Tuberous sclerosis: a genetic study

SARAH BUNDEY AND KATHLEEN EVANS

From the M.R.C. Clinical Genetics Unit, Institute of Child Health, London

Tuberous sclerosis is an autosomal dominant condition, but with a varied clinical picture. In the severe and fully developed form, the patient is a mentally defective epileptic with adenoma sebaceum and retinal phakomata. He may also have other typical skin lesions such as shagreen patches, white naevi, and subungual fibromata. However, milder forms occur, without mental retardation or epilepsy.

There have been several clinical studies in the past, many of which relate to selected populations and therefore emphasize the severer aspects of the disease. Critchley and Earl (1932), Dawson (1954), Nickel and Reed (1962), Reed, Nickel, and Campion (1963), and Zaremba (1968) have produced careful studies of patients with tuberous sclerosis, all seen personally, and all drawn from mental institutions. Ross and Dickerson (1943) collected 23 personal cases, who had presented to hospital with epilepsy. Lagos and Gomez (1967) recently have reviewed the records of a large series of 71 cases from the Mayo Clinic from 1935 to 1964.

Borberg (1951) from Copenhagen, and Nevin and Pearce (1968) from Oxford, have made two good population studies of tuberous sclerosis. The cases in these two series were drawn not only from hospitals and mental institutions, but also from dermatological clinics. These papers give a more balanced picture of the condition; for example 11 of Borberg's 37 cases and six of Nevin's 18 cases were of normal intelligence. Nevin and Pearce's series was based on currently diagnosed cases; Borberg's was taken from the previous 20 years, and his cases comprise a much older age group (ranging from 10 to 74 years). The wide range of clinical manifestation in tuberous sclerosis is well illustrated in Nevin and Pearce's paper as summarized in Table I. Among their patients there is a higher incidence of phakomata than in other series, presumably because patients had their pupils dilated before their eyes were examined.

Many families, with two or more affected members, have been described and in particular Dickerson (1951), having reported three families of his own, reviewed the literature relating to familial cases to date. Where such families are reported, it is clear that inheritance occurs as an autosomal dominant,

with no skipped generations. However, many patients do not reproduce, owing to the severity of their illness. Thus in any survey of tuberous sclerosis, only a few families with affected relatives will be found. The proportions of sporadic cases in published series is shown in Table II. About 80% of cases of tuberous sclerosis are 'sporadic' or 'isolated'—that is, have no other affected relative. These cases do not differ clinically from the familial cases, and are very probably examples of new mutations at the same gene locus.

The diagnosis of tuberous sclerosis is generally made on patients who have presented with neurological symptoms, and who are then found to have adenoma sebaceum. In other patients adenoma sebaceum may be the presenting complaint. However, this lesion is very variable in its age of onset (see later) and may be absent when the patient is first seen. Without adenoma sebaceum, the diagnosis of tuberous sclerosis may be made on finding a retinal phakoma, which is characteristic of tuberous sclerosis; or on neuroradiological evidence suggesting several paraventricular calcified tubers; or on finding characteristic histology after brain biopsy or necropsy. Making the diagnosis in symptomless relatives is more difficult and, when adenoma sebaceum is absent, other skin lesions become important. Butterworth and Wilson (1941) state that shagreen patches and subungual fibromata are specific for tuberous sclerosis. Recently attention has been drawn to the combination of infantile spasms with white naevi, as being one of the earliest manifestations of tuberous sclerosis (Gold and Freeman, 1965; Crichton, 1966; Harris and Moynahan, 1966). It was partly in order to assess the significance of skin lesions other than adenoma sebaceum that the present survey was planned.

AIMS OF PRESENT SURVEY

Genetic counselling in tuberous sclerosis depends upon recognition of the disease in relatives. The important question is what are the minimal manifestations, in a parent of an apparently sporadic patient, or in a sib of a patient, which show that they are heterozygous for the gene and so at risk

TABLE I
RANGE OF CLINICAL MANIFESTATIONS IN TUBEROUS
SCLEROSIS¹

<i>Clinical features present</i>	<i>Aged 5 or under (5 patients)</i>	<i>Aged 6 or over (13 patients)</i>
Adenoma sebaceum	2/5	13/13
Mental deficiency	5/5	6/13
Epilepsy	5/5	10/13
Shagreen patches	2/5	13/13
Subungual fibromata	0/5	7/13
White naevi	5/5	6/13
Café-au-lait patches	0/5	5/13
Retinal phakoma	5/5	9/13

¹From Nevin and Pearce, 1968.

TABLE II
PROPORTION OF SPORADIC CASES IN PUBLISHED SERIES

<i>Author</i>	<i>Total number of cases where family history available</i>	<i>Number with an affected parent</i>	<i>Percentage of isolated cases</i>
Gunther and Penrose (1935)	20	6	70
Critchley and Earl (1932)	20	4	80
Borberg (1951)	37	5	86
Stevenson and Fisher (1956)	9	2	78
Zaremba (1968)	40	11	72
Nevin and Pearce (1968)	16	4	75
Present series	71	10	86

of having affected or further affected children? The main aim of this study was to answer this question. We also wished to study the variability of the disease in families; to learn the distribution of the age of onset of adenoma sebaceum; to estimate the proportion of cases that could be ascribed to new mutations; and to assess possible maternal or paternal age effects in sporadic cases.

METHODS

Index patients were collected from The Hospital for Sick Children (Diagnostic Index, 1951 to 1967, and records of the Neurophysiology Department); from The National Hospital for Nervous Diseases (Records and Pathology Departments, 1947 to 1967); and from St. John's Hospital for Diseases of the Skin (Diagnostic Index, 1951 to 1967). The criteria used for inclusion were the presence of adenoma sebaceum; a retinal phakoma; or the diagnosis of tuberous sclerosis made on cerebral biopsy or at necropsy. Using these criteria, and the sources given above, a total of 96 cases was obtained.

The source of each individual case is shown in the Appendix. Two cases were found at both The National Hospital and St. John's Hospital. They have been included in The National Hospital series only.

In the present series there is a higher proportion than usual of severe childhood cases. This is because of the interest in the Neurophysiology Department at The Hospital for Sick Children in following up children with infantile spasms, where Pampiglione (1968) found that, of 350 children attending with infantile spasms, nearly a tenth subsequently developed signs of tuberous sclerosis.

We planned to interview the 96 initial cases, but it was not possible to trace the addresses of 11 of them, and these were not found by searching for death certificates over the last 10 years. Another three patients refused to participate and a further 11 patients were excluded because they lived far from London. Thus 71 patients or their relatives were traced and interviewed: 63 were living and eight had died at the time of the survey.

