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The Rubinstein-Taybi Syndrome

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The Rubinstein-Taybi syndrome was first described in 1963. The main clinical features are mental retardation, broad thumbs and great toes, a characteristic facies, and a high-arched palate. Rubinstein and Taybi (1963) described 7 cases in the United States. Since then, small groups of patients and single examples of this syndrome have been reported in the United States (Coffin, 1964; Taybi and Rubinstein, 1965; Johnson, 1966; Kushnick, 1966), Canada (Robinson, Miller Cook, and Tischler, 1966), England (Jancar, 1965; Berg, Smith, Ridler, Dutton, Green, and Richards, 1966; McArthur, 1967), France (Job, Rossier, and de Grandprey, 1964), South America (Latuff, Yamin, and Quintero, 1964), and Italy (Principi, 1966). Up to the present, reports of a total of 41 cases have been published, and Rubinstein presented the combined findings of 31 cases at the International Copenhagen Congress on the Scientific Study of Mental Retardation in 1964. It has become clear that this syndrome is a recognizable clinical entity.

Berg *et al.* (1966) and Giroux and Miller (1967) have described in detail the dermatoglyphs of 6 and 19 patients, respectively, with the Rubinstein-Taybi syndrome. Berg *et al.* (1966) observed a low mean ridge count on fingers, an extra triradius on the tip of the thumbs, high frequencies of patterns in the thenar, hypothenar, and third interdigital areas of the palm, and a lateral displacement of the f triradius in the hallucal area with or without an associated e triradius. Giroux and Miller (1967) found patterns in the thenar/interdigital I area of at least one palm in 16 of 18 patients (89%) with Rubinstein-Taybi syndrome compared with 11% in a control sample of 1000 Canadian schoolchildren. Giroux and Miller (1967) also observed a high frequency of patterns in the hypothenar and third interdigital areas of the hand, a high frequency of arches on the digits of the hand, large *atd* angles, and unusually long and distorted loops in the hallucal area of the feet. Penrose analysed the dermal patterns of an additional case (Jancar, 1965) in which hypothenar patterns were present though none of the other unusual dermal patterns were seen.

In this paper we present observations on 17 further cases of the Rubinstein-Taybi syndrome.

Material and Methods

The series consisted of 17 patients. One patient was found in the Outpatient clinic of Kingston General Hospital. The remaining 16 were discovered by inspection of the face and hands of all the patients in three institutions for the mentally retarded in Ontario. The case history was reviewed and a clinical examination carried out. The hands and feet of all but one patient were printed and their dermal patterns were analysed. The thumbs and fingers of 10 patients were reprinted with special attention to the tips of the fingers because of the extra triradius reported by Berg *et al.* (1966).

Results

Frequency. A total of 4838 patients in the three residential institutions were screened for the Rubinstein-Taybi syndrome and 16 cases were found. Assuming that all cases were discovered, this is a frequency of about 1 in 300 in the institutionalized, mentally retarded population of Ontario.

Age and sex. The age and sex distributions of this series and of other published cases are shown in Table I. The youngest patient in our series was 6 years and the oldest was aged 49 years. There were more females than males at all ages except in the age-group 20–29 years. The institutional population studied was known to contain an excess of males, but despite this the preponderance of females with the Rubinstein-Taybi syndrome in our series was not significant (Table II).

Family history. Well-documented family histories were available in nearly all cases. The mean maternal age at the time of birth was 28·9 years with a range of from 18 to 37 years; the mean paternal age was 32·0 with a range from 22 to 41

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TABLE I

Age and Sex Distribution of 53 Patients with the Rubinstein-Taybi Syndrome

Age-group (yr.)	Published Series*		Present Series		Total	
	M	F	M	F	M	F
0– 4	5	6	—	—	5	6
5– 9	7	7	1	5	8	12
10–19	2	4	1	4	3	8
20–29	1	3	3	1	4	4
30–39	—	1	—	1	—	2
40–49	—	—	—	1	—	1
Totals	15	21	5	12	20	33

* These series give the age and sex of the patients (Rubinstein and Taybi, 1963; Coffin, 1964; Job *et al.*, 1964; Taybi and Rubinstein, 1965; Jancar, 1965; Robinson *et al.*, 1966; Kushnick, 1966; Principi, 1966; Johnson, 1966; Berg *et al.*, 1966; McArthur, 1967).

