J. med. Genet. (1964). 1, 2.

A Family Study of Aortic Stenosis*

HERMIEN E. ZOETHOUT, R. E. BONHAM CARTER, AND C. O. CARTER

From the Thoracic Unit and Medical Research Council Clinical Genetics Research Unit at The Hospital for Sick Children, Great Ormond Street, London

Congenital aortic stenosis is no longer only an anatomical diagnosis, but also a haemodynamic one, since it is now possible to measure pressure gradients between the left ventricle and the ascending aorta. Not every anatomical abnormality causes a significant obstruction to the blood flow from the left ventricle.

Anatomically three types can be distinguished.

(1) Supravalvar, in which there is a narrowing of the aorta 1–3 cm. beyond the aortic valves.

(2) Valvar, in which there may be partial fusion of all commissures or total fusion of 1 commissure: this often causes the valve to appear bicuspid.

(3) Subvalvar: this may be a fibrous ring or a diaphragm below valve level or a diffuse muscular narrowing of the left ventricular outflow tract.

Infants with aortic stenosis often present with heart failure, and sudden death or death from left heart failure is not uncommon. In older children symptoms are found related to insufficient coronary or body circulation on exertion, such as attacks of pain in the chest or abdomen, dizziness, syncope, pain in the legs, and tiredness at the end of the day. The presence of symptoms indicates a severe degree of stenosis. All patients have a systolic murmur. A minority (10% according to Keith, Rowe, and Vlad, 1958) have a diastolic murmur suggesting some degree of incompetence. Often a thrill is felt. A systolic ejection click is considered to indicate a valvar stenosis.

In children, the heart commonly appears normal on radiography unless there is aortic incompetence or cardiac failure. Enlargement of the ascending aorta suggests a post-stenotic dilatation. The electrocardiogram often, but not always, shows features suggesting left ventricular hypertropy. Sometimes ST segment and T-wave changes are present constituting a so-called strain pattern.

The most common associated cardiac abnormalities are coarctation of the aorta and patent ductus arteriosus. Less frequent are abnormalities of the mitral, tricuspid, and pulmonary valves. Fibroelastosis is also associated with aortic stenosis. Calcified aortic stenosis, important in adults, is hardly ever seen in children.

Congenital aortic stenosis may also be associated with non-cardiac abnormalities in certain genetic syndromes; for example, Marfan's syndrome and von Recklinghausen's disease*. Supravalvar stenosis has recently been reported as part of a stenosis in which there is also mental retardation and a characteristic facial appearance (Beuren, Apitz, and Harmjanz, 1962). Aortic stenosis has been found associated with idiopathic hypercalcaemia in children. Black and Bonham Carter (1963) have presented several examples of aortic stenosis associated with the facies of severe infantile hypercalcaemia.

The incidence of congenital heart disease among all live births probably approaches 1% (Richards, Merritt, Samuels, and Langmann, 1955), and the incidence of aortic stenosis among all cases of congenital heart disease is about 3% (Wood, 1956; Keith *et al.*, 1958); therefore approximately 1 in 3,000 to 1 in 4,000 live births have aortic stenosis.

Material and Methods

The present family study is based on 126 patients in 123 families attending the Hospital for Sick Children between January 1951 and April 1963. These 126 patients were selected from a total series of about 300 on the basis of certainty of diagnosis and of a domicile within the London area. The family histories were taken from the patients and on occasion from other relatives in their homes or when attending the congenital heart clinic. In 12 cases only, all belonging to Group I (see below), was a questionnaire used rather than personal interview.

For the purpose of the survey, the index patients were re-examined and a number of their brothers and sisters were also examined.

The patients were subdivided into three groups

* Received April 1, 1964.

* The association of aortic stenosis with von Recklinghausen's multiple neurofibromatosis is noted for the first time in this series (R.E.B.C.)

TABLE I

CLINICAL DATA ON GROUP I PATIENTS: 18 ALL DECEASED

	No.
Age at death (yr.)	
< 1	7
1–5	5
6–9	3
10 +	3
Necropsy	
Complex heart lesion	11
Uncomplicated	4
Main symptoms	
Cardiac failure	5
Attacks of pain	3
Dyspnoea	2
Easily tired	1
Main signs	
Systolic murmur	17
Diastolic murmur	5
Systolic ejection click	2
Systolic thrill	2
Chest radiograph	
Cardiac enlargement only	9
Ascending aorta also enlarged	3
Electrocardiogram	
Left ventricular hypertrophy pattern	13
Right ventricular hypertrophy pattern	4
ST segment and T wave changes	8

Group I: 18 patients who died between January 1951 and April 1963 with aortic stenosis or a complex heart lesion of which aortic stenosis formed a part.

