sleeping lightly; viadril, 250 mg. (total, 650 mg.); ears now pink. N_2O/O_2 (3/1) begun; patient intubated. 11.45: on table, almost apnoeic; B.P. 170/70, pulse 120. 11.50: abdomen opened; fluid in peritoneum (stomach contents); carcinoma of stomach found with many secondaries in liver; B.P. 150/80, pulse 150. 12.05: operation very difficult on account of secondary involvement of mesentery, peritoneum, colon, etc., and adhesions between all these organs. Blood transfusion begun. The perforation could not be found. Three pints (1.7 litres) of fluid were aspirated from the peritoneum and the heart began to fibrillate (B.P. 100/60, pulse 118, respirations 36). Methylamphetamine hydrochloride, 30 mg., restored the B.P. to 120/80. At 12.30, the perforation not having been found, the peritoneum was closed. One-half was sutured with ease. The patient now began to tighten up. Suxamethonium, 50 mg., relaxed him at once. The operation was completed at 12.40; the patient was then pale, but pink, with a dry skin. The pulse was of good volume but fibrillating. Death occurred on the fifth post-operative day.

Very Satisfactory Anaesthetic: Case 12.—Woman aged 32. Operation: medial rectus recession. Premedicated with omnopon, $\frac{1}{2}$ gr., and scopolamine, 1/150 gr. B.P. 110/70. At 9.59, viadril, 750 mg. (B.P. 130/65, pulse 120). 10.02, asleep. 10.04: N_2O/O_2 (3/1) begun. 10.06: intubated. 10.12: patient nearly apnoeic (B.P. 115/60). 10.20: breathing regular and of adequate volume. 10.25: operation completed, N_2O/O_2 stopped; coughed immediately. At 11.00 the patient was seen in the ward, sleeping. Easily aroused, she asked—although the conjunctival sac of the affected eye was filled with blood—“Have I been done?” and when reassured said, “Lovely; I’ve been asleep.”

Unsatisfactory Anaesthetic: Case 6.—Man aged 75. Operation: herniotomy and repair; orchidectomy. A very fit, well-built man who appeared younger than his years. B.P. 180/80. At 11.04, viadril, 750 mg. 11.12: patient was “just asleep,” N_2O/O_2 (5/1) begun. 11.17: not relaxing; viadril, 250 mg. 11.22: unable to intubate. 11.30: viadril, 250 mg. 11.35: intubated; still coughing. 11.40: relaxing (B.P. 100/60). 11.45: methylamphetamine hydrochloride, 20 mg. 11.48: patient still coughing (B.P. 110/70). 11.50, N_2O/O_2 still running at 5/1; patient resented cord being pulled. 11.53: orchidectomy complete; operation proceeding with difficulty. 12.10: gallamine triethiodide, 80 mg. 12.15: B.P. 120/80, pulse 100. 12.25: operation completed, neostigmine, 25 mg., atropine, 1/100 gr. (0.65 mg.), patient began to cough immediately. N_2O cut off.

On consideration of Case 6 it was thought that the viadril when being injected into the tubing of the drip was going up into the saline bottle. As a result the routine was instituted of closing off the tubing by means of a clamp whilst the injection was actually being given, a few millilitres at a time; stopping the injection; opening the clamp to dilute the viadril; then repeating the process as often as necessary until the full dose had been given.

Summary

A steroid, viadril (21-hydroxypregnane-3:20-dione sodium succinate), has been used as an anaesthetic in 19 cases. The pharmacology of the drug is discussed and the mode of administration described. Usually premedication was with omnopon and scopolamine, and maintenance by nitrous oxide and oxygen. In some cases relaxants were also given.

Viadril anaesthesia resembles normal sleep; relaxation is fairly good and bleeding usually much reduced. The patient is fully awake in an hour or so after operation, feeling well and without pain. Hormonal effects are absent and vomiting is rare.

Disadvantages are the slowness of induction and the risk of thrombophlebitis in the injected arm. Measures to combat these are suggested.

Details of the 19 cases are tabulated, and three case histories given to emphasize special points.

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FAMILIAL TUBEROUS SCLEROSIS

BY

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Tuberous sclerosis was first diagnosed in 1880 by Bourneville, who described the case of an epileptic imbecile who died of the disease; and the disease was named after the discoverer. The fully developed disease is manifested classically by infantile epilepsy, mental defect, and the characteristic facial eruption of adenoma sebaceum. It is a rare hereditary disorder of tissue growth, in which many different tissues may be affected and many varying clinical syndromes found. It may be familial, and such an afflicted family is described.

