Clinico-pathological Conference

TWO CASES OF TUBEROSE SCLEROSIS

Demonstrated at the Royal Alexandra Hospital for Sick Children, Brighton

Thursday, December 8, 1960

Chairman: Dr. E. D. Scott, O.B.E., M.D., M.R.C.P.

Hon. Consultant Physician, Royal Alexandra Hospital for Sick Children

DR. SCOTT: The two children to be considered tonight are alive and well and, indeed, will be presented during the course of the conference. Will Dr. Mann now introduce the first case, please?

The first patient was then introduced by Dr. Mann.

DR. T. P. MANN: Sally R., aged 8 years, was first admitted to the Royal Alexandra Hospital for Sick Children on December 22, 1953, at the age of 15 months with convulsions and was found to have a staphylococcal pneumonia affecting the right middle lobe. This diagnosis was largely based on the radiological appearances which will be demonstrated by Dr. Rubin in a moment. The day after admission she was found to have a left hemiparesis, which has since persisted. Various drugs were tried for her pneumonia—sulphadimidine, penicillin, chlortetracycline, terramycin—and she eventually responded dramatically to erythromycin, which had just become available in 1953. The *staphylococcus aureus* isolated from her throat swab was resistant to all antibiotics in use at that time, but sensitive to erythromycin.

She was in hospital for three months recovering from this severe illness. Some two months after admission she was noted to have extra-systoles and the ECG showed these to be supra-ventricular in origin. About this time on two separate days she became unconscious with twitching of the right limbs and phenobarbitone and phenytoin were given for a short period. I should perhaps mention, in view of more recent events, that abdominal distension was commented upon in the notes during her convalescence—the entry says ‘habitual distension’—and this was thought to be related to chronic constipation.

Seven months after discharge from hospital she had brief epileptic seizures on two successive days. Convulsions have not recurred since then (October 1954).

In May of this year Sally was asked to attend our newly created Cerebral Palsy Clinic because of her hemiparesis. She had made excellent

progress in the intervening years and was walking well, a point we were able to confirm.

On examination: Positive findings and significant negative ones in this child, now aged 7 years 8 months were as follows: She had left hemiparesis, her left limbs being smaller than her right. There was astereognosis affecting the left hand and two-point discrimination was faulty here. Her fundi and visual fields were normal. It was at this examination that the presence of disseminated and variegated skin lesions was first noted, the most striking finding being tell-tale facial adenoma sebaceum in the typical butterfly distribution (Fig. 1). Over the left forehead was a so-called shagreen patch and in the left nasal labial fold a flame-shaped naevus which had been treated over a period of years with Thorium X varnish without improvement. Over the trunk there were several small flat pigmented areas and a number of raised pink-fawn-coloured lesions of varying size, the largest being a plaque below the left scapula. There was a single depigmented patch over the antero-lateral aspect of the right arm. The facial adenoma sebaceum was of the ‘Pringle type’, each little warty papule having a telangiectatic element. The chin was affected as well. Another noticeable feature at this examination was gum hypertrophy, there being several pedunculated gingival excrescences in the region of the incisor teeth (Fig. 2); beneath these lesions the enamel was eroded. I should mention that phenytoin had not been taken for six years.

In August of this year Sally was presented at one of our quarterly Child Neurology Clinics which hold in Brighton in association with Guy's Hospital. Professor P. E. Polani agreed with the diagnosis of tuberose sclerosis and drew our attention to a large right-sided renal mass. A few days later after radiological assessment a right nephrectomy was carried out by Mr. S. H. C. Clarke.

Since the operation Sally has made good progress and it is our impression that the gum hypertrophy and the individual lesions over the cheeks and chin

FIG. 1.—Case 1—Sally R. Adenoma sebaceum.

FIG. 2.—Case 2—Sally R. Gum hypertrophy.

FIG. 3.—Case 1—Sally R. Retrograde pyelography.]

have regressed. In the latter situations the vascular component of each papule now seems less noticeable.

A final point is that there is no family history of tuberose sclerosis or its various *formes frustes*.