Group II: 21 patients who were surgically treated for aortic stenosis between January 1951 and April 1963 and are still alive.

Group III: 87 patients on whom a diagnosis was made of aortic stenosis on clinical grounds only.

TABLE II

CLINICAL DATA ON GROUP II PATIENTS: 21 ALL SURGICALLY TREATED AND ALIVE

	No.
Age at operation (yr.)	
< 1	1
1–5	4
6–9	5
10 +	11
Types of operation	
Transventricular	8
Open operation	13
Diagnosis at operation	
Valvar stenosis	19
Subvalvar stenosis	2
Associated cardiac abnormalities	3
Main symptoms	
Cardiac failure	1
Attacks of pain	3
Syncope	1
Dizziness	3
Dyspnoea	1
Easily tired	1
Main signs	
Systolic murmur	21
Diastolic murmur	5
Systolic ejection click	5
Systolic thrill	16
Chest radiograph	
Enlargement of ascending aorta	7
Cardiac enlargement	1
Electrocardiogram	
Left ventricular hypertrophy pattern	17
ST segment and T wave changes	11

Cardiological data on the 18 patients in Group I are listed in Table I. The diagnosis was made in 11 of these before death, and in 7 the aortic stenosis was only found at necropsy. In all, 15 came to necropsy, and only 4 of these were found to have an uncomplicated aortic valvar stenosis.

The 5 patients in whom cardiac failure was present were all infants under the age of 1 year. The 1 patient in whom no cardiac murmur was heard died at the age of 1 week with anal atresia. Four patients had no chest radiograph. Of the remaining 14, 12 showed cardiac enlargement and 3 in addition showed enlargement of the ascending aorta. The electrocardiogram usually showed left ventricular hypertrophy; of the 4 patients showing a right ventricular pattern, 1 had severe pulmonary stenosis, the other 3 were infants with complicated heart lesions. Seven patients died suddenly; 5 died at an operation to relieve aortic stenosis; 5 died in heart failure, in some cases caused by respiratory tract infection; 1 died as mentioned above, with anal atresia.

Cardiological data on the 21 patients in Group II are listed in Table II. The transventricular valvotomies were done in the Hospital for Sick Children; the open heart surgery in various other hospitals.

All patients in the group are leading a normal life, at the time of writing. Nearly half of the total number of patients had symptoms before the operation. Cardiac failure was present in the one patient under 1 year old. Of the 3 who have associated cardiac abnormalities, one is thought to have mitral incompetence, another had a coarctation of the aorta resected before the valvotomy was done, and a third was noted to have a supravalvar narrowing at the time of transventricular valvotomy.

All patients had a systolic murmur; a preoperative diastolic murmur was present in 5. All patients in whom an ejection click was heard had valvar stenosis. The abnormalities on the chest radiograph, present in 8 of the 11 patients so examined, consisted of enlargement of the ascending aorta in 7 and an enlargement of the heart shadow in one. One of the 4 patients in whom the electrocardiogram did not suggest left ventricular hypertrophy was found to have a peak systolic gradient across the aortic valve of 160 mm. Hg.

Cardiological data on the patients in Group III are listed in Table III. Recent radiographs of these children had not been taken as they were all doing well. None of these patients had a history of rheumatic fever. A systolic murmur, incidentally found, caused each child to be brought to the hospital. In 75 of 87 patients the murmur was found before the

TABLE III

CLINICAL DATA ON GROUP III PATIENTS: 87 ALIVE AND NOT TREATED SURGICALLY

	No.
Age at time of survey (yr.)	
< 1	0
1–5	25
6–9	35
10 +	27
Associated cardiac abnormalities	
Coarctation	4
Coarctation and aberrant right subclavian artery	2
Coarctation and patent ductus	1
Patent ductus	2
Main symptoms	
Attacks of chest pain	2
Easily tired	1
Pain in legs	1
Main signs	
Systolic murmur	87
Diastolic murmur	9
Ejection click	45
Systolic thrill	60
Electrocardiogram	
Left ventricular hypertrophy pattern	58
ST segment and T wave change	8

