

On the Inheritance and Development of Clinodactyly

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IN MAN, as in other animals, the external characteristics of the integumentary system are the most easily studied from the genetic point of view. And many such traits are known (Cockayne, 1933). The most easily studied internal system is obviously the endoskeleton, since it determines the shape and form of the organism and any change or modification of it is readily noticed. In the case of the skeleton, as no doubt in other organ systems, most hereditary differences are dependent upon multiple factors. The gradational variability in the absolute and relative size of the bones and parts of the face is unquestionably the genetic basis for the inexhaustible variety of the human countenance. There is considerable gradational variability also in the skeleton of the appendages as shown by the radiological examination of twins and triplets (Buschke, 1935).

Of the many hereditary skeletal defects which stand in sharp contrast to the normal, only a relatively few involve the skull, while the overwhelming majority affect the skeleton of the appendages. A possible explanation is that any considerable change in the skull might be lethal. However, there is another possibility. It is well known that many mutants affect the bristles in *Drosophila melanogaster* and other species while this is not the case in *D. hydei* (as shown especially by Spencer, 1949), although the latter species has also been extensively studied from the genetic point of view. Briefly, it happens that all parts of the organisms are not equally plastic and this, although a problem in genetics and evolution, is still largely unsolved, (see discussion by Muller, 1949). Its solution, no doubt, awaits a more detailed knowledge of how genes act and interact to produce their effects. In addition to ease of detection, the mutant traits of the skeleton, in contrast to other internal traits, can be most readily studied by the X-ray technique to obtain considerable knowledge in developmental terms of how the genes act. And this can be supplemented by the present high state of knowledge on the histogenesis of bone.

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The following report is on clinodactyly, or "crooked little fingers". It attempts to analyze all the available data to determine the mode of inheritance and secondly to discuss the trait from a developmental point of view. This task is facilitated by the publication (Bell, 1951), of a monograph on hereditary digital anomalies and by the radiographic atlas of standard plates of normal development of hand and wrist by Greulich and Pyle (1950) from birth to complete maturation of the skeleton.

Of the many forms of digital anomalies reported in the literature the bone deformity in the middle phalanx of the fingers is among the most prevalent. Moreover, the deformity in the middle phalanx of the 5th finger appears less variable than some other digital anomalies, and so has been proposed as one of the more favorable traits for linkage studies in man.

In the monograph mentioned Bell has made a classification of the various types of brachydactyly and classifies as A_3 the trait discussed here. It involves a shortening of the middle phalanx of the 5th finger, especially on the radial side, which in turn leads to a radial deflection of the terminal phalanx, while the remaining digits are normal. These cases should not be confused with other types of crooked little fingers as presented by Hefner (1924, 1929, 1941), Koenner (1924), Moore and Messina (1936), and Stoddard (1939).

We have observed at least two cases in which the radial inclination of the fifth digit included the two terminal phalanges instead of only the terminal phalanx. These cases are not included in the following analysis. Bell's pedigree #17 is also not included in the pooled data discussed below. Although she classifies it under her type A_3 , yet it is clearly not a case of uncomplicated clinodactyly, since syndactyly as well as unilateral manifestation are involved.

THE DATA

The pedigrees collected and recorded by us (Figure 2) were made by a visual inspection of the hands. In five individuals the trait was recorded by correspondence. In every case we made certain that only the little finger was involved and that the curving was radial. Moreover, we made certain that this bending began from the interphalangeal joint of the middle and distal phalanx, i.e., the distal phalanx was tilted radially. The majority of the cases of clinodactyly are readily identifiable. If there is a doubt as to whether or not the case is clinodactylous, one can be almost entirely certain that it is not. It is somewhat like dwarfism. If there is doubt as to whether a person of short stature is a dwarf, the probability is overwhelming that he is simply at the extreme low end of the curve of normal variability. As a matter of record a large number of normal little fingers which have been observed by us have some slight degree of radial curvature. Clinodactyly produces no impairment on the movement of the hands. Further, X-ray studies of some of these cases show that all of the rest of the phalanges of the hands are normal.

