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Skeletal maturation
diabetes mellitus
epiphyseal maturation

Skeletal Maturation in Juvenile Diabetes Mellitus

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Extract

Skeletal maturation has been examined in a group of diabetic children using their nondiabetic siblings as controls. Serial examinations were done over a five-year period.

The diabetic children have a significantly retarded bone age, whether assessed by examination of the hand or of the foot. However, their nondiabetic siblings had comparable retardation of skeletal maturation. Thus, in comparison with his normal sibling, the skeletal development of the diabetic child does not appear to have been affected by his disease process.

There is no significant difference between the development of the hand and the foot for either group of children. When the skeletal maturation of the hand and foot is compared for each child, the correlation is 0.998.

No significant trend can be demonstrated for the relation between skeletal development discrepancy and chronological age. The initial retardation of about six months at ten years of age and the progressive retardation of about one and a half months during the next three years of life are equivalent to a decrement of a half month in skeletal age for each year of chronological age since birth.

Speculation

The moderate, but significant, retardation of both groups of children when compared to the published standards requires explanation. These groups follow a pattern similar to that reported for the children in the longitudinal study of growth in Denver. The most likely factors producing these patterns are the result of sample or standard selection. The children used for the standards in the Atlases were predominantly from families whose socioeconomic level was definitely above average, whereas the diabetic population was more normally distributed in this context.

The high correlation between hand and foot in this series indicates the importance of using the detailed assessment technique described in the Atlas Standards and used for this study. Furthermore, the high degree of correlation found between the hand and the body as a whole by Reynolds and Osakawa [19] would suggest that the hand or the foot is equally representative of total body skeletal maturation.

Introduction

Skeletal maturation has been examined in a group of diabetic children using their nondiabetic siblings as controls. Serial examinations were done during a five-year period.

Although studies of skeletal development in juvenile diabetes have been reported, the results are disparate, and suitable controls have not usually been included [2, 16]. In the present report, in addition to evaluating the effect of a major chronic illness on skeletal development using sibling controls, maturation of the hand has been compared with that of the foot in both groups of children. The hypothesis leading to this latter comparison was based on the fact that in diabetes mellitus, vascular disease is generally seen in the lower extremities before it is seen in the upper; thus any alteration in blood flow occurring prior to adolescence could be reflected by a disparity between the maturation of the hand and the foot.

Methods

The experimental subjects were the patients registered in the Children's Diabetes Clinic of the University Hospitals of Cleveland during the period 1956–1962. The control subjects were nondiabetic siblings of patients. In each family, one sibling was randomly selected for study and all comparisons were made between the child with diabetes and his own sibling. No attempt was made to match the sex of patient and control since the method used for comparisons obviates the established differences in maturation between males and females. In 23 families, one or more additional siblings were examined on at least one occasion. Roentgenograms of the right hand and foot of each individual were obtained at approximately yearly intervals.

These films were assessed by one of the authors of the Atlas used [24] in the manner outlined in the Radiographic Atlas of Skeletal Development of the Hand and Wrist [8]. In this method, age equivalents are assigned to each center visible in the region under study, and an unweighted mean is utilized as the skeletal age. Thirty-one separate centers are evaluated in each fully developed hand, and 21 centers in each developed foot. The standards of reference for the hand and wrist are in the 1959 edition of the Atlas of GREULICH and PYLE [8]; and for the foot, in the 1962 edition of the Atlas by HOERR, PYLE and FRANCIS [12]. Each film was assessed individually and without knowledge of the age or disease-state of the child. The roentgenograms of the hand and foot of an individual child were examined as independent data.

The terminology to be followed in this paper is defined as follows:

Diabetic–D: diabetic child.
Sibling–S: one randomly selected, nondiabetic sibling in family.
Hand age—HA: skeletal age equivalent based on a radiograph of hand and wrist.
Foot age—FA: skeletal age equivalent based on a radiograph of foot and ankle.
Initial—I: first radiograph obtained in study.
Final—F: last radiograph obtained in study.
Chronological age—CA: chronological age at the time of radiograph.
Diabetic age—DA: duration of diabetes since time of diagnosis.