TABLE IV

ASSOCIATED NON-CARDIAC MALFORMATIONS OF INDEX PATIENTS

Group	Serial Number and Sex	Malformations
I	2 (M)	Cataract, mental retardation
	4 (M)	Anal atresia; left atrial appendage
	14 (F)	Dwarfism
II	26 (M)	Syndactyly left hand
	39 (M)	von Recklinghausen's disease
	30 (F)	Turner's syndrome
	41 (F)	Turner's syndrome
III	152 (M)	Mental retardation, hypothyroidism
	128 (M)	Anisochromia
	130 (M)	Talipes equinovarus
	161 (M)	Hypospadias
	151 (M)	Bilaterial malrotation of kidney
	186 (M)	Funnel chest
	146 (F)	Lobster claw deformity both hands
	167 (F)	Marked asymmetry face and hands
	179 (F)	Large capillary naevus on chest and hands

TABLE V

SEX DISTRIBUTION BY GROUP, AND PRESENCE OF ADDITIONAL LESIONS

Group	All Cases		Complex Lesion Excluded	
	Boys	Girls	Boys	Girls
I	11	7	2	2
II	12	9	10	8
III	56	31	49	28
Total	79	47	61	38

age of 6 years. Only 4 patients have symptoms that could be related to the heart condition.

Associated cardiac abnormalities were present in 9 patients. Of these, 4 had a coarctation which had been resected in 3; 2 had an aberrant right subclavian artery as well as a coarctation, both of which have been treated by operation; 1 patient had a coarctation and a patent ductus. Patent ductus only was present in 2, complicated by pulmonary hypertension in 1 of them.

Associated Non-cardiac Malformations. The associated non-cardiac malformations in the 126 index patients are listed in Table IV. Apart from the known association with Turner's syndrome (2 patients), the rubella syndrome (1 patient), and the newly described association with von Recklinghausen's disease, there is no marked association with any other type of defect. The total number of non-cardiac malformations, however, excluding the known associations, is still more than one would expect in a random series of children of similar age distribution.

Genetic Findings

Sex-ratio. The sex distribution of each group is shown in Table V. Taking all the three groups together, there is a total of 78 boys and 48 girls, and when complex heart lesions are excluded the proportion is 61 to 39. The sex ratio in either case is 1·6. This is similar to, but lower than, that in other series: Edwards and Jones (1962) reported a sex ratio of 2, Braunwald, Goldblatt, Aygen, Rockoff, and Morrow (1963) a sex ratio of 4. Two girls in Group II and one in Group I have been diagnosed as having Turner's syndrome.

Parents. There are no instances of parental consanguinity and no parents gave a history of congenital heart defect.

Twins. Six index patients were twin-born, which is close to the expected proportion of 1 in 40. A deceased boy in Group I (16) had a surviving twin brother, who had a patent ductus ligated and was later shown to have pulmonary stenosis and mitral incompetence. This pair were concordant for the presence of, but not the type of, heart malformation. The description by the parents left no doubt that this pair were dizygotic. Another boy in Group I (9) had an unaffected twin sister. Two boys in Group III (143 and 176) had unaffected twin sisters, a girl (148) had an unaffected twin sister, the pair differing in many characters and being clearly dizygotic. A

TABLE VI

THE NUMBERS OF AFFECTED INDIVIDUALS AMONG THE SIBS OF INDEX CASES

		Older Sibs				Younger Sibs				Total Sibs			
		Brothers		Sisters		Brothers		Sisters		Brothers		Sisters	
		Affected	Total	Affected	Total	Affected	Total	Affected	Total	Affected	Total	Affected	Total
Group I	Male	0	5	0	1	0	10	0	3	0	15	0	4
	Female	0	2	0	0	0	0	0	6	0	2	0	6
Group II	Male	0	8	0	12	0	6	0	12	0	14	0	24
	Female	0	2	0	3	1	7	1	6	1	9	1	9
Group III	Male	0	33	1	26	1	21	2	26	1	54	3	52
	Female	1	18	1	19	1	12	1	15	2	30	2	34
Total	Male	0	46	1	39	1	37	2	41	1	83	3	80
	Female	1	22	1	22	2	19	2	27	3	41	3	49

boy (187) had an unaffected twin brother—once again the pair were clearly dizygotic.

Sibs. The number of non-twin full sibs is shown in Table VI. The 3 families each with 2 index patients (112 and 113, 164 and 165, 177 and 178) are counted twice, once for each index patient. Details of the sibships are shown in the Appendix. The classification of sibs as unaffected was based in the majority of instances on information from the parents. It was possible, however, to examine 85 of the 253 sibs, and 2 of these 85 (sibs of patients 114 and 170) were found to have an unsuspected and symptomless heart lesion.

