Hereditary Multiple Exostosis

L. SOLOMON

Royal National Orthopaedic Hospital and the Hospital for Sick Children, Great Ormond Street, London

MULTIPLE EXOSTOSIS (diaphysial aclasis) is a heritable disorder affecting the endochondral skeleton during the period of growth. It is characterized by thickening and deformity of the growing bone with the formation of numerous cartilage-capped exostoses clustered around the areas of most active growth (Figs. 1, 2). Thus, the juxtaepiphysial regions of the tubular bones, the ribs, pelvis, and scapulae are the most heavily affected areas, while the vertebral bodies, the patellae, and the carpal and tarsal bones are usually unaffected.

The bones involved are often diminished in length, giving rise to certain characteristic deformities in approximately two-thirds of affected individuals (Solomon, 1961). Most of these deformities are illustrated in Fig. 1; there is a shortness of stature, asymmetry of the pelvic and pectoral girdles, bowing of the forearm with ulnar deviation of the wrist, and subluxation of the radio-humeral joint due to inequality of growth of the radius and ulna, and valgus deformities of the knee and ankle similarly caused by tibiofibular inequality.

The earliest lesions are normally discovered during the first five years of life; some abnormality is almost certainly present at birth in most cases. Cartilaginous in origin, each bony projection retains a cap of actively growing cartilage and may continue to enlarge by endochondral ossification throughout the period of growth. After closure of the epiphyses, most of the cartilage ossifies, the cap is reduced to a thin lining, and no further increase in size is to be expected. If cartilaginous activity recurs after this time, it must be regarded as neoplastic. Indeed, a certain proportion of cases (estimates vary from 1 to 25%) undergo malignant change to chondrosarcoma.

The occurrence of the disease in several members of the same family was noted in the first case of multiple exostosis described in the medical literature (Boyer, 1814). As the disease became more generally recognized, a fairly constant hereditary pattern began to appear. In 1925, Stocks and Barrington were able to collect 1124 case histories from the medical literature; in 727 of these cases, drawn from 163 families, there was a history of other members of the family being affected. From a simple analysis of the reported cases, they came to the following conclusions: (1) Approximately two-thirds of all patients with multiple exostosis were known to have had an affected relative, usually one of the parents. (2) There was no instance of a father transmitting the disease without himself being affected. However, transmission of the disease through an unaffected female occurred in one-quarter of the cases when inheritance was through the mother. (3) The sex ratio of all cases

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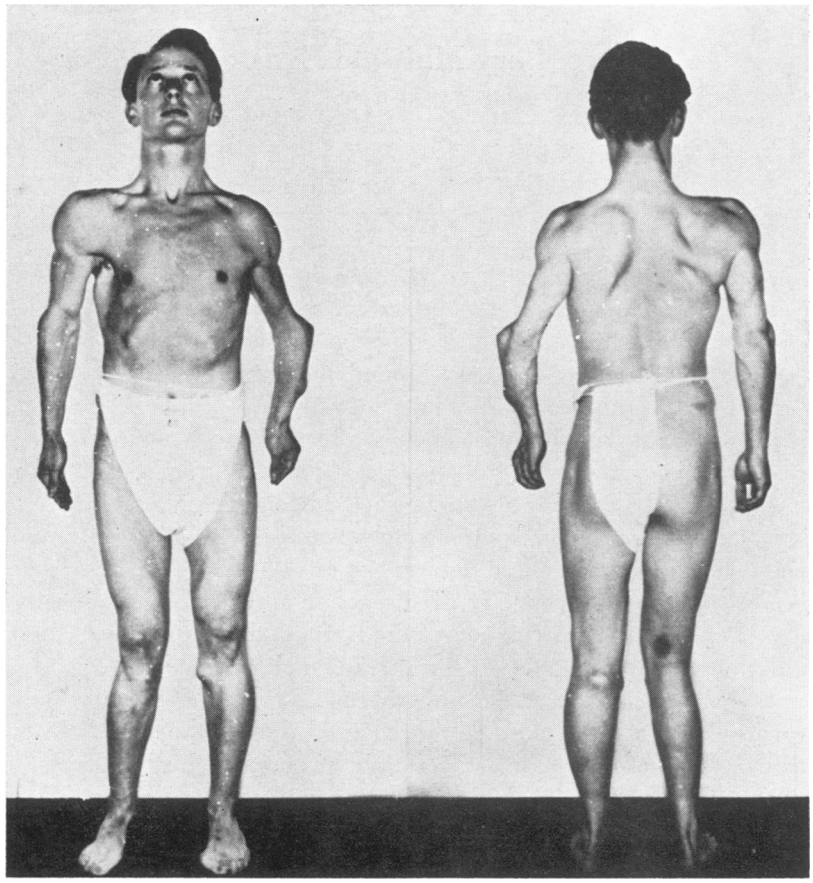

