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COMMUNICATIONS

A CASE OF TUBEROUS SCLEROSIS
WITH "PHAKOMATA"

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THE term "tuberous (or tuberos) sclerosis" is applied to a complex clinical picture, in which retarded mental development (often in company with a primitive type of schizophrenic psychosis—) is combined with epileptiform seizures and adenoma sebaceum of the face; associated with these are "tuberous" sclerotic areas of the brain, and sometimes tumours of the liver, kidneys, heart, gastro-intestinal tract and retina.

The clinical conception has been of gradual development.

v. Recklinghausen (1863) examining the body of a newly born child found a large number of sclerotic areas in the brain and several myomata growing from the heart muscle. Bourneville (1880) described similar sclerosed areas of brain in an epileptic idiot and gave them the name of tuberous sclerosis, because of their resemblance to pieces of potato. His patient had "acné rosacée et pustuleuse" of the face. The skin condition known as sebaceous adenoma was first described by Balzer (1885-6).

Pringle (1890) gave an excellent description of adenoma sebaceum, and it is interesting that his patient was described as undersized with "intelligence decidedly below par." . . . "Neither the patient

nor her mother who accompanied her was particularly bright intellectually." He quoted a case seen by his friend Dr. Hallopeau, in which there were "limited intelligence and mobile temper." Sherlock (1911) noted the connection of tuberous sclerosis with adenoma sebaceum, fits, and feeble-mindedness. He applied the name "epiloia," which he thought a suitable name, as "it is short, unmeaning, distinctive, and capable of forming an adjective."

It has been observed that the mental state is usually a primitive catatonic schizophrenia.

According to Critchley and Earl (1932) tuberous sclerosis is heredofamilial and commoner among the "lower classes." There is usually a bad family history, the patients' relatives often having suffered from psychopathic states if not from symptoms definitely attributable to tuberous sclerosis. The fits may be "grand mal," "petit mal," or "Jacksonian." The patients are undersized, often with misshapen or protruding ears. Their hands may be simian in type with incurved little fingers. Catatonia is often found. A peculiar restlessness is common, sometimes with amazingly complicated repetitive hand movements. In addition to the adenoma sebaceum of the face with its thinning of the dermis and overgrowth of the sebaceous glands, there may be bronzing, café au lait patches or neuro-fibromata of the skin. Hall (1940) reports a case associated with a possible neurofibromatous bony lesion and another with rheostosis.

Critchley and Earl (1932) state that most of these patients die in the second decade of life from pulmonary disease, status epilepticus, or cachexia. Two cases have, however, been reported in which the patients were aged 47 years (Lind, 1924) and 75 years (cited Wilson 1940) respectively.

The small sclerotic masses in the brain, the potato-like consistence of which gave rise to the term "tuberous" are usually of a size intermediate between that of a small pea and that of a broad bean. They are of the colour of brain tissue and are consequently more easily recognised by touch than by sight. Most commonly they are situated in the cortex, but they occur also in the white matter, and not infrequently protrude into the ventricles, where a group of them may produce the appearance which Lind called "candle guttering." Histologically they show giant cells of a primitive type similar to undifferentiated neuroblasts, and an overgrowth of glial elements. Changes, similar in type, but milder in degree, are found in the intervening brain tissue where no sclerosis is recognisable. In rare cases larger intracranial masses are found, and there may be signs of raised intracranial pressure. Critchley and Earl (1932) described a case in which papilloedema was observed during life and at the post-mortem examination a gliomatous tumour the size of a walnut was found in the posterior

part of the third ventricle. Koch and Walsh (1939) mentioned that their patient had pallor of the optic discs characteristic of receding papilloedema, and X-ray examination of the skull showed signs of increased intracranial pressure with erosion of the sella turcica, tuberculum sellae and sphenoid.

The tumours of the heart are usually rhabdo-myomata. Although large kidney tumours of the Grawitz type have been noted, renal neoplasms are more often fibromata or adenomata arising from undifferentiated elements of the Wolffian ridge. Most authors state that the tumours of the liver are mixed tumours. The rare tumours of the gastro-intestinal tract are myomata.

