

HEREDITARY ONYCHO-OSTEODYSPLASIA

Survey of a Family Exhibiting this Syndrome
and Review of the Literature

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HISTORICAL NOTE

The earliest record of nail dystrophy associated with skeletal dysplasia would seem to be the description by Chatelain in 1820 of a patient who exhibited congenital anomalies of the nails, elbows and knees. More than half a century later, Little (1897), in an article on congenital abnormalities of the patella, quoted a family described by Sedgwick, in which, over four generations, 18 persons were found to have no thumb nails and no patellae, thus suggesting that such combined ectodermal and mesodermal defects could be hereditary in nature. A short annotation by Wrede in 1909 is the first record of a hereditary defect involving the elbows in addition to the knees and nails. In the English literature, in 1912, Firth corroborated Wrede's observations by publishing an account of two families in which nail, elbow and knee anomalies were clearly transmitted on a hereditary basis. Wrede and Firth noted that the characteristic feature of the elbow abnormality was a congenital dislocation of the head of the radius associated with limited extension, supination and pronation, while, in the knee, the commonest anomaly was hypoplasia or absence of the patella with or without a tendency to recurrent dislocation.

The first attempts at a really detailed study and description of this triad of abnormalities were made by Osterreicher (1931) and Turner (1933). The latter, in addition, attempted to enlarge the confines of the syndrome. He noted that some affected subjects exhibited marked

flaring of the iliac crests together with prominence of the anterior superior iliac spines. He also suggested that some cases showed anomalies of the shoulder, wrist, ankle and foot. Whether or not he was correct in these latter observations is doubtful but time was to amply justify his description of the pelvic lesions. In 1946, Fong, during routine pyelographic investigation of a patient, observed the presence of conical projections arising from the dorso-lateral aspect of the blade of the ileum. He called these structures "iliac horns." No mention was made of any other associated abnormalities in the patient described. A few years later, Mino et al (1948) and Thompson et al (1949) quite independently of each other observed and described the presence of these iliac horns in association with anomalies of the nails, knees and elbows, the lesions being definitely of a hereditary nature in two of the four families described. Further reports over the next few years left no doubt that this tetrad of anomalies of the nails, knees, elbows and pelvis constituted a definite clinical entity and, furthermore, the syndrome was clearly hereditary. Due to the predominance of nail and knee changes in affected patients, the popular name of nail-patella syndrome has been applied to the condition, but, it should in fact be more correctly referred to as "hereditary onycho-osteodysplasia."

Genetic studies suggested that the syndrome was transmitted as a non-sex linked dominant inheritance and in 1951 Pfandler & Cottet undertook a detailed survey of a very

large family in an attempt to establish whether or not any obvious linkage factors could be demonstrated. They found that there was statistical evidence for linkage between the nail-patella syndrome and the colour of the hair and also the blood group factor N. They failed to obtain statistical proof of any linkage with the ABO blood groups, but that such linkage does, in fact, exist has been clearly demonstrated in a massive survey of 9 families by Renwick & Lawler (1954) and Lawler et al (1957).

The purpose of the present paper is to report a further family exhibiting this syndrome, the family being of special interest in that the anomaly would seem to have appeared as a spontaneous mutation in the mother of the propositus. In addition, as extensive a review of the literature as possible has been undertaken in order not only to discover the total incidence of the syndrome but also to amass a series of affected subjects, sufficiently large to allow of analysis, in order to determine the frequency with which the individual anomalies of the tetrad occur and in what combinations. Finally, in view of the fact that from time to time a large number of subsidiary anomalies has been described as occurring in association with the main tetrad of lesions, an attempt has been made to assess the significance of these other abnormalities and define their relationship to the main syndrome.

CASE REPORTS AND FAMILY SURVEY

The propositus (IV₂, Fig. 1) was discovered merely by chance due to his admission to Edinburgh Royal Infirmary on account of a strangulated inguinal hernia. During routine physical examination he was noted to have anomalies of the elbows and knees and he volunteered the information that his mother and sister were similarly affected. With his mother's help, it was possible to construct a geneological table of the family over four generations (Fig. 1). Only the three subjects already mentioned were known to be definitely affected by the syndrome but the great-grandmother of the propositus (I₁), who is deceased, was said to have had abnormal nails.

In view of the fact that other authors have clearly shown that this anomaly is transmitted as a dominant characteristic with 100 per cent. penetrance, it was considered that, in order to carry out a survey of the family, it would only be necessary, in the first instance, to examine the siblings of the propositus and his mother, together with all the members of the second generation. If any further affected persons had been found in the course of this limited survey, the field of investigation would have been extended. Each individual was subjected to a full clinical examination, and X-rays were taken of the hands, knees, elbows and pelvis. A note was taken of any other associated abnormalities. As some observers have suggested that renal changes can be associated with the syndrome, enquiry was made with regard to the past history of any renal disease and a specimen of urine

GENEALOGICAL TABLE OF REPORTED FAMILY

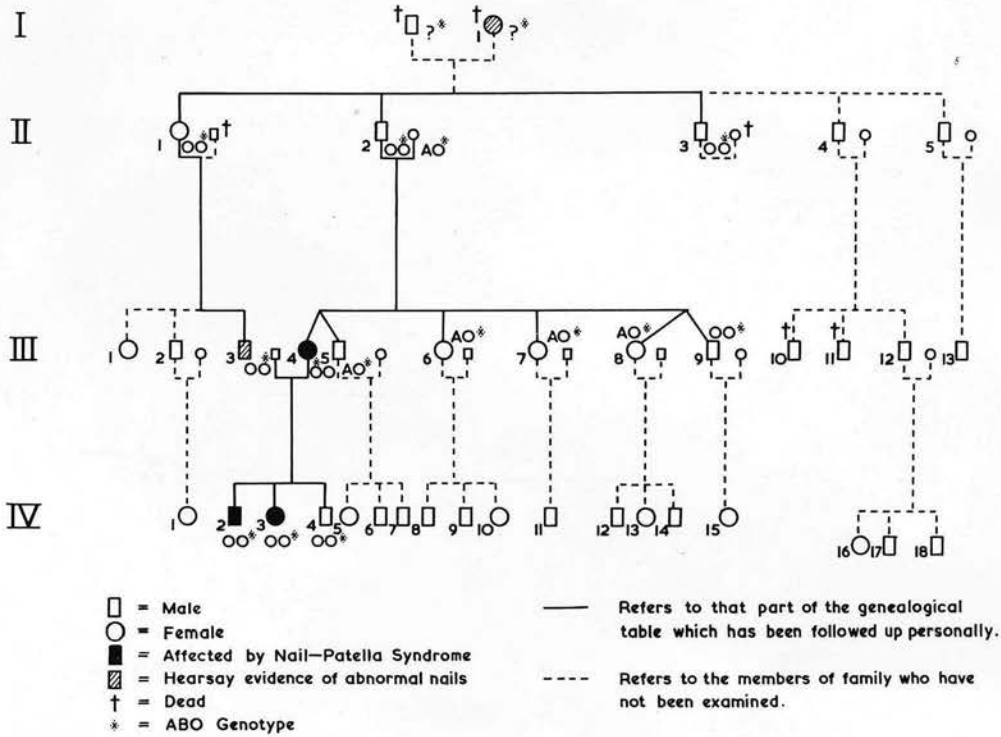


Fig. 1

from each case was tested for the presence of protein and casts. Blood was also sent for detailed grouping.

The great-grandmother of the propositus (I_1), who was said to have had abnormal nails, was unfortunately deceased. There was unanimous agreement that she exhibited no joint dysplasia but family opinion was divided with regard to the presence of the nail dystrophy. II_3 denied having observed any nail changes in his mother, but II_1 and II_2 stated that her nails were abnormal though they would not commit themselves as to whether the changes were identical to those exhibited by III_4 and IV_3 . Considerable doubt must be cast on the significance of this type of hearsay evidence, especially since II_1 stated that her son, III_3 , also showed the nail anomalies. On investigating this, it was found that he showed congenital koilonychia of all the finger nails with none of the characteristic features peculiar to the nail-patella syndrome. Moreover, he showed no skeletal changes at all and must clearly be considered as not being affected by the abnormality.

Two members of the second generation (II_4 and II_5) were not seen personally. II_4 refused to attend for examination but case records were available from a previous admission to hospital and these recorded no abnormality of the nails or skeleton. Moreover, there was no incriminating hearsay evidence from the other members of the family as to his exhibiting any of the stigmata of the syndrome. This also applied to II_5 , who had not been heard of for 13 years. Attempts were made to contact him at his last known address

in Canada but no reply was received.

A.B. (II₂), the grandfather of the propositus, was in poor health and was unable to attend for examination at hospital. When visited in his home, no clinical evidence of the syndrome was found. Moreover, portable X-rays of his knee and elbow joints revealed no abnormality. Pelvic X-rays were not taken but, as will be mentioned later in reviewing the literature, no case has ever been reported in which pelvic anomalies have been the sole manifestation of the syndrome. These negative findings in the grandfather of the propositus render it extremely unlikely that the great-grandmother of the propositus (I₁) exhibited the dystrophic nail changes characteristic of onycho-osteodysplasia.

The grandmother of the propositus (i.e. the wife of II₂) was also examined and she too showed no evidence of any congenital abnormalities. There was, moreover, no history of any of her relatives having been affected.

The findings in all the patients personally examined are listed in Table I. As will be seen from the latter, only three persons were found to exhibit the changes characteristic of onycho-osteodysplasia. These three cases will be described in detail.