Certain patients have been particularly pertinent to the study of minimal clinical manifestations of the disease in adults. These include all the patients from St. John's, and some of the adult patients from The National Hospital. They have been seen personally (S.B.), and extra investigations arranged on a few. For the remainder, clinical details were obtained from hospital notes, supplemented by inquiry from the patient or the patient's mother about the age at which certain signs first appeared.

Clinical and electroencephalographic findings on cases 4, 5, 25, 43, 44, 48, 49, 55 and 62 (numbered in Appendix) were described in a paper by della Rovere, Hoare, and Pampiglione in 1964.

Family histories were obtained in the homes from the patients or from a parent (usually the mother, often both parents). Further members of the family were consulted when necessary. In assembling the family tree, questions were asked about fits or mental retardation in other members of the family, and in particular the presence or absence of skin lesions, including pimples on the face, moles, café-au-lait patches or white spots. Eight living parents were known through hospital records to have adenoma sebaceum, and this was confirmed. Eighteen further parents were reported by themselves or their spouses to have other skin lesions. These parents were seen by one of us (S.B.), and the findings are given in Table III. It was not possible to examine all the remaining 95 living relatives, but 74 other parents (46 mothers and 28 fathers) were examined at random during the survey by one or other of the authors, and no skin lesions were found which had not already been reported. Any other relevant information about relatives was verified through physicians, hospitals, or death certificates. The same criteria for making a definitive diagnosis of tuberous sclerosis in relatives were used as for index patients—namely, the presence of adenoma sebaceum or of a retinal phakoma.

RESULTS

VARIETIES OF CLINICAL PICTURE The clinical details

TABLE III
SKIN LESIONS IN FIRST DEGREE RELATIVES OF SPORADIC CASES

Family no.	1 large (>5 mm) mole	Several large moles	1 café-au-lait patch	Vitiligo	Other
2		Father			
14	Mother				
18	Father				
19	Mother				
22			Mother		Father has white naevus on back
23	Mother		Sister		
34		Father			Mother has fading telangiectatic patch on neck Father has four lipomata on forearms and buttocks
39				Mother	
42		Father			
45	Father	Mother			Father has one fibroma on anterior abdominal wall
46		Father			
50			Mother		
53	Father				
59	Brother		Mother	Brother	
60			Sister		
61		Mother	Sister		

of the 71 patients are presented in Appendix I. Great variation in clinical manifestation was found. Twenty-six patients (37%) were in the normal range of intelligence—that is, with an IQ of more than 70. All those patients with mental retardation also had fits, apart from one exception, a child who died at 18 months. Sixty-three patients (89%) had fits, and among the 46 where the age and mode of onset were known, 40 (87%) had infantile spasms. This high figure is probably related to the mode of ascertainment of the cases from The Hospital for Sick Children. The ages of appearance of adenoma sebaceum, when known, in the present series and in Borberg's, are given in Table IV. There were three adult patients (cases 57, 35, and 37) out of 26 index patients over the age of 20, without adenoma sebaceum, at 21, 28, and 31 years respectively; and there were two secondary cases (family 70, Fig. 1) in whom adenoma sebaceum did not develop until 32 and 35 years. Case 57 is a severely defective epileptic girl, who had removal of part of her left parietal lobe at the age of 13, on account of frequent severe fits, and the preoperative finding of intracerebral calcification in this region. Histology of the lump removed revealed tuberous sclerosis. She also has a depigmented naevus and subungual fibromata. Case 35 is a severely defective epileptic woman, who has a retinal phakoma typical of tuberous sclerosis, but who has no skin lesions, and no calcification on radiographs of the skull. Case 37 is a young man of normal intelligence, who, at the age of 22, had a craniotomy and removal of part of his right temporal

TABLE IV AGE OF APPEARANCE OF ADENOMA SEBACEUM IN INDEX PATIENTS		
Years	Present series (53 cases)	Borberg, 1951 (22 cases)
0-11/12	2	} 8
1- 5	32	
6-11	9	10
12-20	8	0
20-30	1	1
Absent at 30	1	3

lobe, because of severe frequent fits, with left-sided neurological signs and radiographic evidence of a right temporal space-occupying lesion. Histology showed tuberous sclerosis. At present he has no fits, but retinal phakomata have developed over the past year. Of the two secondary cases in family 70, in which adenoma sebaceum developed late, one also has a subungual fibroma, while the other has no additional clinical signs. White naevi were present in 32 out of 39 children (82%) under the age of 10 years who were examined; and in 10 out of 27 patients (37%) over 10 years. Wilson (1969) has suggested that this lowered incidence of white naevi in adults as compared with children may be related to the increased incidence

FAMILY 27

FAMILY 70

FAMILY 69

FIG. 1. *Family 27* I₁ Not seen. Said to have been of average intelligence, with no history of fits or of a facial rash. Died at 74 years of age. Cause of death (after necropsy) given as 'aortic incompetence; bronchopneumonia'. I₂ Not seen. Said to have been of average intelligence, with no history of fits or of a facial rash. Died at 49 years of age. Cause of death given as 'carcinoma of stomach'. He had previously been investigated in hospital. II₁ Stillbirth. II₂ Had fits as a child. IQ is now 80. She has adenoma sebaceum on the face, a retinal phakoma, and calcification on radiographs of the skull. II₃ (National Hospital No. A18058.) Has had fits for some years. He has also been under psychiatric care for a psychosis. He has adenoma sebaceum, and fibromata, café-au-lait pigmentation, and white naevi on the trunk. Fundi are normal. II₄ Twin sister who died at 7 days. III₁ She is under permanent care in a mental subnormality hospital, with severe mental deficiency and epilepsy. She has adenoma sebaceum, lumbar shagreen patch, and café-au-lait pigmentation. Her fundi are normal. III₂ Case 27.

Family 69 I₁ Has adenoma sebaceum, no fits. Low intelligence, poor and reluctant witness. Says she had 11 siblings who all died very young with epilepsy. II₂ Died aged 23. Death certificate: 'tuberous sclerosis'. II₃ Died aged 15. Death certificate: 'epiloia'. II₄ Died aged 7. History brain tumour, not verified. II₅ Died aged 26. Death certificate: 'epiloia'. II₆ Adenoma sebaceum. (No details available about her six children.) II₇ Stillborn twin. II₈ Died aged 3. Death certificate: 'epilepsy, tuberous sclerosis'. II₉ Died aged 6 months. Death certificate: 'acute capillary bronchitis'. Coroner's pathologist reports that brain showed definite evidence of tuberous sclerosis. II₁₀ Died aged 10. Death certificate: 'cerebral compression, cerebral tumour'. Hospital reports epilepsy and mental backwardness. II₁₁ Fits, adenoma sebaceum (reported by mother, but not verified). II₁₂ Case 69.