The basic statistic used for analysis was the algebraic difference between the skeletal age equivalent of the hand (HA) or foot (FA), given in months, and the chronological age (CA) in months (HA–CA or FA–CA). Therefore, a positive value indicates that the skeletal age was advanced for the chronological age and a negative value would signify that the skeletal age was retarded in relation to the chronological age. In the comparison between diabetic and sibling, the comparison is between the diabetic's skeletal-chronological age difference and the sibling's skeletal-chronological age difference. A positive value means that the diabetic's skeletal age is more advanced (or less retarded) for his chronological age than is that of the sibling.

Two examples should clarify this procedure:

Diabetic		Sibling	
CA	HA	CA	HA
110 months	120 months	70 months	74 months

Diabetic (HA–CA) = +10 months
Sibling (HA–CA) = +4 months
Diabetic–sibling = +6 months

Diabetic		Sibling	
CA	HA	CA	HA
107 months	100 months	121 months	111 months

Diabetic (HA–CA) = −7 months
Sibling (HA–CA) = −10 months
Diabetic–sibling = +3 months

Similar comparisons were made between the skeletal age for the hand and foot, as well as for the skeletal age minus chronological age difference when last examined, and the difference when first examined.

The summary and abbreviations for these comparisons are as follows:

D = diabetic; S = sibling

$D\text{–}HA_I$: initial assessment of the skeletal age equivalent of a diabetic's hand-wrist film.

$D(HA\text{–}CA)_I$: extent of advancement (+), or retardation (–) of the skeletal age of the diabetic's hand compared to his chronological age at the time of the original evaluation.

$D\text{–}S(HA\text{–}CA)_I$: difference in the advancement (+) or retardation (–) of the diabetic's hand age compared to that of his own sibling at the time of the initial films.

$D(HA\text{–}FA)_I$: the advancement (+) or retardation (–) of the skeletal age of the diabetic's hand compared to his foot at the time of the first examination.

$D(HA\text{–}CA)_{F\text{–}I}$: maturation of the skeletal age of the hand compared to the increase in chronological age. A positive value indicates that skeletal age development was accelerated during the period of the study, and a negative value, the reverse.

The management of the diabetic state in the children was under the direction of the Pediatric Diabetes Clinic of the University Hospitals of Cleveland and is described elsewhere [22].

Table Ia. Individual data for 30 diabetics (values given in months)