Investigations

Radiology (Dr. J. Rubin). A chest X-ray at the beginning of January 1954 showed consolidation of the right middle lobe, within which there were two large rounded translucent shadows due to either cavitation or air cysts. A few days later the consolidation was much denser and the translucent shadows had fused into one large cavity measuring $1 \times 1\frac{1}{2}$ cm., the appearances being those of abscess pneumonitis, such as is seen in staphylococcal infections. Subsequent serial radiographs showed slow resolution, but by August 1954 only minimal residual changes were present.

A plain film examination of the skull in January 1959 revealed no abnormality.

Intravenous and retrograde pyelography were performed on August 5, 1960. The mass discovered in the abdomen the previous day was confirmed to be a huge space-occupying tumour of the right kidney. The renal pelvis was grossly deformed and elongated and the enlarged calyces separated and clubbed (Fig. 3). The right ureter was displaced downwards and forwards by the right renal mass. The left kidney appeared to be

within normal limits. Both kidneys were functioning. X-ray examination of both hands and feet showed no bony changes. A recent chest film was considered normal, the high position of the diaphragm due to the abdominal mass probably accounting for the slight apparent broadening of the heart shadow.

Electroencephalography (Dr. W. A. Kennedy). A resting record showed absence of alpha activity over the right hemisphere with a spike focus in the right Sylvian region. A Secondal record confirmed the presence of the spike focus and showed gross reduction of the barbiturate-induced fast activity throughout the right hemisphere. These records suggest a macroscopic lesion of the right hemisphere which is presumably related to the illness at 15 months and unrelated to the tuberose sclerosis.

A recent ECG was normal and there was now no evidence of arrhythmia.

The other day Sally was examined by Mrs. J. M. Williams in the Department of Psychological Medicine at Guy's Hospital and found to be of average intelligence. In her report she says: 'This little girl found most ingenious ways of overcoming the difficulty of having one almost useless hand. She showed remarkable persistence and is indeed a "trier" '.

Pathology

DR. R. I. K. ELLIOTT: The renal tumour removed at operation was a large ovoid mass measuring $15.5 \times 10 \times 9$ cm. and weighing 1,030 g. Cut open, it was found to consist of yellowish-pink tissue traversed by grey gelatinous trabeculae; the texture was soft, almost brain-like, and there was an area of hæmorrhagic breakdown 3 cm. in diameter, eccentrically placed in one pole. The tumour was enclosed in a firm capsule which on close inspection proved to include a narrow zone of greatly thinned renal tissue, as though the tumour had arisen in the substance of the kidney and expanded to force it outwards. Medially, this zone was thicker and within it deformed calyces and a much distorted, thinned and elongated renal pelvis could be identified. There was no evidence of direct infiltration of renal tissue by the tumour; a tenuous, but distinct, fibrous capsule separated the two throughout.

In sections the tumour has a remarkably uniform pattern of cords and rounded masses of cells with abundant granular cytoplasm, separated only by vessels and delicate membranous septa, producing an appearance resembling liver. The picture is that, in fact, of an unusually large, but histologically benign, renal tubular adenoma. Significantly, however, close examination shows that other abnormalities are present. In the thinned renal tissue are scattered small collections of adipose cells, like

FIG. 4.—Case 1—Sally R. A small lipomatous area in the renal cortex (H. & E. $\times 50$).

FIG. 5.—Case 1—Sally R. The renal adenoma showing the capsule and a group of foam cells (H. & E. $\times 150$).

tiny lipomata (Fig. 4); and not infrequently small retention cysts occur. In the tumour capsule small bundles of smooth muscle cells occur amongst the collagen, and there are blood vessels, often disproportionately large and numerous. In the tumour itself similar collections of vessels and smooth muscle cells are found in the trabeculae, and there are also groups of foam cells standing out sharply against the adenomatous tissue (Fig. 5). Sometimes, too, the adenomatous areas show foci of more irregular pattern, with marked nuclear variations, or foamy distension of the cytoplasm. Although these changes pass almost unnoticed on casual inspection, they are important because they serve to link this tumour with the commoner types of renal lesion found in tuberose sclerosis.

At the operation the opportunity was also taken of removing one of the gum lesions, which proved to be a mushroom-like pedunculated nodule on a short stalk. Sections show marked hyperplasia of the covering squamous epithelium, but the main bulk of the nodule is composed of vascular fibrous tissue somewhat resembling a granuloma pyogenicum, and infiltrated by lymphocytes and plasma cells which are most thickly distributed in the central fibromatous area. There are no glandular inclusions and no giant cells.