TABLE II

Sex Distribution of 16 Patients with the Rubinstein-Taybi Syndrome in Relation to the Sex Distribution of the Population Screened

Patients	Male	Female	Total
With Rubinstein-Taybi syndrome ..	5	11	16
Without Rubinstein-Taybi syndrome	2864	1958	4822
	2869	1969	4838

χ^2 (Yates' correction) = 3·146; 0·1>p>0·05.

years. One child was the result of incest between father and daughter; there were no other instances of consanguinity. There were 50 sibs of the 17 cases, and all were reported as mentally normal; there was no history of mental retardation in other members of the family. Two mothers had each had two miscarriages each. There was no obvious relation of this syndrome to birth order, and in at least 8 families there were known younger normal sibs.

TABLE III

Summary of Main Findings in our 17 Cases

Clinical Features	No.
Mental retardation	17
Broad thumbs and toes	17
High arched palate	16
Microcrania	16
Short stature	16
Antimongoloid slant	14
Hyperactive reflexes	14
Abnormal gait	14
Strabismus	13
Other broad fingers	13
Beaked nose	12
Flat occiput	10
Deviated nasal septum	9
High eyebrows	8
Sternal anomalies	8
Ear anomalies	6
Ptosis	6
Hirsutism	6
Epicanthic folds	5

Clinical examination. The clinical signs found in our patients are listed in Table III. Some of these features will be considered in more detail.

Mental retardation and disposition. All our patients with the Rubinstein-Taybi syndrome were mentally retarded. This was to be expected from the method of case finding in 16 of the cases, but the 17th case found in out-patients was retarded also. The intelligence quotient (IQ), measured in a number of different ways, varied from 15 to 59, with a mean value of 36. This corresponds to what has been found by others: in over three-quarters of the reported cases the IQ or developmental quotient (DQ) has been less than 50. The highest DQ recorded is 86 in a patient aged less than 1 year by Johnson (1966); while Rubinstein and Taybi (1963) described an 8½-year-old boy with an IQ of 80.

Most of our patients had a happy disposition; after initial shyness they were friendly and eager to co-operate. These impressions were confirmed by the reports of the nursing staff and correspond with the observations of others (Rubinstein and Taybi, 1963; Coffin, 1964; Robinson *et al.*, 1966).

Broad thumb and toes. The presence of broad thumbs was a criterion of selection so that all our cases had this clinical sign. The thumbs were disproportionately broad in relation to the size of the hands, but the degree of broadness varied from patient to patient. The most constant features were broadness, shortening, and flattening of the distal phalanx with flattening of the nails (Fig. 1). In 2 of our patients there was outward or radial displacement of the terminal phalanx which itself had a spatulate appearance (Fig. 2). Thirteen of our patients also showed a similar broadness and flattening of the distal phalanges of the other fingers.

All our patients were found to have enlarged and broad great toes: in 5 there was hallux valgus. Paronychia of both toes and fingers was common, and in 3 patients the great toe-nails had been removed because of repeated infections. There was no obvious broadness of the remaining toes.