Genetic No.	Initials	Age	Sex	Nail Dystrophy	Knees	Dysplasia of Elbows	Pelvis	Past History of Renal Disease	Urine Examination Protein Casts	Blood Grouping			Other Anomalies
										ABO type	RL Factor	RL Genotype	
II ₁	I.B.	74	F	-	-	-	-	-	Trace	0	+	cDe/eDE	-
II ₂	A.B.	73	M	-	-	-	?	-	Trace	0	-	cde/cde	-
Wife of II ₂	E.B.	69	F	-	-	-	?	-	Not tested	A	+	cDe/cde	-
II ₃	J.B.	71	M	-	-	-	-	-	-	0	+	cDE/cde	-
III ₄	E.S.	45	F	+	+	+	+	-	-	0	+	CDe/ede	Rudimentary 6th left digit. Moved in infancy
Husband of III ₄	W.G.	49	M	-	-	-	-	-	-	0	+	CDe/cde	-
III ₅	J.F.B.	45	M	-	-	-	-	-	-	A	+	not done	-
III ₆	T.M.	42	F	-	-	-	-	-	-	A	-	cde/cde	-
III ₇	M.K.	37	F	-	-	-	-	-	-	A	-	cde/cde	-
III ₈	M.V.	34	F	-	-	-	-	-	-	A	+	CDe/cde	-
III ₉	R.B.	34	M	-	-	-	-	-	-	0	-	cde/cde	-
IV ₂	W.S.	17	M	-	+	+	-	-	-	0	Not done	Not done	-
IV ₃	S.S.	13	F	+	+	+	+	Acute nephritis at 10 yrs. No trouble since	-	0	-	cde/cde	-
IV ₄	A.S.	12	M	-	-	-	-	-	-	0	+	CDe/CDe	-

TABLE I. Showing the findings in the members of the family who were subjected to examination as detailed in the text.

Emily S. (III₄), the mother of the propositus.

This patient was found to have abnormal nails and dysplasia of the knees, elbows and pelvis.

Nail Dystrophy

Her thumb nails (Fig. 2 a & b) were less than half the normal length and showed numerous longitudinal cracks. The distal ends of the nails were broken and ridged, the whole nail appearing extremely brittle. Furthermore, the terminal pulp of the thumb extended round from the volar aspect on to the dorsal surface of the digit, distal to the dystrophic nail (Fig. 2b). As a result of this, the patient had difficulty in picking up pins or other fine objects. Her other finger nails were less severely affected but all, with the possible exception of those of the little fingers, were narrower than usual and showed longitudinal cracks. These changes were especially marked in the index and ring fingers. Another interesting abnormality was the absence or poor development of the dorsal skin creases over the distal I-P joints and the limited flexion at these joints (only 30 - 40°). There was no abnormality of the toe nails. Radiographs of the hands showed no skeletal anomaly.

Elbow Dysplasia

Examination of the elbows revealed marked prominence of the radial heads especially on the right, so much so that, in flexion, the tip of the elbow, when viewed from the lateral side, was formed by the dislocated head of the radius and not by the olecranon (Fig. 3). Both elbows showed, also, an increased "carrying angle" (Fig. 5a) and extension was

limited by 30° on the right and by almost 40° on the left (Fig. 4). Supination on both sides was practically nil and pronation was only possible through about 30° . Radiographs of the elbows revealed, on both sides, posterior dislocation of the head of the radius, the latter being rather hypoplastic with elongation of the radial neck. The capitulum and lateral epicondyle of the humerus were hypoplastic, while, in comparison, the medial epicondyle was markedly prominent.

Knee Dysplasia

The knee joints showed loss of the normal patellar prominence, though on palpation a small patella could be definitely felt on both sides. In flexion, the anterior aspect of the joints assumed a very characteristic square outline. The patellae did not dislocate laterally and there was no abnormality of the patient's gait, though she volunteered the information that, as a child, she had been much longer in learning to walk than her brothers and sisters.

X-ray examination revealed extremely small, oval patellae, the appearance being especially striking in the axial view (Fig. 6 a & b), which also emphasised the relatively hypoplastic lateral femoral condyles. Conversely the medial femoral condyles were large and prominent, as were the tibial tubercles.

Pelvic Dysplasia

Radiographic examination of the pelvis revealed the presence of bilateral iliac horns (Fig. 7). No anomaly of

the iliac crests or undue prominence of the anterior superior iliac spines was to be observed.

Other Anomalies

The patient exhibited no other abnormalities. The only point of interest in her past history was that at birth she had been found to have a rudimentary sixth digit on the left hand. This had been removed in infancy.



Fig. 2a

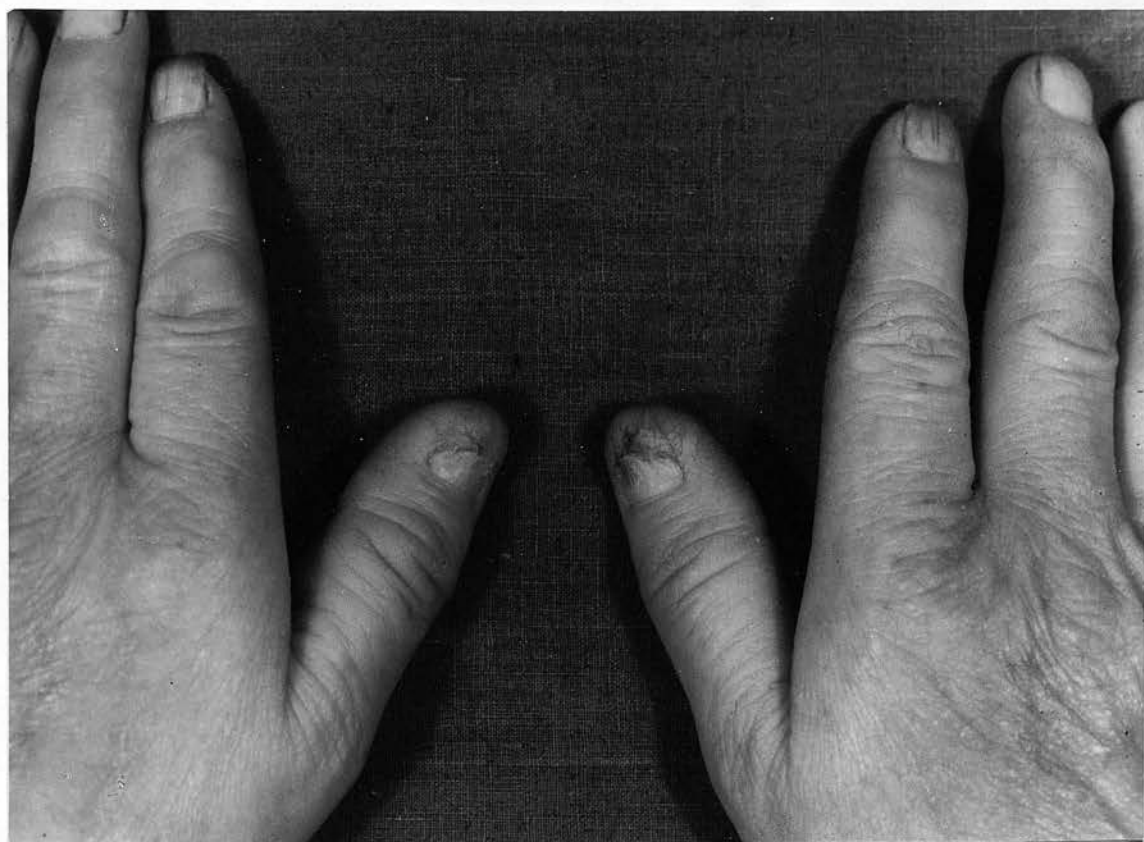


Fig. 2b

Fig. 2. Case III₄. Photographs showing dystrophy of thumb and finger nails.



Fig. 3. Case III₄. Right elbow showing prominence of dislocated radial head.



Fig. 4. Case III₄. Right elbow showing maximum extension.



Fig. 5a



Fig. 5b

Fig. 5. Case III₄. A-P and lateral views of both elbows.



Fig. 6a. Case III₄. A-P and lateral views of right knee.

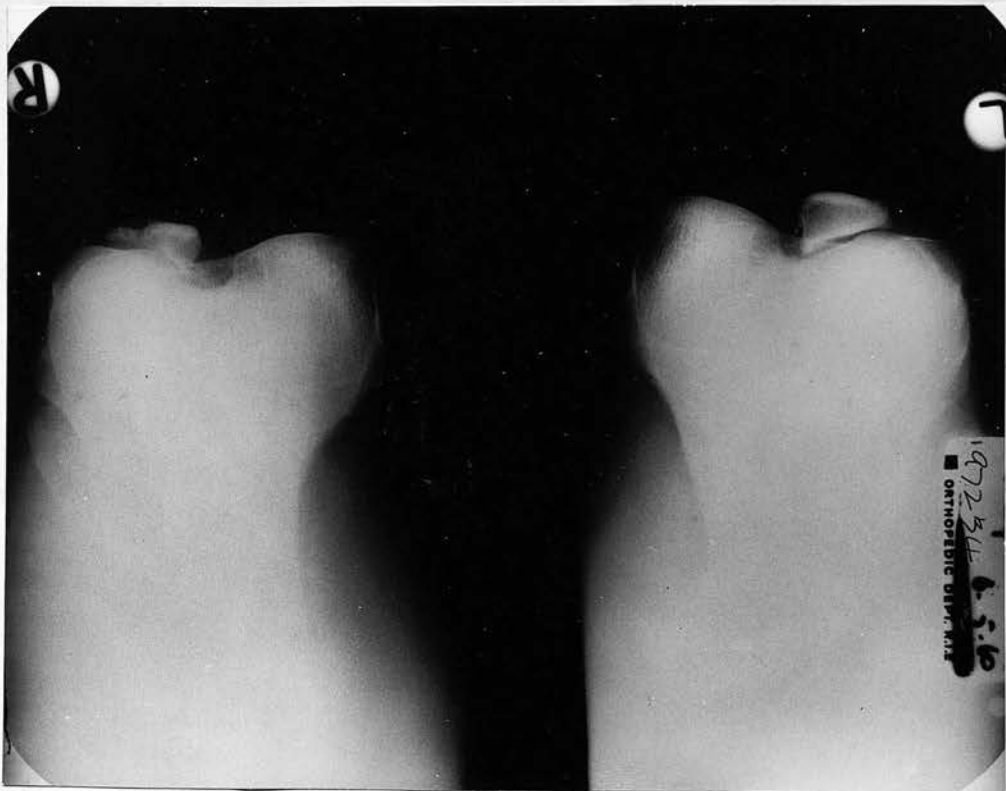


Fig. 6b. Case III₄. Axial views of both knees.



