These cases present great variety. The degree of scorbutic change in the fetus was not proportional to the length of the period of intra-uterine dieting with scorbutic food. These changes, too, as regards intensity were considerably smaller than those in the skeleton of the mother. Thus, for instance, in one case after a diet of oats and water for twenty-two days, the offspring being alive and apparently fully developed (weight seventy-one grams), only isolated hemorrhages in the marrow and scarcely any perceptible reduction of osseous substance could be discerned under the microscope; whereas in another case, also after twenty-two days of experimental diet, the two young ones were born with pronounced Barlow's disease. They were still-born, undersized, apparently belonging to the first half of the period of pregnancy, although at the commencement of the experiment the stage of pregnancy, by palpation of the abdomen, seemed to be fairly advanced. It is, however, an extremely difficult matter to determine the exact stage of a litter.

Figures 1 and 2 show the microscopic structure of this case. They are microphotographs of one of the upper extremities. As in the other instances, there is no change in the cartilage. In the proliferative zone, the columnar zone, and the calcified layers of the cartilage, we find conditions that come within the scope of physiological variation. Destruction of cartilage has taken place almost symmetrically, by the formation of long columns of calcified ground substance that are partially connected into a network. These pillars sometimes continue subchondrally to the center of the bone. No

[4] As regards the purely technical aspect of the experiments, it may be stated that the bones were hardened in formol immediately after death, and subsequently partially decalcified in Müller's fluid. The method of staining employed was principally hematoxylin and eosin.

traces of osseous tissue can be found in the central or subchondral parts or in the zone of primary marrow spaces. Osteoblasts are also absent. The wide medullary spaces and the central medullary cavity are filled with structural marrow (*"Gerüstmark"*), consisting of fine fibers, spindle and stellate cells (medullary substance), in which only scattered specific osteomyelon cells are to be found.

The corticalis consists of a thin, osseous strip scarcely wider than a single row of osseous units where no apposition of osteoid tissue is discernible. In the center of the humerus a complete oblique fracture has taken place. The ends of the fracture have been displaced. The distal end has slipped along the outer surface of the upper one, and lies close to it, while the proximal end is wedged into the loose tissue of the cubital angle. At this spot copious and recent hemorrhage had taken place. We find here, moreover, numerous pigment cells. The periosteum, although torn, was not detached from the osseous tissue by the hemorrhage. At the seat of fracture there was hyaline degeneration of the periosteum and reaction was not discernible. At this point in the bone marrow connective tissue was beginning to be loosened.

In all the bones examined in this case abnormal length and persistency of the calcified columns of cartilage, deficiency of bone formation and medullary substance were found, and also fresh fractures and infractions in nearly all the long cylindrical bones. Even the scapula was fractured and only the ribs were whole. In all cases the hemorrhages were of small extent and few in number. Osteoclasts were very rare.

In reviewing these facts we must note that we are dealing with a case where the fetus corresponded to an earlier stage of development than could be expected from the time during which the pregnancy had been observed and the experimental dieting had lasted. The fetus, both macroscopically and microscopically, was backward in development.

On microscopical examination a perfectly normal appearance of the cartilage was revealed. The region of the endochondral ossification showed a deficiency of bone formation, since neither old nor recent osteoid tissue was discernible. The marrow was a typical medullary substance with few osteomyelon cells. As a rule, hemor-

rhages were rare. The periosteal formation was also diminished. Furthermore, if we take into consideration the fact that in numerous bones fractures and infractions of an undoubted intra-uterine origin were found, with merely a slight reaction from the periosteum and medulla, it is evident that we have all the symptoms of a fully developed case of Barlow's disease.

The second fetus of the case in question showed the same signs of the disease in an advanced stage. It is unnecessary to discuss the remaining cases of this group, as nearly all exhibited the disease to a lesser extent.

