

PROGRESSIVE LENTICULAR DEGENERATION:

A FAMILIAL NERVOUS DISEASE

ASSOCIATED WITH

CIRRHOSIS OF THE LIVER —

together with an

EXPERIMENTAL RESEARCH

INTO THE

ANATOMY AND PHYSIOLOGY

of the

LENTICULAR NUCLEUS —

by

S. A. KINNIER WILSON:

MA '97: B.Sc. '03: M.B. Ch.B. '02 —

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PREFACE.

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THIS Thesis for the degree of M.D. of the University of Edinburgh consists of two parts.

The first part contains a full and detailed account of what is practically a new nervous disease, to which, for reasons which will hereinafter become evident, I propose to give the name of PROGRESSIVE LENTICULAR DEGENERATION. This disease is familial, in the sense that it may attack more than one member of a family, but it is not hereditary: it may also occur sporadically. It always occurs in young people, either in an acute or a chronic form. As far as my present knowledge goes it is invariably progressive and fatal, its duration ranging from six months or a year to as long as five or six years, or possibly longer. The clinical symptoms form a complex which, once the physician is familiar with it, can be readily recognised, and which is of the greatest interest and importance, constituting as it does what I consider to be a practically pure corpus striatum syndrome. In a word, we have bilateral tremor of both upper and lower extremities and sometimes also of the head and trunk, a tremor which is rhythmical usually, but occasionally irregular, and which increases with volitional movement: we find pronounced spasticity of the limbs and of the face, the latter being usually set in a spastic smile--as my illustrations will show--and in the later stages contracture develops: there is great dysphagia and dysarthria, the latter eventually degenerating into the most complete anarthria: there is spasmodic laughing (rire spasmodique) and emotionalism. As a result of the extraordinary degree of stiffness of the musculature there is considerable disturbance of equilibrium. We find, however, little or no true paresis or paralysis, inasmuch as most, if not all, ordinary movements can be executed, though it may be slowly and feebly. In some cases certain mental symptoms, of a transitory nature,

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manifest themselves, and their significance will be duly discussed. In spite of the great degree of motor weakness and helplessness, the abdominal reflexes are conserved and a double flexor response is obtained. In other words, we have in this affection, where it occurs in a pure and uncomplicated form, an EXTRA-PYRAMIDAL MOTOR DISEASE, the importance of which is apparent not only because of its rarity, but also by reason of the light it sheds on such diseases (to specify only one) as paralysis agitans.

The pathology of the disease is as striking as the clinical syndrome. The lesion, as a glance at the photographs will show, is a bilateral symmetrical softening in the lenticular nucleus, involving more particularly the putamen: the globus pallidus is implicated to a less extent. In addition the external capsule is commonly included in the area of disease, whereas the caudate nucleus is scarcely touched, and--most important of all--in a pure case the internal capsule is absolutely intact. The optic thalamus escapes. If we examine the diseased areas minutely we shall find that a change commences apparently round the terminal lenticulo-striate vessels, as a result of which the lenticular nucleus begins to shrink and atrophy: its cells disappear and its fibres are replaced by glial tissue, the laminae medullares and internuncial fibres gradually becoming less and less recognisable: in advanced cases the nucleus breaks down entirely, and a cavity formation is the result. There is no sign whatever of syphilitic disease of the vessels, all of which are patent; in fact, gross vascular disease is conspicuous by its absence. We are not dealing with anything like thrombosis in the distribution of a particular blood vessel: on the contrary, the extraordinary selective action of the morbid agent will be readily appreciated when we remember that the lenticular nucleus is supplied from more than one source. Yet here we have one collection of grey matter singled out, and others left intact. Compared with this bilateral symmetrical DEGENERATION OF THE LENTICULAR NUCLEUS the other changes found in the central nervous system are slight and relatively unimportant: they will, however, be duly recorded in their place.

What must be considered, however, the most curious and the most remarkable feature of this familial disease is the constant presence of a profound degree of cirrhosis of the liver. This HEPATIC CIRRHOSIS does not reveal itself by any symptoms during life, but it is always found post-mortem. It is mixed in type, being both multilobular and monolobular. As far as it is ever possible to exclude anything, syphilis and alcohol as morbidic agents can be entirely excluded. This association, in young people, of cirrhosis of the liver with bilateral symmetrical softening of the lenticular nucleus constitutes the disease from the pathological standpoint: clinically the symptoms are exclusively nervous. Other organs (thyroid &c,) show changes of secondary importance, which will be described subsequently.

Progressive lenticular degeneration, as I propose to call it, is to all intents and purposes a disease unknown to the profession. As far as I can discover from exhaustive examination of the literature that may bear on the subject, there has been no recorded case since 1890, i e for no less than twenty one years, with the very doubtful exception of one reported by Anton of Halle, under the title of "Dementia choreo-asthenica, with juvenile nodular cirrhosis of the liver", some three years ago. This is really a case of congenital syphilis, in all probability. The total number of cases of this disease that have been published amounts to only six. Of these: -

2 (brother and sister) were reported by Sir William Gowers in 1888 under the name of "Tetanic chorea, associated with cirrhosis of the liver".

1 reported by Dr Ormerod in 1890.

3 (two brothers and a sister) reported by Professor Homen of Helsingfors in 1890.

Dr Ormerod called his paper "Case of cirrhosis of the liver in a boy, with obscure and fatal nervous symptoms". Homen described the condition as "A peculiar disease occurring in three members of a family in the form of a progressive dementia, probably lues hereditaria tarda". All these six cases were fatal. In Gowers' cases no lesion of the central nervous system was found. In Ormerod's there was sym-

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metrical bilateral softening in the putamen. In Homen's the same area was affected in all three, together with sundry other changes to be referred to later. All six had marked cirrhosis of the liver.

Since 1890 there has been no further light thrown on the mystery of the disease, nor has there been any adequate pathological investigation, so that the subject has remained a terra incognita.

In this Thesis I shall describe three cases of the affection which I have personally observed and diagnosed, and in each of which I have made a post-mortem examination.

The first case (S.T.) came under my observation in 1905, and died on July 28, 1908. At the autopsy I found what I had diagnosed during life--as far as I am aware, the first time the disease has ever been diagnosed during the lifetime of the patient--viz. bilateral degeneration of the lenticular nucleus, coupled with cirrhosis of the liver.

The second case (D.P.) came under my observation in 1906 and died on March 3, 1907. In her case cirrhosis of the liver and a slighter degree of lenticular change were discovered.

The third case (E.P.) a brother of the above, came under my observation in 1907. As he went to live in Switzerland I paid a visit to him in Spring 1910, and made an exhaustive examination. On September 20, 1910 he died, near Lausanne, and I went out again to perform the autopsy. I brought all the material home, and in his case also I found bilateral lenticular degeneration, coupled with hepatic cirrhosis.

In addition to these three personal cases, I have obtained the record of two other cases of the disease, one of which occurred in the family described by Sir William Gowers, but which has not hitherto been published, as the notes were lost years ago. By a piece of good fortune I discovered the mother of the family, an old lady of nearly seventy, and from her I obtained the details of this new case. The other is one referred to by Ormerod in his paper of 1890: the notes of the case, not hitherto published, are preserved in the National Hospital, Queen Square, London.

Thus I am in a position to add five cases to those already reported, and by a clinical and pathological invest-

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igation which has extended over four years I hope to have been able to add materially to our knowledge of a little known subject. I have made a complete pathological examination of my material in a way that has not previously been attempted, since modern methods of research have been at my disposal, and I have correlated the clinical and the pathological features of the disease in an entirely new manner. Thus I have been able materially to elucidate a rare disease which from its remarkable nature opens up a whole field of pathology in which very little work has as yet been done.

Realising how many problems of anatomical and physiological interest are suggested by a disease that selects the corpus striatum and leaves the pyramidal tracts unaffected, eighteen months ago I commenced an experimental investigation into the anatomy and physiology of that structure, under the aegis of Sir Victor Horsley, in his laboratory at University College, London. The second part of this Thesis, therefore, contains the record of a long series of experiments on monkeys and cats, which is not yet quite completed. Using the instrument of Clarke and Horsley we have made electrolytic lesions in the putamen and globus pallidus, and the whole of the material has been worked up by myself. The results obtained up to date are fully described in the second part. It will be seen that they throw <sup>some</sup> ~~much~~ light on the pathological physiology of some of the symptoms of PROGRESSIVE LENTICULAR DEGENERATION.

The accompanying Index will explain the plan of the Thesis, and the order in which the material is handled. The following recapitulation, however, will serve for a "bird's eye view" of the field. An historical introduction gives an account, in chronological order, of the six previously recorded cases, and this is followed by a clinical and pathological description of my own cases. With these as a basis, we proceed to a comprehensive study of the disease and of its problems. Results and conclusions are summarised. The vexed question of the functions of the basal ganglia is fully discussed, and the new light thrown on it by my cases is

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indicated. Analogies with other nervous diseases are drawn. Experimental evidence from personal observations is described in full. A concise and complete sketch of the disease is supplied. In an appendix previously recorded cases are given in detail. Final conclusions are stated.

I wish here to express my grateful thanks to Sir William Gowers, Sir David Ferrier, and Dr Ormerod, for permission to utilise their notes on the cases I have observed, which were at one time or another under their care: to Dr W.H.B. Stoddart of Bethlem Royal Hospital for similar permission, as also to Dr G.W. Smith of Virginia Water Sanatorium. I owe a very great deal of help in the experimental work to the kindness of Sir Victor Horsley, who has performed my operations for me, and has assisted me in many ways.

The whole of the pathological investigations have been made by myself. The cutting of the brain of case I in serial section, its preparation, staining, and mounting have been done by myself. All the photography, clinical, and pathological, is my own work.

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*[The following text is extremely faint and illegible, appearing to be a reprint of a medical case report or a series of notes. It contains several paragraphs of text, but the characters are too light to transcribe accurately.]*

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CHAPTER I.

HISTORICAL.

THE first two recorded cases of the disease which forms the subject of this Thesis we owe to the clinical acumen of Sir William Gowers, who in the year 1888 published in his well known Manual the following paragraph, under the title "Tetanic Chorea" (vol II, page 656):-

"A case was recently under my care that presented symptoms intermediate between those of chorea and tetany. The disease was fatal, and no lesion was found after death. The patient was a boy aged ten. A brother was said to have died from some affection similar to that from which this child was suffering. There was a history of three other relations having suffered from maladies resembling chorea. In this patient the disease commenced gradually seven months before death. The symptoms consisted of tonic spasm, which was continuous, and varied by paroxysmal attacks of similar but more intense spasm. The face was involved on both sides, so as to cause a constant peculiar smile. The tongue was pressed back against the palate in such a manner as to impede swallowing and prevent speech. The arms were extended, pronated, and rotated inwards, so as to bring the back of the forearms outwards, while the fingers were generally slightly flexed at all joints, but at times were extended and slowly moved in the irregular way characteristic of athetosis. The legs were extended at all the joints, the feet being over extended in talipes equino-varus, and the toes were flexed. At times the spasm at the hip became flexor, so that the extended legs were raised off the bed. The muscles of the trunk were also involved in the spasm. At first the left side was the more severely affected, but afterwards the spasm became equal on the

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two sides. The electric irritability of the muscles was normal, and there was no mechanical excitability of the nerves. There was considerable pyrexia during the more severe stage of the disease. The boy steadily emaciated, and died from exhaustion. The whole central nervous system appeared normal to the naked eye, and no distinct morbid appearances could be discovered on microscopical examination. I have not been able to find a description of any similar case."

This bare outline of an historic case, <sup>for</sup> as the earliest recorded instance of a new disease must always be <sup>historic,</sup> is altogether too meagre: the fact that the boy was found to have cirrhosis of the liver is not even mentioned, as its significance was not at that time appreciated. The original notes, however, preserved in the National Hospital, Queen Square, London, are remarkable for their fullness and accuracy of description, and in particular for the wealth of illustration incorporated with them. Copies of the drawings and old and partly faded silver prints with which the notes are enriched will be found below, ~~and also in the Appendix.~~

Not long after, the sister of case I, a girl of 15, came under the observation of Sir William Gowers, suffering from identical symptoms, which ran an identical course, and terminated fatally in a few months. Realising the great interest of the condition, Sir William Gowers republished the cases in the Review of Neurology and Psychiatry, <sup>for</sup> 1906, in fuller detail, under the heading, "Tetanoid chorea and its association with cirrhosis of the liver". In the opening paragraph of this communication the following passage occurs:

"These cases were under observation many years ago, and their record has been waiting for other facts that might elucidate their mystery, but waiting in vain. They are now presented in the hope they may direct further attention to these strange forms of disease".

From the original notes of these two cases I have made the following precis, in which the cardinal features of the condition as observed by Sir William Gowers are succinctly described from the clinical and pathological standpoints.

CASE I.

Sydney M., aged 10 years, was admitted to the National Hospital, Queen Square, London, on October 5th, 1886, under the care of Dr Gowers.

The patient was the eighth of 14 children, and had had no illnesses except typhoid fever, at the age of three. An uncle on the father's side was said to have been affected in the same way as the patient, and to have recovered after an illness of 12 months. The eldest brother had died at the age of 15 of some form of paralysis. (This is the case whose notes have been lost, but whose history I have obtained from the mother of the family, still living at the age of 69. It will be found below among the new cases. There is no doubt it belongs to the series. S.A.K.W.)

The symptoms began gradually, without exciting cause, three months before the patient was admitted to the hospital, with clumsiness and awkwardness of the hands: about the same time involuntary movements of the arms and legs commenced. On admission constant slowly changing movements in the limbs attracted attention, as well as a generalised spasticity. A contraction of the zygomatics caused a continuous smile, now greater on one side, now on the other. The mouth was usually held spasmodically open, and the tongue generally back in the mouth: occasionally it was slowly protruded. When told to shut his mouth the patient used to push the lower jaw up with his hand, then the spasm of the muscles would seem to give way and he would close his mouth easily, but it returned to the widely open position in a minute or so. A great degree of dysphagia was present, and also of dysarthria: his speech was usually almost unintelligible, but occasionally he could utter words or sentences more distinctly, especially in the morning. As he lay in bed he often made a low whining sound.

The muscles of the neck, trunk, and limbs were all involved, in varying degree, in the generalised tonic spasm: sometimes involuntary movements not unlike athetosis occurred in the fingers, at other times the arms and hands were definitely tremulous. The extremities were in a state of

contracture, the fingers flexed, the forearms pronated, while the feet were extended and inverted, and the toes flexed: in spite of the great degree of spasticity occasionally it relaxed sufficiently to allow the contractures to be overcome. Voluntary movement was interfered with by the spasm to a less extent than might be anticipated: the patient could take hold of any object with little difficulty. He was able to walk, although the heels were usually off the ground, but sometimes they came down and he walked naturally. There was no sphincter impairment. The knee jerks were present: ankle clonus was not obtained. The plantar reflex was "slight". (This was long before the days of insight into the significance of the plantar reflex). The cremasteric reflex was active: the abdominal was not elicited. Sensation was everywhere normal. The optic discs were normal: the mind was clear: the patient could write down what he was unable to articulate, and evidently understood everything that was said to him.

During the first few days after admission some improvement occurred, but thereafter the patient became steadily worse. His temperature rose, and continued highly irregular. <sup>[Figure 9]</sup> He became drowsy, and began to pass his urine and stools into the bed. The dysarthria and dysphagia increased: the spasmodic contractions of the musculature intensified: the extremities became more definitely contracted. Emaciation set in rather rapidly, he gradually sank into a more and more helpless state, all the symptoms aggravated, and after 11 weeks from the date of his admission and 6 months from the commencement of the symptoms he died.

A post-mortem examination was made: naked eye investigation of the brain, cord, and membranes revealed nothing abnormal. The liver was noted to be firm, hard, and lobular, and was evidently cirrhotic. Portions of the cortex, cord, peripheral nerves and muscles, examined microscopically, did not show any departure from the normal.

A glance at the accompanying photographs, which have been reproduced from the original silver prints, kindly loaned me by Dr T. Wilson of the General Hospital, Birmingham

ham, who was Resident Medical Officer to the National Hospital at the time, will serve admirably to take the place of fuller description. It must be remembered they were taken before the days of instantaneous photography, hence the tremulous movements of the arms are well shown: indeed, for my purpose, this is almost to be preferred, as it accentuates a contrast between the spastic tonic smile and wide opened mouth and the tremors of the upper limbs. The contractures of the hands and feet are well seen. The progressive emaciation can be readily appreciated. The drawings are copied from the original sketches in the notes, depicting the condition of the distal portions of the limbs. [Figures 1-8].

No one who compares these photographs of twenty five years ago with the series illustrating my own cases can fail to be struck by the almost startling resemblance between them. The same spastic smile, open mouth, tremors, contractures, emotionalism, are portrayed by the unerring camera in such a fashion as to render comment needless.

In the light of subsequent knowledge the points to emphasise in Sydney M.'s case are the following: -

A boy of ten suffers from an acute and fatal illness of six months' duration, whose features suggest strongly it is of a toxic or toxi-infective nature. The only certain pathological condition found post-mortem is cirrhosis of the liver. Nevertheless the clinical symptoms are exclusively nervous, are from the outset severe and progressive. They consist of dysarthria and dysphagia, emotionalism, generalised spasticity of the musculature of face, trunk, and extremities, tremulous and sometimes irregular involuntary movements of the limbs, without any true paralysis, as most ordinary movements can be performed--though this accentuates the involuntary <sup>movements</sup> contractures that can at first be overcome, but gradually establish themselves, permanently, and emaciation. Sensibility is intact, and there is no indication of interference with the pyramidal system.



X

Fig. 1.

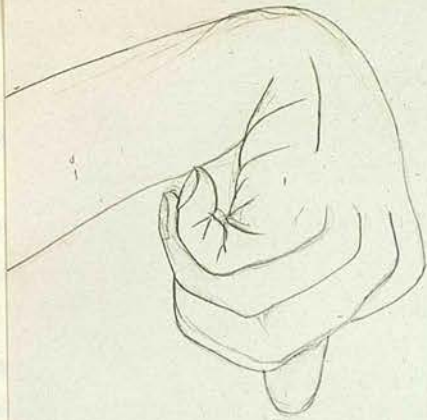


Fig. 2



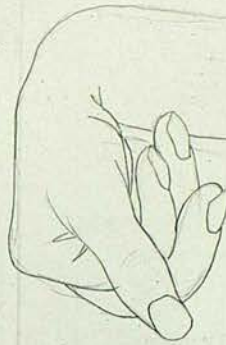
Fig. 3

Copied from the old silver prints in the possession  
of Dr. Wilson of Birmingham —  
They represent S.M. as on admission to the  
National Hospital, Queen's Lane, London — October 1886.



Oct 30<sup>th</sup> / 86

Fig. 4.



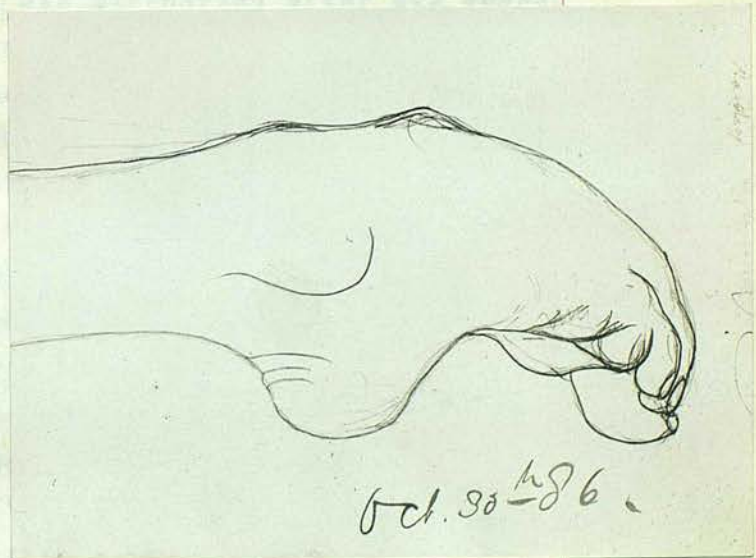
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Fig. 5.

X



Fig. 6.



Oct. 30<sup>th</sup> - 86

Fig. 7.

X

Drawings copied from the originals in the notes prepared in the National Hospital.  
Photos copied from old silver prints -



Fig. 8.

Charlotte M., aged 15, the sister of Sydney M., was admitted to the National Hospital on August 29th, 1888, under the care of Dr Gowers.

She had always been a healthy girl. Menstruation began about a year before, and was quite regular for seven months, then ceased abruptly.

For the last nine months she had been getting listless and lethargic, and disinclined to do anything. Her speech was noticed to become thick and indistinct, and occasionally saliva escaped from her mouth. On admission she was seen to be a heavy looking girl, with mouth generally open and lower lip hanging down, and she was easily excited to laughter. Her tongue was found to be tremulous. She presented no other sign, and no evidence of organic disease of the central nervous system. Accordingly she was discharged after six weeks, but a month or two later involuntary movements of the limbs commenced, and progressed steadily, so that she was "always on the work". She used to be able to write well, but her caligraphy rapidly deteriorated, so as to become almost illegible. She was readmitted to the hospital on January 2nd, 1889. On examination the striking feature was the more or less constant rhythmical tremor of arms and legs. As she lay in bed there was constant regular movement of the feet, with alternating flexor and extensor movements at the hips and knees. Similar rhythmical movements, consisting of alternating contractions of flexors and extensors, occurred in the arms. They could occasionally be stopped for a few seconds by voluntary effort. The lower extremities were rigid and contracted, and passive movements caused some pain.

The illness ran a steady downhill course. The patient became emaciated and febrile: <sup>[Figure 10]</sup> the tremors persisted, the rigidity increased. No sign of organic nervous disease was present, in the ordinary sense, except that the knee jerks could not be elicited, presumably because of the rigidity. Death took place on January 30th.

On pathological examination no definite morbid appearance was found in the brain or cord, but the liver showed an advanced degree of cirrhosis, strands of connective tissue enclosing nodules of varying size.

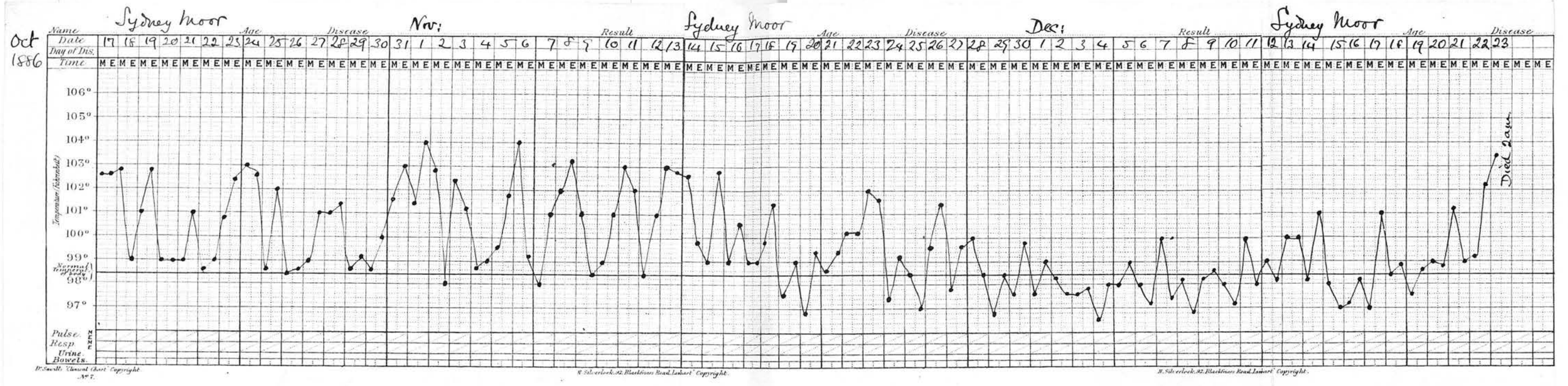


Fig. 9.

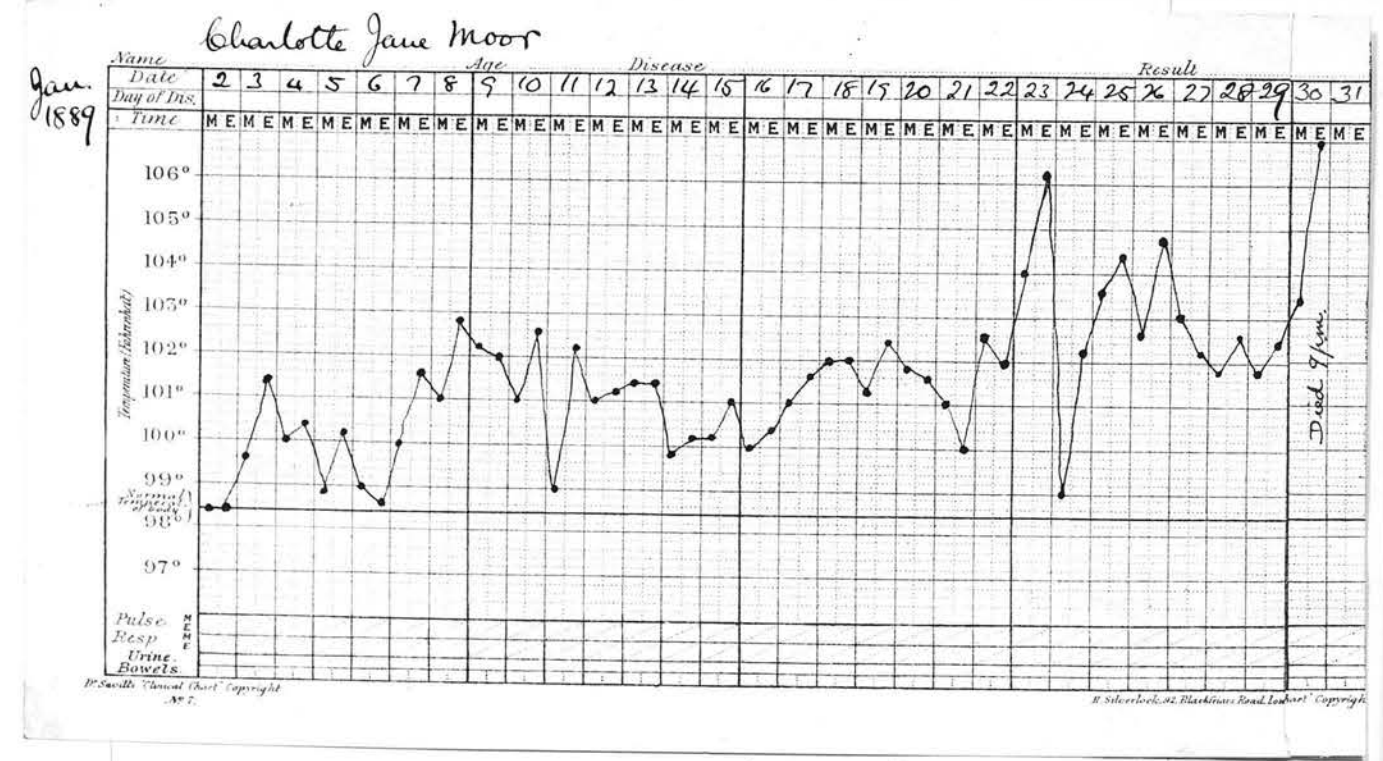


Fig. 10 5 1/2"

Temperature chart of S.M. & C.M. from the originals in the Maternal Hospital

Both from the clinical and the pathological aspect the resemblances between this case and the previous one are of the closest. In spite of the grave and progressive nature of the nervous symptoms no obvious lesion was found in the brain or cord to account for them, whereas an entirely latent and unsuspected hepatic cirrhosis was discovered. It is a curious feature of the disease that in all the recorded instances, as well as in my own series, the cirrhosis has not revealed itself by any of the usual signs. Of this second case it may be remarked that the involuntary movements were less irregular, more definitely rhythmical and tremulous, than in the first case. We shall see later that on this point the resemblance to the new instances of the disease reported in this Thesis for the first time, is perfect. Although Sir William Gowers has described these cases as "tetanoid chorea", the involuntary movements were never really choreiform, while the epithet tetanoid is intended to specify a clinical appearance solely, and not a pathological relationship.

### CASE III.

The third case was recorded by Dr Ormerod in the St. Bartholomew's Hospital Reports for 1890. The clinical notes of the case were made without any knowledge of ~~these~~<sup>the</sup> cases at the National Hospital: the resemblances, therefore, are all the more striking. I cannot do better than quote the resumé of his case given by Ormerod in the opening paragraphs of his paper.

"A boy, aged ten, previously healthy, is admitted with the following history. He has been getting ill gradually for three or four months. The symptoms alleged are, in order of their development, weakness of right hand and arm, with cramped position of the fingers, soon followed by difficulty of speech. "Drawing" of the face, then an unnatural gait. Speech gets worse: he seems "silly": has some difficulty in swallowing. Gait gets much worse. Lastly, some affection of left arm and hand.

The existence of these symptoms is verified after admission--a clumsiness of the right hand, with flex-

ion of the thumb into the palm, and a tendency to rigidity at the knees, with uncertain, stiff gait, is noted. The only marked symptom, however, is inability to speak. He is not aphonic: he understands all that is said to him, but says nothing, except on some rare occasions, when he speaks quite intelligibly. He has difficulty in protruding his tongue.

In about three weeks paroxysms of pain, with contractions, begin in the left hand: he takes to ~~shrieking~~ shrieking. In ten days more he becomes very noisy, and apparently idiotic. The facial spasm becomes more marked. Nevertheless his symptoms are so vague, and apparently so much under his own control, that it seems probable that there is no organic lesion to account for them.

This view, however, is negatived by the advent of more serious events. For six or seven weeks from the time of admission he becomes feverish: pulse very frequent: profuse sweatings. The legs become permanently drawn up, the right hand becomes weak, and like the left.

His mental condition appears to get worse, and he lies howling all the day long. Finally, an acute bed sore and signs of cystitis appear. In spite of a certain temporary remission, his condition gets worse, and the poor child dies, miserably emaciated, and his limbs distorted by contracture. Death takes place about four months from the time of his admission, and some seven or eight months from the commencement of his symptoms.

Post-mortem certain slight changes are found in the nervous system, but he has well-marked atrophic cirrhosis of the liver".

These changes in the nervous system, though designated "slight" by the author, are of the greatest significance. They consisted in a bilateral and in every way symmetrical area of softening occupying the putamen or outer section of the lenticular nucleus, extending for about an inch in an antero-posterior direction, and involving chiefly the ex-

Walter S. (Ormeau)

Age 10

Dec

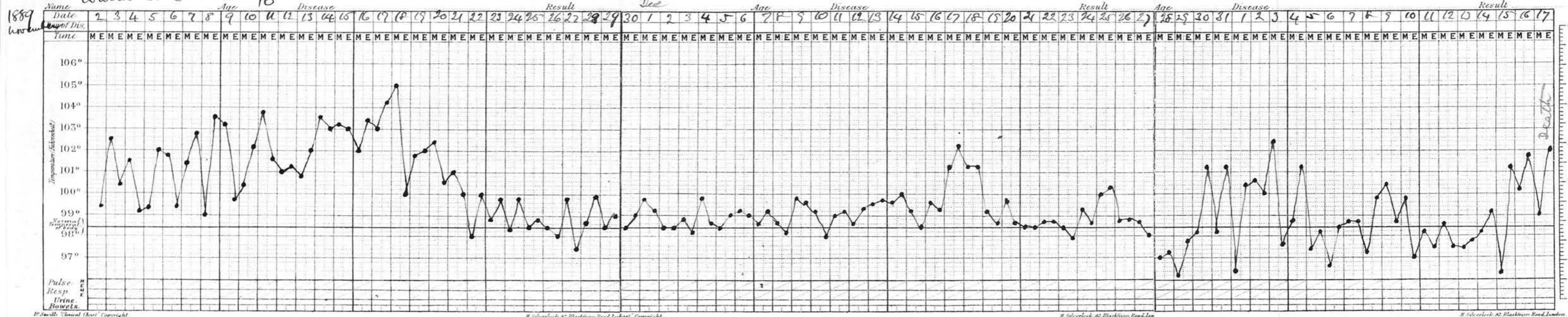
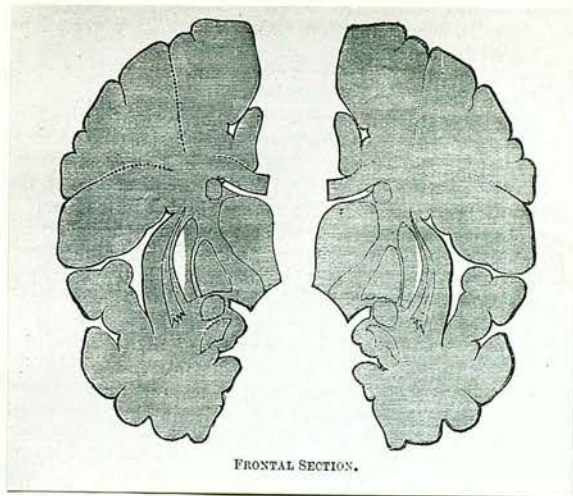


Fig. 11.

Temperature chart of W.S. (Ormeau's case)  
taken from St. Bartholomew's Hospital Reports, 1890—



X

Fig. 12.

Bilateral lenticular softening in Omerod's case  
(St. Bartholomew's Hospital Reports, 1890).

ternal part of the putamen. The tract of disease on the right side was smaller in extent than that on the left. The accompanying figure is a reproduction of the drawing given Figure 12 in Ormerod's paper, and shows the appearances on frontal section at the level of the optic commissure. Microscopically the affected areas were found to consist of closely packed lymphoid cells, in which a few vessels ran, and are supposed by the author to have been inflammatory. The spinal cord was perfectly normal. In the liver the characteristic appearances of cirrhosis were present, although the cells of the lobules were less degenerate than might have been expected, while amid the connective tissue growth bile ducts were very numerous, and very prominent objects.

No one who peruses this brief sketch of these three cases now more than twenty years old, can fail to appreciate their astonishing similarity. Indeed, they form a special group by themselves, for the cases published by Homen, as well as those of my own series, are more chronic, <sup>and</sup> more slowly progressive; less dramatic, if the expression be allowed, yet none the less fatal, and more or less identical in their pathology with that one of Ormerod's that we have just described. These first three cases occurred in young people, beginning in an insidious way without apparent cause, and were characterised by dysarthria, dysphagia, spasticity of the musculature, involuntary spasmodic movements, (sometimes slow and tonic, oftener clonic and treaulous,) contractures, and emaciation: the patients were obviously seriously ill, with high irregular fever, great helplessness and weakness, yet both Ormerod and Gowers were struck by the fact of the occasional variability of the symptoms, and point out how readily and reasonably they might have been regarded, at least to begin with, as "functional", i e hysterical. There was a curious disproportion between the clinical appearances and actual signs, that is to say objective signs, of organic nervous disease. I may remark in this connection that two of my own cases were at one time thought to be hysterical, and treated accordingly. It is, I believe, simply because we have been so ignorant of the symptomatology of extra-pyramidal motor affections that mistakes of this

sort have occurred. No one doubts today that paralysis agitans is an organic disease of the nervous system, yet it is not so long ago that its accepted place in the textbooks was with neurasthenia and hysteria.

Before passing on to the next group, viz. those described by Homen, we may note that Ormerod specifically draws attention to the following three points: -

1. The presence of a cirrhotic liver in so young a subject:
2. The absence during life of all ordinary symptoms of cirrhosis of the liver:
3. The presence of severe and fatal nervous symptoms in a case where the nervous lesions found post-mortem were comparatively insignificant.

We shall be better able to discuss these problems when we have become acquainted with the results of my own pathological investigations, as I believe they will materially aid us in this respect. Nor need we be embarrassed at the apparent absence of any definite positive findings in Gowers' cases, for in the first place the acute nature of the malady may not have allowed time for the development of changes that could be recognised, and in the second place histology has made considerable strides since the eighties of last century.

CASES IV, V, and VI.

Under the somewhat cumbersome title of "Eine eigenthümliche bei drei Geschwistern auftretende typische Krankheit unter der Form einer progressiven Dementia, in Verbindung mit ausgedehnten Gefassveränderungen (wohl Lues hereditaria tarda)", Professor Homen of Helsingfors published in the "Neurologisches Centralblatt" for 1890, the same year as Dr Ormerod's paper, appeared, and again more fully in the "Archiv für Psychiatrie" for 1892, an account of an apparently unique and unknown disease, which for various reasons but in spite of the lack of positive evidence he concluded might be a manifestation of delayed hereditary syphilis, a disease in which a sister and two brothers ~~were~~ out of a family of eleven, were affected, which ran a steadily progressive

course and in each instance ended fatally. Its duration in these cases was 3½, 6, and 7 years respectively. The clinical picture presented by the disease, and the pathological changes found post-mortem, were not only identical in all three, but on all essential points offer the closest analogies to the description already furnished of the English group.

The following resumé of the cases, <sup>made</sup>~~taken~~ from Homen's second paper (Archiv für Psychiatrie Bd XXIV Hft I, 1892), includes the main features of this remarkable familial affection.

CASE IV (Homen's no. II).

Alfred K. was born in December 1866 and enjoyed perfect health up to the age of twenty. Without any apparent reason he then began to suffer from a general listlessness, and loss of appetite, and at the same time he seemed to become slow in his mental processes, and, generally speaking, more "simple". After about six months his gait was noticed to be getting stiff and uncertain: his articulation became indistinct, and tremor appeared in the arms and hands and became more and more pronounced. The stiffness, dysarthria, and tremor advanced to such a degree that the patient was reduced to a state of helplessness.

On admission to hospital the chief symptoms and signs were as follows: -

The youth had a rather childish and stupid expression, the facial muscles being fixed and stiff: he seemed to understand everything that was said to him, but he scarcely ever spoke, and then always slowly: there was slight difficulty in moving the tongue. As he lay in bed the head was seen to have a slight more or less constant to and fro movement: the mouth was almost always open, the lower jaw tremulous: both arms and hands were contracted, the former being somewhat flexed at the elbows and the fingers flexed proximally but extended distally: they were very stiff and passive movements were with difficulty impressed on them. The right hand was less affected than the left. A slow slight tremor of the hands from the wrists, in a radio-ulnar direction, was constantly observable: sometimes it was rotatory: a rhythmical tremor of alternating flexion and extension was

often noticeable at the elbow. The lower extremities were also somewhat contracted, and when the patient was put on his feet he required strong support, and even then the rigidity made progression almost impossible. Tremor of the legs was very frequently noticed, especially when any voluntary movement was executed, chiefly consisting of alternating flexion and extension at knee and ankle. Voluntary effort always aggravated the tremor of the arms. There was some wasting of the muscles: sensibility was intact.

The condition became steadily worse. Occasionally the patient spoke a few words distinctly, but he gradually became more and more inarticulate, as a rule simply giving vent to unintelligible sounds. The contractures increased: the tremors became generalised, and were sometimes observed in "attacks" which lasted for five or ten minutes and involved the whole musculature. Saliva escaped from the opened mouth. Attacks of clonic and tonic spasm spreading over the limbs of a minute's duration, occurred during the last few weeks of life. Emaciation set in, bed sores appeared: sphincter control was forgotten, the patient passing everything beneath him. Difficulty in eating and swallowing increased: the temperature rose slightly, and on the 13th of September 1890 he died, having scarcely reached the age of 24.

At the autopsy the grey matter of the frontal convolutions was thought to be slightly atrophic or thinned, but the brain was of good size, weight, and shape: on horizontal section the middle <sup>zone</sup> section of each lenticular nucleus was found to be softened and discoloured over an area of about one centimetre in length and breadth. Slight sclerotic patches were discovered in the aorta and some of its main branches. The liver showed an advanced degree of cirrhosis.

Of the microscopical examination the following points will suffice for our present purpose. There was possibly some slight diminution in the myelinated fibres of the cortex in the frontal regions. While the pia mater was somewhat thickened, there was no small cell infiltration, or only slight and scattered: the blood vessels in the grey and white matter of the cerebrum were in many places irregularly thickened and hyaline or sclerotic in appearance: fine granules

staining black with osmic acid were often noted in the vessel walls. The thickening seemed to be due to the presence of fine granular masses of this description. While occasionally small round cells were found in the neighbourhood of vessels they were few in number by comparison with the appearances in a brain of a general paralytic, used as a control. The arteries of the middle cerebral distribution--lenticulo-strate, &c--were examined specially, and showed the same hyaline or sclerotic alterations: there were small collections of granular material, sometimes homogeneous-looking, sometimes with nuclei, which lay round the elastic lamina, and occasionally bulged into the lumen of the vessel.