Family History

The composition of the family is shown in Fig. 1. The family is mainly domiciled in Malta, and is compounded of mixed Anglo-Maltese racial stock. The heredity is com-

FIG. 1.—Family tree, showing four members affected with tuberous sclerosis. The ages of living members examined are shown. The grandfather married his first wife's sister.

plicated by the two marriages of the grandfather, who married his deceased wife's sister. The four patients affected by tuberous sclerosis are all alike, showing the typical facies, and anxious family inquiry is made whenever a child is born into the family. All other members of the family are of normal facial appearance and are reputedly healthy.

Case 1

This young girl died in convulsions at the age of 14 years in 1935. Zahra Neumann (personal communication) states

that the girl had suffered all her life from major epilepsy, and that the attacks increased in severity with the onset of puberty. She had a developmental asymmetry of the face, but did not show the lesions of adenoma sebaceum. She suffered also from congenital heart disease, and from retarded mental and physical development. No post-mortem examination was made, so the diagnosis of tuberous sclerosis as the cause for the congenital epilepsy is inferential.

Case 2

This patient, a woman of 39, is the mother of five children, including Cases 3 and 4. She is the half-sister of Case 1, having the same father, and their respective mothers being siblings. As a child she suffered from major epilepsy, and in early adult life from minor epilepsy. She was slow and late in development and was backward in her speech, and for many years she had a bad stammer. She was always shy and retiring when young on account of her peculiar skin condition and stammer. She has never suffered from any other illnesses.

FIG. 2.—Case 2. Photograph showing pronounced adenoma sebaceum.

When examined her face showed a pronounced degree of adenoma sebaceum (Fig. 2). The lesions covered the whole face and forehead anteriorly. They were largest

around the naso-labial folds, where some of them were of the size of a split-pea, and others protruded as pedunculated excrescences above the skin. They were discrete and pinkish in colour. They diminished progressively in size peripherally, until they could be picked out as small elevated pinheads above the skin, which contained telangiectatic capillaries.

The adenoma sebaceum had been present as long as she could remember, and the lesions had increased imperceptibly in size over the years. Some of the larger adenomata with well-developed pedicles had been treated by the constriction of horse hair around their bases.

Physically she is now a very healthy woman, with no other congenital signs. There are no associated congenital abnormalities, and radiographs of the skull and extremities and of the lung fields are all normal.

Mentally she presents as a woman of average intelligence, alert and lively, and quick in her responses to novel situations or to formal tests. She is stable and well balanced, runs her house and family affairs very capably, and can plan her future course of action ahead. She has a normal pleasant personality, and is an excellent mother to her five children.

Case 3

This patient, a schoolboy aged 13, is the second child of Case 2. He was a full-term infant of a normal and easy birth, but his mother could tell at birth that he was going to have "her kind of skin." He developed well until he was 9 months old, when he began to have major epileptic fits. These fits were very violent and exhausting, and occurred about once a fortnight for two years. He frequently cut and bruised himself during these convulsions, and was admitted to hospital on several occasions for suture of scalp injuries. He never received any sedative or anti-convulsant therapy for his epilepsy, but gradually after he

was 3 years old his seizures became less intense and less violent, dying away completely at the age of 4. He has been completely free from all epileptic attacks for nine years.

After the onset of epilepsy he regressed mentally and developmentally and became grossly retarded. He was unable to walk until he was 5½ years old, and he could not frame a coherent sentence until he was 7. But since that age he has developed with increasing rapidity. He is now in the fourth form at school and participates keenly in normal school activities. He is bilingual and can read and write English and Maltese.

Physically he now presents as a healthy active schoolboy of slight build and pre-pubertal development. He has multiple small lesions of adenoma sebaceum covering the nose and cheek and beard areas. The lesions are slowly becoming more evident, and increase in size after any trauma. He has various traumatic scars on the forehead, and occipital alopecia where an infected dermoid cyst was excised at the age of 6 years. He also has an area of alopecia in the right parietal region, where the skin is thickened and lustrous. He has no other physical or congenital abnormalities.

Psychologically he is a quiet and shy boy, who speaks English with a pronounced Maltese intonation. As Maltese is his "natural" language, exact reliance cannot be placed upon intelligence testing, but his mental age is estimated to be in the region of 8½ years (chronological age 13½ years).