The litters comprised in group II were also premature. The weight was somewhat more than that given above; as a rule, between twenty-five and thirty-five grams. These figures were rarely exceeded. Thus in two cases in which birth occurred after twenty-one and twenty-two days respectively, the weights of the fetuses in one were sixty-four and sixty-eight grams, and in the other fifty-five and thirty-three grams. Of these litters only the latter exhibited marked scorbutic changes in the bones, in the form of medullary substance, sparse hemorrhage in the marrow, and markedly diminished osseous formation; whereas in the first litter, with the exception of loose teeth no changes were discernible in the skeleton, even with the aid of a microscope.

In the second group, too, the death of the mother took place comparatively often, five times out of seventeen, on the twelfth to fifteenth day of the experimental diet, and long before the expected time of delivery. The fetuses which were found in the uterus of the dead mothers all showed a stage of development approximately corresponding to the end of the first half of the period of pregnancy. Even after a lapse of twelve days these fetuses exhibited traces of a slight diminution of osseous formation. It is noteworthy that in one case a fetus showed advanced symptoms of Barlow's disease, exactly as described above, as early as the fifteenth day of experimental dieting; yet in this instance I observed the infraction of the corticalis in the subchondral zone, as is typical of Barlow's disease. The seat of infraction was the inner and upper end of the ulna, where it touches the head of the radius, and this fact may be of

importance as regards the origin of the fracture through intra-uterine movement.

Regarding the atypical seat of the fractures and infractions in these intra-uterine cases, they may perhaps be explained by assuming that the seat of fracture has moved towards the center by reason of the later growth of the bones. The pigment cells at the seat of fracture show that mainly older fractures are under consideration. The fact that in the case described an oblique fracture has taken place, agreeing entirely with one occasioned by indirect violence—by forcible bending—makes it probable, however, that the seat of the fracture is not dislocated by growth of the bone, but has taken place in the spot where it was found. The abundant fresh hemorrhage in this case also strengthens our argument. This difference in the seat of the fractures may be explained as follows: The predisposing factor of typical subchondral fractures in Barlow's disease may be sought in the circumstance that in this newly formed osseous zone a locus minoris resistentiæ is formed by the disease, which is, however, not the case with intra-uterine fractures, the corticalis being equally thin everywhere. It is noteworthy that there are no fractures of the ribs.

The origin of an intra-uterine fracture may be explained in this disease as well as in osteogenesis imperfecta as a mechanical action caused by contraction of the muscles (intra-uterine movements).

The results of my experiments prove beyond doubt that we can produce experimentally in the guinea pig embryo during its fetal existence a disease characterized by all the main features of true Barlow's disease.

In the third group of my experiments, comprising four cases from a later stage of pregnancy, the fetal skeleton, having reached a further development, displays a more marked picture of the disease, which resembles the scurvy of the adult animal still more. The secondary changes, however, are not so pronounced as those found in adult guinea pigs that were fed on oats and water until death.

The cases comprised in group III are all remarkable for the high degree of development of the fetus. They all appear to be fully developed and alive at birth. The weight was fifty-five to sixty-five grams.

The duration of experimental dieting, intra-uterine and extra-uterine, was as follows:

Case 1, 23 dys. intra-uterine, 5 dys. extra-uterine (mother's milk, oats, and water).
Case 2, 13 dys. intra-uterine, 16 dys. extra-uterine (mother's milk, oats, and water).
Case 3, 8 dys. intra-uterine, 7 dys. extra-uterine (mother's milk, oats, and water).
Case 4, 14 dys. intra-uterine, 5 dys. extra-uterine (mother's milk, oats, and water).