The spinal cord was normal.

The only remark that need be passed at this stage, in reference to the microscopical findings, is that the vascular alterations cannot be said to resemble in any way an endarteritis obliterans: in fact Homen never uses the word in his description, and never refers to actual changes in the intima.

CASE V. (Homen's no. III).

Wilhelm K. was born on August 8th 1870. He grew up a plump and healthy boy till the age of twelve: then, in the autumn of 1882 he began to complain of a general feeling of tiredness, and his memory and mental powers seemed to deteriorate. His gait, <sup>at</sup> ~~the~~ the same time, became somewhat uncertain, and about a year later his articulation became defective. His arms became stiff to move, so that he had difficulty in making use of them, and simultaneously tremors developed in them, while the lower extremities began to become spastic or rigid. Very gradually contractures appeared, more especially at the knee and hip. After three or four years of this, the patient was so helpless as to be bedridden: he scarcely ever spoke, and then only with difficulty and great indistinctness: his mouth was usually open and saliva drooled from it.

On December 11th, 1888, he came under the observation of Homen. It was noted that his speech was reduced to the enunciation of an occasional inarticulate and unintelligible

sound, yet he sometimes managed to express some words with comparative clearness, especially if he was excited or disturbed. He lay in bed with his limbs contracted and drawn up, and yet by an effort of the will they could be very considerably extended, though not completely. Tremor was particularly well marked in the hands and arms, less obvious in the head and lower extremities. He passed his urine and stools into the bed. Emaciation was pronounced. The pupils reacted to light: cutaneous reflexes were present, but the tendon reflexes could not be tested because of the contractures. Some small bedsores appeared. The patient gradually sank and died on October 17<sup>th</sup>, 1889, aged 19 years.

At the autopsy a horizontal section through the hemispheres showed that the optic thalamus, caudate nucleus, and internal capsule were perfectly normal, whereas symmetrically placed in each lenticular nucleus was an area of softening and degeneration that had resulted in a cavity formation. This cavity was about 3 centimetres long and spread downwards and backwards to the lower extremity of the nucleus. The tissues round it were thickened. Rather more than one half of the nucleus, in breadth, was involved in the lesion. No other pathological change was visible to the naked eye. A few small sclerotic patches were found in the aorta, more particularly in its abdominal portion. The liver was in a condition of advanced cirrhosis.

Microscopically, the blood vessels of the brain were in some places irregularly thickened by the presence of granular or homogenous masses between the membrana fenestrata and the intima: this granular change was apparently of a fatty nature in some instances, in other places it seemed to be more definitely cellular. Other blood vessels seemed to be widened. Small round cell vascular infiltration was practically absent.

Round the diseased area in each lenticular nucleus the neuroglia was thickened, and cellular: but no microscopical alterations were discoverable in the other basal ganglia or in the internal capsule. The spinal cord was normal.

CASE VI (Homen's no. I).

Anna K., the eldest member of the K. family, was born on July 26th, 1862. She was a perfectly normal and healthy child and girl, who never suffered from any special illness, and who had menstruated regularly at a normal age.

Towards the end of the year 1882, when she was 20 years old, identical symptoms to those from which her brothers had suffered appeared in her case, viz. headache, tiredness, loss of appetite, weakness, and impairment of memory. A few months later her walking became defective, and her catamenia ceased. Then generalised stiffness and spasticity of the trunk and limb musculature set in, and her speech became less distinct. Very gradually the arms and legs contracted, the elbows, hips and knees being the joints chiefly affected, and tremor developed in the arms and hands. As a result she became so helpless that she had to take to her bed. Dysphagia was a marked feature of the case. Her mouth was usually open, and saliva escaped from it.

On August 29th 1888 she came into hospital. She lay in bed helpless and apathetic, with a silly expression on her face: indifferent to her surroundings, she passed everything underneath her: she could not speak, as a rule giving vent to a few inarticulate noises from time to time, yet occasionally she appeared to wake up and then could articulate one or two words, though with difficulty. She died from inflammation of the lungs on October 19th 1888, at the age of 26.

On post-mortem examination the middle parts of both lenticular nuclei were found to be spongy and softened in consistence, and to be of a speckled patchy greyish yellow appearance. The liver was profoundly cirrhotic.

Microscopically the central portion of the lenticular nucleus, on each side, over an area of about one to two centimetres long and one centimetre broad, was discovered to be in a state of commencing disintegration, with disappearance of nerve fibres and cells, and slight small cell infiltration. A few small circumscribed endarteritic changes were noted in the sylvian vessels.

The accompanying photographs are reproduced from Homen's paper: fig. 13 represents his second case, taken about 18 months before his death: fig. 14 is his third case, taken about four months before the fatal termination. The latter conveys an excellent idea of the condition of the patient: the fixed smiling expression, open mouth, emaciation, and contractures of arms, hands, feet and legs are well shown.

Such, then, are the three cases observed and described by Homen, which form a clinical picture of so definite a type that it is difficult to imagine how any one familiar with the author's publication could fail to diagnose the condition if occasion arose. We can only conclude that either the paper has been lost sight of, or that the affection is characterised by extreme rarity, for as far as I know no other instance of the disease has been recorded since, during the last twenty years. (I shall refer at the end of this chapter to Anton's case, published in 1908. While it presents definite analogies to the disease under discussion, I am not convinced that its inclusion in the series is justifiable). The resemblance of Homen's group to the other three is very close. If we except the duration, and the fever, there is little else in which the two sets of cases differ. We have the same insidious onset, without apparent cause, in young people who have always enjoyed good health, the same steady progression, without any remissions, of symptoms mental and nervous, until the patient is bedridden and helpless, the same dysarthria, involuntary movements, rigidity and contractures, the same emaciation and fatal issue. If we go into a little more detail, we find that Homen is struck by the odd way in which the patient is able to articulate at one time better than another, as also by the fact that in spite of contractures there was often a still fairly wide range of voluntary movement, if an effort is made; from the negative standpoint, there are no ocular symptoms, the pupils reacting to light, there is no objective sensory disturbance, no particular alteration in the reflexes, beyond the difficulty in eliciting the knee jerks owing to the muscular condition, no impairment of "le langage intérieur". On very insufficient grounds, as I believe, Homen came to the conclusion that

Arch. f. Psychiatrie etc. Bd. XXIV.

Taf. III.

No. II. Juni 1889.

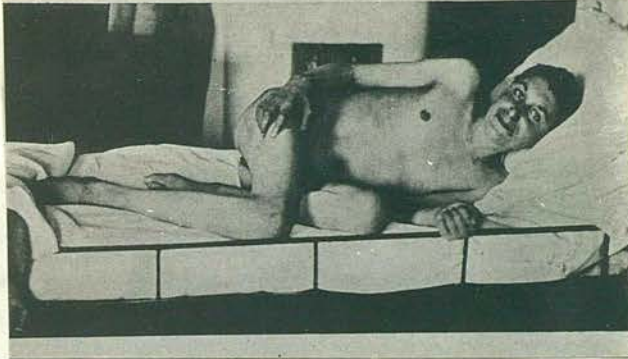


Fig. 13.

No. III. Juni 1889.



Fig. 14.

Homier's Case II + Case III, from  
Archiv für Psychiatrie, 1892.

X  
Original  
Archiv für Psychiatrie

he was dealing with one of the manifestations of syphilis hereditaria tarda; he could obtain no parental history of syphilis, nor did any of his cases present syphilitic stigmata. From the pathological point of view, moreover, his descriptions do not suggest syphilitic endarteritis. Unfortunately there is not a single illustration of any of his preparations, so that we must judge to the best of our ability from the evidence furnished. This evidence we shall examine fully in a subsequent chapter.

Towards the end of his article Homen declares that the clinical phenomena find a complete explanation in the results of the post-mortem investigation, but when we proceed to scrutinise his correlation of the two we note it is open to a great deal of criticism. The tremors and spasticity or rigidity he attributes to cortical irritation, as also the contractures, though probably in the later stages of the disease the nutritional element entered into ~~these~~ their causation: the difficulty in speaking, and in swallowing, the open mouth and sialorrhoea, are all dependent more on the general intellectual deterioration than on any local factor, and similarly with the incontinence of urine and faeces.

It is evident that he assigns much more significance to the slight diminution in the myelinated fibres of the frontal region, the slight changes in the cells of the cortex, the scattered and irregular alterations in the cerebral blood vessels, than to any other pathological defect. In spite of the fact that every one of his cases was found to have bilateral lenticular softening he does not even refer to it specifically, much less attribute any of the clinical phenomena to its presence! There is no hint of any possible importance to be attached to it, not a word on the association of dysarthria and involuntary movements with disease of the basal ganglia, no distinction drawn between pyramidal and extra-pyramidal motor disturbance. After working at the subject for more than four years I may be allowed to say how fully I appreciate the splendid contribution of Homen, but the more I study it the more convinced I am that he entirely failed to grasp the essential and fundamental features of this remarkable disease in the light of cerebral function and physiology. Twenty years, of course, have witnessed

great advances in our knowledge of the central nervous system, and we today have entered into this inheritance. Homen does not seem to have realised the fact that his cases were all bedridden and almost immobile for months before they died: we read nothing of possible terminal infections, nor of the grossly defective nutrition, influencing the pathological element in the disease. The remarkably interesting association of cirrhosis of the liver with degeneration of the lenticular nucleus and not of other nuclei is not so much as mentioned.

We need not delay, however, over defects which seem very obvious at this distance of time: we owe Homen a debt of gratitude for his masterly descriptions, but enough has been said to show that as far as the interpretation of the phenomena is concerned his insight is not sufficient, and this chapter of the disease, therefore, must be rewritten.

I have referred more than once to an article by Professor Anton which appeared in the "Münchener medizinische Wochenschrift" for 1908, under the title "Dementia choreo-asthenica mit juveniler knötiger Hyperplasie der Leber". In this communication Anton describes the case of a young girl of 14, whose development was very backward, as she corresponded in size to a child of 8, and who had always been weak and easily tired. In her early years at school she had been noted for making faces, inattention, unmannerly behaviour especially at meals. Her gait gradually became stumbling, her control over her limbs ineffective: she let things fall out of her hands, and her handwriting deteriorated. When she came under observation it was remarked that she stuttered: involuntary choreiform movements occurred, interfering with voluntary acts: her gait was ataxic. The reflexes were increased. Her mental condition varied very much: she seemed facile and simple, but tired readily and became uncommunicative. Gradually her physical condition weakened: glycosuria was present. Her speech became dysarthric, she kept her mouth open, and often had attacks of impulsive laughter: her limbs sometimes trembled, but amorphous and incoordinate movements were more frequent. Mentally she degenerated profoundly, becoming definitely demented. Towards the end convulsive at-

tacks occurred, with conjugate deviation of the eyes to the right. She died from symptoms of heart failure.

At the autopsy the first left frontal convolution, and part of the second, were softened, extending from almost the frontal pole to a point about 2 centimetres in front of the precentral convolution. The pons was atrophied. The right suprarenal was atrophic in its lower third. The genitalia were infantile. The liver was typically cirrhotic, in nodules varying greatly in dimensions, and hypertrophied. On microscopical examination there was marked thickening of cerebral blood vessels, especially in the frontal regions, but also in the cerebellum. The softening in the left frontal lobe was a gumma. The putamen on both sides was softened, and the external capsule partially. The antero-mesial part of the optic thalamus was poor in both fibres and cells. Small cell infiltration was noted more particularly in the cerebellum.

This case is interesting from several points of view, and it presents certain analogies to the cases already mentioned, which need not again be specified. Pathologically, however, there seemed to be no doubt of the syphilitic nature of the case: it must, therefore, be classified as congenital cerebral syphilis. The frank infantilism, the glycosuria, the complete dementia, find no counterpart in any of the other cases, or in my own. It is of value, however, for this reason, that part both of the clinical and of the pathological features is in harmony with the findings in the other cases, especially Homen's, to which indeed Anton refers.

Such, then, in brief, are all the recorded cases of the disease which I propose to call "Progressive lenticular degeneration". They constitute a little known chapter in nervous pathology, but from their very incompleteness are suggestive. The problems which they present it will be the purpose of this Thesis to attempt to elucidate.

CHAPTER II.

C L I N I C A L C A S E S .

In this chapter the clinical histories of three personally observed cases are given in detail. Their pathology will be fully described in the next chapter.

The first case that came under my notice (S.T., case I), was in the National Hospital, Queen Square, London, under the care of Sir David Ferrier, in 1905. At that time I was not aware of the cases which have been sketched in the previous chapter, but I was quite conscious ~~at the time~~ that in S.T.'s case we were dealing with a strange nervous disease which did not correspond to any type with which I was familiar. Sir David Ferrier remarked at the time, moreover, that while it bore certain resemblances both to disseminated sclerosis and to paralysis agitans, it was quite distinct from either. A year later my second case (D.P., case II) came into Hospital under the care of Dr Ormerod, and whenever I saw her I recognised that her condition was exactly and entirely identical with that of case I, and said so to my colleagues in the residency. It was this case that gave the clue to the mystery, for, as the reader will learn for himself, she died not long afterwards, and at the post-mortem, made by Dr Stodart of Bethlem Hospital and myself, we discovered an unsuspected cirrhosis of the liver. Sir William Gowers, meanwhile, had republished his two cases in the Review of Neurology, and I felt that they threw the illuminating ray, for which I had been waiting, over the darkness that enshrouded the others. I followed up case I without delay, and in her case, a year later, made an autopsy and discovered what I fully expected to find, viz. cirrhosis of the liver and lenticular degeneration. Case III was the brother of case II, and from beginning to end he was under my observation: in his case also similar pathological findings were obtained at the autopsy.

I am in a position, therefore, to report the full clinical and pathological results of three personal cases of progressive lenticular degeneration, in two of which I made the diagnosis during life, and conducted all my research

in the light of knowledge gained by a study of the cases of twenty years ago.

Two other cases, IV and V, will be found in this chapter. Case IV is that of a patient referred to by Sir William Gowers as the eldest brother of his own two patients: "he was in the National Hospital six or seven years before, and died from some form of paralysis at the age of 15". By dint of searching and following up clues I managed to come across the mother of the M. family, an old but very vivacious lady of seventy, and from her lips obtained this history, which therefore makes the story of the M. family complete.

Case V is referred to in Dr Ormerod's paper as follows:-

" a boy aged 13 was under the care of Dr Gee (at St. Bartholomew's Hospital) with ascites, anasarca, enlargement of the spleen, and purpuric spots on the legs. ...It was noticed before he left that he walked very badly. Subsequently he was admitted to Queen Square Hospital, under Dr Buzzard, for nervous symptoms, mainly consisting of contractions of the limbs. He died, and the only definite lesion found post-mortem was cirrhosis of the liver." This case has never been published in extenso, so that I am able to utilise it to render the record as complete as possible.

Case V presents certain features which distinguish it from the others, and in fact I am not sure, as in Anton's case, that we are dealing with identically the same disease, but the resemblances are sufficiently close to warrant its insertion. In any case, I believe it sheds light on the etiology of the condition by analogy, if not directly, and for that reason I consider it valuable.

CASE I.

Gertrude Sylvia T. was born on October 19 th 1878. She was the youngest but one of the following family of nine: -

1. Dorothy, born 1859: living and well:
2. Louis, born 1861: do.
3. Arthur, born 1862: died in infancy.
4. Francis, born 1868: died of diphtheria 1883.
5. Fanny, born 1869: died in infancy.
6. Max, born 1875: living and well.
7. Walter, born 1876: do.
8. Gertrude Sylvia, born 1878: died 1908.
9. Ursula, born 1881: died in infancy.

FAMILY HISTORY.

Father died aged 68 of appendicitis. He had always been a healthy man, and is said to have been "highly strung", and of a somewhat neurotic temperament. Mother died, aged 65, of cancer. There was no history whatever of any form of venereal infection in the family: as far as it is ever possible to exclude anything, syphilis could be definitely excluded.

PREVIOUS HISTORY.

The patient was always a perfectly healthy girl, the only recorded illness being diphtheria at the age of 5. Her catamenia commenced when she was 14, and continued regularly for a year or two: thereafter she suffered from a certain amount of dysmenorrhoea for some years, but after the age of 20 the periods became more regular again. She was always a well developed active girl, and used to be an excellent swimmer. Her mental development was rather above the average: she was fond of literature and at school was considered to be very original-minded.

PRESENT ILLNESS.

In 1899, when the patient was 21 years old, and during a sojourn on the Continent, she had an attack of jaundice, of about five weeks' duration, but further details as to this illness are not forthcoming. For some years thereafter she suffered at intervals from slight swelling of the legs, which used to be puffy round the ankles, and she "used to make dints in them with her fingers". There were no other

symptoms, and she was never laid up or incapacitated in any way by it.

In May 1904, when she was 25 years old, she went to live in Schwalbach, and while there it was noticed for the first time that her right hand shook a little as she was writing, and that her articulation was not as clear as it had always been. She began to slur her consonants and the ends of her words. She seemed quite well in her general health, and her friends were at a loss to account for the symptoms.

By September of the same year her condition had changed definitely for the worse. There was a change in her disposition: she became restless, and appeared "unable to settle to anything", and it was remarked how very easily she was provoked to laughter, the most trifling incidents causing her to smile spasmodically. The tremor became much more pronounced: it was noticed on both sides, and in the arms as well as the hands and fingers. Her speech became more slurring, and a certain slight difficulty in swallowing developed.

At the end of the year she was seen in consultation by Dr., now Sir David, Ferrier, who was at once struck by the curious appearance of the patient, her almost silly smile, her more or less constant tremor, and a certain fixity of expression which led him to wonder whether he might not be dealing with a case of incipient paralysis agitans. Examination convinced him that there were no signs whatever of organic disease of the central nervous system, in the ordinary sense: there was no nystagmus: the reflexes were normal: a double flexor response was present. Recognising that he was not dealing with any well known nervous condition, he sent the patient into the National Hospital, Queen Square, London, where she was admitted under his care, for further examination and observation, on February 24th, 1905, being then 26 years old:

She remained in the Hospital for almost two months, and during this time was repeatedly examined. At no time during her stay were any of the accepted signs of organic nervous disease present, so that more than once the suspicion that her condition was hysterical crossed the minds of those of us that examined her. Yet it was early borne in on myself that the progressive nature of the case excluded hysteria,

and as disseminated sclerosis, another possible diagnosis, was not at all probable, the question of the exact nature of disease was left an open question.

The clinical picture which the patient presented was a very striking one. With a perpetual smile on her face, her mouth open, her limbs shaking, she moved slowly about the ward, often making very personal and apposite remarks about her fellow patients; at other times she kept her bed, unable or refusing to speak when urged to do so. Her mental condition was curious: she showed an abnormal cheerfulness incompatible with the serious nature of some of the other symptoms: sometimes the expression on her face was fatuous or silly, at other times considerable interest in things that would appeal only to an educated mind. She told me, for instance, that she had been learning Norwegian, and ~~that~~ when opportunity arose she intended to pursue her studies in that language.

As for the dysarthria, so marked a feature of her case, there was no word which she could not pronounce more or less distinctly on different occasions, yet she was frequently unable to pronounce test words, and often her speech after a minute or two simply became unintelligible. There was sometimes distinct difficulty in swallowing, but this symptom also was characterised by variability. Her handwriting was unreadable, owing to the constant tremor of her extremities, a quick, fine, rhythmical tremor which at some times seemed to vary with the attention paid it, but at other times was unmistakably of organic type, increasing with muscular effort. It was always well seen in the finger-nose test. The legs were affected with a similar tremor, also more noticeable during muscular effort. Her gait was usually slow and uncertain: her muscles were weak in proportion to their development, but there was no voluntary movement which the patient was unable to perform. The musculature, on the other hand, showed a slight degree of stiffness, especially in the fingers, which were constantly extended distally and flexed proximally.

[Figure 18]

In spite of treatment the patient lost weight while in Hospital, and left on the 19th of April, practically in the same condition as when she entered it: if anything, a little worse.

In the summer of the same year, 1905, her increasing weakness and the possibility of her requiring nursing care for a lengthy period caused her friends to procure her admission as a voluntary boarder to the Holloway Sanatorium, Virginia Water. Here she remained for about 2½ years.

During that time the progress of the disease was slowly but steadily downwards: yet for a long time her general nutrition was satisfactorily maintained, and she passed a sunny existence, to all outward appearance, always smiling and cheerful, and interested in her visitors and in everything going on round her. From the careful notes of Dr Sheila Ross, under whose more immediate care the patient was during her stay in the Sanatorium, one or two excerpts will be sufficient to indicate the steps by which the illness progressed.

“August 17, 1905. The hands are becoming definitely contracted. The fingers of the right hand are flexed at the metacarpo-phalangeal joints while the phalangeal joints are extended: the terminal phalanx is hyperextended especially in the third finger. The tongue is protruded with some difficulty, but is not tremulous. Patient walks unsteadily, and turns with some difficulty: there is well marked tremor in the legs, more particularly when she is fatigued. It is not easy to understand patient’s conversation. Her manner is childish, but this is accentuated by her habit of using as few words as possible in conversation, owing to her difficulty of articulation.

August 31. The tremors are more marked in the right limbs than in the left. Sometimes they are severe.

October 25. The patient now spends almost the whole day on a couch, as her gait is very uncertain. Swallowing becomes more difficult, and she is occasionally dirty, especially in the morning: for the first half hour after waking she seems stupid, incapable of emptying her bowel or her bladder, and as a result is sometimes wet and dirty. All the deep reflexes are normal: there is a double flexor response. The pupils react well to light.

January 3, 1906. Patient’s gait is feeble and stiff: her limbs are contracted and rigid. Speech is very defect-

ive: she usually spells out words on a card instead of speaking: but occasionally, if suddenly asked a question, she responds in a few words readily. Saliva dribbles constantly from her mouth, and swallowing is very difficult. The coarse tremor of the right hand has increased, and on the left side tremor and contractures of the fingers are more noticeable. Patient menstruated last month.

April 21. Mentally she is very self-absorbed, constantly calling the nurses to her, and annoyed unless their whole attention is given to her. She can walk a little, on her toes chiefly, if supported by two nurses. In spite of the severe dysarthria she occasionally brings out a few words fairly smartly. Her physical condition is good.

October 27. When making any muscular effort saliva dribbles from her mouth and she appears to be unable to swallow it. Has menstruated again."

In view of the conclusion I had by this time come to, that the case was one to be relegated to the category of Sir William Gowers' so called "tetanoid chorea": in other words, that it was a case where cirrhosis of the liver would be found post-mortem, I took an early opportunity of going down to Virginia Water to examine the patient, whom I had not seen for something like two years, for myself.

I saw her on March 14th, 1907, when she was about 28½ years old, and made the following notes at the time.

Cerebral and general.

The patient looks remarkably plump and well: she is exceedingly sunburnt, and gives an impression of good health. She is able to get up daily, and walk a little, only a few paces, but she can neither dress nor feed herself. She takes an intelligent interest in what is going on: recognises her friends and visitors, her nurses, the doctors, and often endeavours to speak, but never with any persistence. She knows quite well when she is physically comfortable or the reverse. Her disposition is more than ever facile, docile, almost childish: she never cries, but on the other hand laughs on the slightest provocation, in fact without any provocation. Her features are usually fixed in a fatuous smile, showing

most of her teeth. Her mouth is always open, her lips retracted, her jaws apart. Saliva escapes from her mouth. She looks, at a first glance, and until one begins to examine her carefully, a happy, indifferent, fatuous imbecile, lost to the world and living in a restricted microcosmos of her own. It is quite clear, however, that the impression first conveyed is erroneous. [Figure 15]

She recognised me at once, although we had not met for two years, and proceeded to spell out my name on her alphabet, which she did quite correctly, her fingers and forearm in a violent tremor the while. Her attention and memory were remarkably good: she proceeded to remind me of incidents that had happened during her stay in the National Hospital, and even of one or two of her former fellow patients. It is true that her means of conveying to me what was in her mind were not particularly effective, but the defect was solely one of execution. During the whole of my examination she never failed to appreciate what I requested her to do, and obeyed to the best of her ability. She did not complain of anything: she had no headache or giddiness.

Speech.

There is, to all intents and purposes, a condition of speechlessness in her case, entirely on account of the dysarthria, I should think. She never speaks at all under ordinary circumstances, preferring to use her alphabet, at which she is quite an adept. When she spoke on my request, what she said was unintelligible. I could not catch a single word. As her mouth was fixedly open, her lips and tongue stiff and almost immobile, the sounds seemed to come directly from her throat: it was curious to hear her "speaking" when her face remained completely motionless. I was told, however, that sometimes when the patient seems quite at her ease, and not consciously making an effort, the articulation improves a little, and some words can be distinguished.

There is neither word blindness nor word deafness: there is no paraphasia. The aphasia is really an aphemia, but the defect is entirely on the executive side. Writing is impossible.



Fig. 15.



Fig. 16.

S. T. at Virginia Wake 1907.

[Photographs taken with focal plane camera; exposure  $\frac{1}{1000}$  sec. in order to escape the effect of the constant tremor, which was violent at the time].

a, horrid dull day - very heavy & yet  
 clammy. Father's pain is better but  
 he is Bonny a bit too.  
 Mr Lemon has his hands in a sling  
 now. The de Lisle comes this afternoon  
 Genie has longed to meet him.  
 We are going to purchase Brunswick  
 Black to day. Leppard's butter is better.  
 Miss D had a good  
 A bright spot in a clouded life!  
 Edith goes to Glaston in October.  
 She is working hard at present.  
 Sherr is in hospital with lungs, but

Fig 17.

I want you to make  
 3 women black & pink  
 The white one  
 The one ~~you~~ you made  
 down bit.  
 When can you see  
 or

X

Fig 18.

Handwriting N.S.T.

Fig 17: in 1904.

Fig 18: in 1906.

Cranial Nerves.

2. Vision is good. There is no restriction of the visual fields. The optic discs are normal.

3.4.6. The pupils are regular and equal, of medium size, and react well to light and on accommodation.

All ocular movements are good in range and free in all directions. Convergence is quite good. The patient, however, is unwilling or unable to sustain any of the movements for longer than a few seconds. It is noteworthy, too, that when left to herself her eyes "dance" slightly ere her gaze comes to rest on a given object. On testing her, however, there is no nystagmus whatever, in any direction.

5. The corneal reflex is present on both sides. There is no impairment of sensation over the face. The muscles supplied by the motor fifth contract well: she can close her jaws, and bite, voluntarily, but the movements are certainly slow, and she appears incapable of sustaining the effort, for her jaws open again as soon as they are closed. She cannot move her inferior maxilla well from side to side.

7. The ordinary expression of the patient's face is well seen in the accompanying photograph. There is a spastic smile which is rarely relaxed, and is often aggravated into a spasmodic laugh. The upper part of the face moves well on volition: the orbicular muscles of the eye contract: patient can wrinkle her forehead, frown, &c, satisfactorily: the lower part of the face, however, is stiff and almost immobile: she cannot whistle, cannot purse her lips up, cannot blow out her cheeks. She can bring her lips together slowly, but the movement is not sustained.

[Figure 15]

9.10. There is considerable difficulty in swallowing, the food escaping from the corners of the mouth, or remaining on the tongue. Sometimes choking results. The palate moves well and symmetrically on phonation. It also moves when the fauces are tickled.

11. The muscles supplied by the eleventh nerve are very hypertonic, but patient is able to turn her head to the right or the left, slowly.

12. The tongue is thin and looks atrophic: it is narrower in its middle part, relatively, than at the anterior part: it is slowly protruded with considerable tremor, but there is

no tremulousness or fibrillation of the surface, nor is it puckered or fissured.

Motor system.

General muscular nutrition is fair. There is some general wasting of the muscles: the small muscles of the hands are thin, more particularly perhaps on the left side. The arms as a whole are thin.

Tone. The examiner is at once struck with the generalised spasticity of the muscles of the neck, trunk, and limbs. As a result of this, passive movements are accomplished with some difficulty. It is more pronounced in the upper than in the lower extremities. Thus if the arm be taken and passively flexed at the elbow the tone of the triceps is such as to give the observer a sense of considerable resistance, and a similar phenomenon occurs when the arm is passively extended. The same thing may be observed practically at any joint. The neck muscles are very rigid: even when the patient lies down the sternomastoids are not relaxed. When one of the legs is taken and passively shaken, the observer's hands grasping it proximally, the whole limb feels stiff and moves en bloc. Direct muscular excitability is increased.

Power. Voluntary movements are greatly hindered by the spasticity. Yet the patient can by a voluntary effort flex and extend at all joints, can abduct and adduct at hip and shoulder, can rise to a sitting position with difficulty, can move fingers and toes. The movements which are least good are those at joints where contracture is most marked, viz. at elbows and fingers more particularly. The leg movements are relatively better than the arms. The actual power of the voluntary movements is certainly below the normal. They can be easily resisted by the examiner.

Contractures. There is definite contracture of both biceps: the long flexors in both forearms, specially the right, are contracted: the left hand has adopted the interosseal position of paralysis agitans: on the right, the forefinger <sup>the second</sup> is extended and the thumb opposed to ~~them~~; the other fingers are flexed into the palm. The terminal phalanges of the left fingers are hyperextended. In the legs there is some contracture at hips and knees, and the feet incline to the position of equino-varus. By careful passive movement,

[Figure 16]

however, it is possible to overcome much, though not all, of the contracture. The segments of the limbs where it seems most established are the distal. It is a curious fact that though the patient sits in a chair with the general attitude of a double hemiplegia with contractures there is still considerable voluntary command over the muscles, and by an effort the limbs can all be straightened to a certain extent.

Tremor. Undoubtedly the most interesting feature of the case from the motor standpoint is the never ceasing tremor. The patient sits in the sun or lies in bed with a perpetual smile, and with tremors of the whole body that seem equally interminable. Even though she appears to be in a state of rest, i e , well supported at all joints, the tremor never disappears. It is at once aggravated by any volitional effort, however slight, and it is made almost violent in such tests as the finger-nose test. It is particularly well seen when the patient endeavours to pick out letters on her alphabet.

In type it is usually quick and rather coarse, i e through a range of not less than an inch. Often the excursion increases considerably. It consists of a true alternating regularly rhythmical contraction of any given muscular group and its antagonists. In the arms the greatest movement is from the elbows: the fingers and wrists are very stiff, and move with the tremor from the upper arm. There is also, however, some interosseal tremor and slight tremor of the forefinger and thumb approaching to a rotatory type. The head moves with a slight to and fro tremor, and so does the trunk. In the legs the tremor is very well seen indeed: even when they are at rest in bed it never ceases, and is at once aggravated by the slightest voluntary effort. The chief movement is one of flexion and extension at the hip, knee, and ankle, through a fine range, which is greater for the ankle than for the hip. There do not appear to be separate movements of the toes. I could not cause the tremor to cease entirely by supporting the whole of the limb, but undoubtedly it could thus be diminished in degree.

Coordination. There is no real incoordination to be made out, as the patient is able to direct her limbs in any given direction that is practical, in view of the spasticity. When put on her feet she tended to fall in any direction, not from ataxia, but from the stiffness of her musculature interfering with her ability to keep her balance. When put in an upright position on the edge of her bed she fell backwards in a lump, the attitude of her limbs not altering in the slightest.

Sensory system.

No subjective or objective change to be noted. The patient does not complain of pain or paraesthesiae, and on objective examination with the usual methods (touch, pain, temperature, deep sensibility) no definite alteration can be established.

Reflexes.

All the deep reflexes are difficult to obtain, no doubt because of the rigidity. They are present, however, though not brisk, and apparently equal on the two sides.

The abdominal reflexes are diminished on both sides, left more than right. An extensor response is obtained on the left side, and a flexor response on the right. There is no ankle clonus. If the foot be pressed up on either side, the rhythmical alternating tremor of flexion and extension does not alter appreciably.

There is usually some incontinence: it is not constant.

Gait.

The patient requires very strong support, and can then walk a few paces, on her toes at first, more or less, but she gradually gets her heels down. The movements are stiff, tremulous, and uncertain to a degree.

During the rest of the year her condition deteriorated step by step. Yet there was still an element of variability in the symptoms, often noted in regard to sphincter control. The dysarthria degenerated into anarthria, the contractures increased, and the patient began to lose weight. The tremor persisted without any change.

During the patient's stay at Virginia Water she was on several occasions especially examined from the point of view of the functions of the liver. Notwithstanding that the conviction was borne in on me that the case was one of what I call progressive lenticular degeneration, and that a cirrhotic liver would be found post-mortem, there were no symptoms whatever of the ordinary kind associated with hepatic ~~liver~~ cirrhosis. In particular, there was neither ascites, nor oedema, nor distended veins, nor was there ever any icterus even of slight degree. The liver was not palpable below the costal margin: its dulness in the nipple line on the right side appeared if anything to be somewhat diminished. There were no symptoms referable to the stomach: no indigestion or sickness.

On January 29th 1908 the patient left the Holloway Sanatorium to go and be with her sister near Oxford. She was examined before leaving, but no signs of physical disease, apart from the nervous system symptoms, could be discovered.

During the Spring of that year her nutrition began to fail considerably, and she became much thinner: with this increasing emaciation the contractures seemed to become worse, and all the symptoms were aggravated. She was utterly helpless, dependent on others for everything, anarthric and dysphagic, but at the same time she remained quite clear mentally, suffered from no delusions, was able to understand all that was said to her and to express her wants in a way that could be understood by those around her.

In July 1908, she was moved to be by the sea at Hunstanton. On Saturday July 25th she was suddenly seized with an acute attack of haematemesis, vomiting 4-5 pints of blood. On Monday July 27th she brought up a further 2 quarts of blood, and, sinking gradually, died on Tuesday evening, July 28th 1908, aged 29 years, and after an illness of rather more than 4 years' duration.

RESUME OF THE CLINICAL HISTORY OF CASE I.

A young woman of 21, whose family history is entirely negative, and who has never suffered from any particular illness, who has always been intelligent and physically active, has an attack of jaundice of about five weeks' duration, the exact details of which are not forthcoming, and at intervals thereafter, for about two or three years, has occasional swelling of the ankles, without being in any way incapacitated thereby, Four years later, at the age of 25, she notices that her right hand shakes a little as she is writing, and her articulation becomes a little slurring. In the course of a few months her friends notice a considerable alteration in her general condition: she is restless, unable to settle to anything, easily provoked to laughter, constantly smiling and unnaturally cheerful. At the same time the tremor spreads to both arms and hands, her caligraphy deteriorates greatly, her articulation is definitely impaired, and she has some trouble in swallowing.

At the age of 26 she is examined by a neurologist, who can find no signs of organic disease of the nervous system, and notes that there is no nystagmus and obtains a double flexor response. Nevertheless the condition is steadily progressive; the tremors are accentuated, the dysarthria and dysphagia increase, a generalised stiffness of the musculature reveals itself, and the fingers begin to assume certain attitudes of contracture. Her mental condition is one of facility, docility, almost childishness: she is easily amused, and constantly laughing: her mouth is open and saliva occasionally escapes involuntarily. In spite of the almost silly expression on her face her memory and perception are quite good: she has neither delusions nor hallucinations, she is very observant and often makes apposite remarks about those with whom she is associated. The symptoms are characterised by a curious variability: her articulation and swallowing seem sometimes to improve, and there is no true paralysis, in the sense that all voluntary movements can be carried out, though slowly. Yet she is undoubtedly more helpless than at first, and this shows no sign of improvement.

During the next two years the disease slowly progresses.

While for a long time bodily nutrition is well maintained the other symptoms increase in severity. Her features are fixed in a perpetual smile, her mouth is wide open and the sialorrhoea is more marked than ever, she is anarthric and dysphagic: yet with voluntary effort the mouth can be slowly closed, the tongue slowly protruded, the palate rises on the attempt to articulate; the pupils react briskly to light, the ocular movements are free and the optic discs are normal. The muscles become more and more rigid, the arms and to a less extent the legs fixed in attitudes of contracture, which can be to some extent, but not entirely, overcome by passive movement: as a result the patient is extraordinarily helpless, one might almost say "muscle bound", but again volitional effort will show that a considerable range of movement is still possible. The tremor is absolutely constant, often wide in range and severe in degree: it affects all muscular groups in the limbs, especially the extremities, but includes the lower jaw, head, neck and trunk. No sensory change can be detected: the deep reflexes are present, without being exaggerated, there is no ankle clonus: the abdominal reflexes are diminished, and the flexor response on the left side has changed to extensor, the other remaining as before. Defect of control over the sphincters, probably of central origin, appears.

Eventually emaciation sets in: the patient is reduced to a profound degree of helplessness, is contracted, speechless, incontinent: nevertheless her mental condition remains clear, she understands everything and endeavours to express her wants. An acute attack of haematemesis ushers in the end, and she dies at the age of 29, after an illness of rather more than 4 years. With the exception of the initial symptoms 9 years previously, there have been neither symptoms nor signs referable to disease of the liver, in spite of the fact that this is suspected during life and confirmed at the autopsy.

CASE II.

DAISY P. was born on March 6th, 1887. She was the eldest of a family of six, whose ages and order are as follows, (at Christmas 1910)&-

- 1. Daisy: died in 1907. (my case II).
- 2. Edgar: died September 1910. (my case III).
- 3. Alice, aged 21: quite well.
- 4. Dorothy, aged 18: quite well.
- 5. Arthur, aged 17: quite well.
- 6. Godfrey, aged 15: quite well.

FAMILY HISTORY.

The sole factors of any possible significance are that the maternal grandfather became alcoholic in old age, and that a maternal uncle and aunt died of phthisis, the former at 35, and the latter at 28. There was no history of any nervous disease in the family: no history of syphilis on the part of either parent: nor gonorrhoea. The mother had no miscarriages. At Xmas 1910 both parents are alive and healthy.

PREVIOUS HISTORY.

The patient was a healthy, well nourished child, so much so that she was called "Dumpy" by her parents. She was even tempered and docile. and there were no mental peculiarities to lead to a suspicion that she was in any way different from other children. She never suffered from any serious illness at any time. She went to school, after private tuition, at the age of 14, and gave exceptional promise of doing well. While she was a well set up girl, with a fine head of dark hair, she never had menstruated.

PRESENT HISTORY.

About the summer of 1904, when she was at school and aged 17, it was noticed that she became rather untidy in her dress, where formerly she had been scrupulously neat. At the same time she began to lose flesh, rather rapidly, and she looked more delicate than had ever been ~~at~~ noticed before. At the same time her caligraphy, which had always been good, deteriorated, and became "spidery". This was because of inability to control the fine movements of her hands, and because of a quick tremulous movement of the fingers. She

~~took to writing in pencil instead of ink.~~



took to writing in pencil instead of ink, and failed to obtain the same number of marks at school as formerly. This condition was ascribed to overwork and the schoolmistress allowed her to do as she liked. The condition was progressive, however, and in June 1905 she was removed from the school and her parents took her to live with them in Italy.

It was then noticed that the articulation began to fail: there was a tendency for the lower jaw to drop, so much so that her parents would constantly say, "shut your mouth, Daisy", which command she would instantly obey, but in a short time the mouth was open again. There was a degree of general muscular weakness observable, more particularly on the right side. It appeared to be "heavy", nevertheless she could walk as much as four miles without feeling tired at the end of it. Yet there was an element of awkwardness in her gait which had not been previously present. At the same time her hands became more tremulous than ever, especially if she felt that she was being watched. Her conversation became simpler, less intellectual, more childish: "her younger sister had to be a mother to her". In October 1905 she developed some delusions. She chanced to pick a grape in one of the Italian vineyards and thought that she was therefore wanted by the police. She also thought that her father was a prisoner of the Pope. This delusional state, which was accompanied by some motor excitement, lasted for a few days.

All the symptoms, the tremor, weakness, dysarthria, slowly increased in intensity. At the beginning of 1906 she occasionally suffered from spasmodic bursts of tears. Once when asked to make a choice from some articles for a present, she could only smile in a spasmodic silly manner.

The patient not improving, she was brought to England in the beginning of May 1906, and seen by Dr W.H.E. Stoddart, of Bethlem Royal Hospital, who after careful examination considered the case a nervous and not a mental one, and sent her to the National Hospital. When Dr Stoddart saw her he noted the following points: -

She was a tall well-built girl of dark complexion, with a profusion of dark hair reaching to her waist. There was some pigmentation or discolouration in various parts of the

body, especially round the ankles. She was not anaemic, but she had obviously lost much flesh. The tongue was dry and coated with a brown fur, and the breath somewhat offensive, but the teeth were normal.

