HEREDITARY DISTAL FORELEG CURVATURE IN THE RABBIT

II. GENETIC AND PATHOLOGICAL ASPECTS

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An inherited skeletal abnormality of the rabbit in which the lower segment of the foreleg was permanently curved has been described in the preceding paper (1). This curious condition developed during the period of active bony growth and the bowing was well defined as early as at 6 weeks of age. The convexity of the curvature was directed inward toward the body and the paws assumed a flipper or seal-like position. From the results of physical and x-ray examinations it was found that the distal epiphyseal cartilage of the ulna was the site primarily affected and changes elsewhere appeared to be secondary to or have resulted from the ulnar lesion. The progressive development of the ulnar lesion up to 2 to 3 months of age was followed by comparatively rapid regression of it with healing at 3 to 4 months of age.

The deformity was noted in the early days of the rabbit colony long studied in The Rockefeller Institute. It was first observed in the offspring of pure bred Beveren rabbits and almost at the same time in certain families of pure bred Belgian and French Silver rabbits. The familial character of its distribution was noted again after several years when another example was observed in the progeny of recently purchased pure bred Dutch rabbits. That the abnormality had in fact an hereditary basis was soon evident and the results of breeding tests showed that all offspring of affected parents likewise developed the deformity (1).

The results of further studies on the genetic aspects of the abnormality as obtained from F1, F2, and backcross test breeding experiments are described in the present report. It also contains the observations made at postmortem examination and the results of the microscopic study of representative organs and tissues, particularly those of the foreleg bones.

Pathological Findings

The postmortem examination of the rabbits with hereditary foreleg bowing deformity revealed nothing of note other than the lesion of the distal epiphysis

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of the ulna, the bowed ulna and radius, and the positional changes of the carpus and paw. There was a questionable enlargement of the parathyroid glands. It will be recalled that the development of the deformity from its first clinical manifestation of enlargement of the distal ulna epiphysis to the final state of permanent foreleg curvature was not associated with any disturbance or unusual feature of body growth or of general physical condition (1). A possible thickening of the distal epiphysis of the radius was sometimes noted in x-ray photographs but it was thought that the slightly increased shadow of this area was most probably of the nature of a reaction to the strain of curvature of the immature bone, the curvature itself resulting from the firm attachment of the developing radius to the progressively curving ulna (1).

The changes observed in the distal foreleg bones will be described in the following order. Many of the illustrations are accompanied by x-ray photographs taken at various ages. The material selected for illustration was obtained from rabbits of the deformed Beveren, Belgian, and French Silver stocks.

1. Fresh and dried foreleg bones of adult cases.
2. Split bones from rabbits 5 to 11 weeks of age; histologic sections of 3 of these specimens from rabbits 7 and 8 weeks of age.
3. Histologic sections of developing and progressing lesions from rabbits 10 days to 3 months of age.
4. Histologic sections of regressing and healed lesions from rabbits aged 2 to 4 months.

General Postmortem Observations.—The state of nutrition was excellent. The skin and subcutaneous tissues and the superficial and deep fat deposits were normal. In certain cases of extreme bowing deformity with extensive marked twisting and flattening of the lower foreleg bones, the surface in contact with the ground was not the paw but the wrist or lower foreleg segment or even occasionally the elbow, the skin of the contact area becoming calloused and denuded of hair (Fig. 3 in the preceding paper). With one exception the muscles including those of the diaphragm showed nothing unusual. Along the median surface of the radius the muscles appeared to be less well developed than normal. This feature was noted particularly in the 2nd and 3rd month of age and occasionally in older cases. The condition of the superficial and deep lymph nodes, the thymus, and spleen appeared to be normal, and so too with the bone marrow, viscera, cranial cavity and its contents. The viscera appeared normal. The thyroid and pituitary glands showed nothing of note.

The external parathyroid glands of some rabbits during the period of development of the foreleg deformity, that is from 2 or 3 weeks to approximately 3 months of age, were rather large and opaque, the color of some glands being pale beige or ivory or pale yellowish pink. There were no obvious accessory nodules of parathyroid tissue. The adrenal glands of some rabbits in this period of developing deformity tended to be large; the appearance of the surface and cut section was normal. The number of available organ weight determinations is unfortunately not sufficient for a basis of comparison and one cannot say whether there was parathyroid and adrenal enlargement.