DR. SCOTT: Will Dr. Cree please present the second case?

The second patient was then introduced by Dr. Cree.

DR. JEAN CREE: Paul M., aged 6 years, was born normally at full term. Apart from possible whooping cough at the age of one month, he behaved normally until he was 8 weeks old, when he was admitted to the Royal Alexandra Hospital for Sick Children because of convulsive movements which affected the left limbs predominantly. During the first 48 hours spent in hospital he

had some 20 such attacks, each lasting one to two minutes, all more marked on the left side. There was no true loss of consciousness during these episodes. Examination at this time revealed no abnormality once the seizures were controlled. Lumbar puncture yielded a clear normal fluid. X-ray of the skull was normal. Phenobarbitone was commenced and he had only one convulsion in the next six months, which led to an increase in the dosage of anti-convulsant. At the age of 14 months he started having frequent brief grand mal attacks, when he would sit and stare for about half a minute. There would be no falling and no convulsive movements. These attacks were controlled with the help of phenobarbitone, Epanutin and Diamox.

His early milestones seemed normal, but as a toddler he became hyperactive with difficult behaviour. At the age of 33 months it was noted that his speech was retarded, but his development seemed otherwise within normal limits. At the age of 4½ years he exhibited very difficult behaviour and was hyperkinetic. Examination revealed no abnormal signs, but he was now definitely retarded.

In June of this year he had a generalized convulsion, following which he was unconscious for several hours. His treatment was now changed to Mysoline 250 mg. mane, Epanutin 30 mg. b.d., and Diamox 125 mg. mane. He was now 5½ years old and was found by the educational psychologist, Mr. Gordon Whitehead, to have a mental age of 4 years 7 months, giving an I.Q. of around 80.

In October of this year a rash over the face typical of adenoma sebaceum was noticed for the first time in the medical outpatient clinic. The eruption had the same distribution as described

FIG. 6.—Two small areas of intra-cranial calcification.

in the first case, although it was less obvious. Other skin lesions were as follows:

A shagreen patch over left forehead, near the hair line.

Three small discrete nævoid areas all less than $\frac{1}{2}$ cm. in size over left chin and side of face.

Small raised light fawn-coloured papules over right forehead, both eyelids and back of trunk.

Some 20 or more areas of vitiligo over the trunk, the largest being in the right hypochondrium and measuring approximately $1\frac{1}{2} \times \frac{1}{2}$ in. A few similar patches over both arms and one in the left popliteal fossa.

A *café-au-lait* spot to the right of the umbilicus and another in the sacral region.

A few deeply pigmented spots over the left side of abdomen.

A streak of white hair over the left side of the scalp.

He was admitted recently to the Children's Hospital for observation and investigation, which included skin biopsy of the facial lesion. In the ward he was found to be a restless, noisy but likeable child. His central nervous system appeared normal. No epileptic attacks occurred. His eyes were examined by Mr. Thorne Thorne, who reported a small central cataract in the right eye, but both fundi were healthy. Incidentally, Paul's parents are intelligent healthy people and he has two brothers aged 9 and 11 years who are normal. There is no family history of epilepsy, mental retardation, psychotic disturbances or skin disorders.

Investigations

Radiological (Dr. J. Rubin). X-ray examination of the skull in 1955 revealed no abnormality. Recent plain films of the skull showed two small areas of calcification rather central in position above the pituitary fossa and best seen in the lateral projection (Fig. 6). No bone changes were evident. A ventriculogram (Mr. F. L. Davies) was not entirely satisfactory in precisely localizing the position of the calcifications, but there was some suggestion that they were in the soft tissue projecting up into the floor of the left lateral ventricle, just posterior to the foramen of Munro. There was no evidence of hydrocephalus, but it was difficult to exclude some deformity of the right lateral ventricle.

IVP and chest X-ray examinations were negative.

A recent ECG showed right bundle branch block. An EEG two days ago was normal.

Pathology

DR. ELLIOTT: This skin biopsy, taken by Mr. H. Elliott-Blake from the naso-labial fold, is very satisfactory, except in one particular: there is no undue prominence of vessels. Although the rash on the cheeks in this boy appears telangiectatic, clearly in this fold it was not. Apart from this, the characteristic changes of tuberose sclerosis are well shown.

