

AN ABSTRACT OF THE THESIS OF

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Title: A CLINICAL AND GENETIC STUDY OF TUBEROUS
SCLEROSIS

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Tuberous sclerosis is a serious heritable human disorder that involves many organ systems. It was first recognized as a disease entity over a century ago. Its mode of transmission in familial cases has been fairly well established to be that of a single gene locus autosomal dominant trait. However, the majority of cases reported in the medical literature have been found to be of de novo mutational origin. The finding of a high proportion of these sporadic cases was confirmed in the present study and is consistent with the markedly lowered fertility of affected individuals.

The population of the Oregon State Fairview Hospital and Training Center, the state institution for the mentally retarded, was investigated relative to the incidence of patients with tuberous sclerosis and the clinical, radiological and genetic aspects of the ten propositi were evaluated. Two parents of the ten index cases were

found to be affected with the disease thereby bringing the total of ascertained cases to 12. This number of affected residents represents an incidence in Oregon of about 1 per 175,000 and this estimate is probably lower than the actual frequency of tuberous sclerosis in the state. Yet, this incidence is approximately comparable to that reported in several published reviews of tuberous sclerosis in other countries.

Physical and radiographic examinations were accomplished for the index cases. All available relatives (77 percent of living relatives) of the propositi were examined and photographed. Skull x-rays of the two affected parents revealed intracranial calcifications typical of the disorder.

A majority of the ten propositi exhibited dermatological lesions such as a typical facial rash, fibromata of the fingers and toes, "sharkskin-like" plaques, depigmented areas and café-au-lait spots. All affected individuals were found to display x-ray abnormalities with intracranial calcifications being the most frequently found radiographic lesion.

Implications derived from this study regarding genetic counseling of affected persons and their families are discussed with emphasis on the importance of a thorough genetic history, complete medical examination of the patient and of close relatives; and, where indicated, selected x-rays of the affected person and relatives considered to be possible carriers of the trait. The wide spectrum of expressivity for

this condition must be borne in mind when carrying out a genetic analysis.

With the present limited knowledge regarding the causation of "spontaneous point mutations" and the lack of effective measures to prevent such de novo genetic aberrations, it is not feasible to diminish the frequency of sporadic cases of tuberous sclerosis. On the other hand, correct diagnosis and appropriate genetic counseling should allow a significant decrease in the transmission of this trait to the progeny of affected persons and should permit reassurance of relatives of sporadic cases regarding the risk of recurrence in these families. However, the usual precautions pertaining to the designation of any affected individual as a sporadic rather than a familial case must be followed and this admonition is particularly relevant to a heritable disorder with marked variability of expressivity as is the case for tuberous sclerosis.

A Clinical and Genetic Study
of Tuberous Sclerosis

by

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A CLINICAL AND GENETIC STUDY OF TUBEROUS SCLEROSIS

INTRODUCTION

Tuberous sclerosis, although a relatively rare human affliction, is a grave hamartomatous disorder that is manifest in many diverse tissues and organs. This condition has been recognized for over a hundred years. The famous German clinician Von Recklinghausen (as cited by Critchley and Earl, 1932) was the first to describe the "potato-like" tumorous lesions of the brain in scientific literature in 1862. The French neurologist, D. Bourneville, described a case in 1880 of a 14 month-old child with focal seizures since birth, facial lesions and whose brain displayed the lesions typically associated with this disorder (as cited by Borberg, 1951 and Chao, 1959). The classical triad includes: epilepsy, a characteristic facial rash, and mental retardation. Bourneville (1880) described the first two findings of this triad and the condition was referred to for years as "Bourneville's Disease." By 1900 (according to Chao, 1959) Bourneville had reported ten patients with the typical brain lesions associated with mental deficiency. He suggested the term "la sclérose tubéreuse" or "tuberous sclerosis" and his designation has persisted and is the name generally accepted throughout the medical world for this pathological entity.

Pathology

Tuberous sclerosis was originally recognized to involve the skin and the central nervous system with fibro-angiomatous tumor-like lesions. These nodules in the brain were early considered to be the cause of both the epileptic seizures and the mental retardation and this explanation for these neurological signs (found in most of the more severely involved cases) continues to be accepted. Following Von Recklinghausen's and Bourneville's descriptions of the disease in the latter half of the last century, further investigations led to the discovery of the involvement of other organs such as the eyes, heart, liver, kidneys, lungs, pancreas, and skeleton with firm, often rubbery, nodules. There have also been reports of possibly associated endocrinopathies and metabolic disorders in cases of tuberous sclerosis. In February, 1972, Sareen et al. reported the frequent occurrence of endocrine and metabolic abnormalities among seven patients with the disease who were institutionalized in Washington State.

Review of Literature

This condition has been found in all major racial groups. For example, Singer (1971) found the classical triad in 26 Chinese in Hong Kong and Shukla (1968) reported tuberous sclerosis in (Eastern) Indians. Singer found the incidence of familial and sporadic cases of

tuberous sclerosis in the Hong Kong Chinese population to be comparable to that reported in various areas of the United Kingdom. Besides its incidence in humans, tuberous sclerosis has been reported to be found in the brain of a Rhesus monkey by Unterharnscheidt in 1968 (as cited by Zaremba, 1967).

Most investigators have considered the genetic mode of transmission in the familial cases of the disease to be consistent with that of an autosomal dominant trait (McKusick, 1968). There is a fairly high percentage of sporadic or de novo mutational cases, ranging from about 30 percent to above 80 percent in various surveys, and the frequently found wide variability of phenotypic manifestation (expressivity) within affected families has led some genetic investigators to postulate other than a simple dominant genetic mechanism for the disorder. For example, Gunther and Penrose (1935), based on their study of 23 cases, proposed that the condition was transmitted by irregular dominance with the action of "modifying genes" to explain the unexpected ratios of involved offspring and the variability of expressivity of the multiple clinical manifestations of the disease. Many affected relatives show only the incomplete or "forme fruste" signs. However, more recent genetic studies, while not explaining the mechanism of the striking variability of clinical findings often noted (this variable expressivity not being confined, of course, to this particular heritable human disorder) have obtained data on the incidence of tuberous

sclerosis that correlate reasonably well to those expected for a "single gene locus" dominant disorder.

Some of these more extensive investigations include: Borberg's review in 1951 of 37 cases in Denmark, Zaremba's review of 26 cases from 23 institutions in Poland in 1967, and the English study of 71 cases from the London area by Bunday and Evans in 1969. "Skipped generations" have not been found in any of the reviewed reports cited in the Bibliography, nor was any reference to failure of penetrance noted in the literature that was reviewed by the writer.

Purpose of the Investigation

After consulting the Medical Department of the state institution for mentally retarded persons in Oregon, Fairview Hospital and Training Center, and the Genetics Division of the University of Oregon Medical School, it was learned that neither a genetic nor a clinical investigation of tuberous sclerosis had evidently been accomplished in Oregon. It was decided to carry out a study of this condition using residents at the Fairview Hospital and Training Center as index cases since patients with moderately severe degrees of involvement with this disorder are generally found as residents of such institutions. It was planned to analyze certain variables among these patients and their first degree--and, when feasible, their more distant--relatives. Among the major parameters to be evaluated were the incidence of

apparently sporadic cases, the ratio of affected siblings to established cases, the average maternal and paternal ages at the time of births of the affected individuals, the incidence of skeletal lesions recognizable on x-rays, and the ages of onset of the signs of skin and central nervous system involvement. It was also planned to compare these data with those of several published series to determine the degree of similarity, or any differences, between the findings in this survey and those of the studies found in medical and genetic literature.

ASCERTAINMENT OF INDEX CASES, CLINICAL
MATERIAL, AND METHODS OF STUDY

With the assistance of the Medical Staff and the Records Department at the Fairview Hospital and Training Center, the medical records of current residents at that institution in the summer of 1971 were searched for possible cases of tuberous sclerosis and, from a total hospital population of about 2,200, 11 individuals were suggested as possibly having this condition. They were examined by the writer and their medical records and x-rays were studied in detail. Only one resident was considered to not sufficiently fulfill the diagnostic criteria for tuberous sclerosis. Thus, at the time the study was initiated in July, 1971, there was a total of ten residents comprising the ascertained index cases of tuberous sclerosis at the state institution for the mentally retarded in Oregon. One of the propositi, a 16 year-old girl (L. H.), expired in November 1971 at the University of Oregon Medical School with the cause of death ascribed at autopsy to large brain lesions typical of tuberous sclerosis. The incidence of 0.45 percent of the hospital population is reasonably close to the 0.3 percent incidence of tuberous sclerosis reported for similar institutions in England (Gunther and Penrose, 1935), but lower than the 1.1 percent incidence reported by Zaremba (1967) for the residents of Poland's "institutions for severely retarded children in the age

range of 3-18 years" (Zaremba, 1964). The apparent discrepancy between the incidence in Polish institutions and that found in Oregon and in England may be explicable, at least in part, by the restricted age range of patients in the Polish institutions. That is, due to the shorter life expectancy among individuals afflicted with tuberous sclerosis, institutions limiting their admissions to children would be expected to have a higher proportion of cases. There may also be a significant difference in the composition of the patient populations in the Polish institutions as compared to those in England and in the present study. On the other hand, of course, the incidence may actually be higher in Poland than in Oregon and England.