FIG. 1. The characteristic lesions in hereditary multiple exostosis (Pedigree 3, II-1). This figure is reproduced by courtesy of the *Journal of Bone and Joint Surgery*.

showed a 7:3 preponderance of males. (4) Affected fathers had a much higher incidence of affected sons among their children than did affected mothers. (5) "Enchondromata may occur in some members of a family and exostoses in others, and any kind of admixture of the two disorders in families or cross-inheritance between them seems to be possible."

Since Stocks and Barrington did not examine any of the cases themselves, the accuracy of the sources upon which they drew is of the greatest importance. Unfortunately, even the most reliable accounts of those times often contained examples which, by present-day criteria, would not be regarded as hereditary multiple exostosis. For example, Ehrenfried (1915, 1917), the most important of the early American writers on this subject, stated (Case 1) "Both ilia show a peculiar series of radiating striations about the crests" and (Case 2) "The upper ends of the humeri show irregular enlargement . . . with longitudinal striation. The metacarpals and phalanges show irregular enlargement and vacuolation" and again (Case 3) "The shoulders show the characteristic striated elongation of the upper end of the humerus." These are the

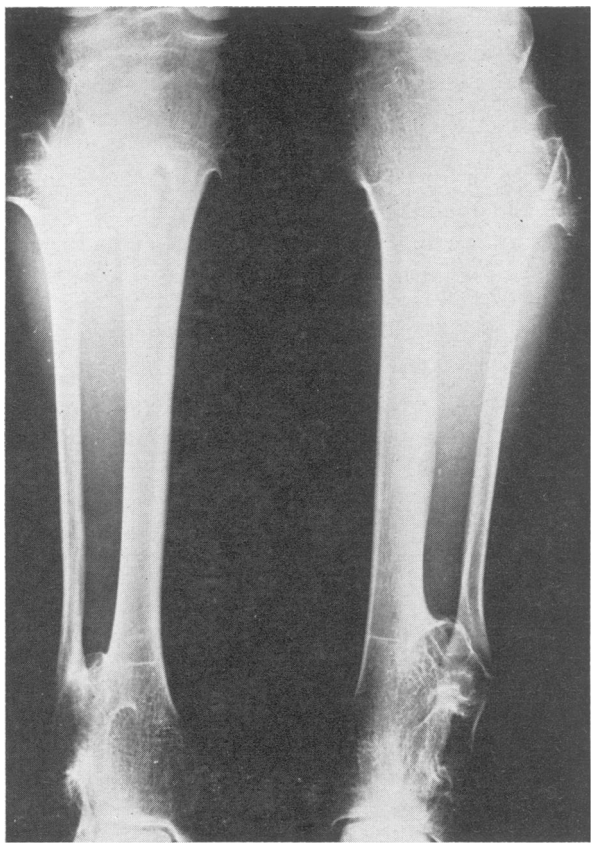

FIG. 2. Radiograph of the tibiae and fibulae in a case of hereditary multiple exostosis (Pedigree 18, III-26).

radiological signs of dyschondroplasia (multiple enchondromatosis). On the other hand, sessile exostoses, appearing as areas of 'vacuolation' when viewed end-on in the radiographic projection, were often called "enchondromata." This may account for the last conclusion quoted above. Enchondromatosis is now known to be a distinct and separate entity which never occurs with hereditary multiple exostosis.

Likewise, the family histories in the early reports were usually unconfirmed. There is considerable doubt about the statement that the disease can be passed to a child by an unaffected mother. Stocks and Barrington quote 13 pedigrees showing this phenomenon; not one is convincingly proved, however. In Pedigrees 45, 129, 137, and 156, there is no indication whether or not the female subject concerned was examined. In Pedigrees 13, 17, 19, 127, 151, and 159, the authors admit that the subject in question was not examined.

Although Stocks and Barrington did not, themselves, undertake any formal mendelian analysis of these cases, the pedigrees suggest that the disorder was transmitted by an autosomal dominant gene, with the female transmitter occasionally remaining unaffected. Incomplete manifestation of the disease

in the female was reflected in a diminished ratio of affected to unaffected females in the families concerned.