Her general aspect was striking. Her mouth was almost constantly wide open, and her face wore a perpetual smile. The hands and arms were affected with a tremor that varied greatly in intensity from time to time, sometimes coarse, sometimes fine and scarcely noticeable. Owing to weakness and stiffness of her muscles, she tended to fall to the right when standing or walking, or even when attempting to sit upright in a chair. She was childish in her behaviour: laughed many times during the course of examination and did not appear to realise the gravity of her condition. Her memory was unimpaired, and perception was perfectly good.

On May 11th, 1906, the patient was admitted to the National Hospital, Queen Square London, under the care of Dr Ormerod, where she remained for almost a month.

She was carefully examined on various occasions. She presented a striking clinical picture, some idea of which may be obtained from the accompanying photograph. With mouth open, and a perpetual smile, she walked about the ward, moving slowly and tending to fall to one or other side, usually the right: she made childish remarks about trifling things in language almost unintelligible because of dysarthria, slurring her consonants and curtailing her last syllables, yet it was odd how this speech defect could be overcome by an effort of the will. Her general appearance suggested a mental defect which was not nearly so pronounced as a superficial glance might convey. As I sat on her bedside one day, I said jokingly, "why, you're just a little girl", to which she replied quickly and with little or no articulatory defect, "I'm not a little girl", as though to impress me with the fact that her looks belied her. Her attention was poor: ophthalmoscopic examination was difficult because of her unwillingness or inability to keep her eyes still. Her spasmodic laughter was remarkably on the slightest provocation the smile on her face would broaden visibly and a curious laugh, with no "tone" in it, would escape in bursts.

[Figure 20]



X

Fig 19.  
D.P. aged 16, before the onset of the disease.  
(from a photograph kindly loaned me by her parents)



X

Fig. 20  
D.P. in the National Hospital, aged 19.  
(May 1906)

The expression on her face was often rather stupid, and this was especially the case if the otherwise fixed smile relaxed. There were no defects in the domain of the cranial nerves. The pupils reacted briskly to light. The optic discs were normal, and there was no defect of ocular movement, in particular no nystagmus. Facial movements could be carried out voluntarily, but somewhat stiffly: she was unable to whistle, and when left to herself kept her mouth constantly open. The palate moved normally, and there was little actual difficulty in swallowing. The tongue movements were not well executed: it was protruded slowly, but came out straight.

All voluntary movements were well performed in strength and range. There was an increased degree of tonicity in the muscles, but no contractures at this stage. When the upper extremities were at rest little or no tremor was noticeable, but when the patient made any voluntary movement it became very marked--a coarse tremor of hands and fingers, about four or six to the second, through a range of one or two inches. It was well seen in the finger-nose test. Exactly the same sort of tremor was present in the legs. Very occasionally, as patient sat up in bed, a similar tremor, but finer in range, was observed to affect the trunk. There was no muscular wasting.

In spite of the patient's volitional control over her musculature, there appeared to be a rather disproportionate motor helplessness. When left to herself she would fall or roll about: owing to a generalised stiffness she could not or would not use her muscles to help herself, or keep herself from falling. (This is seen in the photograph, if the vertical lines of the curtain at the back are compared with the oblique position of the long axis of the patient's body.) Her gait was slow, uncertain, stiff: her feet were kept apart, yet she had difficulty in maintaining equilibrium.

[Figure 20]

Sensation, subjective and objective, was perfectly normal. All the reflexes, cutaneous and deep, were normal. A double flexor response was constantly obtained.

As the patient's condition did not ameliorate, and because of difficulty in getting her to take her food, she was transferred to Bethlem Hospital, under the care of Dr Stoddart, on June 6th of the same year, 1908, being then 19 years old. From that date, until her death the following

March, I had many opportunities of observing the progress of the disease, of which the following notes will convey some idea.

For some time she had to be tube-fed, being apparently under the impression that her food was poisoned, but this passed off and she did her best to take food voluntarily. She had, however, the greatest difficulty in swallowing it, and a few days before her death the dysphagia was so complete that tube-feeding had again to be resorted to. It is worth remarking that even when the dysphagia was greatest some efforts at swallowing were executed more easily than others, and that the reflex was present throughout.

Up to the end of 1906 the spasmodic smile was fairly well marked, but during the last two months of life it gradually diminished, and the facies became characterised by a complete absence of expression. The lower jaw dropped still more: even during sleep the mouth was wide open.

The tremor of the extremities became increasingly severe: its excursion was sometimes as much as three inches. Towards the end the tremor of individual fingers was more prominent than ever: it was usually antero-posterior, but sometimes lateral, the rapidity being about six to eight a second. The tremor of the legs and trunk persisted. Weakness of the limbs increased almost daily: as late as the beginning of January 1907 the patient was still able to stand, though only with assistance, but thereafter her helplessness became so pronounced that she was kept in bed. After this, contractures of the limbs set in with comparative rapidity: at the elbows, hips and knees the limbs were drawn up. The spine became very rigid. For some months before her death she was unable to protrude her tongue. The weakness and tremor were throughout more marked on the right side. In spite of every effort to maintain her general nutrition the patient gradually became emaciated, but there was no local muscular atrophy, nor was there more general wasting of the musculature than could at first be accounted for by the almost continual rest in bed, but towards the end the emaciation became extreme. Sensation remained normal throughout.

The knee jerks were moderately exaggerated throughout. There was no ankle clonus at any time. The abdominal reflexes were never abolished: they were obtained on February 27th, four days before the patient's death. The plantar reflexes remained of the flexor type on both sides, although during the last three days of life some variability was noted. During the early months of the year some weakness of the anal and vesical sphincters set in, not, however, of local significance, in all probability: the patient usually indicated when she experienced a call to stool, and was therefore generally kept clean: but if, at the moment, there happened to be no nurse in the room, the dejecta were passed into the bed.

From the time when the patient went down to Bethlem Hospital drooling of the saliva was a prominent symptom. At first handkerchiefs were used as bibs, but eventually it became necessary to employ a large towel, so profuse was the sialorrhoea. It was a remarkable fact that during the last week of the patient's illness this flow of saliva entirely ceased.

On the evening of February 24th the temperature rose to 101.2, and sibilant râles could be heard in various parts of the chest. Two days later there was a patch of dulness at the apex of the lower lobe of the right lung. The temperature varied from 101 to 103. During the last two days the respirations became somewhat hurried, and were accompanied by dilatations of the alae nasi. The patient gradually sank and died on the evening of March 3rd, 1907, being then 26 years old, all but three days.



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RESUME OF THE CLINICAL HISTORY OF CASE II.

A girl of 17, in whose family history no factor of any pathogenic significance can be discovered, and with a clean bill of previous health--the solitary feature to be recorded being that she has never menstruated--is noticed to develop a fine tremulous movement of the fingers, so that her handwriting deteriorates, to lose flesh, and to fail rather in her school work, so that she does not obtain the same marks as formerly.

Some six or nine months later, her age being 18, it is seen that her articulation is becoming defective, and that she tends to keep her mouth open. A general muscular weakness appears, and the tremor of the hands increases. Her conversation becomes simpler and rather childish, and she suffers from one or two delusions, which do not, however, persist.

Rather more than a year from the onset of the disease, the tremor, weakness, and dysarthria have become more pronounced. She has occasional attacks of spasmodic weeping, but far more constantly her face wears a stiff, spastic smile, her mouth is always open, her limbs show a more or less constant rhythmical tremor, which increases with muscular effort, and she has great difficulty in maintaining her equilibrium, owing to a generalised weakness and stiffness of the musculature. She laughs at the most trifling incidents, and often, indeed, without apparent cause, but on careful examination and observation it is found that she is not in reality suffering from that degree of mental impairment which her appearance suggests. She presents no sign whatever of organic disease of the central nervous system, the pupillary, cutaneous, deep, and organic reflexes are all normal.

In about two years, or less, from the beginning of the disease, dysphagia becomes evident: she seems to be very helpless, falling about, unable to maintain her balance, her muscles are both weak and hypertonic, but there is no true paralysis, as all voluntary movements can be performed, though slowly. The tremors and dysarthria become extreme. In spite of her perpetual smile and silly appearance, her

perception is good and her memory unimpaired.

During the next few months, and in the latter part of her twentieth year, the disease runs a downhill course. Saliva escapes from her open mouth. Her musculature increases in spasticity: her face is fixed and expressionless: her weakness and helplessness are profound. Contractures appear at elbow, knee, and hip: the tremor of fingers, arms, trunk, and legs becomes coarser in type, and is often violent: the dysphagia and dysarthria are such that the maintenance of her nutrition is a serious problem, while her speech is unintelligible, and in fact she scarcely utters a single word. Examination shows that there is no involvement of the pyramidal system, for the abdominal reflexes are always obtainable, and a double flexor response is constantly noted. Sensation is intact: the ocular movements are free, there being no nystagmus.

At length, miserably emaciated, contractured, and helpless, she dies from broncho-pneumonia, aged 20 years all but three days, and three years from the commencement of the illness. Notwithstanding the fact that she has been exhaustively examined by various members of the medical profession, there are never any symptoms referable to the liver, nor has she presented any signs of an objective character that might be associated with disease of that organ.

CASE III.

EDGAR P., the eldest brother of the patient Daisy P., whose case is no. II in my series, and the second member of the family in order of birth, was born on May 14th, 1888.

PREVIOUS HISTORY.

With the exception of whooping cough at the age of nine the patient had a perfectly normal childhood and boyhood. He was active and intelligent, and never had anything the matter with him. He went to school in Taunton at the age of 12½ years, and had an excellent scholastic record. Here he remained, doing exceedingly well, till Easter 1906, when certain symptoms unexpectedly appeared, to the great surprise and distress of his relatives.

PRESENT HISTORY.

During the spring months of the year 1906, when the patient was almost 18 years old, he had been working very hard for an examination, and broke down under the strain. He found he could not concentrate his attention on his work. He was a keen sportsman, and had been playing football all winter, but games had to be given up. An attack of excitement, accompanied by hallucinations of hearing suddenly ensued, and he became unmanageable. On two medical certificates he was admitted to Bethlem Hospital, London, on April 11th, 1906.

These certificates contained the following statements:-

"The patient is very excited and emotional: says he is being influenced, willed, or hypnotised to do certain things: is quite sure that God is working a miracle on his behalf. Says he has heard God and the devil talking to him simultaneously, and does not know which voice to obey. Is frightened because although he has been baptised he is not now certain whether that has secured his salvation", &c.

On examination at the hospital he was seen to be a tall well developed young fellow with a dark complexion. He presented no symptoms whatever of organic disease of the central nervous system. His speech was normal: there was neither rigidity nor tremor: the pupils reacted briskly: all cutaneous and deep reflexes were normal. The urine contained no

abnormal constituents. On the day after admission he already appeared to be more rational, and his temperament was noted as being bright and cheerful. He admitted that about ten days previously he had heard the voice of God speaking to him, but now thought it might have been a dream. Voices in his ears which he heard then he said might possibly have been those of other people in the building.

During the summer his condition gradually improved. At intervals he was hallucinated, and at these times he became excitable and restless, laughing and crying alternately, and suffering much from insomnia. By the end of July 1906, with the exception of these attacks which lasted about a week, he was more himself again, and from that time he improved steadily. He was so well that on February 5th, 1907, he was sent to the Bethlem convalescent home at Witley, not having shown any symptoms for months previously. He was discharged recovered on April 3rd, 1907, and went out to Italy to his parents.

Although submitted to several careful neurological examinations by Dr Stoddart, he never showed the slightest sign of organic disease of the nervous system: and the diagnosis of exhaustion or toxic psychosis seemed entirely justified. A good prognosis was given.

During the summer of 1907 he was very well. He took long walks and climbs, being away for twelve hours at a time, and never gave cause for any anxiety on the part of his parents. He was quiet and reserved, it is true, but he always had been of a rather retiring disposition.

Towards the latter part of the year, when he was 19, however, other symptoms made their appearance and progressed with rather alarming rapidity. He began to have difficulty in speaking and swallowing, and his mother noticed how constantly a thin stream of saliva used to escape from the corner of his mouth. Further, his hands became tremulous, and his handwriting became very bad. He never complained of anything, no pains, headache, or giddiness, yet in three months time his whole appearance had altered for the worse.

During 1908 the disease advanced steadily. The tremor became generalised, the dysarthria more pronounced, so that he rarely spoke at all, the difficulty in swallowing did not diminish, and he had a constant tendency to let his mouth

open, sometimes widely, without apparently being aware of the fact. His limbs, more particularly the legs, became stiff and weak, but there was no paralysis at all, in the ordinary sense of the word, as he could move them well enough, and could walk about without any assistance. He was sent to be under the care of Dr Raymond at Chexbres, near Lausanne, and in a letter from his father, dated, November 18th, 1908, from which the following passages are culled, I received some information as to the patient's condition.

"...His main difficulty now is that he swallows badly and that his articulation is very imperfect indeed. He is still troubled with an abnormal flow of saliva. Still, compared with his previous condition, I think there is improvement in each of these directions. When I saw him I certainly understood him better than some months previously, but articulation is most defective still. ....As to his ability or inability to walk, and stiffness of legs, of which you ask, I think there is some improvement. During the two days that I was with him we walked and even climbed a good deal, and it was I, not he, who always tired first. Dr Raymond thinks that there is nothing wrong whatever with the boy's mental condition. Certainly in long and searching conversation, and in his various letters home we never see the slightest sign at all of mental trouble. I do not think that I can say that the mind is equal to vigorous work. He reads a great deal, but does not ask for deep books. His memory seems exceptionally strong. He writes very badly, and, if possible, gets someone to write for him. But he sent us last week an eight page dictated letter, sensible, bright, and full of interest, exactly reproducing his thought as he gave it. This may have been dictated at more than one sitting, but it certainly means that the boy is quite able to express himself upon all ordinary lines, and, further, that he managed, whether with or without difficulty, to make his amanuensis clearly understand, at his dictation, eight pages of matter. Of his own handwriting I send you a specimen herewith. (See fig. 30). .... He looks to me a little stouter....."

During 1909 the illness progressed slowly but steadily in a downward direction, and at the beginning of 1910 it became clear that there could be only one end to it, and that perhaps not very far off. I cannot do better than quote some sentences from a letter from the patient's father, dated May 27th, 1910.

"..... I am sorry not to be able to give you a good report of Edgar's progress. As far as I am able to judge the mind is perfectly clear, and I think on the whole the lad is happy. But there is a very distinct and marked failure in physical strength. ....The symptoms are very greatly aggravated since I last wrote you. He seems to have lost almost entirely control of his motor nerves. The effect of this is that he cannot grasp, that he swallows with so great difficulty that it is a serious matter to get him fed, and his power of articulation is so very slight that one can hardly understand a single word he utters. Dr Raymond has given him a kind of tablet with the alphabet in letters each about 1 1/2 in. square, at which he tries to point, to spell what he wants to say, but in any attempt to indicate a letter with his finger, the trembling, I could almost say the vibration, of his hand is so violent that it has to be held and steadied before it can reach a desired letter. He has lost control in some measure of the physical functions of the body in a way which makes the care of him difficult for others. He is wonderfully patient and of a happy disposition, though one can see that he suffers very much, naturally, at not being able to express himself.....This fact of itself, you will note, proves a considerable measure of balance of mind. ....Edgar cannot now get his hand anything like steady enough to write a stroke, the poor fingers, when he tries to hold pen or pencil, shaking, or rather swinging, with a swing of two or three inches, or even more. His limbs are somewhat emaciated. He is not now strong enough to walk many paces....."

As the patient had not been seen by any neurologist since the onset of the symptoms of progressive lenticular degeneration in the Autumn of 1907, it appeared to me very desirable to investigate his condition for myself. Accordingly an early opportunity was taken of paying a visit to the sanatorium where he was living, and the greater part of Saturday June 4th, 1910, was spent in examining him. The following description is based on the notes which I made at the time.

Cerebral and general.

As I walked round the corner of the building and came upon the patient sitting in a lounge chair in the sun, the impression I received was one not easily to be forgotten. He was leaning back with a fatuous smile on his face, his mouth wide open and the saliva dribbling from it onto his chest, his arms and hands contracted and drawn up, and moving to and fro ceaselessly with a quick rhythmical tremor, his toes tapping the ground with a similar rhythm, his whole attitude one of complacent imbecility. If, however, this first impression was one of the utter hopelessness and helplessness of the patient, it was not long ere one perceived that it was to a certain extent erroneous. It is true he had apparently no idea who I was, although we had met several times previously, and he did not show any signs of interest or recognition when I spoke to him of his mother. On the other hand, he evidently knew familiarly the various inmates and members of the staff of the place, and he certainly could pick out with accuracy the various photographs of friends scattered about his bedroom.

[Figure 23 re]

His mental state was one of extreme facility: he was as docile as a child. He did whatever he was told to do with a brief involuntary explosive laugh. Aware of his mental condition some of his fellow patients would say, "open your mouth, Mr. P.," and this he would at once do, to the accompaniment of bursts of laughter. He laughed constantly while he was being examined, yet when he noticed that one of the legs of my camera was unsteady he at once put out his left hand to hold it, though the movement was slow.

He read the English journals every day, and used his alphabet quite intelligently. He knew where everything was

in his bedroom, or round about him, that was required for his use, although his gestures to indicate what he wanted seemed to me to be poor. Others, however, more familiar with him, could understand perfectly. He was hugely pleased with any little attention paid him: if his mouth were wiped he passed at once from his smile to his laugh. When his reflexes were being tested he burst into a loud "rire spasmodique", and I got a most distinct impression that he remembered that sort of thing having been done before. He was perfectly acquainted with the use of all sorts of articles with which I tried him: he was, however, unable to do anything for himself, his movements being so very slow and laboured.

It was very difficult to be sure whether he was correctly oriented in time and space: he appeared to be well enough aware of what was going on in his own little world. It was curious how quickly he noticed things: when I helped to dress him after examination he corrected me several times in my manner of doing it. He seemed entirely content and perfectly happy: there did not appear to be the least insight into his condition on the part of the patient. Nor could I interpret any of his actions or gestures as indicating that he suffered mental pain at being unable to express himself. He appeared to have little initiative or spontaneity, although, I suspect, this may have been partly due to his own consciousness of his helpless condition.

As for his general physical condition, he was tremendously unburnt, but very thin. There was <sup>not</sup> an ounce of fat on his body. The outlines of the muscles and tendons were everywhere clean cut. The vertebral spines were very prominent. The face was comparatively well nourished. The genitalia were well developed, and there was a good deal of pubic hair. The feet were somewhat oedematous, and the ankles a little puffy, but this oedema could not be dimpled with the finger. There was no abnormality, however, of heart or circulation.

Perhaps the most striking feature of his case was his complete helplessness, and the indifference bred of a knowledge of this. He sat in the sun in the chair, rolling over to one or other side if he lost his balance, the extraordinary spasticity of his musculature making the effort to recover himself almost useless. I found him thus, on one occasion,



X

Fig 21.  
E.P. aged 16 - (from photo loaned me by his parents)

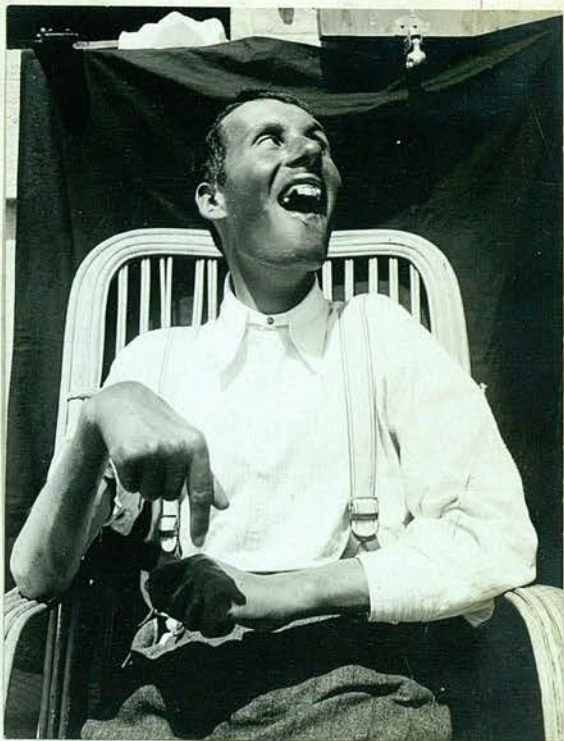


Fig 22.

Fig 23.

Figs 22-28 were taken at Chevres, Switzerland June 4<sup>th</sup> 1910.  
Exposure of all,  $\frac{1}{250}$  second, to minimize the effect of the unceasing tremor.

(Figure 22)

leaning right over the arm of his chair, the fixed smile on his face, apparently content to hang thus until he was found and put back in position. His indifference was sometimes remarkable. On several occasions he kept his mouth wide open long after I had finished asking him to do it: he similarly kept his tongue protruded for several minutes. Occasionally the smile relaxed and the vacant expression became less obvious, but he never seemed to express any other emotion, made no visible facial response when I gave him messages from his parents, or when I finally said goodbye.

Speech.

During the whole time we spent together he said only three or four words, of which two were, "I will". These words seemed to come from his throat, after the fashion of a ventriloquist, for there was not the slightest appreciable movement of lips or tongue. His anarthria was complete. So too, practically speaking, was his speechlessness: he made no effort whatever in response to my urging him at least to attempt it. Nor did he appear distressed at this.

On the other hand, he used his alphabet with perfect correctness, spelling out such words as "doctor" without any difficulty. He appeared to be able to read quite well, and to understand what he read. He never once failed in the whole of the examination to perform correctly what he was asked to do--with the exception of the aphemia--although: of course the movements were exceptionally slow. There was no apraxia to be detected, and no agnosia. It struck me as being affording a remarkable contrast, this apparent idiocy and fatuousness compared with his quickness in appreciating everything he did or said or asked. When I proposed going inside he at once tried to get on to his feet: when I asked for a towel he indicated where to find one: when I asked him to do this or that for the purposes of photography he cooperated with the greatest intelligence. Thus to apply the term dementia to characterise his mental condition would be inaccurate. Caligraphy was impossible. Various drawings of familiar objects, however, he recognised easily.



July 24.



July 25.



July 26.

Co9

Cranial nerves.

2. Vision was good. Visual fields were good. The optic discs were emmetropic and presented no visible abnormality.

3.4.6. All ocular movements were good in all directions: there was not the slightest trace of nystagmus. Sometimes the ocular movements seemed better sustained than at other times, but this was solely a question of attention. When the patient moved his eyes about of his own accord, and not to command, it was noted that there was occasionally some unsteadiness in fixing an object: this, however, was only momentary.

The pupils were regular, equal, and of medium size; they reacted briskly to light, and contracted well on accommodation.

5. Corneal reflex was brisk on both sides. There was no sensory impairment over the face. The motor fifth muscles contracted well. The masseters contracted so that the patient could close his mouth, but the movement was slow and not well sustained, as the patient was so constantly in the habit of keeping his mouth widely open. Opening of the mouth against resistance was unexpectedly powerful. The whole of this musculature was hypertonic, and the patient had difficulty in moving his jaw from side to side.

7. Except when the patient's face was contracted into a broad smile, he had an utterly stolid, mask like facies, all the facial lines round his mouth being obliterated, and the latter simply an aperture in the mask: the lips themselves, however, do not hang much. Frequently he wrinkled his forehead and made other movements of the upper face, but his mouth never moved in the slightest except when he went off into the smile or laugh, which, it is true, occurred almost every minute. On attempting to whistle only a feeble contraction of the orbicular muscles was detected, and he was quite unable to make any sucking movements. When urged to show his teeth, i e to retract the corners of his mouth, he indulged invariably in a spasmodic laugh, so that it was difficult to gauge the amount of voluntary movement. He could wrinkle the forehead, frown, close eyes tightly, quite well to order. It may be said that there was complete paralysis of expression, and pronounced bilateral feebleness of the lower face. When the muscles contracted into a smile

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it was always a stiff, tonic contraction, which never relaxed quickly, and often remained fixed, as it were, one might almost say pinned, on the patient's face. The fact that the lips did not hang down showed the tonicity of the musculature.

8. Hearing was normal on both sides.

9. The palate moved quite well, and symmetrically, in the effort to phonate. The patient usually succeeded in saying "ah" very fairly. The palatal reflex was present on both sides. Swallowing was very bad indeed. He could not make the movement of swallowing, on request. Water he swallowed in gulps, noisily, and a great deal of it was swimming about in his mouth and running out at the corners. He was unable to approximate his lips sufficiently to grasp the edge of the vessel.

11. No paralysis of the muscles supplied by this nerve was noted.

12. The tongue was thin, and narrower from side to side in its middle section than nearer the tip. When he protruded it to command, there was marked to and fro tremor as he moved it slowly forward, but he managed to get it right out, and once it was well out the tremor ceased. Lateral movements were also performed, though very slowly. There was no fibrillary tremor whatsoever, nor was it cracked or fissured.

#### Motor System.

Development. The general muscular development was very fair, but at the same time the musculature had obviously been shrinking, and was in a state of poor nutrition. There was no local muscular atrophy to be observed anywhere, and no fibrillation.

Tone. All the skeletal muscles, practically without exception, felt very firm to the touch, and this spasticity or hypertonicity was probably one of the reasons for the slowness of the patient's voluntary movements. There was always a certain difficulty in impressing any passive movement on a limb, but it could be overcome. If the arm was taken and passively extended and flexed quickly at the elbow, insufficient relaxation impeded the movement: if it was done more slowly, there was no difficulty at all. When any limb was

placed in such a position as to relax the muscles as completely as possible, it was still found that they felt firm, though not to the same extent, on palpation. When the patient was voluntarily contracting say the left biceps, in the effort to flex at the elbow against resistance, the left triceps never relaxed entirely, though it became for the moment less tonic.

The abdominal and the leg muscles were similarly rigid: palpation of the abdominal viscera was for this reason not easy.

The results of this generalised rigidity were rather curious: the patient seemed to be enclosed, as it were, in a solid muscular covering. Hence he fell about en bloc: his back moved en bloc: sitting on the edge of his bed he would slowly lose his balance, and fall over in a solid mass on to his side, often to his huge delight, at least in the presence of a visitor. The neck muscles were always in a markedly tonic state: even when he lay with his head back on the pillow the sternomastoids did not relax. It was quite clear that the condition of the musculature had a great deal to do with the difficulty experienced by the patient in maintaining his equilibrium.

Speaking generally, the rigidity was more marked in the trunk and proximal sections of the limbs, whereas the tremor was most noticeable in the distal portions of the limbs, and affected the proximal joints and the trunk to a much less extent.

It cannot be said that there was any myotonia, in the strict sense of the word. For although relaxation was slow, it was no slower than voluntary contraction: they were alike in this respect: nor was there any distinction between flexor and extensor groups, or between any muscular group and its antagonists, in the matter.

Contractures. The hands and arms were, when left to themselves, held invariably in the position to be described. On the right side the forefinger was flexed at the metacarpophalangeal joint, but extended distally, and similarly with the thumb. These two fingers were in apposition, whereas the other three fingers were flexed at all the joints. The wrist was flexed to a right angle, the forearm semi-pron-

[Fig 24]



Fig 27.

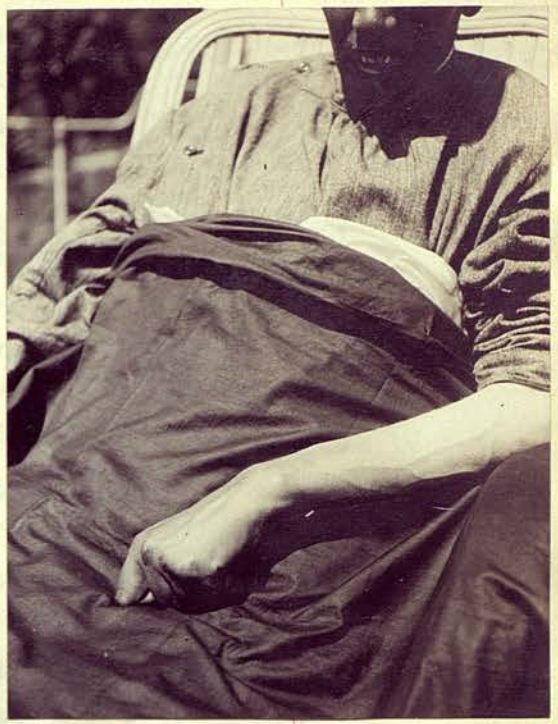


Fig. 28.

read it.  
 Yesterday Uncle Edgar sent me the  
 Jan. number of the Shirley Mes-  
 senger.  
 I had such a nice letter from  
 Father which arrived on the 25<sup>th</sup>  
 of Dec.  
 Also a budget from the children  
 at home.

Fig 29.

Handwriting before the onset of the disease.

Strength  
 Mr. ... sent me a priced  
 account of some of your  
 ... of ... will you?  
 ... going to send me  
 that sketch of ... which  
 in your last letter you said she  
 ...  
 ... MRS ...  
 arrived yesterday.  
 Did ... get his ...  
 and the stamps & his ...  
 Long ...  
 ...  
 ...  
 ...  
 ...  
 ...  
 ...

Fig 30.

Do. after the disease was established.

ated and flexed on the upper arm, which was adducted at the shoulder. The whole position of the arm was suggestive of the attitude adopted by a contracted hemiplegic limb, while there was a distinct resemblance to the attitude of paralysis agitans in the hand.

The left hand was curled up, with the thumb held inside the flexed first and second fingers: the wrist was not so much flexed as on the right side: the arm was flexed at the elbow and adducted at the shoulder.

[Figure 28]

The lower extremities were flexed at the knees, not to a great extent: the feet were somewhat inverted and the heels drawn a little up. The toes were slightly flexed.

The attitude of the extremities is well seen in the accompanying photographs. [Figs 22, 23, 27, 28]

As has been said, if the patient was left to himself, such were the apparent contractures of the limbs, and they never varied. But the remarkably interesting thing was that these contractures, typical though they were, could both actively and passively be overcome. Passively there was little resistance, so that the degree of true permanent contracture could be estimated. It was found that the right arm could not be completely extended at the elbow, nor could the legs be straightened at the knees. Apart from this, the limbs could be passively moved in any way. Moreover, if the patient were given time, he could overcome these attitudes of contracture himself. He could open and close his right hand, flex and extend the fingers, abduct and adduct the same, &c, in fact he could make any movement at any joint, but slowly, not strongly, and always to the accompaniment of tremor. He could overcome the habitual position of the lower extremities in a similar way. In spite of the extraordinarily spastic appearance of the face there was no true contracture of any of the facial muscles, or muscles of the throat and neck.

[Compare Figs 24 + 25]

Power. All voluntary movements executed by the patient were certainly weak. There was no doubt of this. All could be easily resisted by the examiner: the strongest relative movement seemed to be depression of the lower jaw.

In the arms the range of voluntary movement was very good, and, considering the contracted appearance of the limbs,

at first somewhat unexpected. The grasp was better on the left side than on the right: the left biceps was stronger than the right, whereas the right triceps was a little stronger than the left.

All voluntary movements of the legs were relatively better, but not of normal strength. On the whole the flexor groups were weaker than the extensor groups. Adduction at the hip was much stronger than abduction.

In any voluntary movement there was a jerky action usually to be observed: when the patient voluntarily adducted his legs it was by a series of jerks, apart from the gross action tremor which was constantly present. He seemed to be unable to sustain any movement for longer than a second or two, although encouraged or urged to do so: relaxation began and once the voluntary effort weakened the involved muscles passed into the ordinary unceasing tremor.

All the muscular groups of the body were tested as far as could be done, and, speaking generally, it may be said that the left side was weaker than the right, and not so tremulous as the right.

Tremor. Undoubtedly the most striking motor phenomenon in the case was the highly typical rhythmical tremor of the arms and legs. As the patient sat in the sun a ceaseless oscillatory to and fro, up and down, movement of his extremities at once caught and riveted the attention. This tremor was a perfect example of a true tremor, i.e. of a rhythmical alternation in contraction of a given muscular group and its antagonists. Its rate varied from 4 to 6 a second: it rarely quickened, perhaps to 8 a second. Its range or excursion was also variable: as a rule this did not exceed an inch in the case of the fingers, but with any muscular effort e.g. in picking out the letters on his alphabet the range was as much as three inches. On exertion the tremor became wide and quick: left to itself it was slower and finer.

In the arms the chief tremors were: alternating flexion and extension at the elbow, flexion and extension at the wrist, with the frequent addition of a slight alternating pronation and supination, causing a sort of rotatory tremor: the finger tremor was chiefly flexion and extension, some-

times with the addition of an opposition and adduction element in the case of the thumb. In the legs there was alternating flexion and extension at the knees, though this was of very short range: there was more obvious flexion and extension at the ankles, and most noticeable of all was the tremor of the toes. The lower jaw was also, unless the mouth were at its maximum of opening, rhythmically moving up and down through a fine range. When the patient sat up on the edge of his bed there was a distinct to and fro movement of the body in an antero-posterior direction.

Speaking generally, the tremor was much more noticeable distally than proximally, being in this respect the contrary of the the rigidity, as has already been remarked. When any muscular effort was made, the tremor in the corresponding groups increased in degree and rapidity, and often spread: thus by making the patient squeeze my fingers in his hands I could cause the tremor of the lower extremities to augment. With the finger nose test the tremor was easily aggravated, but there was this difference in the two sides: on the left side the patient put the forefinger to the nose in the usual way, to the accompaniment of a tremor increasing in range, and in doing this, of course, the contracture attitude of the hand was relaxed, but on the right the hand in its contracted attitude was always put en bloc to the nose.

When it is said that the tremor increased with voluntary action it must be remembered that the patient was incapable of sustaining any voluntary effort for more than a few seconds, hence the increase in the rate and excursion of the tremor was always transient, and of brief duration. When the the finger or the hand reached the nose the tremor at once became less marked, although the limb was being held in the desired position.

A number of experiments were made to see if by supporting and relaxing all the joints of a limb the tremor would disappear. It was possible in this way, and by quietly encouraging the patient to divert his attention from what was being done, to cause the tremor to cease, in toto, for a few seconds. This was effected in the right arm, for instance. When it was left to itself, extended and still, without any interference on the patient's side the limb almost immediately began to shake again, at first quietly, but with ever in-

creasing force, and at the same time it began to contract again at the joints, with the result that ere many seconds had elapsed it was back once more in the accustomed position, and shaking as before. The tremor which was the most difficult to cause to disappear was a fine interosseal tremor, coupled with the somewhat rolling tremor of the forefinger and thumb.

Coordination. No real incoordination was to be observed. Even when the tremor was severe the patient could direct his forefinger to his nose correctly enough. The occasional irregularity of movement of the eyes could not be called ataxia. There was no static ataxia, either, in the strict sense. When he stood upright, closure of the eyes made no difference to his equilibrium.

Sensory system.

The patient did not complain of any abnormal subjective sensations, and objectively no alteration in any form of cutaneous or deep sensibility could be detected.

Reflexes.

A slight jaw jerk was present. The tendon reflexes of the upper extremities were not easy to elicit, because of the tonic condition of the muscles. They were obtained, however, and were equal on the two sides. The abdominal reflexes were present, equal, active, and readily obtainable from all four quadrants. The knee jerks and achillis jerks were brisk, and equal: there was no ankle or other clonus. The plantar response was an unmistakable double flexor type. In regard to the organic reflexes, the patient was reaching the indifferent stage. The patient's attendant put the bottle to him at regular intervals: if this was not done he passed urine "involuntarily". There was no doubt, however, that he could pass urine naturally: probably his helplessness was sufficient to account for the methods adopted. There was no incontinence of faeces.

Gait.

This was a very interesting and instructive performance. As the patient was helped to his feet he lent hard on the supporting arm, moving stiffly and clumsily, and ready to

fall in any direction, as the maintenance of balance was somewhat hazardous: at the same time there was a perfect riot of tremor. At first he was certainly rather on his toes, but in a short time the heels came down, and with shuffling steps, not unlike a "démarche à petits pas", he proceeded, tending usually to fall forward. Nevertheless he improved with the effort, and was able to go up and down two steps, and walk along a corridor, slowly, laughing and shaking the whole of the time. He was totally unable to walk unaided.

Such, then, was the condition of the patient when I visited him in June 1910.

During the summer he remained much the same, but towards the autumn, without obvious reason, he began to fail rapidly. He became definitely worse about the beginning of September. Up to that time he had been getting up daily, and sitting as usual in the sun the greater part of the day. He developed an irregular temperature which ran up to nearly 104° F, suggesting possibly some sort of septic absorption. The difficulty of feeding the patient became acute. Slight sores appeared over the heels, trochanters, and sacrum. These were, however, more superficial abrasions than real bedsores. The tremors of the limbs, especially of the arms, became more violent than ever, and the contractures much more marked. General emaciation rapidly set in.

Yet the patient maintained complete consciousness to within a couple of hours of his death. He recognised all those around him: and knew quite well where he was. He was able as usual to express his wants by his alphabet. When asked if he wished anything to drink, he was able, though in extremis, to indicate his desires rationally. During these weeks he was incontinent of urine and faeces.

He died on the afternoon of September 20th, 1910, being then 22 years of age.

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RESUME OF THE CLINICAL HISTORY OF CASE III.

A youth of 17, the brother of the patient whose case is no. II, of entirely normal mental and physical development, active and athletic, breaks down through overwork for an examination, suffers from auditory hallucinations, becomes excited and unmanageable, and is removed to Bethlem Hospital, where a diagnosis of toxic psychosis is made. This illness is of comparatively brief duration, and the patient makes a complete recovery therefrom, never showing any analogous symptoms at any subsequent period. No signs of organic disease of the central nervous system are noted. In less than a year he is discharged recovered, and appears in good general health.

About four or five months later, the patient being 19 years old, other symptoms of a totally different nature make their appearance, and progress rather rapidly. He begins to have difficulty in speaking and swallowing, and it is noticed that a little saliva escapes from the corners of his mouth. At the same time his hands become tremulous and his handwriting deteriorates. In the course of three months his whole appearance has altered for the worse. The tremor is generalised: his dysarthria is such that he rarely speaks at all, and what he says is scarcely intelligible, and he has a constant tendency to keep his mouth wide open. The dysphagia also increases.

In the next year the disease runs a slow downward course. The patient's musculature becomes very stiff, so that his helplessness is considerable: his face wears a constant fixed smile: he is very cheerful, and often breaks into spasmodic laughter: the tremor of the limbs is severe and constant, and increases on exertion: the defect in articulation amounts practically to anarthria. Yet there is no obvious mental impairment beyond a certain childishness which shows itself in the readiness with which he is amused. He is able to read, understands everything that is said to him, indicates his wants, and evidently has a degree of intelligence of which a glance at his physical appearance gives little hint.

From this point the progression of the disease is even more noticeably in a downward direction. When he is just turned 22 years, about 2 1/2 years from the onset of the illness, and 3 months before the end, an examination shows the following as the most noteworthy points:-

He has a fixed smile on his face, and bursts frequently into involuntary laughter: his mouth is wide open and the saliva drools from it: he cannot swallow, yet his palate moves well and he can protrude his tongue slowly but completely: he cannot articulate at all, though he can phonate "ah" fairly well: he can perform upper facial movements well, lower facial movements very badly: he has no nystagmus, and his pupils react briskly to light. He is very thin: his muscles are all hypertonic and he has an attitude of contracture, chiefly flexor, in the arms and legs: yet this contracture can be overcome passively, and also actively, although voluntary movements are very slow: there is no true paralysis, yet the patient is extraordinarily helpless, falling and rolling about off his chair, owing to the muscular stiffness and weakness combined: his hands and arms, feet and legs, and to a less extent his trunk, show a ceaseless rhythmical tremor, which increases with exertion. The muscular rigidity is more marked proximally, the tremor distally. There is no disturbance of sensation. The abdominal reflexes are brisk and a double flexor response is obtained, accepted proofs of the integrity of the pyramidal tracts. With the help of an alphabet he is able to express his wants: he evidently appreciates all that is going on round him: his observation is quick, and he understands everything that is said to him.

[Figs. 22, 24]

Three months later, he becomes more acutely ill, his temperature rises, he becomes much weaker, emaciation rapidly progresses, bedsores and more permanent contractures develop, and he dies, conscious to within an hour or two of the end, at the age of 22, after an illness of three years' duration.

At no time during his illness, or before, has he shown any of the ordinary symptoms or signs of cirrhosis of the liver.

CASE IV.

Samuel M., the eldest member of the M. family, was born in 1864, and was quite well as a child. He developed in a normal manner, physically and mentally, and enjoyed good health till the age of nine. At this age he got an accidental wetting in the Regent's canal, and soon after developed typhoid fever. It was a severe attack, lasting, with relapses, over the better part of six months.