Family 70 I₁ Case 70. II₁ After a severe head injury at 14 years, he became difficult and uncooperative and liable to fits of aggression. Epileptic fits commenced at 27 years of age, and at 31 he had a right temporal lobectomy on account of his uncontrolled epilepsy. Histology showed no evidence of tuberous sclerosis. Since then he has continued to have fits and is an aggressive and uncooperative man. He has no adenoma sebaceum, and radiographs of the skull show no calcification. II₃ She is of normal intelligence and there is no past history of fits. She has adenoma sebaceum, which developed at 35 years of age, and a subungual fibroma on her left hand. Fundi are normal. II₄ He died at 2 years of age with meningitis after whooping cough. II₆ He is of average intelligence and has had no fits. Adenoma sebaceum developed at the age of 32. There are no other skin lesions and the fundi are normal. II₇ Said to have had similar spots on her face, which were diathermied as a child. Now in Australia. III₁₋₁₀ These children, aged between 3 and 27 years of age, are all said to be normal.

of café-au-lait patches in adults (see Nevin and Pearce's data in Table I). Wilson has suggested that the abnormal melanocytes in white naevi (Fitzpatrick, Szabó, Hori, Simone, Reed, and Greenberg, 1968) may in adult life produce more melanin than elsewhere, and so a café-au-lait patch may develop where a white naevus used to be. However, 12 mothers were asked whether their children's café-au-lait patches had previously been paler, and they all denied this.

Retinal phakomata were looked for without prior pupillary dilatation, and were found in 19 patients, all of whom had evidence of neurological disease (epilepsy or mental deficiency or both). The youngest age at which a phakoma was seen was 4 months. Intercranial calcification was present in 33 out of 64 patients (52%) who had radiography; the earliest age at which it was observed being 1 year. In one adult patient (case 36) calcification was present in the absence of neurological symptoms, yet in another adult patient (case 35), who had severe mental deficiency and fits, intracranial calcification was absent.

The symptoms and signs in the patients in this series did not appear to be progressive, apart from the mental deterioration in infants after infantile spasms, or in older patients after status epilepticus; or when a space-occupying lesion developed, as in cases 9, 27, 37, 57, and 67. Otherwise the patients' clinical condition remained static.

Distinguishing between patients with a parent affected (cases 5, 8, 10, 12, 15, 27, 36, 38, 58, and 69) and those without, there was no significant overall difference in clinical manifestation between the two groups (Table V).

FAMILY FINDINGS *Patients with a parent with adenoma sebaceum* In seven families (5, 8, 10, 12, 27, 36, and 69), a mother had tuberous sclerosis, and in two families (15 and 38), a father had the condition. In one family (58), it is very probable that the mother, now dead, had adenoma sebaceum, although this is unconfirmed. The diagnosis in the nine confirmed cases was made on the finding of adenoma sebaceum. One would expect the disease to be mild in these parents, for they would not otherwise have re-

produced. In fact, adenoma sebaceum and other skin lesions were the only clinical manifestations in four parents, while the other five had, in addition, fits in childhood which have disappeared in all but one parent. In four parents, tuberous sclerosis was so mild that it was not until the parent accompanied his or her child to the out-patient clinic that the diagnosis was first made. In the other five cases, the diagnosis had been made previously.

In these 10 families, there was a total of 18 sibs of the index patient, of whom nine were undoubtedly affected, and two more (in family 69) probably so. The affected sibs are mostly from family 69 (Fig. 1) in which seven sibs certainly, and two probably, had tuberous sclerosis out of a sibship of 10. In the remaining families, of eight sibs, two were affected, and two were still in the risk period at 1 and 2 years of age respectively. Altogether, there were three families (27, 58 and 69) where two or more sibs are affected. These are the only families in the whole series where a second sib is affected. In family 27 (Fig. 1), presumably one of the grandparents (I_1 or I_2) of the index case must have carried the gene for tuberous sclerosis. Unfortunately, they are both dead, and we have not been able to obtain further information about them, apart from that on the death certificates. A grandparent in three further families (5, 8, and 36) was reported as having a facial rash, similar in description to adenoma sebaceum, and one of these grandparents (family 5) also has fits and 'cystic disease of the lungs'.

Three index patients in this group (8, 36, and 58) have had four children, now aged 38, 30, 4, and 2 years, and one of these (case 36) has tuberous sclerosis.

Patients with parents who did not have either adenoma sebaceum or other unequivocal evidence of tuberous sclerosis The remaining 61 patients (86%) had parents without adenoma sebaceum. There were no affected sibs in these families, and no evidence of tuberous sclerosis in aunts, uncles, or grandparents. Four index patients in this group (11, 51, 70, and 71) have had 11 children, aged from 47 to 1 years, of whom two definitely, one probably (family 70, Fig. 1), have tuberous sclerosis and while a 1-year-old child with spots on her face may have the condition

TABLE V
CLINICAL MANIFESTATIONS IN RELATION TO WHETHER OR NOT PARENT AFFECTED

	<i>IQ less than 70</i>	<i>Epilepsy</i>	<i>Skin lesions alone</i>	<i>White naevi</i>	<i>Retinal phakoma</i>	<i>Skull x-ray calcification</i>
Cases with an affected parent	6/10 (60%)	8/10 (80%)	1/10 (10%)	4/8 (50%)	1/10 (10%)	4/8 (50%)
Cases without an affected parent	39/61 (64%)	55/61 (90%)	4/61 (7%)	38/58 (66%)	18/60 (30%)	29/56 (52%)

(family 51). This incidence, three or four out of 11, is consistent with a 50:50 risk to offspring, in a disease in which there is a variable age of onset.

We paid particular attention to the presence of skin lesions in close relatives. Of the 122 parents of these isolated cases, 113 were living at the time of the survey, and nine had died. Detailed clinical information was available about 92 of the living parents. Eighteen of these had skin lesions which are described in Table III. Although none of these parents had adenoma sebaceum, in view of the possible late onset of this lesion (Table IV and Fig. 2), we have tabulated (Table VI) the ages of the parents at the time they were seen. One parent, the father of case 19, had a white naevus on his back, which had been present from birth. This measured roughly 6 cm by 6 cm and was clinically similar to the white naevi seen in patients.

TABLE VI

AGE OF 113 LIVING PARENTS OF SPORADIC CASES AT TIME OF SURVEY, AND AGE AT DEATH OF NINE WHO HAD DIED

	Years							
	20-24	25-29	30-34	35-39	40-49	50-59	60-69	70+
Alive	1	8	13	13	51	20	4	3
Dead					2	1		6

The fundi of 48 parents were examined; no phakomata were seen. One father (case 48) had a patch of choroiditis in his left fundus. Three parents had had fits; in two cases these occurred in association with a fever, at 1 year and at 18 months, and in the third, fits occurred at 3 years and have not recurred.