Besides a complete medical history and examination, including an x-ray survey, of the ten institutionalized index cases, all of the living parents, except one whose whereabouts is unknown, and a majority of the living siblings (22 of 33) were examined and photographed by the writer. A complete family medical history, including second and third degree relatives, was obtained from the parents of each propositus. Only one of the parents of the ten propositi was known to be deceased (death by accident) at the start of the study and photographs of him and the unlocatable father of two affected sisters were obtained. Another parent, the father of A. B., expired during the course of the study from carcinomatosis with the primary site undetermined. Photographs as well as medical and socio-educational histories of all the

siblings of index cases who were not examined were reviewed and no significant abnormalities among these 12 full-sibs and two half-sibs were elicited. Many of these siblings had moved out of the state. In none of the siblings who were not available for examination was there a history of epilepsy, facial rash or other significant skin disorder; nor was any mental retardation reported among them. Thus, a total of 40 of the known surviving first degree relatives (a total of 52 parents and siblings) or 77 percent of the living first degree relatives were personally examined and photographed by the writer in search of any stigmata that might suggest the possible presence of tuberous sclerosis.

Skeletal x-ray surveys that included radiographs of the skull, spine, pelvis, knees, hands and feet were taken of all the ten probandi and skull x-rays were also taken of the two parents who were considered likely to be affected with the disease. All of the x-rays were evaluated by a certified radiologist as well as the writer (an orthopaedist).

Since cytogenetic studies of many patients with this disorder have been reported in the medical literature and have consistently been found to be normal, index cases and their relatives are not karyotyped. All medical records of the ten probandi were carefully reviewed by the writer, and any abnormalities of pregnancy, birth, neonatal, pediatrics, and adult histories were noted.

RESULTS

After all of the propositi had been examined and x-rayed and the available relatives had been examined and, where indicated, x-rays taken, the findings were compiled for analysis. Included in Table I are the salient historical, clinical, and radiographic findings of the survey of the ten propositi with tuberous sclerosis and their families. In Table II, the main findings obtained from the medical and familial histories are summarized.

All the propositi were white, evidently with primarily Northern European ancestry. (It should be noted that this is the racial and national background of the majority of the residents of Oregon and thus the ten propositi would appear to be representative, from the standpoint of racial and national origin, of the general population of the state.)

Familial Incidence of Tuberous Sclerosis in the Ten Index Cases

Incidence of other first degree relatives with tuberous sclerosis was found for two of the ten propositi; that is, the familial incidence was 20 percent. Therefore, the incidence of sporadic cases of tuberous sclerosis in this survey was 80 percent.

Table I. Summary of Findings of Physical and X-Ray Examinations and of Medical and Familial Histories

Index Case	Age	Age at onset of		Degree of Mental Retardation	Family History	Abnormal X-Ray Findings	Skin Changes Besides Adenoma Sebaceum	Other Physical Findings	Age of the Parent at Birth		Order of (Live) Birth
		Epilepsy	Adenoma Sebaceum						Mo.	Fa.	
1. S. McQ. (Female)	23	1 year	Mild facial rash noted at about 15 years	Moderate	Mother has skin and intracranial lesions of t. s. Younger sister died due to lesions of tuberous scler.	Typical intracranial densities. Slight cortical thickenings of the fingers	Lumbosacral shagreen spot and several pigmented naevi	Moderate degrees of pes planus and genu valgum or "knock-knee"	29	25	1st of 2 sisters (both were affected)
2. R. H. (Male)	14	3 months	8 years	Moderate	Father has typical facial rash, intracranial calcifications and prob. marginal intelligence	Intracranial calcifications	Subungual fibromata of four toes		19	25	1st of 6
3. J. M. (Male)	23	4 months	5 years	Severe	Unremarkable	Intracranial calcifications, old non-union of carpal navicular densities of fingers, toes	Lumbosacral shagreen spot, "white spots," and fibromata of fingers and toes	Clinodactyly of little fingers Pes planus (flat feet)	25	26	1st (only pregnancy)
4. L. O. (Male)	30	2 months	about 20 years	Severe	Unremarkable	Faint frontal intracranial calcifications	Fibromata of both 5th toes, "white spots" on back and large pigmented naevi		27	32	2nd of 4
5. V. T. (Female)	21	8 months	Atypical of tub. sclerosis: mild rash since teens	Moderate	Unremarkable	Intracranial calcifications, skull is thickened 2 mm. density of rt. middle finger, cyst of metacarpal	A few scattered small "white spots" or "leukoderma"	Mild lower dorsal kyphosis	27	29	3rd of 8

Table I. (continued)

Index Case	Age	Age at onset of		Degree of Mental Retardation	Family History	Abnormal X-Ray Findings	Skin Changes Besides Adenoma Sebaceum	Other Physical Findings	Age of the Parent at birth		Order of (Live) Birth
		Epilepsy	Adenoma Sebaceum						Mo.	Fa.	
6. S. A.	26	3 months	By age	Moderate	Essentially unremarkable except for history of "harelip" in a sister	Multiple calcific intracranial densities	Lumbosacral shagreen spot, "white spots" on back and extremities, fibromata of both hands, left foot	---	25	29	2nd of 4 (all daughters)
7. L. H. (Female)	Died in 1971 at age of 16	6 months	3 years	Moderate	Essentially unremarkable but siblings have mild acne (within normal) and diabetes on maternal side	Some increased density of distal portions of proximal phalanges of fingers, mild shortening, metacarpals 4+5	"White spots" on back and lower limbs, fibromata of two left fingers	Slight kyphosis, mild strabismus (esotropia)	23	23	1st of 3
8. D. K. (Female)	14	5 years	At about	Marked	Unremarkable	Intracranial calcifications, intracalvarial density at the coronal suture on right side (of the skull)	Fibromata of both second toes; mild increase in pigmented naevi	Slight pes planus	22	23	4th of 6
9. A. B. (Female)	39	1 year	No rash typical of tub. sclerosis, more like "freckles"	Moderate (I. Q. of 41)	Unremarkable except that a nephew has had a brain tumor (not like tuberous sclerosis)	Faint intracranial calcifications, tiny densities in phalanges of fingers	Few small "white spots" on back	Mild hemiparesis, had tuberculosis with left upper lobectomy	32	37	4th of 5 (all sibs are brothers)
10. D. P. (Female)	17	2 months	4 years	Moderate (I. Q. of 34)	Unremarkable except that one brother, a twin, had seizures till age 2-1/2 years (born premature)	Lucent lesions of 5th toes, tiny dense lesions in phalanges of hands, scoliosis with spina bifida 1st sacral	Fibroma of right great toe, several small "white spots" of lower limbs, large pigmented naevus of abdomen	Mild degree of exophoria, marked scoliosis (1st noted age 11)	34	30	1st of 3 (but 2 maternal half-sibs preceded pt.)

Table II. Summary of Findings of Medical and Familial Histories

The mean age of the ten propositi	22.2 years (14 to 39)
The mean age of the onset of epilepsy	11.2 months (2 to 60)
The mean age of the onset of adenoma sebaceum	7.9 years (3 to 20)
The mean maternal age (at time of birth of propositi)	26.3 years (19 to 34)
The mean paternal age (at time of birth of propositi)	27.9 years (23 to 37)
The mean birth order of the propositi	2.2
The mean number of live births per family of propositi	4.4
The female to male ratio of the ten propositi	7:3

Table III. Summary of Dermatological Findings in the Propositi

Skin Changes Suggestive of Tuberous Sclerosis	Found In
Adenoma sebaceum (the remaining two had facial changes atypical of this disease)	8 of 10 propositi
Shagreen spots (all at the lumbo-sacral area)	3 of 10 propositi
Depigmented areas ("leukoderma" or "white spots")	7 of 10 propositi
Subungual and/or periungual fibromata	7 of 10 propositi
Café-au-lait spots or naevi (the other five had one or more small pigmented naevi)	5 of 10 propositi

Dermatological Findings

The incidences of the various cutaneous disorders recognized to be associated with tuberous sclerosis are indicated in Table III.

Other Significant Clinical Findings

One patient (A. B.) had undergone a lung lobectomy for tuberculosis, another (D. P.) had instrumentation and a spinal fusion for marked scoliosis, and a third (S. A.) had undergone an operation for a polycystic kidney tumor that was found to be characteristic of tuberous sclerosis nephropathy and another surgery for a "prominent hip bone" in childhood. No repeating pattern to these abnormalities was recognized. Two cases of strabismus were noted among the ten propositi.

Parental Ages and Birth Orders

The mean maternal age at the time of the propositi's births was 26.3 years and the mean paternal age was 27.9 years. These mean ages are well within the normal ranges of parental ages for the period covered by the births of these patients.¹

The mean order of birth of the ten propositi was 2.2, or 0.5 below the 2.7 mid-way point between 1.0 (for the first-born) and 4.4 (the mean number of births among the families of the propositi). This small

¹Source: Oregon State Health Division

deviation from the expected mean of birth orders among the ten families is not statistically significant (by the t-test with $0.30 < P < 0.40$).

X-Ray Findings

Abnormal x-ray findings suggestive of the diagnosis of tuberous sclerosis were noted in all ten index cases and in the two parents recognized to display clinical signs of tuberous sclerosis. The frequencies of bony abnormalities among the ten propositi that are either pathognomonic for or commonly found in persons affected with tuberous sclerosis are shown in Table IV.

Table IV. Incidence of Radiographic Findings

	No. of Propositi
Intracranial calcifications	7 of 10
Abnormally thickened calvarium	1 of 10
Phalangeal lesions (lucencies and/or punctate densities)	6 of 10
Metacarpal shortening	1 of 10
Metacarpal radiolucency	1 of 10
Metacarpal cortical thickening (as reported by Holt and Dickerson, 1952)	none

Other radiographic findings, considered to be probably incidental, included: a non-union of an old carpal navicular fracture (in

R. H. whose wrist was found to be normal on physical examination) and the aforementioned cases of moderately severe scoliosis and pulmonary tuberculosis.