Rather less than a year later, when he was ten years old, it was noticed that his fingers and hands were beginning to shake when he used them in any muscular effort, and that he could not walk properly. His gait began to be somewhat shaky. The condition gradually got worse. About a year or so from the commencement of the illness, he began to suffer from an articulatory defect, and swallowing became difficult. In the course of another year the extremities became contracted, and he had to be fed and nursed by others owing to his helplessness. He used to keep his mouth open, and to "make a groaning noise". He was admitted to the National Hospital some time in the year 1878, but the notes cannot be found. He was discharged unimproved, and was taken home, where his condition steadily deteriorated. He was "reduced to skin and bone", and so helpless that "he could not move hand or foot". Anarthric, dysphagic, emaciated and contracted, he lay in bed with all his limbs "constantly on the work". He died in 1879, aged 15 years all but a few days, after an illness of about 4½ years' duration.

There was no post-mortem examination.

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CASE V.

Christopher J., aged 13, was admitted to the National Hospital, Queen Square, London, under the care of Dr Thomas Buzzard, on January 18th 1889, with the following history.

Two years before, for no obvious reason, the boy began to have difficulty in walking: he dragged his feet along the ground instead of lifting them properly, and his feet toes turned in slightly. About the same time he had to leave the choir in which he sang owing to "loss of voice". It was not that his voice broke, but he could not phonate properly.

A few months after the commencement of the illness some discolouration of the lower extremities was noticed. Bright purpuric spots appeared on the skin and faded gradually. At intervals ever since, crops of these spots have appeared. There was no fever, but the joints were sometimes slightly swollen. Since then, the patient has gradually become weaker on his legs.

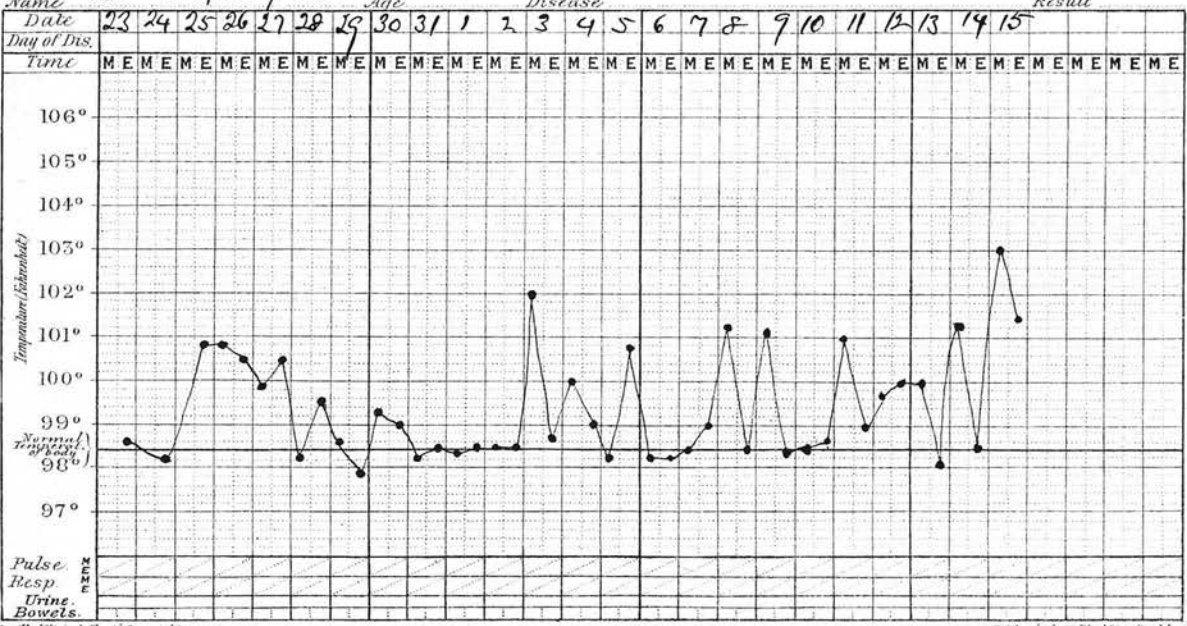
About 13 weeks before his admission he had oedema of the legs, and scrotum, and some ascites. These symptoms improved. About a month ago he had some difficulty in controlling the action of his sphincters. Formerly he was a bright and intelligent boy, in the sixth standard, but since the illness commenced he has been duller and more stupid, noticeably so during the last month.

The patient was an only child: the parents were perfectly healthy: the mother had had no miscarriages.

On admission he was seen to be pale and rather delicate-looking. His mental condition was striking: he was very emotional, at one time laughing, at another, crying: He was slow in answering questions, and the saliva often dribbled from his open mouth. He was slow in understanding what was said to him, but did everything correctly that he was asked to do. There was some general wasting of the musculature, most evident below the knees, and there was some contracture at the ankle, as the patient was unable to move that joint or only to a very little extent. The toes were in a state of more or less constant rhythmical tremor. Passive movements at the ankles were not easy of execution, and caused the patient

1889  
Jan

Name *Christopher Johnson* Age *13* Disease \_\_\_\_\_ Result \_\_\_\_\_



H. Sawdell's 'Clinical Chart' Copyright. No. 7.

H. Silverlock, 92, Blackfriars Road, London.

Fig 31.

Temperature chart of C.J., from the original notes in the National Hospital, dated 1889.

pain, though not of any severity. He could move the legs well, but less well distally than proximally. The deep reflexes in the legs were increased, and there was a tendency to ankle clonus on both sides. The plantars were "brisk".

In the arms all movements could be carried out, but were undoubtedly weaker than normal. The arm reflexes were active and equal. The abdominal and epigastric reflexes also were brisk, and equal on the two sides. The pupils, optic discs, and ocular movements, were all normal.

The illness progressed rapidly: the boy's emotional state became more aggravated: he laughed or cried on the slightest provocation. His legs became more contractured, and were constantly drawn up at the knees and hips. Constant sudden involuntary movements of the lower extremities occurred: they were abruptly drawn up and rather more slowly relaxed. The arms in their turn became rigid: the left arm began to contract up, and there were sudden involuntary alternating movements of pronation and supination to be observed. The same thing was noticed in the right arm, to a less extent.

Oedema and ascites set in and on February 14th the child died.

If we summarise this case briefly, its salient features are as follows: -

A little boy of 18, who has always been healthy, and intelligent, begins to have difficulty in walking, and his voice alters: he becomes gradually more emotional, laughing or crying at the merest trifle: his mouth is open and saliva dribbles away: his muscles waste and become rigid, and then the extremities contract, the legs first, and later the arms: there is rhythmical tremor of the feet and toes, and attacks of involuntary spasmodic movements in the upper extremities, usually of an alternating type (pronation and supination, flexion and extension): he loses control over his sphincters. The abdominal reflexes remain brisk, however, a significant fact. Emaciation sets in, and he dies after an illness of about two years' duration.

He has shown very definite signs at intervals of defect of liver function, but there are no evidences whatever of congenital syphilis.

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CHAPTER III.

P A T H O L O G I C A L F I N D I N G S I N T H E  
P E R S O N A L C A S E S .

In this chapter I give the complete pathological investigation of three personal cases of progressive lenticular degeneration whose clinical history has been recorded in the previous chapter. In addition, there is a brief account of the pathological findings in case V, that is to say the case referred to by Ormerod in his paper, the details of which, have not hitherto been published. In Case IV there was no pathological examination.

The harmony in the pathological findings of the personally observed cases is no less convincing than the similarity in their clinical features. It is true that I am not able to give as complete a pathological investigation of case II as I should have liked, but there is ample evidence that its place with the others is beyond all cavil. Cases I and III are identical, pathologically, except that the latter is not so advanced as the former. The specificity of the lesion is strikingly manifest. It is, in fact, a fortunate circumstance that the degree of pathological change is not so great in case III, for clinically the patient was just as profoundly affected as the patient whose case is no. I. By this means we are able to learn better what pathological change to associate with the clinical symptoms, and due reference will be made to this important point in a subsequent chapter.

There are certain features of the pathology of the three personal cases which I may very briefly emphasise by way of introduction. In the first place, there is no pathological evidence whatsoever that the cases are syphilitic: in fact, syphilis may be excluded pathologically as I believe it can and must be clinically. Secondly, there is no pathological evidence that the disease is congenital: there are no anomalies of development of any kind. Thirdly, the pathology furnishes proof that a selective morbid agent of a quite peculiar and apparently unique sort must have been at work.

CASE I.

The autopsy was performed at 9 p. m. on the evening of Wednesday, July 29th 1908, 25 hours after the death of the patient.

The body was greatly emaciated, and rigidity was marked, but there were no bedsores or abscessions. Postmortem lividity was pronounced.

On opening the calvarium the dura was noted to be neither adherent nor discoloured: its veins and sinuses were engorged, but otherwise normal. The subarachnoid spaces and cisterns were greatly distended with cerebrospinal fluid. The arachnoid was observed to be somewhat "milky" at the base of the brain, in particular across the interpeduncular space. The arteries at the base presented no visible abnormality. The pons, cerebellum, medulla and cord seemed normal on a rapid inspection. The membranes of the cord were not thickened. As the cranial nerves were cut through they appeared to be quite normal.

The brain and cord were immersed in 10% formalin. They were weighed the next day, with the following result:

- brain complete: 1850 grammes.
- cerebellum, medulla, and pons, together: 146 grammes.
- cerebrum: 1204 grammes.

The heart and lungs were normal, except that the latter were somewhat congested. There were old pleural adhesions, few in number, on the left side posteriorly.

The liver, when removed from the abdomen, presented a very striking appearance, seen in figures 32, & 33. It was intensely cirrhotic: the whole of its surface was covered with irregular rounded nodules of liver tissue, about the size of hazel nuts, surrounded by bands of connective tissue, of varying width. Some nodules were considerably smaller. The capsule of the liver was not obviously thickened, except in one or two places. There were no adhesions to the neighbouring viscera. The organ was not bilestained, and was perhaps rather lighter in colour than ~~usual~~ usual. On making a transverse incision through it, it was seen to be cirrhotic from one side to the other: it was divided up into nodules

X Reduce to  $\frac{1}{2}$  area

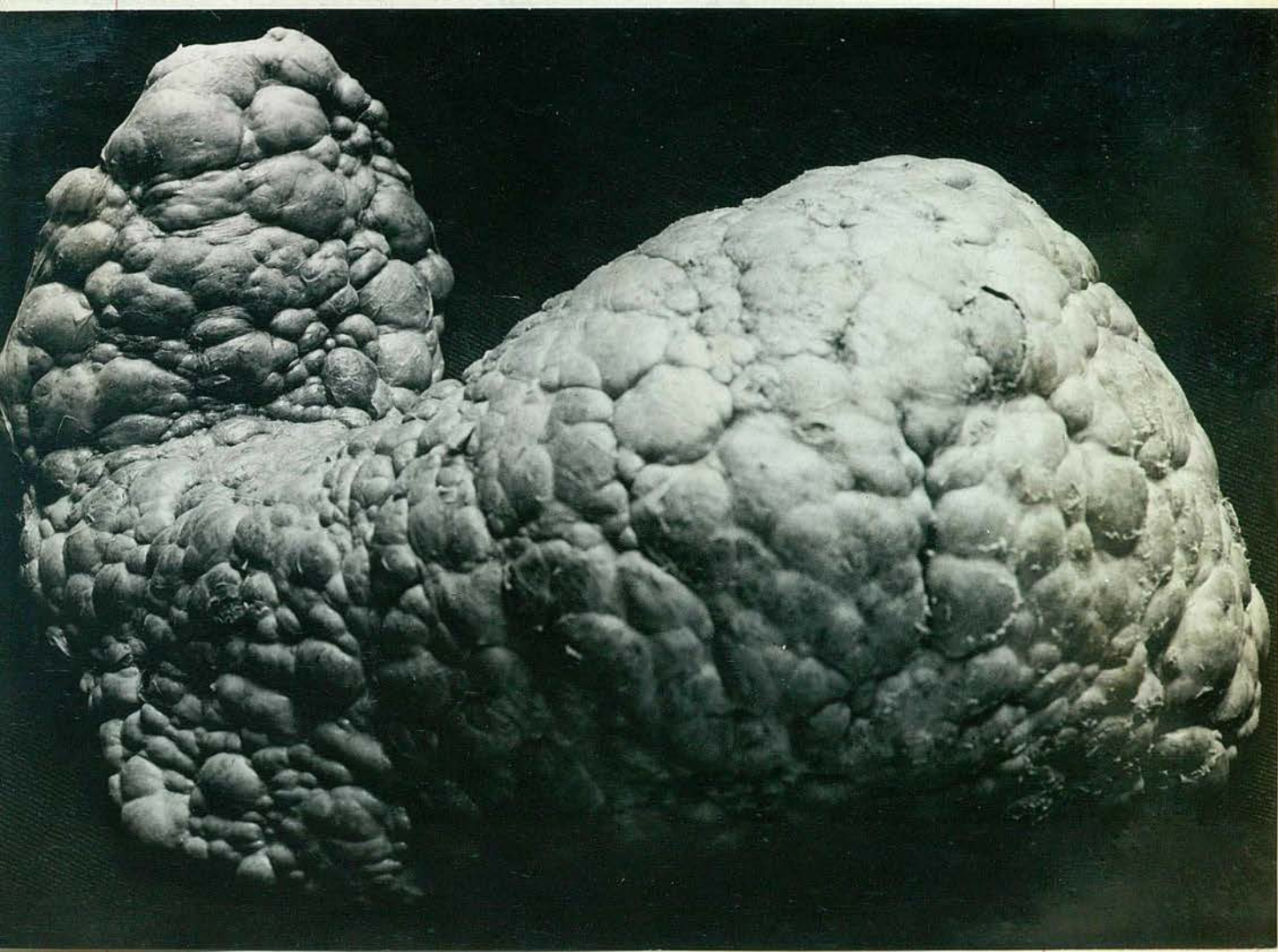


Fig 32.  
(about natural size)  
live in case of S.T.

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to

X Reduce by  $\frac{1}{2}$  area



Fig 33.

Liver in case of S.T.  
(about natural size)

varying in size from a shilling to a threepenny piece, or less, between which was a great deal of connective tissue overgrowth, sometimes of considerable width, especially in the deeper parts of the viscus. There was much thickening along the portal tracts. The cirrhosis was characteristically multilobular.

The weight of the liver and gall bladder was 1380 grammes. It was firm and preserved its shape. The gall bladder did not show any abnormality.

The spleen was not obviously enlarged: it was firm, and rather congested: its cut surface on section seemed normal.

The kidneys were normal. The suprarenal on the left side, pieces of the following muscles: -right thenar eminence, left biceps, left flexor sublimis digitorum, left extensor communis, together with a piece of the left lobe of the thyroid, were taken for subsequent examination.

The pancreas and the intestines were unaltered. The stomach was three parts full of dark liquid blood: its mucosa was greatly congested, but no ulceration was discovered, and a rapid search for a ruptured vessel or vessels was unsuccessful.

There was no ascites.

MACROSCOPICAL EXAMINATION OF THE BRAIN AND CORD.

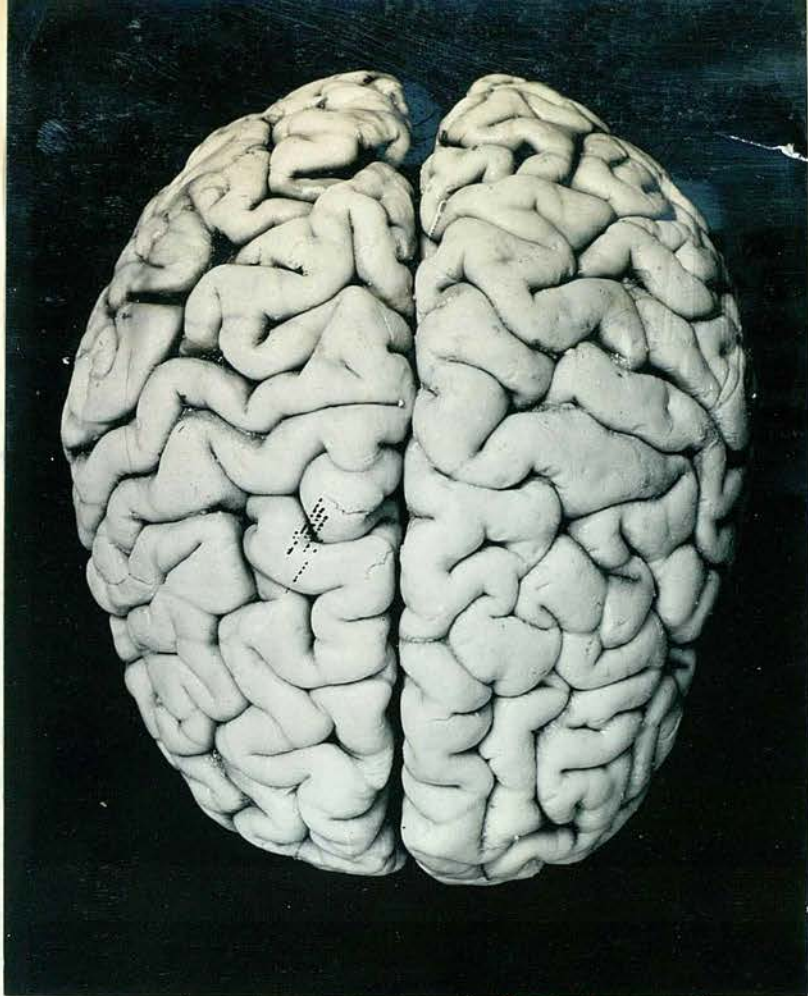
After hardening in formalin the brain was stripped of its membranes. These were not adherent anywhere. Pieces of the middle cerebral artery and its branches were taken for microscopical investigation.

The cerebral hemispheres were perfectly well developed, and did not show any atrophy or undue spacing between the convolutions. The pattern of the latter was normal. In particular, the frontal lobes were not the seat of any obvious pathological change. The corpus callosum was divided in the mesial plane, when the mesial aspect of the hemispheres was examined, and found to be quite normal.

[Fig 34, 35]

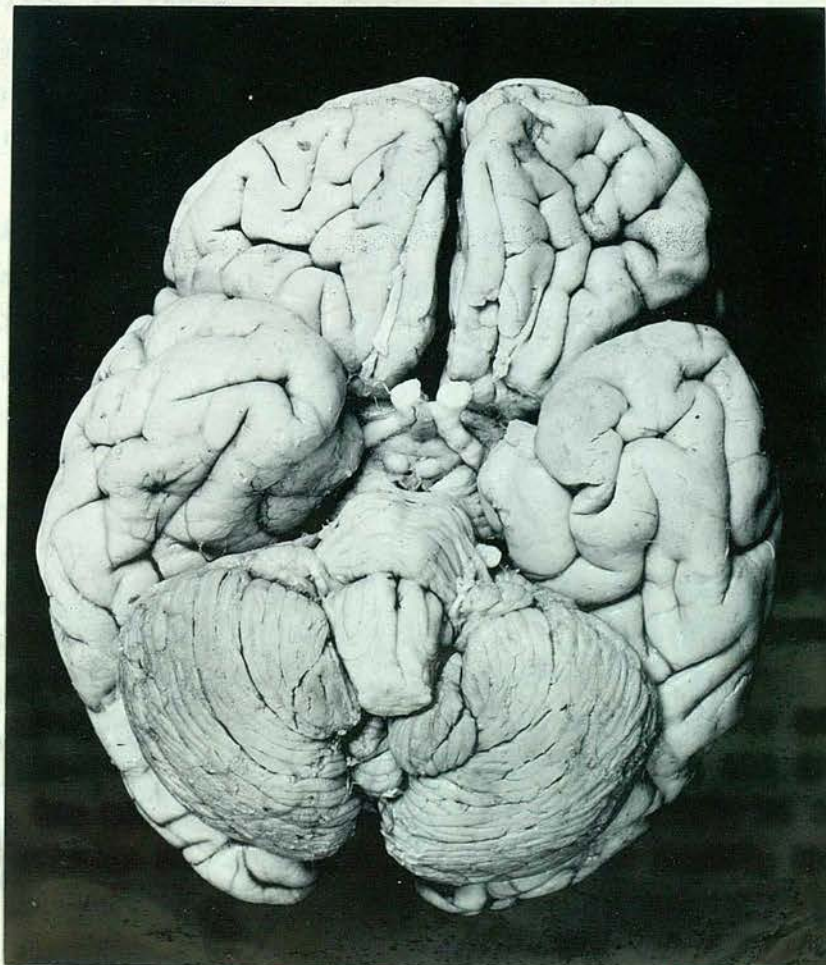
Each hemisphere was then cut across by Professor Marie's coupe d'élection, a section which passes under, and just touches, the extremities, anterior and posterior, of the corpus callosum as it appears on the mesial aspect, and is

89



X Reduce  
by  $\frac{1}{3}$

Fig 34. Brain n S.T. from above (Case I)



X reduce  
by  $\frac{1}{3}$

Fig 35. Base of brain n S.T. (Case I)

carried horizontally outwards to the lateral aspect of the hemisphere. When this was done, the remarkable picture that is reproduced in figures 36 + 37 was revealed.

The eye is at once caught by an extraordinary bilateral and symmetrical cavitation of the lenticular nucleus: it rivets the attention by its degree of severity when the rest of the cut surface of the hemisphere is practically normal. The cortex and the white matter of the hemispheres do not present any abnormality, the thalami are of perfectly good size and shape, the internal capsules stand out clearly (with an exception, to be noted immediately) while the putamen and globus pallidus have almost entirely disappeared, and in their place is a crumbling cavity.

Right side.

The whole of the right putamen, with the exception of its anterior fifth, and the globus pallidus, with the exception of its extreme inner part, have vanished, and the small sections that do remain are obviously soft and disintegrated. Their place is taken by a cavity lined with irregular dirty brown tissue debris, which subsequent examinations show to extend practically from the upper to the lower limit of the lenticular nucleus. Its greatest dimensions are  $2\frac{1}{2}$  centimetres long by  $1\frac{1}{4}$  -  $1\frac{1}{2}$  centimetres wide. It does not contain any fluid. The outer margin of the cavity is formed by a steep wall which corresponds strictly to the outer aspect of the nucleus, and it is sharply differentiated from the claustrum and island of Reil convolutions, which, although microscopical examination may show they are slightly degenerated, certainly do not present any sign of loss of substance. Posteriorly the cavity comes to an end at a point corresponding to the posterior end of the nucleus, and its inner wall is formed by the internal capsule, except at the anterior part, where a little globus pallidus remains.

The external capsule in its middle third is thinned and has undergone loss of fibres. The caudate nucleus is a little shrunken, and not so "full" as in a normal brain, but compared with the destruction of the lenticular nucleus it is well preserved, and its fine fibres can be easily distin-

R



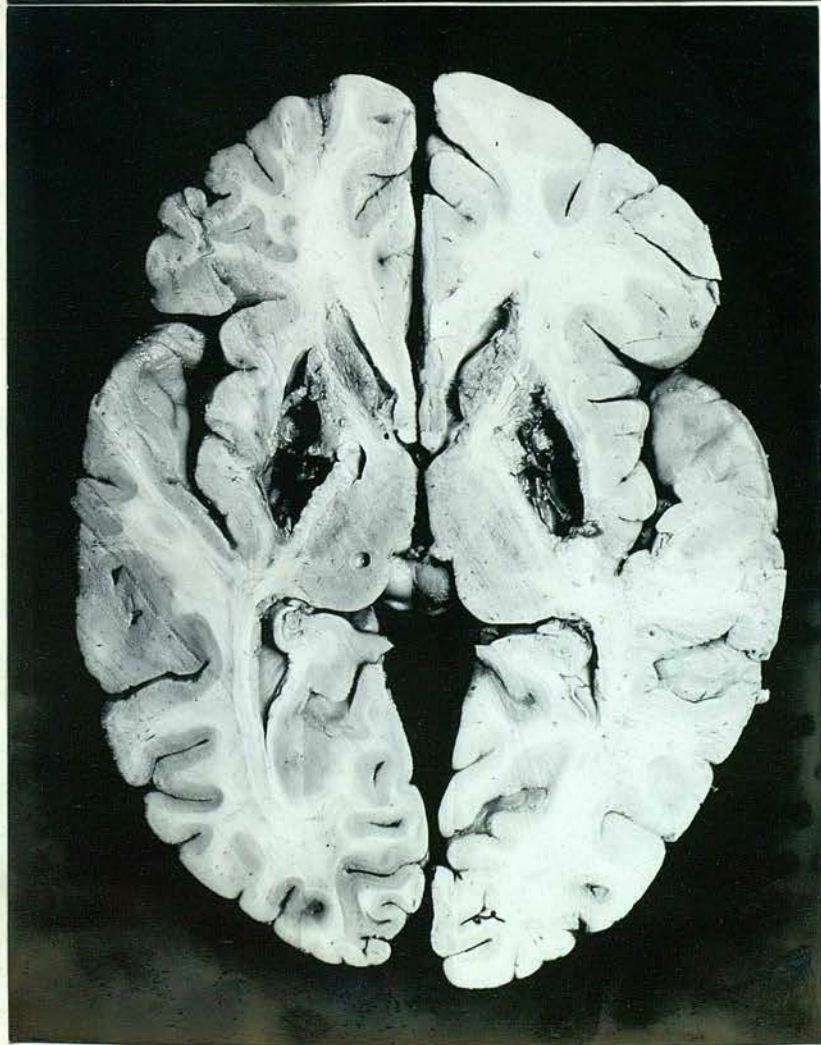
L

X

Fig 36. Horizontal section through brain of case I: upper surface:

(slightly reduced from natural size)

L



R

Fig. 37. do. do. under surface

92  
guished.

The internal capsule is untouched: its anterior and posterior limbs look perfectly normal. A few fine internuncial fibres from the extreme anterior part of the putamen, running mesialwards, can still be seen. The optic thalamus is to all appearance perfectly normal. It is not atrophic or shrunken in any way. The rest of the section presents no visible morbid appearance.

Left side.

The cavity formation on the left side is almost identical with that on the right. It is, however, even more severe. It occupies the whole of the lenticular nucleus area, with the exception of a small portion of the globus pallidus anteriorly and to the inner side. It extends right back to the point at which the nucleus comes to an end. On the outer side the cavity has destroyed part of the external capsule, at the junction of its middle and posterior thirds, and has extended into the claustrum very slightly. Anteriorly, on this outer side, the crumbling debris of the nucleus has fallen away from the "bed" in which the nucleus lies, leaving a clean cut edge to the cavity which is well brought out in the photograph. On the inner side the cavity has undermined the internal capsule at its genu, and a small extension from the main part has made its way across the capsule, separating but not destroying the fibres, at least not in any degree, as we shall learn later.

The cavity walls are highly irregular, dark brown in colour, in some lights shiny: the debris that is left is soft and granular. Subsequent investigation shows that on this side also the cavity occupies almost the whole extent of the lenticular nucleus in a vertical direction. In one or two places thin strands of shreddy material still bridge it across, more particularly towards its anterior end. Its dimensions are  $2\frac{5}{8}$  centimetres long by  $1\frac{1}{4}$  centimetres broad. The diameter of the little prolongation of the main cavity across the internal capsule is 7 millimetres. There is no brownish slough in this little subsidiary cavity, and no sign whatever of softening round it.

The internal capsule, anterior limb, is normal. At the

genu we meet the cavity prolongation already described. The posterior limb of the internal capsule looks quite normal, though it appears somewhat undermined by the cavity: the retrolenticular segment is normal.

As on the right side, the caudate nucleus seems rather small, and less rounded than usual, but it is not softened: in fact it appears well preserved, and its internuncial fibres stand out prominently. The latter have all disappeared from what is left of the globus pallidus on this side.

The optic thalamus contains, towards its posterior and inner side, a small shallow almost circular depression, like a little punched out hole, which is sharply defined, has no softening round it, and is not connected with the main cavity at all. Its diameter is 3 millimetres. Otherwise this ganglion is normal to all appearance: it is not atrophic or shrunken in the least.

The convolutions of the island of Reil do not show any obvious loss of substance.

The rest of the section presents no visible morbid appearance.

There is no internal hydrocephalus, and no ependymitis. The whole of the visible cortex on these sections appears of good depth.

The spinal cord seemed on naked eye investigation to be of normal appearance. Its transverse sections, at various levels, were of good size, and did not show any trace of degeneration. The membranes were not obviously thickened, unless it were that the pia-arachnoid was a little "milky," chiefly along the posterior aspect of the cord.

MICROSCOPICAL EXAMINATION OF THE CENTRAL NERVOUS SYSTEM.

1. MUSCLES.

Sections were stained by the following methods: haematoxylin-eosine, haematoxylin-van Gieson, and Weigert-Pal for intramuscular nerves, counterstained with eosine.

Speaking generally, the muscle fibres were all of good size, and all about the same size. There was no disparity in this respect. There were no hyaline changes: no splitting of fibres: no loss of longitudinal or cross striation. What was

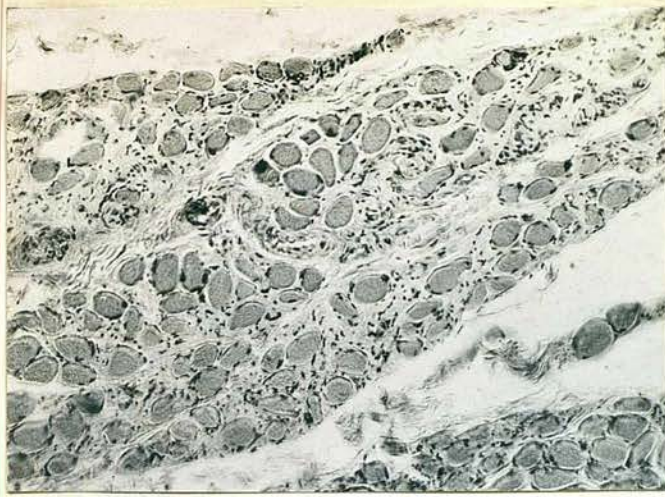


Fig 38. Transverse section of left. flex. pub. dip: case I



Fig 39. Longitudinal section from same muscle - case I

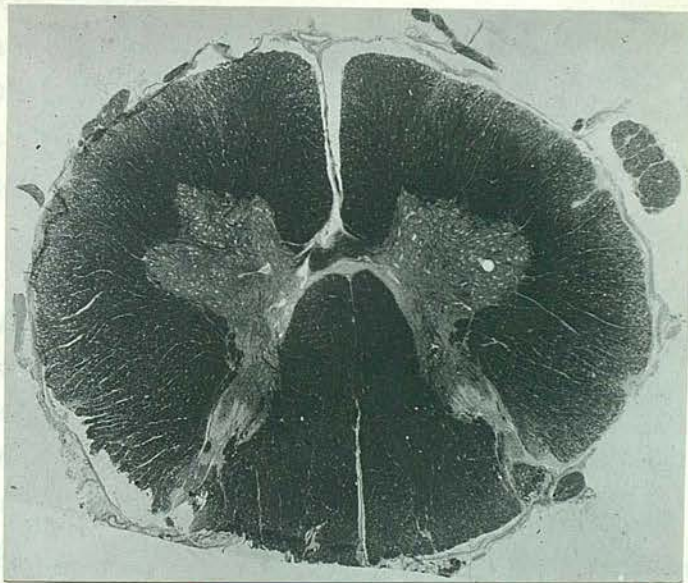


Fig. 40. Cervical cord (weight)

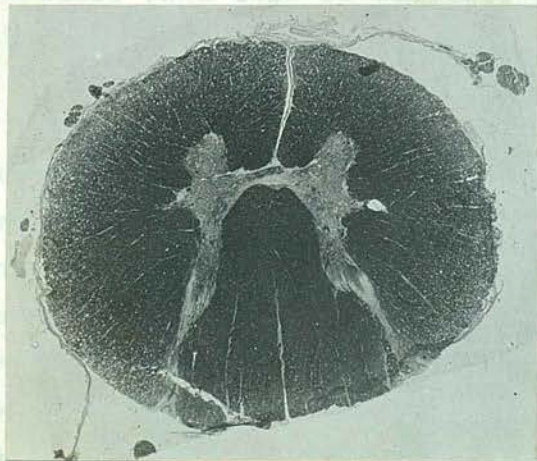


Fig 41. Dorsal cord (weight)

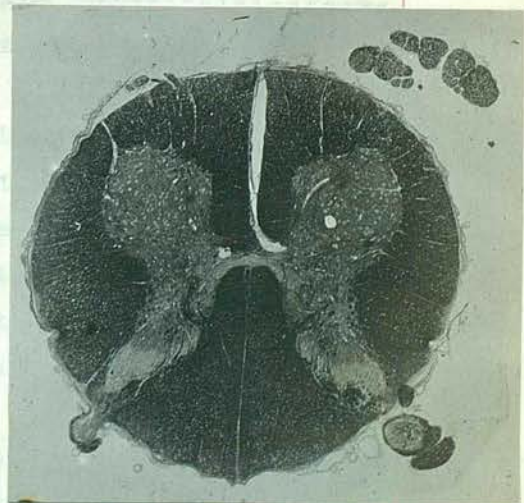


Fig 42. Lumbar cord (weight)

all from case I.

Reduce each of these by  $\frac{1}{2}$

chiefly remarked was a frequent change in the contour of the fibres, whereby they became much more rounded, and less polygonal or polyangular than usual. In addition to this change, the muscle fibres were often less closely packed together, and a degree of commencing interstitial change was frequently observed. One of the sections in which this was most marked (<sup>left flex: post: digitorum</sup> ~~right thenar eminence~~) is shown in figure 38.

In some places the sheath nuclei were much increased in numbers (figure 39). The muscle spindles were normal, and no change was discovered in the intramuscular nerves.

2. PERIPHERAL NERVES.

These were not separately examined.

3 SPINAL CORD.

The histological methods utilised were Weigert, Weigert-Pal, Nissl, haematoxylin-eosine, haematoxylin-van Gieson.

a. Fibres.

A glance at the series of photographs from sections stained by Weigert's original method will show that there is no systematised degeneration in the cord. The pyramidal tracts are normal throughout, and stain deeply and equally. There is no shrinkage of the white columns, and although there is a trace of marginal loss of fibres it is scarcely to be classed as pathological, it is so slight. The fibres of the grey matter also stain well, and are not reduced in number. The complete integrity of the pyramidal paths in the cord is a remarkable fact when we remember the utter motor helplessness of the patient, the contractures, tremors, and spasticity.

[Fig 40-42]

b. Cells.

These were carefully examined at various levels. In the first place, as can be seen from the figures, they are present in good numbers; they preserve their normal grouping, moreover. The majority of them, in both cervical and lumbar enlargements, are of good shape and staining reaction. A number, however, are rather drawn out, and stain more deeply than usual, apparently owing to some shrinkage of the achromatic part of the cytoplasm, whereby the tigroid elements are brought more closely together, thus explaining the darker hue of the cell. Such cells retain their nucleus,

[Fig 43-44]

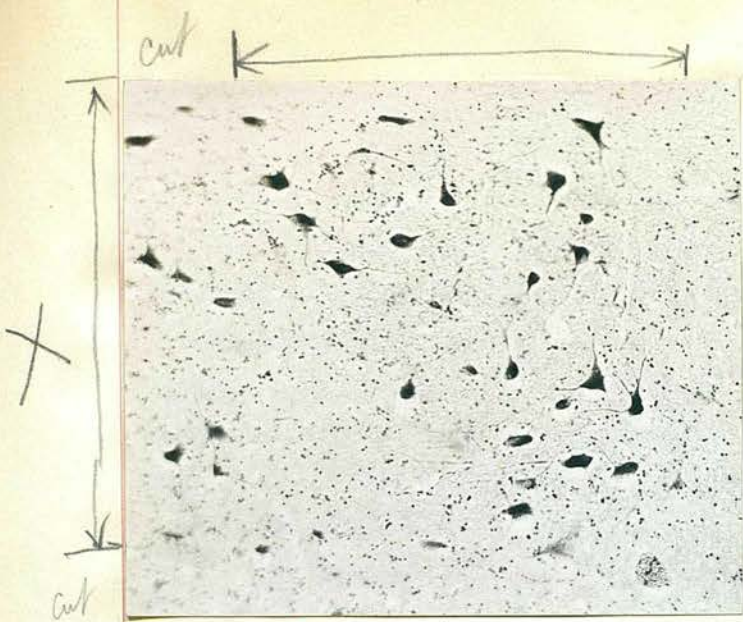


Fig 43. Cells from anterior horn in cervical region (Nissl). Case I



Fig 44. Do. Do. lumbar region. Case I.

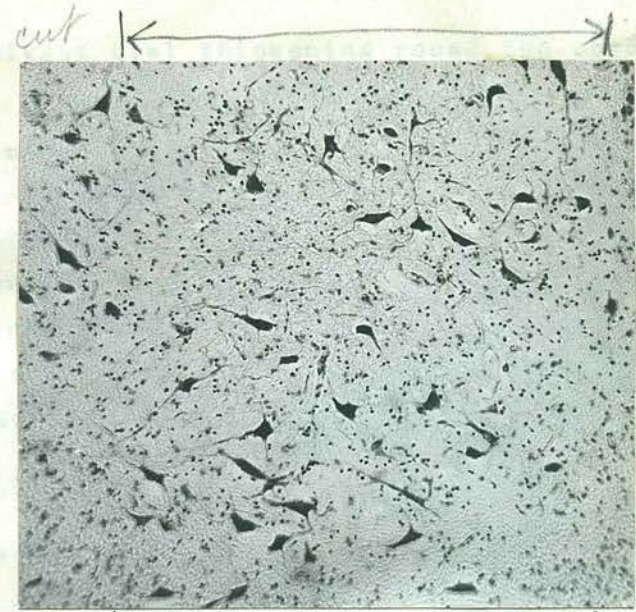


Fig 45. ~~Do. Do.~~ Hypoglossal nucleus R. sick - (Nissl's method). Case I

Note the change associated with the comparative resorption & immobility of the tongue: yet at same time the number of cells is practically unaltered.

and there is no reason to suppose that they have lost their function completely. They are often met with in chronic diseases of the nervous system, in which the patient has not the full functional use of his limbs. Other cells, much fewer in number, show commencing pigmentary degeneration. Others still show the changes that are associated with a more acute degenerative process, viz. pulverisation of the chromatin bodies round the nucleus, eccentricity of the latter, and disappearance of its membrane. Such cells usually appear somewhat swollen. In this case their presence may be indicative of a terminal infection.

On the whole, the actual numbers of the anterior horn cells are slightly reduced compared with a healthy, i e normal, cord.

c. Meninges.

There is slight pial thickening round the cord, more especially in the cervical region. It is important to note however, that small cell infiltration is conspicuous by its absence. Neither in the meninges, nor round the spinal vessels is there the faintest trace of this inflammatory reaction. the spinal vessels themselves are entirely normal: they are not thickened in any of their coats, nor can anything approaching endarteritis be discovered. The intramedullary vessels are similarly healthy.

4. MEDULLA OBLONGATA AND PONS.

The same methods were utilised for these as for the examination of the cord.

With Weigert-Pal's stain for medullated fibres no change could be detected. The pyramids stained normally, and were not atrophic: they did not appear to have undergone any loss of fibres at all. In the position of the descending mesencephalo-spinal tracts no defect could be found. Monakow's bundle, on either side, seemed normal. The olives, restiform bodies, fillet, &c, were to all appearance normal. (Figs 46, 48)

The cells of the motor cranial nuclei were investigated by Nissl's method. Figure 45 shows the appearance of the cells of the right hypoglossal nucleus. It will be seen at once that there is no obvious loss of cells, distinguishing the condition at once from an ordinary bulbar palsy. Many

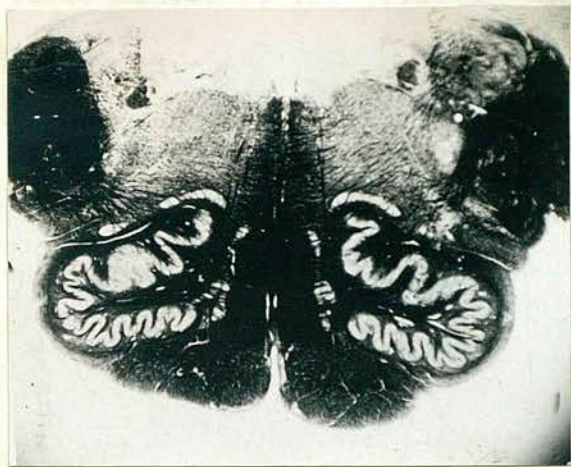


Fig 46. Transverse section  
of cerebellum in Case I  
(Weigert-Pal)  
Pyramid normal.