The normality was determined merely by inspection in a comparison with the radiographic atlas mentioned. There is at present no standard series of measurements of sizes and angles of inclination for the phalanges of the normal hand

Figure 1 shows a photograph of a typical case of clinodactyly. These hands belong to one of the identical male twins illustrated in Figure 2, case D, II 5. In Figure 1, notice that the degree of curvature is remarkably uniform in both little fingers. The distal phalanx inclines radially, forming an angle of nearly 20° . The degree of radial curvature may be determined by the angle formed between the mid-longitudinal line of the distal phalanx and the mid-longitudinal

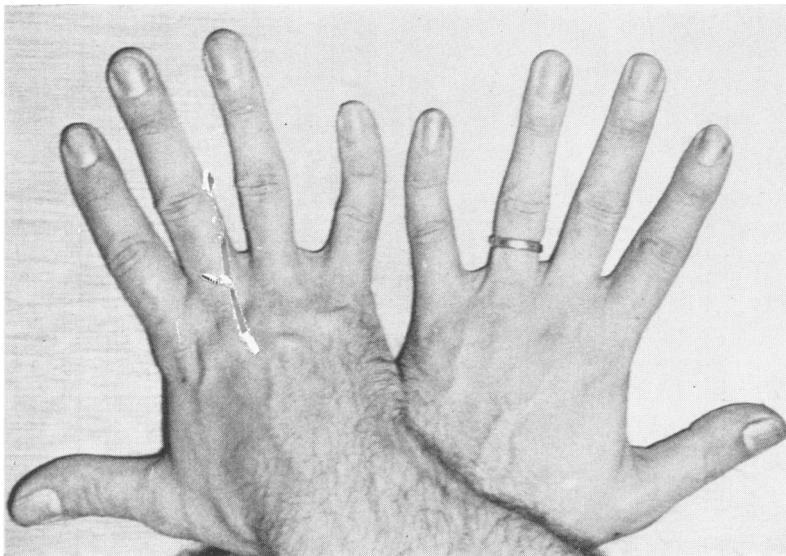


FIG. 1. Photograph illustrating a typical case of "crooked little fingers" or Clinodactyly. The left and right hands of this individual have been crossed to facilitate the comparison of the radial curvature in the two little fingers.

line passing through middle and proximal phalanges. Angle measurements made from the three X-ray photographs are undoubtedly much more accurate and range from 15° to nearly 30° . No attempt was made to collect other associated traits in these individuals. However, webbed toes occur between the 3rd and 5th digit in both identical twins and in the daughter in Figure 2, case D, II-4 and 5, III-2.

Figure 3, *A* and *B*, illustrates two X-ray photographs taken of the hands of two sisters found in case E, II-1 and 2, (Figure 2). *A*, was about 20 years old and *B* was about 10 years old. In *A*, the older girl, all of the phalanges of both hands are normal except for the middle phalanx of the 5th finger. This phalanx is slightly shorter on the radial side, forming a visible slanting on its upper

surface. As a result of this slanting, the normal distal phalanx sets in a radial inclined position. The hands of her younger sister, *B*, clearly show all normal phalanges with their respective unfused epiphyses, a condition which is normal

