TUBEROSE SCLEROSIS TREATED BY DEEP IRRADIATION

By

BRIAN H. KIRMAN, M.D., D.P.M.

From The Fountain Hospital, Tooting, London

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EPILOIA occupies an intermediate position between the neoplasms on the one hand and other diseases, such as Huntington's chorea and Tay-Sachs disease, which are system disturbances, presumably based on a metabolic disorder. The lesions in the disease-complex of epiloia might at first sight appear mainly neoplastic in form. Thus the brain nodules have the form of gliomata. Polycystic kidneys may be classed as neoplastic (Jeanbrau, 1928; Vines, 1949). In some cases a frank hypernephroma may develop (Kirpicznik, 1910; Berg, 1913; Ferraro and Doolittle, 1937). The rarely encountered heart lesions may take the form of rhabdomyomata, whereas the skin lesions of the face which are pathognomonic of the disease are described as sebaceous adenomata (Figs. 1 and 2), i.e. benign neoplasms of the sebaceous glands of the face in the area to either side of the nose. In fact the facial eruption is seldom simply adenomatous but is complicated by elements of an angiomatous or warty nature. The heart lesion may likewise involve a variety of elements.

Some of the abnormalities which are less commonly found in epiloia are definitely not neoplasms. This particularly applies to the form of the disease which shades off into von Recklinghausen's disease (e.g. the mother of Dickerson's cases 4 and 5) and which is characterized by "café au lait" patches of skin pigmentation or by "peau de chagrin". The latter condition, however, is not unlike some pre-cancerous states of the skin.

A fundamental difference between epiloia and most neoplasms is that the majority of the tumours found in this disease are present at birth although often manifesting themselves later (Stewart, 1935). This does not apply to the skin eruption on the face, which usually appears between the 3rd and 8th years of life. A second difference lies in the fact that in full blown cases of the disease a vast number of tumours are present whereas the majority of neoplasms are initially solitary. In this respect epiloia may be likened to conditions such as Hodgkin's disease or to multiple tumours of known infectious origin such as those of verruca vulgaris or molluscum contagiosum. The similarity to the latter condition lends support to the suggestion made by Professor Penrose that epiloia may be at least in part a reaction to a virus infection, rather than being, as commonly suggested, wholly explicable as determined by a Mendelian dominant character, partially expressed.

The former hypothesis could also be used to explain the fact that epiloia, unlike most neoplastic conditions, has a familial tendency in some cases, re-appearing, though in very diverse forms, in two or even three generations (Dickerson, 1951; Marting, 1941). Shelmire (1918) has recorded adenoma sebaceum in 5 members of one family. On the analogy with certain plant diseases (Cayley, 1928) it can be assumed that a placenta-passing virus affects

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FIG. 1.—Patient D.J. showing typical distribution of adenoma sebaceum in "butterfly"-shaped area.
Photographed by Dr. L. Crome.

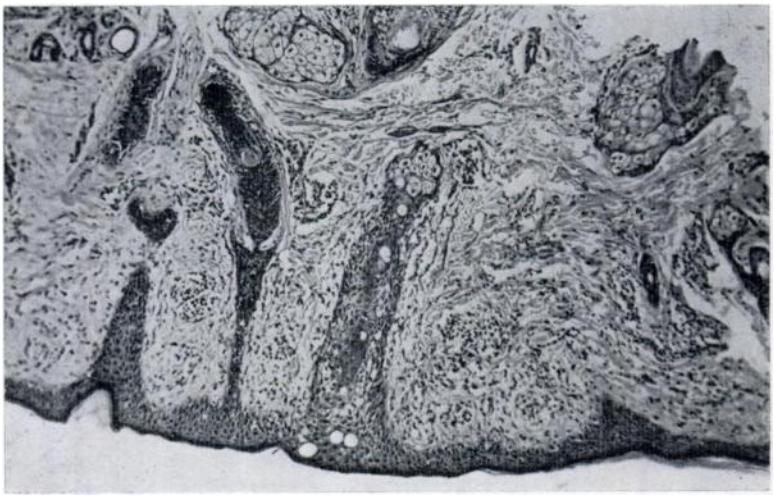


FIG. 2.—Section of rash of adenoma sebaceum from patient D.J. showing that the hypertrophy of the skin is by no means confined to sebaceous elements.
Photographed by Dr. L. Crome.

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the new individual at an early stage in development, thus accounting for conditions which are thought to be hereditary. The suggestion advanced by Quill and Marting (op. cit.) that given forms of epiloia, e.g. with sub-ungual tumours, are inherited, does not conflict with this suggestion, since a similar problem occurs in syphilis where the neurotropic variety appears in members of one family (Moore, 1947). It may be possible to test this hypothesis by animal inoculation.