Pair No.	CA_I	$CA_{F\text{–}I}$	DA_I[1]	DA_F	$(H\text{–}C)_I$	$(H\text{–}C)_{F\text{–}I}$	$(F\text{–}C)_I$	$(F\text{–}C)_{F\text{–}I}$	$(H\text{–}F)_I$	$(H\text{–}F)_{F\text{–}I}$
2	109	42	91	133	– 1	– 2	– 1	0	0	– 2
4	135	19	50	69	–27	4	–24	6	– 3	– 2
5	122	36	0	36	5	–11	4	– 2	1	– 9
8	108	11	59	70	–21	– 3	–16	– 6	– 5	3
9	132	11	14	25	–16	0	–18	1	2	– 1
11	152	23	109	132	–22	5	–22	7	0	– 2
14	94	40	14	54	–12	– 1	–13	2	1	– 3
17	154	13	83	96	–20	– 5	–20	– 3	0	– 2
18	59	25	0	25	15	– 3	6	– 2	9	– 1
19	76	47	42	89	6	– 8	6	– 3	0	– 5
22	115	43	44	87	–20	15	–19	11	1	4
23	120	15	13	28	– 6	– 3	– 8	– 1	2	– 2
25	52	15	22	37	– 4	– 2	– 3	– 3	– 1	1
27	79	13	12	25	– 3	2	– 1	3	– 2	– 1
31	23	29	16	45	2	– 3	1	– 4	1	1
33	140	15	45	60	10	3	10	3	0	0
35	79	33	59	92	–37	– 4	–37	– 7	0	3
36	100	25	17	42	–16	5	–14	3	– 2	2
37	28	11	18	29	– 6	– 4	– 7	– 2	1	– 2
38	113	34	16	50	–14	– 2	–15	– 5	1	3
39	142	25	56	81	2	10	2	11	0	– 1
44	71	39	28	67	–11	2	–11	6	0	– 4
45	122	27	28	55	– 3	4	– 5	0	2	4
46	31	14	0	14	– 1	– 2	– 3	– 3	2	1
47	100	25	45	70	5	– 8	6	– 5	– 1	– 3
48	142	12	13	25	14	0	13	– 9	1	9
50	43	12	12	24	–18	– 2	–21	– 3	3	1
51	138	42	52	94	1	–14	6	–16	– 5	2
53	73	24	23	47	–17	– 7	–19	– 7	2	0
54	113	26	15	41	–11	– 2	– 9	– 5	– 2	3
$\bar{x}$	99	25	33	58	– 7.5	– 1.2	– 7.7	– 1.1	0.2	– 0.1
SE $\bar{x}$	7	2	5	6	2.3	1.1	2.2	1.1	0.5	0.6
p					< 0.01		< 0.01			

[1] DA_I = Duration of diabetes upon initial evaluation; DA_F = Duration of diabetes upon final evaluation; see text for definition of other terms

In the course of this study, radiographs were obtained on 76 diabetic children and 55 matched siblings. Studies were performed on an additional 45 siblings from 23 of the original 76 families. In only 30 families were there at least two sets of useable films for the hand and foot for both the diabetic and the sibling. Thus a basic group of 30 families could be evaluated for every variable. For any single variable, however, a larger number of individuals was available. Therefore, the results are given both for the basic group of 30 in each case, as well as for the total number of individuals for whom there is the information in question.

Results

The individual data for the 30 diabetics for whom complete data were available are given in table Ia. The differences for each variable between the diabetic and his sibling are listed in table Ib. Individual datum for sibling controls can be calculated by comparing the appropriate numbers in these tables. The summary of these figures, as well as the summary for the larger group which were available for each specific calculation, is given in table II. In this table, the data for the diabetic children are shown directly in the first set of

Table Ib. Diabetic-Sibling Differences: Diabetic value minus sibling value

Pair No.	CA_I	CA_{F-I}	$(H-C)_I$	$(H-C)_{F-I}$	$(F-C)_I$	$(F-C)_{F-I}$	$(H-F)_I$	$(H-F)_{F-I}$
2	– 3	5	7	10	7	11	0	– 1
4	–22	0	–27	0	–24	3	– 3	– 3
5	79	1	5	– 9	5	– 1	0	– 8
8	86	– 1	–13	2	– 7	– 1	– 6	3
9	77	– 1	–33	3	–31	6	– 2	– 3
11	–19	– 4	– 7	8	– 7	10	0	– 2
14	–20	– 8	– 2	4	– 5	6	3	– 2
17	21	1	– 2	– 6	– 4	– 4	2	– 2
18	21	2	15	8	12	9	3	– 1
19	–32	5	– 1	–10	3	– 8	– 4	– 2
22	55	1	– 6	19	– 1	13	– 5	6
23	33	0	14	– 2	13	– 2	1	0
25	– 1	2	–14	– 2	–11	– 7	– 3	5
27	–12	0	15	0	12	5	3	– 5
31	–14	– 2	5	4	4	4	1	0
33	40	– 5	– 6	–17	– 6	–17	0	0
35	–15	– 1	–12	11	–11	5	– 1	6
36	–29	0	8	– 1	5	0	3	– 1
37	–51	0	–13	– 5	–18	– 2	5	– 3
38	2	– 4	11	– 7	10	– 9	1	2
39	45	– 4	13	10	9	15	4	– 5
44	28	2	7	13	8	16	– 1	– 3
45	–14	1	– 9	12	– 7	9	– 2	3
46	9	0	– 1	– 2	– 1	– 2	0	0
47	–26	– 4	5	– 3	6	2	– 1	– 5
48	41	0	17	2	18	–10	– 1	1 2
50	–28	– 1	1	2	– 2	0	3	2
51	103	3	0	–11	7	–12	– 7	1
53	–12	– 2	– 3	– 2	– 6	1	3	– 3
54	–40	4	– 8	4	– 6	1	– 2	3
$\bar{x}$	10	– 0.7	– 1.1	1.2	– 0.9	1.4	– 0.2	– 0.2
SE $\bar{x}$	7	0.5	2.2	1.5	2.0	1.5	0.5	
p	No means significantly different from 0							