Gross Skeletal Observations.—The skeleton was normal with the exception of the ulna and radius, the ulna-carpus articulation, and the position of the forepaw. At about 4 to 6 weeks of age, both the ulna and radius showed a considerable lateral curvature. Less pronounced
curvatures in the anteroposterior plane were also often present and as the condition progressed, flattening or “dishing” of the bones were observed. In older marked cases various degrees of twisted bones were frequently seen.

The area of deepest dishing was the central or distal portion of the anterior surface of the shaft. These features of bowing, twisting, and flattening of the radius and ulna are illustrated in the photograph of the partly dissected lower forelegs of a rabbit 1 year, 2 months, of age (Fig. 1); the anterior or upper surface of the left foreleg and the posterior or under surface of the right foreleg are shown. In addition to the distorted outlines of the leg bones, the photograph shows the abnormal position of pronation of the paw.

Other examples of the deformity are illustrated in the photographs of dried bone specimens of a Beveren rabbit aged 7 months (Fig. 2) and of a French Silver rabbit aged 3 months (Fig. 3). The similarity of the condition in the French Silver rabbit to that in the Beveren breed is obvious. For comparison, a photograph of a dried specimen from a normal rabbit aged 2 years, 5 months, is reproduced in Fig. 4.

The deformed Belgian stock is represented by the photograph of the dried foreleg bones from a rabbit aged 2 months (Fig. 5); an area of the distal ulna was cut away to expose the widened epiphyseal cartilage. The pronounced lesion of the epiphysis at 27 days of age is shown in the x-ray photograph reproduced in Fig. 6 and it will be noted that the abnormality in this Belgian rabbit appears to be entirely comparable to that observed in the Beveren breed.

Another example of typically deformed foreleg bones is shown in the photograph (Fig. 7) of the dried specimens from 7 litter mates aged 80 days; 2 other litter mates with similar bowing were killed at 60 days of age. Both parents belonged to the Beveren flipper stock and showed well marked bowing. All 7 specimens depicted in Fig. 7 show a considerable lateral curvature, most pronounced in the sixth specimen; an x-ray of these bones taken at 36 days of age (Fig. 8) gives an excellent idea of the character of the early marked ulnar epiphyseal lesion. In the other 6 specimens (Fig. 7) a good grade of deformity obtained. An x-ray of the leg bones of the second specimen at 36 days of age (Fig. 9) indicates an ulna involvement almost as marked as that shown in the specimens of Fig. 8. The character of the practically healed ulnar epiphyseal lesion and the well marked bowing of both leg bones at 80 days of age, the day the rabbits were killed, are well brought out in the x-ray photograph of the second specimen reproduced in Fig. 10.

Longitudinal section of the deformed foreleg bones of rabbits 1 to 3 months old revealed the conspicuous lesion of the distal epiphysis of the ulna. The changes which were first discernible at 2 to 3 weeks of age increased very rapidly for 1 to 2 months and thereafter rapidly regressed so that by 3 to 4 months of age the epiphysis had an essentially normal appearance. The characteristic feature of the actively progressing lesion was a marked increase in the thickness and width of the cartilage, together with irregularities of outline particularly of the inner margin where frequently they were very pronounced, a projection, for example, extending well into the metaphysis or even the diaphysis. The semipaque greyish white cartilage contained occasional dots or tiny streaks of a semitranslucent faintly bluish tint, while its periphery particularly along its inner margin was outlined by an opaque white rim or band of variable width. The cut surface of the distal epiphysis of the radius had an essentially normal appearance except for possible slight thickening of the cartilage. The
cortex of both the ulna and radius became somewhat thickened. The cut surfaces of the split bones showed to advantage their lateral curvature while unevenness of surface level indicated the extent and degree of bone twisting and flattening.

A photograph of both forelegs, one intact and the other with longitudinally sectioned ulna and radius, from 5 deformed rabbits 7 to 8 weeks old and of a normal rabbit 7 weeks old gives an excellent idea of the appearance of the affected bones at the height of development of the active condition (Fig. 11). Four of the abnormal rabbits belonged to a flipper Beveren litter and the fifth was a Belgian animal. Also reproduced are x-ray photographs of foreleg bones of 2 of the Beveren stock rabbits taken 3 days before the animals were killed (Figs. 12 and 16); of the Belgian rabbit taken 2 days before (Fig. 19); and of the normal rabbit taken on the same day (Fig. 14). Photomicrographs of legbone sections of these animals are also depicted (Figs. 13, 15, 17, 18, 20, and 21).