It is of special interest to note that one (L. H.) of the three patients in whom intracranial calcifications were not noted on skull x-rays expired during the course of this study with the typical brain lesions associated with tuberous sclerosis described as the primary cause of death as determined at autopsy. In other words, the absence of abnormal findings on skull x-rays did not indicate that significant cerebral lesions were likewise absent. This lack of correlation between the x-ray and autopsy findings relative to cerebral lesions in patients with tuberous sclerosis has also been reported in other surveys.

Review of Familial Histories for the Eight Apparently Sporadic Index Cases

Except for two (R. H. and S. McQ.) of the ten index cases, detailed interrogations regarding the possible presence of minor signs or incomplete forms of this disorder in the pedigrees of these propositi failed to reveal any history suggestive of other affected family members. The usual broad spectrum of medical conditions that is expected to be elicited by interviews of this nature was obtained including: a scattered incidence of diabetes, psychosis (not suggestive

of tuberous sclerosis as the underlying etiology), and several cases of "psoriasis" (but not suggestive of adenoma sebaceum or fibromata of the fingers or toes). The nephew of one patient (A.B.) underwent brain surgery for a medulloblastoma (not considered to be related to tuberous sclerosis in its pathogenesis). Only one case of "epilepsy" was reported in a first degree relative of the ten propositi. This case was in the younger full-brother of a 17 year-old female proband (D.P.) and the brother, a fraternal twin who was born prematurely by breech presentation and who is now 15 years old, has not had any seizures since he was two and one-half years old and has not had medication for seizures since that time. It is felt that his seizure history was probably related to the insults sustained by his brain at the time of his premature birth rather than to a possible etiology of tuberous sclerosis. He currently displays no stigmata suggestive of tuberous sclerosis.

There was no history of significant abnormalities during gestations of the propositi such as exposure to large amounts of x-radiation or drugs.

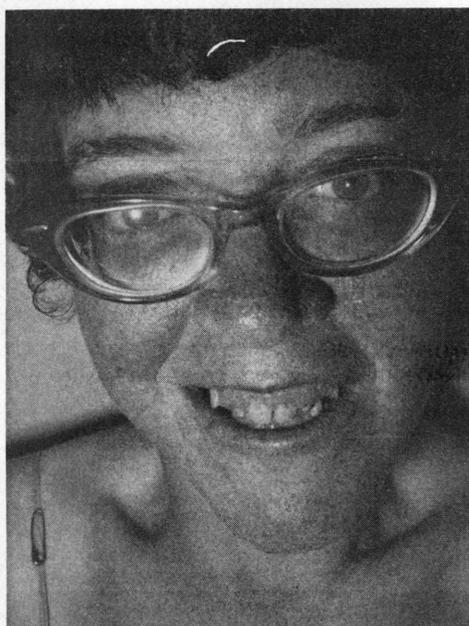
Analysis of the Two Familial Index Cases

Case Number 1. (S. McQ.)

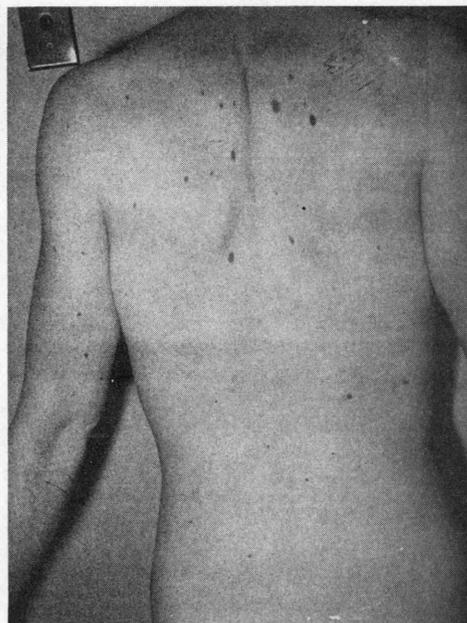
This 23- year old female displayed typical dermatological and radiographic (of the skull and hands) findings of tuberous sclerosis and

moderately severe retardation. The onset of seizures was reported to have occurred at the age of one year. She is the elder of two sisters (there were no brothers) and her younger sister (K. McQ.) expired at the Fairview Hospital and Training Center in 1967 with the cause of death ascribed to typical brain lesions of tuberous sclerosis: "several nodular protuberances arising from the surface of the brain." K. McQ. had experienced the onset of seizures at the age of one and one-half years and also had "typical skin lesions" of tuberous sclerosis. A congenital defect of the aortic cusps with stenosis was also found at autopsy, and this was presumably the cause of a cardiac murmur heard during her life. Auscultation of the chest of the surviving sister (S. McQ.) failed to reveal a significant murmur.

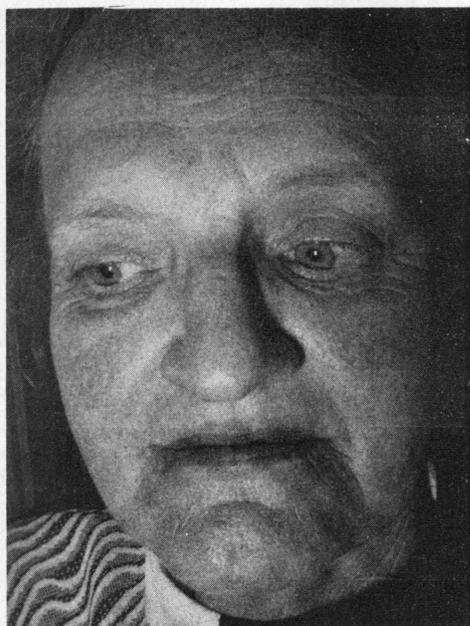
The mother of these sisters is now 52 years old and she and her mother (the maternal grandmother of the affected sisters) were examined and photographed. Their father, who was evidently Canadian, is reported to have "disappeared" when the sisters were two years and one year old, respectively. His photograph (see Figure 1) reveals no obvious facial lesions. However, stigmata of tuberous sclerosis, previously unsuspected, were detected in the mother of these two sisters. She remarried after the "desertion" of her first husband but she did not have any more children. It is of interest that her face displays a mild malar and nasal rash (see Figure 1) that resembles the *proposita's* facial eruption, and both are fairly typical of tuberous



a. S. McQ.



b. S. McQ. Showing Pigmented Naevi



c. The Mother of S. McQ.



d. The Father of S. McQ.

Figure 1. Family of S. McQ.

sclerosis, that is, of adenoma sebaceum. The mother also has a typical "shagreen patch," a sharkskin-like area, over her lumbosacral region and a similar "patch" was found at this location on her daughter's lower back. However, the mother has no history of seizures and appears to have above-average intelligence. She is employed as an executive secretary.

A genetic finding of this family that is probably unrelated to the tuberous sclerosis is the rather high degree of myopia that was reported for both the daughters and the mother but was not found in the maternal grandmother. Skull x-rays of the mother were taken as a part of the study and they demonstrated the presence of previously unrecognized multiple intracranial calcifications that are typical of cases of tuberous sclerosis, thereby providing an example of radiographically demonstrable cerebral involvement in this condition without associated epilepsy or mental retardation; that is, just the opposite of the situation found in the 16 year-old girl (L. H.) who expired during the course of the study with large cerebral lesions in whom cerebral calcifications had not been noted radiographically.

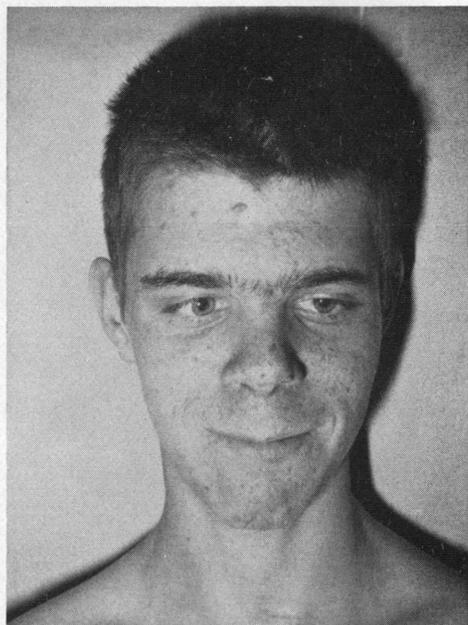
The maternal grandmother, now 81 years old, had eight children who are now widely dispersed in various states. She was found to be normal except for obesity and the history of adult-onset diabetes. Both she and her daughter (the mother of the two affected sisters) disclaimed any knowledge of a facial rash, depigmented spots, "shagreen

patches, " subungual or periungual fibromata, etc. in any of the seven uncles and aunts of the two girls afflicted with tuberous sclerosis.

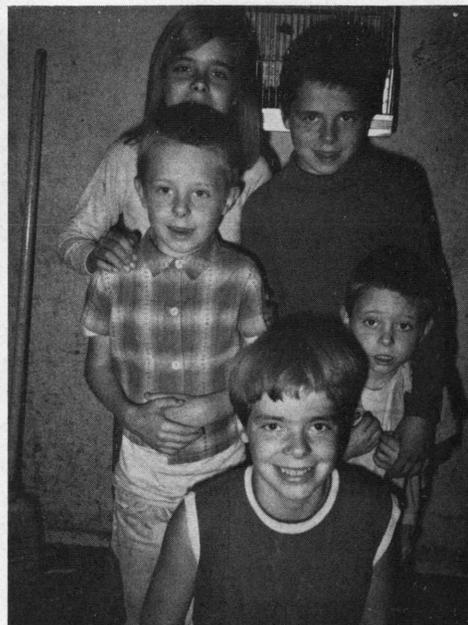
The maternal grandfather of these girls was reportedly normal in regard to any stigmata of tuberous sclerosis and died at the age of 73 years following a fractured hip. Thus, it is suggested that the tuberous sclerosis trait arose by mutation in either the maternal or paternal gametogenic divisional sequence contributing to the genetic composition of the mother of the affected girls and that this defective gene was transmitted to each daughter with the subsequent rather severe manifestations of the disease found in both the elder daughter, now 23 years old, and the younger daughter who expired in 1967 due to complications of tuberous sclerosis.