One of the striking features of the rash is the presence of raised nodules. They are formed by hyperplastic overgrowth of a group of dermal

FIG. 7.—Case 2—Paul M. Adenoma sebaceum. Biopsy of naso-labial fold (H. & E. $\times 22$).

papillæ, coupled probably with some tissue œdema. The overgrowth is affecting exclusively the fibro-vascular core of the papillæ; the sebaceous glands, which lie at a deeper level, play no part in it.

This is an area of the skin in which, in a normal person, large and prominent sebaceous glands would be expected. In this boy the glands are not prominent; this is because the individual glands are small; but there are many more of them and they cluster about the follicles like bundles of grapes (Fig. 7). One of the follicles, opening amongst the hypertrophied papillæ, is much dilated and contains several lanugo hairs instead of the normal one or two. Others, at a deeper level, are immature and have become dilated to form small cysts.

Discussion

DR. SCOTT: Will Dr. Mann now open the discussion by giving us a brief historical review of tuberose sclerosis?

DR. MANN: Von Recklinghausen was the first to describe tuberose sclerosis in its cerebral form. In 1862 he reported the co-existence in a stillborn baby of sclerotic brain lesions and myomata of the heart muscle. His account reminds us that we are dealing with a developmental disorder.

The title 'tuberose sclerosis', which nowadays is accepted as the generic name for the various forms of this diffuse disorder, was coined by Bourneville in 1880 because of the potato-like appearance of the cerebral lesions. He was the first person to give a comprehensive description of the disease. In a series of communications between 1880-98 he reported the association between sclerotic brain foci at autopsy and mental subnormality and epilepsy in life; also the frequent occurrence in these cases of renal tumours of a primitive mixed form. Bourneville also noted

the co-existence of facial adenoma sebaceum in cases of tuberose sclerosis. The earliest descriptions of the facial eruption are usually attributed to Balzer and Ménétrier (1885) and Pringle (1890), but it appears that it was Rayer who, as long ago as 1835, first described the rash (Dawson, 1954), and in 1851 Addison and Gull at Guy's Hospital were undoubtedly familiar with this skin condition. Incidentally, two varieties of adenoma sebaceum are recognized today: the 'Pringle type', in which telangiectatic elements are prominent, as in these two children, and the 'Balzer type', which is largely avascular.

Bourneville's descriptions were given from a pathological point of view and it was not until the turn of the century that the full clinical syndrome as we know it today emerged so that diagnosis in life became feasible. About this time, too, atypical forms of tuberose sclerosis became defined, often occurring amongst the relatives of cases with the classical disease.

Mr. S. H. C. CLARKE: As the urologist I am only concerned with the renal aspects of this case.

Firstly, should this kidney have been removed? When I saw this child it was difficult to know how long the tumour had been present. It had only been noticed a few days previously and therefore malignancy had to be seriously considered. In retrospect, I wonder if nephrectomy was the correct treatment. The tumour was benign and on studying the literature (Moolten, 1942; Inglis, 1954; Le Brun, Kellet and Macalister, 1955; Eikenboom, 1957; Weaver and Carlquist, 1957; Beck and Hammond, 1957; Taylor and Genters, 1958; Perou and Gray, 1960) all the cases reported have been benign, although Moolten (1942) refers to three cases reported in earlier literature as having metastases. Although most authors have removed the tumours, malignant change is rare. Taylor and Genters (1958) and Beck and Hammond (1957) treated cases conservatively, even after spontaneous hæmorrhage, with very good results. They are frequently bilateral (Perou and Gray, 1960). In this case, although the pelvi-calyceal pattern is grossly deformed, the kidney has good function, as seen on the five-minute intravenous pyelogram. If she develops a hamartoma in the remaining kidney, it might shorten her life. On the other hand, it was a large tumour, extending from under the right costal margin to below the iliac crests and from the right loin to the left of the umbilicus, and who knows what effect it was having on her? There is a high incidence of spontaneous hæmorrhage (Le Brun *et al.*, 1955; Taylor *et al.*, 1958). I should be very interested to hear what Professor Polani thinks. In the absence of tuberose sclerosis the difficulty is in diagnosis.