There were 79 liveborn sibs born before the index patient and 58 born after. It was felt that in many cases, family limitation had occurred after the birth of the affected child, as several mothers had been advised not to have further children, and some had found the burden of a severely mentally retarded child too great to consider having further children. Out of the total of 137 liveborn sibs, information was obtained about 100, and skin lesions were present in six of these (Table III). One sister had febrile convulsions as an infant. There was a neurological disorder in three sibs, and one sib was a mongol (families 49, 29, and 65). In family 49, an older sister (now 23 years) is mentally backward (ESN) and has a non-progressive pontocerebellar disorder; the second child, the mongol boy, died at 18 months of pneumonia; the third is the index patient. The parents, and older sister, have all been seen and they show no stigmata of tuberous sclerosis. In family 29, a maternal half-

sister died at 23 years of age of a midline brain tumour, associated with hypopituitarism and suprasellar calcification; she died at home and no necropsy was carried out. She had previously been seen at The National Hospital (No. 93012) where the diagnosis of possible craniopharyngioma was made. The mother in this family has been seen and is clinically normal. In family 65, an older sister died at 5 years with mental deficiency and spasticity attributed to birth trauma. There are five normal sibs in this family.

There was no consanguinity among the parents of isolated cases, and no index patient was a twin.

PARENTAL AGE AND BIRTH ORDER From 1938 onwards, the Registrar General gives tables where mothers' ages at maternity are tabulated against birth order. We have used these national figures for comparison with the data in families with tuberous sclerosis, using only those families where the index patient was born in 1938 or later, and where the parental ages are known. There are 56 such families. The comparison is shown in Table VII. The mean maternal age of our cases is 28.95 (S.E. 0.81), compared with an expected mean maternal age when standardized for birth order, of 27.76. Table VII shows that the χ^2 for the distribution of maternal age is 8.25, which is significant at the 5% level. However, as there is no consistent trend relating number of cases of tuberous sclerosis to either low or high maternal age, and as there is no significant difference from expected in the mean maternal age, we consider that there is probably no real maternal age effect.

Table VII also shows that there is no significant effect of birth order in isolated cases. The mean

TABLE VII

MATERNAL AGE AND BIRTH ORDER, COMPARED WITH THOSE OF BIRTHS IN THE SAME YEAR IN ENGLAND AND WALES

<i>Maternal age</i>	<i><25</i>	<i>25-29</i>	<i>30-34</i>	<i>35+</i>	<i>Total</i>
Index cases	14	26	6	10	} 56
General population	19.04	17.78	11.35	7.83	
$\chi^2 = 8.25 \quad \text{DF} = 3 \quad 0.05 > P > 0.2$					
<i>Previous children</i>	<i>0</i>	<i>1</i>	<i>2</i>	<i>3+</i>	<i>Total</i>
Index cases	28	15	6	7	} 56
General population ¹	22.71	17.71	8.03	7.55	
$\chi^2 = 2.19 \quad \text{DF} = 3 \quad 0.7 > P > 0.5$					

¹Standardized for maternal age.

rank is 2.59 (S.E. 0.22), compared with an expected mean birth rank, when standardized for maternal age, of 2.34. Family limitation would not be expected to give any apparent birth order effect by this method, in contrast to the Greenwood-Yule method, in cases due to fresh mutation.

Paternal age figures are given in the Registrar General's tables only for 1962 and onwards, and so index cases born earlier than 1962 cannot be directly compared with national figures. However, before this date, yearly tables are given in which husbands' and wives' ages are tabulated at time of marriage. Study of these tables shows firstly that over the 30 years 1938 to 1968 there has been little change in the age difference between husbands and wives, although over this period there has been a lowering both of mean age at marriage, and of mean age at maternity. Secondly, comparison of the 1959 to 1961 ages at marriage with the 1962 to 1966 ages at maternity, shows that there is in the two groups a very similar distribution of husbands' ages, against wives' ages, until the wifely age of 40. After 40, the ages of fathers are lower than the ages of husbands. Data illustrating these two points is shown in Table VIII. The figures for the ages of fathers of patients with tuberous sclerosis are shown in the last column and there is no significant deviation from expected. The mean paternal age in our series is 31.52 (S.E. 0.96), compared with an expected mean paternal age, when standardized for mother's age, of 31.87 years.

DISCUSSION

In the past there has been uncertainty over the minimal manifestation of tuberous sclerosis in adults; the possible significance of skin lesions alone and their relationship to the severer form of the

disease. In particular, it has been debated whether the presence of adenoma sebaceum is essential for the clinical diagnosis of tuberous sclerosis. The variable age of appearance of adenoma sebaceum among the patients is shown in Table IV, and in Fig. 2, where the proportion of patients with adenoma sebaceum in each age group is shown. While about 50% of affected children had adenoma sebaceum by the age of 5, there were three patients who did not have adenoma sebaceum in adult life. Two of our secondary cases and three of Borberg's cases developed adenoma sebaceum after the age of 30. In addition, one of Borberg's cases (no. 7) was considered to have tuberous sclerosis of the lungs, yet at 62 years she had no cutaneous signs, yet had an imbecile daughter who suffered from epilepsy and adenoma sebaceum. Schnitzer (1963) described a 62-year-old woman, who had no cutaneous evidence of tuberous sclerosis, yet who had tubers of the brain, kidneys, and lungs at necropsy.

It is clear that adenoma sebaceum, though uncommonly, may be absent in a patient with tuberous sclerosis. However, when present, it is generally accepted that adenoma sebaceum is specific for tuberous sclerosis (see later discussion). Can the same be said for other skin lesions?

White spots, which have long been described as a clinical manifestation of tuberous sclerosis, have recently been recognized as an important early sign in children (Gold and Freeman, 1965; Crichton, 1966). These early and characteristic lesions, which have variously been called depigmented naevi, white naevi, and white macules, should be carefully distinguished from vitiligo. Fitzpatrick *et al.* (1968) have drawn attention to the distinguishing features, both clinical and pathological. White naevi have a smooth, oval outline, are about $\frac{1}{2}$ to 8 cm in size,

TABLE VIII
MEAN AGE OF HUSBAND; AT TIME OF MARRIAGE 1938-61; AT TIME OF PATERNITY 1962-66; COMPARED WITH AGE AT PATERNITY OF CHILD WITH TUBEROUS SCLEROSIS

Age of wife	1938	1948	1956	1957-61	Mean 1938-61	1962-66	Tuberous sclerosis 1938-67
<20	23.63	23.59	22.92	22.63	23.14	22.4	24.7 (3) ¹
20-24	25.84	25.50	24.99	24.87	25.03	26.1	25.4 (11)
25-29	28.90	29.51	29.37	29.32	29.27	30.1	29.7 (26)
30-34	33.49	34.59	34.60	34.68	34.44	34.8	33.3 (6)
35-39	39.46	39.29	39.70	39.86	39.58	39.4	43.1 (5)
40-44	46.19	45.12	45.04	45.26	45.29	43.6	44.6 (5)
45-49	51.35	50.64	50.02	50.35	50.59	47.3	no cases

¹Number of cases in each group is given in parentheses.