Facies. The facial characteristics of the patients with the Rubinstein-Taybi syndrome were similar to those described by others. Most patients showed a strong resemblance to one another (Fig. 3). The main features were antimongoloid slant to the eyes (seen in 14 of our 17 patients), some degree of

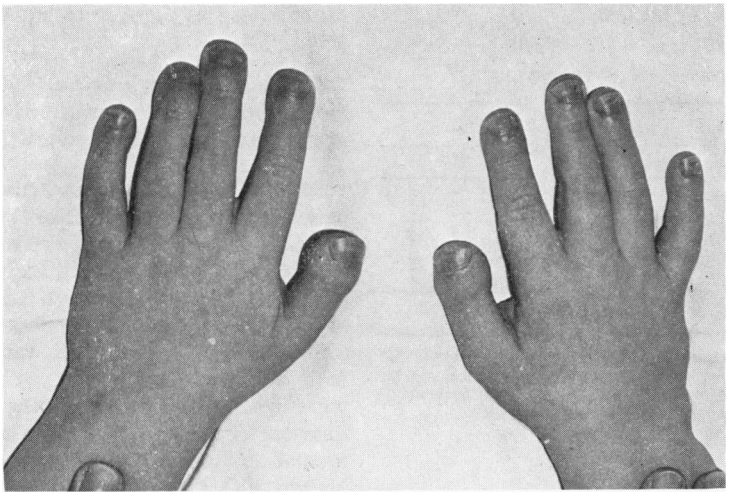

FIG. 1.—*Typical hands in a case of Rubinstein-Taybi syndrome.*

strabismus (13 patients), and a prominent beaked nose (12 patients). In addition, 8 patients had high arched eyebrows, 6 had low-set ears, 6 had some degree of ptosis, 5 had epicanthic folds, and 4 had very long eyelashes. One patient had unilateral microphthalmia, and another had bilateral polar cataracts. A broad flat base to the nose was seen in 3 patients. A naevus flammeus was present in 2, and in 2 more patients a naevus flammeus had been present when they were younger.

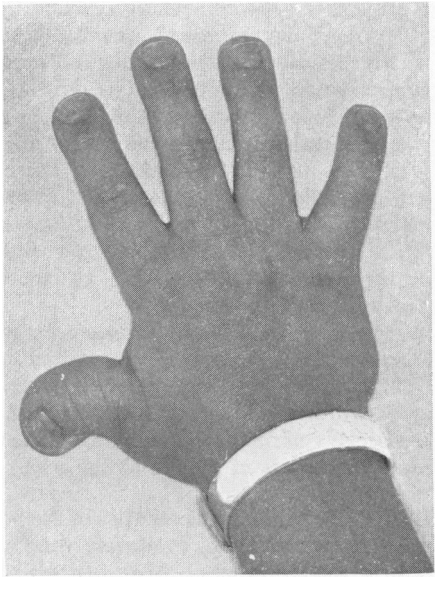

FIG. 2.—*Radial displacement of terminal phalanx of thumb as seen in 2 patients with the Rubinstein-Taybi syndrome.*

Mouth and nose. A high arched palate was seen in all but one of our patients. In 8 patients the palate was extremely high and narrow, the so-called 'steeple palate' (Fig. 4). In 9 patients there was a marked deviation of the nasal septum. There was a characteristic nasal quality to the voice in those patients who were able to speak.

Head size. In nearly all other previously reported cases there has been microcrania, this usually being measured by a reduced head circumference. Berg *et al.* (1966) calculated the cephalic index of their patients and found this ranged from 0·70 to 0·85. In our patients the head circumference was measured, and in 15 out of 17 the measurement was less than the 10th centile for the age. There was marked flattening of the occiput in 10 patients.

Stature and gait. All of our patients had short stature, 13 were below the 3rd centile and the remaining 4 were between the 3rd and 20th centile.

A common finding in the history was lateness in learning to walk, and 2 of our patients aged 6 years and 9 years were unable to walk without support. An abnormal characteristic gait was noted in 14 out of the remaining 15 patients who were able to walk.

FIG. 3.—*Six patients with the Rubinstein-Taybi syndrome.*

Movement was awkward, with flat feet and hips and knees slightly flexed.