Fig. 7. Case III₄. A-P of pelvis showing bilateral iliac horns.

William S. (IV₂), the propositus.

This patient showed no abnormality of the finger or toe nails and X-rays of the hands and pelvis similarly revealed no dysplasia. He exhibited, however, very gross elbow and knee changes.

Elbow Dysplasia

The contours of both elbows were highly abnormal, the heads of the radii being extremely prominent, especially on the right. Extension was limited by 40° on both sides and the deficiency in supination and pronation was similar to that observed in the mother.

Radiographs of the elbows showed assymetrical skeletal abnormalities on the two sides. On the right there was marked postero-lateral dislocation of the head of the radius (Fig. 8), while on the left there was gross "mushrooming" and irregularity of the radius with marked hypoplasia and irregularity of the capitulum of the humerus. The superior radio-ulnar joint was clearly dislocated, but the radius still articulated with the hypoplastic capitulum.

Knee Dysplasia

The knee joints also presented a highly abnormal appearance, the square outline in flexion being very marked, as was the prominence of the tibial tubercle. There also appeared to be marked external rotation of the tibia on the femur. The patient walked with a rather abnormal waddling gait. Most of the movement appeared to come from below the knee and the feet tended to be thrown outwards at each step. He was well aware of this abnormality of function and was

rather sensitive about it. The patellae were very small but there was no history of dislocation.

X-rays confirmed the above changes and showed a bipartite patella on the right and some prominence of the medial femoral condyle (Fig. 10).



Fig. 8. Case IV₂. A-P and lateral views of right elbow showing postero-lateral dislocation of radial head.



Fig. 9. Case IV₂. A-P and lateral views of left elbow showing markedly deformed radial head and hypoplasia of capitulum.



Fig. 10. Case IV₂. A-P and lateral views of right knee.

Sheila S. (IV₃), the sister of the propositus.

The lesions in this patient were much less marked than in the other two.

Nail Dystrophy

The thumb nails were shorter than usual and showed longitudinal ridging. The other nails were rather narrower than usual and showed an occasional longitudinal crack. Once again, the poorly defined dorsal skin creases over the distal I-P joints and the diminished range of movement at these joints was noted. X-rays of the hands were entirely negative.

Elbow Dysplasia

The abnormalities in the contour of the joints was comparatively slight though she lacked about 30° of extension on both sides. Supination and pronation were also limited but less severely than in her mother and brother. Radiographs revealed bilateral posterior dislocation of the heads of the radii with rather hypoplastic humeral capitula (Fig. 11).

Knee Dysplasia

Examination of the knees again showed hypoplastic patellae and this was confirmed on X-ray (Fig. 12 a & b).

Pelvic Dysplasia

Radiographic examination showed bilateral iliac horns, and of considerable interest is the presence on each horn of an epiphyseal centre of ossification.



Fig. 11. Case IV₃. A-P and lateral views of left elbow. Note lateral curve of coronoid process of ulna.



Fig. 12a

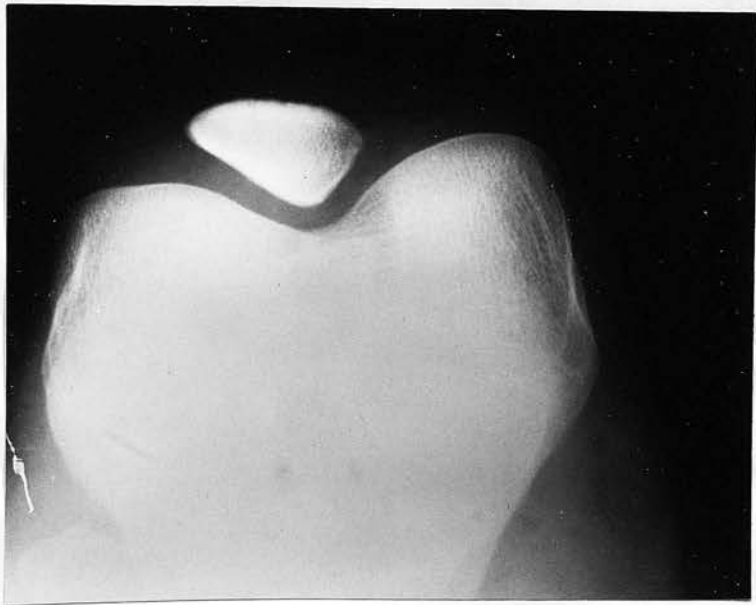


Fig. 12b

Fig. 12. Case IV₃. A-P, lateral and axial views of right knee.



Fig. 13. Case IV₃. A-P of pelvis showing bilateral iliac horns. Note the bilateral epiphyseal centre of ossification.

Past History

At the age of 10 years the patient had developed acute nephritis and was in the Royal Hospital for Sick Children for five months. Thereafter, however, she made a complete recovery and at the time of her examination a specimen of urine was found to have an S.G. of 1.032, and there was no evidence of proteinuria or of casts.

Passing reference might be made at this point to the fact that II₁ and II₂ showed a trace of proteinuria but, as both subjects had arteriosclerosis and cardiac failure, this could hardly be regarded as significant of any inherent renal disease.

ABO Linkage

The number of affected persons is obviously too small to allow of any study of blood group linkage but if we assume that this syndrome does exhibit ABO linkage as demonstrated by Renwick & Lawler (1954), it is clear that the abnormal gene must be linked to group O in this particular family.

SURVEY OF THE LITERATURE

An extensive survey of the world literature has revealed a total of 44 families, in each of which at least one or more persons exhibit the changes characteristic of onycho-osteodysplasia. The details of the individual family reports are shown in Table II. The series as a whole comprises more than 400 affected persons.

(Note: In order that a family might be included in this series, it was essential that the affected members, taken as a group, should exhibit the nail dystrophy and at least two of the three types of skeletal anomaly characteristic of the syndrome. Such criteria may be rather arbitrary but they at least ensure some degree of uniformity in the families selected for study. Moreover, such strict selection may be highly justified since it is by no means certain that families which persistently manifest only certain facets of the whole syndrome (e.g. Sedgwick's - see introductory historical note) are in possession of the same abnormal genetic factors as those in whom the full blown syndrome is apparent).

ANALYSIS OF RESULTS

Genetic Factors

With the exception of two apparently sporadic cases of the condition, in which no definite family history was forthcoming, and also of Family 16 in which, on the evidence

CASE NO.	CASE INDEX AFTER FERWICK ET AL.	AUTHOR	DATE	GENERA- TIONS AFFECTED	SIZE OF FAMILY	SEX RATIO OF FAMILY	AFFECTED PERSONS TOTAL	MALES	FEMALES	MAIL DYSPLASIA	NUMBERS OF CASES SHOWING KNEE DYSPLASIA	FELVIC DYSPLASIA	COMMENTS
1		Wrede	1909	3	13	7	6	4	2	6	6	1	
2		(a) Pirth (b) Lester	1912 1936	3	7	2/8	5	2	3	6	7	6	4
3	C	Thomson (quoted by Pirth)	1912	2	11	6/4	3	3	6	6	6	1	
4		(a) Trauner & Reiger (b) Orul	1925 1931	4	30	16/14	5	5	10	9	3	9	
5		Osterreicher	1931	5	21	10/11	7	4	11	11	10	9	24 showed arthrolyplasia but details not given.
6		Turner	1933	4	37	13/24	5	19	24	24	?	?	Only 9 showed arthrolyplasia. Details not given.
7		"	"	4	41	22/19	13	14	27	27	7	7	24 showed arthrolyplasia but details not given.
8	R	Rutherford	1933	3	27	13/14	6	3	9	9	5	-	Only 9 showed arthrolyplasia. Details not given.
9		Montant & Eggermann	1937	4	22	13/9	5	10	8	8	9	7	Details given of only 1 subject.
10		Sever	1938	23	7	7	72	22	24	1	1	1	Details given of only 1 subject.
11		Senturia & Senturia	1944	4	60	30/30	11	19	30	1	1	1	?
12		Montagard	1945	3	14	6/8	1	2	3	2	2	2	?
13		Mino, Mino & Livingstone	1943	4	7	7	5	5	10	10	10	10	?
14		Thompson, Walker & Weems	1949	1	7	7	7	7	7	4	2	3	Felvic details only given in 2 cases.
15		"	"	2	7	7	3	1	4	2	2	1	Details of other sisters not given.
16		"	"	1	7	7	7	7	7	1	1	1	?
17	B	Hemkina & Smith	1950	5	28	12/16	11	8	19	19	19	9	Details given of only 2 subjects.
18	L	Waldorwenok	1950	5	55	32/20	15	7	22	21	14	13	Details given of only 2 subjects.
19		Brizley & Burke	1950	5	15	8/7	3	4	7	2	2	2	?
20		Rocherath	1951	3	12	6/6	3	3	6	4	5	4	?
21		Prhallor & Ootet	1951	4	51	36/15	14	1	15	15	15	10	?
22		Book	1952	3	12	3/9	-	5	5	5	5	4	?
23		Wetler & Welach	1952	4	88	51/37	6	7	13	12	11	10	?
24		Donaguis & Hildault	1954	2	7	3/4	1	2	3	3	3	2	?
25		Forcella	1954	2	7	7	3	-	3	3	3	3	?
26		Bates	1954	2	6	4/2	4	2	6	6	6	6	?
27	A	Remick & Lemler	1954	5	62	30/32	15	10	25	7	7	7	?
28	D	"	"	6	65	23/35	12	18	30	7	7	7	?
29	P	"	"	2	2	2/0	2	-	2	2	2	2	?
30		Osauk	1954	3	11	8/3	3	1	4	4	3	3	?
31		Flechowaki	1955	4	10	3/7	2	7	9	8	2	1	?
32		Mengind	1955	4	8	4/4	4	3	7	7	4	5	?
33	G	Jamson, Lemler & Remick	1956	5	93	52/41	18	7	25	19	17	11	?
34		Broder	1956	3	8	5/3	5	3	8	4	4	4	?
35	H	Lemler, Remick & Waldorwenok	1957	4	62	30/32	5	8	13	7	7	7	?
36	J	"	"	33	9	4/5	11	23	24	7	7	7	?
37	K	"	"	4	28	14/14	5	2	7	7	7	7	?
38		Love & Baier	1957	5	7	7	7	7	7	4	4	4	?
39		"	"	71	7	7	7	7	7	1	1	1	?
40		Paqgali	1957	4	39	23/16	9	7	16	10	10	10	?
41		Heriel et al.	1960	3	14	4/10	1	6	7	7	4	5	?
42		"	"	7	7	7	7	7	7	7	7	7	?
43		Leoroux, Phillippon & Poirier	1960	3	8	2/6	2	3	5	5	4	1	?
44		McCluskey	1961	5	7	7	1 (4?)	4 (-?)	McLear 5	1	1	1	?