Case Number 2. (R. H.)

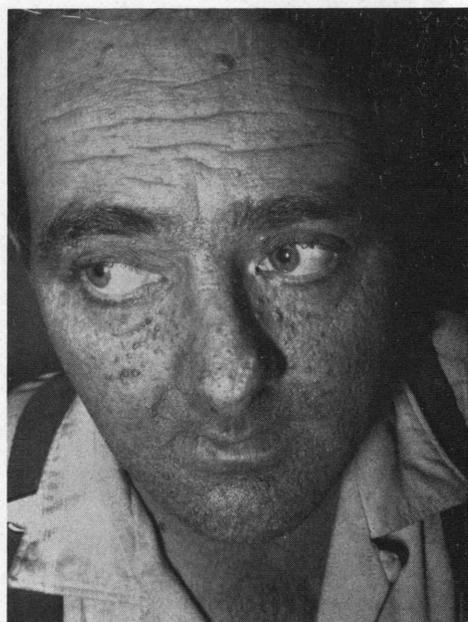
This 14 year-old boy, the youngest of the ten propositi, was the first-born of six children, with two spontaneous abortions in the first trimester of undetermined cause also reported. His father displays a facial rash that is typical of tuberous sclerosis and similar to the rash noted on the face of the propositus (see Figure 2). Skull x-rays of both the propositus and his father revealed the presence of typical multiple intracranial calcifications. Neither the propositus nor his father displayed "shagreen" or depigmented skin patches but in both of them subungual fibromata of four toes (not the same toes) were



a. R. H.



b. Siblings of R. H.



c. Closeup of the Father of R. H.



d. The Parents of R. H.

Figure 2. Family of R. H.

found. The son also displayed a mild increase, that is, above the normal range, in the number and size of pigmented naevi. The father's skin was negative for this sign.

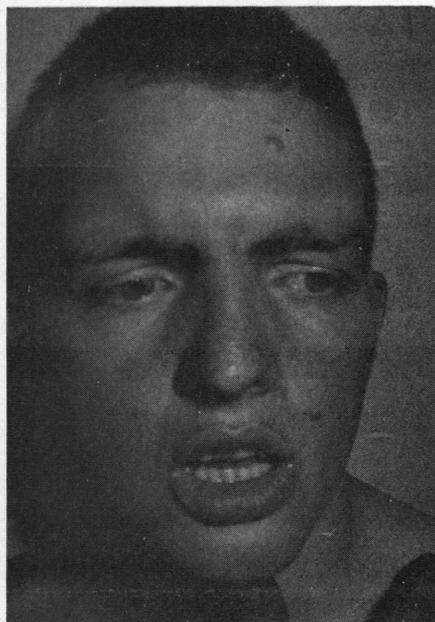
The propositus had the onset of epileptic seizures at the age of three months. These seizures are now well controlled. His father, now 39 years old, disclaimed any history of seizures, "fainting spells" etc. and the father's mother and sister both confirmed this point. The patient is moderately retarded but can communicate verbally fairly well. His father, unemployed for many years, reportedly attended school as far as the seventh grade and has been described by a social worker to be "hostile, uncommunicative... and is intellectually limited." His right leg is about one and one half inches shorter than the left leg. This reportedly resulted from poliomyelitis sustained at the age of four years according to his mother. The mother, paternal grandmother, one paternal aunt, and all five siblings of the propositus were examined and photographed. None were found to display any stigmata of tuberous sclerosis. The paternal grandmother reported that the paternal grandfather died in 1956 at the age of 48 years of "the dropsy and a little of everything wrong with his right and left ventricles." No photographs of this paternal grandfather of the propositus are available, but the patient's grandmother denied that her deceased husband had any of the cutaneous manifestations or other signs of tuberous sclerosis, such as seizures. The mother's side of

the pedigree of the propositus was likewise negative for any history suggestive of even a limited "forme fruste" of tuberous sclerosis. The mother of the propositus has four siblings and they, as well as her parents, are all reported to be living and well.

The five siblings of the propositus are aged 5 to 12 years. Except for their being of somewhat smaller than average stature (the father is five feet four inches tall and the mother is five feet seven inches tall) and the suggestion of questionable nutrition, all were considered to be within the normal range on physical examination. No skin lesions were found and none had a history of seizures.

As in the case of propositus number one (S. McQ.) described above, it is suggested that the trait for tuberous sclerosis made its first appearance in the genotype of the father but did not, at least not as yet, reappear in any of the subsequent five (reportedly full) sibs of the propositus.

Photographs of the remaining eight propositi (the apparently sporadic cases) and their families are included in Figures 3-10.



a. J. M.



b. The Hands of J. M.
(Note the fibromata on fingers)



c. The Mother and Aunt of J. M.

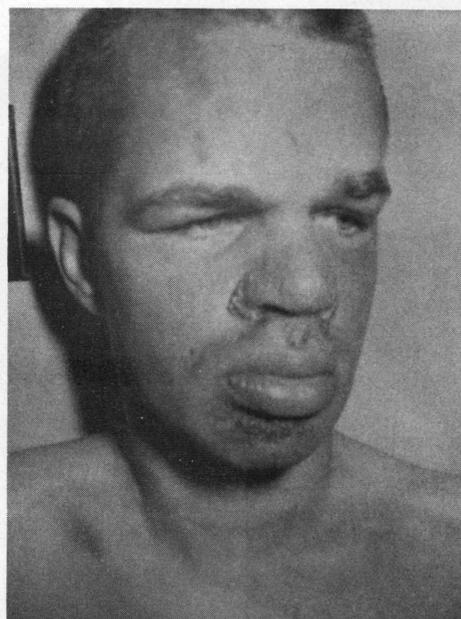


d. The Father of J. M.
(Deceased)

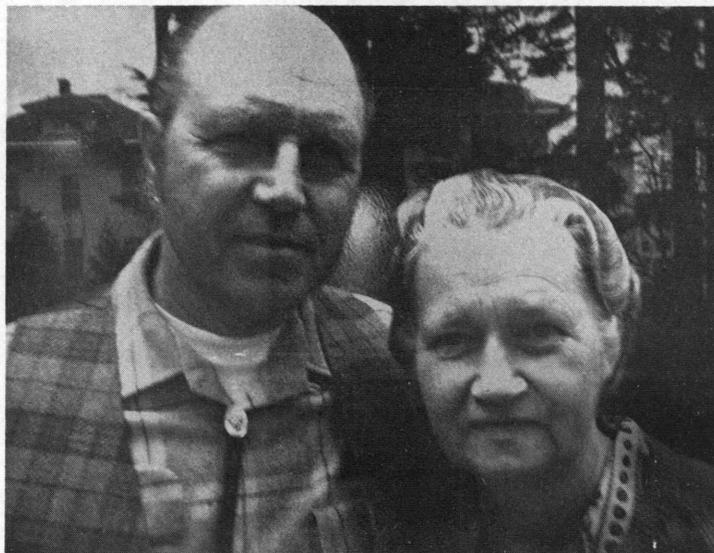
Figure 3. Family of J. M.



a. L. O.
(Note the large naevi)

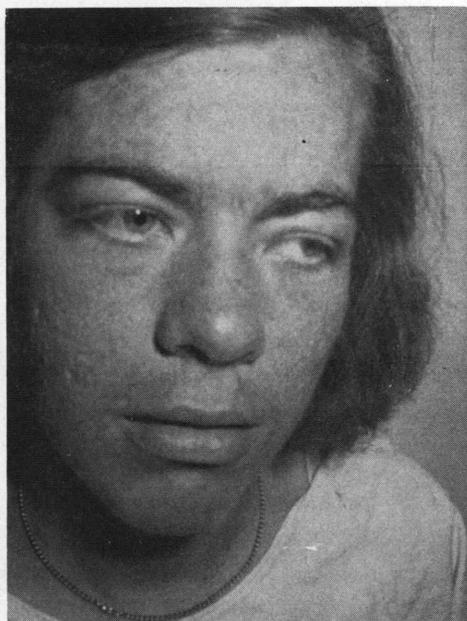


b. L. O.

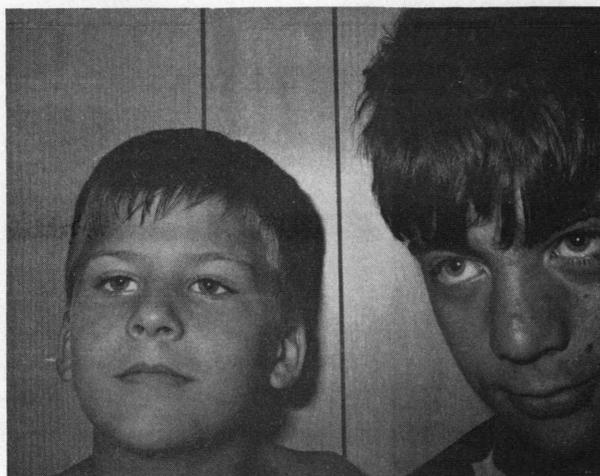


c. The Parents of L. O.