Next, I should like to point out that cases of

tuberose sclerosis do not necessarily die in adolescence, some of the reported cases were in women in their forties (Beck *et al.*, 1957; Taylor *et al.*, 1958). Hamartoma of the kidney can occur without signs of tuberose sclerosis (Eiken, 1957; Le Brun and Kellett, 1955; Taylor and Ginters, 1958; Perou and Gray, 1960) and need not be apparent in childhood, one reported case being in a man of 68 (Eiken, 1957).

Finally, I should like to take this opportunity of thanking Dr. Mann very much for asking me to take part in the discussion and also for asking me to deal with the case. I hope the ultimate outcome will be happier than we all fear.

MR. B. THORNE THORNE: Ocular signs of tuberose sclerosis are rare. Critchley and Earl in their account (1932) found one case showing ocular tumours in 29 cases of generalized tuberose sclerosis.

Ocular signs are of two kinds: firstly, papilloedema resulting from increased intracranial pressure; secondly, tumours of the retina and/or optic nerve. These tumours are of varying size, from pin-point to more than the diameter of the optic disc. They are raised and nodular, giving the appearance of a mulberry, but greyish-white in colour, and undergo cystic degeneration. These cysts burst and their contents are scattered about the vitreous, and it is thought that they become attached again to the retina and begin to form further tumours.

I will leave Mr. St. Clair Roberts to describe the histological appearance of the retinal tumours from a case which he had the opportunity of examining at Oxford.

MR. D. ST. CLAIR ROBERTS: I would like to show some sections of the right eye of Mrs. A.B., who was a patient of Dr. E. M. Buzzard at the Radcliffe Infirmary, Oxford, and who died in September 1956. Fig. 8 shows the family tree.

She was mentally dull and had fits. She suffered from rheumatoid arthritis, which was thought to be the cause of her death. She also had tuberose sclerosis of the brain and eye and a leiomyoma of the kidney.

There were two children. H.B. was in a mental defective colony, had fits, cerebral calcifications and adenoma sebaceum, but no eye lesion. B.B. was stillborn and had tuberose lesions in the brain, cystic changes in the kidney and a rhabdomyoma of the heart.

Fig. 9 shows the position of a tuber adjacent to optic disc. It lies mainly in the inner ganglion cell layer of the retina and, though well demarcated macroscopically, microscopically it blends into the surrounding retina. There are varying densities of cells with large collections of calcium deposits.

Under greater magnification can be seen the characteristic large cells, some being multinuclear and forming a syncytium; elsewhere there are vacuoles. Surrounding these large cells are many fine tortuous fibrils staining blue with PTAH. It is thought that these large cells are abnormal glial cells and the fibrils glial fibrils.

DR. RUBIN: No discussion of tuberose sclerosis would be complete without reference to the bone changes which occur very frequently in adult cases. I have found mention of bone changes before puberty in only two cases. These are (1) the secondary manifestations in the skull due to raised

FIG. 8.—Family tree of patient with tuberose sclerosis.

FIG. 9.—Whole eye section. Tuber adjacent to optic nerve.

← Optic Nerve

intra-cranial pressure, which are due to the rare event in which a sub-ependymal node has caused obstructive hydrocephalus, and (2) fibrocystic expansion of a rib in a boy of 10 years reported by Dr. Whitaker. Even after puberty the association of bone changes may not be found unless specifically looked for, but they occur in most cases and when found in conjunction with calcification in the brain (which is the commonest single radiological sign) they are very suggestive of tuberose sclerosis. These bone changes are thus of great diagnostic importance. They have recently been reviewed by Whitaker and Hawkins (1959). Briefly, patchy sclerosis of the skull and of long bones, or more generalized thickening of the skull, may be found. More typical changes are encountered in the hands and feet. Small cyst-like translucencies are seen in the phalanges and there may be surface erosions, pitting, periosteal warts or localized thickening. The undulated irregular cortical thickening of the shaft of the metatarsals is particularly noteworthy.

In the lungs a reticular type of shadow may be encountered in the lower half of both lung fields or there may be more generalized cystic changes, the appearances being those of 'honeycomb lung disease'.