Table II. Details of the 44 families gathered from the literature.

available, the condition can only be said to be familial, it is clear from Table II that the syndrome is hereditary in nature, most of the families having exhibited the anomaly over several generations. For example, Renwick & Lawler (1954) in family D were able, by hearsay evidence, to trace the abnormality back through six generations and there are several instances where five generations have been involved. Moreover, the syndrome has never been known to "skip" a generation, and we find that approximately half of the offspring of these families exhibit the dysplasia. If we summate the membership of the 33 families where the total family size is actually quoted in the literature, we obtain a total group of 969 people of whom 391, i.e. 40 per cent., are affected by the dysplasia. The sex ratio (males/females) in this group of 969 people is 1.06. In the case of affected individuals, we find that in 41 families there was a total of 216 males to 209 females.

The above findings amply corroborate the impression of previous investigators that onycho-osteodysplasia is transmitted as a non-sex-limited, dominant inheritance with 100 per cent. penetrance.

Variability of the Syndrome

Not all affected persons show the complete tetrad of anomalies (see Table II). In the collected series, 252 subjects are described in sufficient detail to allow of analysis with regard to the incidence of the individual manifestations of the syndrome. The results are shown in Table III.

Total Number of Affected Patients	Number of Cases Showing			
	Nail Dystrophy	Knee Dysplasia	Elbow Dysplasia	Pelvic Dysplasia
252	234	201	148	75

Table III. Showing relative incidence of the different anomalies in 252 affected persons.

Series	Total Number of Affected Patients	Patients Exhibiting							
		Nail Dystrophy		Knee Dysplasia		Elbow Dysplasia		Pelvic Dysplasia	
		No.	%	No.	%	No.	%	No.	%
Touraine's Series (1943)	135	131	97%	102	79%	58	43%	-	-
Present Series	252	234	93%	201	80%	148	59%	75	30%
Corrected Series (A)	219	213	97%	194	89%	137	63%	-	-
Corrected Series (B)	120	116	97%	111	93%	81	68%	79	66%

Table IV. Incidence of each anomaly as found in 4 different series (see Text.)

It is clear that the nail dystrophy occurs most commonly, the knee dysplasia being next in order of frequency. The elbow and pelvic changes occur less frequently. The results obtained in Table III are strikingly similar to those found by Touraine when he carried out a similar review of the literature in 1943 (Table IV). At that time, pelvic anomalies were not recognised as part of the syndrome, but, more recently, Lawler, Renwick & Wilderwanck (1957) suggested that iliac horns are usually to be found in 30 per cent. of all affected persons, which agrees exactly with the results in Table IV. It must be remembered, however, that the anomalies exhibited by many of the subjects included in Table III were only determined by rather distant hearsay evidence. Such evidence will undoubtedly enhance the predominance of the more easily recognised anomalies such as the nail dystrophy, while neglecting the obscurer manifestations of the syndrome. If poorly documented cases of this type are excluded from the series (Corrected Series A), we find little change in the percentage incidence of the various anomalies save for a slight increase in the number of cases exhibiting elbow dysplasia. If we restrict the series still further and only include patients examined personally by authors who were clearly aware of and on the outlook for the full tetrad of lesions (Corrected Series B), we find that there is a more marked increase in the incidence of elbow changes and a striking rise in the incidence of pelvic dysplasia, two out of three affected individuals showing the latter (Table IV).

The variability of expression of the syndrome may be analysed from a rather different angle. Instead of dealing with the incidence of the individual manifestation of the tetrad of anomalies, we may classify the reported cases according to the various combinations in which the anomalies occurred. In Table V, Corrected Series A (219 cases) has been analysed with regard to the incidence of the various combinations of nail, knee and elbow anomalies, while in Table VI are tabulated the results of analysis of Corrected Series B (120 cases), this time pelvic anomalies being included in the permutation.

It is of interest that just under 50 per cent. of reported cases show the full tetrad of lesions, while only four cases exhibited skeletal dysplasia without associated nail dystrophy. No cases have been reported in which elbow, knee or pelvic dysplasia occurred as the sole manifestation of the syndrome. It is interesting to note that the propositus of the family recorded in this paper is the only reported case in which elbow and knee dysplasia has been the only sign of the condition and it is all the more interesting in that the dysplasia of these two joints was more severe than in the other two cases which exhibited the full tetrad of anomalies.

Not only does this hereditary syndrome vary in its expression with regard to the site and number of the anomalies exhibited, but also the individual lesions at any one site may vary greatly in severity from one patient to another, and from one limb to the other in the same patient. This

	TYPE OF DYSPLASIA							TOTAL
	Nails Only	Knees Only	Elbows Only	Nails and Knees	Nails and Elbows	Elbows and Knees	Nails Elbows and Knees	
NUMBER OF CASES	11	1	-	70	14	5	118	219

Table V. Incidence of the various combinations of anomalies in Corrected Series A.

	TYPE OF DYSPLASIA															TOTAL
	Nails Only	Elbows Only	Knees Only	Pelvis Only	Nails and Elbows	Nails and Knees	Nails and Pelvis	Elbows and Knees	Elbows and Pelvis	Knees and Pelvis	Nails Elbows and Pelvis	Nails Elbows and Knees	Nails Knees and Pelvis	Elbows Knees and Pelvis	Nails Elbows Knees and Pelvis	
NUMBER OF CASES	3	-	-	-	4	14	2	1	-	1	-	19	19	2	55	120

Table VI. Incidence of the various combinations of anomalies in Corrected Series B.

will be clearly seen when in the ensuing paragraphs the pathology of the lesions is discussed.

PATHOLOGY

Nail Dystrophy

The commonest type of nail dystrophy is that exhibited by Emily S., the mother of the propositus, i.e. the thumb nail is very short and small with a brittle texture and longitudinal cracking. The other finger nails are affected in varying degree, the dystrophy as a rule becoming less marked in the more medial digits, the little finger being, in fact, only rarely affected. In other cases, however, the nail may be bifid (Desbuquois, 1954) or show hemiatrophy. The latter abnormality would seem to occur only in the thumb nail and for some reason it is usually the ulnar side of the nail which is absent (Osterreicher, 1931; Mortant & Eggermann, 1937; Pfändler & Cottet, 1951). In the most severe cases, the thumb nail may be completely absent (Osterreicher, 1931; Margini, 1955). Very occasionally the index finger nail may also be absent (Böck, 1952; Desbuquois, 1954).

The colour of the nail may be altered to a brownish or black shade (Trauner & Reiger, 1925; Osterreicher, 1931). The dystrophy may involve the toe nails in addition to the finger nails and here, too, it is the big toe nail which is most commonly involved.

Table VII shows the incidence of the various forms of

Site of Dystrophy	Thumb			Index Finger		Other Fingers	Big Toe	2nd Toe	Other Toes
Nature of Dystrophy	Absence of Nail	Hemi-Atrophy	Other Abnormalities	Absence	Other Abnormalities	Unspecified	Unspecified		
Number of Cases	28	19	96	4	95	43	23	20	9
	143			99		43	23		

Table VII. Incidence of the nail dystrophy tabulated according to site and nature of anomaly.

Total Number of Cases	Number of cases showing				
	Absent Patella	Hypoplastic Patella	Subluxation of Patella	Complete Dislocation	Recurrent Dislocation with Flexion
143	20 (1 unilateral case)	124	31	14	21

Table VIII. Incidence of various forms of knee dysplasia.

the nail dystrophy in 143 cases drawn from the literature.

It is important to realise that the anomaly is not entirely confined to the actual nails. The whole tip of the thumb or finger shares in the abnormality. There is an absence of the dorsal crease over the distal interphalangeal joint and flexion is limited at this joint. The terminal pulp of the digit is carried round the tip on to the dorsal surface distal to the dystrophic nail and the resulting smooth, fusiform type of finger tip, devoid of nail edge, causes great difficulty in lifting fine objects such as pins.