This unusual sex incidence was not observed by Langenskiold (1925) in the series which he reported, nor did it occur in the large family reported by Vanzant and Vanzant (1942). In this family of 78 members, there were 65 siblings; the ratio of affected to unaffected males was 18:15, of females 17:15.

Nevertheless, the main conclusions of Stocks and Barrington have never been seriously questioned. The fact that males are affected more than twice as often as females has been widely accepted as one of the curious anomalies of the disease.

In 1948, Harris studied the data of Stocks and Barrington and came to the conclusion that, although the abnormality was transmitted as a simple dominant, the disease was often suppressed in the female by a second, autosomal modifying gene. He proceeded to test this hypothesis against the data of Stocks and Barrington and was able to predict correctly the sex ratio of the affected offspring of different groups of matings as well as the frequency of different parental pairs among the 163 families quoted.

In a genetic study of 21 patients (six families) with diaphysial aclasis, Krooth, Macklin, and Hilbish (1961) gave special consideration to this question, but their series was too small to test Harris's hypothesis. No further studies along these lines have been reported; the entire subject is due for a critical re-evaluation.

MATERIAL AND METHODS

All available records at the Hospital for Sick Children and the Royal National Orthopaedic Hospital were collected for study if indexed under any of the following headings: hereditary multiple exostosis, multiple exostosis, diaphysial aclasis, exostosis, osteochondroma, ecchondroma, enchondroma, chondroma, chondromatosis, dyschondroplasia, Ollier's disease, and chondrosarcoma. In most instances, an examination of the case notes and the available radiographs was sufficient to separate those with true multiple exostosis (diaphysial aclasis) from the others. Doubtful cases were not included until they had been examined by the author.

Records of 78 patients were found. Thirteen of these patients could not be traced, four were known to have died, and nine declined to attend the follow-up clinic. The remaining 52 patients were examined in detail both clinically and radiologically.

In each case, after the propositus was interviewed, a tentative pedigree was drawn up. Every report of an affected family member was confirmed wherever possible by interview, correspondence with the physician, or from other hospital records. Relatives reported unaffected by the condition were not routinely examined. Exceptions were the reputedly unaffected parents of any children thought to have the disease. Since it is generally believed that unaffected females can transmit the disease to their children, every effort was made to submit these cases to radiological proof. Before completing the pedi-

TABLE 1. DETAILS OF 39 FAMILIES WITH HEREDITARY MULTIPLE EXOSTOSIS

Pedigree number	Proband	Sex	Parent affected	Grandparent affected	Siblings		Children		Cousins	
					Aff.	Unaff.	Aff.	Unaff.	Aff.	Unaff.
1	III-7	M	Father	Doubtful	0	1	0	0	2	5
2	III-4	F	Father	—	0	0	0	0	2	3
3	II-1	M	Father	Unknown	1	1	1	1	Unknown	
	III-1	F	Father	Grandfather	0	1	0	0	0	3
4	II-5	M	Neither	—	0	3	1	1	Unknown	
	III-5	M	Father	—	0	1	0	0	0	5
5	II-3	M	Neither	—	0	4	1	1	0	0
	III-5	F	Father	—	0	1	0	0	0	4
6	III-1	M	Mother	—	1	2	0	0	0	12
7	III-11	M	Mother	—	1	1	0	0	0	4
8	IV-10	F	Mother	Grandmother	0	1	0	0	1	7
9	III-35	M	Mother	Grandmother	7	4	2	0	Uncertain	
	IV-14	M	Father	Grandmother	1	0	0	0	4	10
10	III-1	M	Neither	—	0	0	1	1	0	0
*11	II-4	M	Mother	Unknown	0	3	0	0	Unknown	
12	III-2	M	Neither	—	0	1	0	0	Unknown	
13	III-1	F	Mother	Doubtful	0	0	0	0	1	0
14	III-3	M	Neither	—	0	2	0	0	0	0
15	III-4	M	Neither	—	0	1	0	0	0	8
16	III-2	F	Father	Grandfather	0	2	0	1	0	6
17	III-2	F	Father	Grandfather	1	0	0	0	0	5
18	III-26	M	Father	Grandfather	0	0	0	1	9	16
19	IV-26	F	Mother	—	0	1	0	0	0	12
20	III-9	F	Neither	—	0	2	0	0	0	16
21	III-8	F	Father	—	0	1	0	0	0	6
22	III-3	M	Father	Grandfather	1	0	0	0	0	4
23	III-8	F	Neither	—	0	1	0	0	0	6
*24	II-3	F	Neither	—	0	2	0	0	Unknown	
25	III-11	M	Neither	—	0	4	0	0	0	25
26	III-4	F	Neither	—	0	3	0	0	0	1
27	III-9	M	Neither	—	0	1	0	0	0	12
28	III-3	F	Father	—	0	1	0	0	0	2
29	III-1	F	Father	Grandmother	2	1	0	0	0	0
	IV-2	F	Mother	Grandfather	2	0	0	0	0	3
30	III-2	M	Neither	—	0	1	0	0	0	8
31	II-5	F	Neither	—	0	4	1	0	0	6
	III-4	F	Mother	—	0	0	0	0	0	7
32	III-1	M	Neither	—	0	1	0	0	Unknown	
33	III-5	F	Mother	—	1	0	0	1	0	4
34	III-6	F	Mother	Grandfather	1	1	0	0	2	2
35	III-9	M	Neither	—	0	3	0	0	0	13
36	II-6	F	Father	Unknown	2	5	1	0	Unknown	
	III-12	M	Mother	Grandfather	2	4	0	0	1	8
*37	IV-5	M	Father	Grandfather	0	2	0	0	0	0
*38	III-7	F	Father	—	0	8	0	0	0	4
39	III-1	M	Neither	—	0	0	0	0	0	4