DR. ELLIOTT: We call this condition 'tuberose sclerosis' not simply because Bourneville, who first began to piece it together as an entity, was mainly interested in its cerebral manifestations,

but also because these do tend to dominate the clinical picture, the more so as age advances. I am most grateful to Professor P. M. Daniel and Dr. Sabina Strich, of the Maudsley Hospital, for the loan of illustrative photographs and sections.

Two main types of lesion occur. The first is the 'tubers' which Bourneville described, are nodular indurations of the gyri of the cerebral cortex which in the fresh brain are more readily felt than seen. In the fixed state, when such gyri are cut across, these thickenings appear as nodules with diameters ranging from 0.5 to 3 cm., of potato-like colour and texture, not encapsulated but quite clearly defined (Fig. 10). There may be only a few, or as many as 30. Microscopically they consist of a dense proliferation of glial fibres which shades off, less perceptibly than one would expect into the contiguous brain. Scattered through this glial mat are curious giant cells which vary considerably amongst themselves in pattern, being neither clearly neuronal nor clearly glial in origin and less frequently small calcareous concretions.

The second type of lesion occurs beneath the ependyma of the third and lateral ventricles as button-like protrusions which may become complex and confluent, the so-called 'candle gutterings'. Like the cortical lesions, they are mainly composed of glial fibres with scattered giant cells but usually they show many more calcareous inclusions (Fig. 11).

FIG. 10.—Coronal section of brain showing a prominent tuber just above the corpus callosum.

The wide variety of tissue other than the brain affected by tuberose sclerosis, and the variety of different appearances seen within a single tissue, well exemplified by the multiple skin lesions in these two cases, combine to make it difficult to lay down a general statement about the pathology of this disease. I think it is important to make a distinction between large, actively growing tumours deriving from a single-cell type, like Sally's renal adenoma, which are neoplasms; and the smaller more static lesions like the nodules of adenoma sebaceum, the brain nodules, the cortical lipomata in the kidney, and so on, which are haphazard aggregates of tissue, rather than autonomous developing units. The great majority of the lesions found in tuberose sclerosis are of the 'haphazard aggregate' type. We call them hamartomas, by which we imply malformations resulting from erratic development of normal tissue components, and distinguish them from true neoplasms. When we consider the matter, the essential character of tuberose sclerosis subsists in these hamartomas. Had Sally presented initially as a renal tumour, we would have found the neoplasm and recognized it as an adenoma; that would be no grounds at all for considering a diagnosis of tuberose sclerosis. Then we would look further and see the abnormal vessels and muscle fibres and the cortical lipomata; at once tuberose sclerosis would spring to mind, and so we would go back and look for further evidence of malformations and find our diagnosis confirmed. What common thread unites these scattered and almost infinitely variable lesions? I see it as a failure of tissue organizer control at a comparatively peripheral level—to borrow a term from British politics, tuberose sclerosis is a Borough Council defect.

MR. CLARKE: In the literature I have studied

FIG. 11.—Section of a 'candle-guttering' showing gliosis, giant cells and calcareous bodies (Nissl stain $\times 80$).

since I knew this case was to be discussed most of the renal tumours in tuberose sclerosis are described as lipomyoangiomas. Is this equivalent to what you call hamartoma?

DR. ELLIOTT: Yes, I think these mixed lesions are always hamartomatous.

MR. CLARKE: A pure adenoma must be considered a rarity, then?

DR. ELLIOTT: Yes, I think one of this size must be.

DR. SCOTT: We have Dr. John Stead with us tonight. Perhaps he would say something briefly about the psychiatric aspects.

DR. J. STEAD: In this condition there is a very variable incidence of mental subnormality, which when it occurs can be of any degree, but does not have clinical features which distinguish it from other types of subnormality. Progressive deterioration is described, but is not by any means inevitable, except perhaps in those cases in which epilepsy is severe; hence there is no need to be unduly pessimistic about the future of the two children we have seen this evening.

Those suffering from subnormality or severe subnormality are liable to psychotic breakdown, but the incidence of psychosis is not, so far as I know, greater than in other subnormals. They are also liable to mental changes in consequence of tuberose lesions becoming malignant.

I hope someone will take up the genetic aspects of this disease, which seem to be unusual and interesting. The incidence of subnormality is hard to estimate in a disease with such very variable manifestations, but it is seen in about 5% of subnormals in hospitals. Compared with the other aspects of this disease, the psychiatric aspects are not perhaps of such outstanding interest.