columns and for the difference between the diabetic and sibling in the second set of columns. Student's t was used to evaluate the significance of the means.

From these results, it is clear that the diabetic children have a significantly retarded bone age, whether assessed by examination of the hand or of the foot. However, it is also apparent that their nondiabetic siblings had comparable retardation of skeletal maturation. Thus, when the diabetic child is compared to his sibling, his skeletal development does not appear to have been affected by his disease process.

There is no significant difference between the development of the hand and the foot for either group of children. When the skeletal maturation of the hand and foot is compared for each child, the correlation is very high. This is shown in figure 1, which is based on the initial assessment of skeletal ages for the hand and foot. The diabetics and siblings have been combined since there does not appear to be any significant difference in the correlation for the two groups. The correlation coefficient for hand age vs foot age is +0.998 ($N = 117$) ($p < 0.001$). The equation for the regression for these data is HA = 0.003+1.005 FA or FA = 0.305+0.992 HA (FA and HA in months). The value for the constant in either case is not significantly different from 0, and the value for the slope does not differ significantly from 1.0.

When the differences between hand age and chronological age are compared with the differences between foot age and chronological age for the diabetics, the correlation coefficient is +0.98 ($N = 66$) ($p < 0.001$), and it is the same for the siblings ($N = 51$).

Because of the close similarity between the hand and foot evaluations of skeletal maturity, the remaining results are presented for the hand age data only.

Figure 2 presents the degree of advancement or retardation in skeletal development for the diabetic children as a function of chronological age at the time of the first examination. Although there is a significant retardation for the total group (table II, line 1), there does not appear to be any specific relation between delay or advancement and chronological age. The figure does illustrate that the variance changes little with age. The same relation exists when the data for the nondiabetic sibling are examined. The diabetic child and sibling are also similar when comparing the change in skeletal maturation from the time of the initial examination to the time of the final study $(HA–CA)_{F–I}$ (table II, line 2) and relating this to chronological age.

No significant trend can be demonstrated for the relation between skeletal development discrepancy and chronological age. The initial retardation of about six months at ten years of age, and the progressive retardation of about one and a half months during the next three years are equivalent to a decrement of a half month in skeletal age for each year of chronological age since birth.

Further comparison between diabetic and sibling is shown in figure 3. In this figure, the difference between the skeletal and chronological age of the diabetic child is compared with the difference for his sibling. The correlation coefficient for these variables is 0.44 which is significant with $0.01 > p < 0.001$ ($N = 54$).

