A CASE OF MULTIPLE NEUROFIBROMATA ASSOCIATED WITH A TRUE ANGIONEUROFIBROMA OF THE ACOUSTIC NERVE, JACKSONIAN EPILEPSY AND OSTEOPOROSIS.

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THE subject of multiple neurofibromata or von Recklinghausen's disease is too interesting from a pathological point of view to need any excuse for recording the following case, with some considerations thereon.

CLINICAL HISTORY.

W. B. G., age sixty-six, was admitted to the Sunderland Mental Hospital as a certified patient on December 9, 1924. The medical certificate stated that, "He is very troublesome, jumping out of bed and wandering about naked, keeping the other patients awake and using 'awful' language. He is very irritable and requires continual watching. Is very violent, throws utensils about and threatens attendants."

Family History.—Patient was one of three children. His two brothers are both alive and well, ages forty-eight and fifty-four. His sister died, age fifty-seven, from diabetes. The patient's wife has had five children, of whom four are living; a boy died in infancy, and is said to have had 'only one lung.' A daughter, age twenty-seven, has been epileptic since she was seventeen, is married, and has had five children, of whom three were stillborn. We were unable to obtain an interview with her. His parents were both healthy; no history of insanity or nervous disease is obtainable.

Previous History.—About the patient's early history little is known. He did not go to school, and was unable to write. Why he did not attend school is not known, but both his brothers were at school. The patient had been epileptic since he was forty, i.e., for twenty-six years. His fits were generally confined to the left side, and occurred usually without warning. He had occasional generalized seizures. The attacks appeared to start round his mouth, his wife stating that there was drooping of the corner of the mouth and twitching of the muscles just

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as he was beginning to have each fit. During late years he became more and more quarrelsome and bad-tempered. At times he was very noisy. In the intervals between the seizures he was fairly reasonable, and was fond of the theatre, especially Shakespearian plays. He had been a steady worker all his life, first as an iron-moulder, and then as a scavenger. He took a moderate amount of alcohol. There was no history of venereal disease.

Condition on Admission.—The patient was in a weak state, and was confined to bed during the whole of his stay in hospital. He was a thin man, 5 ft. 2 in. in height, and weighed 130 lb. His temperature was normal. Physical examination revealed the presence of multiple tumours on both arms, from wrist to shoulder, there being some seven or eight palpable in each arm (*Fig. 1*). These tumours were obviously situated along the course of the principal nerves. Careful examination of the rest of his body failed to reveal any others. They were diagnosed as multiple neurofibromata, were not adherent to the skin, and were freely movable. There was slight pigmentation of the skin over the right shin, but no other cutaneous abnormality.

FIG. 1.

Circulatory System.—The pulse was regular, of high tension, and the vessel wall was thickened. Pulse rate 80. The second cardiac sound was accentuated, but there was no enlargement of the heart. The systolic blood pressure was 180, the diastolic 130.

Respiratory System.—Rate 22. There was an area of dulness at the right apex, and some fine crepitations in both lungs.

Alimentary System.—There was little to remark, except some furring of the tongue.

Genito-urinary System.—The urine was amber-coloured, acid reaction, sp. gr. 1.018; neither sugar nor albumin was present.

Nervous System.—Owing to his mental condition it was very difficult to examine him in anything like a thorough manner.

Cranial Nerves.—Vision was obviously impaired. The right palpebral fissure was narrower than the left, there being slight ptosis of the right lid. The pupils were regular, concentric, and reacted to light. The sympathetic, oculocardiac, and consensual reflexes were all normal. The reaction to accommodation could not be obtained owing to the patient's mental condition. The fifth nerve was normal. There was some impairment of the facial musculature on the right side, the corner of the mouth drooping somewhat. As far as could be ascertained, the patient was deaf on the right side.

In the upper extremities there did not appear to be any abnormality of function that could be demonstrated. The lower extremities and trunk were normal.

The mental condition was one of severe dementia. He was very difficult to rouse, would not answer any questions, and was noisy and troublesome on many occasions, disturbing the other patients at night. He had attacks of Jacksonian epilepsy which as a rule affected only the left side, and always involved both the arm and the leg. There was usually loss of consciousness. On more than one occasion he had an attack of generalized epilepsy. The seizures occurred as follows :—

Dec. 11, 1924	.	2 seizures.	March 16, 1925	.	20 seizures.
Jan. 6, 1925	.	35 "	" 17 "	.	2 "
Feb. 8, 1925	.	18 "	" 31 "	.	1 "
" 10 "	.	1 "			

During the intervals between the attacks the patient was very surly, and would hardly speak to any one. He lay under the clothes, and would only rouse himself to feed. He gradually became weaker and died on March 31, 1925.

PATHOLOGICAL EXAMINATION.