PROFESSOR P. E. POLANI: In addition to the names that have been mentioned to describe the condition from which the two patients just demonstrated are suffering, the term 'epiloia' has had wide use. This term was coined by Sherlock in 1911 or 1912 to describe the syndrome of mental deficiency, epilepsy, adenoma sebaceum, nodular sclerosis of the cerebral cortex and tumours of the kidneys and other organs. The name has a classic ring to it, but is, in fact, a newly coined word. Firstly, something should be said about the frequency of epiloia in the general population and its inheritance causation. Epiloia has been estimated to have a frequency of about 1 in 30,000 and it is inherited as a Mendelian autosomal dominant condition. However, it is estimated that about one in every four cases arises *de novo*; consequently this is attributed to mutation. Epiloia would thus have a reasonably high mutation rate of about 1 in 120,000 per individual per generation. Although there have been described a few pedigrees of families where epiloia seems to be present in some members of the family and Von Recklinghausen's neurofibromatosis in others, the two disorders are considered distinct. Von Recklinghausen's neurofibromatosis has a 10 times higher incidence and about 10 times higher calculated mutation rate. Although neither Von Recklinghausen's neurofibromatosis nor epiloia can strictly be considered lethal conditions, they are associated, however, with diminished reproductive efficiency of the concerned individual and the high mutation rate is supposed to replenish the reservoir of these diseases which would otherwise gradually become eliminated.

Let me turn now to some specific remarks concerning the two patients who were demonstrated: Firstly, looking at Sally it is interesting to note that the lesion on her back—the large, slightly raised, softish, pigmented and slightly hairy plaque—does resemble somewhat an initial plaque of molluscum fibrosum. Both Sally and Paul show vitiligo, which, although described in these disorders, is not a very common feature of them as far as I remember. I shall later return to the apparent regression of some signs in Sally following nephrectomy, but I would like to stress the fact that both epiloia and neurofibromatosis are clinically progressive disorders. Their signs may be absent or very minimal in early life and become apparent or much more obvious as the individual grows older. The clinical manifestations of the disorder are likely to become observable, particularly at puberty and during pregnancy. The reason for this exacerbation of signs is not known. It may be of some interest to comment on the cardiac arrhythmia which Sally had in infancy and on the electrocardiographic changes in Paul's case because of the association

which has been reported between cardiac tumours called rhabdomyomata and epiloia. The association has been reported also between sub-endocardial fibroelastosis and epiloia by Crome (1954), who has also made the interesting observation that the rhabdomyoma cells resemble morphologically the cardiac changes may account for a proportion of neonatal or infantile deaths in children with this disorder.

The question was raised as to whether removal of the renal tumour in Sally's case was necessary in view of the fact that such tumours would appear to be very seldom malignant. I would think, however, that on the grounds of its size and the possibility of necrosis within the tumour removal of it was perfectly justified. In this connection it is interesting to note that there appears to have been some regression of the skin lesions in Sally's case after nephrectomy. Also the hyperplasia of the gums appears strikingly less after the operation. The tumour was demonstrated to be a mature-looking tubular adenoma. The apparent partial regression of physical signs, in association with a mature-looking tumour, raises the possibility of the tumour having been responsible for the production of a substance with activity on the clinical manifestations of the disorder. Although this is speculative, the speculation does not appear too far-fetched in view of the known natural history of the disorder, which tends to exacerbate, as I have said, at certain periods of life, when marked hormonal changes are known to occur. The nature of the hypothetical substance is, of course, obscure. However, in view of the well-known hypertrophy of the gums which follows the administration of Epanutin, it is tempting to think that some substance with a similar mechanism of action may be involved. It should be noted that Epanutin has a recognized extra-cerebral action, particularly on the adrenal cortex (Staple, 1951). At any rate, it would be interesting if any blood pressure changes have been recorded as between the pre- and post-operative period. The question has been raised as to whether the condition in these two children is likely to be progressive. It appears that in epiloia there is a certain slow progression of the disease and that the progression is more likely in patients with seizures. Furthermore, progression of clinical manifestations is possible in association with the hormonal changes of puberty and pregnancy. The other question that has been raised is that of the nature of the hemiplegia in Sally and whether it should be taken that this *ipso facto* proves the presence of tuberose sclerosis of the cerebral cortex or even within the brain. The hemiplegia in Sally had a post-natal origin following a severe illness associated with fever and it is difficult to know what part, if any, the presence of

tuberos sclerosis might play in this way, or whether one can take the hemiplegia to be indicative of the presence of tuberos sclerosis. On the whole, it is tempting to think that a pre-existing lesion of the brain might have favoured the hemiplegia in association with a severe general illness with fever. It is to be noted that neuro-

logical manifestations indicative of focal cerebral deficit have been noted in association with epiloia.