The population figures are taken from the Registrar General's tables 1938-66.

FIG. 2. Estimated percentage of cases at each age in which adenoma sebaceum is present.

are paler than the surrounding skin, and may occur anywhere on the body. They are areas which are present from birth and which have never pigmented, although they may not be first noticed until the surrounding skin is suntanned. The pathology of these white naevi is very unusual, consisting of melanocytes but no melanin pigment. Vitiligo on the other hand is an acquired lesion occurring on exposed areas; it is more extensive, often bilateral, is dead white in colour, and has a very irregular outline. Histologically, melanocytes in an area of vitiligo are very few or absent. Moynahan (1969) considers that these congenital amelanotic naevi are pathognomonic for tuberous sclerosis, and certainly their unusual histology, which is otherwise seen only in albinism, suggests a metabolic block. However the usefulness of white naevi as a definitive sign of tuberous sclerosis remains uncertain, in view of the finding of Zaremba (1968) that, out of 1,013 children from mental institutions, white naevi were present in 3.3%, and these were mostly over the age of 10 years and so unlikely to be as yet undiagnosed cases of tuberous sclerosis. We found a white naevus, in the absence of adenoma sebaceum, in only one of the parents in the series. He has only one affected child (case 19) and we cannot be certain

whether he is a genetic carrier for tuberous sclerosis or not.

Other skin lesions which are probably more indicative of tuberous sclerosis are the shagreen patch and subungual fibromata. Butterworth and Wilson (1941) state that these two lesions are specific for tuberous sclerosis. A shagreen patch was the only abnormal skin manifestation in a man of 42 who had three children with probable tuberous sclerosis (Bunday, Dutton, and Wells, 1969).

Less helpful signs are the café-au-lait patch, and moles, since these occur frequently in the general population. Crowe and Schull (1953) found that one café-au-lait patch of more than 1.5 cm in diameter was present in 8 to 9% of a mental hospital population, and two café-au-lait patches were present in 1%. Fifty-three patients with tuberous sclerosis were included in their control group and did not differ from the main group. Nicholls (1968) found that the number of moles (pigmented thickened areas, more than 2 mm in diameter) increased with age, and that the mean number of moles per child in the 16 to 17 age group was 23. In view of these two sets of observations, we think that the incidence of café-au-lait patches, moles, and vitiligo in first degree relatives of patients in this series does not

differ from the incidence in the general population. In general, we feel that adenoma sebaceum, shagreen patch, subungual fibromata, and possibly white naevi, indicate a heterozygote for tuberous sclerosis, but that moles, café-au-lait patches, and vitiligo do not carry the same significance.

GENETICS The hypothesis of simple dominant inheritance fits the current findings. We consider the 61 patients (86%) with normal parents are examples of new mutations and that these are similar, both clinically and genetically, to the familial cases. There is no suggestion from the family data that individuals may be heterozygous for the gene without clinical manifestation, for there are no examples of a 'skipped' generation, nor of a 'normal' parent of an index patient having two affected children. In each of the three families (27, 58, and 69) where more than one sib is affected, one parent had adenoma sebaceum. Gunther and Penrose (1935) described three families with more than one sib affected; Borberg (1951) described three such families; Zaremba (1968) four families; and Nevin and Pearce (1968) three families with more than one sib affected. In all these cases, a parent had adenoma sebaceum. Dickerson (1951) described three sibships of multiple cases of tuberous sclerosis: in two families a parent had adenoma sebaceum, and, in the third, the parents were not fully examined. In reviewing the literature relating to familial cases, we can find no example where both parents of two affected sibs have been fully examined and neither has been found to have adenoma sebaceum. We feel, therefore, that clinically normal parents of an affected child may be reassured, and given a good risk for subsequent children. It is clearly possible to carry the gene without adenoma sebaceum, but this is uncommon and another manifestation of the gene is likely to be present.

The situation where adenoma sebaceum occurs alone in a healthy adult has been discussed by Bjornberg (1961). He considers that adenoma sebaceum is always part of the tuberous sclerosis complex, and that such patients should be given the 1 in 2 risk of having a child with tuberous sclerosis. Borberg agrees with this comment. There is a scarcity of families with adenoma sebaceum alone described in the literature, and where such families are described, the patients and their relatives have not been carefully examined for other evidence of tuberous sclerosis. Of nine patients presenting at St. John's Hospital on account of adenoma sebaceum, four cases (11, 36, 51, and 63) also have evidence of neurological involvement (fits or calcification on radiographs of the skull); two cases (11 and 58) have a child with neurological involvement in

addition to adenoma sebaceum; one case (70) has two children with skin lesions alone (one with adenoma sebaceum and a subungual fibroma; and the other with solely adenoma sebaceum); case 71 has one normal child; and cases 7 and 28 have not yet had families of their own. If we consider the variability between generations in 10 families (5, 8, 10, 12, 15, 27, 36, 38, 69, and 70), we find that, of five parents with skin lesions alone, four have produced children with evidence of neurological involvement in addition to skin lesions. Of the four parents with skin lesions and fits occurring only in childhood, all have had children with neurological abnormality, and the one parent who continues to have fits has a severely mentally retarded epileptic boy. It appears that there is little similarity in the manifestation of the disease within families, and that adults with skin lesions alone run a considerable risk of having an affected child with neurological lesions in addition to skin lesions.

SUMMARY

A family study has been made on 71 cases of tuberous sclerosis collected from three hospitals. Affected relatives in an earlier generation were found in 10 families. The remaining 61 cases (86%) were considered to be examples of new mutations; in these families, no association with higher parental age was observed.

There was great clinical variability and this was both between and within families. Parents with adenoma sebaceum alone are very likely to have an affected child with neurological lesions. We considered that, for genetic counselling, adults with adenoma sebaceum, or a shagreen patch or subungual fibromata, or possibly white naevi, should be given the 1 in 2 risk of affected children.

No family of two affected sibs has been observed in this series without one parent having adenoma sebaceum. In counselling parents who have one affected child, but who do not have adenoma sebaceum or other characteristic skin lesions, they may be told that the condition in their child is very probably the result of a new mutation, and that the risk of recurrence is small.

Our grateful thanks go firstly to Dr. C. O. Carter for his help and advice throughout the study. We are also pleased to acknowledge the help of Dr. G. Pampiglione for information on the patients seen in the Neurophysiology Department of The Hospital for Sick Children; and we are grateful to Professor R. W. Gilliatt, Dr. John Wilson, and Dr. R. S. Wells for their comments and criticism in the preparation of this manuscript. We thank the consultants of The National Hospital, St. John's

Hospital, and The Hospital for Sick Children for allowing us to study the families of patients under their care.