Case 4

This boy aged 8½ years is the youngest son of Case 2. His mother was well during the pregnancy and free from virus infections, and had a normal easy delivery. He weighed 7 lb. 4 oz. (3.3 kg.) at birth, and was breast-fed for six months. He was apparently normal at birth, and his mother thought his facial appearance was normal. All the early milestones of physical development were passed normally; he walked when he was 18 months old; he was talkative, and spoke many common words.

He developed petit mal at 3 years, and had two or three attacks daily for a period of nine months. In an attack he would suddenly stand quietly, run to a chair or bed, stare into emptiness, and then make repeated swallowing and shivering movements; if he was approached by his parents he would push them away. Each episode lasted about two minutes, and was followed by an unnaturally deep sleep for at least two hours. There was no tongue-biting or involuntary micturition. He was treated with sedation by phenobarbitone tablets for three years. Five years have elapsed since his last attack. He started to develop the early lesions of adenoma sebaceum when he was 3 years old, coincident with his attacks of petit mal.

At a recent examination he had a pink raised facial rash of butterfly pattern distribution, with discrete red pin-point spots especially prominent by the naso-labial folds. His physical development was normal, his vision and hearing were good, and there were no abnormal physical signs in any system. Radiological examinations of the skull, hands, and lung fields were normal.

His speech was normal until the onset of his epilepsy, but from then onwards he retrogressed steadily. He gradually spoke less and less, until he appeared to his mother to have forgotten how to speak. It was the inability to talk at the age of 8½ years that induced his mother to seek medical advice and led to the whole family coming under review. He then had a vocabulary of about 40 words, all of them common objects which he could recognize in life or in pictorial representation, and to which he could ascribe the correct name; and for these words his phonation and articulation were distinct. But for the rest of the time he made unnatural crowing noises and jabbered gibberish. He understood and obeyed simple commands, such as "clap your hands."

In his habits he is cleanly and his sphincteric control is good. He always dresses himself and manages to use a

knife and fork capably. He is placid and good-natured in temperament, without any psychotic tendencies, nightmares, or tantrums. He has never been to school or undergone any special or institutional training. He lives at home, and each morning he performs much of the routine housework, the sweeping and dusting, and drying of dishes, and does the shopping and fetches the groceries. On occasion he exhibits a striking form of stereotyped movement, a compulsive obsession to moisten objects with saliva and polish them vigorously, and other forms of repetitive hand and finger play. In summary, his vocabulary and behaviour and responses to requests are similar to those of a mongol child, and probably correspond with a mental age of about 2 years.

The remaining three children in the family are all unaffected by tuberous sclerosis. The eldest son is lively and intelligent and well developed, and is the hope of the family. The twin girls are bright self-possessed young ladies of good average intelligence. They all speak English and Maltese with equal facility.

Discussion

Tuberous sclerosis is a rare disease, but with increasing recognition of its salient features and clinical manifestations it is being diagnosed more frequently. The incidence in America has been estimated at about 1 in 500,000 in the general population (Ross and Dickerson, 1943). In London the incidence of tuberous sclerosis with mental defect is about 1 in 300,000, and the milder forms without mental defect probably occur equally often (Dawson, 1954). All surveys show an approximately equal sex incidence. The family here reported contains the first cases diagnosed in Malta.

Tuberous sclerosis is a congenital disorder in which tumour-like masses are found in large numbers in many of the tissues of the body. These lesions are not confined to tissues of a single germinal layer, for the abnormalities of skin and brain are ectodermal and those of the kidneys, heart, and lungs are mesodermal in origin. The lesions are remarkably non-progressive and show little tendency to grow in size during life. The cutaneous lesions of adenoma sebaceum may not be apparent at birth, and often become prominent only when the normal adolescent development of the sebaceous glands takes place; but after puberty they remain static and may even regress slightly. There is no evidence that these multiple tumours could be caused by a placenta-passing virus or that there are any exogenous aetiological factors. Tuberous sclerosis is a true tissue dysplasia, beginning in the earliest months of foetal life.

Dickerson (1951) has published a complete review of the familial occurrence of tuberous sclerosis. When a family is affected cases may be found in different generations, and many members may be sufferers. In one family which he reported there were eight cases; and in a family subsequently reported by Dawson (1954) a mother and 9 of her 12 children were affected, most of them suffering from mental defect and epilepsy.

The precise pattern of inheritance has been investigated by Penrose (1938), who concluded that the disease was transmitted by a dominant gene. The great clinical variation in the heterozygous state he explained by the existence of modifying genes in the same zygote, which might lead to abortive forms or might even completely mask the dominant gene. The homozygous state has never yet been reported.