Dr. R. I. K. Elliott expresses his appreciation to Dr. Roger Pugh for his comments on the renal adenoma. The contributors wish to thank Mr. S. T. Higgins for his help with the reproductions.

REFERENCES

- ADDISON, T., and GULL, W. (1851): On a Certain Affection of the Skin, Vitiligoidea: (a) Plana, (b) Tuberosa, *Guy's Hosp. Rep.*, 2nd series, **7**, 267.
- BALZER, F., and MÉNÉTRIÉR, P. (1885): Etude sur un cas d'adénomes sébacés de la face et du cuir chevelu, *Arch. physiol.*, 3rd series, **6**, 564.
- BECK, R. E., and HAMMOND, R. C. (1957): Tuberos Sclerosis: Renal and Osseous Manifestations, *J. Urol. (Baltimore)*, **77**, 578.
- BOURNEVILLE, D. M. (1880-81): Sclérose tubéreuse des circonvolutions cérébrales: idiote et épilepsie hémiplegique, *Arch. Neurol. (Paris)*, **1**, 81.
- CRITCHLEY, M., and EARL, C. J. C. (1932): Tuberos Sclerosis and Allied Conditions, *Brain*, **55**, 311.
- CROME, L. (1954): The Structural Features of Epiloia, with special reference to Endocardial Fibroelastosis, *J. clin. Path.*, **7**, 137.
- DAWSON, J. (1954): Pulmonary Tuberos Sclerosis, *Quart. J. Med.*, **23**, 113.
- EIKEN, W. C. (1957): Renal Hamartoma, *N.Y. St. J. Med.*, **57**, 3675.
- HAWKINS, T. D. (1959): Radiological Bone Changes in Tuberos Sclerosis, *Brit. J. Radiol.*, **32**, 157.
- INGLIS, K. (1954): The Relation of the Renal Lesions to the Cerebral Lesions in the Tuberos Sclerosis Complex, *Amer. J. Path.*, **30**, 739.
- LE BRUN, H. I., KELLETT, H. S., and MACALISTER, C. L. O. (1955): Renal Hamartoma, *Brit. J. Urol.*, **27**, 394.
- MOOLTEN, S. E. (1942): Hamartial Nature of the Tuberos Sclerosis Complex and its Bearing on the Tumour Problem, *Arch. intern. Med.*, **69**, 589.
- PEROU, M. L., and GRAY, P. T. (1960): Mesenchymal Hamartomas of the Kidney, *J. Urol. (Baltimore)*, **83**, 240.
- PRINGLE, J. J. (1890): A Case of Congenital Adenoma Sebaceum, *Brit. J. Derm.*, **2**, 1.
- RECKLINGHAUSEN, F. VON (1862): Ein Herz von einem Neugeborenen, welches mehrere, theils nach aussen, theils nach innen prominirende Tumoren(myomen) trug, *Monats Geburtskunde*, **20**, 1.
- SHERLOCK, E. B. (1911): 'The Feeble-minded'. London: Macmillan.
- STAPLE, P. H. (1951): Action of Diphenyl-Hydantoin Sodium on the Adrenal Gland, *Lancet*, **i**, 1074.
- TAYLOR, J. N., and GENTERS, K. (1958): Renal Angiomyolipoma and Tuberos Sclerosis, *J. Urol. (Baltimore)*, **79**, 685.
- WEAVER, R. G., and CARLQUIST, J. H. (1957): Rare Tumours of Renal Parenchyma, *Ibid.*, **77**, 351.
- WHITAKER, P. H. (1959): Radiological Manifestations in Tuberos Sclerosis, *Brit. J. Radiol.*, **32**, 152.