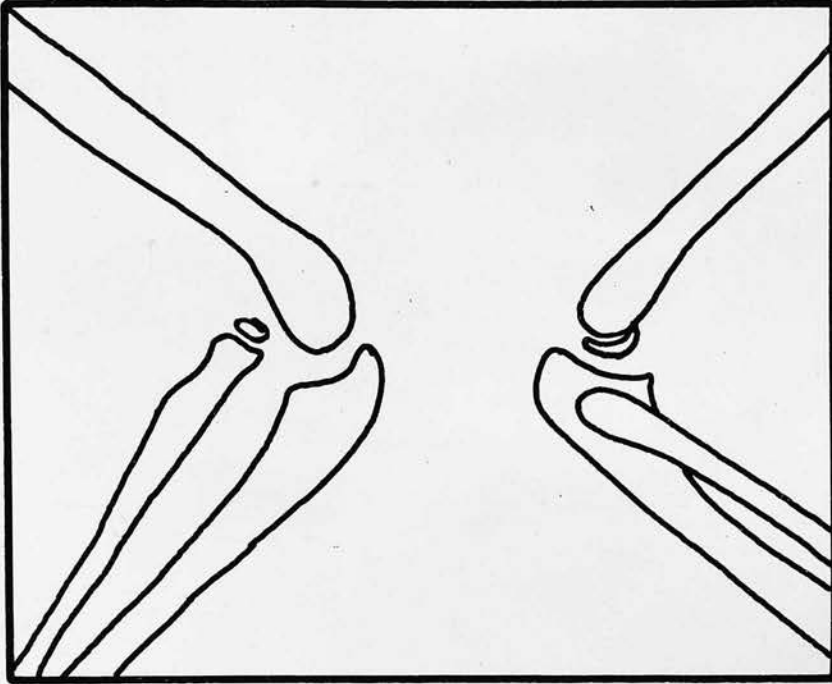
Some authors have also described the occurrence of laxity of the ligaments at the metacarpo-phalangeal and interphalangeal joints so that marked hyperextension may occur. This was most noticeable in the family reported by Montant & Eggermann (1937) in which, in 5 out of 10 affected persons, extension at the finger joints was possible to 90°. Less severe examples of ligamentous laxity have been reported by Roeckerath (1951), Piechowski (1955), Mangini (1955), Pasquali (1957) and McCluskey (1961). Radiographs of the hands have in no case shown any bony abnormality to account for the changes at the metacarpo- and interphalangeal joints. They must presumably be due to some anomaly of the connective tissue of the digits. Cosack (1954) was so impressed by the diffuse nature of the changes in the terminal parts of the digits that he put forward the somewhat heretical suggestion that the nail anomaly itself might be due, not to an ectodermal defect but to a defect of the underlying mesoderm.

Arthrodysplasia

Elbow Joints.

Little requires to be added to the description already given of the anomalies shown by the three cases reported earlier. The essential abnormalities are limitation of extension, supination and pronation, usually associated with dislocation of the head of the radius. The neck of the radius tends to be elongated and the head hypoplastic. The hypoplasia appears to affect the whole of the lateral side of the joint, as the capitulum and lateral epicondyle of the humerus are definitely smaller than usual. It is undoubtedly this hypoplasia of the lateral side of the joint which accounts for the marked cubitus valgus deformity shown by many of the affected subjects. The dislocation of the radius is usually postero-lateral but two cases of unilateral anterior dislocation have been reported (Wilderwanck, 1950; Roeckerath, 1951) (Fig. 14).

In a few cases, there may merely be dysplasia of the bones without actual dislocation as was seen in the left elbow in the case of William S., the propositus (also Trauner & Reiger, 1925; Osterreicher, 1931). Asymmetrical anomalies in the elbows is fairly common (Trauner & Reiger, 1925; Montant & Eggermann, 1937; and see Figs. 8, 9 and 14). The ulna takes little or no part in the dysplasia though occasionally there has been described a curious lateral sweep of the coronoid process towards the radial neck on the A-P view (Fig. 11) (also Trauner & Reiger, 1925; Wilderwanck, 1950). In the present author's opinion, two possible



Line Drawing to show assymetrical elbow
dysplasia. (After Roeckerath, 1951)

Fig. 14

explanations exist for this appearance. The first is that the lateral surface of the coronoid process, deprived of the modelling influence of the radial head, becomes hypertrophied at the site of what normally is the superior radioulnar joint. Alternatively, it may be that the cubitus valgus deformity of the elbow and the posterior radial dislocation are associated with a slight degree of external rotation of the forearm, so that in the A-P view one is looking at the coronoid process from an oblique angle. Lester (1936) suggested that the lowest part of the humeral shaft tended to be angled forward very slightly in affected subjects and that this is in part explained by the limitation of extension. However, this has not been substantiated by more recent investigators.

The actual cause of the limitation of movement at the elbow joint is not by any means certain although soft tissue contracture undoubtedly occurs in many cases. In some subjects, however, good movement may exist with severe skeletal abnormalities (Piechowski, 1955; Osterreicher, 1931), while the reverse may also apply (Mangini, 1955). The functional disability is seldom severe enough to prevent the subject undertaking normal manual work. There would appear to be an increased liability to osteoarthritic change in this type of dysplasia, the degenerative changes occurring at a relatively early age (Trauner & Reiger, 1925; Osterreicher, 1931; Wedler & Welsch, 1952).

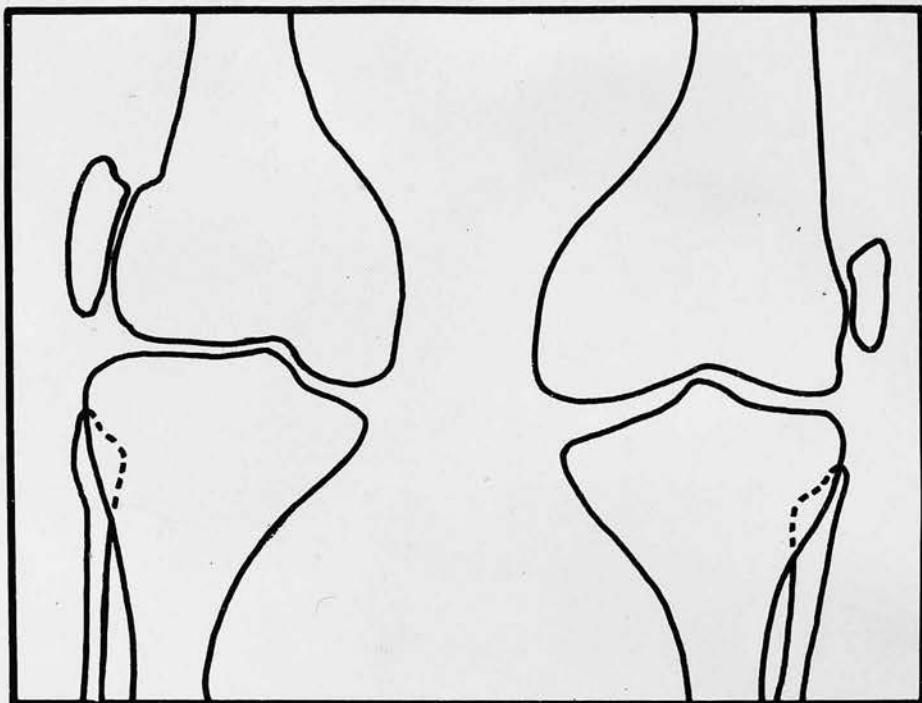
Knee Joints

The commonest feature of the dysplasia of this joint is the hypoplasia or absence of the patella, yet the whole joint may share in the dysplasia. The lateral condyle of the femur tends to be hypoplastic and due to this some of the affected subjects suffer from dislocation of the patella. The latter may be complete, as in the case recorded by Sever (1938). More often, however, the patient suffers from recurrent dislocation during flexion of the joint (Rutherford, 1933; Turner, 1933). This may cause severe functional disability when running or in descending stairs. For example, one of the cases described by Montant & Eggermann could only walk downstairs backwards or sideways. Those suffering from recurrent dislocation of the patella are practically the only affected persons who come under medical supervision, primarily because of this hereditary syndrome. Some require operative treatment (McCluskey, 1961).

In some cases, the patella is permanently in a subluxated position, usually rather lateral and inferior so that it lies over the joint line and overlaps both the lateral tibial and femoral condyles (Montant & Eggermann, 1937). Such lesions may or may not be associated with recurrent dislocation. The patellar lesions are quite often asymmetrical with regard to the severity or type of dysplasia (Montant & Eggermann, 1937; Desbuquois & Bidault, 1954).

The medial condyle of the femur is usually large and prominent and may extend beyond the margin of the tibial condyle for some little way. This medial hyperplasia may

give rise to marked genu valgum deformity noted by several authors (Rutherford, 1933; Lester, 1936; Sever, 1938). In some cases the medial surface of the shaft of the tibia sweeps upwards and medially towards the large medial condyle in a very characteristic way (Lacroix et al, 1960), while the plateau of the condyle may slope downwards and medially or may even be grooved (Wedler & Welsch, 1952). Sever, in 1938, reported a case in which these latter observations were combined with complete dislocation of the patella, the latter articulating with the lateral condyle of the femur (Fig. 15). This would appear to be the most severe expression of the knee dysplasia. In some cases the tibial tubercle is markedly prominent (Osterreicher, 1931; Turner, 1933; Wilderwanck, 1951). The latter suggested that this was a compensatory mechanism for the loss of the patella in improving the angle of insertion of the ligamentary ^{um} patellae. Forcella (1954) has, however, pointed out that the whole condylar area of the tibia is angled backwards relative to the rest of the metaphysis of the tibia (see also Fig. 10). Several cases also show marked external rotation of the tibia on the femur (Montant & Eggermann, 1937; Broder, 1956; and present case). In external appearance, the knee shows, in extension, a transverse ridge across the joint line due apparently to the underlying infra-patella pad of fat (Meriel et al, 1960). In the flexed position, the knee shows a characteristic flat, square outline. The fibula does not share in the dysplasia to any extent, but some authors have considered that the fibula head is rather



Line Drawing to show advanced knee dysplasia.
(After Sever, 1938)

Fig. 15

- Note:
1. Large medial femoral condyles.
 2. Sloping plateau of medial tibial condyle.
 3. Inward sweep of upper medial surface of tibia.
 4. Complete lateral dislocation of patella.

poorly developed (Turner, 1933). In one very remarkable case, severe knee abnormalities were associated with complete medial bowing of the fibulae behind the tibiae (Lacroix, 1960). Another case in which an arthrogram was performed showed a discoid cartilage. It is important to note, however, that these anomalies have been recorded in only one case each and that this is far too scant evidence to say that such anomalies are potentially part of the syndrome. Indeed, the reverse is likely to be true.