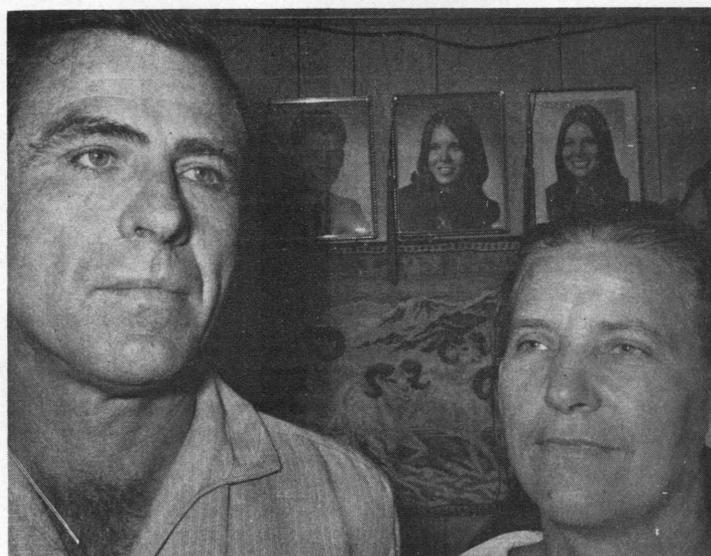
Figure 4. Family of L. O.



a. V. T.
(Rash is not typical of adenoma
sebaceum)

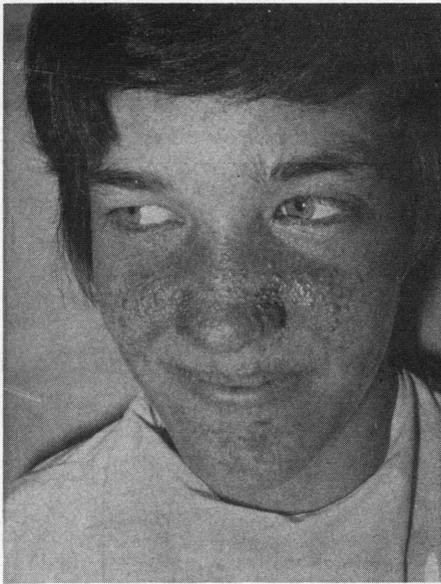


b. Brothers of V. T.

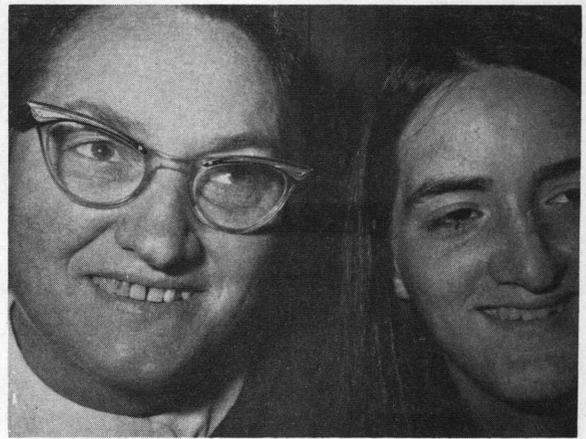


c. Parents of V. T. with Photos of Three Siblings

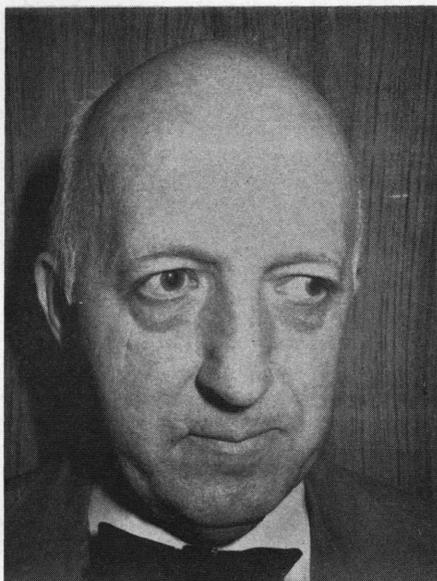
Figure 5. Family of V. T.



a. S.A.



b. The Mother and Sister of S.A.

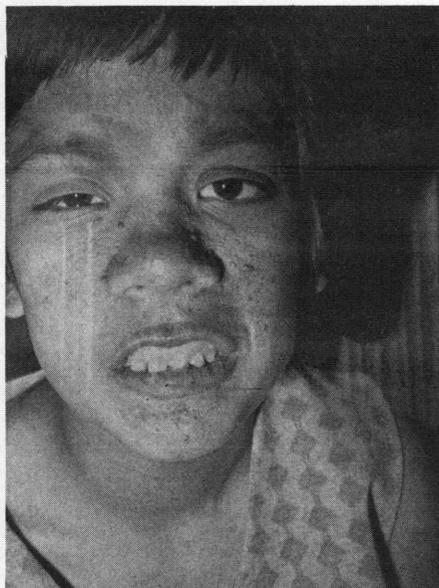


c. Father of S.A.

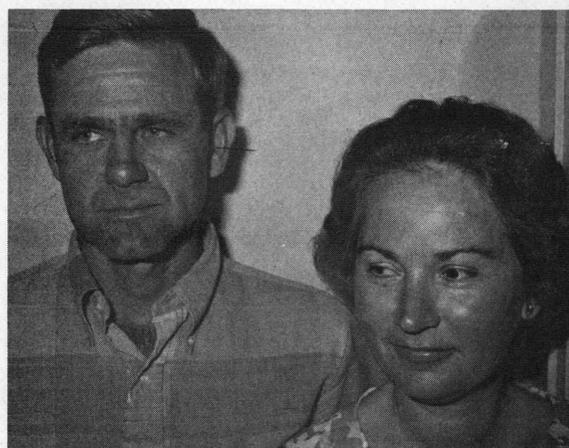


d. A Sister and a Niece of S.A.

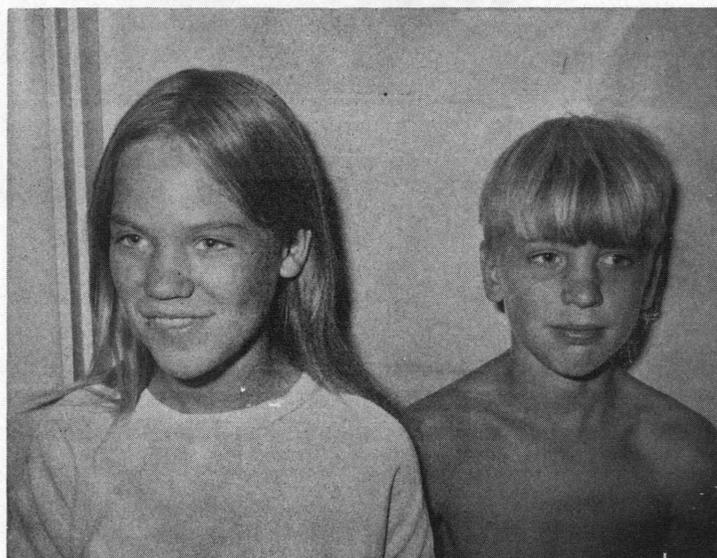
Figure 6. Family of S.A.



a. L. H. (Deceased)

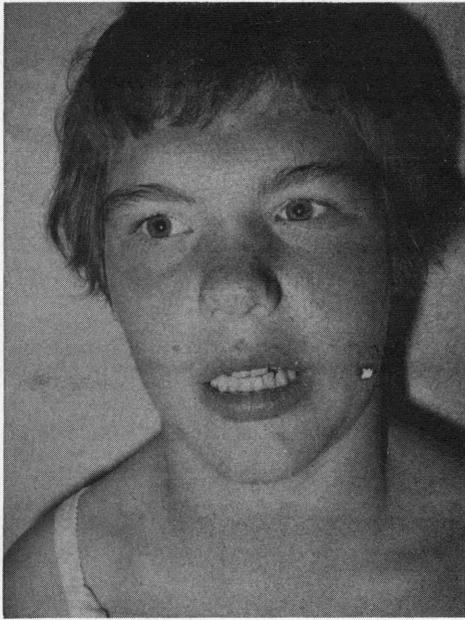


b. The Parents of L. H.

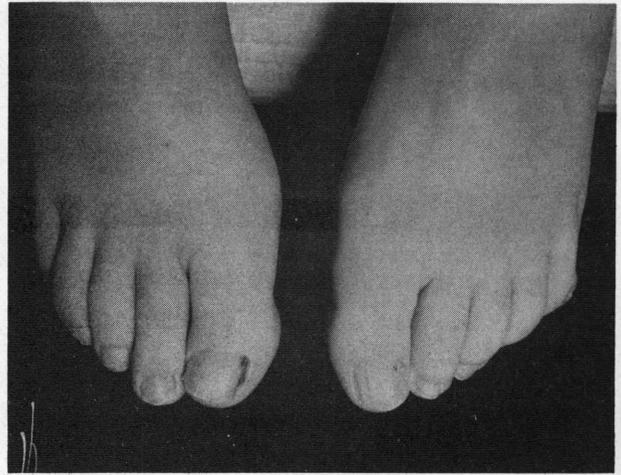


c. The Siblings of L. H.

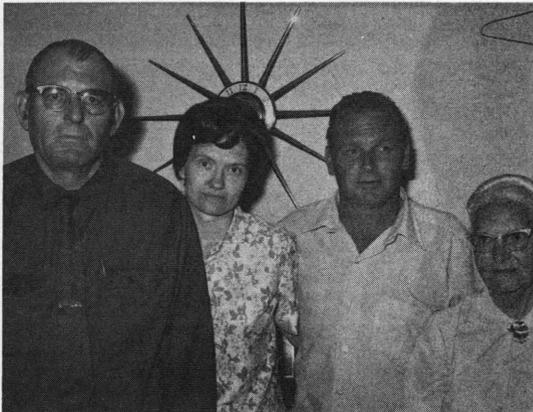
Figure 7. Family of L. H.



a. D. K.



b. Feet of D. K.
(Note the Periungual Fibromata)

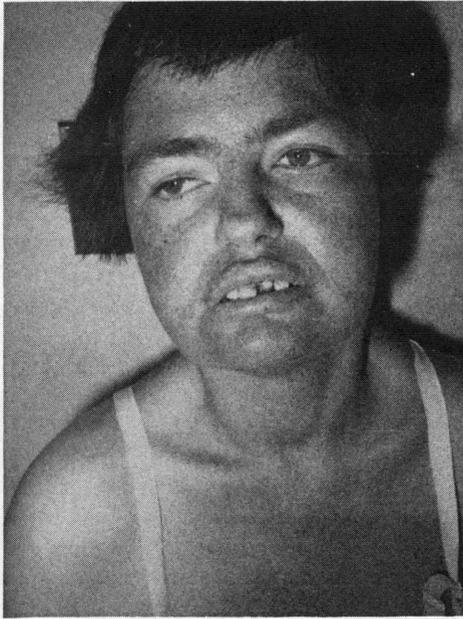


c. The Parents and Paternal Grandparents of D. K.