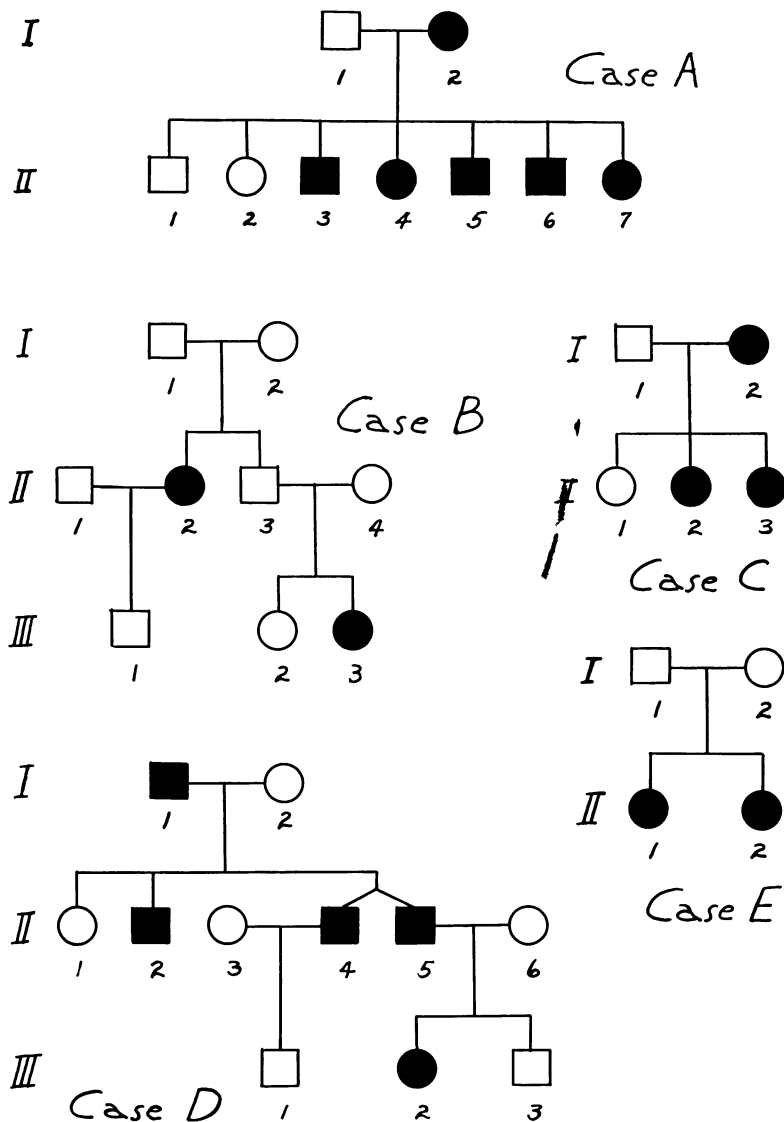


FIG. 2. Pedigrees of "crooked little fingers" or Clinodactyly

for children of this age, except for the middle phalanx of the 5th finger. Here we note an under-developed ossification area on the upper radial position of each of these phalanges. Figure 4 *B*, an enlargement made from Figure 3 *B*,

illustrates this condition more clearly. The arrows point at the unossified areas on the radial side of each middle phalanx of the 5th finger. These areas appear