Reference has already been made to the abnormal gait shown by William S., the propositus reported in this case. It has also been noted that the mother was apparently late in learning to walk. Debuquois and Bidault (1954) reported an interesting example of the latter disability in a child who exhibited a divorce between the rate of progress with regard to intellectual development, e.g. speech, and its progress in the development of ambulation, the child being unable to walk until 23 months old.

Table VIII shows the incidence of the knee dysplasia in a series of 143 cases.

Pelvic Dysplasia

Turner was the first to draw attention to the abnormal pelvic appearance in some of his affected subjects. He noted that the iliac crest appeared to be flared outwards with marked prominence of the anterior superior iliac spines and marked concavity of the lateral aspect of the blade of the ileum. These findings were substantiated by Lester three years later. It is of interest that retrospective examination of the published pelvic X-ray in Turner's paper definitely reveals the presence of iliac horns.

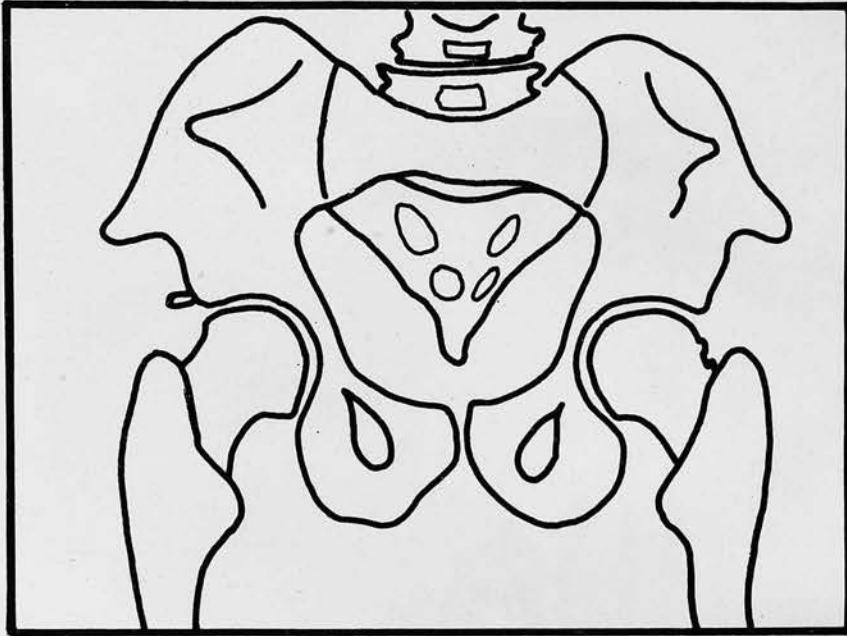
These structures are conical bony projections, oval in cross section, which jut out from the dorso-lateral aspect of the ileum. They were first described by Kieser in 1938 as part of a hereditary syndrome involving nail dystrophy, widespread muscular and connective tissue dysplasia, together with limited elbow movement due to soft tissue contractures (there were no skeletal abnormalities of the elbows or knees).

As mentioned in the historical note at the start of this paper, iliac horns were next described and called by their name for the first time by Fong in 1946. Three years later their association with the rest of the manifestation of the nail-patellar syndrome was amply demonstrated by Mino et al (1948) and Thompson et al (1949). They apparently are present very early in life, having been noted in a 6 months old baby. They would also appear to ossify in continuity with the blade of the ilium. However, as noted earlier, in Sheila S., the sister of the propositus,

there may be a secondary centre of ossification at the tip of the horn. This was previously recorded in a 14 year old child by Hawkins & Smith (1950). The horns vary greatly in size and may be visible, palpable or impalpable (Wedler & Welsch, 1952).

Böck (1952) attempted to ascertain their exact position on the ilium relative to the known landmarks of the gluteal lines by comparing X-rays of his patients with X-rays of iliac bones of similar size on which the gluteal lines had been marked with radiopaque dye. He found that the base of the bone lay either in the path of or just to one side of the middle gluteal line, midway between the anterior and posterior iliac spines. Moreover, the long axis of the oval base of the horn lay at right angles to the gluteal line. Hence they would not appear to be merely an exaggeration of the gluteal ridge. The authorities in comparative anatomy, quoted by Fong (1946), and the personal communication from Fraser quoted by Hawkins & Smith (1950) could shine no light on the origin of these structures. They resemble no structure found in any other mammal. The horns are usually symmetrical but rarely may be unilateral (Hawkins & Smith, 1950; Wedler & Welsch, 1952).

The iliac horns are the most common manifestation of the pelvic dysplasia. In the series collected from the literature, in 75 cases exhibiting pelvic anomalies, iliac horns were present in 65 cases, while the outward flaring of the iliac crest and the prominence of the anterior superior iliac spines only occurred in 37 cases. When the crest and



Line Drawing of Pelvis to show iliac horns
and flaring of Iliac Crest.

(After Roeckerath, 1951)

Fig. 16

Spine

Abnormalities are fully developed, the pelvis assumes a characteristic winged appearance, the ilium being likened by Lacroix (1960) to "an elephant's ear."

Other Anomalies

A great number of anomalies have been described from time to time as occurring in association with the nail-patella syndrome. There has been a tendency with certain authors to regard any such coincidental anomaly as part of the syndrome itself. In most cases, however, there is very little convincing evidence to support such hypotheses. Whereas the tetrad of abnormalities which characterise onycho-osteodysplasia recur in family after family with remarkable constancy, these other subsidiary anomalies are chiefly remarkable for the erratic and inconstant nature of their appearance. In attempting to assess the significance of these other anomalies, I have classified them into four categories:-

1. Doubtful anomalies.
2. Postural defects.
3. Sporadic anomalies.
4. Associated hereditary abnormalities.

1. Doubtful anomalies

This group largely consists of a series of abnormalities described by Turner in 1933, when he attempted to enlarge the

bounds of the nail-patella syndrome. He believed that certain other affected subjects showed anomalies of the wrists, shoulders, ankles and feet. For example, he stated that the medial malleoli were extremely prominent in some cases, while the neck of the talus was truncated and poorly developed. It would appear that Turner was not an expert on skeletal radiographs since he failed to recognise that the elbow dysplasia was associated with dislocation of the head of the radius and that the iliac horns were present in certain members of the family, though in his published X-rays these abnormalities are clearly visible. Consequently, one may doubt just how valid his observations were when it came to appreciating the range of normality in the appearance of bones and joints. Moreover, though subsequent authors have perpetuated his beliefs in their own writings, none has produced convincing X-ray evidence of the supposed abnormalities, nor is it stated by how many affected persons these changes were exhibited.

Perhaps the shoulder changes which he described merit fuller discussion, as they have also been referred to by Lester (1936), Mino et al (1948), Cosack (1951), Mangini (1955) and McCluskey (1961). The shoulder dysplasia is said to be characterised by a hypoplastic, pointed acromion, and coracoid process, a poorly developed upper end of humerus, and a small, triangular scapula. In other cases, the lateral edge of the scapula is said to be hypertrophied and thick, its outline being convex instead of concave, while the usually convex medial margin appears concave, the

whole blade of the scapula being rather narrow and triangular. It is of interest, in this connection, that shoulder X-rays of Emily S., the mother of the propositus (Fig. 17), and of the propositus himself (Fig. 18) tend to exemplify these anomalies. The mother's scapula is small, while the humerus has rather poorly defined bony prominences at its upper end. The scapula of the propositus, moreover, exhibits the thickened lateral margin and the change in outline of the scapula blade described above. I would submit that no published X-rays show changes more extreme than demonstrated in Figs. 17 and 18, and yet the radiologist who reported on these films had no hesitation in regarding them as being within normal limits. Furthermore, it must be remembered that even slight rotation of the scapula will, on the A-P view, produce the exact change of contour as described above (see Fig. 19). In view of these facts, the present author is inclined to believe that persons affected by the nail-patella syndrome exhibit no inherent dysplasia of the shoulder joint.

2. Postural defects.

Thirteen subjects in the whole series of 252 persons have been reported as showing pes planus, while 16 exhibited an excessive lordosis. The latter was especially marked in the family of Wedler & Welsch (1952). Thirteen examples of flat feet in a series of 250 people would not appear to be in any way unusual! Moreover, in those cases with severe knee dysplasia and marked external rotation of the leg or