Autopsy showed a poorly nourished man with decubitus on sacrum and inside of upper thigh. Rigidity and lividity were not marked. The liver was small and atrophied, weighing only 31 oz. There was an old infarct in the spleen, which was very hard and cartilaginous. Both kidneys were atrophied, with a marked increase of perirenal fat. The adrenals appeared normal. The pancreas, stomach, gallbladder and intestines showed nothing abnormal. A large tubercular cavity was found in the apex of the right lung, and some old fibrotic patches and some hypostatic congestion in the base. The left lung was congested in the lower lobe. The heart was in surprisingly good condition, the valves being healthy and the muscle firm and of good appearance.

The cranial vault, when cut into with the saw, felt very soft. None of the other bones showed any marked softening. The pelvis was normal.

Meninges.—On removal of the calvarium, the dura was found to be adherent to the bone over considerable areas. The whole of the dura was very much thickened and discoloured, there being a wellmarked pachymeningitis hæmorrhagica interna. Lying along the right Sylvian fissure and foot of the Rolandic fissure was an endotheliomatous thicken-

FIG. 2.

ing which occupied an area of about 10×10 cm., and was about 0.5 cm. thick. This covered the anterior end of the superior temporal gyrus and the operculum. Lying on the superior frontal gyrus was a small nodular growth about $3 \times 1\frac{1}{2}$ cm., which was attached to the dura and came away with it, leaving a depression lined by pia of about 1 cm. in depth. This depression lay anterior to the leg area, in the intermediate precentral area of Campbell, or partly in area 6 of Brodmann, and partly in area 8. In the falx cerebri, between the two anterior poles, was an endotheliomatous nodule the size of a small pea. This lay opposite the middle of area 32 of Brodmann, and was probably of no clinical importance.

Brain.—There was considerable general atrophy of the frontal and parietal regions. Some distortion of the gyri round the depression in the intermediate precentral area of Campbell was noticed. The gyri under the diffuse tumour covering the Sylvian fissure were somewhat distorted. The convolutional pattern of the brain was of ordinary type. Careful examination of the meninges of the cord and cauda equina failed to show any endotheliomatous or other abnormal structure.

Cranial Nerves.—A small tumour of the right acoustic nerve

FIG. 3.—Scale in inches.

was found, pressing on the pons (*Fig. 2*). It was hard, about the size of a small walnut, and pale yellowish grey in colour, with areas of degeneration. None of the other cranial nerves presented any abnormality.

Peripheral Nerves.—All the larger nerves in the arms had tumours on them (*Fig. 3*). These varied in size from mere fusiform dilatations of the nerve to a large tumour, weighing 5 oz., on the right median nerve. Unfortunately the endocrine glands were not submitted for microscopical examination.

HISTOLOGICAL REPORT AND NOTES.*

The following tissues were examined histologically :—

1. Fibroneuroma from median nerve. This appeared to be composed entirely of loose areolar and fibrous tissue of perineural origin, and no nervous tissue could be demonstrated.
2. Growth from dura mater. This was undoubtedly an endo-thelioma.
3. Growth of eighth nerve. This was a very interesting tumour.

FIG. 4.—Showing angiomatous structure.

It was a true angiomatous neurofibroma, and contained glial tissue. The fibrous tissue was found to be undergoing metaplastic transformation, and resembled the “gliomes polymorphes angiomateux” of Alagna.¹ There was no evidence of malignancy. A tendency to hydropic change was remarked (*Figs. 4 and 5*).

This tumour presented the characteristics of eighth nerve tumours ; these growths have been described from time to time under a varying nomenclature, much depending upon the portion or portions of the tumour examined.

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Cushing² points out that certain characteristics are common to these neoplasms, and he distinguishes them from other growths originating in the cerebellopontine angle. The chief characteristic is the combination of fibrous zones, in which nuclei tend to dispose themselves in 'palisades' or whorls, with a loose reticular tissue containing glia-like fibrils in which fat and hyaline metamorphoses commonly occur. The vascular tissue is rarely as prominent as it was in this case.

From these findings it is apparent that generalized neurofibro-

FIG. 5.

matosis, isolated tumours of the eighth nerve, and endotheliomata of the meninges are correlated in some way (Wishart,³ Fraenkel and Hunt,⁴ Funkenstein⁵).

4. Portion of cerebellum showed no abnormality.
5. Portion of rib showed a certain amount of osteoporosis.

THEORETICAL CONSIDERATIONS.

The whole question of neurofibromatosis is interesting, but not a little is obscure. The explanation of the association of a general fibromatosis of the peripheral nerves, whether it is merely of one or two

nerves, or as extensive as occurs in molluscum fibrosum, with acoustic tumours, whether they are unilateral or bilateral, and with meningeal endotheliomata, is not yet forthcoming.