Half of the patients suffering from tuberous sclerosis have no relatives at all affected by the disease. These cases must have arisen by mutation, and if it were not for the high mutation rate the disease would have died out rapidly owing to its dysgenic effect.

One interesting factor in the heredity of such a pleomorphic disease is that in many families the pattern of the disease remains remarkably constant. Thus the prognosis for the younger children and infants may be assessed and evaluated by a careful examination of any affected relatives, and all members of the family should be sought out and

examined. In addition to this main hereditary pattern of the classic disease, the inconstant and rarer manifestations of tuberous sclerosis are also hereditary. Particular families have been described in which such features as nail-bed tumours, cystic phalanges, retinal tumours, shagreen skin patches, renal tumours, cystic lungs, and laryngeal polyps have all proved hereditary (Dickerson, 1951). In each family the pattern of transmission may be complicated by formes frustes in apparently unaffected members.

The diagnosis of tuberous sclerosis in a florid case of infantile epilepsy and mental defect should become obvious when the lesions of adenoma sebaceum appear. But it has now become apparent that tuberous sclerosis is a very pleomorphic disease, with lesions in many different structures and with diverse modes of presentation, which often render diagnosis difficult. Patients may present with epilepsy, with mental retardation in a child, with dyspnoea in an adult, with swellings in the loins, with facial lesions, or in many other different ways. Careful examination will almost always show other stigmata of tuberous sclerosis, although occasionally the diagnosis may be made only by finding relatives with adenoma sebaceum or other conclusive features of the disease. Thus when an adult presents with dyspnoea or spontaneous pneumothorax, and is found to have radiographic changes of honeycombing of the lungs, or when a child presents with haematuria and abdominal pain, and is found to have renal tumours or polycystic kidneys, then tuberous sclerosis must be considered in the differential diagnosis.

Confirmatory evidence is most likely to be found in the skin or the eyes, or by radiographic examination of the skull and extremities. In the skin the commonest and most obvious stigma is adenoma sebaceum. Other common diagnostic features are the patches of thickened shagreen skin, often 3-4 in. (7.5-10 cm.) in diameter, located usually in the lumbar region, and multiple subungual fibromas and haemangiomas. Ophthalmoscopic examination often discloses the retinal phakomas which are seen as several small round white plaques, about half the size of the optic disk. Plain x-ray examination of the skull reveals in 80% of cases multiple areas of low-density intracranial calcification, and scattered sclerotic plaques can be seen in the cranial vault in 40% of cases. Holt and Dickerson (1952) have demonstrated characteristic changes in x-ray films of the hands and feet in 66% of cases. These consist of localized cyst-like areas of bone destruction in the phalanges and irregular periosteal new bone formation along the shafts of the metacarpal and metatarsal bones. Careful examination of individual cases of tuberous sclerosis will often reveal other types of skin lesions, visceral tumours, or congenital abnormalities, but none of these are constant enough to confirm a clinical diagnosis.

The prognosis in tuberous sclerosis is poor, but is not as gloomy as is usually stated. Russell Brain (1951) declares that "most patients finally reach a mental state comparable with that of an advanced stage of schizophrenia. A few remain stationary at the mental level of a low-grade mentally defective patient. Death occurs early, usually before the age of 20, although some patients survive into the third and fourth decades." This is an accurate and succinct account of the course of the classical disease, and is especially true of those patients in mental deficiency institutions; but it is not a true picture of the disease as a whole, where increasing experience has shown that mild forms of the disease occur as often as the severe forms (Dawson, 1954). Mental defect probably occurs in only half of the cases, and some patients with retarded development improve surprisingly with adolescence. Although probably most tumours of tuberous sclerosis are present at birth, they often do not manifest themselves until later in life, while the pulmonary form of the disease always presents in adult life.

The prognosis in any afflicted patient may be assessed more accurately by a careful investigation and study of

other members of the family. This will often bring to light several undiagnosed cases, and, as the disease in any one family tends to breed true to type, the management of the individual is assisted by further knowledge of the family.