None of the 28 sibs of index patients in Group I was affected. None of the 38 sibs of male index patients in Group II was affected, but 1 girl (27) with valvar aortic stenosis had a younger sister with an apical systolic murmur of organic type, but a normal electrocardiogram; it is certain that this girl has a congenital heart lesion, but the type is not yet established. Another girl in Group II (40) with valvar aortic stenosis had a younger brother, dying at the age of 4 days; a hospital diagnosis of cyanotic congenital heart disease was made and this was the certified cause of death, but there was no necropsy, and the type of lesion was not established.

Of the 3 pairs of sibs in Group III in which both members of the pairs were index patients, the pair of girls, 112 and 113, both had a clinical diagnosis of coarctation of the aorta and aortic stenosis; this was confirmed at operation and in addition an aberrant right subclavian artery was found. The brother and sister pair, 164 and 165, both have signs of aortic stenosis and normal electrocardiograms. The brother and sister pair, 177 and 178, both have signs of aortic stenosis and an electrocardiogram indicating left ventricular hypertrophy. A boy (114) with signs of aortic stenosis has a younger sister diagnosed as having aortic stenosis because of an apical systolic murmur and electrocardiographic evidence of left ventricular hypertrophy. A boy (170) with coarctation of the aorta and signs of aortic stenosis has a younger brother with a systolic murmur at the base of the heart and electrocardiographic evidence of left ventricular hypertrophy.

In summary, among the sibs of male index patients, 1 in 84 brothers and 3 in 82 sisters were affected. Among the sibs of female index patients, 3 in 47 brothers and 3 in 51 sisters were affected. The total incidence is 10 in 253, i.e. 4% or, if the patients with known aetiology are excluded, and those with rubella syndrome (2), von Recklinghausen's disease (39), and Turner's syndrome (30 and 41), the incidence is 10 in 246, 4·1%.

Similarity of Heart Defects in Sibs and Twins. In patients 112 and 113 the lesions proved to be strikingly similar. In patient 164 and his sister 165, patient 177 and his sister 178, patient 114 and his sister, the lesions are very probably similar. Patient 170 and his brother are probably concordant for aortic stenosis but not for coarctation. Patient 27 and her sister are possibly similar, but the diagnosis of aortic stenosis is not yet established in the younger sister. In contrast, patient 16 and his twin brother certainly, and patient 40 and her brother very probably, had different lesions.

TABLE VII

MATERNAL AGE AND BIRTH ORDER COMPARED WITH THOSE OF BIRTHS IN THE SAME OR ADJACENT YEARS IN ENGLAND AND WALES

	Maternal Age (yr.)							Birth Order						
	15–19	20–24	25–29	30–34	35–39	40+	Total	0	1	2	3	4	5+	Total
Index cases	7	33	37	32	11	5	125	53	44	16	7	3	2	125
General population	5·34	35·30	40·45	25·98	13·75	4·18		49·25	38·26	18·99	8·84	4·37	5·29	

$\chi^2 = 3{\cdot}07$; D.F. 5; $0{\cdot}9 > p > 0{\cdot}5$. $\chi^2 = 4{\cdot}48$; D.F. 5; $0{\cdot}5 > p > 0{\cdot}1$.

Maternal Age and Birth Order. There are no significant indications of maternal age or birth order effects. The maternal age distribution and the birth order distribution are shown in Table VII and there compared with an expected distribution based on the Registrar-General's figures for similar years of birth.

The mean maternal age is 28·4 and the mean birth order is 0·95 as compared with expected figures of 28·3 years and 1·17. The mean paternal age was 32·30 years.

Pregnancy Events. Only 4 mothers gave a history of infection in pregnancy, the infections being rubella in the first month (2), hepatitis in the second month (36), influenza in the third month (8), and mumps in the fourth month (34). Only in the first instance is the pregnancy event likely to be related to the heart defect.

Season of Birth. There is no definite indication that aortic stenosis shows any seasonal variation. The distribution of the whole group was, first quarter 38, second quarter 34, third quarter 26, and fourth quarter 27.

Discussion

The series now reported is the first systematic study of the families of patients with aortic stenosis.

The sex-ratio 1·6 is of the same order as, but lower than, other series. Edwards and Jones (1962) found a sex-ratio of 'exactly 2' and Braunwald *et al.* (1963) a sex-ratio of 4·0.

The co-twins of index patients in this series provide little information as none were monozygotic. There were also no cases of aortic stenosis in the monozygotic twin series of Uchida and Rowe (1957) and Lamy, Grouchy, and Schweisguth (1957).