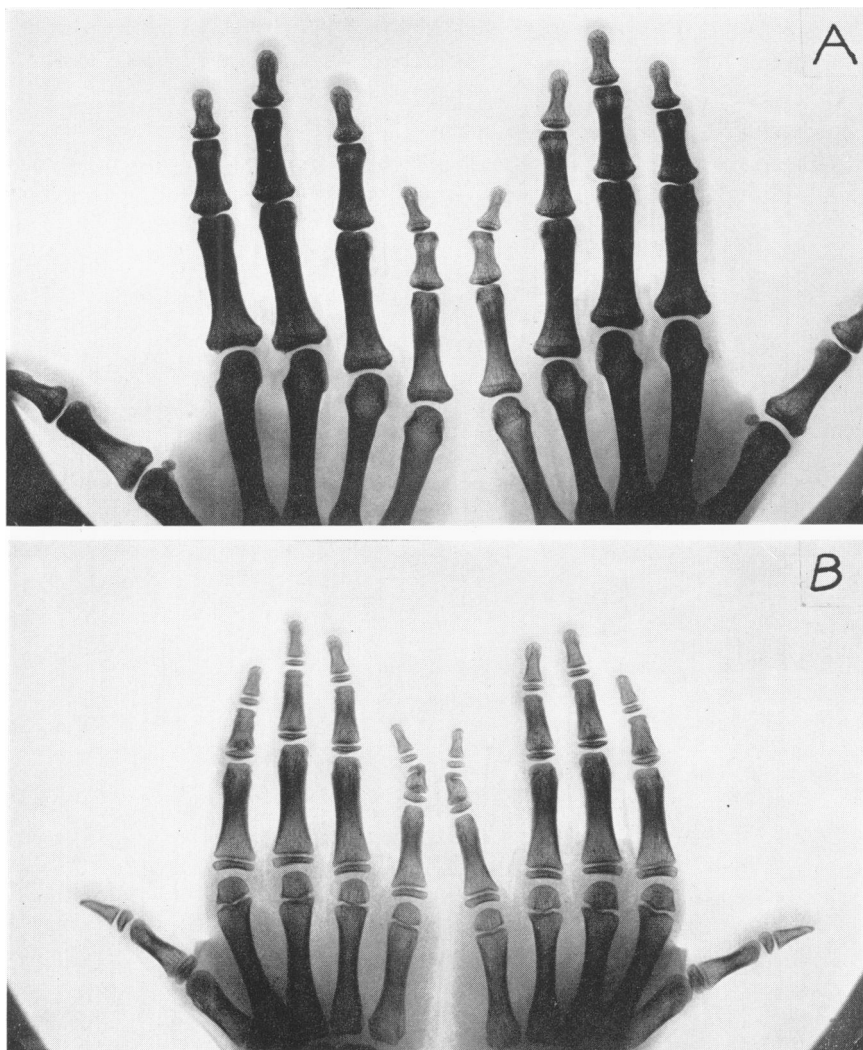


FIG. 3. X-ray photographs of the hands of two sisters with "crooked little fingers" or Clinodactyly. The older sister, *A*, is about 20 years of age. The upper surface of the middle phalanx of both little fingers is slanted radially causing the distal phalanx to incline radially. *B*, the 10-year old sister shows similar inclination of the little fingers. Note the underdeveloped ossification area in the middle phalanx of both little fingers. (See Figure 4, *A* and *B* for detail views).

to be still in a cartilaginous stage. Figure 4 *A* shows a radial view of the left and right "crooked little fingers" of the 20 year old sister. The ossification of these areas is already completed at this age. This view, 4 *A*, also shows that the inclination is not of the flexion type.

These facts seem to indicate that clinodactyly is a definite case of developmental arrest of the ossification center. This slowing-down process of ossification might possibly begin at any time after the ossification center appears during the embryonic life and extend well beyond 10 years of age. Moreover, this arrest is restricted to a definite area of the middle phalanx of the 5th finger.

Figure 5 illustrates a variation of clinodactyly. Figure 5 *A* shows an X-ray photograph of the hands of a 4-year old girl with a definite but mild case of clinodactyly. She is the daughter of one of the identical twins with clinodactyly,

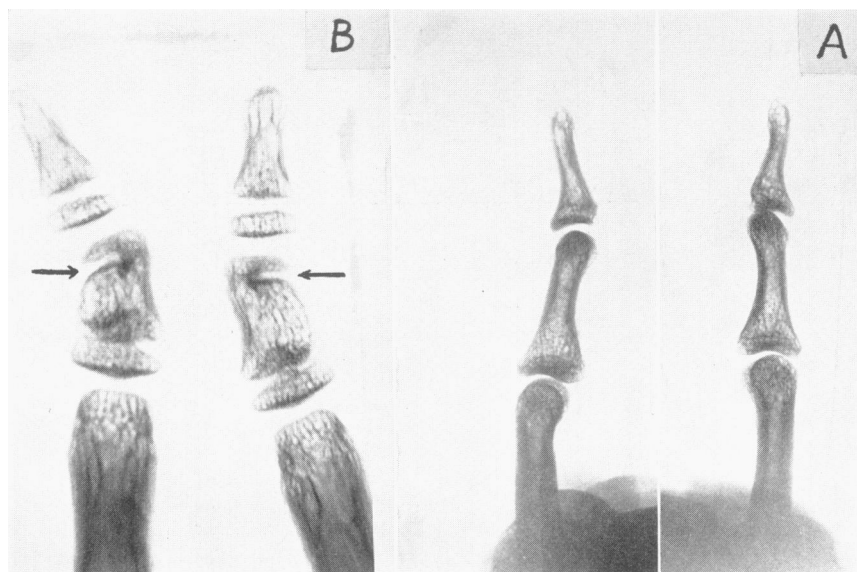


FIG. 4. X-ray photograph enlargements, *A*, radial view of the left and right "crooked little fingers" of the 20-year old girl. Notice there is no inclination in the direction of flexion. *B*, shows the left and right "crooked little fingers" (5th) of the 10-year old sister. Note the underdeveloped ossification area in the upper radial region of the middle phalanx (pointed out with arrows). For complete view of the hands see Figure 3, *A* and *B*.

illustrated in the pedigree chart in Figure 2, case D, III-2. As one can see the radial bending of the little finger in this 4-year old is not as severe as the 10-year old illustrated in Figure 3 *B*. A detail view of the two little fingers, Figure 5 *B*, shows that the ossification of the upper radial area of each middle phalanx is already completed, while in the 10-year old this area is still in cartilage stage. The only evidence we see is a small dent in each of these phalanges as pointed out by arrows in Figure 5 *B*. It seems evident, therefore, that in clinodactyly the degree of radial bending is related to the length of the period of delay of the ossification process. In the 10-year old girl the radial bending is quite severe and the ossification is not complete, while in the 4-year old the bending is much