Dermatoglyphs. It was possible to obtain palm prints of 16 of our 17 patients, and some of the typical patterns are illustrated in Fig. 5. Detailed results of the dermatoglyphic findings are presented in Tables IV and V.

Comparisons of dermal pattern frequencies in our series are made in Tables VI and VII with those frequencies reported by Berg *et al.* (1966) and Giroux and Miller (1967) and frequencies in the same Canadian control sample reported by Giroux and Miller. The findings in the three series are in general agreement. The frequencies of thenar/interdigital I patterns in our series and that of Berg *et al.* were not as high as that in the series of Giroux and Miller, but are greater than that of the control. The mean *atd* angles in the present series (Table V) were not different from controls nor, however, were they different from the series of Berg *et al.* (1966). In addition, in the present series there were more loops (31%) in the second interdigital area than in controls (3%), which may have some significance (Table VII). Two of our patients and one of Berg *et al.*'s had a radial loop on the third digit of the left hand. This pattern occurs on the third digit of the left hand in only about 2% of the Canadian control. Jancar (1965) reports a radial loop on the fourth digit of the right hand, an even rarer pattern which occurs in less than 1% of the control population. An extra triradius was not observed on the tips of the thumbs, as described by Berg *et al.* (1966), but was observed on the two fifth fingers of one patient. Distorted and unusually long distal loops, as described by Giroux and Miller (1967) in their patients, were observed in the hallucal area of the feet in 11 of our patients.

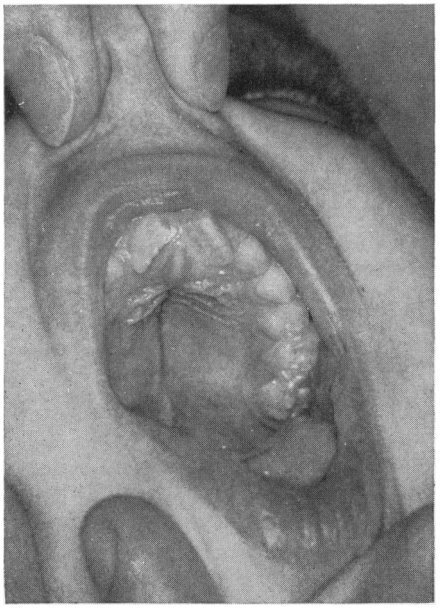

FIG. 4.—*Typical high arched palate ('steeple palate') seen in 8 cases of Rubinstein-Taybi syndrome.*

Other clinical findings. Hyperactive tendon reflexes were found in the lower limbs of 14 of our patients and 4 of these had sustained ankle clonus; in 7 patients the upper limb reflexes were also much increased. Sternal abnormalities have been