The most remarkable feature of these cases was the slight development of the secondary changes in the zone of ossification, which is so marked in human cases of Barlow's disease. This results from the slighter hemorrhage in the bone marrow, and in consequence the lesser disturbances of the circulation in the zones of subchondral and primary marrow spaces. In these cases, too, even after sixteen days of extra-uterine life, there results a symmetrical destruction of cartilage, with no changes in the cartilage, even in the bones where usually we find the highest degree of change; *viz.,* the ribs and extremities of the knee joints. The newly formed columns of calcified primary cartilagenous substance are more scarce than in normal animals; they are usually short and thick; only a few continue subchondrally as more substantial osseous columns. The subchondral spongiosa consists of scattered, isolated, somewhat small calcareous columns, on which only small quantities of osseous substance are deposited. Neither here nor in the zone of primary marrow spaces are there any traces of osteoid tissue. Osteoblasts are also rare, and exclusively spindle-like in shape. The corticalis is very thin, especially in the subchondral zone.

In nearly all cases we can trace subchondral infractions of the corticalis, and also isolated broken cartilage columns. These fractures are most pronounced in the offspring of the second case, which were influenced by the injurious diet for thirteen days *intra uterum,* and sixteen days *extra uterum,* and lived longest of all the animals experimented upon.

In the ribs, and particularly in the tibiæ, there were subchondral fractures with extensive, fresh hemorrhages in the periosteum and bone marrow. The circumstance that the epiphysial centers of ossification of the bones contained extensive fresh hemorrhages in the marrow proves that the latter were not only of traumatic nature, but

also were due to a hemorrhagic diathesis. Also the characteristic formation of medullary substance in the subchondral zone in all cases leads us to the conclusion that in these cases the changes in the skeleton increase not only with the duration of experimental feeding, but first and foremost with the mechanical strain on the skeleton of the extra-uterine animal. This seems to be directly confirmed by the circumstance that infractions and extensive hemorrhages were lacking in one of the offspring of case 1 of this group, which was killed immediately after birth, after twenty-three days of intra-uterine life, while diminished formation of bone and formation of medullary substance were discernible.

DISCUSSION.

From the experiments here described it is evident that a disease of the skeleton may be produced not only in the pregnant guinea pig, but also in the fetus, by feeding the mother exclusively on oats and water. The condition thus produced is characterized as Barlow's disease by the diminished or even non-existing formation of bones, by the existence of hemorrhages in the bone marrow, by the formation of medullary substance, and by the occurrence of fractures.

During the first half of the period of pregnancy the lack of the conditions necessary to sustain life, occasioned by the special diet, is so marked that the animals die almost at the beginning of the period of experiment, and in these cases microscopic examination of the skeleton shows only hemorrhages and thrombosis in the bone marrow.

In group II of my experiments I succeeded in keeping the animals alive for a somewhat longer period. In these cases, too, the fetuses were undeveloped, apparently belonging to the first half of the period of pregnancy, and were frequently still-born. In these cases I found, besides hemorrhages in the marrow, a more or less marked reduction of bone formation, in some instances complete cessation, a development of typical medullary substance and even undoubted intra-uterine fractures.

More marked secondary changes of the bones occurred after birth only by the consequent mechanical strain on the skeleton, the animals

being deprived continuously of the necessary materials for normal development of the bones, by dieting them on milk from a scorbutic mother, and on oats and water only. These secondary changes consisted in larger fractures in the epiphysial zone, indications of a more or less pronounced zone of decay, more extensive hemorrhages in the periosteum and bone marrow, and a reaction of connective tissue by the osteomyelon, corresponding exactly with a fully developed case of Barlow's disease as seen in adult animals after twenty-eight days of an oat diet. No case, however, showed a more marked disturbance of the endochondral reduction, or change in the cartilage proper.

On comparing the cases of Barlow's disease in the mother animal and in the offspring, it is seen that the life of the fetus is not of longer duration than the life of the mother, and this is true in cases fed with scorbutic food during the intra-uterine life, as well as in cases in which this period is succeeded by a period of postnatal scorbutic feeding. None of the fetuses were alive for more than twenty-eight days; that is, they have the same duration of life as the adult animals under the same conditions. On this point, mothers and young animals give the same results.