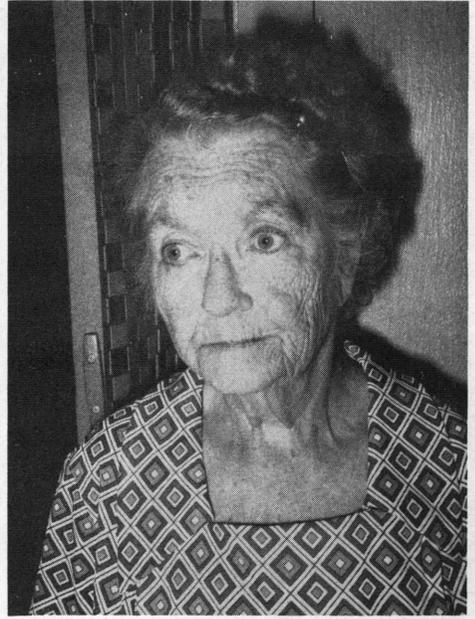


d. The Siblings of D. K.

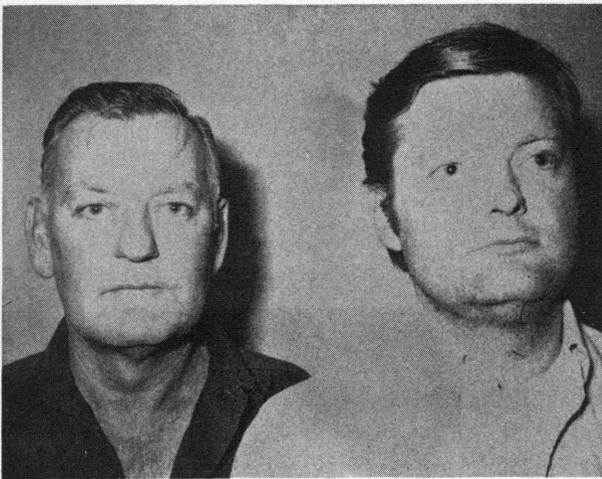
Figure 8. Family of D. K.



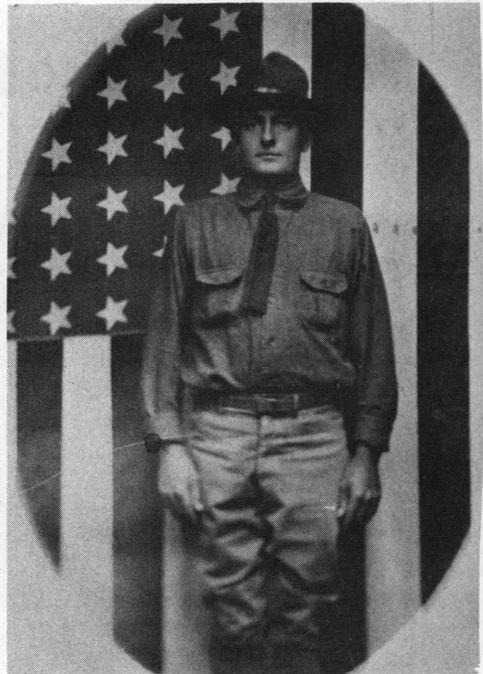
a. A. B.



b. The Mother of A. B.

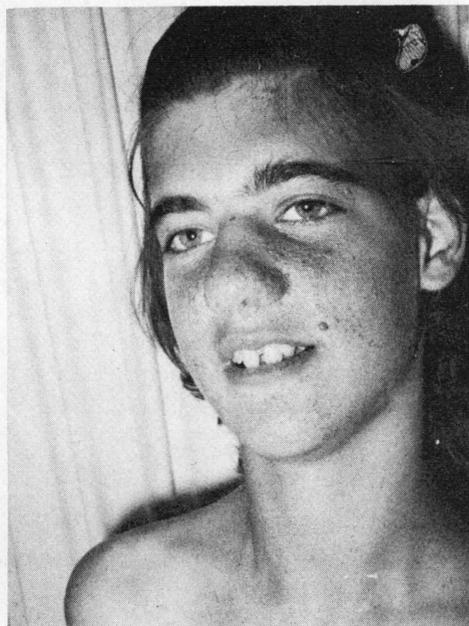


c. Brothers of A. B.



d. The Father of A. B.
(Deceased)

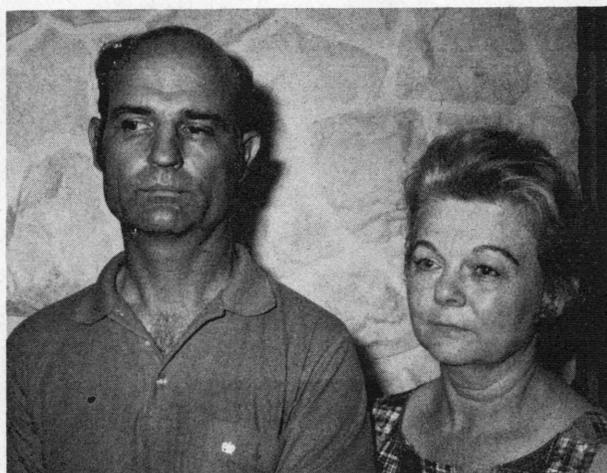
Figure 9. Family of A. B.



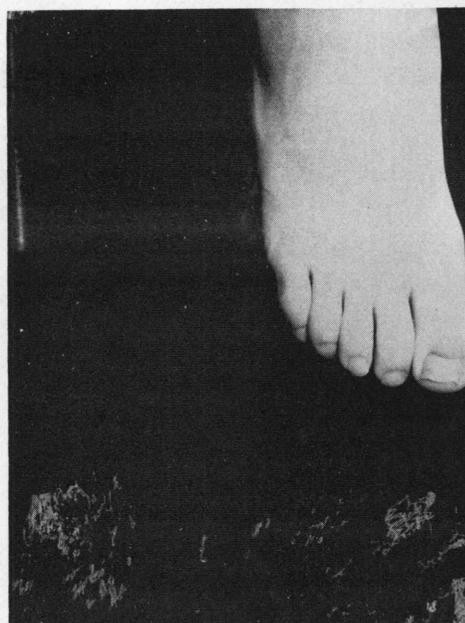
a. D.P.



b. D.P.
(Note Spinal Deformity)



c. The Parents of D.P.



d. Right Foot of D.P.
(Note large fibroma
on the great toe)

Figure 10. Family of D.P.

DISCUSSION

Familial Incidence of Tuberous Sclerosis

The familial incidence found in the present relatively small series is in the range of incidences reported in the larger surveys comprised of series of about 20 to 100 index cases. Comparison of the familial incidence in this study of ten current cases of tuberous sclerosis in an institution for the mentally retarded and several investigations from Europe and Hong Kong is depicted in Table V.

Table V.. Incidence of Familial Cases

Study	Percentage of Familial Cases
Present survey	80
Gunther and Penrose, England (1935)	70
Critchley and Earl, England (1932)	80
Borberg, Denmark (1951)	86
Zaremba, Poland (1968)	72
Stevenson and Fisher, Northern Ireland (1956)	78
Nevin and Pearce, England (1968)	75
Singer, Hong Kong (1971)	65

However, the failure to recognize the stigmata of even a "forme fruste" case among the five siblings of case number two (R.H.) would tend to raise some doubt as to the premise of a "simple autosomal dominant" character of this trait. That is, on the assumption that

both the propositus and his father carry the dominant gene for tuberous sclerosis, each child of the father should have a 1 in 2 probability of receiving the trait from him; therefore, the probability that five consecutive offspring of the affected father would "escape" transmission of this trait is $(1/2)^5$ or 1 in 32. When any such unexpected incidence of a presumed autosomal dominant trait appears in the offspring of an affected parent, and when the penetrance for such a trait is recognized to be very high as is the case for tuberous sclerosis, the possibility of inaccurate paternity of the unaffected offspring is sometimes advanced as an alternative explanation to the lack of penetrance or delayed manifestation of the trait or the unlikelihood by probability theory of a consecutive series of offspring in whom the trait appears to be absent. The available information does not allow further discussion of these possible explanations. The combined data from other investigations suggest that this disorder is inherited in familial cases as an autosomal dominant trait with segregation that is generally consistent with that characterization.

Sex Incidence

Until Vaas (1940) compiled a large series of 232 cases from the published reports as of 1940, it was generally believed that there was a predilection for male incidence of tuberous sclerosis. Vaas, however, found nearly equal numbers of reported cases for males (118)

and females (114). Since that time, the larger reported series of tuberous sclerosis cases have shown the incidence to be comparable in the sexes, thus refuting the previously held concept of sex linkage for the disorder. The observed sex incidence of the ten propositi in the present study, seven females to three males, is not a significant deviation from the over-all expected one to one ratio by sex since consultation of probability tables indicates that the ratio of three males to seven females would occur with a probability of 17 percent when the general probability for sex incidence is 50-50.