REFERENCES

- Bjornberg, A. (1961). Adenoma sebaceum. Review, case reports and discussion of eugenic aspects. *Acta derm.-venereol. (Stockh.)*, 41, 213-223.
- Borberg, A. (1951). Clinical and genetic investigations into tuberous sclerosis and Recklinghausen's neurofibromatosis. *Acta psychiat. scand.*, Suppl. no. 71.
- Bunday, S. E., Dutton, G., and Wells, R. S. (1969). In preparation.
- Butterworth, T., and Wilson, M. (1941). Dermatologic aspects of tuberous sclerosis. *Arch. Derm.*, 43, 1-41.
- Crichton, J. U. (1966). Infantile spasms and skin anomalies. *Develop. Med. Child Neurol.*, 8, 273-278.
- Critchley, M., and Earl, C. J. C. (1932). Tuberous sclerosis and allied conditions. *Brain*, 55, 311-346.
- Crowe, F. W., and Schull, W. J. (1953). Diagnostic importance of café-au-lait spots in neurofibromatosis. *Arch. intern. Med.*, 91, 758-766.
- Dawson, J. (1954). Pulmonary tuberous sclerosis and its relationship to other forms of the disease. *Quart. J. Med.*, 23, 113-145.
- della Rovere, M., Hoare, R. D., and Pampiglione, G. (1964). Tuberous sclerosis in children: An E.E.G. study. *Develop. Med. Child Neurol.*, 6, 149-157.
- Dickerson, W. W. (1951). Familial occurrence of tuberous sclerosis. *Arch. Neurol. (Minneapolis)*, 65, 683-702.
- Fitzpatrick, T. B., Szabó, G., Hori, Y., Simone, A. A., Reed, W. B., and Greenberg, M. H. (1968). White leaf-shaped macules. *Arch. Derm.*, 98, 1-6.
- Gold, A. P., and Freeman, J. M. (1965). Depigmented naevi: the earliest sign of tuberous sclerosis. *Pediatrics*, 35, 1003-1005.
- Gunther, M., and Penrose, L. S. (1935). Genetics of epiloia. *J. Genet.*, 31, 413-430.
- Harris, R., and Moynahan, E. J. (1966). Tuberous sclerosis with vitiligo. *Brit. Derm.*, 78, 419-420.
- Lagos, J. C., and Gomez, M. R. (1967). Tuberous sclerosis: reappraisal of a clinical entity. *Proc. Mayo Clin.*, 42, 26-49.
- Moynahan, E. J. (1969). Personal communication.
- Nevin, N. C., and Pearce, W. G. (1968). Diagnostic and genetical aspects of tuberous sclerosis. *J. med. Genet.*, 5, 273-280.
- Nicholls, E. M. (1968). Genetic susceptibility and somatic mutation in the production of freckles, birthmarks and moles. *Lancet*, 1, 71-73.
- Nickel, W. R., and Reed, W. B. (1962). Tuberous sclerosis. *Arch. Derm.*, 85, 209-226.
- Pampiglione, G. (1968). Some inborn metabolic disorders affecting cerebral electrogensis, in *Some Recent Advances in Inborn Errors of Metabolism*. Edited by K. S. Holt and V. P. Coffey. Livingstone: Edinburgh.
- Reed, W. B., Nickel, W. R., and Campion, G. (1963). Internal manifestations of tuberous sclerosis. *Arch. Derm.*, 87, 715-728.
- Ross, A. T., and Dickerson, W. W. (1943). Tuberous sclerosis. *Arch. Neurol. Psychiat. (Chic.)*, 50, 233-257.
- Schnitzer, B. (1963). Tuberous sclerosis complex. *Arch. Path.*, 76, 626-632.
- Srevenson, A. C., and Fisher, O. D. (1956). Frequency of epiloia in Northern Ireland. *Brit. J. prev. soc. Med.*, 10, 134-135.
- Wilson, J. (1969). Personal communication.
- Zaremba, J. (1968). Tuberous sclerosis; a clinical and genetical investigation. *J. ment. Defic. Res.*, 12, 63-80.

APPENDIX I

CLINICAL INFORMATION ON THE 71 INDEX PATIENTS

Family no.	Mental deficiency	Epilepsy*	Adenoma sebaceum*	White naevus*	Other skin lesions	Retinal phakoma*	Calcification on skull x-ray*	Other
<i>Patients from St. John's Hospital for Diseases of the Skin</i>								
7	0	0	+(3-4)	+	+	0	0	
11	0	+(7/12)	+(3)	NE	NE	0	NE	
28	0	0	+(12)	0	+	0	0	
36	0	0	+	0	+	0	+(20)	
51	0	+(20)	+(5)	+	+	0	+(20)	
58	0	0	+	+	+	0	0	
63	0	+	+	+	+	0	+(16)	
70	0	0	+	0	+	0	NE	
71	0	0	+	+	+	0	NE	
<i>Patients from The National Hospital, Queen Square (hospital number in parentheses)</i>								
6 (57893)	+	+(3/12 IS)	+(infancy)	0	+	0	0	
8 (80092)	IQ 75	+(13)	+	0	+	0	0	
9 (68830)	+	+	+(19)	0	0	0	+(18)	
10 (26305)	IQ 61	+	+(teens)	NE	NE	0	NE	
27 (A37049)	IQ 81	+	+(16)	+	+	+(16)	+(16)	
29 (A29073)	IQ 92	+(9)	+(16)	0	+	+(16)	+(16)	
30 (28078)	+	+(3/12 IS)	+(4)	+(1)	+	+(5)	+(3)	
31 (A4465)	IQ 91	+	+(15)	0	+	+(15)	0	
32 (80067)	IQ 92	+	+(4-5)	0	0	+(20)	+(20)	
34 (50879)	0	+(13)	0	0	0	0	0	d. 17 yr.
35 (48627)	IQ 44	+	0	0	0	+(21)	0	Diagnosis at necropsy
37 (1064)	0	+(18/12)	0	0	+	+(29)	+(22)	Excision r. parietal lobe 1960, on account of epilepsy. Histology revealed TS
38 (482)	IQ 54	+(7)	+	NE	NE	0	+(16)	
52 (A13754)	IQ 91	+(8)	+(9-10)	0	+	0	+(38)	
56 (72140)	0	+(8)	+(4)	+	+	+(20)	+(9)	
57 (67418)	IQ 44	+(6/52 IS)	0	+	+	0	+(13)	Excision part I. parietal lobe 1960, on account of epilepsy. Histology revealed
66 (A25052)	+	+	+(4)	+	+	+(18)	+(21)	
67 (A3746)	0	0	+(21)	0	+	0	+(33)	d. 31 yr after craniotomy for removal r. frontal tumour. Diagnosis of TS confirmed at necropsy