Another difference between the tumours of epiloia and common isolated tumours is that the former have little tendency to grow. This is true in general, but there are exceptions to the rule. The disease indeed may occasionally present with the classical picture of a cerebral neoplasm (e.g. the mother of Dickerson's cases 4 and 5). The established case of epiloia in this static form may occasionally be complicated by symptoms suggestive of a growing cerebral tumour.

These considerations led to the view that it would be logical to attempt the treatment of certain cases of epiloia by means of deep X-ray therapy. One of the difficulties which confronts the treatment of this disease is that the majority of the patients are either hopeless idiots or suffering from such a mild, abortive form of the disease (e.g. the mother of Dickerson's cases 1 and 2, see also Walsh, 1947), that such drastic treatment as deep irradiation is not indicated. None the less in those of its victims whose condition is threatened with deterioration as a result of increase in size of one of the gliomatous masses, such treatment, it was considered, should be tried, especially in view of a report by Friedman (1939) who states that after irradiation of the head of a patient with tuberose sclerosis fits ceased for at least two and a half years, the patient remaining normal mentally and working as a clerk. He used in the first stage of treatment "a total dose of 850 r to each of 4 fields". In the second stage "850 r in divided doses to each lateral field". Kessel (1949) recommends that any surgery in tuberose sclerosis should be followed by X-ray therapy. In the case of Koch and Walsh (1939) irradiation was administered but the patient, after 7 months, was no better. This, however, was a case where the patient had become almost completely blind before treatment.

Case Report

This case was reported briefly previously prior to treatment (Kirman, 1949).

D.J., born 6.iv.40. Male.

The patient is the only member of the family known to be affected by the condition. There is no family history of epilepsy, mental defect or adenoma sebaceum. The father is a road-sweeper, the mother a charwoman. The home is a poor one. The parents are in good health. The patient is the last-born of five. The siblings are as follows (1952):

1. Girl, died at 6 years of diphtheria.
2. Boy, died at 4 years of diphtheria.
3. Boy, aged 15, at work.
4. Boy, aged 14.
5. Patient.

Both parents were aged 42 at the patient's birth. The mother was well during pregnancy. The birth was quick and easy. Birth weight was 9 lbs. He was bottle fed. At 12 months he walked and at 15 months is said to have talked. No abnormality was noted until 18 months when he began to have epileptic fits for which he was taken to hospital. He is said to have been unconscious for two days. The parents attributed the fits to the explosion of a land mine. He is said to have teethed normally, to have become clean in his habits and to have learnt to use a spoon prior to admission to the Fountain Hospital.

He was admitted 27.ix.45. At that time he was already said to be deteriorating both mentally and physically. He could not wash or dress and had frequent attacks of petit mal. He said only a few words. He knew his name but not his sex or age. He could not copy a straight line or match colours. After admission he was found to be faulty in his habits. He could walk well and wandered round the ward although there was a left talipes equino-varus with left hemiparesis. The Wassermann Reaction and parallel test were negative. The cerebro-spinal fluid showed 7 lymphocytes per cubic millimetre, 35 mg./100 cc. protein, negative Wassermann reaction and Lange test.

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Soon after admission he had a succession of fits, going into status epilepticus. He continued to have both major and minor attacks. He was able, however, to attend the occupation centre where at first he made some slight progress though his mental level was noted to vary from day to day—possibly owing to sub-clinical fits. In 1946 the rash of adenoma sebaceum was noticed, beginning with a patch of partial baldness with induration of the scalp, followed by a lesion with a typical paranasal distribution.

In 1947 he was still able to walk though unsteadily and on a broad base. He talked to other children and occasionally answered questions from the staff. He could use his paretic hand a little. An electro-encephalogram (E.E.G.) showed an abnormal record with irregular dominant delta activity. Some "sharp waves" were seen in the posterior areas of both hemispheres where the greatest abnormality was found. The delta activity had the greatest amplitude and slowest frequency in the left occipital lobe.

A radiological examination of the skull showed a small calcareous deposit in the left hemisphere.

In August, 1947 a rapid deterioration occurred following a series of fits. He was then found to have a paresis of the right (i.e. his good) hand which had now become almost useless. His gait acquired a high-stepping character. He became very ataxic, appeared dazed and could not understand anything said to him. A month later the right hemiparesis was worse than the old established left weakness. From that time on he never spoke again. He made efforts to feed himself with his left hand but these were unsuccessful.

An eye examination at that time showed a phakoma over the left macula.

At this stage deep irradiation was suggested but the view of the radiotherapist, who was consulted at that time, was that the tumours would probably be completely insensitive and that the treatment would inflict "unnecessary discomfort on the patient". (This was not the view of Dr. R. M. Patterson who saw the patient at a later stage.)