On the other hand, both macroscopic and microscopic changes in the skeletons of the fetus, although pronounced, were evidently less than those in the adult animal. Thus the zone of decay was always lacking and, accordingly, the secondary changes in the cartilage. Therefore the offspring that were born alive were lively and active. Several points must be considered in order to explain this circumstance. I am inclined to believe that the first cause is the vital independence of the fetus in the uterus. In the case of diseases occurring spontaneously, as well as in injury occasioned by experiment to pregnant individuals, the damage to the organism of the fetus is always less than to that of the mother. We know that the state of nourishment of the mother does not in the least correspond in normal pregnancy with that of the new-born child. On the other hand, Goldmann's[5] experiment with vital staining proves directly that during the development of the fetus there is established a "kind of

[5] Cited by Wolff, B., in von Meyer and Schwalbe, Studien zur Pathologie der Entwicklung, Jena, 1913, i, 50.

center," to which "certain nutritious substances, *e. g.*, glycogen and fat, are directly attracted from the maternal organism."

Moreover, remembering that pregnant animals show a more advanced state of the disease in their bones at an earlier period of defective diet than is the case with non-pregnant animals, it appears that by a reduction of the amount of the essential components of diet, the fetus absorbs a comparatively high percentage of those substances, by reason of its superior intensity of assimilation.

Another important cause of the lesser development of osseous changes in the fetus is no doubt to be found in the circumstance that its protected position in the uterus wards off all but a few minor mechanical influences. This is shown again by the circumstance that very few days of extra-uterine existence are sufficient to produce marked symptoms of Barlow's disease even in cases where at birth the disease occurs only in a latent state. I was able to trace only slight disturbances of the skeleton in the case of young animals of the third group that were killed immediately after birth.

In these experiments we notice the high percentage of premature births and of still-born litters. I do not know whether any corresponding phenomenon has been observed in human beings during scorbutic epidemics, nor are there any accounts of cases of congenital Barlow's disease in the medical literature; and considering the long period of development of this disease in human beings and the rapid recovery caused by suitable diet, this circumstance is not remarkable. Judging from the complete correspondence of the disease in human beings and in guinea pigs, we must assume that such cases may exist. On the other hand, Cheadle and Poynton[6] mention scorbutic offspring whose mother suffered from the same disease.

With reference to the etiology of Barlow's disease when produced *intra uterum,* there is no doubt that unsuitable diet occasions a species of pathological assimilation that equally influences the organism of both mother and offspring. We may presume that a certain substance is lacking in the food, which substance is equally essential to both mother and infant. Yet even these experiments disclose

[6] Cheadle, W. B., and Poynton, F. P., in Allbut, C., and Rolleston, H. D., A System of Medicine, 1909, v, 898.

nothing as to the real nature of this action, whether directly on the bone-forming elements of the osteomyelon or by way of some inner gland secretion, or perhaps by a species of intoxication. It has occasionally been shown that by an insufficiency in the mother of a gland with inner secretion, a vicarious hypertrophy of the same gland occurs in the fetus. Thus the thyroid gland in the fetus is hypertrophied when that gland is removed from the mother (Halsted and others).

We may imagine something of the same kind in the case before us, but I have found nothing macroscopically that would lead to such an interpretation. No microscopic examination, however, has been undertaken with this in view. Undoubtedly the fetus cannot remain alive for a longer period than the adult animal, nor can it defend itself against the development of the disease.

At the same time, experiments made for the purpose of determining a possible failure of some secretive gland in adult animals gave no positive results. By the addition of various preparations of glands influencing the growth of bones (thyroid, hypophysis, thymus, parathyroid) to the oats and water diet, no positive results were obtained in a single case, either *per os* or parenterally. Nor did I succeed in influencing the disease by parenteral introduction of defibrinated blood from normally fed guinea pigs, in which presumably secreted substances from all the glands are present.

On the other hand, no experimenter has so far succeeded in a direct demonstration of the possible lacking substance in scorbutic diet. In this connection it is interesting to recall Schmorl's[7] investigations on Heubner's dogs, in which by a diet deficient in phosphates he found the symptoms of a disease that showed great likeness to Barlow's disease, but which could not be identified with it. Experiments which I have performed on adult guinea pigs point in the same direction, inasmuch as I did not succeed in checking the development of the scorbutic phenomena by adding phosphorated cod liver oil to the oats diet.