*Pedigrees 11, 24, 37, and 38 are insufficiently reliable for statistical analysis.

gree, at least one member from an older or younger generation was interviewed and the information cross-checked against the original record. Altogether 84 relatives of propositi were examined, 40 of them both clinically and radiologically and 44 clinically but not radiologically.

Of the original 52 index patients, two were adopted children and another four were unable to give any relevant family history. The remaining pedigrees are summarized in Table 1, but numbers 11, 24, 37, and 38 are insufficiently reliable for analysis of the kind proposed by Harris. The findings in the other 35 families (42 propositi) are presented here.

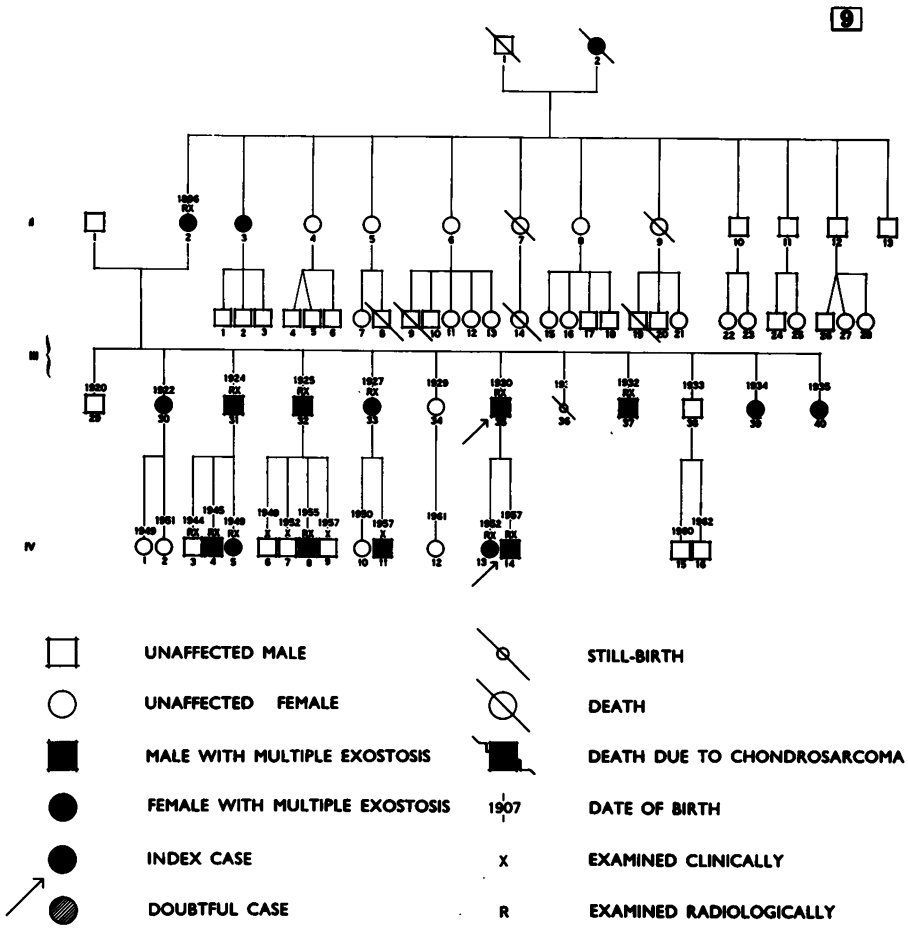

FIG. 3. Pedigree of Family 9.