Deterioration continued. He became doubly incontinent and unable to walk without assistance, though he still showed his tongue on request and was delighted to be allowed to scribble with a pencil on request. In 1949 he had a complete right hemiplegia with considerable paresis on the left side.

In March, 1949 he received 2,000 r on alternate days 4 doses on each side to each motor cortex. This therapy was given at Charing Cross Hospital at the suggestion of Dr. Frank Elliott under the direction of Dr. R. M. Patterson. In April, 1949 he showed no particular change. He made a poor attempt at walking. He appeared very lethargic. He was spoon-fed and made no shift to obey simple instructions. On the Merrill-Palmer Scale he scored an I.Q. of 18 and on the Stanford-Binet 20. When tested he was friendly and tractable. He made some slight effort at speech. Subsequent testing showed little significant change.

In May, 1949 the E.E.G. report from the Maudsley Hospital was as follows: "The whole record remains grossly abnormal. The dominant activity is of slow irregular delta waves which show poor organization over the whole cortex, save for a tendency for the waves to be sometimes bilaterally synchronous. Traces only of normal alpha activity are seen. The record suggests a gross generalized cortical disturbance, possibly secondary in the main to some cerebral lesion." The record was found to bear some resemblance to those of cases of sub-acute encephalitis.

Present Condition

He remains a low grade imbecile. He still does not talk. His comprehension is very limited. With his good hand (the left) he will point to his nose, chin and hair on request, but not his ears. When asked to point out another patient mentioned by name, he does not do so. He can feed himself with the left hand. He is clean in his habits if supervised. He cannot walk. Physically he is a cripple with spastic diplegia, more marked on the right. Both feet are held in equinus position. At thirteen he is excessively fat and heavy (Fig. 3) though in good general health. The adenoma sebaceum, as is usual at the age of puberty, has become more obvious with dilatation of the superficial blood vessels. The blood pressure is 110/74. The urine contains a very faint trace of protein and on culture there is a heavy growth of streptococcus viridans and of staphylococcus albus. The blood groups are as follows:

ABO	Rh	MN	S	P	Lewis	Kell	Lutheran
A_1	R_1r	N	−	+	−	−	−

The record of epileptic fits is as shown in the accompanying diagram. He received small doses of phenobarbitone intermittently in 1948 and 1949 but no other medicine.

COMMENT

In the present case no benefit resulted from the treatment apart from a reduction in the number of fits which may be a coincidence. It may be, however, that if treatment had been given earlier, when it was first suggested, irreversible destruction would not have taken place. Clearly, in any such case treatment should be given as soon as it is decided that it is indicated. Only in this way can an estimate of its value be explored. The development of symptoms in this case

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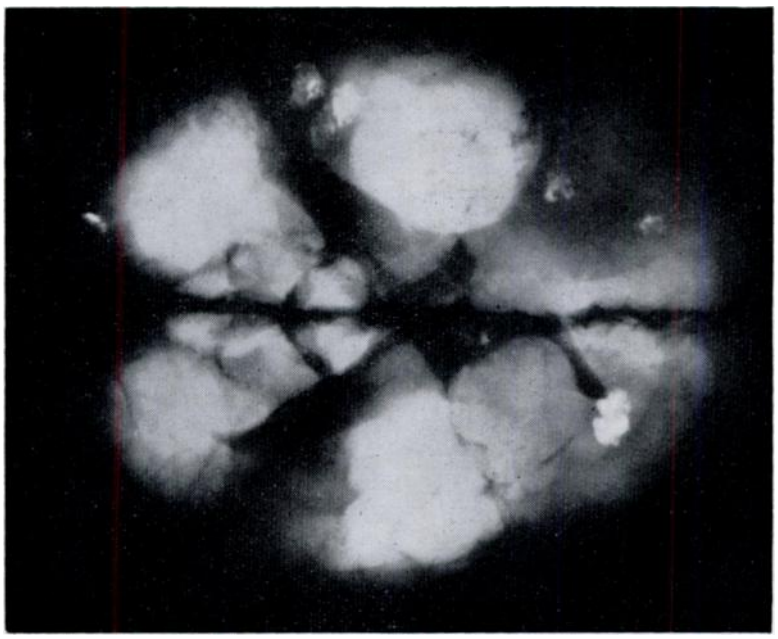


FIG. 3.—X-ray of brain after removal from another case of tuberose sclerosis showing diffuse distribution of the partially radio-opaque lesions.