The proportion of sibs of index patients found affected with congenital heart disease in this series, i.e. 4·0% with standard error of 1·1%, is a minimum figure since it is possible that a few more sibs would have been found affected if all sibs, instead of about one-third, had been examined. This proportion is somewhat higher than that which has been found in family studies of index patients with mixed types of congenital heart disease: for example, McKeown, MacMahon, and Parsons (1953) found 1·8% in sibs born after index patients, Polani and Campbell (1955) 2·3% in sibs born after index patients, and Lamy *et al.* (1957) 1·5% in sibs. The proportion of sibs affected in this series is also higher than that found in family studies of specific types of malformations: 1·2% for patent ductus (Anderson, 1954), 2·1% for patent ductus (Polani and Campbell, 1960), 1·1% for atrial septal defect (Campbell and Polani, 1961b), and 0·4% for coarctation (Campbell and Polani, 1961a). Some of these published series, however, are not comparable with the present survey in that most of the family data for them were collected by a questionnaire and few sibs were examined.

The findings for the proportion of sibs affected are not striking in relation to the over-all incidence of congenital heart disease at birth, which in people of north-west European ancestry probably lies between 0·5 and 1%.

Much more striking, however, is the family concentration of the same type of malformation in the sibs in this and other series. The incidence in the general population of aortic stenosis, as mentioned above, is probably less than 1 in 3,000 births.

It may be concluded that genetic factors play some part in the aetiology of congenital aortic stenosis, as in other types of congenital heart malformations, and that these factors are specific for the individual type of cardiac malformation.

Summary

A family study of 126 index patients with aortic stenosis in 123 families is reported. These patients attended The Hospital for Sick Children between January 1951 and April 1963. Of these, 18 patients were dead, 21 had been treated surgically and were alive and well, 87 had a diagnosis made on clinical grounds only. A summary of the clinical findings in each group is given. Maternal age, birth order, and season of the year had no detectable influence.

There were no instances of parental consanguinity. The sex-ratio is 1·6, a rather lower sex-ratio than has been found in other series.

Six index patients had dizygotic or probable dizygotic co-twins of whom one only had a congenital heart disease, and this was of different type from that in the index patient. No index patient had a monozygotic co-twin.

Of the sibs of the male index patients 1 in 84 brothers and 3 in 82 sisters had congenital heart defects. Of the sibs of female index patients, 3 in 47 brothers and 3 in 51 sisters had congenital heart disease. The total proportion of sibs affected was 4·0%. In 8 out of 10 instances, the affected sib had a lesion probably or certainly including aortic stenosis.

It is concluded that the incidence of aortic stenosis in the sibs of index patients is about 100 times that in the general population, but that the incidence of other cardiac malformations in sibs is little more than that in the general population.

We wish to thank Dr Gerald Graham for his help and advice, and Mrs K. A. Evans for help with the visits to the families and with the analysis of the data.

REFERENCES

Anderson, R. C. (1954). Causative factors underlying congenital heart malformations. I. Patent ductus arteriosus. *Pediatrics*, **14**, 143.

Beuren, A. J., Apitz, J., and Harmjanz, D. (1962). Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance. *Circulation*, **26**, 1235.

Black, J. A., and Bonham Carter, R. E. (1963). Association between aortic stenosis and facies of severe infantile hypercalcaemia. *Lancet*, **2**, 745.

Braunwald, E., Goldblatt, A., Aygen, M. M., Rockoff, S. D., and Morrow, A. G. (1963). Congenital aortic stenosis. *Circulation*, **27**, 426.

Campbell, M., and Polani, P. E. (1961a). The aetiology of coarctation of the aorta. *Lancet*, **1**, 463.

——, and——(1961b). Factors in the aetiology of atrial septal defect. *Brit. Heart J.*, **23**, 477.

Edwards, F. R., and Jones, R. S. (1962). Congenital aortic stenosis. *Thorax*, **17**, 218.

Keith, J. D., Rowe, R. D., and Vlad, P. (1958). *Heart Disease in Infancy and Childhood*. Macmillan, New York.

Lamy, M., Grouchy, J. de, and Schweisguth, O. (1957). Genetic and non-genetic factors in the etiology of congenital heart disease. *Amer. J. hum. Genet.*, **9**, 17.

McKeown, T., MacMahon, B., and Parsons, C. G. (1953). The familial incidence of congenital malformation of the heart. *Brit. Heart J.*, **15**, 273.