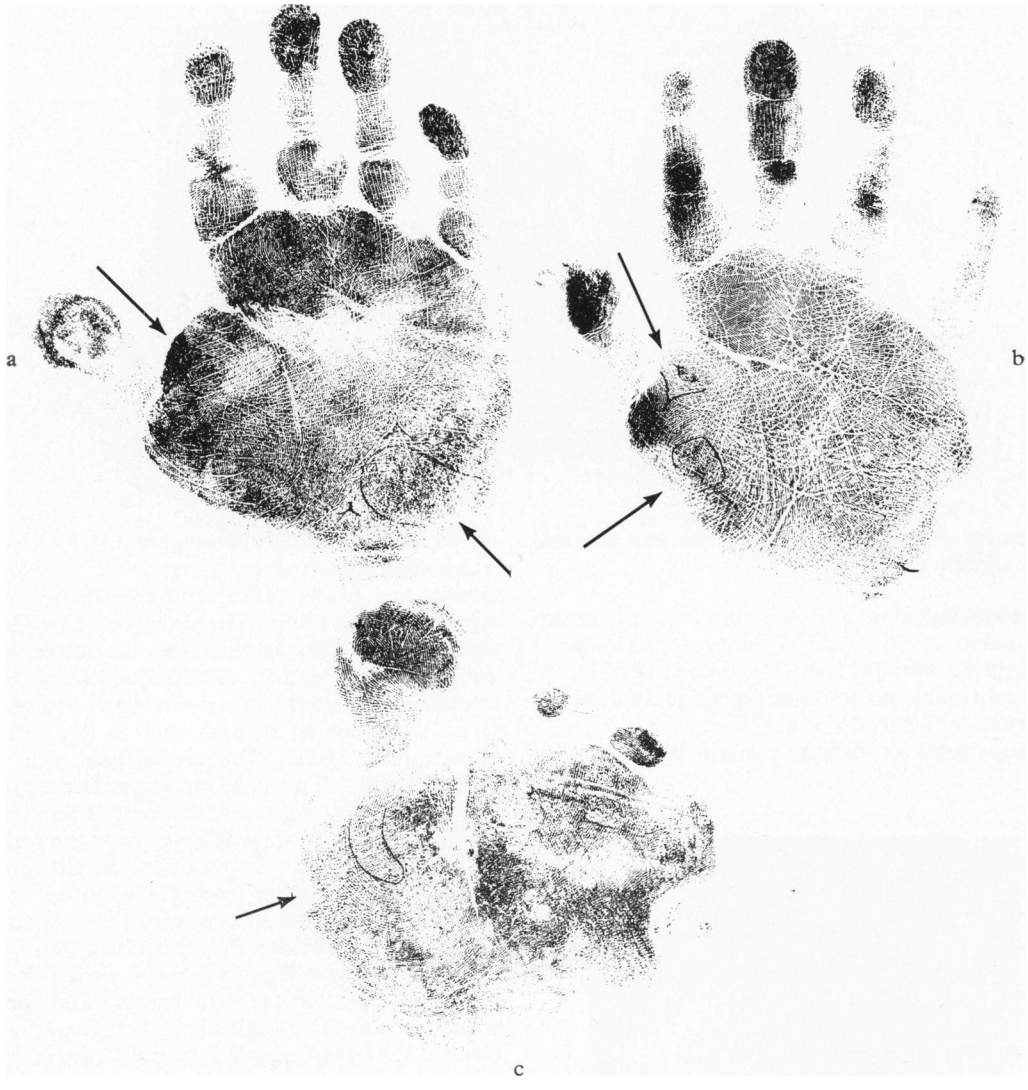

FIG. 5.—(a) *Palm print to illustrate a whorl in the 1st interdigital area and an ulnar loop in the hypothenar area; two patterns which are frequent in patients with Rubinstein-Taybi syndrome.* (b) *Palm print to illustrate patterns in the thenar/1st interdigital areas common in patients with Rubinstein-Taybi syndrome.* (c) *Foot print to illustrate the distorted loop commonly observed in the hallucal area of patients with Rubinstein-Taybi syndrome.*

noted in 6 of the previously published cases, and in our series 8 patients had varying degrees of pectus excavatum. Only 1 of the 5 male patients had both testes in the scrotum. 6 of the patients were markedly hirsute. 5 had a history of neonatal respiratory difficulties and 5 had repeated upper respiratory infections. In addition, there were heart murmurs in 4, muscular hypertonicity in 3, hyperextensibility of the joints in 3, and areas of vitiligo in 2 patients.

Chromosomal studies of the leucocytes in 3 of our patients revealed normal karyotypes in 2 of them; in the third patient an apparently large 16th chromosome was observed: however, this abnormal chromosome was also present in 6 of this patient's close relatives who were all clinically normal (N. E. Simpson, 1967, unpublished data). A large 16th chromosome has been observed in other normal individuals (Court Brown, Jacobs, and Brunton, 1965).