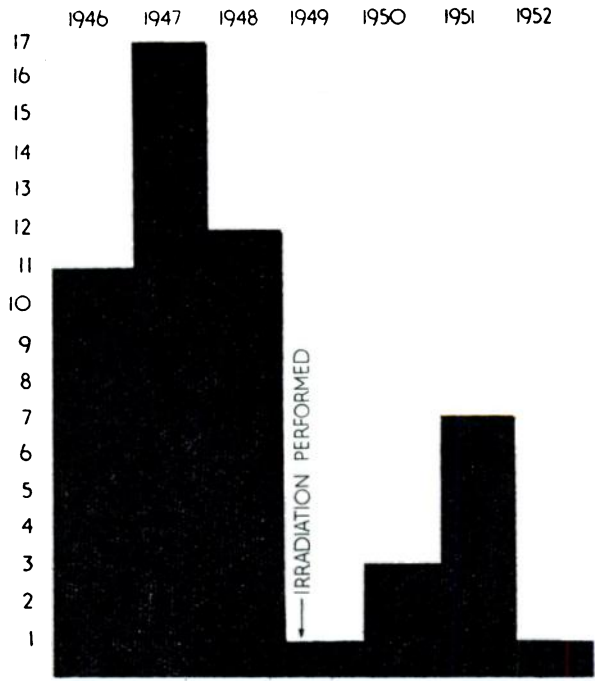


Diagram showing incidence of epileptic fits recorded before and after deep X-ray therapy to head in tuberose sclerosis.

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particularly in 1947 suggests that one of the lesions had begun to spread, producing the additional right hemiplegia and other worsening of symptoms. It seems feasible that radiotherapy at this stage might have halted or even reversed the deterioration.

The pattern of the brain tumours differs sharply from that of many tumours and congenital abnormalities (Fig. 4). The more usual histological findings are

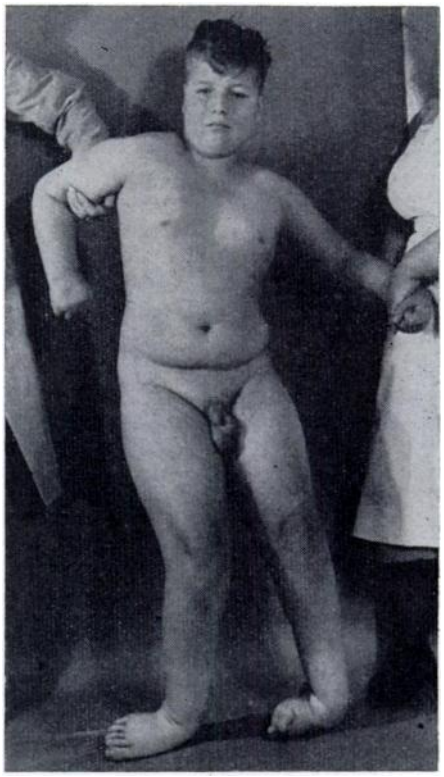


FIG. 4.—Patient D.J. showing very marked adiposity which developed after deep X-ray treatment at the time of puberty. Also note bilateral spastic diplegia with club feet. Photographed by Mr. J. E. Stevens.

described by Biggart (1949). These include a marked disturbance of the architecture of the brain and the presence of strikingly abnormal cells of uncertain origin and classification. In most of the nodules there is little evidence of active growth—a fact in keeping with clinical observations which suggest that only rarely does a particular mass acquire neoplastic properties. It is notoriously the sub-ependymal masses which do this. Potter (1952) illustrates one of these tumours. Even the more rapidly growing, highly cellular portions of tissue shown here have extremely diverse composition unlike that of a simple glioma.

Globus and Kuhlenbeck (1942) report a series of cases showing every degree of transition between tuberose sclerosis which they describe as "disseminated spongioneuroblastosis" and frank solitary tumours of the type of medulloblastoma. They consider that all these tumours arise from certain areas of the stratothalamic sub-ependyma which are rich in cell nests, notably the lamina terminalis. They demonstrate to their satisfaction by Nissl staining that at least

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some of the giant cells both in tuberose sclerosis and in single tumours of this area are neuroblasts, hence the term neuroblastoma. All the tumours in this series were actively growing and rapidly fatal. In view of these facts no previous deduction about radiosensitivity seems possible and evidence on this point can only be obtained by experience. The very limited value of surgery in tuberose sclerosis (Kessel, 1949) and the difficulty of approach to tumours most of which arise from the strio-thalamic region is an additional reason in favour of more extensive trial of radiotherapy in appropriate cases.

SUMMARY

A case of epiloia treated with deep X-ray therapy is reported. The number of fits has been conspicuously less since treatment but there is no improvement in the mental state or in the paralysis. It is suggested that a more extensive trial of deep X-ray therapy in epiloia should be made, especially in those cases beginning to show signs of deterioration. Possible radiosensitivity in the disease is discussed in relation to the morbid anatomy and histology.

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