Neurofibromatosis has been attributed to an intoxication, a local nervous infection, and to an intrauterine neuritis; according to Brissaud and Feindel it is due to a congenital malformation of the ectoderm. Cornil and Ranvier⁶ postulate an instability in differentiation of the nerves, and point out its resemblance in this respect to the myopathies. In both cases there appears to be a predisposition which, influenced by toxins or injuries, gives rise to the pathological conditions found.

In view of more recent work, particularly Bielschowsky's⁷ study of heredodegenerations, it appears very probable that neurofibromatosis ought to be included in his second group, viz., dysplasias with blastomeric complications, under which he groups tumour formation and tuberosc sclerosis. Bassoe and Nuzum,⁸ in 1915, reported a case of neurofibromatosis with areas in the brain analogous to those of tuberosc sclerosis. Bielschowsky,⁹ in a recent article, maintains that in general neurofibromatosis there is a lack of differentiation and failure of migration of the spongioblasts. Such is the case in syringomyelia, and it is an interesting fact that syringomyelia and tuberosc sclerosis are sometimes found in the same patient. He considers that from an etiological standpoint tuberosc sclerosis, neurofibromatosis and syringomyelia have a common hereditary constitutional "Anlage." When there are lesions in the cerebellum in neurofibromatosis, as has been reported by Maas, Nowicki and Orzechowsky, the picture is almost identical with that of tuberosc sclerosis. In the present case no lesions were found in the cerebellum. The almost invariable association of multiple fibromata with acoustic nerve tumours and meningeal endotheliomata, the frequent hereditary occurrence of neurofibromatosis, and, in this particular case, the occurrence of an angiomatous structure in the acoustic tumour, all suggest a heredodegeneration. In the present instance the tumour of the acoustic nerve resembled fairly closely what has been described as an acoustic tumour by Henschen¹⁰—the admixture of fibrous areas with reticular areas. The 'palisade' arrangement of the nuclei in the fibrous areas is not quite typical, but there are areas of hydropic fibrous tissue which accord well with what Cushing describes.²

Crouzon¹¹ includes neurofibromatosis in his ninth group of "maladies familiales atypiques" as being exceptionally hereditary, the other two diseases mentioned by him in this group being Sydenham's chorea and epilepsy.

Parkes Weber¹² recently described a case of neurofibromatosis with a true suprazygomatic meningocele, with a hairy naevus close to it. Gastronuova¹³ states that neurofibromatosis may be associated with congenital lipomata, plexiform neuromata, syringomyelia and other

dystrophies, including bony malformations. Leontiasis has been occasionally associated with neurofibromatosis.

It is not beyond possibility that there may be some endocrine factor at work. The frequent association of pigmentation of the skin may be of sympathetic or of endocrine origin.

The points in favour of endocrine involvement either primarily or secondarily are, in the first place, the skeletal changes. Pearce-Gould, in 1918,¹⁴ reported bony changes resembling osteomalacia. The present case simply presented porosis in the portion of rib examined and obvious softening of the calvarium, which was not examined microscopically.

Osteomalacia is probably due to dysfunction of the endocrine glands, but which glands are at fault it is hard to say. Some are inclined to blame the pituitary. Erdheim,¹⁵ in 1907, attributed osteomalacia to disease of the parathyroids, and Todyo,¹⁶ in 1912, agreed with this up to a point, but did not find hyperplasia of the parathyroid in all cases of osteomalacia. Secondly, neurofibromatosis associated with acromegaly has been reported by Wolfsohn and Marcuse¹⁷ in 1912, and by de Castro¹⁸ in 1916. Lier,¹⁹ in 1913, reported a case with dystrophia adiposogenitalis. In this connection it is interesting to note that Jeanselme²⁰ reported a case of neurofibromatosis with craniofacial asymmetry and a small sella turcica. Sanz,²¹ in 1916, reported a case of neurofibromatosis with dystrophia adiposogenitalis, and he is inclined to put the two conditions in the same group of "les dystrophies endocrino-sympathiques." Barber and Shaw,²² in 1922, reported a case of neurofibromatosis with hypophyseal tumour, which was possibly a tumour of the optic chiasma pressing on the hypophysis. Thirdly, Bosquet,²³ in 1913, published a case of an Addisonian form of neurofibromatosis and mentions six previous cases in the literature. Vignolo-Lutati,²⁴ in 1916, reported a case with Addisonian symptoms, possibly due to affection of the sympathetic branches by a fibrosis, with consequent adrenal insufficiency.

In conclusion, I beg to thank Dr. M. A. Archdale for permission to publish this case, and Dr. H. A. Cookson for the histological notes and the microphotographs.

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