GENETIC STUDIES

Sex ratio. The sex ratio of the 42 propositi was 22 males to 20 females. Among the secondary cases examined, there were 21 males and 20 females with multiple exostosis.

Children. Eight of the 15 children of propositi were affected—four males and four females.

Parents. One parent was affected in 26 of the 42 cases, the father in 16 and the mother in 10. A typical large family is represented by the pedigree in Fig. 3. The 16 propositi with neither parent affected might be attributed to mutation. This group had 31 sibs, all unaffected. No case was encountered where an aunt, uncle, cousin, or grandparent was affected when both parents were free of the disease.

Sibs. Among the patients with an affected parent, there were 52 sibs, 23 affected and 29 unaffected. There was an equal incidence of males and females in each group (Table 2).

TABLE 2. SIBLINGS OF INDEX PATIENTS WITH AFFECTED PARENTS (26 CASES)

Sex	Affected	Unaffected
♂	11	15
♀	12	14
Total	23	29

Grandparents. There was some evidence of a grandparent being affected in 12 of the 26 cases with an affected parent. (In two cases, information could not be obtained.) Only one of these was examined and verified by the author, three were verified by another hospital or the family doctor, five were reliably reported by an immediate relative, and three were hearsay reports. There was no instance of a grandparent but not a parent being affected.

Children of affected aunts and uncles. There were 52 children of affected aunts and uncles and 197 children of unaffected aunts and uncles. Of the former group, 22 children were themselves affected; of the latter group none was found to be affected. Particular attention was paid to the children of unaffected female relatives. In three cases where typical lesions were found in the children, the mother, after denying the presence of exostoses in herself, on radiological examination was found to be affected.

Intrafamilial resemblance. The type and distribution of the lesions showed no tendency to intrafamilial resemblance except in one family (Pedigree 34, Fig. 4). In the six affected members of this family who were examined (II-1, 2; III-2, 3, 4, 6), the lesions occurred predominantly in the hands; before radiological examination, most of these patients were unaware of the presence of exostoses elsewhere. In each case, the common sites at the ends of the long bones were only mildly affected by exostoses, and the characteristic deformities associated with this disease were not present. An uncle of the propositus (II-5) was not examined, but the author heard of him by chance. He was known to be selfconscious about the "lumps and swellings on his hands."

ACID MUCOPOLYSACCHARIDE EXCRETION

The pathogenesis of multiple exostosis has been considered in detail elsewhere (Solomon, 1961, 1963). However, one aspect in particular has received increasing attention in recent years. In 1960, Lorincz reported that the urinary excretion of acid mucopolysaccharides (AMPS) was greatly increased in multiple exostosis and suggested that this was due to a disorder of connective tissue AMPS metabolism. As the same observation has been made in Hurler's syndrome, Lorincz's suggestion was regarded as significant and important. The investigation was repeated in 20 subjects of the present series: 13 affected patients and seven unaffected sibs from Families 5, 9, and 38. Their ages ranged from 3½ to 64 years.

The method used for estimating urinary AMPS was that described by Di Ferrante and Rich (1956). Each value was expressed as a ratio of AMPS (glucuronic acid) to creatinine in any given sample of urine; these were plotted against the normal standards of Teller *et al.* (1962). The results are shown in Fig. 5.

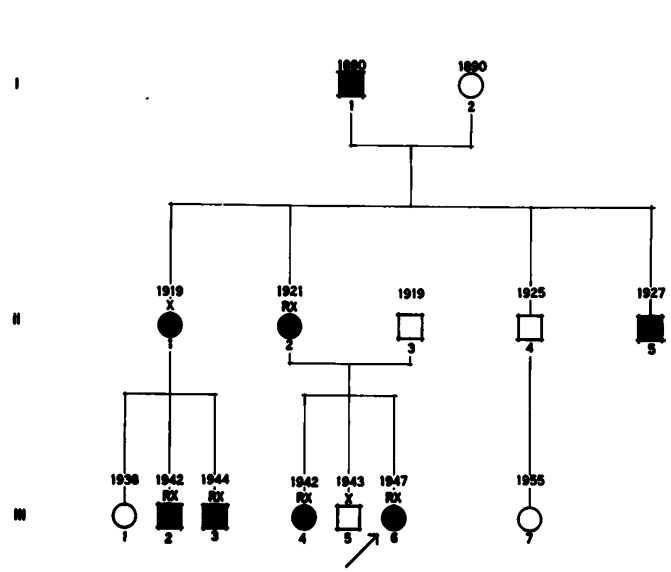

FIG. 4. Pedigree of Family 34.