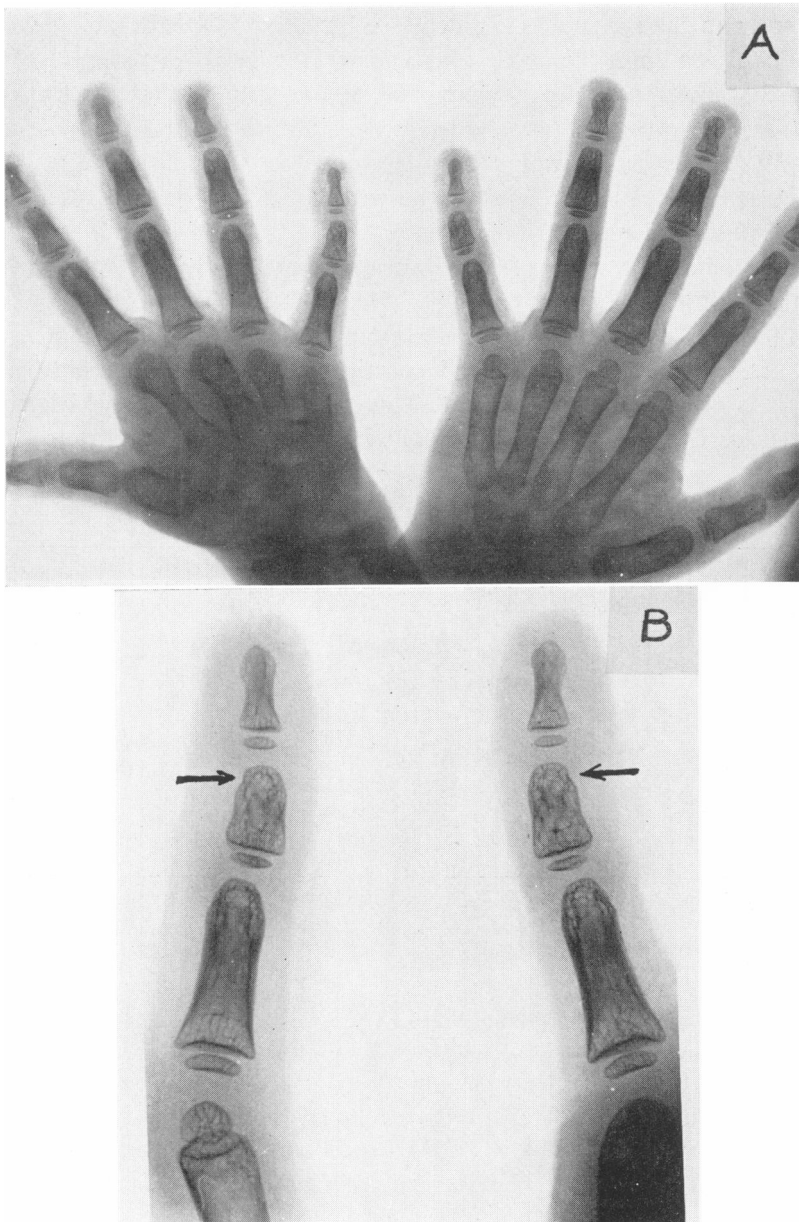


FIG. 5. X-ray photographs of the hands of a 4-year old girl with a mild case of clinodactyly. *A*, complete view of the left and right hands, showing a slight but definite radial bending of the little fingers. As seen in *B*, a detailed view of the two little fingers, the ossification of the upper radial area of the middle phalanges is already completed, only a small dent (pointed out by arrows) is seen in the radial region of these two phalanges.

less severe and the ossification is already completed. One might naturally have expected that the X-ray picture for the 4-year old would show a still

earlier stage in the incomplete ossification. But as mentioned this is definitely not the case. The possible explanations for this from a genetic point of view are first that multiple alleles may be involved, or secondly, that genes at different loci are concerned, or perhaps most plausibly, the effect is one of several modifying factors, which would at the same time explain the slight lack of penetrance. Clearly no decision can be reached on the basis of the present data and observations.