In order to determine whether the correlation between the diabetic child and his nondiabetic sibling was altered by the disease process, a comparison between nondiabetic siblings was made in the 23 families in which an additional nondiabetic sibling had been examined. In these families, the correlation coefficient between the diabetic child and the original nondiabetic sibling was 0.364 and the correlation between the two nondiabetic siblings was 0.358. These are not signifi-

Table II. Skeletal development related to chronological age[1]

	Diabetic		Diabetic-sibling difference	
	N = 30	N = (Max)[2]	N = 30	N = (Max)[2]
$(HA–CA)_I$	–7.53[3]	–4.22[3] (74)	–1.13	–1.54 (54)
$(HA–CA)_{F–I}$	–1.20	–1.46 (59)	1.17	1.13 (38)
$(FA–CA)_I$	–7.73[3]	–5.13[3] (67)	–0.93	–1.23 (47)
$(FA–CA)_{F–I}$	–1.10	–1.87 (52)	1.37	1.32 (31)
$(HA–FA)_I$	0.20	–0.36 (66)	–0.20	–0.23 (47)
$(HA–FA)_{F–I}$	–0.10	–0.15 (52)	–0.20	–0.20 (30)
$(CA)_I$	98.8	111.5 (76)	10.1	12.2 (55)
$(CA)_{F–I}$	24.9	33.6 (62)	–0.7	–1.4 (40)

[1] Values in months

[2] Numbers in parentheses identify number of subjects in each group

[3] $0.01 > p < 0.001$

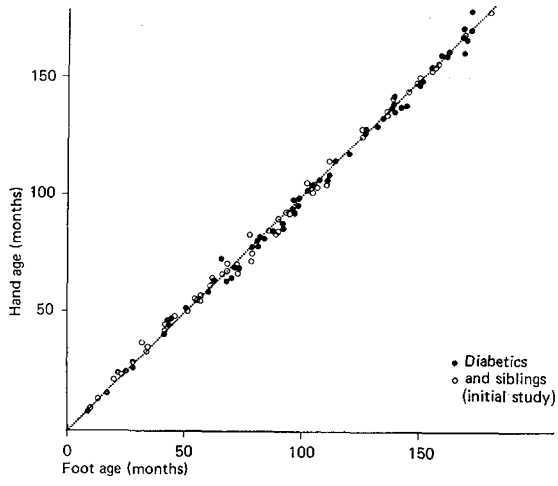

Fig. 1. Correlation between hand age and foot age. These data are for 66 diabetic children and 51 nondiabetic siblings. The data for both groups are combined as there was no statistical difference between them. The correlation coefficient is not statistically different from 1.0 and the origin not different from 0.0.

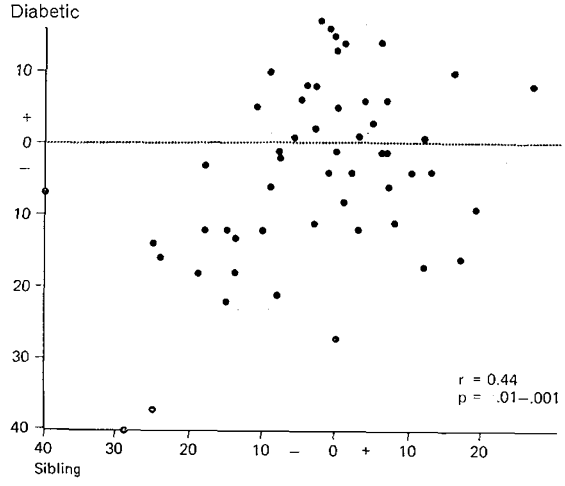

Fig. 3. Correlation between diabetic and sibling. Using the hand age minus chronological age (months) difference for each child, this difference is shown for each diabetic child and his respective sibling. There is a significant correlation of 0.44 for skeletal deviation between diabetic and nondiabetic sibling. (Initial study)

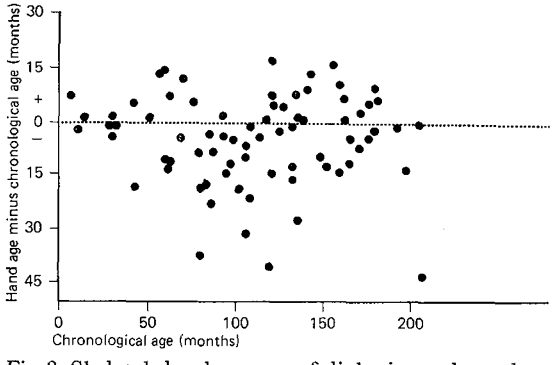

Fig. 2. Skeletal development of diabetic vs chronological age. The difference between skeletal and chronological age for 74 diabetic children is shown as a function of their age at the time of the initial examination. The mildly negative mean (−4.2 months) does not appear to change significantly with age. (Initial study)