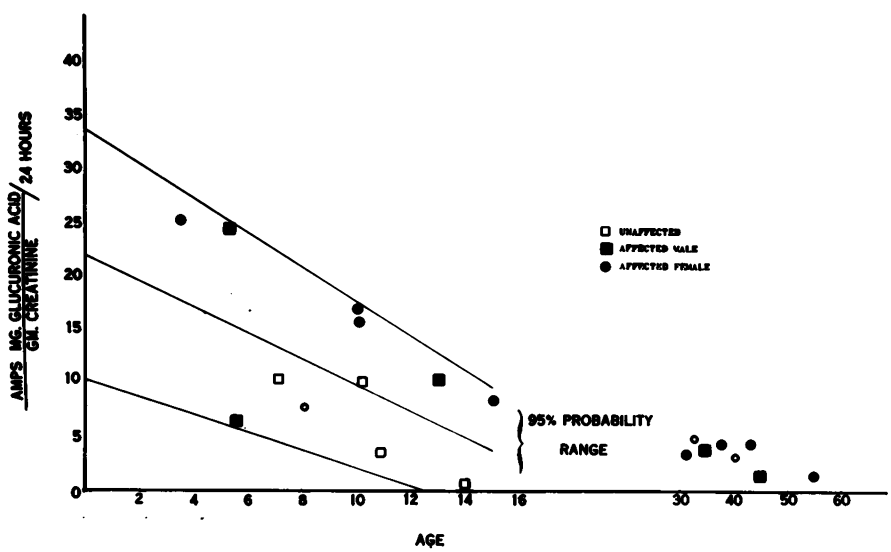

FIG. 5. Urinary acid mucopolysaccharide levels in 13 patients with hereditary multiple exostosis and in seven unaffected sibs.

It is seen here that the values in most of the unaffected sibs fell slightly below the mean. Among the affected patients, those under the age of 16 years had values well above the mean (with a single exception) but still within the 95% probability range. In the affected adults AMPS excretion was not raised.

The finding of a somewhat raised AMPS excretion in children with multiple exostosis does not necessarily point to a specific metabolic abnormality but

could equally well be explained by the greatly increased bulk of cartilage, which is the main source of AMPS. The normal values in adult patients (whose lesions are likely to contain very little cartilage) lend additional support to this view.

DISCUSSION AND INTERPRETATION

Frequency

The frequency of hereditary multiple exostosis is unknown and cannot be estimated with any accuracy from the available data. Krooth, Macklin, and Hilbish (1961) studied this condition in a relatively closed community among the Chamorros on the Pacific island of Guam. They discovered 21 patients in a population of 32,000 and believed that this represented more than 50% of the cases on the island, giving a prevalence of approximately 1:1,000. It is estimated that three new cases are diagnosed each year at the Royal National Orthopaedic Hospital, which specializes in orthopedic diseases and handles approximately 7,000 new patients annually.

The Pedigrees

Forty-two index cases of multiple exostosis are analyzed here. The pedigrees suggest that the disease is usually transmitted by an autosomal dominant gene which always produces detectable effects in the heterozygote.

There are two major differences from the findings of Stocks and Barrington—the almost exact equality of the sex incidence and the complete absence of any instance in which the disease was transmitted by an unaffected parent. On three occasions, the unexpected situation arose in which a mother denied being affected by exostoses but radiological examination showed the presence of the disease. This could account for reports of transmission of the disease by an unaffected mother. Krooth, Macklin, and Hilbish (1961) reported that several adult females in their series had "no clinical signs of the disease" but that radiological examination showed the presence of exostosis. They attribute this in part to greater obesity of the females but also suggest that females are less severely affected.

The possibility of a consistently milder manifestation of the disease in females has been considered, but there was no evidence among 76 subjects examined radiologically that females as a group were less severely affected than males nor has this been reported in the literature. Collateral evidence is provided by the incidence of bony deformities in the patients studied. Moderate to severe deformities occurred in 72% of males and 75% of females with multiple exostosis (Solomon, 1961).