In determining the mode of inheritance of clinodactyly we have combined our data with those presented by Bell (1951) as A_3 -type, except for her pedigree #17. They are listed in Table 1. The combined data involve 15 pedigrees with a total of 51 sibships. Analysis by inspection of the pedigrees indicates that this trait is an autosomal dominant. There are 4 instances in which neither parent shows the trait, denoting a slight lack of complete penetrance. In all

TABLE 1. COMPARISON OF AFFECTED SIBS WITH THEORETICAL EXPECTATION ON BASIS OF SIMPLE AUTOSOMAL DOMINANT (1:1 RATIO)

SIZE OF SIBSHIP (z)	NO. OF SIBSHIPS (n_z)	TOTAL SIBS (zn_z)	AFFECTED SIBS (r)	CORRECTIVE FACTOR (f)	EXPECTED AFFECTED (fn_z)	VARIANCE (s^2)
1	10	10	10	1.000	10.000	—
2	12	24	16	1.333	15.996	2.666
3	10	30	20	1.715	17.150	4.898
4	5	20	14	2.134	10.670	3.911
5	3	15	11	2.581	7.743	3.246
6	2	12	6	3.047	6.094	2.758
7	5	35	25	3.527	17.635	8.335
9	1	9	7	4.509	4.509	2.215
10	3	30	17	5.005	15.015	7.434
Totals	51	185	126	—	104.812	35.643

$$s = \pm 5.95.$$

other cases only one parent is affected. Numerical tests applied on the pooled data listed in Table 1 show unusual results. In spite of the small lack of penetrance there are significantly more affected than expected on the basis of a 1:1 ratio, even after applying the corrective factor (Hogben, 1946) for small family size. The difference between the 126 observed affected and the 105 expected affected is 21, while the standard deviation is slightly under 6. This significant difference might most plausibly be explained if the early published pedigrees were reported merely because of the unusually large number affected.

Also an attempt was made to find the frequency with which clinodactyly occurs in the population, in order to determine the gene frequency. In a study of Heberden's nodes (enlargement of the terminal joints of the fingers owing to hypertrophic arthritis) over the years (Stecher, 1940) and one which is still continuing, there was a total of 4304 white patients over 20 years of age ex-

amined at the City Hospital of Cleveland. Of these 2117 were men and 2187 were women. Only 4 cases of clinodactyly were found; of these 3 were men and one a woman. Although these data do not give an ideal cross section of the population, yet they nevertheless give an indication of the incidence of clinodactyly in the population of Northern Ohio. From these data the incidence of clinodactyly may be taken as approximately 1 in 1,000. Consequently, assuming random mating and genetic equilibrium, the frequency of d , the dominant gene for clinodactyly has a frequency of 0.0005 and for the normal recessive allele r , the frequency is 0.9995. The incidence of heterozygotes in the population is nearly 1 in 1,000. The homozygotes would be expected to occur about 1 in 400,000.

It perhaps should be pointed out that the pedigrees and the numerical test are in agreement with the hypothesis that clinodactyly is a simple autosomal recessive trait. On this basis then with the incidence in the population of 1 in 1,000, the frequency of the recessive gene is 0.032 and for the dominant normal allele the frequency is 0.968. Consequently the frequency of heterozygotes in the population is 0.06 or about 1 in 16. With the population mating at random in regard to clinodactyly then about 1 in 256 marriages should be between heterozygotes and about 1 in 4 of these families would have affected children, i.e. approximately 1 in 1024 marriages. In the 51 sibships there were 4 with neither parent affected. Clearly, on these grounds, the data overwhelmingly favor the conclusion that clinodactyly is an autosomal dominant with a slight lack of penetrance.

DISCUSSION

Clinodactyly should be clearly distinguished from other types of crooked little fingers in that clinodactyly specifically affects the bone formation of the middle phalanx of the 5th finger in a manner that it inclines radially. All other cases of crooked little finger as reported in the literature should be clarified and properly classified at this point. From the study of our data as well as the data presented by Bell (1951), Hefner (1924, 1929, 1941), Koenner (1924), Moore and Messina (1936), Stoddard (1939), and Pol (1921), it seems clear that the inherited types of crooked little fingers may be classified into three general categories; (1), those due to *incomplete ossification*, (2) those due to *abnormal tendons*, and (3) those caused by *fused ossification*. For example, the incomplete ossification type may well be represented by our data as well as those of Pol (1921); the abnormal tendon type may be represented by Hefner's cases, and the fused ossification class by Koenner's data. These three general categories may well apply in classifying digital anomalies of the other fingers. In our opinion this proposal of the method of classifying digital anomalies has the distinct advantage over the method suggested by either Bell (1951), or Stoddard (1939) in that this method is more inclusive. Practically all of the

different forms of hereditary digital anomalies may be classified under any one of the three categories or combination of them.