From the ophthalmic point of view the main interest of tuberous sclerosis lies in the occasional presence of tumours in the ocular fundus which van der Hoeve (1920) first described and named "phakomata" (from the Greek=lentil and hence mole). He described, with illustrations, a cystic degenerating tumour of the optic disc; the cysts appeared and disappeared under observation, and van der Hoeve was later (1923) of the opinion that masses seen elsewhere in the fundus had seeded from the primary lesion. In succeeding papers he described further cases of retinal phakomata, but in none of them were tumours present on the optic disc. Recently Koch and Walsh (1939) have collected accounts of 24 cases of phakomata recorded in the literature in addition to van der Hoeve's cases, and in six or seven of these there were tumours on or partly overlying the disc. In many of the recorded cases the tumours had an appearance similar to that described by v. Herrenschwand (1929) as—"a mulberry composed of glittering white nodules"; in other cases the masses were described as resembling raised white plaques in the retina.

Messinger and Clarke (1937) found six recorded histological examinations of phakomata. There were two such records of phakomata of the optic disc, *viz.*, the cases of van der Hoeve (1923) and Messinger and Clarke (1937) and tumours of the retina had been sectioned by van der Hoeve (1932), Schob (1925), Feriz (1930), Kuchenmeister (1934).

Van der Hoeve (1923) described a tumour of the disc consisting of nerve fibres and a peculiar type of cell. The fibres came from the nerve fibre layer of the retina and broke through holes in the membrana limitans interna. The cells were probably descendants of the first anlage of the retina.

Messinger and Clarke (1937) submitted a section to Miss Ida Mann for her opinion. She thought their disc tumour showed cells which were probably glial in origin, and considered that the cells had been derived from glial cells of the inner neuroblastic layer during the second stage of retinal differentiation which takes place from the sixth week to the third month of intra-uterine development.

Messinger and Clarke themselves considered phakomata as hamartomata.

Glial fibres were present in the cases of Schob (1925), Feriz (1930), and Kuch nmeister (1934).

Brain and Greenfield (1937) described and illustrated the histological appearances of a case of retinal phakomata. It was a "lenticular nodule of cellular or loosely areolar neuroglial tissue, lying in the innermost layer of the retina and bulging the internal limiting membrane." Large rounded cells with clear cytoplasm and eccentric nucleus were found, similar to those occurring in the nodules in the basal ganglia. According to these authors calcified spherules are sometimes seen in the centre of a phakomatous nodule.

The following clinical observation seems worth recording because of the general interest of the disease, the rarity of phakomata on the optic disc, and the problems to which the case gives rise.

E.S., a male, aged 34 years, was admitted to Whipps Cross Hospital on November 10, 1939 and remained there till February

FIG. 1.

Note the worried expression and the adenoma sebaceum of the face.

8, 1940. For several years before his admission he had been an inmate of an epileptic colony. It was known that he had been mentally deficient and subject to fits since early childhood, and much of his life had been passed in homes for the mentally defective. He was sent to the Hospital because of failing vision, as it had been noticed at the Colony that he walked into doors and tables and similar large objects, and apparently did not see them. Because of the patient's mental state it was impossible to obtain any coherent history from him and he made no complaint of his blindness.

He was first seen by one of us (J.P.M.) on November 25, 1939. The only abnormalities found on examination either then or later were concerned with:—

1. His skin, especially on the face (see Figs. 1 and 2.)
2. His mental state.
3. His eyes.
4. His cerebro-spinal fluid.

FIG. 2.

1. Over the whole of the face, except the forehead, there was typical adenoma sebaceum with its numerous little rounded, bead-like swellings. On the forehead there was a large nodule and at the back of the neck and spreading on to the shoulders there were little rounded tags of skin resembling minute neuro-fibromata. A more typical pedunculated neuro-fibroma was present over each scapula and scattered over the trunk there were a number of sessile "moles."

2. The mental state had features suggestive of early mental defect, and others strongly suggestive of dementia praecox. The patient did not know his age, date of birth, or how long he had been in hospital; he did not know ordinary coins; he could not add simple figures correctly, but he could multiply a little, having evidently learnt simple multiplication tables by heart at one time. His emotional state as a rule was one of indifference, though towards the end of his stay in hospital he had one short outburst of "spitefulness" in which he tried to bite the hand of the ward sister, and on other occasions he interrupted conversation with querulous demands for food. Apart from this he scarcely ever spoke spontaneously. He answered questions after a long latent period slowly, and in a voice devoid of animation. He had the worried look of the schizophrenic (Figs. 1 and 2), but he showed no stereotyped movements. Catatonia was well marked; he held his hands in any bizarre position in which they might be placed. To his loss of sight he seemed to be remarkably indifferent. He was unable to co-operate except in the simplest acts of the examination and study of the ocular fundi was greatly impeded by his inability to maintain his attention.