The most conspicuous feature of all the split abnormal bone specimens (Fig. 11) was the greatly expanded and irregular distal ulna epiphysis; it is several times the size of a normal epiphysis. In the specimens obtained from the 4 Beveren litter mates the central portion of the expanded epiphysis comprised about half its total area, its color was a semitranslucent pale faintly bluish grey, its resistance to section firm but not hard and its shape ovoid or roughly triangular. Encircling this central area or core was an opaque whitish collar varying in thickness from a narrow stripe along the outer margin to a considerably wider irregular inner or proximal band. There was a brittle resistance of this tissue to section or probing. Both the ulna and radius showed a well defined lateral curvature, most pronounced in the distal and midportion of the bones. The cortex of the ulna shaft and possibly that of the radius was slightly thickened. The appearance of the distal epiphysis of the radius was normal.

The fifth abnormal specimen (Fig. 11, lower right corner) was obtained from a deformed Belgian rabbit a week older than the 4 litter mates just referred to. The lateral curvature of both foreleg bones was well marked. The distal epiphysis of the ulna was greatly enlarged and most of its area was a semiopaque darkish grey or greyish blue color with a sparse sprinkling of points and tiny streaks of opaque white. Its proximal portion was a comparatively narrow and slightly irregular band of opaque greyish white tissue. There was less of this tissue in this specimen than in those of the 4 Beveren litter mates. The cortical bone of the ulna shaft was somewhat thickened. The cut surface of the radius showed nothing remarkable except a slight thickening of cortical bone.

The x-ray photographs of 3 specimens shown in Fig. 11, 2 from Beveren stock rabbits (Figs. 12 and 16) and the other from the Belgian rabbit (Fig. 19), give an excellent idea of the marked expansion and irregularities of the ulna epiphyseal cartilage, with cupping a very conspicuous feature. The area of calcium opacity is much greater than is found in the ulna epiphysis of normal rabbits.
of the same age group as is shown in the x-ray photograph reproduced in Fig. 14. The cortical bone shadow of the ulna and probably also of the radius is slightly thickened.

The appearance of the sectioned foreleg bones of deformed rabbits of the Belgian and French Silver stocks was entirely comparable with that of Beveren cases. This is well shown in the photographs of the split bones of a 50 day old Belgian rabbit reproduced in Fig. 22 and of an 8 week old French Silver rabbit reproduced in Fig. 26. Conspicuous features in both cases are the greatly expanded distal epiphysis of the ulna and the inwardly directed lateral bowing of ulna and radius, the characteristic manifestations of the developing Beveren deformity. In the x-ray photographs of the French Silver rabbit taken at 43 and 52 days of age (Figs. 26 and 27) the markedly expanded ulna epiphysis with cupping has the same appearance as that of a Beveren deformity of the same stage.

Beginning at about 2½ or 3 months of age the appearance of the distal epiphysis of the ulna became less and less abnormal, the expanded cartilage plate decreased in thickness and width and its margins became smooth and regular while the excessive calcification disappeared. The entire process of regression of the acute ulnar epiphyseal lesion was rapid and in practically all cases no abnormalities could be detected on inspection of the split bone or in x-ray photographs by the time the rabbit was 4 months of age. The bowing deformity of the ulna and radius was, of course, a permanent feature. The other bones of the foreleg, the humerus, the carpal and metacarpal bones, and the phalanges continued to be unaffected except for the pronation position of the paw and variations in the ulna-carpus articulation.

Despite the form and the usual degree of the permanent bowing deformity there appeared to be little shortening of the lower foreleg segment. Although there may have been some reduction in over-all length, it was not obvious except in cases with extreme twisting and rotation of the ulna and radius.

HISTOLOGIC OBSERVATIONS

In the foregoing descriptions of x-ray photographs and postmortem examinations of rabbits with bowed forelegs, it was pointed out that only the distal epiphysis of the ulna was primarily affected and that the other abnormalities, the curvatures of the ulna and radius and the fixed positional changes of paw and wrist, were secondary to the ulna lesions. This conclusion was confirmed by the results of the microscopic study of representative tissues from deformed rabbits of various ages. The histologic appearance of the ulnar lesion will now be described.