The previous analysis clearly leads to the conclusion that clinodactyly is inherited as a simple autosomal dominant. Furthermore, X-ray observations indicate that clinodactyly is a trait which seems to be brought about by a slowing-down process of ossification, specifically in the upper radial area of the middle phalanx of the 5th finger. This slowing-down process might be interpreted from two points of view; (1) as a direct arrest of the bone-forming process, or, (2) as a delay in the orderly transformation of the cartilage cells. According to the first point of view, this arrest may be caused by either a local failure in the supply of the bone minerals, or by a delay in the production of phosphatase in the osteoblasts. This delay extends for quite a long period of time. It may possibly begin sometime after the 83rd day-old embryo and extend well beyond the 10th year of age. Mall (1906) in studying the early human embryos with regard to the time of the appearance of the ossification centers in the phalanges, stated that "the second row are the last phalanges to appear. On the 75th day the center in the second phalanx is well-formed and those of the third and fourth phalanges are each represented as two very small nuclei, the one on the radial side being a little longer than the one on the other side. On the 83rd day a single center appears in the fifth phalanx. It is crescent-shaped with its closed side outwards and the open side directed towards the radial side of the hand. It retains this form, growing only in size in embryos up to 105 days old." If we are permitted to use Mall's embryological observations in further interpreting our results on clinodactyly, then it means that this trait is a result of a developmental arrest of the ossification center of the middle phalanx of the 5th finger.

According to the second point of view, this arrest may be caused by a delayed reaction in the transformation of the cartilage cells. Streeter (1951), in studying the development of the human embryonic humerus during its cartilaginous period, observed that cartilage cells, as they grow older pass through an orderly series of transformations. He recognized five phases. These begin with a proliferation and growth of cells, followed by an extensive vacuolization of their cytoplasm and immediately followed by a formation of intercellular substance, and finally, ending with a liquefaction of disintegration of the cells. The end of this last phase is followed by an invasion of cells derived from the inner coating of the periosteum. These cells progressively fill in the zone of disintegrated cartilage cells, thus transforming the cartilage into marrow and bone. Although these observations were restricted to the development of the humerus, Streeter is of the opinion that all other skeletal parts (enchondral ossification) follow the same basic sequence. He believes that "the chief difference in the manner of their development rests in the extent to which a cartilaginous period intervenes between the primitive mesoblastic tissue and the definitive bony struc-

ture." In genetic terms, the dominant gene for clinodactyly produces its effect by delaying some physiological process in the orderly series of transformations of the cartilage cells, specifically localized in the upper radial region of the middle phalanx of the 5th finger. This condition in turn retards the filling-in of the bone-forming cells. As a result of this series of delays, the radial side of this phalanx is left shorter than normal, thus producing a visible slanting of its upper surface. The ulnar side is also shorter but not as much as the radial side. Consequently, the middle phalanx is shorter than normal and justifies Bell's inclusion of clinodactyly among the various forms of brachydactyly.

SUMMARY

Hereditary "crooked little fingers" have been classified into three groups based on internal causes rather than on outward appearance; (1) *incomplete ossification*; (2) *short tendon*; (3) *fused ossification*. Clinodactyly belongs to the first group.

It is a minor digital anomaly in which the middle phalanx is shorter than normal, but distinctly shorter on the radial than on the ulnar side, with the result that the terminal phalanx of the 5th finger inclines radially somewhere between 15° to 30°. There is no curvature in the direction of flexion. An analysis by inspection of pedigrees and a numerical test on the pooled data from 51 sibships lead to the conclusion that clinodactyly is an autosomal dominant. There is a slight lack of penetrance; in 4 of the sibships neither parent was affected. An X-ray study of several cases, along with Mall's observations on ossification centers in human embryos, and discussed in the light of our knowledge of the histogenesis of cartilage and bone, leads to the conclusion that clinodactyly is the result of a developmental arrest caused either by a delay of the ossification process or by a delay in the transformation phases of the cartilage cells. The best estimate at present of its incidence in the population is about 1 in 1000.

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