In 16 of the 42 propositi, there was no history of either parent being affected, and these could be regarded as sporadic cases. Doubtless, a full radiological examination of all the parents would have disclosed some affected cases among them, so that it is not possible to state with assurance the exact frequency of mutation. In some instances, however, both the parents and the sibs were examined by the author and found to be unaffected. The question as to whether such cases are due to mutation or whether they represent

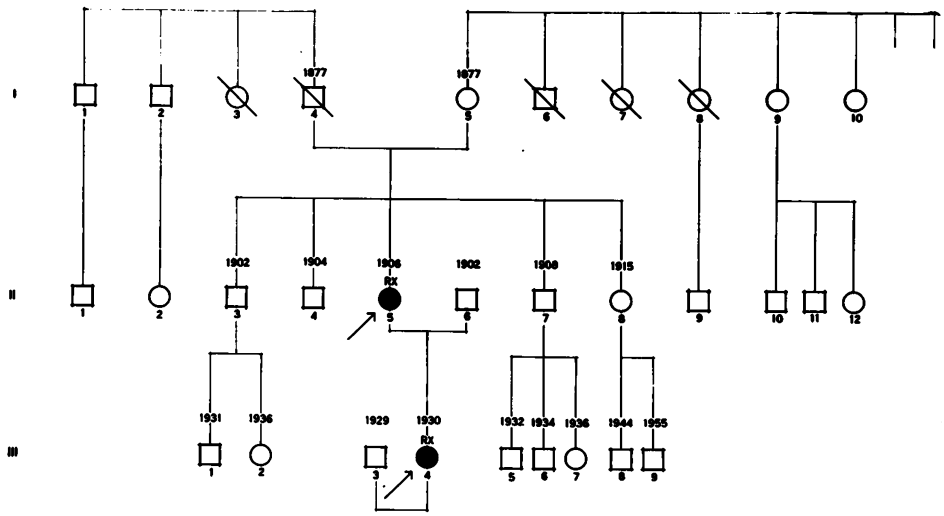

FIG. 6. Multiple exostosis in a mother and daughter with both grandparents unaffected.

phenocopies has not been finally resolved. Convincing proof of mutation would be provided by the occurrence of the disease in a parent and child with grandparents definitely unaffected. This situation was reliably recorded in three families, in one of which the evidence for mutation was very good (Fig. 6). The family history here was supported by a negative post-mortem report in the case of I-4 and a clinical examination of I-5 by the family doctor.

Intrafamilial Resemblance

Pedigree 34 was referred to as showing a strong intrafamilial resemblance in the form and distribution of the disease. In every affected member of this family, the lesions occurred in the hands and fingers with only a few exostoses in the long bones. In no other subject did the abnormality take this particular form. Neither Stocks and Barrington nor Krooth, Macklin, and Hilbish found any correlation between members of the same family for the form or distribution of the disease. The family described here is therefore of unusual interest and suggests the possibility that more than one mutant gene may be concerned in the etiology of the disease.

Consanguinity

There were no consanguinous marriages of affected individuals, but Vanzant and Vanzant (1942) have reported this situation in one family; all seven children of this union had multiple exostosis.

Harris's Hypothesis

In analyzing the data of Stocks and Barrington (1925), Harris (1948) found that, whereas the manifestation rate of the gene for diaphysial aclasis

TABLE 3. THE RELATIVE INCIDENCE OF MULTIPLE EXOSTOSIS IN MALE AND FEMALE SIBLINGS

Pedigree	Affected males	Affected females	Unaffected males	Unaffected females	Total sibship
1 (II)	2	2	2	3	9
9 (III)	4	4	2	2	12
16 (II)	2	1	0	4	7
18 (II)	5	1	3	3	12
21 (II)	2	1	4	2	9
36 (II)	0	3	2	3	8
(III)	2	1	4	0	7
Totals	17	13	17	17	64

among male sibs conformed to the expected 1:1 ratio, female sibs were affected in the ratio of 1:1.66. Furthermore, he observed that the sex ratio among affected children was 1:1 when the mother was affected, 2:1 when the father was affected, and 3:1 when neither parent was affected but the mother was considered to have transmitted the disease.

Seeking to explain these phenomena, Harris postulated that, although diaphysial aclasis was transmitted directly by an autosomal dominant gene, the disease was often suppressed in the female by a second, autosomal modifying gene. He was further reassured, on applying this hypothesis to the original data, to find that he was able correctly to predict the frequency of different parental groupings as well as the sex ratio of the offspring of these groups among the pedigrees of Stocks and Barrington.

The series of cases reported here does not support Harris's hypothesis. The relative incidence of the disease in male and female sibs is shown in Table 3. (Following Harris, only sibships of seven or more individuals are considered.) Of 34 males, 17 were affected and 17 were unaffected, an exact 1:1 ratio. Of 30 females, 13 were affected and 17 unaffected. The difference here is insignificant ($\chi^2 = 0.47$).