APPENDIX I—continued

Family no.	Mental deficiency	Epilepsy*	Adenoma sebaceum*	White naevus*	Other skin lesions	Retinal phakoma*	Calcification on skull x-ray*	Other
<i>Patients from The Hospital for Sick Children, Great Ormond Street</i>								
1	+	+(6/12 IS)	0	+	+	+(1)	0	
2	+	+(4/12 IS)	+(4)	+	+	+(4)	0	
3	+	+(6/12 IS)	+(3)	+(1)	+	0	+(3)	
4	+	+(4/12 IS)	+(4)	+	+	0	+(3)	
5	+	+	+(9-10)	0	+	0	+(8)	
12	+	+(2/12 IS)	+(2)	+	+	0	0	
13	+	+(5/12 IS)	+(1)	+(birth)	+	0	0	Hepatosplenomegaly
14	+	+(7/12 IS)	+(1)	+(birth)	+	+(9/12)	0	Cystic kidneys
15	+	+(7/12 IS)	+(3)	+	+	0	NE	
16	+	+(4/12 IS)	+(2)	+(2)	+	0	NE	
17	+	+(5/12 IS)	+(3)	+(birth)	+	0	0	
18	+	+(4/12 IS)	+(6/12)	+	+	0	+(4)	
19	0	+	+(4)	+(3/12)	+	0	0	
20	+	+(3/12 IS)	+(4)	+	+	0	0	
21	+	+(3/12 IS)	+(4)	+	+	+(6)	+(6)	
22	IQ 94	+(7/12 IS)	+(8)	0	0	0	0	
23	IQ 72	+	+(10)	+	+	0	+(12)	
24	+	+(3/12 IS)	+(6)	+(birth)	+	0	0	Diabetes mellitus
25	+	+(8/52 IS)	+(4)	NE	NE	0	+(2)	d. 10 yr
26	IQ 80	+(3/12 IS)	+(12)	+(birth)	+	+(15)	+(5)	
33	+	+(6/12 IS)	+(11)	0	0	0	+(12)	
39	+	+(4/12 IS)	+(3)	+(birth)	+	0	0	
40	+	+(2/365 IS)	+(3-4)	+(1)	+	0	0	d. 5 yr
41	+	+(1 yr. IS)	+(1)	+(birth)	+	0	+(4)	
42	IQ 77	+(6/12 IS)	+(1)	+(birth)	+	0	+(5)	
43	IQ 72	+(3/12 IS)	+(9/12)	+	+	+(7)	+(6)	
44	+	+(3/12 IS)	+(4)	+	+	0	0	
45	+	+(4/12 IS)	+(2)	+(birth)	+	+(7)	+(11)	
46	+	+(2/12 IS)	+(9)	0	0	0	0	
47	+	+(3/12 IS)	0	+(birth)	+	+(4/12)	0	Congenital heart disease ? patent ductus Aortic stenosis
48	+	+(6/12 IS)	+(1)	0	+	0	+(6)	
49	+	+(3/365 IS)	+(6)	+	+	0	+(2)	
50	+	+(17)	+(13)	0	+	0	0	
53	+	+(4/12 IS)	+(5)	+	+	0	0	
54	+	0	0	0	0	0	0	d. 18/12 Diagnosis of TS made at necropsy
55	+	+(3/12 IS)	+(4)	0	+		+(14)	d. 19 yr. Diagnosis of TS confirmed at necropsy
59	0	+	+(11)	+(birth)	+	0	0	
60	+	+	+	+	+	+(5)	0	
61	+	+	0	NE	NE	0	0	d. 9 yr. Diagnosis of TS made at necropsy
62	IQ 60	+(8/12 IS)	+(3)	+(6/12)	+	0	+(1)	
64	+	+(4/12 IS)	+(3)	+(1)	+	0	0	Cystic kidneys with hypertension
65	+	+(4/12 IS)	0	+(1)	+	+(3)	NE	
68	+	+(8/12 IS)	+(8)	0	0	0	+(8)	Deaf
69	+	+(3/12 IS)	+	0	0	0	0	

CLINICAL INFORMATION ON PROVEN SECONDARY CASES (excluding families 27, 69, and 70)

Family no.	Mental deficiency	Epilepsy*	Adenoma sebaceum*	White naevus*	Other skin lesions	Retinal phakoma*	Calcification on skull x-ray*	Other
5 Mother	0	+	+(9-10)	0	+	NE	NE	
5 Mother's father	0	+	+	NE	NE	NE	NE	d. 42 yr. Death certificate: Congenital cystic disease of lungs
8 Mother	0	+	+	NE	NE	NE	NE	
0 Mother	0	0	+	NE	NE	0	NE	
5 Father	0	0	+	0	0	0	NE	
8 Father	0	0	+	NE	NE	NE	NE	
8 Brother	0	0	+	NE	NE	NE	NE	

* number in parentheses refers to the age in years when a symptom or sign first appeared, if this is known.

† applies onset with infantile spasms.

= not examined.

UNCONFIRMED SECONDARY CASES

This is an elusive family and no further information can be obtained. Mother's mother; mother's mother's brother both had red pimples on their faces. Mother's mother's two sisters died in their teens with fits. Three maternal cousins have fits; it is not known whether they also have facial rashes. (now aged 1 yr) has spots on her face. She has no other skin lesion and her development so far is normal. (deceased) had spots on her face, similar to those on her daughter. No fits. Of average intelligence.