Polani, P. E., and Campbell, M. (1955). An aetiological study of congenital heart disease. *Ann. hum. Genet.*, **19**, 209.

——, and —— (1960). Factors in the causation of persistent ductus arteriosus. *ibid.*, **24**, 343.

Richards, M. R., Merritt, K. K., Samuels, M. H., and Langmann, A. G. (1955). Congenital malformations of the cardiovascular system in a series of 6,053 infants. *Pediatrics*, **15**, 12.

Uchida, I. A., and Rowe, R. D. (1957). Discordant heart anomalies in twins. *Amer. J. hum. Genet.*, **9**, 133.

Wood, P. (1956). *Diseases of the Heart and Circulation*, 2nd ed. Eyre and Spottiswoode, London.

Appendix

The sibships of index patients with aortic stenosis. Index patients are in italics, affected sibs are marked with an asterisk and unaffected sibs who were personally examined are marked with a †. . . . not known, M = male; F = female; m = miscarriage; s.b. = stillborn; d. = died. Twins are in square brackets.

Serial No.	Patient, Date of Birth, and Sibship	Half Sibs		Date of Birth (mth. and yr.)	
		Maternal	Paternal	Mother	Father
	Group I				
1	*F* 5.59 (d. 2.60)	—	—	4.44	. . .
2	*M* 12.57 (d. 2.59); M 12.60; m . . .	—	—	4.37	7.31
3	*F* 12.53 (d. 3.54); F −.56; m . . .; m . . .; m . . .	—	—	2.21	3.30
4	m 9.60; *M* 8.61 (d. 8.61); m 11.62; m 9.63	—	—	7.38	12.34
5	M −.60; *M* 8.62 (d.8.62)	—	—	10.37	12.38
6	*F* 8.60 (d. 2.61); F† −.61	—	M −.41; F −.42	2.22	3.07
7	M −.47 (s.b.); M −.49; *F* 8.51 (d. 3.63)	—	—	−.08	−.06
8	m . . .; *F* 5.58 (d. 6.58); F 2.60; F 8.62	—	—	8.37	3.31
9	[*M* 12.51 (d. 4.61; F 12.51]; M 9.60	—	—	12.17	12.11
10	*M* 3.55 (d. 2.59); m . . .; M† 2.60; M† 4.61	—	—	10.21	−.24
11	*F* 11.53 (d. 12.61); F 2.62; F 2.63	—	—	1.27	1.19
12	*M* 6.55 (d. 8.62); F 1.57; M 10.58; M 12.61	—	—	5.32	3.32
13	F −.48; M −.52; *M* 1.58 (d. 12.60); M† −.60	—	—	2.25	−.24
14	*M* 5.47 (d. 6.61); [F 6.51; F 6.51]; M 1.63	—	—	11.19	1.21
15	M 6.61; *M* 12.62 (d. 1.63)	—	—	2.34	10.32
16	M −.50; m . . .; [*M* 1.53 (d. 11.54); M* 1.53]; [M −.55; M −.55]	—	—	7.25	6.18
17	M 3.39; *M* 4.44 (d. 6.61)	—	—	8.15	−.07
18	m 10.46; *F* 2.47 (d. 1.55)	—	—	1.19	−.18
	Group II				
21	*F* 3.58; F 3.59	—	—	9.36	4.36
22	F† 5.50; m . . .; m . . .; m . . .; *M* 3.54	—	—	4.22	−.21
23	M† −.46; *F* 3.51	—	—	3.22	−.22
24	m . . .; *F* 8.51; F† 4.53; m . . .	—	—	7.18	−.16
25	*M* 3.52; M† 6.55	—	—	1.30	−.23