Thus, the manifestation rate of the gene conformed to the expected mendelian ratio in both males and females of the present series. Moreover, there was no significant difference in the sex ratio of affected offspring of different antecedents. In only one family did the lines of inheritance appear to follow predominantly through males (Fig. 7), although even here there is uncertainty about some of the relatives, such as II-1 who emigrated to America and II-5 who emigrated to Australia "before the First World War." The latter and his three daughters are listed as unaffected.

The sex ratios of the children of affected fathers and affected mothers are further analyzed in Table 4. This is based on the immediate family of each propositus and only sibships of two or more individuals are considered. Among the affected offspring, the ratio of males to females was 11:13 where the father was affected and 10:12 when the mother was affected. The manifestation rate of the disease in each category did not differ significantly, although the numbers are too small to draw a firm conclusion from this observation. A strict comparison with Harris's figures is further limited by the fact that this series did not contain any cases which could be placed in the category

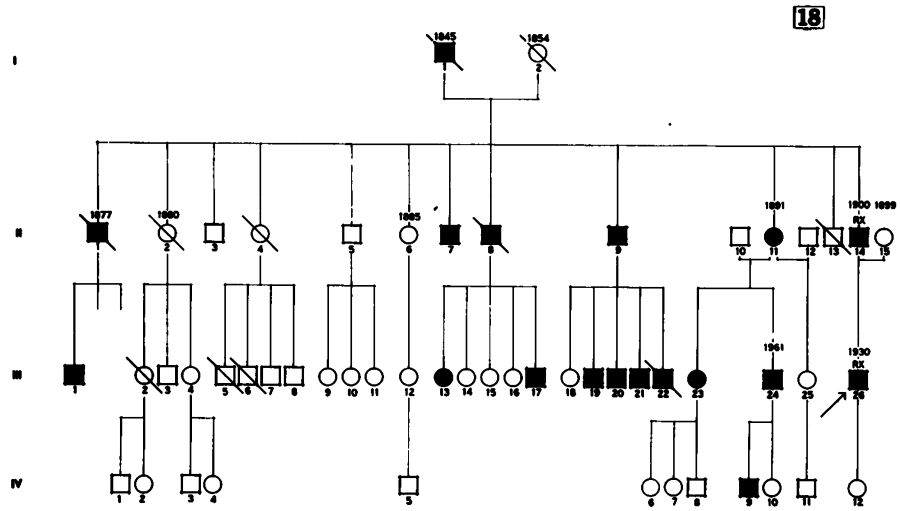

FIG. 7. Pedigree showing inheritance predominantly through the male members of the family.

of "unaffected but transmitting females." However, so far as could be judged, they did not conform to the pattern suggested by Harris's theory.

On the basis of these findings, there was no need to postulate the existence of a second, sex-modifying gene in hereditary multiple exostosis.

SUMMARY AND CONCLUSION

The hereditary characteristics of multiple exostosis have been studied in 42 patients (35 families), of whom 61.9% were found to have inherited the abnormality. Males and females were affected with equal frequency.

The disease was transmitted to approximately half the children of affected parents; there was no tendency for the severity or the multiplicity of the lesions to increase in successive generations.

The findings in this series of patients suggest that most of the cases of multiple exostosis are determined by an autosomal dominant gene with full penetrance. Earlier claims for incomplete manifestation in females and skipping of generations may be due to inadequate examination or errors in diagnosis. The present evidence does not indicate the need to postulate the existence of a second, sex-modifying gene as suggested by Harris (1948).

TABLE 4. THE RELATIVE INCIDENCE AND SEX DISTRIBUTION OF MULTIPLE EXOSTOSIS IN THE CHILDREN OF DIFFERENT AFFECTED PARENTS

Parent Affected	Children			
	Affected Males	Unaffected Males	Affected Females	Unaffected Females
Father	11	6	13	9
Mother	10	8	12	5
Uncertain	2	1	0	6

The possibility that more than one mutant gene may be concerned in this condition finds support in the discovery of one family (Pedigree 34) in which there was a strong intrafamilial resemblance in the form and distribution of the disease.

The suggestion that the disease might be associated with a specific metabolic abnormality resulting in an increased excretion of acid mucopolysaccharides (AMPS) prompted an investigation of the urinary AMPS levels in 13 patients and seven unaffected sibs. The finding of slightly raised values in the affected children under 16 years of age could equally well be explained by the greatly increased bulk of cartilage (the main source of AMPS) in children with multiple exostosis.

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