Fig 47. Cross in Case I:  
(Weigert-Pal)  
Note the absolutely intact pyramidal  
tract.



Fig 48. Upper part of pyramid, Case I.  
(Weigert-Pal)  
Pyramid normal.

reveal that alteration which we have already noted in some of the cells of the anterior horns, viz., "intensification". They are drawn out, stain more deeply, are less easy to differentiate structurally, but retain their nucleus. The processes of the cells are elongated and often rather more wavy than usual.

The examination of the nucleus shows that the "uselessness" of the tongue during life was not due to any atrophic paralysis, or to gross defect of pyramidal mechanism.

The cells of the other motor cranial nerve nuclei examined were found to be similar to those just described.

5. CEREBELLUM.

From the structural point of view, as regards both cells and fibres, this organ was normal. (Figure 49)

6. CRUS.

Weigert and Weigert-Pal sections of the crus cerebri (figure 47) were in every way normal. The pyramidal tract looked perfectly normal, and the <sup>components</sup> ~~sections~~ of the crus on either side of it were similarly unaffected. The tegmentum was unimpaired. The fibres of the red nucleus were normal: they stained deeply, and the nucleus did not in any obvious way--in size, shape, or intensity--differ from the red nucleus in a normal brain, used as a control.

The cells of the red nucleus were examined with Nissl's method, as well as with haematoxylin-van Gieson. They did seem to be abnormal in any way. A number of them were immediately surrounded by parasite glial cells, but not to a great extent.

7. BASAL GANGLIA, INTERNAL CAPSULE, &C, SUBTHALAMIC REGION.

The two hemispheres were subjected to an exhaustive examination and investigation by the method of serial sections. The right hemisphere, with the exception of the frontal and occipital poles, was cut up into slabs, one centimetre thick. These were cut exactly at right angles to the coupe d'election, and 8 such slabs were Mullerised, embedded and cut in cell-

oidin, in complete series from before backwards. Every fourth section was taken and stained either by Weigert's original stain, or by Pal's modification of it. The accompanying photograph gives an idea of the blocks of tissue in relation to the mesial aspect of the hemisphere. [Figure 53]

On the left side the hemisphere, with the exception of the frontal and occipital ~~poles~~ poles, was divided by a number of incisions exactly parallel to the coupe d'election into a series of slabs one centimetre thick. Of these, two were above the plane of the coupe, and two below. The photograph shows their position in relation to the mesial aspect of the hemisphere. They were Mullerised, embedded in cell-oidin, as in the case of the other hemisphere, and cut in complete serial section from below upwards. Each fourth section was taken, and stained as above. [Figure 52]

Figures 51 + 50 were photographed when the right hemisphere was cut into divisions. The first of these represents the naked eye appearance of the anterior aspect of the hemisphere at the line 4---4, and the second at the line 5---5. They portray, in a truly striking manner, the specificity of the lesion in progressive lenticular degeneration. They demonstrate the integrity of the caudate nucleus and the optic thalamus, and the utter cavitation and destruction of the lenticular nucleus. The posterior end of the cavity, looked at from the front, as seen in figure 50, impresses itself vividly on the eye: the uniqueness of the lesion could not be brought out more clearly or convincingly.

For purposes of description I cannot do better than ask the reader to follow the photographs of various sections, taken in order, on the right side from in front backwards, and on the left side from below upwards. [Figures 54-61]

a. Description of the appearances of the lesions on serial section.

Right side. The lesion begins, on vertical transverse section, well towards the anterior extremity of the putamen, on a plane which passes through the tips of the temporal lobes, and at a level where the lenticular nucleus is continuous with the caudate round the anterior fibres of the internal capsule. Here a small hole makes its appearance al-

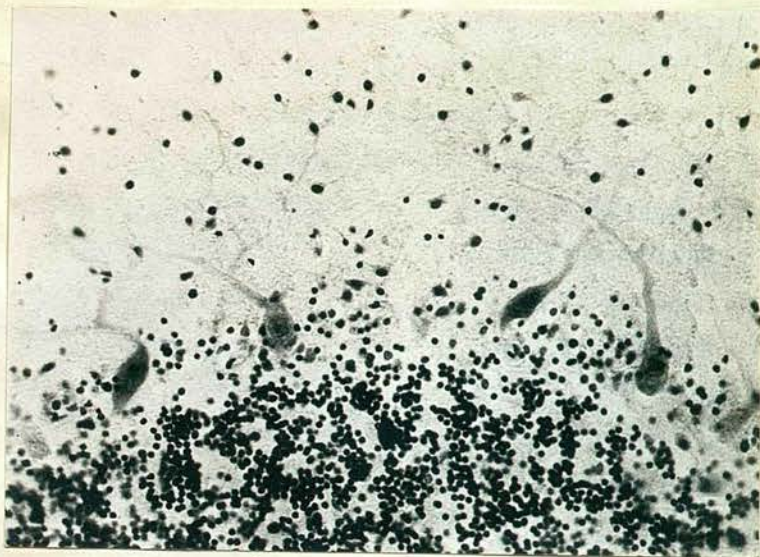


Fig. 49. Cerebellar cortex, Case I.  
(Haematoxylin-van Gieson)  
- normal -

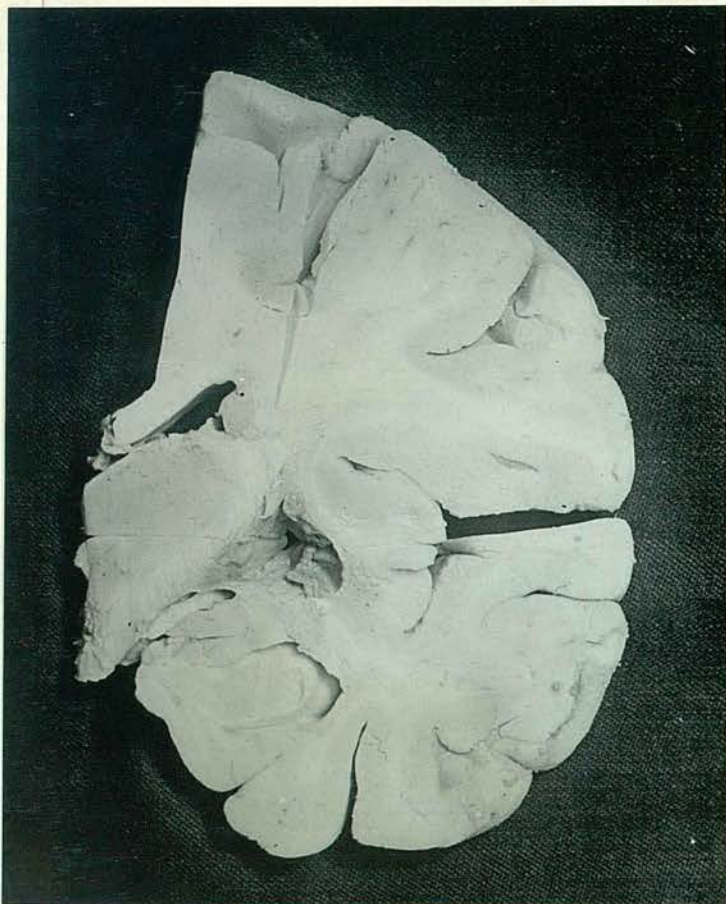
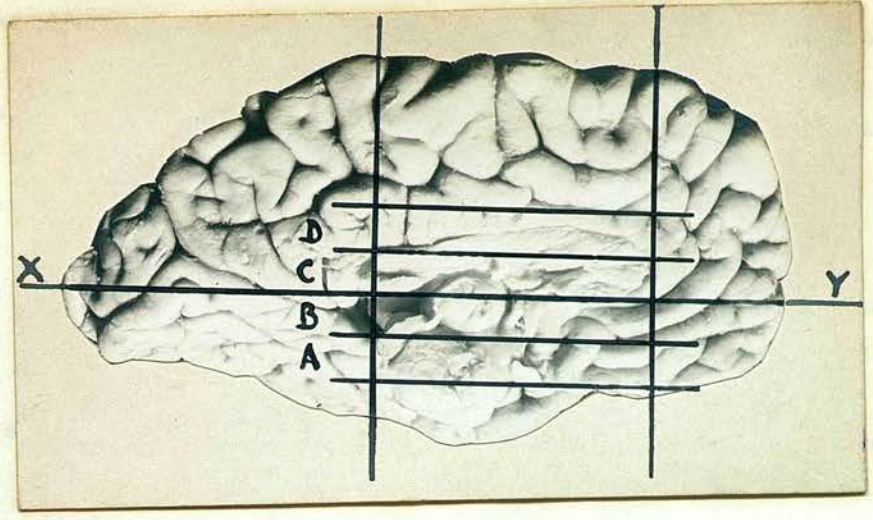


Fig 50. Line 5-5 in fig. 53.  
(about natural size)

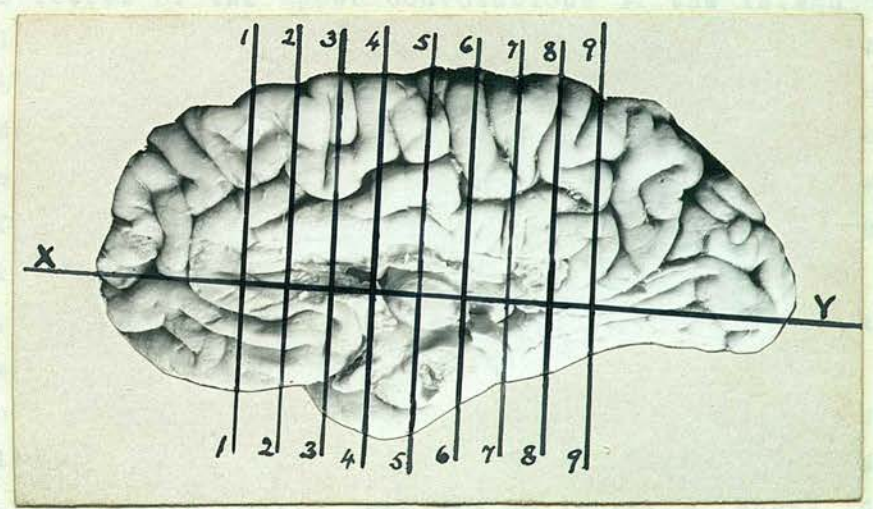


Fig 51. Line 4-4 in fig 53.  
(about natural size)



X

Fig 52. Represents the slabs cut in serial section in the left hemisphere



X

Fig 53. Represents 8 slabs cut in serial section of R hemisphere

X-Y is the coupe d'election in each case

most exactly in the middle of the putamen, and extends by a narrow process into the internal capsule, the fibres of which it separates, but does not appear to destroy. It looks as though the morbid process had extended along one of the "bridges" of grey matter that unite the putamen and the caudate across the capsule.

A few sections further back the lesion is about the size of a split pea, and has a very definitely thickened lining or wall to it, apparently of some duration.

At the level of the anterior tip of the globus pallidus (middle lenticular zone) the lesion is still confined to the putamen. It is rather larger, but remarkably circular. It can be seen that the external capsule stains rather faintly towards its lower part, and is evidently thinned. The external medullary lamina has disappeared. The pencils of fibres passing inwards from the putamen are absent.

Further back, the lesion has spread into the middle zone and destroyed it completely, and has now its greatest diameter in a vertical direction. The internal medullary lamina can be seen, but it does not stain well. The internal capsule is intact, however. The external capsule is somewhat attenuated, and the fibres of the upper convolutions of the island of Reil also seem rather poor. The strio-thalamic fibres which cross the capsule, under a higher magnification, are found to be degenerated in many cases, to be of irregular thickness and staining power: many are moniliform. On the other hand some of the bundles of fibres crossing the capsule are normal: probably some at least of these are coming in a reverse direction, from the thalamus. If the globus pallidus--all that remains of it--is examined its fibres are seen to be in a state of degeneration: they are twisted, distorted, wavy, irregular in thickness: some show a myelin sheath ending in a knob. Many stain badly. They are no longer arranged in close set symmetrical bundles intersecting each other. The ansa lenticularis is found to consist partly of healthy fibres and partly of obviously degenerated fibres. All that is left of the putamen proper is a fibreless ring of degenerated tissue round the cavity.

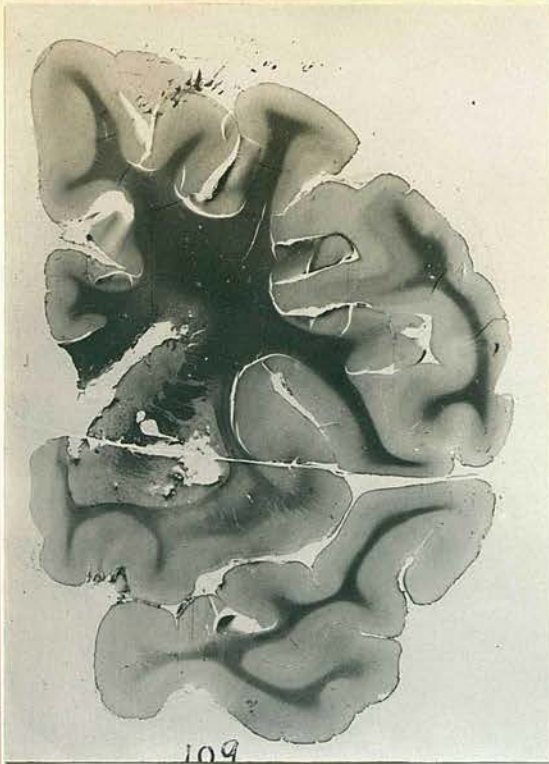


Fig. 54.



Fig. 55

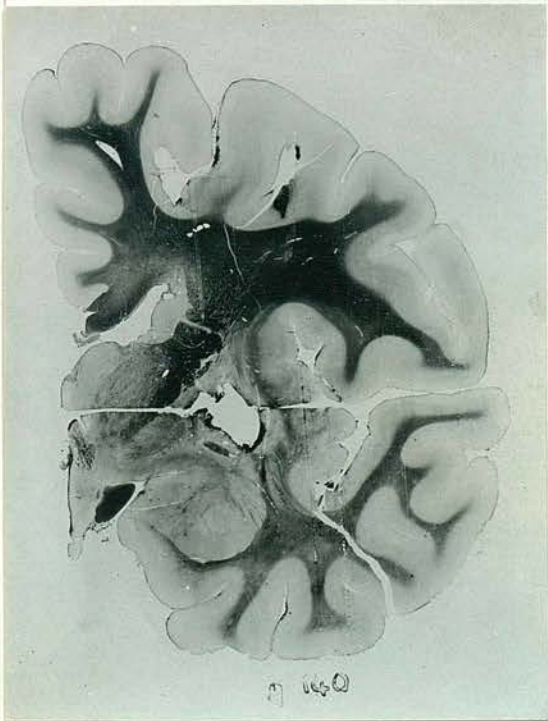


Fig. 56.

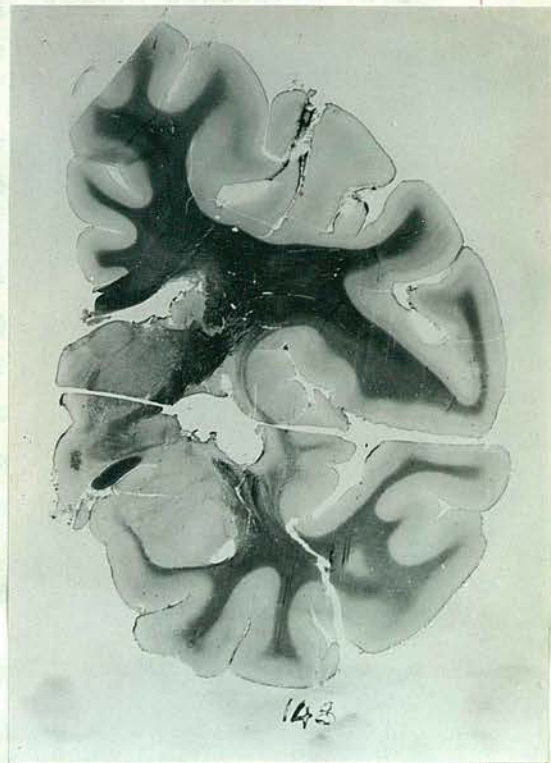


Fig. 57.

(Natural size or very slightly reduced)

A few sections further back we reach the area of maximum disintegration. The putamen and the middle lenticular zone are non-existent, and their place is taken by an irregular cavity which extends close up the internal capsule on the inner side, and to the claustrum on the outer. The internal lamina of the nucleus can be traced, but it is obviously degenerated: the fibres of the internal zone are greatly interfered with, and many of them are in a condition of decay. The capsule has a few degenerated fibres in it, mostly towards that part of it which is going to form the genu. In the ansa lenticularis are a great number of defective fibres, along with some that seem structurally to be normal. It can be traced, staining imperfectly, round the inner end of the capsule, towards the posterior and inferior part of the thalamus. The strio-thalamic fibres present the same features as have already been noted. The fibres under the cortex of the upper convolutions of the island of Reil stain feebly. The external medullary lamina of the optic thalamus is weakened.

The lesion comes to an end by gradually narrowing to a point, just short of the posterior inferior extremity of the putamen.

A scrutiny of these serial vertico-transverse sections shows that there are certain secondary degenerations which require to be studied.

The ansa lenticularis is partly degenerated, but can be followed into the subthalamic region. Here it becomes difficult to trace: apparently some of its fibres joined others coming more directly across the capsule to the upper side of the corpus Luysii, but its prolongation towards the red nucleus could not be made out, presumably because of degeneration.

The corpus Luysii is undoubtedly smaller than normal, and under a high power the fine myelinated fibres contained in it are found to be somewhat reduced in number. Some are moniliform.

The lenticular bundle of Forel (faisceau H), in the regio subthalamica, is also degenerated, but not so much as the ansa, for a number of the fibres passing directly across the capsule from the inner zone of the globus pallidus and going to form part of Forel's bundle seem quite normal.

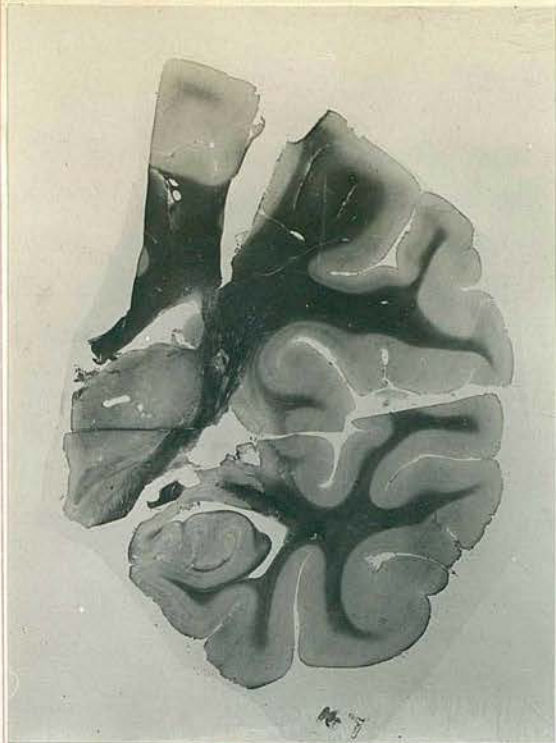


Fig. 58.



Fig. 59.



Fig. 60.



Fig. 61.

(all natural size or very slightly reduced: all Weigert-hal method)  
fig 60 natural size)

As regards the optic thalamus, it has been already remarked that the external medullary lamina is thinned, and poorer in fibres than in the normal brain. The ganglion as a whole is not atrophic at all, and the fibres that skirt its nuclei ~~area~~ are easily traceable. The thalamic bundle of Forel is imperfectly stained.

The caudate nucleus contains throughout bundles of fine fibres passing down and across the capsule, and the majority of these appear quite normal. They appear, however, to be somewhat reduced in number. It is difficult to ascertain if any degenerated fibres pass to it from the putamen.

The internal capsule stains with normal intensity all through the series of sections, except that it contains a few degenerated fibres in the immediate region of the genu.

Türck's bundle is normal.

Retrograde degeneration, or any diffuse degeneration, is so difficult to follow in sections stained by the Weigert-Pal method that nothing can be said of any possible alteration in the corona radiata or in cortical fibres.

Left side. The condition of affairs on the left side so closely resembles that on the right that a briefer description will suffice.

[Figs 61-67]

The lesion extends to the extreme lower and posterior portion of the putamen, behind the anterior commissure, and behind the spot at which the lenticulo-striate vessels enter the hemisphere to run vertically upwards. At a slightly higher level a cavity appears also in the anterior portion of the same outer zone of the lenticular nucleus, and as we pass up we find that these two cavities unite to cause a complete destruction of the putamen and of the outer part of the globus pallidus, leaving a fragment of the inner part at its anterior end. Where the lesion is at its maximum, about the middle of the putamen considered vertically, we find the extension through the fibres of the internal capsule, at its genu, to which allusion has already been made. The little subsidiary cavity thus formed is lined by capsular fibres which stain deeply, but there is no doubt that a number of them in this section of the capsule are degenerate, for the degeneration can be traced. It is not, however, as pronounced as might be expected from the naked eye appearance. The



D1

Fig 61.



C46

Fig 62.



C39

Fig 63.



B31

Fig 64.

(All about natural size)  
Fig 62, 63 - weight; Fig 61, 64, weight (al).

are also two very small holes in the outer part of the optic thalamus, close up to the capsule, as well as the other small punched out depression which is seen in figure 63. The lesion extends almost to the upper limit of the putamen, coming gradually to an end. A minute prolongation into the capsule, or rather, through it, can be seen at the upper termination of the lesion.

It is noteworthy that it is only towards the site of the maximum area of disease that the external capsule is degenerated, for above, it is quite normal, although the putamen is still completely softened. The convolutions of the island of Reil are more involved, i e their fibres with Weigert-Pal stain less well, towards the lower part of the island. The claustrum is invaded apparently only in one place, and the actual convolutions just referred to certainly do not appear to be softened or to have lost any substance.

The internal capsule stains with normal intensity throughout, except that as the fibres converge to form the crus, in the subthalamic region, it can be seen that the genu section is partly degenerated. This degeneration, however, is not at all extensive. The caudate nucleus and optic thalamus are in much the same condition as on the opposite side. They are practically untouched: it is noteworthy that neither subjective nor objective thalamic symptoms were present during life. In the horizontal sections it is clear that the corpus Luysii is shrunken, and smaller than normal: the ansa lenticularis is degenerated: the bundle H of Forel, and the strio-luysian fibres which cross the pyramidal tract more or less at right angles, are partly degenerated: amongst the latter there are a number of normal fibres: the red nucleus does not appear to be either smaller or ~~fewer~~ to contain fewer fibres than in the normal brain. It is difficult to say whether the locus niger shows any pathological change: apparently not. As on the right side, the strio-thalamic fibres are much degenerated, and the external medullary lamina of the thalamus is less marked than it should be. The zone grillagee of Dejerine is not easily distinguishable.

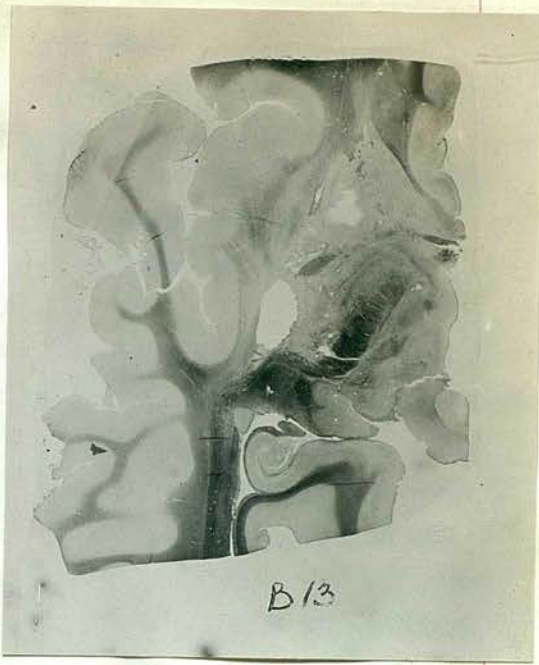
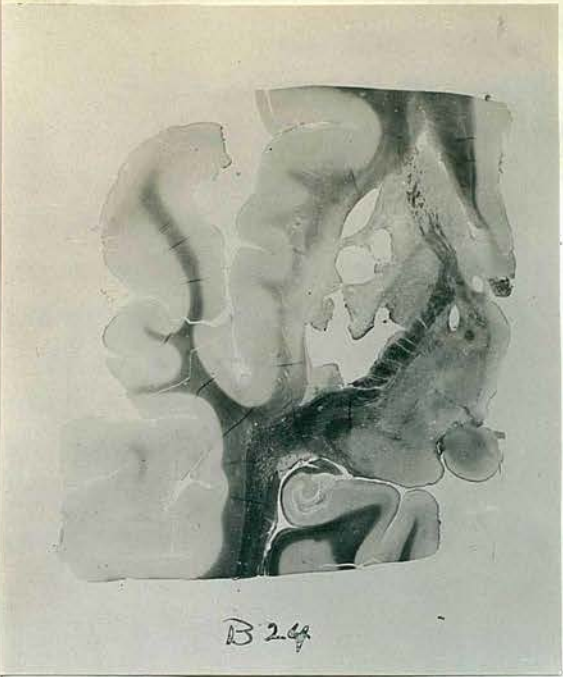


Fig. 65

Fig 66



Fig 67.

(all very slightly reduced.)

Fig 67 - weight  
Fig 65-66, weight-bal.

b. Minute anatomy of the degenerate area.

Under a low power the walls of the cavity are seen to be composed of a thick interlacing network of neuroglia fibres, with neuroglia cells, degenerated myelinated fibres, diseased and fragmented blood vessels and capillaries, all mixed up inextricably. Along the margins of the cavity it is common to come upon such blood vessels as are represented in figures 71, 72. It is noteworthy that while they are reduced to mere debris none of them is thrombosed or occluded. I did not find a single vessel in this condition in more than a score of sections. In some places the cavity wall is very clean cut, firm, and evidently of old formation: in other places it appears to be crumbling away. In the fragment of the globus pallidus that remains a few nerve cells can still be found, staining rather deeply. Here the confusion of degenerated medullated nerve fibres is at its maximum: see figures 69, 70.

In the small areas of putamen and globus pallidus that have not entirely succumbed the condition of the blood vessels was carefully investigated. Some seem to have undergone a sort of hyaline change, their coats staining in a homogeneous way, and being rather difficult to differentiate. In others the muscular and adventitial coats seem thickened in proportion to the intima, which in no instance shows any sign of endarteritis. Not the least indication of small cell infiltration is to be found anywhere, neither round the vessels, in the lymphatic sheaths, nor where the nucleus is degenerated.

[Figs 73-75]

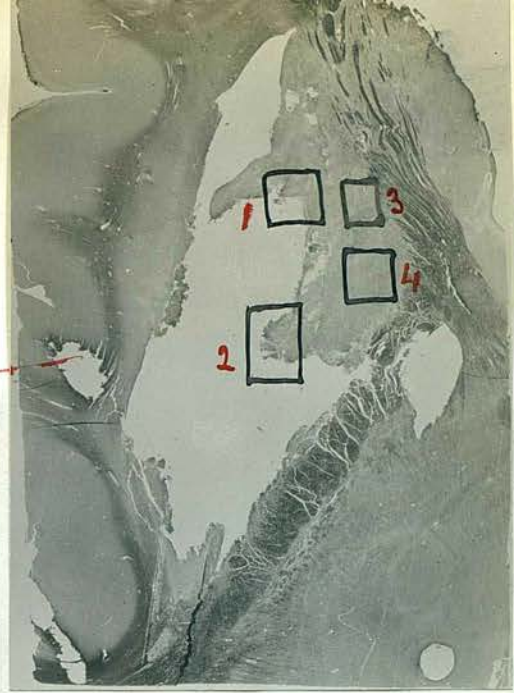
Under a higher magnification Körnchenzellen can be seen in the part of the globus pallidus that is left, but they are not present in numbers.

8. CORTEX CEREBRI.

The cortex cerebri was investigated by Nissl's method, as well as with haematoxylin-van Gieson. Pieces were taken from the motor area on both sides, as well as from frontal, occipital, and temporal lobes.

In the motor area, certain changes were found, more obvious in some places than in others. Figure 80 represents a strip from the precentral gyrus corresponding to the

77



This is from the bottom of the block & is an artefact, not part of the genuine cavity.

1 = Fig 71.  
x 2 = Fig 72.  
x 3 = Fig 69.  
4 = Fig 70.  
} only to be marked on photographs to be called 1. + 2.

Fig 68. maximum lesion L hemisphere of S.T. Case I. (same as fig. 64, higher magnification)

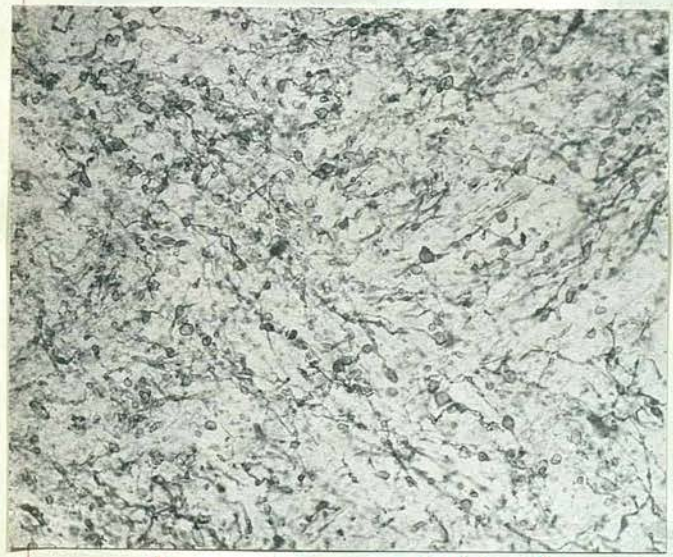


Fig 69. Degenerated fibres from Stria pallida.



Fig. 70. Degenerated fibre from Stria pallida.



Fig. 71. Edge of cavity. masses of dead vessels, neuroglial tissue, neuroglial cells - no nerve fibres or cells.



Fig. 72. Edge of cavity.



Fig 73. Artery from  
Globus pallidus.  
(Haematoxylin-eosin)  
Intima normal-



Fig 74. do. do.  
Normal walls-  
(Plug of bacilli in lumen)  
see below.



Fig 75. do. do.  
Thickened hyaline looking  
middle & outer coats)

left arm area. While some of the Betz cells are normal, others show pigmentary degeneration, with granulation of the tigroid substance, presumably a change of a fairly ~~ext~~ chronic regressive type. Their numbers are not diminished to any noteworthy extent. In a section taken rather higher up, towards the should area, the Betz cells are practically all normal (figure 79). In sections from the leg centres the appearances are more or less normal. Thus in figure 77 (right leg centre) it can be seen that the Betz cells are of normal size, shape, and staining properties. Similarly with the left leg centre (figure 78). The large photograph represents a strip from the right leg centre, and in it the different layers of the cortex can be readily distinguished. There is no poverty of pyramidal cells, and the Betz cells are well preserved. [Fig. 76]

When we remember the complete powerlessness of the patient, the spasticity, tremors, and contractures, the practically normal condition of the cyto-architectonic structure of the motor area, so called, and of the pyramidal tracts, is a fact of the greatest importance and significance.

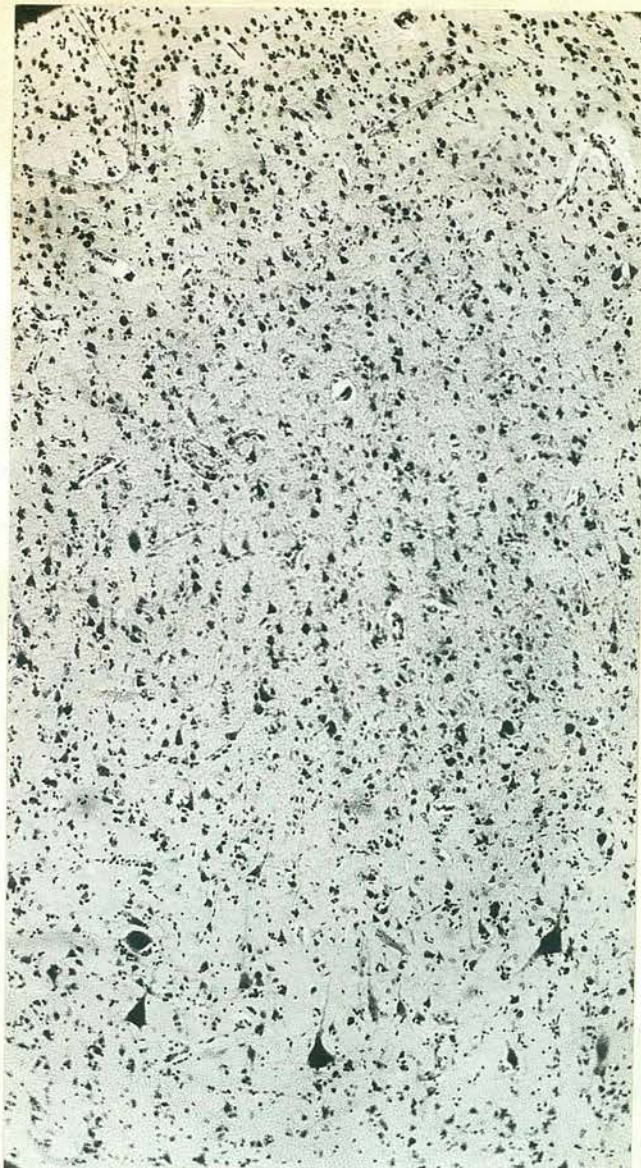
The cortex of other parts of the brain showed changes so minimal that it is difficult to know what importance to attach to them. Undoubtedly occasional pigmentary degeneration of pyramidal cells was seen, but there was nothing even approaching a wholesale disappearance of cells, or confusion of cell layers. Nor was the cortex obviously thinned anywhere.

In no one of many scores of sections examined was there any trace of small cell infiltration of cortical vessels. Nothing more different from the pathological picture of dementia paralytica can be imagined.

In sections of the motor cortex stained by Pal's method for myelinated fibres it was seen that the tangential layer of fine fibres was considerably reduced, but the supraradiary and intraradiary networks were not altered to any extent.

MICROSCOPICAL EXAMINATION OF OTHER ORGANS.

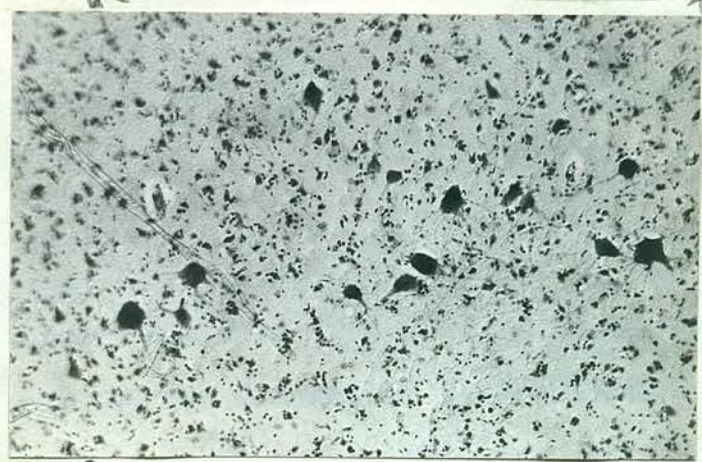
1. LIVER. The histological methods utilised were haematoxylin-eosine, haematoxylin-van Gieson, Weigert's stain for elastic tissue, Sudan III for fat.



← Probin  
of granular &  
stellate layer  
(as in post central cortex)

Betz.

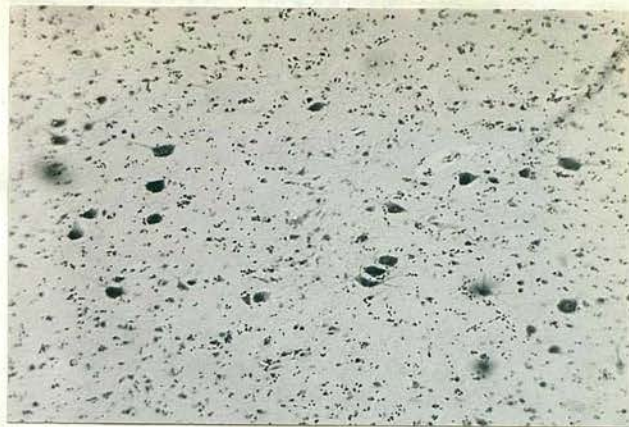
Fig 76. Right leg centre, paracentral gyrus.



Betz.

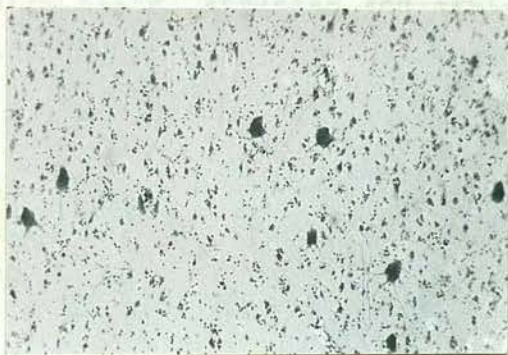


Fig 77. Right leg centre, paracentral lobule.



Belz.

Fig. 78. Left leg cortex, precentral cortex, cut obliquely.



Belz.

Fig. 79. Left shoulder cortex, precentral cortex.



Belz.

Fig. 80. Left arm cortex, precentral cortex, cut obliquely.

(The magnification of figs 78-80 is less than that of figs 76 & 77.)

Under a low magnification the appearance represented in figure 81 was met with. Numerous islets of liver tissue, not a few of which did not contain more than one or two liver units, while others were much larger, were separated from each other by wide strands of cirrhotic tissue, which in some places was mainly fibrous, in others very cellular. Occasionally a few isolated liver cells, as was determined by the method of serial sections, were found, surrounded by cirrhotic strands. There was little indication of any intra-lobular spread of connective tissue, and there was no sign of the monocellular type. In the more cellular areas of cirrhosis abundant bileducts ramified in all directions. (Fig 82)

The condition of the liver cells was highly irregular. Many lobules looked to be normal, the columns of cells being symmetrically radate, staining well and of good size. In other nodules scarcely a single normal cell was found: many were in a necrotic state, shrunken and staining very homogeneously a brighter tint with eosine than normal cells. Everywhere there were evidences of fatty degeneration. On the other hand, more particularly towards the periphery of some of the nodules, regeneration of liver tissue was actively proceeding. Thus it was common to find the nuclei of the cells enlarged: some were dumbbell shaped and evidently about to divide by an amitotic process. Other cells were doubly nucleated. In the regenerating areas metachromatic staining of the nuclei was common. I did not find any definite mitotic figures: apparently this form of multiplication is less frequent than the other. [Figure 83]

The portal tracts and vessels of the organ did not show any particular alteration. A very few plugs of inspissated bile were found. There was no sign whatever of any obliteration of bileducts.

2. The SUPRARENAL did not present any obvious morbid change.

The THYROID showed certain regressive changes in the shape of interstitial overgrowth and diminution of colloid.

There remains to be described only one other pathological condition, but this is a widespread one. In every organ examined, particularly in the liver and in the central ner-



X

Fig 81. Low power view of liver nodules. Case I.  
(Haematoxylin - van Gieson). Magnified 20.

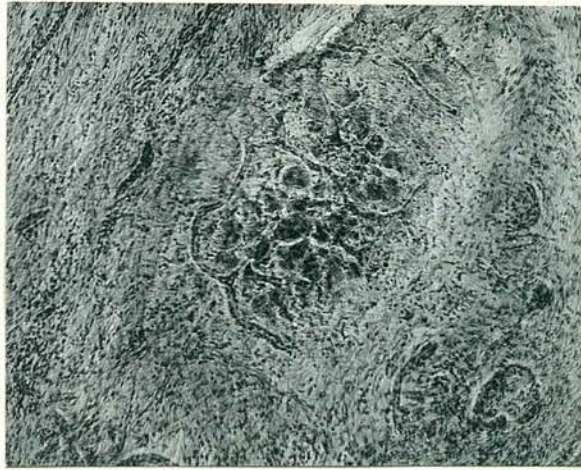
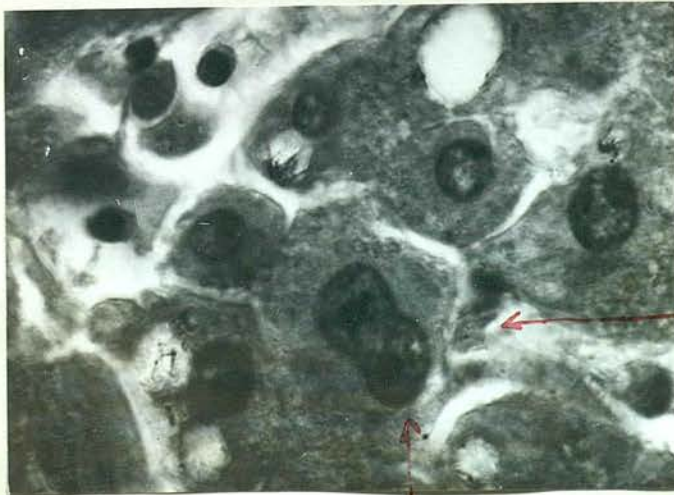


Fig 82. Shows bile ducts ramifying in a small  
islet of liver tissue, surrounded by fibrotic tissue.  
(x110)



liver cell  
dividing amitotically.