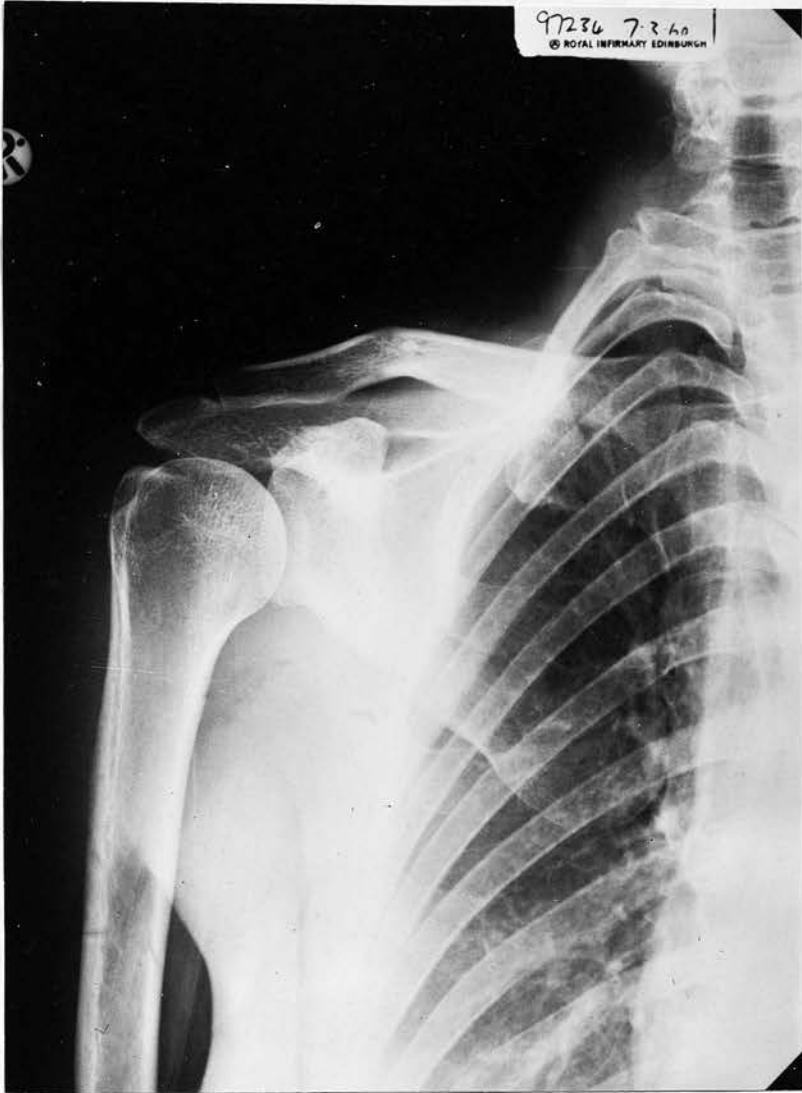


Fig. 17. Case Emily S. (III₄).

X-ray of right shoulder.
Shows a rather small triangular
scapula and rather hypoplastic
upper end of humerus.

N.B. Probably within normal limits.

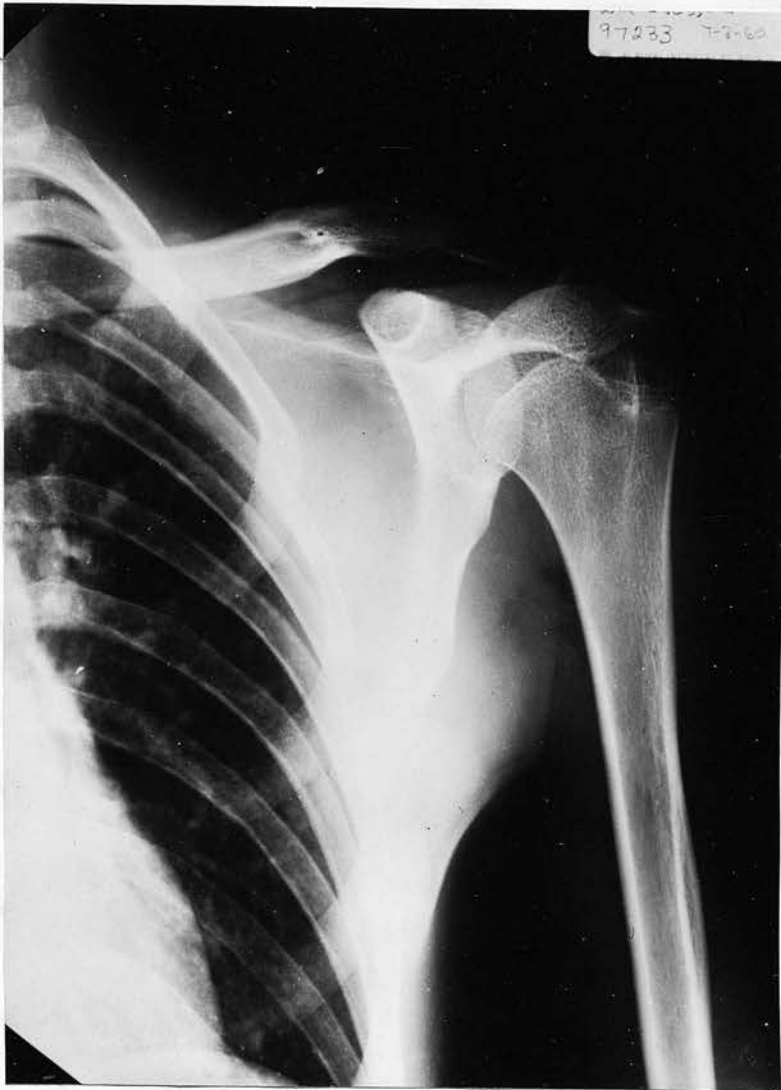
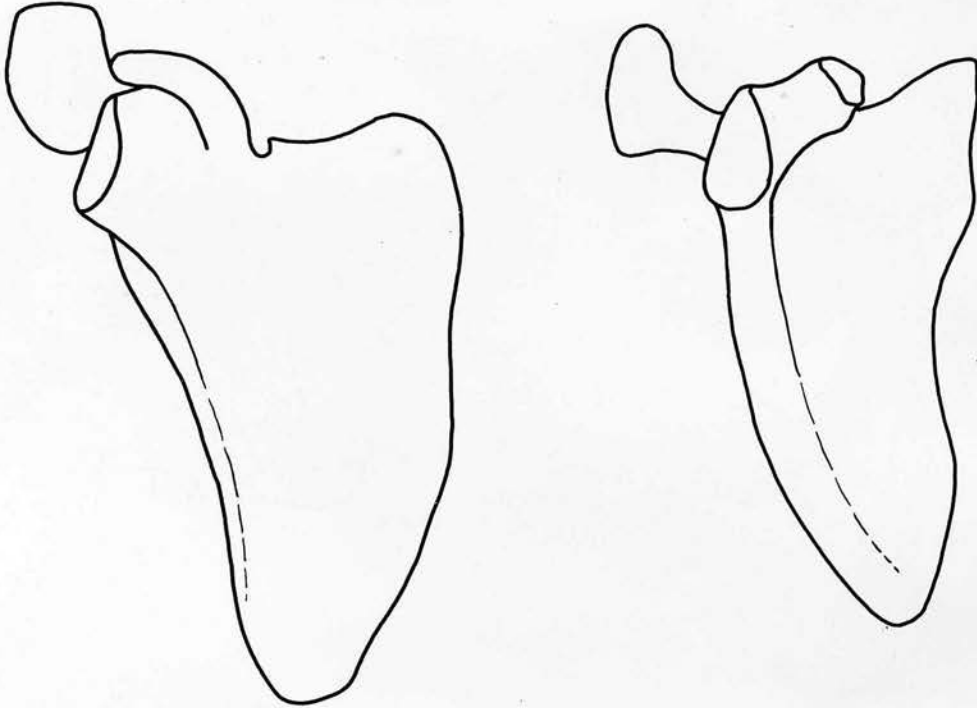


Fig. 18. Case William S. (IV₂). X-ray of left shoulder. Shows a triangular scapula with concave medial margin and thick convex lateral margin. Very short, thick scapula neck. N.B. Again probably within normal limits. Apparent anomalies are probably due to rotation. See Fig. 19.



Line Drawing to show effect rotating the scapula has on its contour and the density of lateral border

Fig. 19

genu valgum deformity, it would not be surprising if these anomalies resulted in postural defects, such as pes planus and lordosis. The opinion of the present author that these latter abnormalities are essentially postural defects resulting from the knee dysplasia is strengthened by the fact that no one has yet described any local manifestation of osseous dysplasia in the lumbar spine or in the foot, of a type which could provide an organic pain for the lordosis or pes planus.

3. Sporadic anomalies.

A considerable number of congenital defects have been recorded as occurring sporadically in the 44 families under investigation (see Table IX).

From this table it will be seen that 44 instances of other congenital anomalies have been recorded, but the incidence of any one of these is very small. Furthermore, there is a comparable, or even higher, incidence of many of these defects in the general populace, e.g. congenital dislocation of the hip, coxa valga and spina bifida. In consequence, this author feels that the occurrence of these anomalies in those affected by the nail-patella syndrome should be regarded as entirely fortuitous.

One of the anomalies, however, does, I think, merit closer investigation. This is the hyperostosis of the inner table of the frontal bone, a highly unusual and characteristic lesion in which, on the lateral skull X-ray, a low, "cauliflower-like" exostosis formation takes place.

TABLE 1X

THE MAIN ANOMALIES WHICH HAVE BEEN REPORTED AS OCCURRING SPORADICALLY IN ASSOCIATION WITH NAIL-PATELLA SYNDROME

	Number of families involved	Total number of patients
Club foot	4	5
Congenital dislocation of hip	2	2
Coxa valga	6	6
Coxa vara	2	2
Spina bifida	2	4
Scoliosis	1	1
Cervical ribs	1	3
Madelung's deformity	2	2
Second metacarpal larger than third	3	3
Rudimentary sixth digit	2	2
Multiple skeletal anomalies in lower limbs	2	2
Hyperostosis of frontal bone	4	4
Small sella turcica	4	4
Epicanthus	1	2
Cleft palate	1	1
Absence of primary dentition	1	1

The phenomenon has been recorded on four separate occasions by Mino et al (1948), Bates (1954), Piechowski (1955) and McCluskey (1961). This evidence is clearly not in any way conclusive of an actual association with onycho-osteodysplasia, yet the highly unusual nature of the lesion is striking and, furthermore, it must be remembered that comparatively few subjects with the nail-patella syndrome will have been subjected to routine skull X-ray. The present author feels that this investigation might well be included in the routine examination of suspected cases of onycho-osteodysplasia. Skull X-rays were taken in the case of Emily S. and Sheila S., the mother and sister of the propositus, but they showed no abnormality. The propositus refused to return for further examination.

4. Associated hereditary abnormalities.

This constitutes by far the most interesting group of associated anomalies. Four such abnormalities have been described:-

1. Congenital contracture of the fingers.
2. Abnormal pigmentation of the iris.
3. The Plummer-Vinson syndrome.
4. Renal dysplasia.