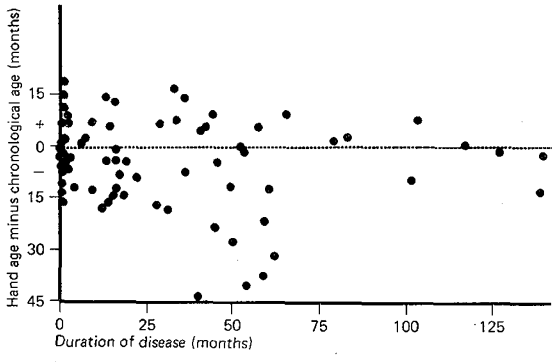

Fig. 4. Changes in skeletal development with duration of disease. Both the initial and final determinations of the degree of skeletal maturation are shown as a function of the known duration of the diabetic process. No tendency other than that attributable to age itself can be observed in the data. (Initial study)

cantly different from each other or from the value of 0.44 for the larger group. The similarity in the values indicates that the disease process does not affect the correlation in skeletal development between siblings.

Discussion

Since the underlying metabolic disorder in diabetes mellitus remains unknown, physiologic variables other than carbohydrate metabolism should be of use in evaluating the nature of the regulation of the diabetic state. One such variable characteristic in children is growth. Skeletal maturation has been used as one measure of growth since the early 1900's [18, 23].

The variations in skeletal development between children can be either genetic or acquired as a result of internal or external environmental factors. The majority of investigators have assumed that individual variation is primarily genetic and this has been confirmed particularly in the studies from the Fels Institute [6, 7]. The finding of a correlation coefficient of +0.4 be-

tween siblings in the present study would also confirm this concept since this value is in keeping with the value expected on a theoretical basis [11].

The use of siblings without overt disease does not represent an ideal control population because of the resultant wide chronological age variation, the presence of an unknown number of prediabetic individuals in the control group, and the high incidence of heterozygosity in the siblings. Nevertheless, the advantages of comparability in other genetic aspects and in the socioeconomic environment of the group were considered to outweigh the disadvantages.

Among the environmental factors which have been considered to affect skeletal development, illness has been controversial. Two investigations have concluded that illness can be an important factor in the alteration of the rate of skeletal maturation [3, 4]. However, studies at Oxford and in Australia have failed to demonstrate correlation between the amount of 'routine' childhood illness and variation in patterns of total epiphyseal development [1, 10, 20].

The role of more serious and chronic illnesses has been less well-examined. Histologic study by PARK has demonstrated that serious prolonged illness can temporarily stop the process of skeletal maturation, but these studies did not specifically examine the radiographic appearances of these changes [17].

In diabetes mellitus, the report of MORRISON and BOGAN in 1927 [16], stated that children with diabetes tended to have a skeletal age which was advanced with regard to chronological age at the onset of their disease. However, after three or more years of illness, the skeletal development was about two years behind the child's chronological age. DANOWSKI has stated that in the patients he has studied, the skeletal development, when compared to the published standards, was somewhat retarded at the onset of illness and remained so throughout its course [2]. The extent of the retardation in DANOWSKI's series is quite comparable to that found in the present study.

From the present serial studies of the skeletal development of the hand and foot, it is clear that the mean skeletal age for the study population is four to seven months less than its chronological age, and there is no significant difference between the diabetic and nondiabetic children. Under the program of diabetic management that was followed, the slight increase with time in the skeletal retardation of the diabetic children was not significant of itself and was even less impressive when compared with a somewhat greater increase in retardation in the nondiabetic sibling. DANOWSKI has also stated that duration of disease did not have a significant effect on the degree of skeletal retardation [2].