Serial No.	Patient, Date of Birth, and Sibship	Half Sibs: Maternal	Half Sibs: Paternal	Date of Birth (mth. and yr.): Mother	Date of Birth (mth. and yr.): Father
	Group II				
26	F −.41; F −.45; *M* 7.49	—	—	. . .	. . .
27	*F* 1.56; M† −.57 F *−.60	—	—	7.36	2.31
28	*M* 8.50; F† 2.52; F† 2.53; F† 5.56	—	—	7.21	8.21
29	F −.45; *M* 11.47; F 1.52; M 7.53	—	—	3.17	−.01
30	F† −.46; *F* 5.47; M −.52; M −.53	—	—	9.11	−.12
31	M 2.45; M 1.49; F 10.50; *M* 1.52	M 4.37; m . . .; M 11.39	—	1.18	2.21
32	m . . .; F† −.45; *F* 6.47; M −.50 (d. −.50); M† −.52; F† −.56	—	—	4.28	−.26
33	*M* 6.49; F† 1.53; M† 7.54; M† 7.56; M† 2.61	—	—	11.23	−.13
34	F −.38; *M* 1.43; M −.45; F† −.47; F −.48	—	—	9.20	−.14
35	M −.44; [F −.47; F −.47]; M −.50; *M* 4.53; F† −.55; F 4.59 (d. 4.59)	—	—	8.22	−.20
36	M −.44; M −.48; F −.51; *M* 2.54; F −.58	—	—	6.18	−.19
37	M −.39; F −.40; M −.44; F −.46; *M* 12.46; F −.53; F −.55	—	—	9.16	−.15
38	*F* 7.48; F† 5.58	—	—	12.17	−.01
39	m . . .; F 7.37; *M* 6.48	—	—	7.17	−.00
40	*F* 3.46; M 3.48 (d. 4.48); F −.50; M† −.58	—	—	8.25	−.23
41	m . . .; F −.40; M −.43; m . . .; *F* 4.47	—	—	1.15	−.15
	Group III				
101	*M* 12.57	—	—	8.27	6.21
102	*F* 12.56	—	—	2.28	−.23
103	m . . .; *M* 3.59	—	—	11.27	3.28
104	*M* 7.53	—	—	−.26	−.22
105	*M* 5.56	—	—	6.24	−.22
106	*M* 7.56	—	—	10.29	−.20
107	*F* 7.52	—	—	3.34	8.28
108	*M* 6.57	—	—	7.34	−.34
109	*M* 3.53	—	—	2.25	11.16
110	*M* 5.54	—	—	8.28	9.27
111	F 2.54 *F* 2.56	—	—	7.28	1.27
112, 113	*F* 1.48; *F* 12.49	—	—	4.16	−.12
114	*M* 10.57; F* 6.60	—	—	5.29	−.28
115	*M* 4.50; F† 4.52	—	—	2.27	−.04
116	F −.56; *F* 9.59	—	—	7.32	−.31
117	*M* 1.55; F† 12.59	—	—	8.32	−.29
118	*F* 6.58; m . . .; M† 12.60	—	—	12.37	1.34
119	*M* 1.50; F† −.54	—	—	12.26	−.25
120	M −.29; *M* 7.50	—	—	9.14	−.13
121	F −.50; *M* 9.55; m . . .	—	—	3.27	−.27
122	F 12.48; *F* 5.51	—	—	4.15	−.11
123	F 11.53; *F* 2.57	—	—	10.23	−.23
124	M −.54; *M* 9.55	—	—	1.24	−.24
125	*M* 5.60; M −.62	—	—	2.35	−.33
126	M 1.54; *M* 9.55	—	—	9.28	−.27
127	M 10.50; *F* 1.56	F −.36; m . . .; F −.41; m . . .; M −.46	—	9.12	8.14
128	*M* 7.56; M† −.60	—	—	6.33	8.27
129	*M* 3.56; M† −.60	—	—	3.22	3.11
130	*M* 12.56; F† 1.58	—	—	9.32	−.29
131	M −.53 (s.b.); *M* 1.56; m −.59	—	—	3.23	4.25
132	*M* 4.58; M −.61	—	—	10.29	−.16
133	M −.51; *M* 6.54	—	—	10.25	12.18
134	*M* 8.58; m −.60; M 7.61	—	—	4.36	−.36
135	F† −.56; *M* 4.57; F† −.59	—	—	3.33	−.25
136	*F* 2.59; F† 7.60; M† 12.62	—	—	3.25	−.27
137	M −.48 (s.b.); *M* 10.49; M −.44	—	—	11.24	−.24
138	m . . .; *M* 3.55; F 2.57; M† 3.63	—	—	5.31	−.30
139	*M* 4.58; F 1.60; F 12.60	—	—	8.33	−.32
140	F† 7.53; *M* 1.56; M† 6.59	—	—	12.33	−.28
141	M −.50; *M* 1.51; F −.56	—	—	5.24	−.20
142	M −.48; *F* 5.51; F† −.56; m −.50; m −.53; m −.59	—	—	4.20	−.13
143	F† −.50; [F† 10.56; *M* 10.56]	—	—	3.30	−.28
144	F 2.55 (d. 2.55); F 9.56; *F* 9.58	—	—	3.31	12.28
145	F† 3.53; F† 1.55; *M* 12.57	—	—	8.20	10.25
146	M −.48; F 11.49; *F* 3.60	—	—	8.22	−.27
147	F −.45; *F* 9.49; M† −.52	—	—	2.24	−.23
148	F 4.50 (s.b.); [*F* 12.52; F† 12.52]	—	—	3.26	−.23
149	M 4.40 (s.b.); F −.47; *M* 4.51	—	—	12.10	−.09
150	*F* 6.51; [F† 6.55; M† 6.55]	—	—	2.20	−.13
151	M 6.51 (d. 6.51); *M* 2.53; F† −.61	—	—	11.34	3.27
152	*M* 7.48; [F −.51; F −.51]	—	—	3.15	10.10
153	M† −.56; m . . .; *M* 2.59; F† −.60	—	—	−.32	−.36
154	M −.50; *M* 11.52; F −.53	—	—	9.28	2.20
155	F −.53; F −.56; *M* 9.58	—	—	5.29	1.27
156	F −.55; *F* 2.59; F† −.62	—	—	12.35	7.29
157	F −.48 (s.b.); F −.50; *M* 1.51	—	—	6.24	10.26
158	F† −.57; *F* 4.59; M† −.62	—	—	2.37	7.29
159	*F* 4.51; F −.52; M† −.56	—	—	6.30	5.24
160	M −.49; M 1.54 (d. 1.54); *F* 5.56	—	—	5.15	−.12
161	F† −.56; *M* 9.58; M† −.62	—	—	4.33	1.27
162	F −.45; *M* 12.49; F −.55	—	—	6.25	4.21