The characteristic feature of the ulnar lesion was the great widening and irregularity of the cartilage plate during the period of progressive bone growth. The older cartilage cells did not degenerate and disappear leaving numerous
spaces into which blood vessels and osteoblasts of the shaft could penetrate as in a normal bone. The cartilage cells persisted and continued to multiply giving rise to an increasingly broad cartilaginous zone. From its inner surface or margin numerous projections of cartilage were found in the metaphysis. Calcification was somewhat delayed and osteoid tissue was abundant. With increasing age, however, spongy bone was soon very prominent. Beginning at about 2½ months of age, the cartilage plate rapidly diminished in thickness and resorption of spongy bone proceeded quickly. By 4 months of age the distal segment of the ulna in the majority of cases had an approximately normal appearance in x-ray photographs, in longitudinally sectioned fresh specimens and in histologic preparations.

The earliest cartilage changes were found in histologic preparations from rabbits in the 2nd week of life; at this age they were not detected in the gross or in x-ray photographs. In the photograph of a 10 day specimen (Fig. 28), the irregularities of the inner margin of the epiphyseal cartilage are comparatively slight but are perfectly definite.

At 4 and 5 weeks of age, the increased thickness and irregularities of the epiphyseal cartilage are prominent features as is well shown in the x-ray photograph (Fig. 29) and two photomicrographs (Figs. 30 and 31) of a 34 day old rabbit. These illustrations should be compared with the x-ray photograph (Fig. 32) and a photomicrograph (Fig. 33) of a normal rabbit aged 35 days. In the deformed rabbit, the increased number and persistence of cartilage cells and the extent of osteoid tissue are well shown (Figs. 30 and 31). The distal epiphyseal segment of the radius in the x-ray photograph (Fig. 29) and in the low power photomicrograph (Fig. 30) shows none of the characteristic abnormalities of the ulna cartilage, but the bowing or curvature of the slender radius is well advanced and more marked than that of the stock ulna.

During the next few weeks, the epiphyseal ulnar lesion continued to progress rapidly and by about 8 weeks of age the enlargement and irregularities of the cartilage were very striking. This characteristic feature of the condition has already been pointed out in the descriptions of sectioned bone specimens and their x-ray photographs, as well as in the description of the clinical manifestations in the previous paper (1).

Four typical examples of the distal ulna segment at 7 to 8 weeks of age are shown in the low power photomicrographs reproduced in Figs. 13, 17, 20, and 23; higher magnification of 3 of the specimens are reproduced in Figs. 18, 21, and 24; and x-ray photographs of 3 of the foelges are reproduced in Figs. 12, 16, and 19. For comparison, an x-ray photograph and a low power photomicrograph of a normal specimen taken at 7 weeks of age are depicted in Figs. 14 and 15. In all these specimens the greatly enlarged massive and irregular cartilage plate of the ulna contrasts very sharply with the narrow uniform plate of the normal rabbit (Figs. 12 and 13). The marked cellular changes in the
cartilage, including the persistence of the cells together with an increased matrix, many cartilage projections or extensions into the metaphysis and a considerable amount of spongy bone, are well brought out in the photographs at higher magnifications reproduced in Figs. 18, 21, and 24.

There were some cases in which the enlargement of the ulna cartilage plate was extremely marked, an example of which is shown in the photomicrograph of a specimen obtained from a 61 day rabbit (Fig. 36). The cartilage was many times the size of a normal plate and had become cone- or pear-shaped; it occupied practically all the metaphysis and extended into the diaphysis. The border had many fine and some larger irregularities. A photomicrograph at a higher magnification (Fig. 37) gives a good idea of the condition of the cartilage in the enlarged plate, its projections and also the relationship of the cartilage projections to the metaphysis and diaphysis of the bone. The character of the cartilage and spongy bone in the metaphysis is shown in the high power photomicrograph depicted in Fig. 38. The character and extent of the pronounced cartilage lesion is also revealed by the x-ray photograph taken at 58 days of age (Fig. 35). An earlier x-ray photograph (Fig. 34) taken 3 weeks previously, that is, at 37 days of age shows well the very extensive and well established cartilage lesion in which cupping is a conspicuous feature.

In both x-ray photographs and in the low power photomicrograph (Fig. 36) the distal epiphyseal cartilage of the radius shows nothing unusual. Curvature of the distal third of this bone, however, is well marked at 2 months of age (Figs. 35 and 36).

BIBLIOGRAPHY

EXPLANATION OF PLATES

No legends for the pictures are available, but the text tells of them sufficiently.
(Pearce: Hereditary distal foreleg curvature. II)
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