The standard deviation in our sample for the skeletal age—chronological age differences is approximately 12 months for both the hand and the foot in both the diabetic and nondiabetic children. The constancy of this value for both areas in both sets of children suggests that deviations of more than 24 months can be considered as abnormal. Thus with a mean value of minus 6 months, only children with skeletal ages 18 months greater than their chronological age or 30 months less than their chronological age would be 'abnormal'. On at least one examination and using these criteria, there were, in this group of 76 diabetics, two children who were abnormally advanced and four abnormally retarded. In contrast, on at least one examination, there were four abnormally advanced siblings and only two retarded ones. These distributions are not significantly different.

The moderate, but significant, retardation of both groups of children when compared to the published standards requires explanation. These groups follow a pattern similar to that reported for the children in the longitudinal study of growth in Denver [9]. The most likely factors producing these patterns are the result of sample or standard selection. The children used for the standards in the Atlases were predominantly from families whose socioeconomic level was definitely above average, whereas the diabetic population was more normally distributed in this context.

Other theoretical possibilities exist, such as a closely linked tendency for mild skeletal retardation and the diabetic geno-type even in what appears to be the heterozygous state; however, there are no data to support or invalidate such a concept.

The possibility that the differences are the result of the evaluation errors discussed by MAINLAND [13, 14, 15] seems unlikely since only one individual evaluated these films, and she has been continuously working in this field for many years and was, in addition, a co-author of both of the Atlas standards involved.

A further area of interest is the relation between skeletal age for the hand and for the foot. In an earlier examination of this relation, REYNOLDS and OSAKAWA, using a different evaluation technique, found correlations generally greater than 0.90 between the hand and the rest of the body, but only 0.60 to 0.78 between the hand and foot [19]. Simple enumeration of ossification centers yields relatively low correlation coefficients between either hand or foot and the rest of the body [5]. The high correlation between hand and foot in this series indicates the importance of using the detailed assessment technique described in the Atlas Standards and used for this study. Furthermore, the high degree of correlation found between the hand and the body as a whole by REYNOLDS and OSAKAWA would suggest that assessment of either the hand or the foot should be quite representative of the total body skeletal maturation. This is corroborated by the close

relation between hand and mean of hand, foot, elbow, knee, hip and shoulder found in the Brush Foundation studies [21].

Finally, it may be of importance to the lifetime management of diabetes that the epiphyses in the hands and feet seemed to be developing at the same rate. The comparisons were started primarily because vascular disease is usually seen earlier in the lower extremities in patients with diabetes mellitus.

Detailed comparison in the sibling pairs of the skeletal ages of similar kinds of bone growth centers, carpals vs tarsals or epiphyses (hand) vs epiphyses (foot) have been made. No unexpected individual differences were observed between the apparent rates of calcification of the anatomically related growth centers. Moreover, both groups of children were quite free from skeletal anomalies.

Summary and Conclusions

1. Skeletal maturation in 76 chi dren with diabetes mellitus and in 78 nondiabetic siblings has been assessed by repeated radiographic examination of the hand-wrist and foot-ankle areas.

2. Both the children with diabetes and their nondiabetic siblings had skeletal ages approximately six months behind the published standards for their chronological age; this was found to be statistically significant. These data provide a basis upon which to question whether the groups used for the published standards are appropriate and truly represent the total normal population of children. The two study groups, diabetic vs sib controls, did not differ significantly from each other; the slight increase in retardation noted over the course of the study was not statistically significant.

3. Duration of diabetes does not appear to affect the level of skeletal maturation.

4. The sibling correlations were +0.4, and this value was not affected by the presence of diabetes mellitus.

5. The skeletal development of the hand and foot was strikingly similar; there was a correlation coefficient of 0.98 between these two areas.

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