As regards the relation between the experimental results given here and the congenital disease osteogenesis imperfecta (congenital osteopsathyrosis) which occurs spontaneously in human beings, and

[7] Schmorl, G., *Arch. f. exper. Path. u. Pharmakol.*, 1913, lxxiii, 313.

which also is due to a diminution of the osseous development, it is clear even from the morphological and symptomatological discoveries in both instances that they differ essentially. The fact that I did not succeed in producing a disease resembling it, even by an alteration in the experiments whereby the injurious influences were less extensive, although allowed to continue for a longer period, is in accord with the above hypothesis. The circumstance is in full accord with the demands for a specific etiology of Barlow's disease, whereas the etiology of osteogenesis imperfecta is still unknown, whether occasioned by an injury to the ovum, or to the embryo at a very early stage.

By adding thirty grams of cabbage, boiled for one-half hour at a temperature of about 110° to 120° C., to the daily ration of oats, Holst and Frölich succeeded in keeping the animals alive for several months; when death occurred as the result of this diet, the animals showed scorbutic changes. As mentioned above, I failed to produce during this modification of the experiments an injury to the bone-forming elements coincident with their formation, which would assert itself in the later development of the skeleton. This diet also resulted in premature delivery; the fetus showed no particular changes in the skeleton; only lesions of scorbutic origin were observed.

These experiments, however, are of special interest on account of another disease of the bones which occurs in human beings during pregnancy; *viz.,* osteomalacia. Although exacerbation always occurs during pregnancy in this disease, I am not aware of any case in which a congenital osteomalacia or rachitic disease has been traceable in the fetus or in full term children of such mothers.

With respect to the total of the examples of congenital rachitis recorded in medical literature, even after eliminating osteogenesis imperfecta and chondrodystrophia fetalis, which were formerly regarded as fetal rachitis, the remainder consists essentially of cases based upon macroscopic observations. On the other hand, no authors, not even Schmorl in the course of his extensive examinations of the skeletons of human fetuses and the newly born, have so far succeeded in finding the pathognomonic aspect of the microscopic diagnosis of rachitis,—excessive periosteal superposition or thickening

and plane extension of the osteoid seams. Nor can the macroscopic appearance of intumescences at the limits of the cartilage be considered pathognomonic for rachitis, because the former exist as secondary symptoms in several osseous diseases; *e. g.*, rachitis, Barlow's disease, traumatic disturbances, and recently the "snuffles" in hogs.[8]

The circumstance that no child suffering from rachitis or osteomalacia has been known to be born of a mother suffering from osteomalacia during pregnancy, even when the disease has lasted throughout the full period of gestation, assuming that this factor will assert itself in future investigations, indicates that the two diseases are fundamentally different both as to their nature and their etiology. It is all the more noteworthy because Hart[9] claims to have discovered a case of rachitis among his cases of Barlow's disease during a series of experiments on monkeys, all of which had been put on the same scorbutic diet, and lived under the same conditions. He assumes a common etiology between Barlow's disease and rachitis.

We are thus concerned, on the one hand, as regards osteogenesis imperfecta with a disease in which an injury to the fetus may occur without any traceable illness in the mother, which seems to indicate a primary injury to the fetus. On the other hand, in osteomalacia we observe that a healthy fetus may be born of a constitutionally diseased mother. By the selective action of the placenta, that is, of the chorionepithelioma, the fetus is able, in the latter disease, to avoid the influence of the factors that are injurious to the mother.

While in the case of Barlow's disease the assumption, as an etiological factor, of a deficiency of some nutritive substance essential to the support of life as well as to the action of the bone-forming cells of the osteomyelon, would appear to be probable, we might perhaps in osteomalacia imagine a hormonic effect. The general relation between various secretive glands and the growth of the bones is well known. Thus, for instance, the disturbance of the function of the hypophysis is connected in some cases with acromegaly (Fischer and others), and in the same way the parathyroid glands are probably closely connected with the disturbances of osteomalacia (Erdheim, Todyo).