TABLE IV

Finger-tip and Foot Patterns in Rubinstein-Taybi Syndrome

Case No.	Sex	Finger-tip Patterns													Foot Pattern	
		Left					Right					Total Ridge Count	Triradius at Tip of Digits		Pattern on Hallucal Area	
		5	4	3	2	1	1	2	3	4	5		Left	Right	Left	Right
1	F	A	A	A	U	U	U	R	U	A	A	71	O	O	W	L^t
2	M	A	U	U	A	A	U	A	A	W	A	34	O	O	L^d	L^d
3	F	A	A	U	R	U	U	R	A	U	U	79			L^d	L^d
4	F	A	U	U	U	U	A	U	U	U	A	79	O	O	L^d	L^d
5	F	W	U	R	W	U	U	U	U	W	U	117	O	O	L^d	W
6	F	W	W	U	U	U	W	U	U	W	W	213	O	O	L^d	L^d
7	F	A	A	TA	A	U	U	A	TA	A	A	25	O	O	L^d	L^d
8	M	U	W	W	W	U	U	TA	W	W	W	160	O	O	L^d	L^d
9	F	U	W	W	W	U	U	W	U	W	U	—	—	—	L^t	L^t
10	M	W	U	W	W	W	W	W	W	U	U	216	O	O	L^d	L^d
11	F	U	U	U	U	U	W	W	U	U	U	125	5th	5th	L^d	L^t
12	M	U	U	W	R	U	U	W	U	U	U	139	—	—	L^t	L^t
13	M	R	U	U	U	U	W	U	U	U	W	—	—	—	W	L^t
14	F	U	W	U	U	U	U	U	U	U	U	—	—	—	L^d	L^d
15	F	A	W	U	A	U	U	U	U	U	A	70	—	—	L^d	W
16	F	U	U	R	R	U	U	W	U	U	U	—	—	—	L^d	W

A, arch; TA, tented arch; U, ulnar loop; R, radial loop; W, whorl; L^t, tibular loop; L^d, distal loop; —, pattern not examined.

TABLE V

Palm Patterns in Rubinstein-Taybi Syndrome

Case No.	Palm Patterns												Total
	Hypothenar Pattern		Thenar Pattern		1st Interdigital Space		2nd Interdigital Space		3rd Interdigital Space		*atd* Angle		
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	
1	O	O	+	O	+	O	+	+	+ ?	+	38·0	38·0	76·0
2	O	O	O	O	O	O	+	+	O	+	37·2	43·8	81·0
3	O	O	O	+	O	O	O	O	O	+	58·1	45·9	104·0
4	O	+	O	O	+	+	O	O	O	O	49·6	47·0 58·2	107·8
5	O	O	+	+	+	+	O	+	O	+	37·0	47·0	84·0
6	O	+	O	O	+	O	O	+	+	+	37·1	37·0 61·6	98·7
7	+	O	+*	+*	O	O	O	O	O	O	43·3 49·1	43·5	92·6
8	O	O	O	O	O	O	O	+	O	+	46·4	43·2	89·6
9	O	O	O	O	O	O	O	O	O	O	48·1	46·0	94·1
10	O	O	O	O	O	O	O	O	+	+	65·2	64·9	130·1
11	+	+	O	O	O	O	O	O	O	O	53·9	49·4	103·3
12	O	+	+*	O	O	O	O	O	O	+	42·4	45·8	88·2
13	O	+	O	O	+	O	O	O	O	+	31·9	35·8	67·7
14	+	—	O	O	O	O	O	O	+	+	45·7	49·5	95·2
15	+	+	O	O	+	O	O	O	+	+	45·0 78·0	46·0 66·0	144·0
16	+	O	O	O	O	O	O	O	O	O	41·5	43·0	84·5

* Pattern opens into interdigital space 1.

+, pattern present; O, pattern absent. Total *atd* angle = total of largest angles.

Chromatography of the amino acids in plasma and urine showed normal patterns in 4 patients. In 1 patient with eczema and recurrent infections, the serum immunoglobulins were studied and found to be normal.