APPENDIX II FAMILY DETAILS ON THE 71 INDEX PATIENTS

Family no.	Source	Sibship	Half-sibs	Children	Father	Mother
1	C	*M 6/66	—	—	3/43	11/41
2	"	*M 3/64	—	—	5/31	4/44
3	"	*F 2/63	—	—	1/16	10/27
4	"	*F 5/58	—	—	5/21	9/27
5	"	*M 12/56	—	—	12/30	5/30
6	N	*F 5/53	—	—	4/22	4/29
7	J	*F 7/46	—	—	2/08 d.-/62	9/20
8	N	*F 6/44	—	F 3/67	-/02 d.-/65	2/17
9	"	*F 4/38	—	—	2/10	4/12
10	"	*F 2/33	—	—	6/08	11/12
11	J	*F 9/44	Mat.F -/37 F-/38	—	10/15	6/20
			M-/40 F-/42	M 5/66 F 11/67	10/15	6/20
			M-/58	(No. 12)		
12	C	*M 5/66 F 11/67	—	—	NK	9/44
						(No. 11)
13	"	M 4/62 *M 4/65	—	—	3/33	5/36
14	"	*M 2/65 F 6/68	—	—	1/27	6/26
15	"	*M 12/64 F 5/66	—	—	8/39	2/43
16	"	*M 5/63 F 12/66	—	—	10/38	12/38
17	"	*F 1/62 M 11/64	—	—	2/21	3/26
18	"	*M 7/61 M 12/62	—	—	3/38	9/39
19	"	F 9/58 *F 6/61	—	—	12/30	7/31
20	"	F 6/47 *F 4/61	—	—	9/19	4/18
21	"	*M 4/60 F 9/61	—	—	2/38	12/42
22	"	*M 5/58 M 5/61	—	—	3/32	7/36
23	"	*F 9/55 M 1/61	—	—	5/30	7/30
24	"	*M 2/54 F 1/56	—	—	3/24	4/25
25	"	F -/47 *M 3/52 d.-/62	—	—	-/22	-/25
26	"	*F 1/52 M 7/55	—	—	1/23	4/23
27	N	F 3/49 *F 7/51	—	—	8/21	1/23
28	J	*F 8/49 M 4/54	—	—	7/22	4/20
29	N	*F -/48 F -/52	Mat.F -/37 M-/41	—	-/18	-/15
			d. -/60			
30	"	M 3/48 *F 6/49	—	—	7/26	4/26
31	"	*F 4/46 F SB -/48	—	—	4/16	11/17
32	"	*M 5/43 F 9/46	—	—	3/13	3/13
33	C	*M 12/43 F 7/51	—	—	1/13	3/15
34	N	*F 10/41 d. 3/58 M 12/43	—	—	10/11	10/14
35	"	M 12/36 *F 2/40	—	—	8/08	10/15
36	J	M 10/30 *F 12/38	—	F 11/64	NK	11/06
						(No. 58)
37	N	*M 1/38 M 9/41	—	—	1/12	7/13
					d. 2/45	
38	"	*M 9/33 M -/32	—	—	6/05 d. 4/68	3/05
39	C	M 11/62 F 9/63 *M 11/64	—	—	3/38	10/39
40	"	F 4/54 *F 3/62 d. 7/67	F 7/64	—	5/35	4/35
41	"	M 4/58 *F 7/60 F 7/64	—	—	3/30	8/32
42	"	M 2/56 *M 2/60 M 9/64	—	—	4/35	4/34
43	"	*F 3/59 M 12/60 F 5/63	Mat. F 3/56	—	10/39	1/35
44	"	F 9/41 M 5/47 *M 1/58	—	—	1/12	4/20
45	"	M 10/52 *M 8/56 F 2/66	—	—	2/28	3/28
46	"	F 2/51 *F 1/55 F 1/65	—	—	9/22	12/24
47	"	FSB 2/54 M 8/63 *M 3/67	—	—	10/20	1/24
48	"	M 1/50 *M 3/54 F 4/62	—	—	5/23	9/26
49	"	F 11/45 M 12/48 d. 2/50	*M 10/52	—	5/20	6/21
50	"	*F 8/47 (M 5/50 F 6/50)	—	—	6/14	5/17
51	J	*F 4/46 F 4/47 F 12/48	—	F 12/67	9/16	1/17

APPENDIX II—continued

no.	Source	Sibship			Half-sibs	Children	Father	Mother	Other affected relatives
N	F 9/13	M 8/16	<u>*F11/25</u>		—	—	10/89 d. -/65	1/86 d. -/65	—
C	<u>*M 6/61</u>	F 7/64	(F 3/67	F 3/67)	—	—	10/39	6/42	—
„	<u>M -/52</u>	M -/55	<u>*F 7/57 d. 2/59</u>		—	—	7/23	3/29	—
„	F 8/43	<u>*M 11/48 d. 4/67</u>	M 1/53	M 2/56	—	—	10/18	11/21	—
N	M 12/41	<u>F 1/42</u>	<u>*M 2/48</u>	M 11/51	—	—	-/11 d. -/56	-/20	—
„	<u>*F 12/47</u>	M 5/49	F 9/52	M 10/59	—	—	9/24	2/25	—
J	<u>M 1/01</u>	M 9/04	<u>*F 11/06</u>	F 9/08	—	M 10/30 F 12/38 (No. 36)	NK	-/81 d. -/38 Mo. Bro.	—
C	M 5/52	<u>*M 8/54</u>	M 12/58	M 11/60	F 8/62	—	3/28	3/28	—
„	F 5/41	<u>M 7/44</u>	F 4/46	F 8/49	<u>*M 6/53</u>	—	1/15	1/11	—
„	<u>*M 12/56</u>	M 12/57	M 4/59	M 12/60	<u>M 1/63</u>	—	-/26	9/28	—
„	<u>M 11/65</u>								
„	F -/52	M -/53	F -/56	M -/58	<u>*F 9/61</u>	—	-/26	-/27	—
„	F -/64				=				
J	M -/38	<u>*M 5/46</u>	M -/50	F -/50	M -/59	—	NK	NK	—
„	F -/61	<u>M -/63</u>							
C	M 7/45	F 1/47	F 1/53	F 6/56	M 10/57	—	4/21	1/28	—
„	M 12/60	<u>*M 8/64</u>							
„	F 8/47	<u>M 8/48</u>	M 10/51	M 12/54	M 3/56	—	4/18	1/25	—
„	F 4/60 d. 2/65		<u>*F 2/65</u>						
N	F 7/23 d. -/43		<u>F 4/25 d. -/64</u>		F 2/27	—	8/94	11/99	—
„	M 11/29	F 9/33	F 1/35	F 9/35	<u>*F 12/43</u>	—			
„	F -/09	M -/11	F -/13	(M -/17 M -/17 d. -/52)		—	2/87	12/90	—
„	M -/19	F -/21	<u>*M -/29 d. -/62</u>		F -/34	—			
C	F 7/51	F 11/54	<u>M 7/56</u>	F 5/57	<u>*M 7/58</u>	—	5/33	11/32	—
„	F 7/59	F 10/61	M 3/63	(F 9/64	<u>M 9/64</u>)	—			
„	M -/21	<u>M -/23 d. 9/46</u>		F -/27 d. 9/42		—	NK	-/02	—
„	<u>M -/28 d. -/34</u>		F 1/31 d. 10/57						
„	(F -/35	FSB -/35)	<u>M -/38 d. 10/41</u>						
„	<u>M 8/40 d. 3/41</u>		<u>F -/42 d. 1/53</u>		<u>M -/46</u>				
„	<u>*M 4/49</u>								
J	<u>*F 11/96</u> (11 others - details not known)					M -/21 F -/23 F 3/25 M -/27 d. -/29 M -/29 M 3/34 F 10/40 F 2/50	NK	NK	—
„	<u>*M 8/17</u> (12 older sibs - details not known)						NK	NK	—

ospital for Sick Children. N = The National Hospital. J = St. John's Hospital.
dex patient. — = Affected. () = twins.