[8] Ingier, *Frankfurter Ztschr. f. Path.*, 1913, xii, 270.

[9] Hart, C., and Lessing, O., Der Skorbut der kleinen Kinder, Stuttgart, 1913.

CONCLUSIONS.

1. Pronounced cases of Barlow's disease may be produced in the fetus as early as ten to fifteen days after the commencement of dieting pregnant guinea pigs with oats and water. There are wide individual variations. The scorbutic changes in the skeleton are greatest in the earlier embryonic stages. The fetuses of that period, with practically no exceptions, die and show marked traces of impeded growth.

2. Fetuses from the later period of pregnancy are born alive, and apparently fully developed, with comparatively slight changes in the osseous system.

3. Even a short extension of the period of extra-uterine dieting on milk from scorbutic mothers and later on oats and water is sufficient to change the latent scurvy into a highly pronounced case.

4. The fetus cannot be kept alive longer than the adult animal, about twenty-eight days, either by intra-uterine dieting alone or by combined intra- and extra-uterine dieting.

5. The mothers show signs of disease at an early period, and are more severely attacked than non-pregnant animals. Death also occurs comparatively often in the first period of gestation.

EXPLANATION OF PLATE 38.

FIG. 1. General view of the humerus, ulna, and radius. At the limits of the ossifying cartilage in the humerus both metaphyses show a close network of calcified primary cartilagenous substance, with normal conditions in the cartilage; there is no endochondral formation of bone. The corticalis is thin throughout. In the middle of the bone there is a dislocated oblique fracture. The proximal piece is wedged into the loose tissues at the angle of the elbow and surrounded by hemorrhages. The periosteum shows hyaline degeneration at the seat of fracture, but no formation of callus. The marrow, which is typical structural medulla, contains a slight reaction of tissue at the fracture.

FIG. 2. The proximal extremities of the ulna and the radius, more highly magnified. Normal conditions in cartilage. (The black spot is due to a fault in preparation.) At the limits of ossifying cartilage, especially in the radius, is seen a close network of calcified primary cartilagenous matter, which continues in long calcified cartilagenous columns. In other sections the latter extend almost to the center of the bone. No endochondral formation of osseous matter is present. There is typical medullary substance throughout the bone. The corticalis is evenly thin, and the ulna shows in the middle of the bone an infraction of the corticalis with a slight thickening of the cambium layer at that point.

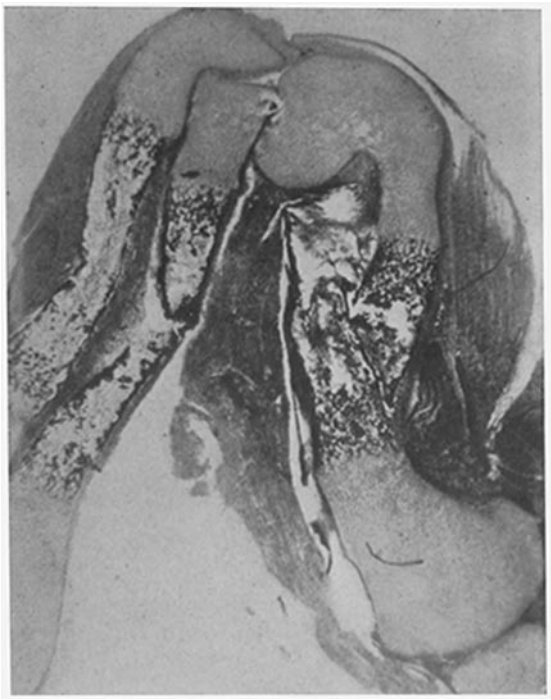

FIG. 1.

FIG. 2.

(Ingier: Barlow's Disease Experimentally Produced.)