Discussion

When Rubinstein and Taybi first described 7 patients with mental retardation and broad thumbs and great toes, they did not exclude the possibility that this association might have been fortuitous. Our own experience agrees with other published reports and suggests that this syndrome is in fact a distinct clinical entity. Although Berg *et al.* (1966) laid stress on the variations between patients, we were struck by the comparative uniformity of the clinical picture. This impression may be partly explained by our case-finding method. Initially

TABLE VI

Number and Percentage of Thenar and First Interdigital Dermal Patterns in Patients with Rubinstein-Taybi Syndrome and a Control

Sample	No. of Palms	Thenar	Interdigital I	Thenar plus Interdigital I	Total
Berg *et al.* (1966)					
No.	12	2	2	1	5
%		16·7	16·7	8·3	41·7
Giroux and Miller (1967)					
No.	36	4	5	18	27
%		11·0	14·0	50·0	75·0
Present series					
No.	32	0	3	9	12
%		0·0	9·4	28·1	37·5
Control*					
No.	2000				
%		4·1	1·6	2·0	7·7

* Control consists of 1000 Canadian schoolchildren.

TABLE VII

Comparisons of Dermal Patterns in Patients with Rubinstein-Taybi Syndrome in Three Series and a Control

Sample	No. of Patients	Percentage of Patients with Pattern				Mean *atd* Angle	% Arches on Digits	Mean Total Ridge Count
		Hypothenar	Thenar/Interdigital I	Interdigital II	Interdigital III			
Berg *et al.* (1966)	6	66·7	50·0	16·7	100·0	53·7±7·0	10·0	84·3±12·2
Giroux and Miller (1967)	18	66·7	88·8		60·5	55·0	17·4	
Present series	16	56·3	56·3	31·3	68·8	48·2±1·8	16·3	
Control*	1000	37·0	11·3	3·0	40·4	49·9	5·3	133·9±1·6

* Control consists of 1000 Canadian schoolchildren.

42 out of the 4838 patients screened were suspected of having the Rubinstein-Taybi syndrome; but later, after more detailed examination, 26 patients were rejected. Like Coffin (1964) we wondered whether some of these 26 patients had an incomplete form of the syndrome. Some variations in the clinical picture may be related to age as Johnson (1966) has suggested: for example, a broad flat nasal root has been most often reported in the younger age-groups.

The frequency of this syndrome in the general population is not known. In institutionalized retarded patients of all ages over 5 years we found a frequency of about 1 in 300. Berg *et al.* (1966) found 3 cases in a similar population of 1600, a frequency of about 1 in 500.

There were twice as many females as males in our series and all the cases reported by Berg *et al.* (1966) were female. However, of the 53 published cases (Table I) 20 are male and 33 are female, which is not a significant preponderance of females.

Since frequencies of some dermal patterns have been shown to be different from a control population in three series, it is important to record the frequencies of dermal patterns in future series of patients until a large enough sample is attained from which a reliable estimate of frequencies may be made. When a reliable estimate is possible, a scoring system based on these estimates and those of frequencies in the population might be devised as an aid to diagnosis of the syndrome.

The unusual dermal patterns suggest that the syndrome has a causative agent which is active early in embryonic life. There is no evidence of single gene inheritance. No consistent history of infection or drug ingestion during pregnancy has emerged from our own or other published case reports. The age of the oldest patients tends to exclude some classes of drugs, for example steroids or antibiotics, as possible aetiological agents. This negative evidence, and analogy with other syndromes with distinct dermatoglyphic patterns, suggests the possibility of a chromosomal abnormality being present in patients with this syndrome. However, examination of the leucocyte karyotypes by current methods has failed to show any abnormality in some of our own and several previously published cases.

Summary

Seventeen cases of the Rubinstein-Taybi syndrome are presented. The clinical features and

family histories are described. An incidence of this syndrome in the mentally retarded population is suggested. The dermatoglyphic findings of 16 of these cases are described and compared with previously published accounts.

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