Fig 83. (x1000)

119

vous system, bacterial invasion was acute. Clumps of short bacilli, structurally rather like the bacillus coli, were seen everywhere in sections of the liver, and were found plugging the vessels of the degenerated lenticular area, in the cortex cerebri and cerebelli, in the spinal cord. The appearances presented are reproduced in the accompanying photographs. The widespread nature of the condition suggests a terminal infection, which we know can take place with extraordinary rapidity. It is probable that the infection was from the alimentary canal, as the patient had neither bedsores nor cystitis. [Figures 84-87]

That the infection is of any special pathogenic significance it is difficult to believe.



Fig 84. Small artery from glomus pallidus, lumen plugged with bacilli (H.V.G)



Fig 85. Clump of bacilli in connective tissue of liver.



Fig 86. Do. higher power.



Fig 87. Do. (x 750)

X

X

121

RESUME OF THE PATHOLOGICAL FINDINGS IN CASE I.

The brain is of good size, shape, and weight. The cerebral gyri are not atrophic, are of normal convolutional pattern, and present no obvious morbid appearance. The membranes are to all intents and purposes normal. The cerebral blood vessels are not thickened or occluded, and show no patches of disease in their walls.

The corpus callosum is divided by a mesial incision and the hemispheres cut through by Marie's coupe d'election. At once the eye is caught by a complete bilateral and symmetrical cavitation of the lenticular nucleus, which is simply non-existent. In the place of the latter, on either side, and more especially in the place of its outer and middle zones, is an elongated cavity, measuring  $2\frac{1}{2}$  centimetres long by  $1\frac{1}{4}$  centimetres wide, with dark coloured crumbling walls, extending from the anterior to the posterior limit of the putamen, and from its extreme lower extremity almost to its upper limit. Only a small piece of the inner zone of the globus pallidus remains. Compared with this utter degeneration of the lenticular nucleus the optic thalamus and the caudate nucleus are perfectly well preserved, except that the former has on the left side a small punched out hole towards its posterior internal section, and the latter is on both sides a little shrunken, and less full and rounded than in a normal brain.

The degenerated area extends close up to the internal capsule on both sides: on the right this seems quite intact throughout, although it turns out to be a little undermined: on the left there is a small prolongation of the cavity across the genu of the capsule, the fibres of which are separated rather than destroyed. Microscopically, however, there is some descending degeneration in the genu fibres.

The external capsule is thinned on both sides, and degenerated in its middle third: the claustrum is slightly invaded on the left side: the cortex of the island of Reil is well preserved on both sides, although microscopically there is some degeneration of the subcortical fibres of its convolutions, towards its posterior part.

The white matter of the cerebral hemispheres is normal. The cortex is practically normal: in particular the origin

of the pyramidal tracts in the Betz cells of the motor area is carefully examined, and the great majority of the latter are found to present no morbid appearance, although some show slight changes.

With the exception of the slight descending degeneration in some capsular genu fibres on the left side, the pyramidal tracts stain normally throughout, and, followed from the motor cortex through the capsule, crus, pons, medulla, and cord, are perfectly normal.

On the other hand, the extra-pyramidal system from the lenticular ~~system~~ nucleus via the ansa lenticularis, to the red nucleus, is degenerated on both sides: the lenticular bundle of Forel (faisceau<sup>n</sup>) is partly degenerated, as are the strio-luysian fibres on both sides: the corpus luysii is smaller than normal. The strio-thalamic fibres are degenerated. The cells of the red nucleus do not appear changed, nor does the nucleus seem altered in its fibre-content.

The nuclei of the cranial nerves are unchanged, except for slight alterations of secondary significance.

The spinal cord, cells and fibres, is normal, except for slight alterations, also of secondary significance.

The same is true of the muscles.

The liver is in an advanced state of cirrhosis: the type is multilobular, but some monolobular cirrhosis is found. In the cirrhotic tissue abundant bileducts ramify. The liver cells are in many instances normal, others are necrosed: many show fatty infiltration and degeneration, others are actively regenerating.

The spleen is not enlarged. The thyroid shows interstitial changes.

There are evidences in all the organs examined, and particularly in the liver and nervous system, of a terminal bacillary infection.

CASE II.

The autopsy was performed by Dr W.H.B. Stoddart on March 4th, 1907, 18 hours after the death of the patient.

The body was greatly emaciated, but there were no bruises or bedsores. The skullcap and the dura mater with its veins and sinuses presented no abnormality. The cerebral arteries at the base of the brain were normal, all patent, and showed no visible thickening or patchy degeneration. There was excess of cerebrospinal fluid on opening the membranes, especially in the subarachnoid spaces. The brain looked oedematous, and the convolutions somewhat separated from each other. It weighed 1275 grammes. The pia-arachnoid appeared slightly thickened in one or two areas.

The bronchial vessels were congested, and there were several patches of pneumonic consolidation scattered throughout both lungs, the largest patch being at the apex of the lowest lobe of the right lung. The heart was normal. The spleen was enlarged, and weighed 312 grammes, but it showed no obvious morbid appearance on section. The kidneys were normal.

The liver presented a remarkable appearance. It was in an advanced state of multilobular cirrhosis, being subdivided up into spherical portions of liver substance about the size of small hazel nuts, held together by bands of cirrhotic tissue. It was firm and tended to preserve its shape. Its weight was 1392 grammes.

The photographs show the naked eye appearances of that organ. [Fig 88-90] One of them (figure 90) was taken after the liver had been in formalin for about twelve months, and it shows the appearance on transverse section. One is at once struck by the irregular size of the nodules, and the difference in their colour: some are much darker than others: many look somewhat mottled. The strands of cirrhotic tissue are notably slender in comparison to the dimensions of the nodules which they enclose. There is some thickening along the portal tracts. The capsule of the organ is possibly slightly thickened.

When it was removed from the body it was not noted to be bilestained: the gallbladder was in a normal condition.

X Reduce by  $\frac{1}{2}$  area 124

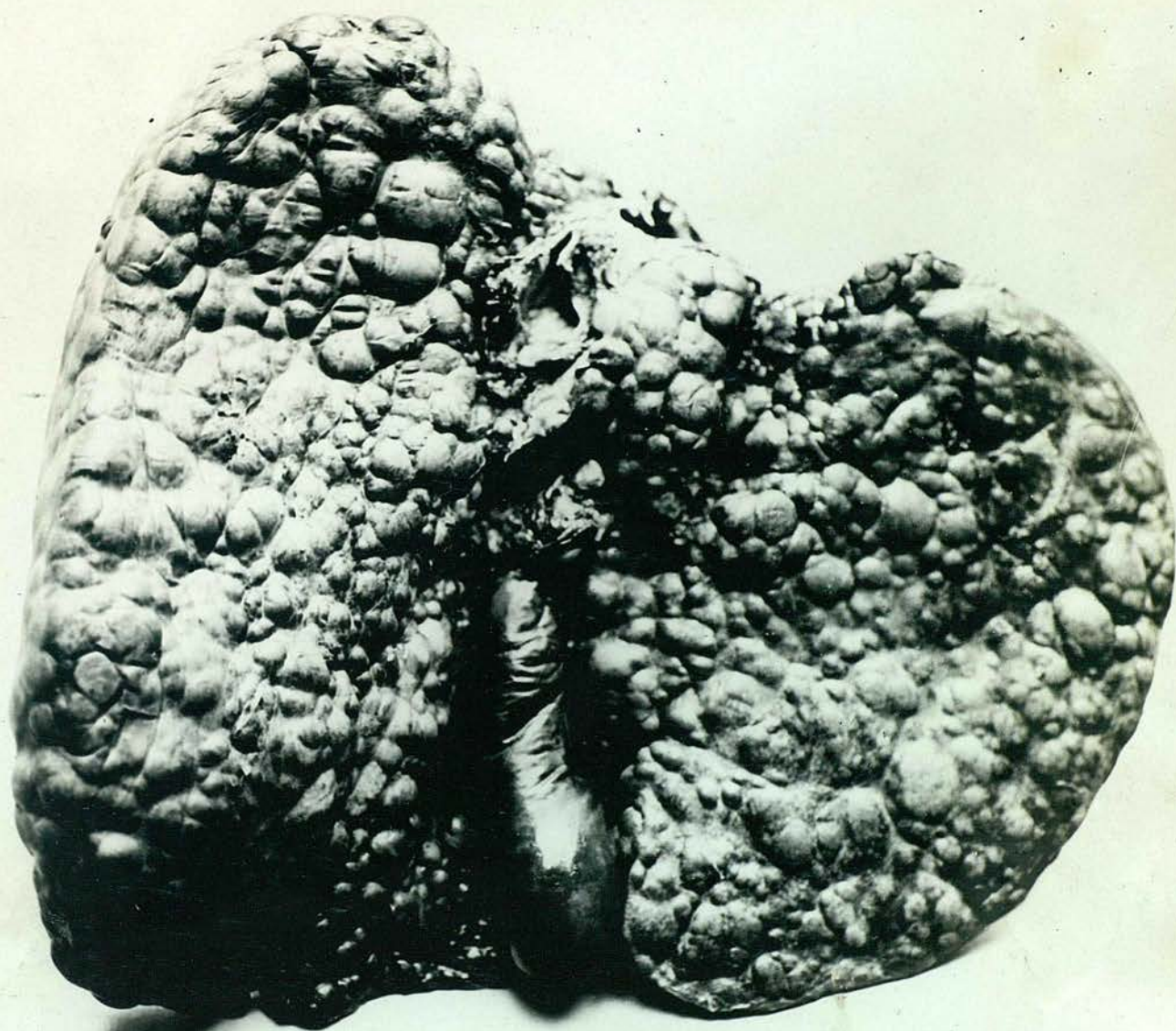


Fig 88. Liver of D.P. Case II  
(slightly reduced from natural size)



Fig 89. Liver in Case II  
(natural size).

X to Reduce by  $\frac{1}{2}$  area



Fig. 90. Tissue in Case II  
( $\times \frac{2}{1}$ )

MACROSCOPICAL EXAMINATION OF THE CENTRAL NERVOUS SYSTEM.

Owing to an unfortunate accident the nervous organs were rendered almost useless for certain methods of investigation, so that to that extent it must be considered incomplete. What I am able to describe, however, will be sufficient to class the case in toto with no. I and no. III.

The brain, when stripped of its membranes, was found to be of perfectly good size, shape, and convolutional pattern. On a transverse horizontal section through the right hemisphere, the putamen was found to be darker in colour than usual, to be somewhat shrunken, and to be soft to the touch. There was not, however, any gross loss of substance. The globus pallidus appeared normal, as was the optic thalamus, the caudate nucleus, and the internal capsule. I am unable to say what the condition on the left side of the brain was, and whether there was any similar degeneration of the outer zone of the lenticular nucleus. On the right side the inter-nuncial fibres from the outer to the middle zone of the nucleus were almost entirely absent, and the outer lamina was not readily distinguishable. The fine fibres of the caudate, however, could be seen easily. The external capsule and the white and grey matter of the convolutions of the island of Reil presented no obvious morbid appearance.

No other change was demonstrable on this section by Marie's coupe d'election. The cerebral cortex appeared to be of good depth everywhere, with the possible exception of the first and second frontal convolutions, where it may have been a little thinned. The white substance of the hemisphere presented no abnormality. There was no hydrocephalus, and no ependymitis.

The pons, medulla, and cord, and the cerebellum, looked quite normal.

MICROSCOPICAL EXAMINATION OF THE NERVOUS SYSTEM.

1. The MUSCLES and the PERIPHERAL NERVES were not examined.

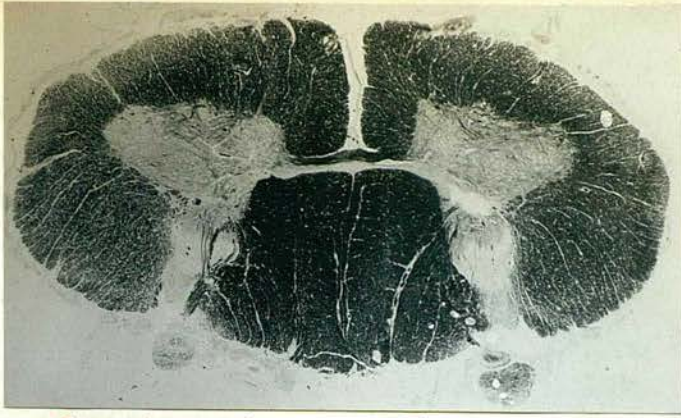


Fig 91. Cervical Cord Case II



Fig 92. Dorsal Cord, Case II



Fig 93. Lumbar Cord, Case II.  
(Fig 91-93, Weigert-Pal.)

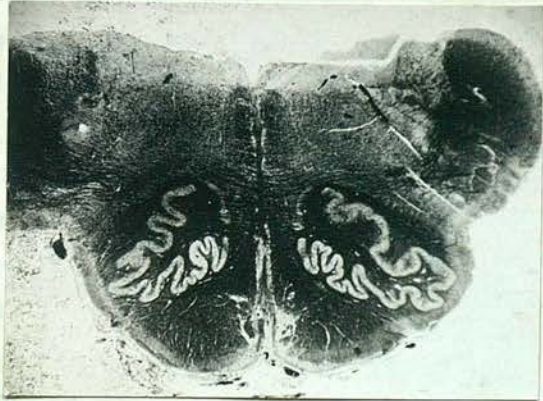


Fig. 94 Medulla, Case II.  
(Weigert-Pal.)

2. SPINAL CORD.

The methods of staining employed were Weigert-Pal, Nissl, and haematoxylin-van Gieson.

The meninges were everywhere normal. There was no trace of pachy- or lepto-meningitis: in particular, there was no small round cell infiltration of any sort. The spinal vessels, both intra- and extra-medullary, were normal, and showed no sign of endarteritis.

The spinal cord, from the point of view of its myelinated fibres, was normal. In particular, there was no trace of any degeneration in the pyramidal tracts, as will be seen by a glance at the photographs. The integrity of the pyramidal system is of great importance in view of the nature of the disease. The medullated fibres of the grey matter of the cord were likewise normal, if perhaps a little sparser.

(Fig 91-93)

Examined by Nissl's method the cells of the anterior horns were found to be present in good numbers, to stain well, and to preserve a normal size and shape in the great majority of them. Some were slightly "sclerosed", i e , shrunken and elongated, stained unusually deeply, but remaining nucleated. Others were in a state of commencing pigmentary degeneration, but there were not any, as far as was noted, that showed an acute form of degeneration associated with eccentricity of the nucleus and pulverisation of the tigroid substance round it.

3. MEDULLA, PONS, AND CEREBELLUM.

The same methods were employed for the examination of these structures as for the cord.

With the Weigert-Pal stain no defect was to be seen in the pyramidal tracts anywhere. They stained deeply, and were not atrophic in any way. The transverse sections of the medulla and pons that were examined seemed normal in all respects. Similarly with the cerebellum, its nuclei and peduncles did not show any deviation from the normal. (Fig. 94)

The nuclei of the cranial nerves, especially the facial and the hypoglossal, showed no pathological change by Nissl's method. The cells were present in good numbers, with normal staining reactions.

4. CRUS CEREBRI.

The pyramidal path in the crus was perfectly normal. The

red nucleus was not altered in its fibre content, or in its cells, as seen when stained with haematoxylin-van Gieson.

#### 5. BASAL GANGLIA AND INTERNAL CAPSULE-

The appended description applies to the right side only, and is of necessity somewhat incomplete.

The histological methods utilised were the same as for the cord.

In the degenerated right putamen we find considerable over-growth of neuroglial tissue, but it does not form a thick feltwork: it is in some places sparse and evidently breaking down. There are great numbers of glial nuclei to be seen, which may give the impression of small round cell infiltration, but must be carefully distinguished from this. In the degenerated area there are no signs of inflammatory reaction. The important feature of sections through the lenticular nucleus is the dearth of nerve cells, both in the putamen and the globus pallidus, but particularly in the former, which is almost cell-less. Körnchenzellen, so-called, are seen in abundance. The condition of the blood-vessels is important. They are neither thickened nor obliterated, but stand out prominently, usually with a wide space round them, and are often apparently somewhat dilated, possibly even a little thinned. There is no trace of endarteritis: the intima is unaltered. Nor is there any thickening of any of the other coats: and there is no indication of anything approaching small cell infiltration. Figure 97 represents a transverse section of one of the lenticulo-striate arteries, removed from the degenerated area and cut separately. It is conspicuous by the absence of any endarteritis. [Fig. 95, 96]

The caudate nucleus shows slight changes not unlike what is found in the putamen: there seems to be an increase of glial nuclei, and fewer nerve cells than in the normal nucleus. But the changes are still slight. The optic thalamus is from the point of view of cells and fibres practically normal.

The internal capsule throughout stained in perfectly normal fashion, and was neither atrophied nor hypertrophied. Both its anterior and its posterior limbs were intact. The

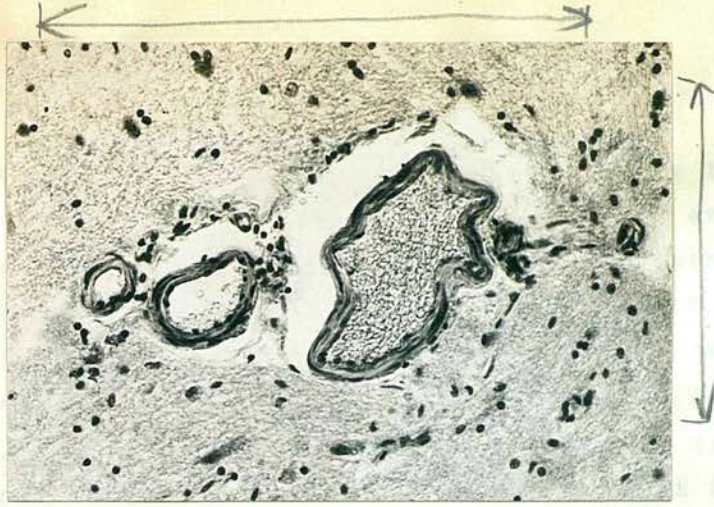


Fig 95. vessels from the right putamen, Case II  
 normal walls (Haematoxylin - van Gieson)  
 No small cell infiltration.

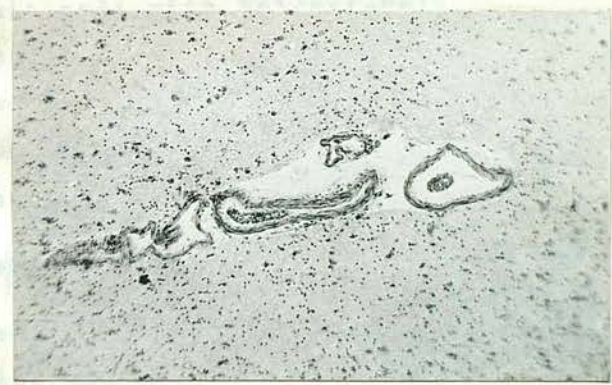


Fig 96. vessels from optic chiasm, Case II  
 normal walls. (low power)

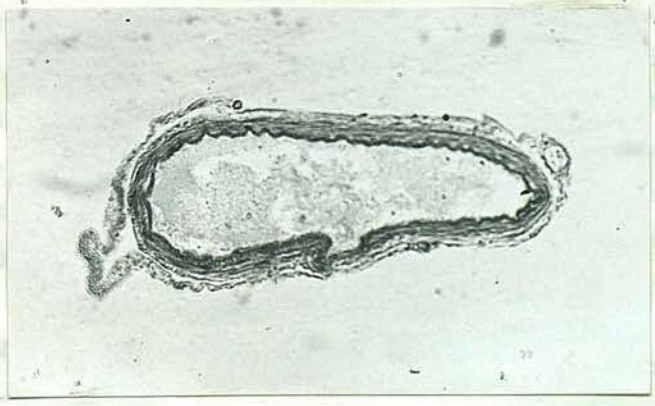


Fig 97. High power transverse section  
 of a leuculo-striate vessel, Case II  
 The vessel is, if anything, thinned.

fibres that cross the internal capsule, running between the globus pallidus and the optic thalamus, were in every respect normal. They stained well, and were not diminished in numbers. The inner lamina, between the middle and inner zones of the lenticular nucleus, was well developed, but the fibres that pass mesially from the putamen were diminished in number, except at its anterior and posterior extremities. The external capsule did not seem to be involved in the seat of the disease, and the fibres of the white matter under the convolutions of the island of Reil was normal, except in one place, opposite the centre of the putamen, where they did not stain well with Weigert-Pal.

In this case, unfortunately, it was impossible to examine further the lower portions of the degenerated area, so that the condition of the ansa lenticularis is not known, nor of the structures in the subthalamie region.

6. CORTEX CEREBRI.

Pieces were taken from both sides of the brain, including in particular the motor area, with both the precentral and the postcentral convolutions. ~~The sections examined are indicated on the accompanying diagram.~~

It may be said at once that from the cyto-architectonic point of view no definite changes could be made out. The Betz cells of the motor area were easily recognisable, present in quantity, and not altered in staining reactions or in morphological characters, except that a few showed commencing pigmentary degeneration, and in a few others the tigroid substance round the nucleus was becoming granular. The cells of the pyramidal layers did not appear to be altered, though round many of them parasite neuroglial cells were to be seen. The depth of the motor cortex was not appreciably different from the normal brain.

The cortex in the other areas examined did not show any pathological change that need be specified.

From the myelo-architectonic point of view only the fibre content of the motor area was investigated, and it proved to be normal, with the exception of considerable diminution in the tangential layer, and to a less extent of the supraradiary

network.

Nowhere in the cortex were the vessels surrounded by small cell infiltration, nor was there any sign of increased neuroglial growth.

#### MICROSCOPICAL EXAMINATION OF OTHER ORGANS.

The only other organ subjected to examination was the liver, which was stained with haematoxylin-eosine, haematoxylin-van Gieson, Weigert's elastic tissue stain, and Sudan III.

Under a low power, one was struck by the varied appearance which the liver nodules presented. Some contained only one or two lobules, the majority contained as many as eight or twelve: some were evidently in full functioning power, as the columns of liver cells were normal, others were totally degenerated and changed into a mass of fat granules. In many places in the cirrhotic tissue immense numbers of small connective tissue cells, and great numbers of so called new bileducts, were to be seen. The cirrhotic tissue was slender and nowhere looked very fibrous. In some places there were delicate strands of connective tissue passing between groups of liver cells. The cells themselves, under a higher magnification, in most lobules stained normally, but in areas where active regeneration was taking place--and of this there was abundant evidence--metachromatic staining was noticed. Regeneration was shown by the presence of enlarged or doubled nuclei: sometimes amitotic division was seen, but I could not find any mitotic figures.

There was no special feature to be noted in the sections stained by Weigert's elastic tissue stain. The picture given with the Sudan III sections was very striking, and explains beautifully the irregular colouration showed in the naked eye photograph reproduced as figure 90. . [Figures 98, 99]

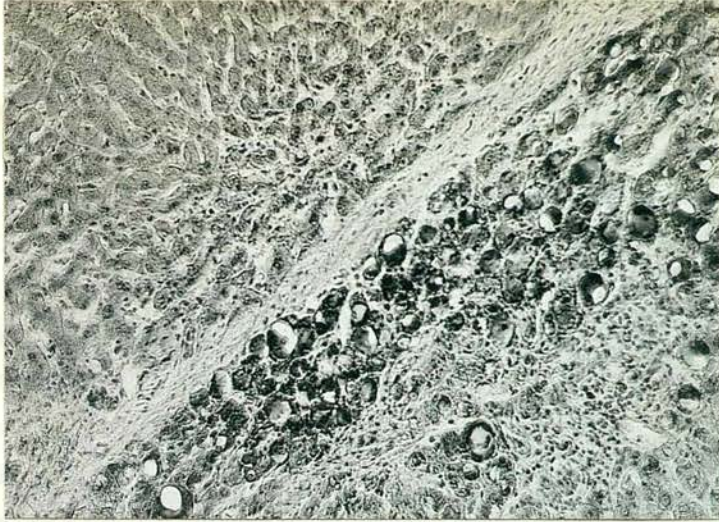


Fig 98. Liver, Case II. (Jordan III)  
 + methylene blue  
 The connective tissue is very narrow.

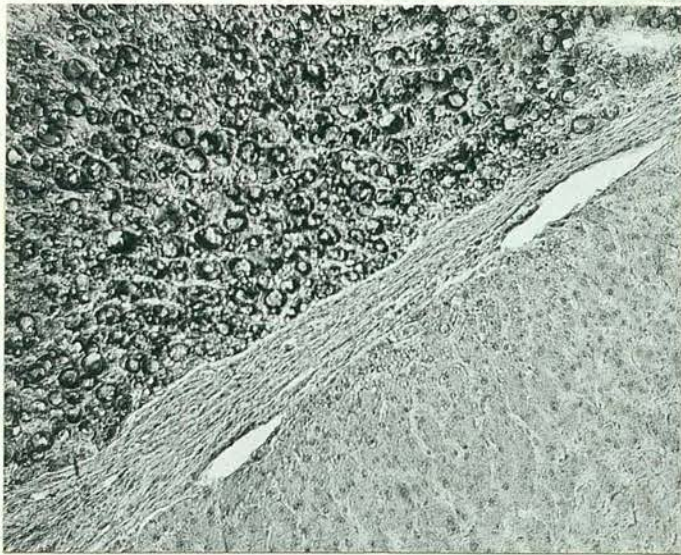


Fig 99. Liver, Case II. (Jordan III)  
 + methylene blue  
 Normal & degenerated nodules side by side.

RESUME OF THE PATHOLOGICAL FINDINGS IN CASE II.

The brain is of good size and shape, and its convolitional pattern is normal. There is no indication of atrophy of the gyri, except that possibly the cortex of the frontal convolutions is a little thinned. This, however, is so slight as to be negligible. The white matter of the hemispheres shows no abnormality. The membranes are normal, except that in one or two places the pia-arachnoid is a little thickened. The cerebral blood vessels present no deviation whatever from a normal state. The pons, medulla, and cord look normal.

On section the right lenticular nucleus is seen to be in a definite state of degeneration: it is atrophic in its outer zone or putamen, shrunken, discoloured, looks friable and feels soft. There is not, however, any cavitation. The globus pallidus does not appear to be impaired: the external capsule is normal. The degeneration in the putamen occupies its whole breadth, but leaves a small portion anteriorly and posteriorly which seems intact. Microscopically we find definite neuroglial changes, overgrowth of glial nuclei and fibres, very definite disappearance of nerve cells from the putamen, and interference with the internuncial fibres from the outer to the inner zones of the lenticular nucleus.

The arteries of the affected area do not show any change, except that they are, if anything, dilated and thinned, in some instances at least. There is no endarteritis of any vessel, and no small cell infiltration.

The internal capsule, the optic thalamus and caudate nucleus are normal throughout, except for very slight commencing changes in the last of these.

The motor cortex is normal, and the pyramidal tracts, examined exhaustively from the Betz cells of the cortex to the anterior horn cells of the spinal cord, are likewise normal. There is no degeneration in the cord, by any method.

The liver is profoundly cirrhotic, though the bands of cirrhosis are relatively slender: many nodules are reduced to masses of fat, but others are actively regenerating. Numerous bileducts course in the cirrhotic tissue.

CASE III.

The autopsy was performed at 7. 30 p.m. on the evening of September 21st, 1910, 27 hours after death. As the body had been kept in the open air, the Sanatorium being at a considerable altitude and the nights very cold, it was in an excellent state of preservation.

Post-mortem lividity was marked. The limbs showed a severe degree of post-mortem rigidity. There were fairly large superficial abrasions over the heels, trochanters, and sacrum. The body was profoundly emaciated, being reduced almost to skin and bone. On the other hand, while the muscles were shrunken to some extent, no local atrophy was noticed: their outlines were unusually distinct beneath the skin.

The calvarium was opened, and the dura was found to be not adherent. The latter was not obviously thickened or discoloured. On its being cut open a considerable quantity of cerebro-spinal fluid escaped, but it was seen at once that all the subarachnoid spaces and cisterns were greatly distended with fluid. As a result the brain looked oedematous and the outlines of the convolutions seemed indistinct through the distended membranes. Over one minute spot at the upper end of the left Rolandic area the dura was adherent to the tissues underneath. The cerebral veins were greatly distended everywhere. Over the base of the brain the arachnoid appeared somewhat thickened, and a little opaque, especially across the pons and the interpeduncular space. Elsewhere that membrane seemed normal, with the possible exception of its portion that covered the anterior parts of the temporal lobes, which also appeared rather opaque. As the brain was being taken out, one got the impression that the pons was rather small in proportion, and that the cranial nerves were rather slender.

Figs 102-104

The brain and cord were at once immersed in a 10% solution of formalin.

The pituitary gland, thymus, left lobe of thyroid, left suprarenal body and kidney, were removed for subsequent examination. The thyroid appeared to be of normal size, and the other organs mentioned above presented no obvious alteration

to the naked eye. The spleen was slightly enlarged, felt firm, and on section showed no deviation from the normal, except that it was congested.

The heart and lungs were normal, except that the latter was somewhat congested. There was a few ounces of clear fluid in each pleural cavity, but no adhesions.

The liver presented a striking appearance, which is seen in the accompanying photographs. It was of medium size, [Figs 100, 101] of good shape, and weighed 1450 grams. It was firm and preserved its shape well when removed from the body. When examined it was at once seen to be in a state of profound cirrhosis: the dome-like upper surface and the under surface were not smooth, but subdivided up into innumerable small raised nodules, in between which were narrow lines where the surface was depressed, corresponding to bands of cirrhotic tissue. The average size of the nodules was perhaps that of a threepenny piece, but they varied considerably. In some places they were more evident and more closely set than in others. There were no signs of hepatitis: the capsule was not thickened anywhere, and there were no adhesions to the surrounding viscera. The organ was if anything rather lighter in colour than usual, but it was not bilstained, nor was the colouration patchy or irregular. Its appearance on transverse section was equally striking. From one side to the other it was subdivided into more or less circular or oval nodules, or islets, most of which were about the same size, and were separated from each other by cirrhotic strands that were quite narrow. In one or two places the cirrhosis approximated to the monolobular type, but it was far more characteristically multilobular.

There was no ascites.

portions of the following muscles were taken for subsequent microscopical examination: muscles of the left thenar eminence: left flexor sublimis digitorum, right flexor carpi ulnaris, right biceps, right supinator longus.

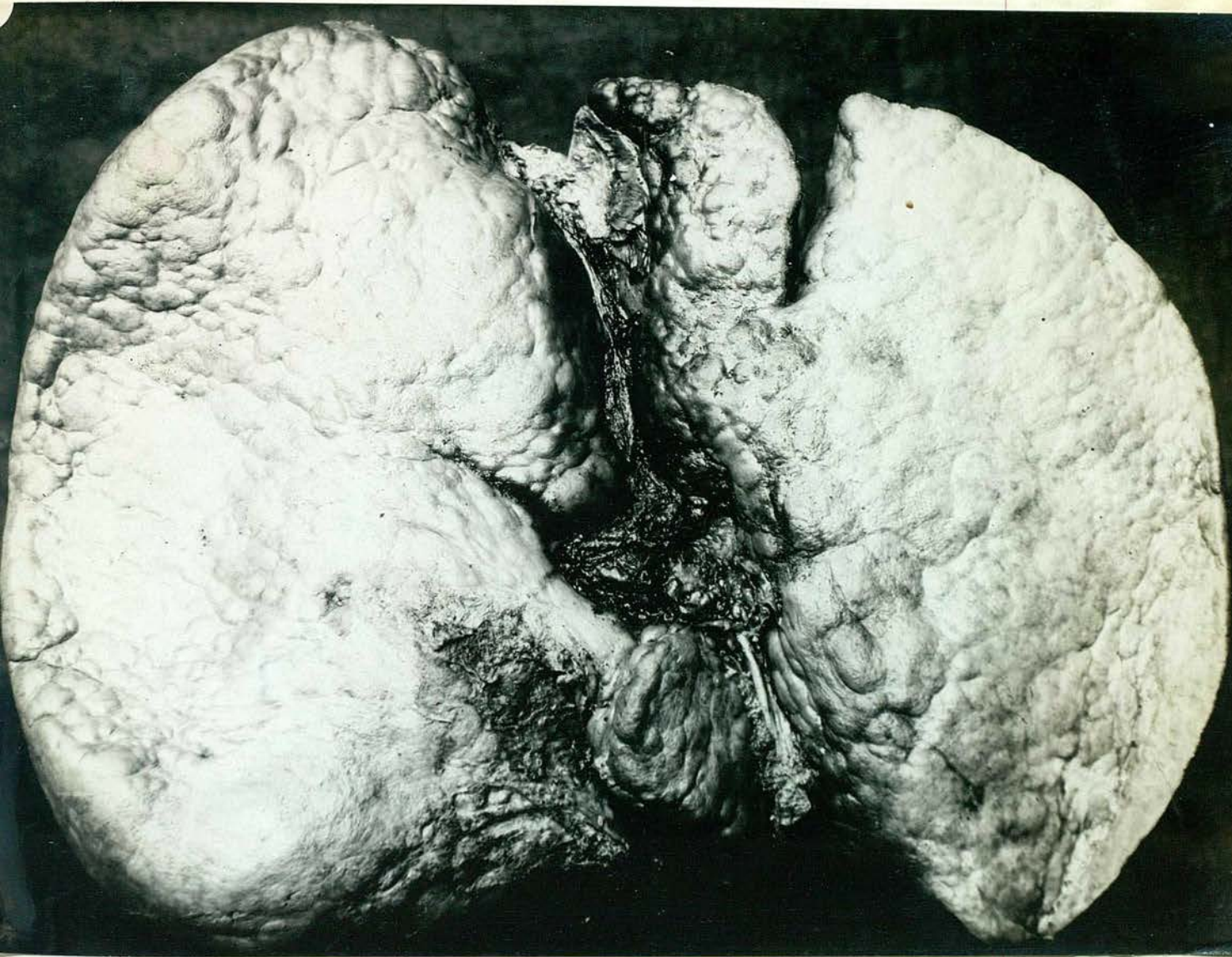


Fig. 100. Liver from E.P. Case III. Under surface—  
(very slightly reduced.)

to 139  
X reduce by  $\frac{1}{2}$  area



Figure 101. Liver, Case III. Transverse section.  
(slightly reduced).

MACROSCOPICAL EXAMINATION OF THE BRAIN AND CORD.

After hardening in formalin the brain was stripped of its membranes. The middle cerebral artery and its branches, as far as practicable, were removed for microscopical examination, from the left side. The weight of the brain thus stripped was 1245 grams: the cerebrum alone weighed 1080 grams, the cerebellum, pons and medulla together 165 grams.

The cerebral hemispheres were well developed and of good convolitional pattern, as can be seen from the photographs. (Figs 105-107, 108, 109.)

There was no obvious atrophy of any of the gyri: there was no undue spacing between them. The corpus callosum was divided by an incision in the mesial plane, and then each of the hemispheres was cut by Pierre Marie's coupe d'election. This is a section which passes by the under surface of each extremity, anterior and posterior, of the corpus callosum as it appears on the mesial aspect, and is carried horizontally outwards to the outer surface. The appearance of the sections, as they appeared to the naked eye, is given in the photographs. One is struck at once by the shrinkage of the lenticular nucleus, right and left, and by the remarkable symmetrical softening in each putamen. [Figures 110 & 111.]

Right side.

The posterior two thirds of the putamen in its complete transverse extent, and to a less degree the corresponding part of the middle zone of the lenticular nucleus are the seat of an obvious softening. The substance of the nucleus appears a little discoloured, and it is friable, pitted, as it were wormeaten. There are a number of fine holes evidently related to blood vessels: many are clean cut, and empty, and round these, i e in the area where these are, the degeneration of the nucleus seems at its maximum. The minute vessels which remain stand out from the surface of the section, are patent, tear very easily, and when extracted leave a small but gaping hole behind. The whole substance of the nucleus in the affected area is shrunken, slightly hollowed out, and clearly in an early stage of definite cavitation. The diameter of the minute punched out holes averages 1 to 1½ millimetres: the length of the area is 2¼ cm., and its

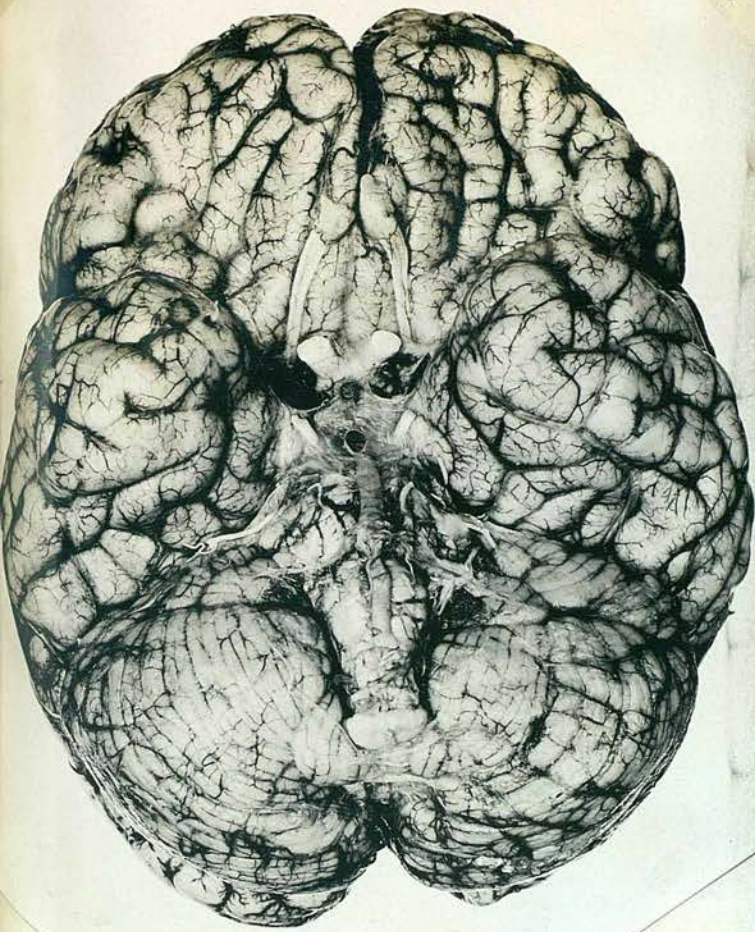


Fig. 102. - (see Fig 102a.)