1. Congenital contractures of the little fingers have been described as occurring sporadically with the nail-patella syndrome (Roeckerath, 1951; Piechowski, 1955; McCluskey, 1961). Wilderwanck (1951) recorded the anomaly in 3 of his 22 cases, the contracture appearing in two

generations. In Trauner & Reiger's family, congenital contractures of the fingers appeared in 6 of 10 affected subjects over four generations. In two cases, moreover, the index finger also showed a flexion contracture similar to that appearing in the 5th digit. It is of interest, however, that in two cases the congenital contracture appeared in a branch of the family not exhibiting onycho-osteodysplasia (Orel, 1931). This suggests that the contracture must be due to a completely different gene from that causing the nail-patella syndrome, the association of the abnormalities being either coincidental or perhaps more likely due to linkage.

2. Iris anomalies. Lester (1936) was the first to draw attention to an anomaly of the iris pigmentation which occurred in two siblings of the family he reported. The outer zone of the iris was pale in colour while the inner zone possessed much deeper pigment arranged in a clover leaf pattern. One of the affected subjects had blue eyes, while the other had brown eyes. Roeckerath (1957) reported the same anomaly of the iris in 5 persons affected by the nail-patella syndrome in two generations. It was found, in fact, in every one of the individuals exhibiting onycho-osteodysplasia who were actually submitted to examination.

Later, Cosack (1954) described the anomaly in three members of his family, but on this occasion ~~only~~ two of these did not exhibit the nail-patella syndrome.

The above reports would tend to suggest that families exhibiting onycho-osteodysplasia are liable in a few cases to

show abnormal pigmentation of the iris. This is of special interest since both Montant & Eggermann (1937) and Pfändler & Cottet (1951) suggested that linkage might exist between the genes controlling the tint of the hair and colour of the eyes and the nail-patellar gene (see later). Hence it may be that the factors responsible for giving rise to the mutation of the gene for onycho-osteodysplasia may also affect neighbouring parts of the same chromosome, and in particular the gene for iris pigmentation. The fact that Cosack (1951) showed that this abnormality could occur in those unaffected by the nail-patella syndrome clearly demonstrates that the anomaly is not, as has been suggested, by several authors, part of the nail-patella syndrome itself, since clearly "crossing over" or, at least, separation of the genetic factors involved has occurred in Cosack's family.

3. The Plummer-Vinson syndrome. Cosack's family (1957) was also remarkable in that all 4 affected subjects exhibited, in addition, dysphagia, hypochromic anaemia and koilonychia. None of the unaffected members of the family exhibited these anomalies. The occurrence of the Plummer-Vinson syndrome was all the more remarkable in that 3 of the affected persons were males, whereas normally the condition is practically confined to females. The genetic relationship of the two hereditary syndromes must be regarded as being most likely a matter of coincidence, since the association has never been reported in any of the other 43 families in the series.

4. Renal dysplasia. Hawkins & Smith's family (1950) exhibited multiple anomalies in addition to the nail-patella syndrome. These included angiomatous lesions, multiple spinae bifidae, especially in the cervical region, pigeon chest, cervical ribs and congenital cataract. In addition, 6 members of the family exhibited signs of renal disease in that examination of their urine revealed persistent proteinuria. One subject actually showed signs of renal failure. Here again, however, one of the 6 subjects exhibiting this anomaly showed no evidence of onycho-osteodysplasia and it seems clear that a different gene must be responsible for the two conditions, though linkage may exist between them. Renal disease has been reported sporadically in other families in the series (Brixey & Burke, 1950; Jameson et al, 1956), but there is little to suggest, as some authors have done, that the presence of the nail-patella syndrome predisposes to or is commonly associated with hereditary renal dysplasia.

GENETIC BACKGROUND

There is no doubt, as noted earlier, that the nail-patella syndrome is transmitted as a non-sex-linked dominant character with 100 per cent. penetrance. Controversy has, however, waged for a long time as to whether the syndrome is the result of the action of a single gene with pleiotropic effect or is due to a group of very closely linked

genes. The earliest of the investigators, Trauner & Reiger (1925) and Osterreicher (1931) favoured the former mechanism but in 1933 Turner suggested that more than one gene might be involved. In his first family, in which all the affected members exhibited nail dystrophy and arthrodysplasia, he thought that a single gene could provide a satisfactory basis for the hereditary transmission of the condition, but in the second family when only 9 out of 27 affected cases showed the joint changes, he felt that there probably were two genes responsible, one controlling the nail anomaly and one the joint dysplasia, the latter being only able to exert its effect when the nail gene was present or, conversely, when a third hypothetical gene was absent. Aschner in 1934 agreed that several linked genes were probably responsible but considered that Turner's hypothesis was quite irrational and untenable, since it implied two entirely different mechanisms for the transmission of essentially the same syndrome. She put forward a very satisfactory theory, which for a long time was fairly generally accepted. She considered that probably four genes were involved, one for each facet of the tetrad, and that these genes were very closely linked. On her theory, variations in the combinations of the anomalies were to be explained on the basis of "crossing over" of certain of the gene factors during meiosis. She still considered, however, that each of the gene factors was pleiotropic to a certain degree, thus explaining the variability in the expression of any one of the anomalies found in the syndrome.

There is clearly one very marked drawback to this theory, and this is that, if variation in the combination of anomalies is due to "crossing over," one would expect that if a given subject had lost the gene for, say, the knee anomaly he would be unable to give rise to offspring exhibiting this anomaly, but in fact, anomalies absent in one generation may reappear in the next. This is seen in Osterreicher's family (1931) where after absence of the elbow dysplasia in the third generation it reappears in the fourth. Similarly, in Trauner & Reiger's family (1925) no knee abnormality occurred in the third generation, whereas when Orel (1931) followed the family up five years later the fourth generation was found, in certain cases, to exhibit the typical knee dysplasia.

Linkage studies also tend to disprove Aschner's theory as they indicate that the nail-patella syndrome is due to a gene, the locus of which can be fairly accurately determined. Pfändler & Cottet (1951) pioneered this line of investigation and gained evidence to suggest that linkage existed between nail-patella factor, blood group factor N and the tint of the hair. A very extensive survey by Renwick & Lawler (1954) and by Lawler et al (1957) of 9 families of large size and covering many generations, has shown that there is definite linkage between the nail-patella gene and that of ABO blood groups. The ABO group with which the nail-patella gene is linked varies from one family to another, there apparently being no predominant association with any one blood group, since the incidence of different

blood groups in those affected by the nail-patella syndrome is largely the same as in the general public (Fraser Roberts, 1959). The recombination value in the 9 families was found to be approximately 10%, and hence it must be assumed that the nail-patella syndrome is due to a gene situated in the same chromosome as the gene for the ABO blood groups at a distance of ten units of "crossing over."

Since the expression of the gene is so highly variable, Renwick (1956) has attempted, by a survey of 7 families, to find out whether any correlation exists in the severity of the nail dystrophy between parents and offspring and between siblings. No correlation could be demonstrated between parents and their children but there was a significant correlation between siblings. According to Renwick, these findings suggest that variations in the severity of the syndrome are due to modifying genes at the same locus as the main gene. In handing on the main gene, the parent of any affected person is prevented from handing on the modifying allele at the same locus. Instead, the anomaly in the offspring will be controlled by the modifying gene contributed by the unaffected parent. Such modifiers are called iso-alleles, that is, normal genes modifying the effect of the main gene at the same locus. Renwick believes that there is evidence that at least three such modifying genes exist in the general populace, any one individual only being able to possess one of them.

Spontaneous mutation.

It is generally assumed that dominant characteristics

of this nature must arise at some point by spontaneous mutation. In man, this is, of course, very difficult to establish definitely (Wilder, 1951). The family reported in the present paper is therefore of considerable interest in that the mother of the propositus would appear to be the first member of the family to exhibit the syndrome. The evidence in favour of the abnormality having arisen in this family by spontaneous mutation is as follows:-

1. The chances of a dominant inheritance being passed through the second and third generations of this family, with only one person affected in each, are 512 : 1.
2. The evidence for the great-grandmother being affected is, as noted earlier, both vague and inconclusive.
3. If she really did carry the abnormal gene, one would have to postulate, since the grandfather of the propositus is normal, that the anomaly had "skipped" a generation, something which has never been recorded in the previous literature, the gene having apparently 100 per cent. penetrance.
4. There is no evidence whatsoever that the grandmother of the propositus, or her relatives, showed any anomaly. There would, therefore, appear to be good grounds for considering that the mother of the propositus was in receipt of a spontaneous mutant from either her father or mother. The ABO genotypes, as noted in Fig. 1 and Table I, did not help

in identifying which parent was responsible since the abnormal gene in this family must be linked to group 0 which was present in the genotype of both her father and mother.

SUMMARY

A brief historical outline of the gradual recognition of hereditary onycho-osteodysplasia has been given.

The investigation of a further family, 3 members of which exhibit changes characteristic of the nail-patella syndrome, has been described.

Forty-four families exhibiting hereditary onycho-osteodysplasia have been collected from the world literature, the whole series comprising over 400 affected persons, details being available, however, for only 252 of these. The manifestations of the syndrome in the latter group have been analysed in order to find the relative incidence of the individual anomalies comprising the syndrome, and of the different combinations in which they occur. It has been suggested that the pelvic anomalies occur much more frequently than has previously been believed.

An account has also been given of various other abnormalities which have from time to time been reported as occurring in association with the nail-patella syndrome and an attempt has been made to classify these and determine their true relationship to the syndrome itself. The present

author's opinion is that, with the exception of a few associated hereditary anomalies which may possibly exhibit "linkage" with the main syndrome, the other subsidiary lesions are almost certainly coincidental.

Finally, a brief account has been given of what is known of the genetic factors involved in the transmission of the syndrome. Evidence has also been presented that there are strong grounds for believing that the anomaly has arisen as a spontaneous mutation in the family reported in this article.

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