Frequency of Occurrence of Mutation
for the Tuberous Sclerosis Trait

It is apparent that the majority of the more affected patients and probably all of those severely affected will not have children to whom the trait may be transmitted. Therefore, unless a distinct majority of affected individuals are only mildly involved with this multifaceted disease (and all the reviewed published investigations that include an analysis of this aspect of the disease, for example, those of Bunday and Evans (1969), Borberg (1951), Gunther and Penrose (1935), Nevin and Pearce (1968), Zaremba (1967) and Lagos and Gomez (1967), suggest this is not the case) a considerable introduction of new cases into the population by mutation would be required to prevent diminution in the frequency of the disorder. Since there are approximate data for

the frequency of the trait for only one or two generations at the most and since the disease has only been recognized for about a century, one cannot make an accurate estimate regarding any current trend relative to either an increasing or decreasing frequency of tuberous sclerosis. However, as in analogous situations of genetic frequency relationships, when no new selective factor, natural or "artificial" (e. g. due to society's interference with human fertility), has been introduced to influence the balance between the various genetic and environmental factors bearing on the frequency of the trait, it seems reasonable to assume that a state of equilibrium, with a fairly stable gene frequency for the tuberous sclerosis trait, has been achieved. Sterilization of affected individuals is a recent development and, because of the high proportion of sporadic cases, cannot be expected to significantly lower the incidence of the disease. The rate of new mutations for the trait presumably approximately offsets the loss of gene frequency due to the infertility of the more severely affected persons. Published reports usually include familial cases with no more than two or three affected generations; thus, normally the trait evidently "dies out" by the fourth and fifth generations. Obviously, the average degree of involvement of affected persons would influence the frequency of the gene in familial cases as compared to sporadic cases. In the presence of a higher average degree of involvement with its concomitant low fertility, a mutation rate as high as the 80 percent found in

the present study could be required to maintain the incidence of the condition among the general population,

In 1954, Dawson found that the number of persons with incomplete forms of tuberous sclerosis was approximately equal to those with the "full-blown" syndrome. He estimated the combined incidence at 1:150,000 in the general population of England and, in 1956, Stevenson and Fisher arrived at the same ratio for the population of Northern Ireland. Zaremba (1967) estimated an incidence of tuberous sclerosis with mental retardation in Poland at 1:22,727. Based on the estimate of incidence of the trait of 1:150,000, the expected number of cases in the State of Oregon, with a population of about 2,100,000 would be about 14. Counting the two affected parents, neither of whom is currently hospitalized, the present study includes twelve affected individuals. The writer is of the opinion that this incidence of 1:175,000 is probably somewhat on the low side since it is believed to be fairly likely that more than two cases besides the ten index cases may be present in Oregon.

The age range for the ten index patients is 25 years (14 to 39 years), or approximately one generation. It appears reasonable to use the population of Oregon at the time of the birth of the youngest patient, that is, in 1957, in the calculation of the ratio of cases of tuberous sclerosis to the total population and this would tend to correct the underestimate for the incidence in the present (considerably

larger) population resultant from the absence of any cases under the age of 14. It seems likely that there are several such cases that perhaps have not yet progressed to a degree of severity that requires institutionalization. The population of Oregon in 1957 was estimated at 1,737,470² and the 12 cases in the current study would represent an incidence of about 1:145,000.

This estimate would, of course, be lower than the actual incidence, since a number of patients with this disease who were living in 1957 have died in the interim. For example, four or five patients at the Fairview Hospital and Training Center who probably had tuberous sclerosis have expired during those 14 years. Seven of the ten index cases were born in Oregon with the birth dates spanning a period from June, 1941 to February, 1957. Therefore, a minimum of seven births in Oregon of persons afflicted with tuberous sclerosis occurred in this period of 16 years during which there were approximately 514,500 births in the state.² With six of the seven affected individuals representing mutational incidence of tuberous sclerosis, the mutation rate for the trait among residents of Oregon would be estimated at a minimum of 0.5×6 per 514,500 or 1 per 171,500 gene loci. This is equivalent to 5.8 mutations per million genes which would reflect a mutation rate for this disease of 11.6 affected births per million births. It is noteworthy that this estimate of mutational

²Source: Oregon State Health Division

frequency for this locus of 5.8 per million genes is roughly comparable to the often cited estimate of the "spontaneous" mutation rate of a single locus of 10^{-5} or 10 per million.

It had earlier been stated that those cases of tuberous sclerosis that are inherited from a recognized affected parent have more severe manifestations of the disorder. More recent studies (Borberg, 1951; Bunday and Evans, 1969; Zaremba, 1967) tend to disclaim this assertion. Although only ten cases are included in the present study, no significant difference of degree of involvement was found in the clinical manifestations of the disorder in the two familial index cases (R. H. and S. McQ.) and the eight apparently sporadic cases. Nor should any inference be made regarding increasing severity of the disorder with successive generations since, by the nature of the ascertainment methods and the likelihood of infertility in the more severe cases, it is inevitable that the affected parents of the familial index cases will generally have involvement of a lesser degree. The variable expressivity among the five recognized familial cases in this study represents a puzzling feature of the disorder (not, of course, an unusual finding among heritable disorders) that has been recognized throughout the approximately 60 years since the familial character of the disease was first described by Berg and Shelmire (as cited by Borberg, 1959 and Gunther and Penrose, 1935). "Modifier" genes were proposed by Gunther and Penrose (1935) as an explanation

for the variable expressivity and epistatic genes have been advanced as possible explanations for the markedly protean character of the phenotypes of the disorder.

Clinical Findings

Dermatological Manifestations

The incidence in the ten cases described in the present study of the various dermatologic lesions often noted as features of tuberous sclerosis is comparable to that reported in several other studies with the possible exception of a higher incidence (50 percent) of patients with café-au-lait spots of significant size and number than was reported in the series of Lagos and Gomez (1967) with only seven percent, in Nevin and Pearce's (1968) series (28 percent) and in Zaremba's study (1967) (17 percent). However, in Chao's (1959) series of eight cases in Texas, an incidence of 50 percent for café-au-lait spots also was found.

The presence of the "butterfly rash" called adenoma sebaceum (actually a misnomer since neoplasia of the sebaceous glands does not comprise the morphology of these fibro-angiomatic lesions) has often been considered pathognomonic for tuberous sclerosis. In his textbook on dermatology, Professor George Lewis (1952, p. 216) stated that the lesions of "adenoma sebaceum" appear early in life and

"accompanying this condition, subungual and periungual fibromata of the fingers and toes may be noted and tuberous sclerosis is not uncommon," evidently implying that the combination of these skin lesions does not necessarily justify the diagnosis of tuberous sclerosis. In the review of the literature accomplished in preparation for this clinical study, the writer repeatedly encountered the assertion that the presence of either, and particularly of both, of these lesions strongly suggests the diagnosis of tuberous sclerosis. It may be that Lewis' somewhat qualified statement resulted from his knowledge of "forme fruste" cases of tuberous sclerosis in which only the dermatologic signs were evident; that is, in patients with adenoma sebaceum and periungual fibromata in whom epilepsy and mental retardation were apparently absent.

Definite adenoma sebaceum was found in eight of the ten (80 percent) *propositi* and in one of the two parents considered to be affected with tuberous sclerosis. Seven of eight of Chao's (1959) series displayed these lesions, with the eighth, a 20 year-old patient, having "bumpy skin around the nose," the facial condition considered by Chao to be atypical of adenoma sebaceum. However, the patient did display a subungual fibroma and a "shagreen patch." The incidence of adenoma sebaceum in the present study and in several published series is depicted in Table VI.

Table VI. Incidence of Adenoma Sebaceum in Patients with
Tuberous Sclerosis

Investigation	Percentage of Adenoma Sebaceum
The present study	80 (in 8 of 10)
Nevin and Pearce (1968)	83 (in 15 of 18)
Gunther and Penrose (1935)	100 (in all of 20)
Zaremba (1967)	90 (in 36 of 40)
Lagos and Gomez (1967)	83 (in 57 of 71)
Chao (1959)	88 (in 7 of 8)
Singer (1971)	100 (in all of 26)

It is of interest that the two patients from the present study (V. T. and A. B.) in whom typical adenoma sebaceum was not present also lacked other dermatologic signs of this disorder. However, both presented mental retardation and epilepsy with onset in early childhood and they also had confirmatory x-ray findings with multiple intracranial calcifications. It is suggested that there may be some modifying factor present in the genetic make-up of these two patients and similar individuals in whom notable skin abnormalities are not found with the result that the potential for cutaneous manifestations of the trait for tuberous sclerosis is somehow suppressed. This speculation is of course hypothetical and essentially merely a restatement of this observed variation in clinical signs.

Table VII allows comparison of the propositi of this study and those of other investigations in regard to the incidence of cutaneous

findings that are generally considered to be less pathognomonic than adenoma sebaceum.

Table VII . Incidence of Cutaneous Lesions Besides Adenoma Sebaceum

Investigation	Number of Patients	Sub- and Peri-ungual Fibromata	Shagreen Patches	White Spots	Café-au-lait spots
		%	%	%	%
Present study (1971)	10	70	30	50	50
Nevin and Pearce (1968)	15	39	83	61	27
Zaremba (1967)	40	55	48	78	20
Lagos and Gomez (1967)	71	17	21	15	7
Chao (1959)	8	13	50	63	50
Sareen <u>et al.</u> (1972)	7	71	57	100	29

The above data reveal a considerable variability in dermatological signs, except for the generally present adenoma sebaceum, for each of the abnormal skin findings tabulated with a range of seven percent for the incidence of café-au-lait spots to as high as 100 percent for "white spots." Although much of this rather striking variability among the six included studies for these skin signs may actually be present, it is suggested that at least some of the wide range of the incidences for the various lesions may be due to a difference in the criteria for inclusion of a particular sign according to the observer. This variability in the interpretation of skin signs

would probably be more significant for the café-au-lait and "white spots" than for the more definite clinical findings of shagreen patches and fibromata of the fingers and toes. There is a distinctly subjective element on the part of the examiner in the diagnosis of the former two signs. On the other hand, as alluded to previously in this paper, the relatively small size of all of the studies except those of Lagos and Gomez (United States, 1967) and Zaremba (Poland, 1967) would lead one to anticipate a moderate degree of variability of these parameters purely on the basis of probability considerations. Regarding the present study, the relatively high incidence of subungual and periungual fibromata is noteworthy and these lesions were found in seven of the eight propositi who presented adenoma sebaceum, thereby rather firmly establishing the diagnosis of tuberous sclerosis.