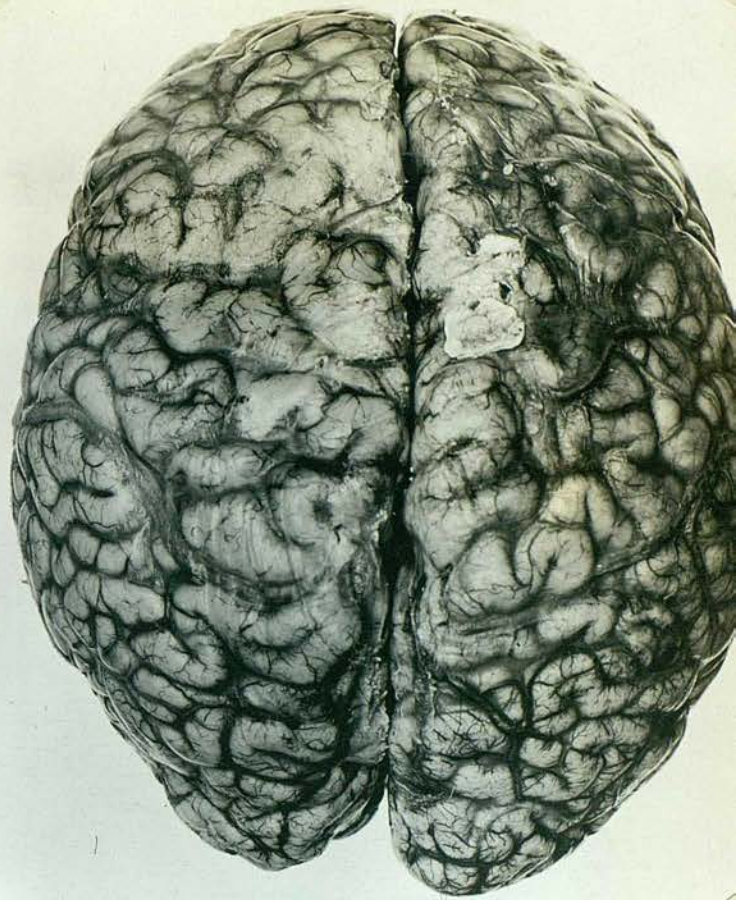


Fig. 103. (see Fig 102a)

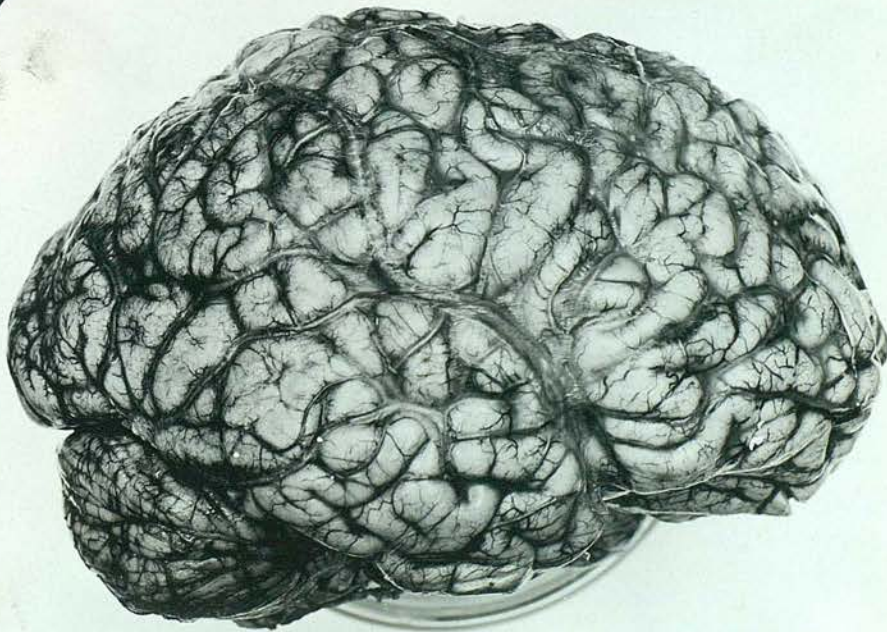


Fig. 104. Brain of E.P. as removed, with membranes on.  
(slightly reduced).  
Arachnoid slightly thickened.  
Note interpeduncular space -

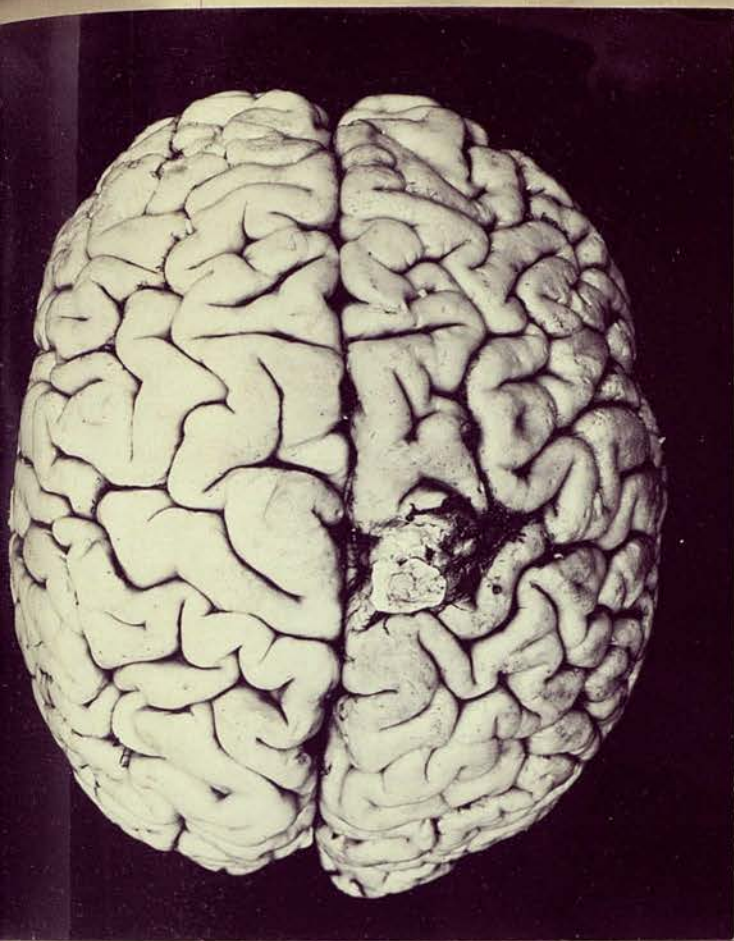


Fig. 105. X (see 107)  
reduce by  $\frac{1}{3}$

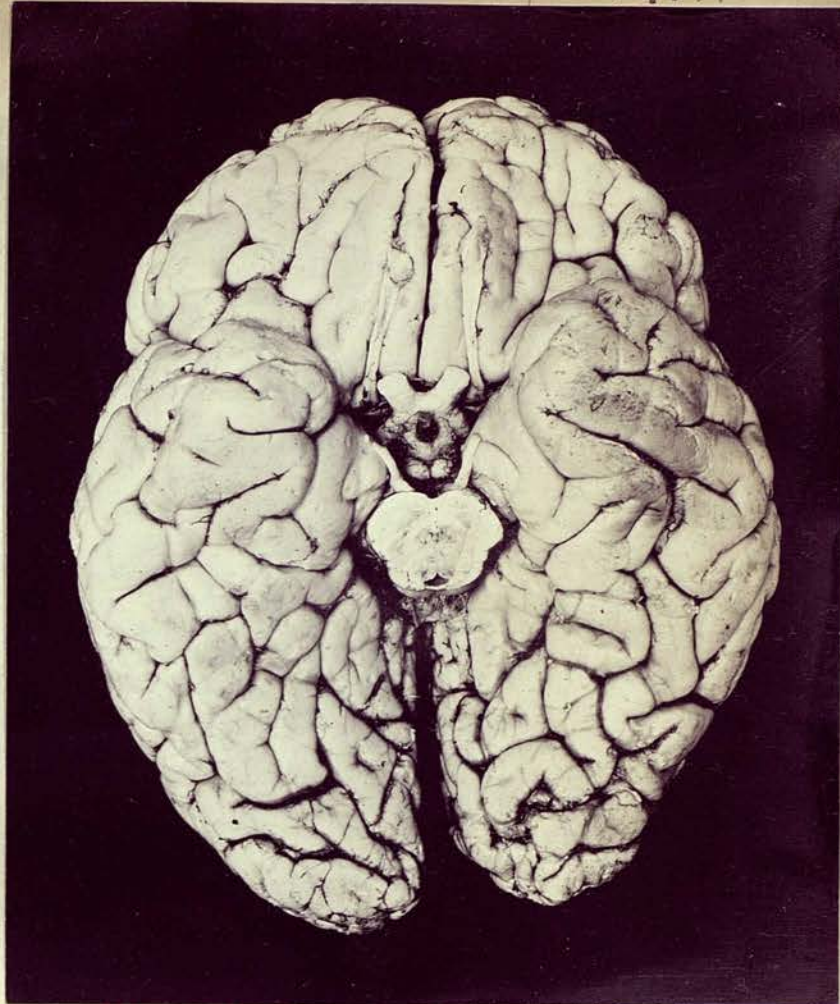
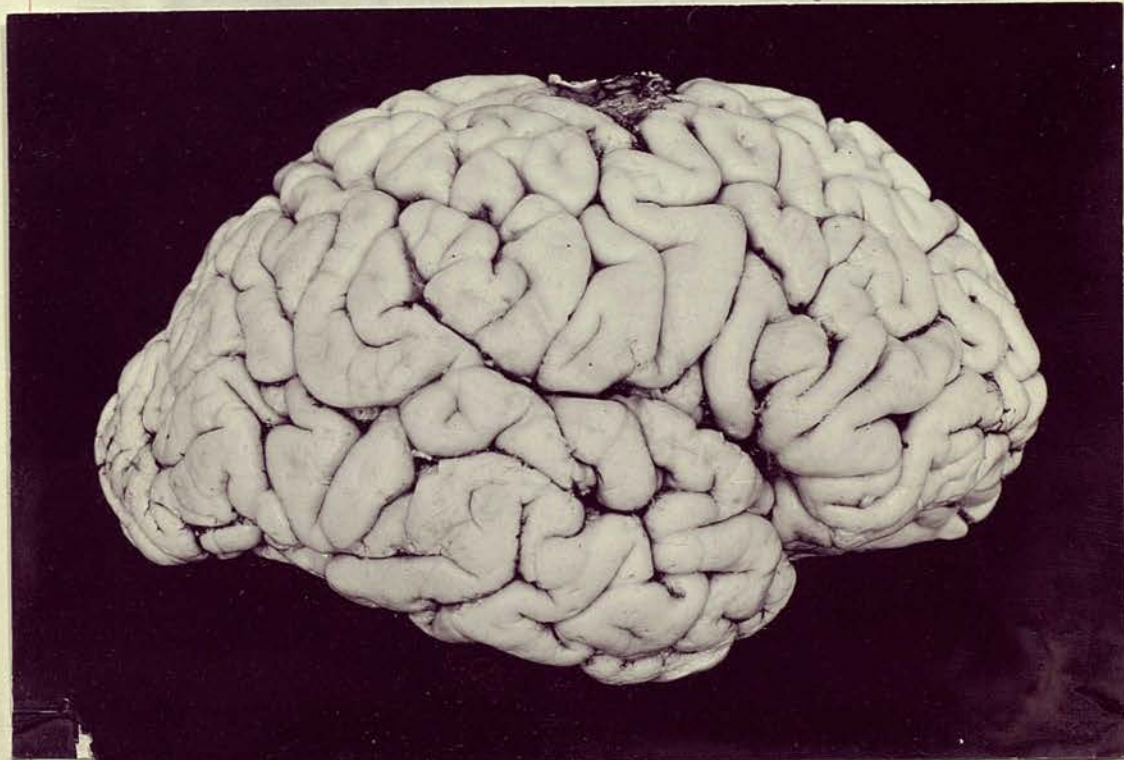


Fig 106. X (see 107)  
reduce by  $\frac{1}{3}$



X reduce  
by  $\frac{1}{3}$

Fig. 107. Brain of Case III, stripped of its membranes. In one place it will be seen the dura & pia were left, in order to section membranes & cortex together. (all slightly reduced).

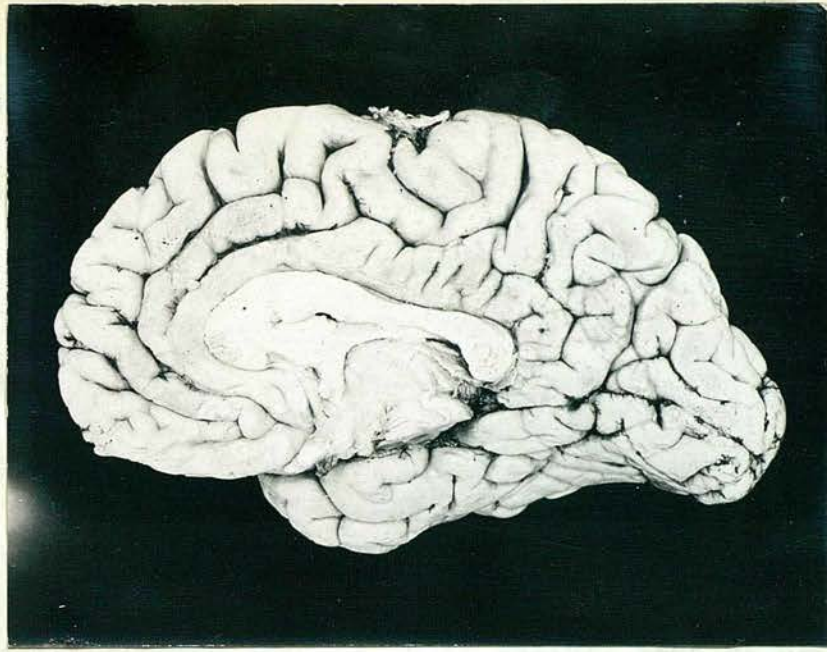


Fig. 108. (no 109)

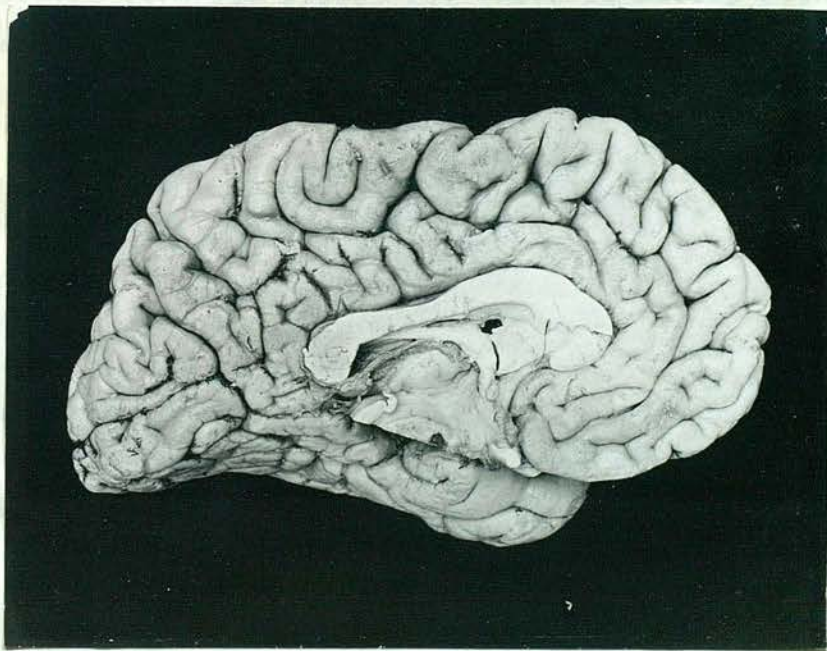


Fig 109. medial aspects of brain of Case III,  
stripped of its membranes.  
(Reduced)

Greatest breadth  $\frac{5}{2}$  cm.

The degenerated section also includes the middle third of the external capsule, so that its white fibres no longer stand out clearly between the claustrum and the outer zone of the lenticular nucleus. The claustrum itself appears normal. The inner zone of the lenticular nucleus (globus pallidus) seems not to be involved at all, while the internal capsule is intact throughout its whole extent. The cortex of the island of Reil looks normal.

It is interesting to note that even with the naked eye it is easy to note that the fine internuncial fibres, so conspicuous a feature of the zones of the lenticular nucleus, have to a large extent disappeared, especially where the area of degeneration is. The outer lamina, made up of fine fibres between the outer and the middle zone, has gone, and the inner lamina, between the middle and the internal zones, is less obvious than in the normal brain.

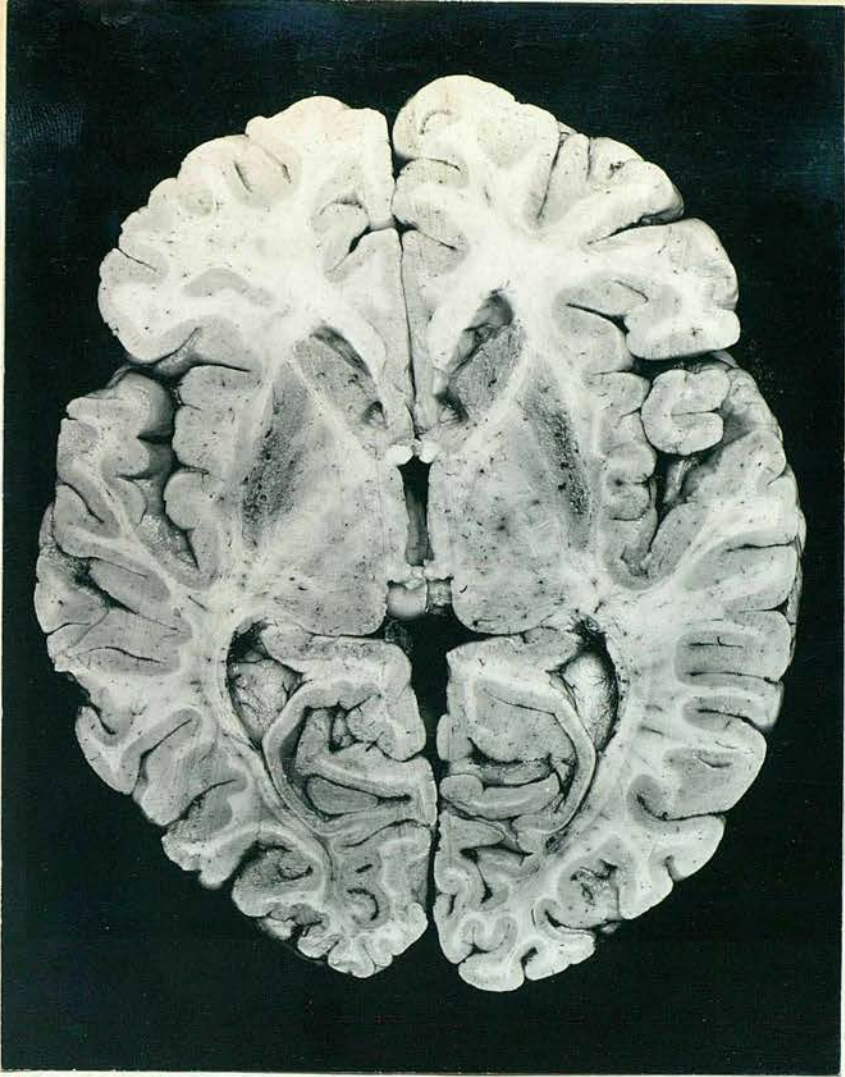
There is no other visible abnormality on the transverse section of this hemisphere. The caudate nucleus is possibly in a slightly atrophic state, but there is really nothing definite to be made out macroscopically. The optic thalamus appears perfectly normal.

Left side.

The condition on the left side is extraordinarily like what obtains on the right. The situation, shape, and appearance of the affected area, the slight cavitation, the punched out little holes, are identical. The affected area has the same slight discolouration, feels soft, friable, and is clearly in a commencing state of disintegration. The globus pallidus, in its mesial zone, seems normal, and feels firm to the touch, as it does on the right. We observe the same disappearance of internuncial fibres and laminal fibres on the left side, as well as a slight involvement of the middle part of the external capsule. Otherwise, there is no change to be noticed. The caudate nucleus and optic thalamus appear perfectly normal: the internal capsule is entirely unaffected.

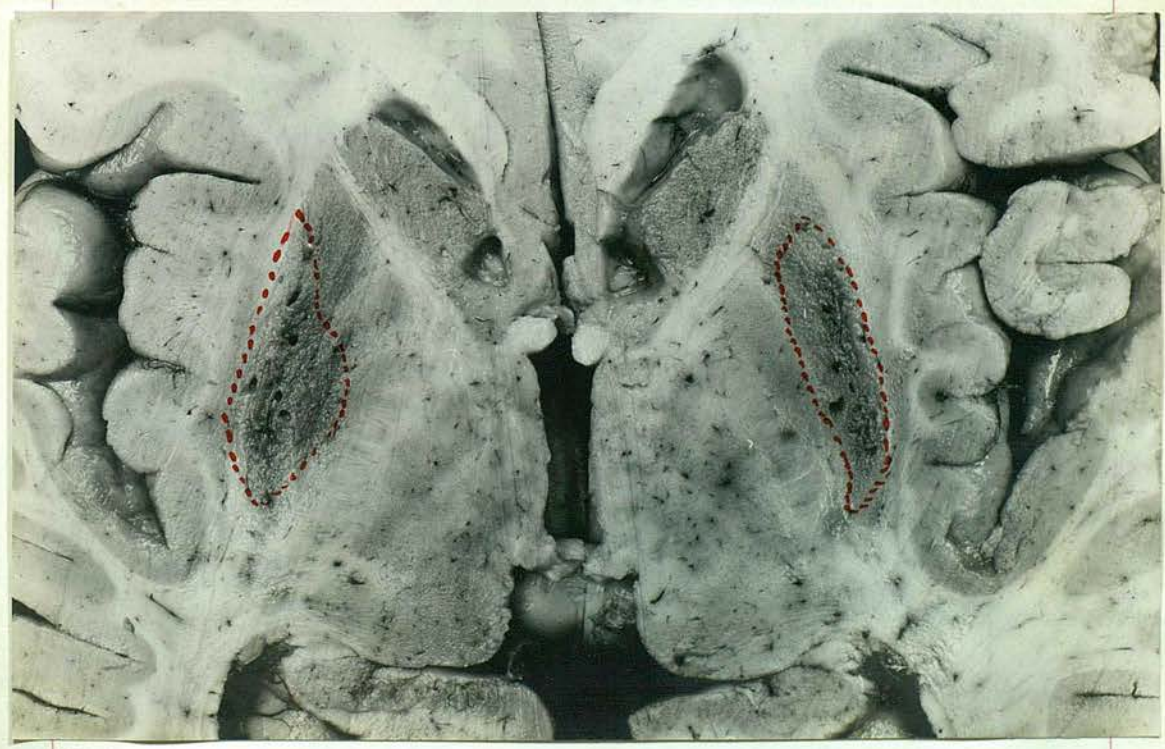
The affected area on this side has the following dimensions:  $2\frac{1}{4}$  to  $2\frac{1}{2}$  cm. long, by 1 to  $1\frac{1}{4}$  cm. broad.

There is no hydrocephalus, and no ependymitis. Possibly the white matter of the occipital lobes is a little narrow-



X

Fig. 110. Coupe d'élection, Case III. (specif reduced)  
Bilateral lenticular degeneration -



X

Fig 111. do. (enlarged)

er than it ought to be. The cortex of the frontal convolutions on both sides, the white matter of the frontal lobes, and briefly the whole of the visible cortex, appears of good depth everywhere.

It is important to compare the naked eye appearances on this section of the hemispheres of case III with the appearance in a normal brain, and also in the brain of a case of cirrhosis of the liver in which there were no nervous system symptoms whatever. By this means I have obtained a double control, which serves to emphasise the unique features of the brain with progressive lenticular degeneration. I have put these photographs together for the sake of comparison.

On the left, in figure 112, we have a photograph of the coupe d'election in a normal brain, and it will serve to remind the eye of the full, rounded appearance of the outer border of the putamen, and to give an excellent idea of the ample proportions of the corpus striatum in a normal individual. The laminae and internuncial fibres can be distinguished readily.

Figure 113, in the centre, is the left hemisphere of case III, cut in exactly the same way. While the optic thalamus is seen to be as well developed as in the normal brain, and the caudate nucleus too, the lenticular nucleus is grossly shrunken and atrophic, especially the putamen: its outer contour is no longer rounded and full, but is straighter, in fact almost slightly concave at one point: it is darker in colour than in the normal state, is perforated with holes, has lost its laminal and internuncial striation to a great extent: the external capsule is thinned, and the white matter of the convolutions of the island of Reil looks a little less distinct than it should, although it does not appear to be wasted. The internal capsule, anterior and posterior limbs, are perfectly good.

Figure 114, on the right, is the coupe d'election of the brain in the case of a boy who died from cirrhosis of the liver, without any nervous symptoms at all. It shows a perfectly normal corpus striatum, and the contrast between it and the previous figure is most instructive.



Fig 112. Normal brain.

NB. Both 112 + 114 ~~had~~ <sup>had</sup> been in Müller + therefore photographs better than 113, which was photographed fresh.



Fig 113. Case III

Also it is a very slight smaller magnification. But the atrophy of the lenticular nucleus is striking - (Fig 113).

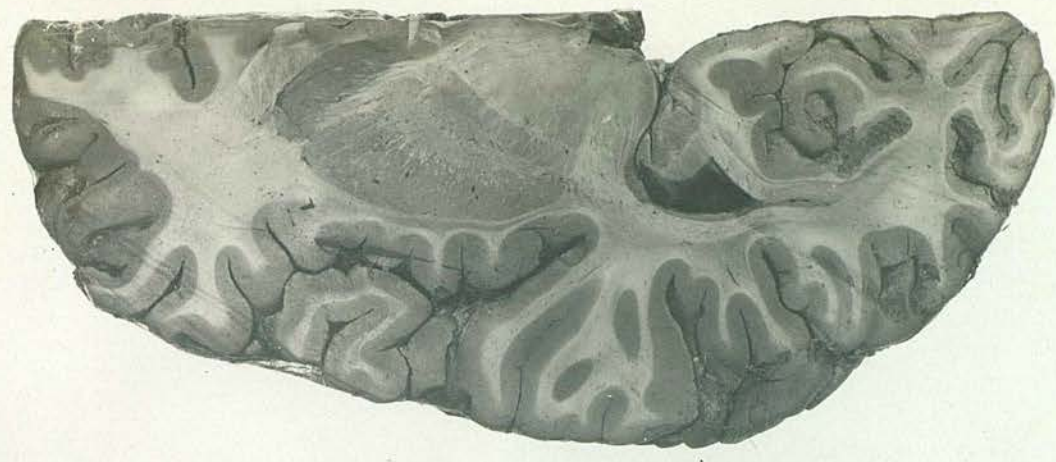


Fig 114. Brain of boy who died from cirrhosis of the liver. No nervous system symptoms whatever.

X

A photograph taken with a higher magnification shows that the caudate nucleus has retained its fibre striation in a normal way, whereas the striation of the lenticular nucleus is most defective. It also shows that the globus pallidus is much less disintegrated than the putamen, and that the internal capsule and optic thalamus on each side are entirely unaffected. The specificity of the bilateral lesion is demonstrated in a convincing way. (Figure 111)

On macroscopical examination the cord did not present any noteworthy feature. It was of good size on transverse section at various levels, and presented no sign of degeneration. The membranes were not thickened, except that the pia-arachnoid looked just a little "milky" in one or two places.

MICROSCOPICAL EXAMINATION OF THE CENTRAL NERVOUS SYSTEM.

1. MUSCLES.

Sections were embedded and cut in celloidin, and stained by haematoxylin-eosine, van Gieson, Pal's method for intramuscular nerves, counterstained with cochineal.

The chief change was that the muscle fibres were in many places rounded, instead of being polygonal, and were rather separated from each other instead of being closely packed. There was a commencing but still slight interstitial change in many of the sections examined: the muscle fibres were surrounded by narrow strands of fibrous tissue with multiplying nuclei of connective tissue corpuscles: see figure 115. In some places there was increase of nuclei in the sheath of the fibres, but, speaking generally, these changes were nowhere advanced. Many parts of the muscles were indistinguishable from the normal. There were no hypertrophied fibres, and none markedly atrophied. They were all about the same size. The fibres all stained well: no alteration in sarcoplasm or myoplasm was discoverable from this point of view. The muscle spindles seemed normal. The intramuscular nerves were not obviously changed. (Fig 116)

2. PERIPHERAL NERVES.

These were not separately examined.

3. SPINAL CORD.

For the cord the methods utilised were Weigert, Weigert-Pal, Nissl, haematoxylin-van Gieson, haematoxylin-eosine.

To take the methods for the myelinated fibres first: the sections stained by Marchi's method, from six different levels of the cord, were negative. There no was indication of degeneration, beyond the presence of a few discrete granules, in any of the columns: in particular, the pyramidal tracts, crossed and direct, and the descending antero-lateral tracts from the brain-stem, showed no change. Of course the illness had been of some years' duration, but on the other hand it was essentially progressive, so that the negative result with Marchi is of significance.

The sections stained by Weigert's original method, of which a series is given in figures 117 - 120, were equally negative. There is no trace whatever of any degeneration in the pyramidal tracts, from the upper to the lower extremity of the cord. Exactly the same result was obtained by Pal's method. The columns are all of good size, and stain deeply. There is in some places an indication of a slight peripheral loss of fibres, round the margin of the cord, but this is so sparse as to be negligible. The myelinated fibres of the grey matter of the cord stain normally.

In view of the almost complete helplessness and powerlessness of the patient, owing to motor defects, the integrity of the pyramidal system in the cord is of the utmost significance.

With Nissl's method (thionin blue) the anterior horn motor cells were carefully examined at various levels. The first point to notice is that there was practically no loss of cells. In all the sections they were present in good numbers, preserving their ordinary grouping; in the majority of cases they were of good size and shape, and stained well. On the other hand, it was clear that many had undergone a change which is well portrayed in the accompanying figures. This change is one which I have frequently met with in any disease of a chronic and progressive nature which is associated with helplessness and with muscular weakness, for instance, an advancing case of tabes. It consists in a slight shrinkage of the achromatic part of the cell protoplasm, so that the Nissl granules are closely packed together, and the cell therefore stains darkly. It is often elongated, and its processes may be less straight than they usually are. But it

[Figures 124-126]

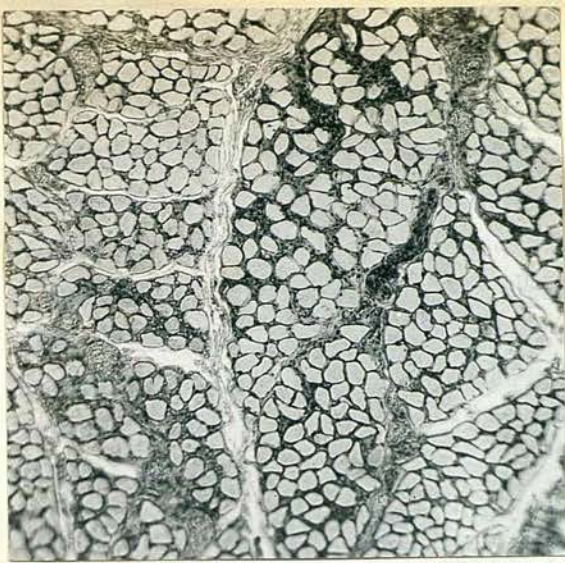


Fig 115. Transverse section  
left thoracic eminence -  
Interstitial changes (low power)

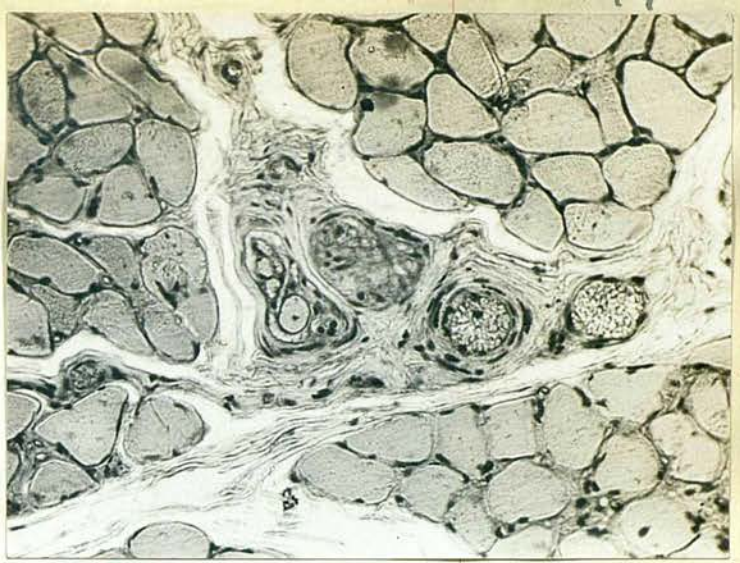


Fig 116. Transverse section right flexor  
Carpi ulnaris - Normal - High power

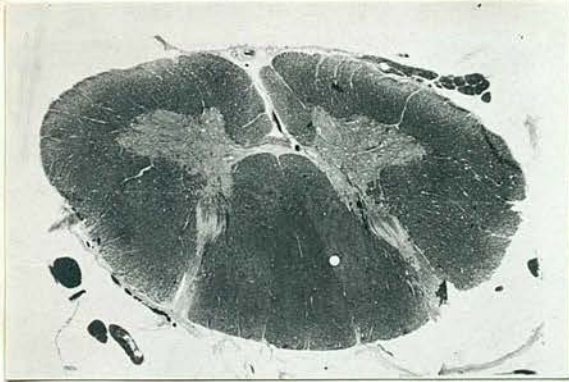


Fig 117. Cervical



Fig 118. Upper dorsal

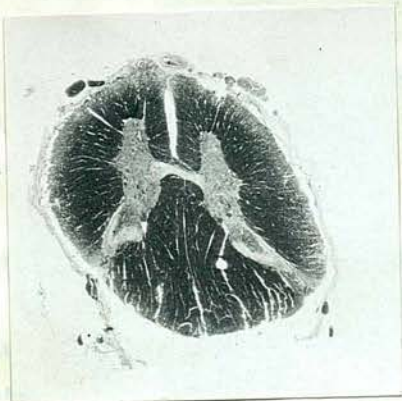


Fig 119. Lower dorsal

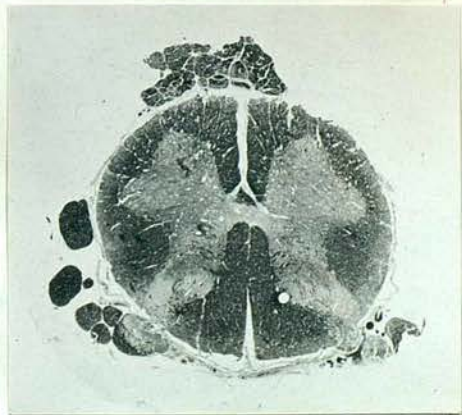


Fig 120. Lumbar

Fig 117-120. Spinal cord case III. (Wright)

does not lose its nucleus: the latter remains nucleolated, and it, too, often takes on the stain more deeply. Such cells were often met with in the Nissl sections of the cord. Others showed some pigmentary degeneration: others again showed commencing degenerative changes of a less chronic type, in which the tigroid substance becomes more finely granulated, specially round the nucleus, stains less well, while the nuclear membrane disappears.

Such as they were, the changes may be said to indicate the results of long continued imperfect use of the musculature, without their signifying any definite local atrophic change. Perhaps some of the more acutely altering cells were associated with the effects of a terminal infection.

With ordinary tissue stains it was seen that some pia-arachnitis, or leptomeningitis, was present, but this was nowhere at all severe. It was irregularly distributed over the cord, but the most significant fact in regard to it was the entire absence of anything like small cell infiltration of the meninges. This was especially looked for, and its complete absence is very important, as we shall see when we discuss the nature of the disease. The blood vessels of the cord, the anterior spinal artery and the intramedullary arterioles, were normal. There was not the least indication of anything resembling an endarteritis.

[Figures 121-123]

MEDULLA OBLONGATA AND PONS.

The same methods were utilised for these as for the cord.

With Pal's stain for medullated fibres no obvious change could be discovered. The pyramids stained deeply, and were not atrophic in any way: the olives, restiform bodies, fillet, &c, all appeared normal. In the pons there was no change that could be described as pathological.

The sections stained by Marchi's method were not so successful: prolonged immersion of the tissues in formalin militates against good results. No characteristic degenerations, however, were found.

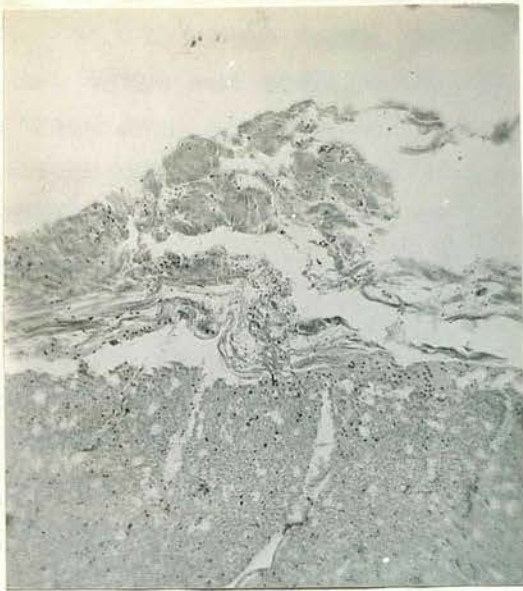


Fig. 121. Slight thickening of  
pra-archuoid - cervical cord.  
(Haemaloxylin - van Gieson)



Fig. 122. Anterior spinal vessel -  
Normal walls -  
(H. v. S)



Fig. 123. Slight thickening of pra-archuoid.  
No small cell infiltration whatever.  
(H. v. S)

In view of the patient's condition during life the nuclei of the lower cranial nerves were specially examined, by Nissl's method. A description of the cells of the hypoglossal nucleus will suffice. If the reader will look at figure 127 he will see that there is no loss of cells, in the first place: in other words, the condition is utterly different from an ordinary bulbar paralysis. The cells stain well and deeply, and the majority are of good shape: others show the same elongated and "intensified" appearance that has been already noted in the spinal cord. They are nucleated, and there is no reason to suppose that they have been functionless: When we remember that the tongue was to all intents and purposes "out of action" during life, but only slightly atrophic, we can readily appreciate the fact that its "paralysis" was not due to any defect in the pyramidal mechanism, but to other causes, and the pathological picture bears witness to the truth of this interpretation.

The cells of the facial and other motor nuclei are similarly numerous, not atrophic, and many show the changes that have just been described. Round a few of the nuclear cells ~~parasite~~ parasite glial cells are found.

CEREBELLUM.

The cells and fibres of this organ seemed quite normal with the same stains as for the cord. The Purkinje cells, granular layer, dentate and other nuclei, presented no departure from similar sections of a normal case, used as a control.

CRUS.

Weigert-Pal sections of the crus cerebri (figure 128) were in every respect normal. The pyramidal fibres were apparently intact, stained well, and were in no respect diminished in quantity, compared with similar sections from a normal brain. The fibres of the nucleus ruber were normal.

With Nissl's method the nucleus ruber was carefully examined. Its cells were not diminished in number: they stained well, and were of normal shape. A great number of them showed round them the presence of parasite neuroglial cells in considerable numbers. Reference will be made to this elsewhere.

(Figure 129)

X



Fig 124. Cells anterior horn  
cervical cord (Mussl)



Fig 125. Cells anterior horn  
lumbar cord (Mussl)

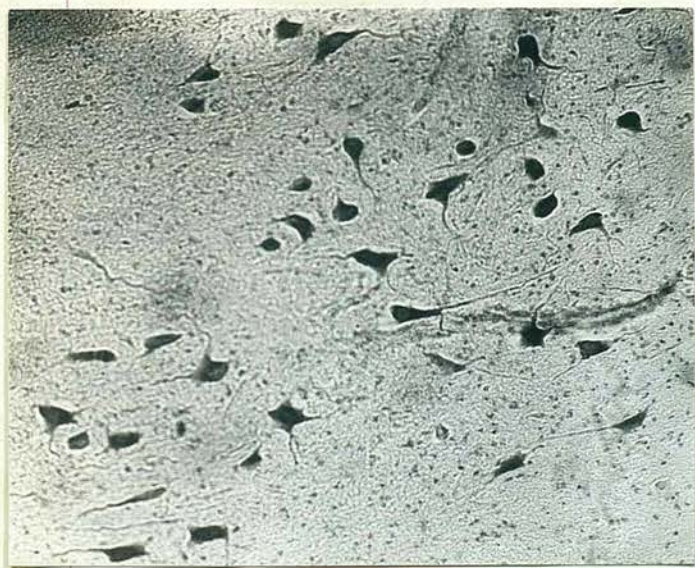


Fig 126. Same as fig 124 - another  
section: higher power.

In fig 124 + 126 same cells are  
of the "selective" type described in  
the text.