Summary

Tuberous sclerosis is a rare disorder of tissue growth, in which many different tissues may be involved. It is hereditary and may be familial: an Anglo-Maltese family is here described in which four members were affected. The classic descriptions of the disease, to which the name epiloia was given, concentrated on the symptom triad of infantile epilepsy, mental deficiency, and adenoma sebaceum of the face, and emphasized the bad prognosis. But only about half the sufferers exhibit the disease in this fully developed form, and milder forms with good prognosis occur just as often as the severe ones. The disease is very pleomorphic, and other common manifestations are renal or retinal tumours, and cystic lungs and phalanges. The disease is probably transmitted by an incompletely dominant gene, and in any affected family the pattern of the disease remains constant. Whenever tuberous sclerosis is suspected or diagnosed in a patient the remaining members of the family should be studied.

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THE BLOOD GROUPS IN PEPTIC ULCERATION

BY

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Evidence continues to accumulate that there is a distinct relationship between the ABO blood groups and certain diseases. The incidence of Group A has been shown to be unduly high in subjects suffering from pernicious anaemia (Buchanan and Higley, 1921), carcinoma of the stomach (Aird *et al.*, 1953), and bronchopneumonia in infancy (Struthers, 1951). Group O has been found to occur with excessive frequency in persons suffering from peptic ulcer (Aird *et al.*, 1954). It has been pointed out (Clarke *et al.*, 1955) that in the latter disease the Group O excess is confined to duodenal ulcer subjects. The present communication on the relationship of the ABO blood groups to peptic ulcer was prompted by previous investigations relating to patients in selected English hospitals. In Scotland, important differences exist both in the prevalence of peptic ulcer in general and in the geographic distribution of the ABO blood

groups. Duodenal ulcers, as opposed to gastric ulcers, are between three and four times more frequent in Glasgow than in London (Doll, 1952); Group O is also present in a slightly greater proportion of the population than in England, Group A being correspondingly diminished.

This communication reports the results of a survey, carried out in Glasgow, into the ABO Rh(D) blood-group distribution in 2,059 patients suffering from peptic ulcer. In 276 of these subjects we have also investigated the maximum acid output of the stomach in relation to the above blood groups.

Collection of Data and Controls

The survey was carried out in two adjacent Glasgow Hospitals. The peptic ulcer clinic of the Western Infirmary supplied information relating to 1,588 cases, collected over the period 1946-55. Data concerning a further 471 subjects were obtained from the Southern General Hospital for the years 1952-5. Both in-patients and out-patients were included. The following items were recorded for each patient: site of ulcer, method of diagnosis, occurrence of previous acute complication, ABO group, sex, age, and place of residence. In 1,606 subjects the rhesus group was also noted.

It is obviously essential in a study of this type to ensure accuracy in diagnosis and in blood-grouping methods. Our criterion of diagnosis in 1,177 cases has been visualization of the ulcer at operation. In the remaining 882 patients the diagnosis has been accepted when a chronic peptic ulcer has been demonstrated by barium-meal examination and has confirmed a presumptive clinical diagnosis. These two groups of patients have been subsequently analysed separately, for we have been interested to discover whether any difference in blood-group frequency existed between patients diagnosed by x-ray examination and treated medically in the first instance, and those, presumably cases of a more severe nature, who required operation at some stage of the disease. The blood groups of the ulcer patients were determined at the Regional Blood Transfusion Centre in Glasgow for the Western Infirmary cases, and in the pathology department, Southern General Hospital, for patients from that hospital. The blood groups were specially determined for this investigation, freshly collected venous blood specimens being used. The ABO group was established by testing both cells and serum. The Rh(D) group was established, using two potent saline agglutinating sera. The control series was provided by 5,898 consecutive new registrations of blood donors at the Regional Blood Transfusion centre made over the period 1952-5. According to their location, the ulcers have been classified as duodenal, including juxtapyloric; gastric; combined gastric and duodenal; and stomal.

An explanation of the excess of Group O in duodenal ulcer patients recorded by previous authors may be that there is an association between possession of blood Group O and excessive output of acid by the stomach (Koster *et al.*, 1955). We have investigated this possibility. The augmented histamine test (Kay, 1953) was carried out on 276 patients in whom the diagnosis of peptic ulcer and the ABO Rh(D) blood groups had previously been established.

Results

The basic data are recorded in Table I. The percentage increase of Group O over controls for each subgroup of cases is indicated in Table II. Although an increase is recorded in each instance, subsequent analysis reveals that only in some of the subgroups is this increase of statistical significance. Certain comparisons have been made within the material, subdividing it in a variety of ways. The primary subgrouping has been according to the site of the ulcer. In addition, our aim has been to ascertain whether clinical severity or site of the ulcer is mainly responsible