Serial No.	Patient, Date of Birth, and Sibship	Half Sibs		Date of Birth (mth. and yr.)	
		Maternal	Paternal	Mother	Father
	Group III				
163	m . . .; F −.58; *M* 5.59; M −.61	—	—	10.32	−.20
64, 165	M† −.57; *F* 12.49; *M* 4.51	—	—	5.12	8.06
166	F 9.56; M 6.58; *F* 5.59	—	—	9.38	−.37
167	M −.45; F −.48; *F* 9.52	—	—	6.24	−.23
168	*M* 12.46; M −.58; F −.59; m . . .; m . . .; m . . .; M −.61	—	—	12.12	8.18
169	F† −.42; M −.43; *M* 10.44; m . . .	—	—	11.24	−.22
170	*M* 3.44; M† −.47; M* −.54	—	—	9.22	−.19
171	M −.57 (d. −.57); *F* 11.57; M −.59 (d. −.59); F −.60 (s.b.)	—	—	6.38	−.37
172	M 2.53; M 12.54; *M* 3.56; F 4.59	—	—	10.24	−.25
173	F† 8.54; *F* 3.57; M† 6.58; M† −.61	—	—	8.29	−.29
174	F −.45; M −.47; M −.50; *M* 11.53	—	—	8.16	−.14
175	M −.51; F† −.52; *F* 12.58; F† −.60	—	—	−.21	−.25
176	F −.39; M −.44; [F† 12.50; *M* 12.50]	—	—	−.19	−.07
177, 178	M −.56; *M* 6.59; *F* 8.60; M† −.62	—	—	4.36	10.27
179	F 1.43; F 10.47; *F* 10.52; F† 1.58; m 11.61; F 1.63	—	—	2.23	11.23
180	M −.52; *M* 6.53; M −.55; M −.58; M† −.60; F† −.61	—	—	10.30	−.28
181	m . . .; M −.38 (d. −.60); M −.44; M 6.48 (d. 7.48); *M* 1.50; M −.54	—	—	2.15	−.11
182	M −.46; *M* 11.52; F −.53; M −.55; F† −.59; F† −.61	—	—	7.26	−.14
183	M −.41; M −.43; M −.45; M −.47; *F* 2.48; F −.53; F† −.55	—	—	3.14	−.01
184	F −.44; M −.46; M −.48; *M* 7.49; M −.51; F −.52; F −.55	—	—	12.16	−.07
185	M −.47; M −.48; F −.49; *F* 1.53; F −.56; F −.58; M −.59; F −.60	—	—	−.27	−.17
186	F −.33; F −.36; F −.39; M −.43; F −.44; M −.50 (s.b.); *M* 7.54; F −.57	—	—	7.13	−.12
187	M −.36; M −.37; F −.40; F −.42; M −.44; M −.47; M† −.51; F −.52; [*M* 5.56; M† 5.56]; F† 12.59	—	—	5.20	1.13