3. On ophthalmic examination, ocular movements were found to be normal. The eyes had perception of light, though it was difficult to discover from the patient any further details of his vision. The ward sister did not think he had any useful vision. His pupils did not react to light.

The right disc (Fig. 3) showed general greyish pallor, blurred margins, and swelling of 1.D. The vessels near the disc showed white lines along their margins. Outside the disc were several white striae as if residual from oedema. Near the right macula was a greyish mottled swelling, about half a disc diameter across, and about $\frac{1}{2}$ D. raised from the surrounding retina. Far out, near the upper temporal vessels could be seen two superficial spots of black pigment. Near the inferior temporal vessels was a small raised white patch in the retina (about 1D. swelling). The outlines were indefinite. Below the disc was a similar white patch. Two smaller white masses could be seen in the extreme nasal periphery.

The left fundus (Plate) showed the disc swollen about 2D. but less pale in colour than the right disc. The margins were blurred.

Illustrating the changes in the left fundus

FIG. 3.

There were white lines along the retinal vessels near the disc. On the disc and situated towards its upper nasal aspect there was a small glistening tumour, more or less globular in shape and slightly pedunculated, $\frac{1}{2}$ to $\frac{2}{3}$ of the disc breadth in diameter, glistening white in colour with a "mulberry" surface, as if composed of numerous minute cysts.

In the retina, up along the nasal vessels, about the diameter of a disc from the edge of the papilla, there could be seen another white swelling (Plate); this was elongated in shape, being about two disc diameters in length and one in breadth; its surface was smooth and raised about 3 D. above the surrounding retina. Peripheral to this tumour, about three disc diameters away, was a small patch of choroidal atrophy.

(4) The cerebro-spinal fluid pressure measured at lumbar puncture with the patient horizontal was 80 mm. fluid. This is lower than the normal reading, which is about 120 mm. fluid. The fluid had a greatly increased protein content—*viz.*: 240 mgms. per cent.

instead of the normal 20-40 mgms. The increase included a "considerable excess" of globulin. The amounts of chloride and sugar were normal, and there were two lymphocytes per cubic mm.

Comment

Comment here may be limited to the ophthalmic features of the case. There is no doubt that the case is one of tuberous sclerosis, and we consider that the globular tumour on the left disc, and the large left retinal tumour are phakomata. In our opinion the smaller white swellings in the right fundus are also probably phakomata.

The loss of vision was almost certainly associated less with the phakomata than with the changes in the discs themselves. It is not proven that these were the result of papilloedema resulting from raised intracranial pressure, because the pressure when measured was in fact below normal and the patient showed no other signs or symptoms of cerebral tumour. We cannot, however, entirely exclude the possibility of a tumour with occasional rises of intracranial pressure. The increase of protein in the cerebro-spinal fluid is somewhat in favour of the presence of a tumour, but may equally well be accounted for by the tuberous sclerosis itself. Very few examinations of the C.S.F. in uncomplicated cases of tuberous sclerosis are on record.

We have to consider also the possibility that the changes in the discs are due to local causes. They may be those of tuberous sclerosis of the nerve heads. It is, however, unlikely that all the abnormal appearances are direct manifestations of this. The phakoma of the left disc is presumably the manifestation of tuberous sclerosis of the nerve head, and for the other changes, which are very different, some other explanation must be sought. An alternative is that tuberous sclerosis of, or near the nerve heads has interfered with the venous return from the discs and given rise to an associated papilloedema, and that the present appearances and the patient's loss of vision are due to a combination of sclerosis and post-neuritic atrophy. If this is so, it is not likely that the changes have occurred quite simultaneously in the two eyes. Because of the patient's defective mentality a loss of vision in one eye would have passed unnoticed to those in charge of him, and the appearances of the discs suggest that the changes in the right eye are older than those in the left.

It is not likely that these problems can be decided until pathological examination is possible.

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The blocks of the colour illustration have kindly been lent by Messrs. Wm. Heinemann, at the request of Mr. R. Lindsay Rea, in the second edition of whose "Neuro-ophthalmology" the picture has recently been published.

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EPIDEMIC SUPERFICIAL PUNCTATE KERATITIS IN MALAYA

An account based on observations of Superficial Punctate
Keratitis which occurred in Selangor, one of the
Federated Malay States, from 1935-38

BY

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SELANGOR, KUALA LUMPUR, FEDERATED MALAY STATES

SUPERFICIAL punctate keratitis was not recognised in this country prior to 1934, during which year the writer met with two cases, one in a European female, and the other in a Tamil labourer. In