X-Ray Findings

Comparison of the x-ray findings among the ten cases was made with those of the comprehensive series of Holt and Dickerson (1952) comprising a review of radiographic changes in 43 patients from the University of Michigan Medical College. These authors found that over 50% of the patients had cerebral calcifications in the region of the basal ganglia. D. W. Smith (1970) reported an incidence of 51 percent intracranial calcifications, and Singer (1971) found an incidence of 65 percent intracranial calcifications in 26 Hong Kong Chinese

displaying the signs of tuberous sclerosis. Lagos and Gomez (1967) reported the same incidence as Smith, that is, 51 percent, among 35 of their patients with tuberous sclerosis who had skull x-rays. The incidence of 70 percent in the present study does not differ significantly, for a series of this size, from the findings in the above cited series, and it agrees well with the 70.6 percent incidence of intracranial calcifications reported in Zaremba's (1967) series of 34 patients. Of 30 patients in the Holt and Dickerson (1952) survey whose hands and feet were x-rayed, two thirds had cystic changes in the phalanges (usually found in the hands) and/or cortical thickening of the metatarsals (and less frequently of the metacarpals). Smith (1970) reported an incidence of cyst-like changes in the phalanges of 66 percent. Sixty percent of the cases in the present series showed phalangeal changes (largely cystic) and this incidence is in agreement with those cited in the preceding two series.

However, the frequently found metatarsal cortical thickening described by Holt and Dickerson (1952) was not noted in any of the ten patients of the present study. Zaremba (1967) did not report any metatarsal or metacarpal changes. He described thickening of the phalangeal cortices in 81.8 percent of the hands of 33 patients and in the phalanges of the feet in 34.4 percent of 32 patients. Also, Chao (1959) stated that he had not found any cortical thickening or cystic changes of the metacarpals, metatarsals, or phalanges on x-rays of the eight

patients in his study.

The rather distinct cortical thickening of about 75 percent greater than the average skull thickness noted in one (V. T.) of the ten propositi comprises an incidence for this finding of ten percent. The figure corresponds reasonably well to the five percent (3 of 66 patients) of cranial thickening reported by Lagos and Gomez (1967) whereas this condition was reported by Chao (1959) to be present in two of the eight patients (25 percent) of his series.

The absence of significant radiographic findings of the knees, hips and spine, except for the single case of marked scoliosis (D. P.), is consistent with other reports of radiographic findings although it should be noted that x-rays of these parts of the skeletal system have not been mentioned in most of the published reports. The only abnormality noted in a carpal or tarsal bone was the radiolucent lesion of the carpal navicular of the youngest propositus, the 14 year-old boy (R. H.). In none of the reviewed published articles that described x-ray findings was mention of any abnormality of the carpal or tarsal bones noted. This boy is occasionally difficult to manage and is often combative and frequently injured. Since the radiographic appearance of the carpal navicular lesion is typical of an established non-union of an old fracture, and since even in normal patients these fractures can occur without recognition of the responsible injury and often with relatively little symptoms, the writer feels that it is

probable that this lesion represents an old fracture rather than a distinct (and yet unreported) manifestation of tuberous sclerosis. However, the latter possibility cannot be entirely excluded.

To summarize the x-ray findings, the type and incidence of abnormalities noted in the radiographs of the skull, feet and hands are generally in agreement with several published studies. However, there are marked differences in the reported incidences of metacarpal and metatarsal abnormalities in the published surveys of patients with this condition. Whereas 60 percent of x-rays of hands of the ten patients in the present study show phalangeal changes (an incidence that is in approximate agreement with several published surveys), no abnormalities of the metatarsals were found. It is for the latter bones that the greatest divergence of reported x-ray changes is noted in the published surveys. The typical findings in the skull x-rays, when present (generally in more than half of the patients in the reviewed surveys as well as in the present study) are quite pathognomonic and can serve to confirm the diagnosis of tuberous sclerosis when it may be in some doubt. Two (A. B. and V. T.) of the ten propositi of this study whose dermatological findings were not typical of tuberous sclerosis had their diagnoses confirmed by skull x-rays that revealed multiple intracranial calcifications.

SUMMARY AND CONCLUSIONS

The population of the Oregon State Fairview Hospital and Training Center was investigated relative to the incidence of patients with tuberous sclerosis and the clinical, radiological and genetic aspects of the ascertained ten affected individuals were evaluated and analyzed. All of the living parents, whose whereabouts were known, of these ten index cases and a majority of the living siblings were personally examined and photographed by the writer.

There may well be cases of tuberous sclerosis of varying degrees of severity among the residents of Oregon that were not ascertained during the course of this study. However, the ten institutionalized and the two non-institutionalized affected individuals detected in this investigation would represent an incidence of about 1 per 175,000 residents in the state and this is in the range of several published reports (1:150,000 in England per Dawson (1954); 1:150,000 in Northern Ireland per Stevenson and Fisher (1956); and 1:170,000 among the approximately 4,000,000 Chinese in Hong Kong per Singer (1971)).

The proportion of sporadic or non-familial cases of 80 percent that was found in this study is consistent with the findings of seven other surveys accomplished in Europe and Hong Kong during the past two decades.

Of the two families identified to display parent-to-child transmission of this trait (in one case, from father to son and in the other case from mother to two daughters) the family of the boy (R. H.) is of interest in that this disorder has not--at least not yet--become manifest in any of the five siblings of the propositus. Possible explanations for this atypical frequency behavior (for a dominant trait that is generally conceded to display complete penetrance) have been considered, including the statistical probability of 1:32 that none of the affected five younger siblings would receive the defective gene on a probability basis of 1:2 for each conception.

Considering that the majority of cases of tuberous sclerosis appear to present the full triad of epilepsy, gross skin disorders and mental retardation with the resultant low fertility of these individuals, the finding of a minority of familial cases (20 percent) among institutionalized persons in this investigation is consistent with the biometric relationships required to maintain an approximately stationary incidence or "equilibrium" of this condition in the general population.

The dermatological manifestations of tuberous sclerosis among the ten propoiti of this study have been tabulated and the incidences of adenoma sebaceum, periungual and/or subungual fibromata, "shagreen spots," "leukoderma" or "white spots," and café-au-lait naevi were within the ranges of several published series. The relatively high (70 percent) incidence of periungual fibromata of the toes

and fingers is noteworthy as is the absence of typical adenoma sebaceum in two of the ten index cases.

Radiographic lesions were found to affect the brains and/or skulls of a majority (70 percent) of the ten patients and were found on examination of the skull x-rays of the two affected parents in the two familial index cases. Six of the ten propositi had abnormal, largely "cystic," changes of the phalanges demonstrable by x-rays. Again, no significant deviations from several published reports of x-ray findings in tuberous sclerosis were noted in this investigation. In both the radiographic and dermatological findings, the pattern of abnormalities was not obviously different in the familial cases as opposed to the sporadic or mutational cases of tuberous sclerosis.

There is no known specific medical treatment for the underlying ectodermal and mesodermal defect or defects that involve so many organ systems, but symptomatic and supportive measures can be helpful for some of the varied symptoms such as seizures and skin disorders. The skeletal lesions are usually asymptomatic and generally do not require treatment.

The genetic data obtained from the present study lend support to the accepted principles of genetic counseling for patients, parents and siblings of persons affected with either a mild form (a so-called "forme fruste" case) or with the "full-blown" triad of tuberous sclerosis. It is of practical importance to point out that this condition is probably

of a sporadic occurrence, a de novo mutation, if neither parent and none of the siblings display any of the clinical signs of this disease and thus subsequent children, or children of siblings of the affected individuals as the case may be, should have no higher risk of recurrence of tuberous sclerosis than is present for the general population. However, caution should be exercised to avoid overlooking relatively minor clinical signs in the parents or siblings; for example, in the present study, the mother of K. McQ. and S. McQ. was evidently unaware that she displayed any dermatological stigmata of this condition. Skull x-rays confirmed the diagnosis of tuberous sclerosis in a "forme fruste," with typical intracranial calcifications demonstrated, in this woman who has normal intelligence and who gave no history of any seizure disorder or other neurological abnormality. In questionable cases of this disorder, radiographic examination of the skull, hands and feet may be helpful in either confirming the diagnosis or in denying the likelihood that a given individual carries the trait.

This hamartomatous disorder is evidently ubiquitous among the races of the world and appears to be largely perpetuated by the occurrence of de novo or sporadic cases. Until much more information is learned regarding the causation and possible prevention of such so-called "point mutations," it will not be feasible to eliminate or even to effectively decrease the incidence of this extremely

disabling condition. However, careful genetic analysis of recognized cases should allow effective counseling of these families and should make possible the prevention of further transmission of this trait in the recognized at-risk population. Such evaluation should also provide a reasonable degree of reassurance for the parents and siblings of sporadic cases who are disturbed regarding the possibility that they may be carriers of this trait in a mild form and thus capable of transmitting it to subsequent children who might manifest the more severe forms of the disease.

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