X



Fig 127. Cells hypoglossal nucleus  
(Mussl) Case III

X



Fig 128. *Crus cerebri* in Case III  
(Wright)

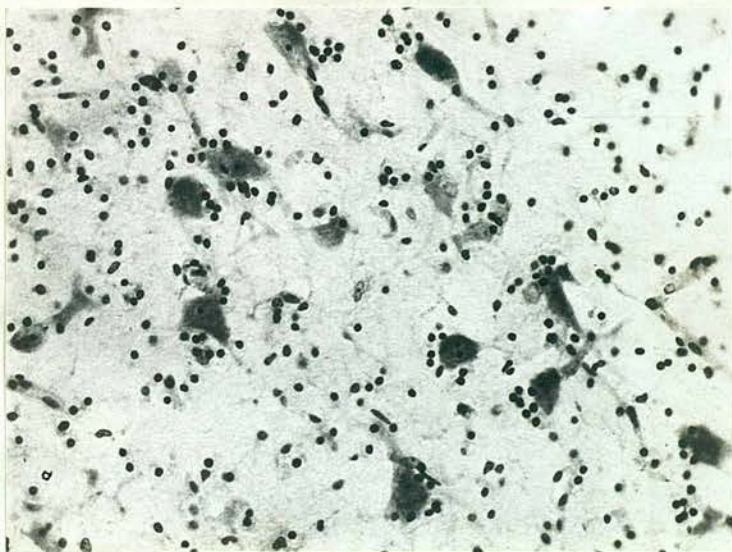


Fig 128. Cells of red nucleus - Case III (Missel)  
Numbers of parasite glial cells  
surround many of the nerve cells -

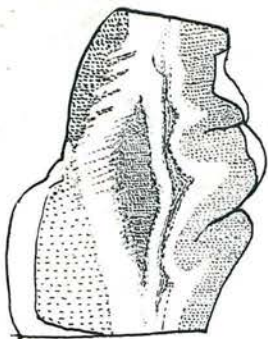
7. BASAL GANGLIA, INTERNAL CAPSULE, SUBTHALAMIC REGION.

On the right side, the central part of the hemisphere was cut into slabs by a series of incisions exactly parallel to the coupe d'election. Some of these were taken for Nissl and ordinary tissue stains, others were Müllerised for Pal and Weigert. On the left side, similar slabs were cut: some were utilised for Marchi, others for a Weigert-Pal series of the subthalamic region.

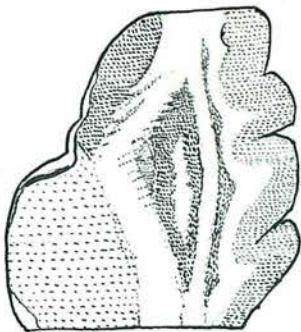
a. Minute anatomy of the lenticular degeneration.

The accompanying series of drawings represent the appearance of the upper aspect of the cut slabs of the right hemisphere, from above downwards, and serve to give as it were a reconstruction of the lenticular degeneration. [Figure 130]

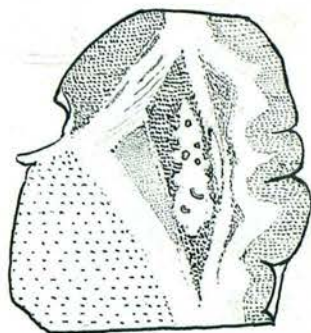
In no. 1 we have the putamen above the level of any visible degeneration, with a normal internal and external capsule, claustrum, &c. In 2. the area of disease has made its appearance, and is seen to occupy a somewhat crescentic-shaped strip of the putamen, towards its outer side, while the beginning of the middle zone (globus pallidus) just appears to its inner side. The external capsule appears intact. In 3 the affected area is broader, occupies posteriorly almost the whole breadth of the putamen, touches the external capsule slightly, and contains in its centre the minute but gaping holes round the lenticulo-striate vessels that have already been mentioned. No. 4 shows us the appearance at the coupe d'election, and corresponds to the photograph reproduced as figure 110. No. 5, a little lower, still shows clearly how the degeneration is related to the lenticulo-striate vessels: it is confined at this level to the putamen, but is already becoming less marked. The globus pallidus appears unaffected, at least directly. As we go down to the base, through nos. 7, 8, and 9, we find that there is no degeneration to be noted, and that where the lenticulo-striate vessels enter the brain they appear to be normal, nor is there any diseased area round them.



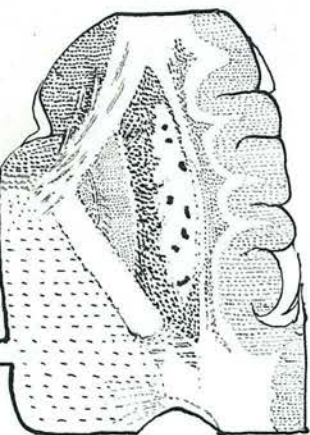
1



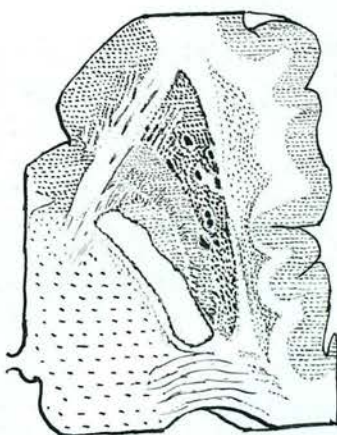
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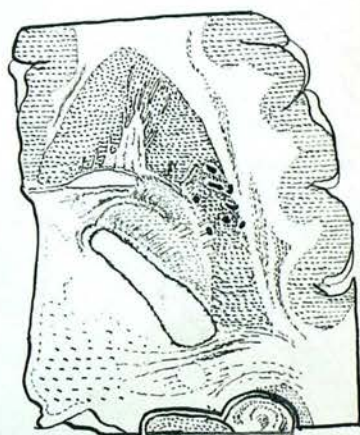
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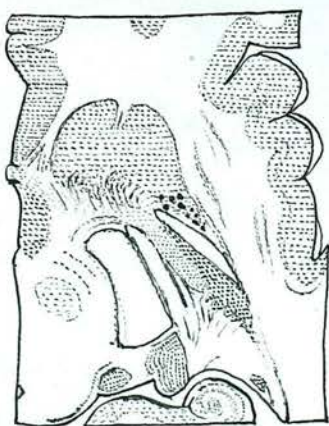
4



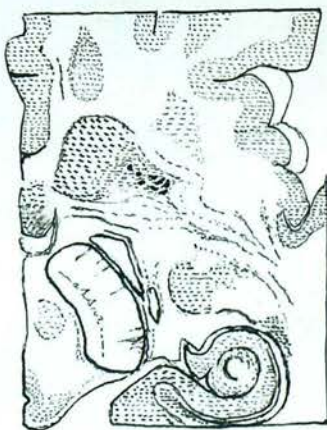
5



6



7



8

Fig 130.  
Upper surfaces of series of plates cut from above downwards  
through the R basal ganglia -

S.A.K.W.

(Natural size)



If now we look at the microscopical preparations of the diseased nucleus, stained with haematoxylin and eosine, we note the following points. With a low power there is a wide strip, occupying almost the whole of the putamen, which stands out prominently and unmistakably. Here there is a pronounced degree of sclerotic change: a great overgrowth of neuroglia has taken place, which in a number of places is commencing to break down. The internuncial fibres from the putamen have disappeared: the cells of the nucleus are few and far between. In and round this area the blood vessels are somewhat dilated and have wide spaces around them, occasioned probably by retraction of the tissues under the action of sclerosis. It is towards the periphery of the degenerated area that the sclerosis is densest: towards its centre it is thinner, and the tissues are necrosing: no doubt definite cavitation would have ensued had the patient lived longer. Figure 131 gives an idea of this low power appearance.

[Figure 131]

With a higher magnification there is seen to be a confused mass of neuroglial overgrowth and tortuous small vessels, forming an amorphous network in which the true nerve elements of the nucleus have been strangled. Figure 132 gives an excellent impression of the density of this change in the putamen, and illustrates well the amorphous character of the degeneration.

Under a still higher magnification we can study the alterations more minutely. The nerve cells of the putamen have almost entirely disappeared: only a few can be discovered. Neuroglial nuclei and cells and fibres form the chief feature in the picture. In some places they are actively growing: in others they are sparse, the tissue is breaking down. Everywhere numbers of the so-called Kornchenzellen can be seen. Where the cells of the putamen can be found, they are usually shrunken and stain very deeply. The bundles of internuncial fibres leaving the putamen to enter the globus pallidus are very difficult to trace. The first lamina medullaris, between the outer and middle zones, is similarly attenuated.

[Figs 134-136]

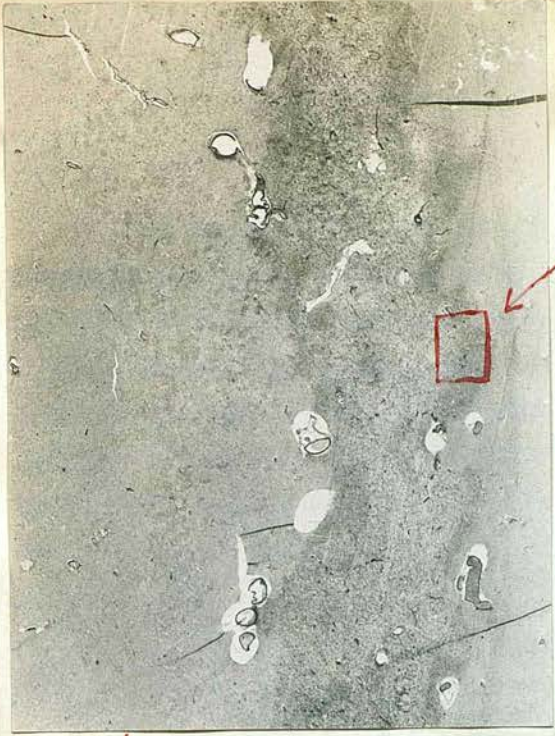


Fig 131. Low power view of degeneration in putamen.

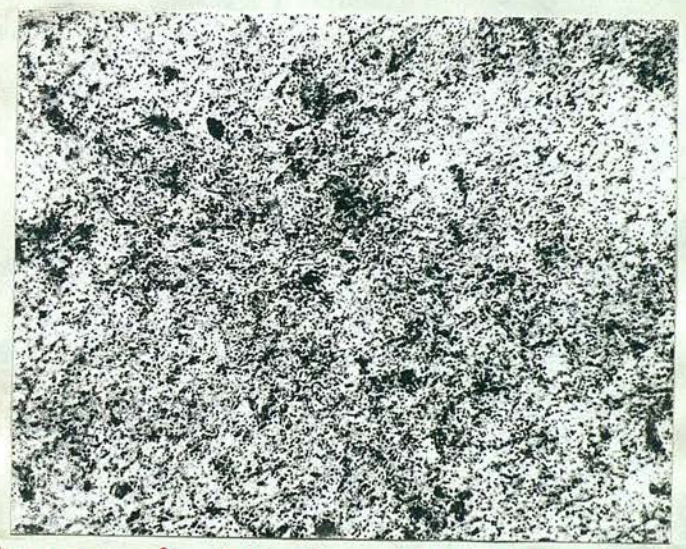
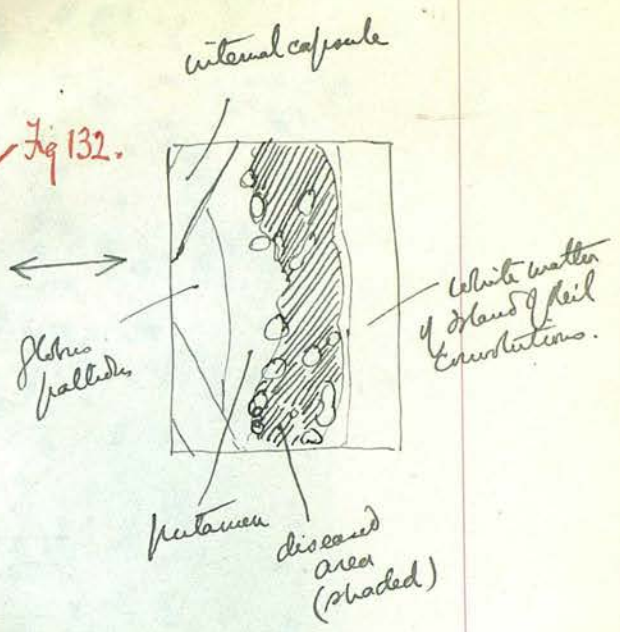


Fig 132. Do. higher power (about x60) to show the neuropil filling + neuronal cell overgrowth.

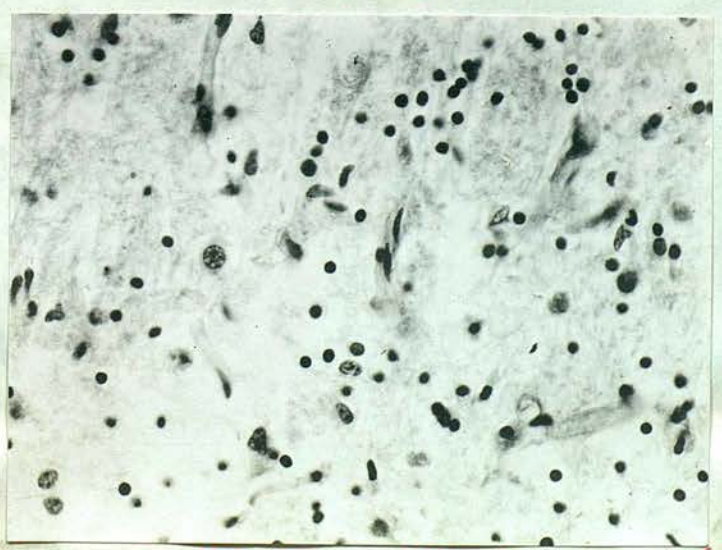
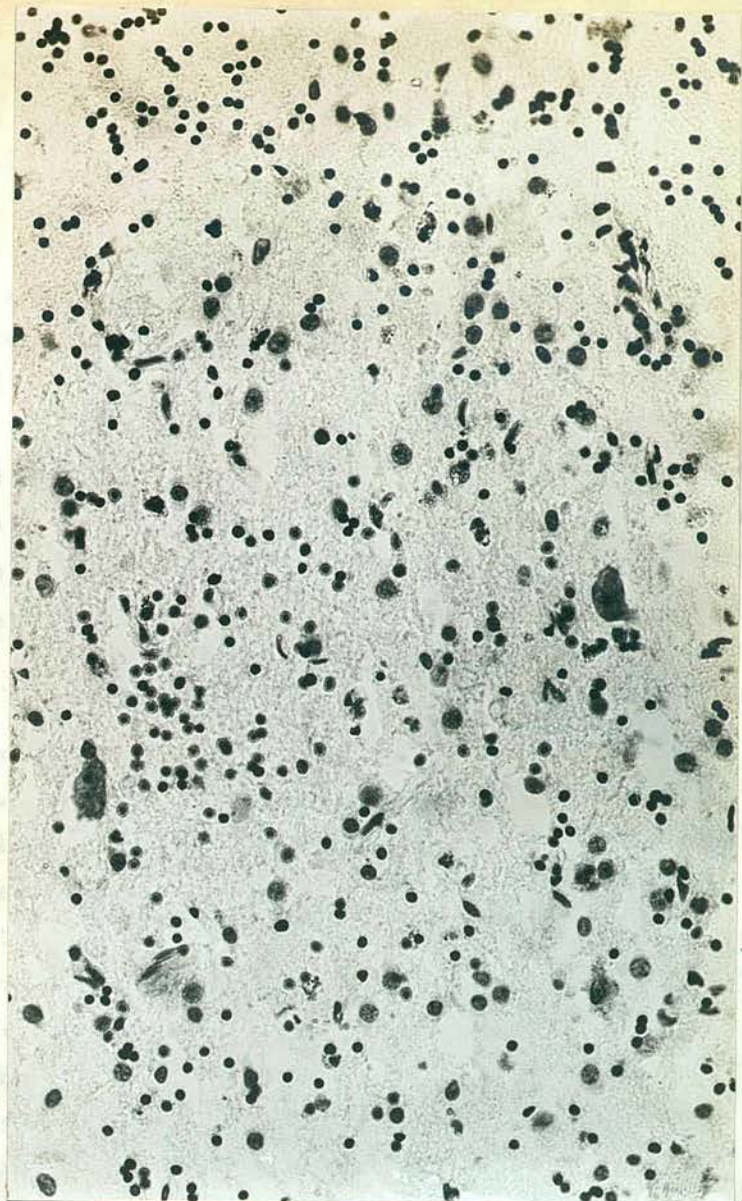


Fig. 133. High power ditto No nerve cells - or only few.



cut X  
cut

Fig 134. Strip from degenerated area (X 450)  
Two new cells - great number of neuroglial cells + Körnerzellen.



Fig 135. Ditto. (X 750)  
mostly Körnerzellen  
new cell.

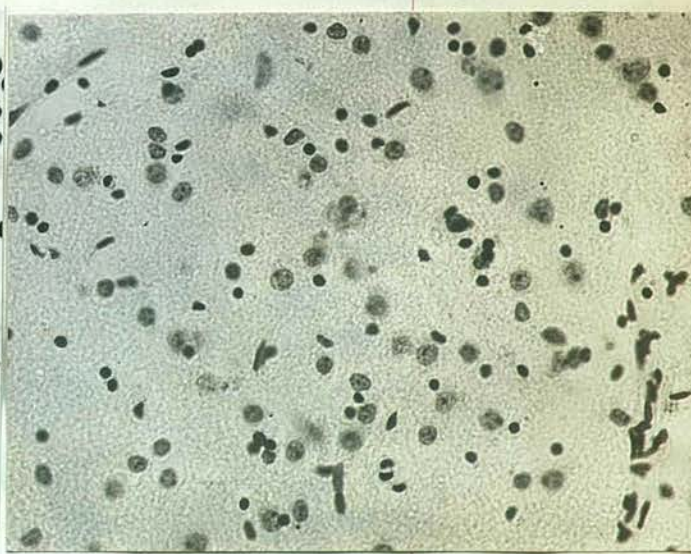


Fig 136. Ditto. (X 450)  
Large number of Körnerzellen  
in field.

(Fig 134-136 by Miss's method)

The condition of the blood vessels deserves special attention. As has already been remarked, under a low power, so far from being thickened or obliterated, they are if anything thinned and dilated. The wide spaces surrounding them are not filled with tissue debris, but are mostly empty, and the edges of the spaces are formed of a feltwork of neuroglia. Towards the centre of the diseased area, however, we do not find the same spacing, and there is a considerable degree of disintegration round the vessels. Under a higher power there is no trace whatever of any small cell infiltration that would suggest an inflammatory reaction. The lymphatic sheaths of the vessels are somewhat dilated, but they do not contain small round cells. The coats of the lenticulo-striate arteries can be seen to be of normal proportions: in no single vessel is there any endarteritis: the elastic lamina is mostly intact, the muscular layer is a little thinned or stretched, the adventitia is in some instances perhaps a little thickened. The arterioles and capillaries, also, are free from any sign of endarteritis. In scores of sections I failed to discover a single obliterated vessel.

All these points are well brought out in the photographs. (figures 137, 138, 139 — ).

Compared with the putamen, the cells of the globus pallidus were much less interfered with: this section of the nucleus lentiformis showed little change beyond a certain increase in neuroglial nuclei and a general increase in its the density of its tissues. Similarly the cells of the claustrum revealed little if any pathological change, and its neuroglial groundwork was practically normal. (figure 137).

Sections from the degenerated portion of the lenticular nucleus, stained with osmic acid, showed the presence of great numbers of phagocytic cells crammed full with minute fat granules, but only where the tissues were actually disintegrating. Round the edges, where the neuroglial overgrowth was densest, these fat cells were not found. ~~See~~ figure .

b. Optic thalamus and caudate nucleus.

No changes in these ganglia, analogous to what obtained in the putamen, could be found. The cells of the different

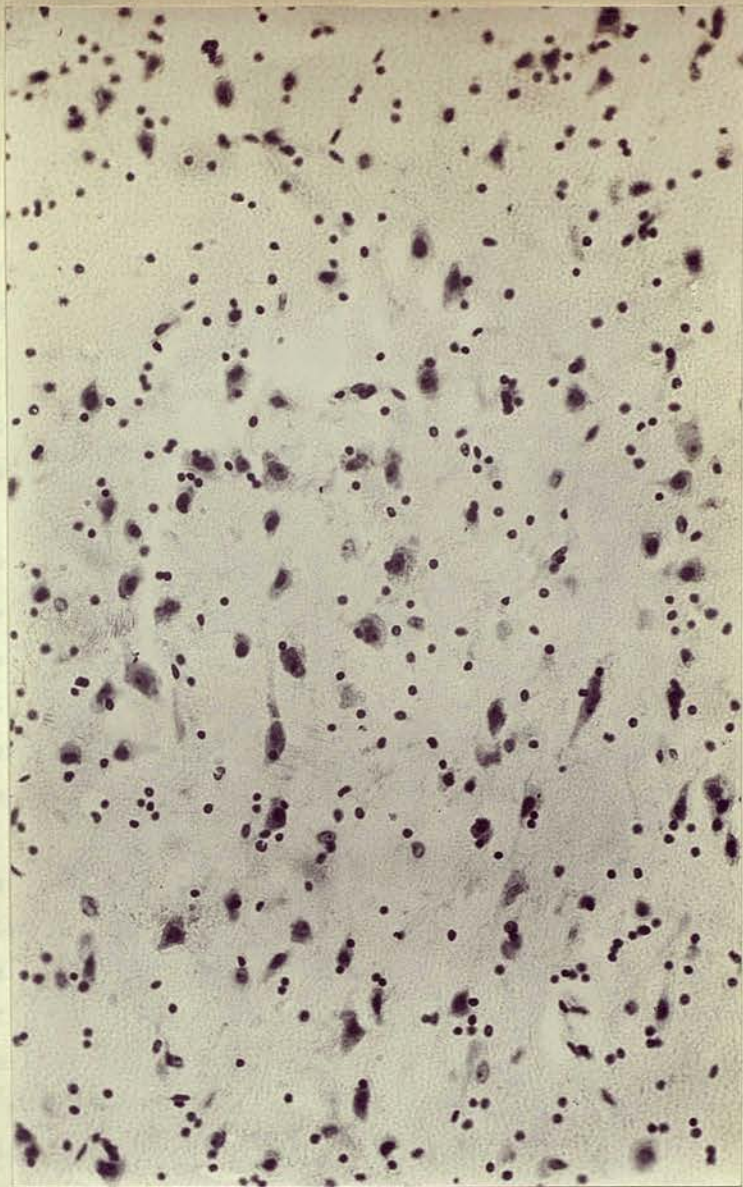


Fig 137. Claustrium - practically normal (x400)  
(Kissel)



Fig 138. Vessels from pulvener -  
low power.



Fig 139. One of the lenticulo-striate  
vessels. It is, if anything,  
thinned. No endothelium whatever.

X

nuclei of the thalamus were for all practical purposes normal, and similarly with the cells of the caudate. There were no neuroglial changes that could be distinguished with certainty.

c. Internal capsule and fibres of the corpus striatum.

By the methods of Weigert and of Weigert -Pal the fibre content of the basal ganglia was investigated.

In a series of sections cut consecutively from above downwards it was seen that the maximum of defect was in the middle third of the putamen, regarded vertically, and to <sup>a</sup> less extent in the upper third: in the lower third there was very much less change. In a section at the level of the upper part of the corpus striatum the internal capsule was perfectly normal, and the pencils of fine fibres passing from the putamen mesially were also normal. A little lower, at the level of the upper margin of the globus pallidus, these fine fibres were still visible, but appeared diminished in number. At the level of the middle of the globus pallidus, regarded vertically, there was an obvious defect of fine internuncial fibres passing from the putamen to the middle zone, and the outer lamina was very incomplete. The inner lamina was more nearly normal, and the fibres from the middle to the inner zone were also nearly normal. The fine fibres coming from the caudate across the internal capsule, anterior limb, to the lenticular nucleus, stained quite well, and did not appear obviously diminished in number. At the anterior and posterior ends of the putamen a number of fine pencils of fibres, passing mesially, were still to be seen. The internal capsule stained in a perfectly normal fashion throughout. The external capsule was deficient in its middle third, but the fibres of the white matter of the island of Reil convolutions were unimpaired. At a lower level, the chief defect was still in the internuncial fibres from the putamen inwards, otherwise the nucleus had a practically normal aspect. At the level of the upper part of the crus, where the red nucleus first appears on horizontal section, little change could be detected. The ansa lenticularis, where it sweeps round the crus, appeared to be somewhat thinned and did not stain so deeply as some of the neighbouring structures, but on the other hand it could not be said to be grossly atrophic.

It was difficult to say whether there was any abnormality in Forel's lenticular bundle, or in the zona incerta. The corpus Luysii did not present any definite change: it was a little smaller than the similar body in the control sections from a normal brain: however, its staining reactions were unaltered. I cut in serial section the whole of the sub-thalamic region on the left side by Marchi's method, but did not obtain any positive finding except that the ansa lenticularis was certainly degenerated. The staining, however, owing no doubt to the tissues having been in formalin so long, was not perfect. The fibres of the ansa could not be traced as far as the capsule of the red nucleus: they passed in that direction, however.

Under a higher power the fibres in the putamen were examined, and many found to be irregularly moniliform, twisted and turned, and altogether their symmetrical arrangement was markedly interfered with.

The fine fibres of the optic thalamus, and the fibres passing across in bundles from the globus pallidus to the outer levels of the thalamus, were not obviously imperfect.

CORTEX CEREBRI.

The left motor area was investigated by a series of pieces taken from it, to include both the precentral and the postcentral convolutions. In addition, the cortex of the island of Reil, as well as of the posterior end of the third left frontal convolution, was taken. Special attention was given to that part of the motor area, at the lower end of the precentral gyrus, from which originate the fibres that innervate the muscles of articulation, via the bulbar nuclei.

An exhaustive examination was made of these sections of the motor cortex. In the accompanying photographs are strips of the cortex of the leg and of the arm area. It will be seen that there is, in the first place, no defect in number, or in shape and staining properties, of the Betz cells. In view of our knowledge of the origin of the pyramidal tracts, this fact is of great significance, when compared with the utter feebleness and helplessness of the patient. Further, it is

*Figures 140-142*

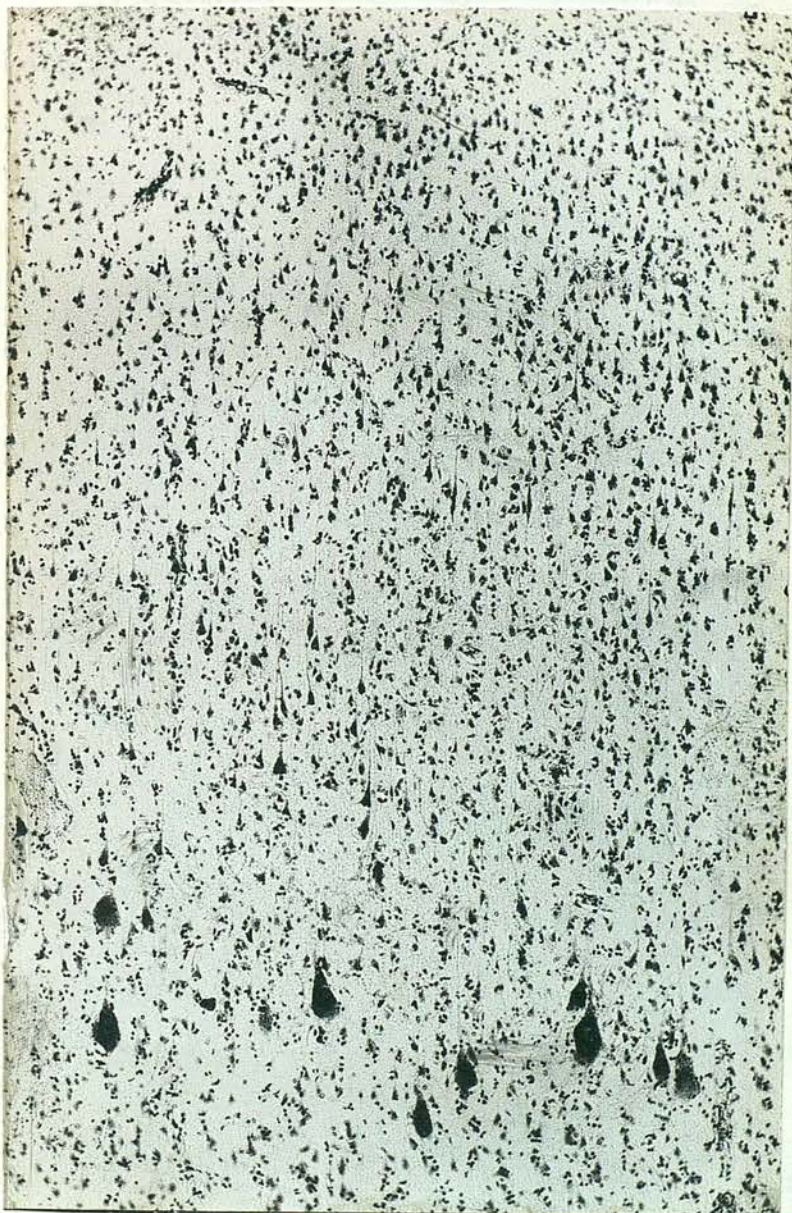


Fig 140. Strip from the leg centre, left precentral  
 convolution - Case III  
 (Misch.)  
 The Betz cells are perfectly normal -

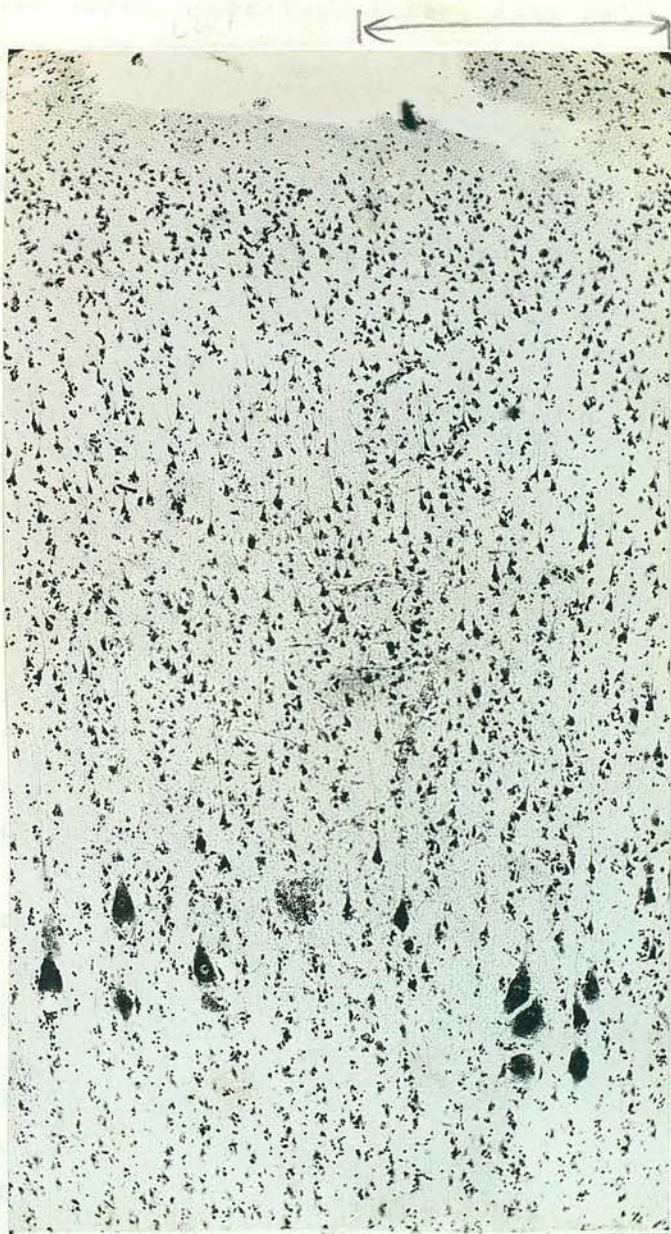


Fig 141. Strip from left arm center, precentral gyrus. (Nerve). The Betz cells are unusual.



Fig 142. Ditto. another section. Normal Betz cells - cut a little obliquely.

X

seen that when compared with sections from a normal brain there is little departure from the normal. The zonal layer, outer granular layer, pyramidal layer, Betz cell layer, and fusiform layer, can be readily distinguished. The stellate or inner granular layer is never marked in the precentral convolution cortex, though it can sometimes be traced faintly.

I am unable to satisfy myself that there is any serious defect of the pyramidal cell layer, though possibly its cells are slightly diminished in number. A number of the pyramidal cells show small collections of glia cells round them.

In the other portions of the cortex examined, there was little or no departure from the normal. In particular, the motor centre for articulation shows no obvious loss of cells, although here the pyramidal cells seem in some instances to be unduly elongated and to stain too deeply.

In no one of many scores of section was there any trace of small cell infiltration of cortical vessels.

The fine myelinated fibres of the motor cortex were examined by the method of Pal. There was some diminution in the fibres of the tangential layer, or zonal layer. It was not so dense and well defined as in the normal brain. On the other hand, the supraradiary and intraradiary networks were apparently unaltered. (figure 143).

#### MICROSCOPICAL EXAMINATION OF OTHER ORGANS.

##### 1. LIVER.

The histological methods employed were haematoxylin-eosine, haematoxylin-van Gieson, Weigert's stain for elastic tissue, Sudan III for fat.

The liver presented a very interesting appearance under a low magnification. Its substance was divided into numerous islets, <sup>of</sup> highly irregular size, most of them including perhaps six or eight lobules, or liver units. Others were so small as to include only one lobule--of these only a few were seen--and in other instances less than one lobule, in fact only a few liver cells, were enclosed in cirrhotic tissue. This fact was determined by the use of serial sections. Speaking generally, the cirrhosis was of mixed, but mainly multilobular, type. Round the islets was cirrhotic tissue in abundance, of varying breadth, much more cellular than fibrous, on the

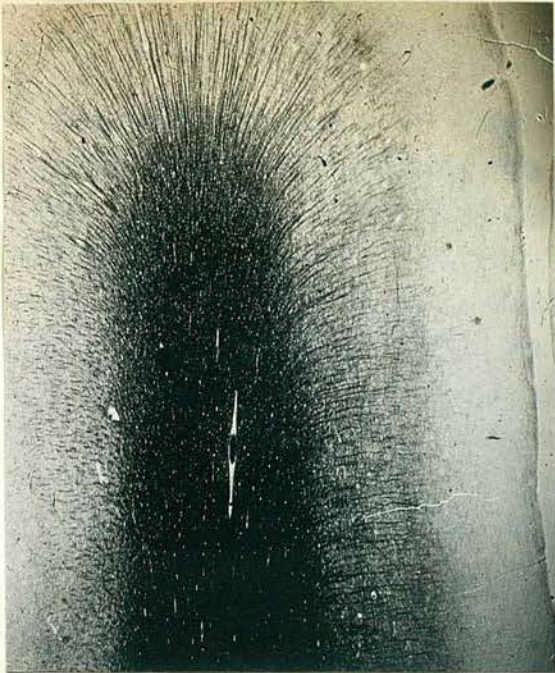


Fig 143. Myelinated fibres of precentral convolution.  
(Vergat Pal.) - low power.

X

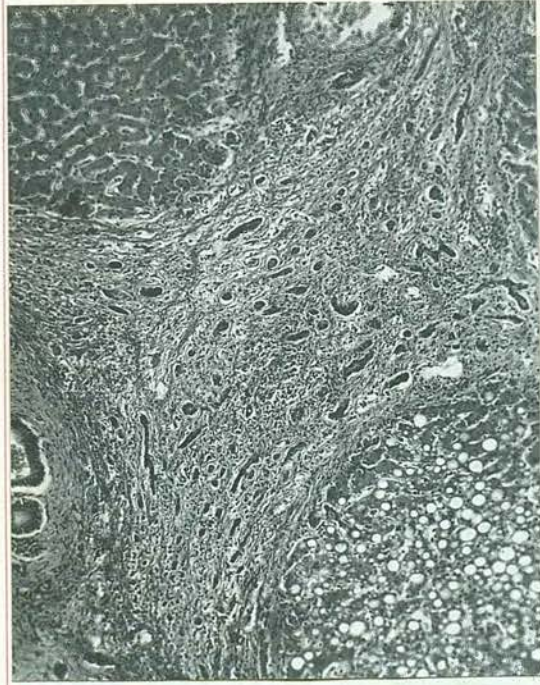


Fig. 144.  
Low power cerebellar tissue,  
with bile ducts. Case III  
(haematoxylin-eosin)

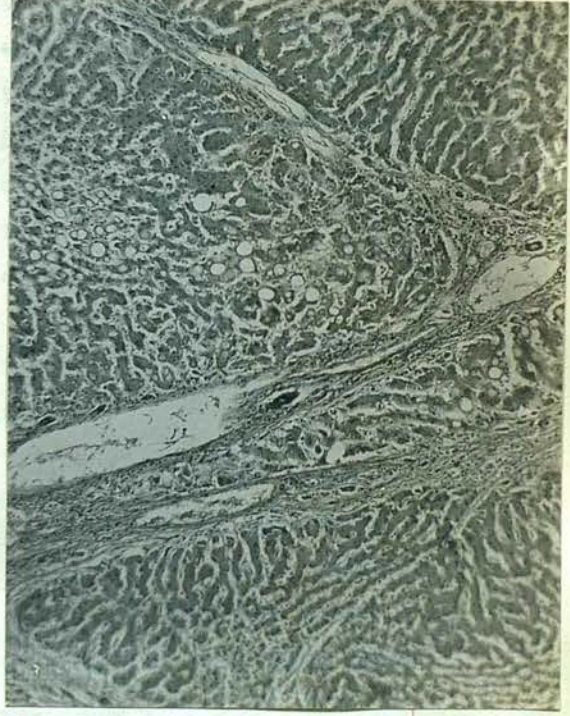


Fig 145.  
Ditto. High variable appearance  
of liver cells.  
Thin bands of sclerosis  
(haematoxylin-eosin)

whole, and containing numerous young connective tissue corpuscles. A very prominent feature of the cirrhotic strands was the presence of so called hypertrophying bile ducts. In some places these were almost the only structure that could be seen in the field. There was very little sign of intralobular cirrhosis: in a few places strands of connective tissue appeared to be dividing up the columns of liver cells, but there was so little of this change as to be negligible.

(Fig 146)

(Figs 144-147)

The curious feature of the cirrhosis was its pronounced irregularity as far as its effects on the liver cells was concerned. While many lobules were normal, others in their neighbourhood were not merely irregularly degenerating, but were sometimes in a state of what appeared to be acute necrosis. The whole of the centre of the lobule would be seen to be losing its cellular structure, and to be staining homogeneously, indicative of some acute chemical change. The liver cells were in many places normal in every way: others in the same lobule might be in a state of advanced fatty degeneration. Stained with Sudan III the picture obtained was striking. Some nodules of cirrhotic tissue contained only fat cells, so to speak, others contained no fat at all.

Abundant evidence was obtained, under a high power, of active regeneration of liver cells. In the regenerating area I often noticed that the nuclei stained irregularly with polychrome blue, some being pinkish, others bluish: sometimes the nucleus was blue with a bright red nucleolus. Here were to be found cells undergoing amitotic division, in most instances, although a rare mitotic figure was here and there seen. Many cells had double nuclei, others hypertrophying nuclei. These varying appearances are shown in the accompanying figures. (figures 148, 149 → ).

One of these is instructive (figure 147) as it shows direct continuity of the hypertrophying bile ducts with columns of liver cells. The portal tracts, and vessels, of the liver, did not present any marked abnormality.

Another feature seen in the liver sections will be noted subsequently.



Fig 146. Bile ducts in the connective tissue.  
(haematoxylin-eosin)

↓

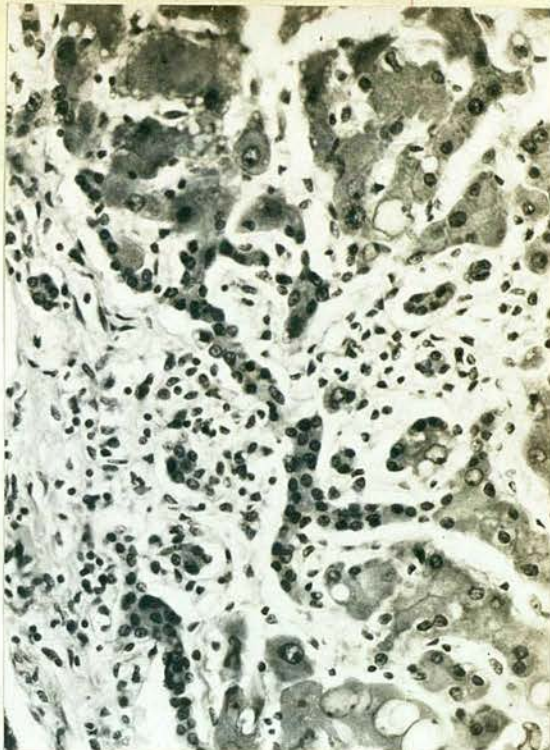


Fig 147. Ducts with columns of diseased liver cells.  
(haematoxylin-eosin)



Fig 148. (x1200)  
Regeneration in liver cells -  
mitotic division -

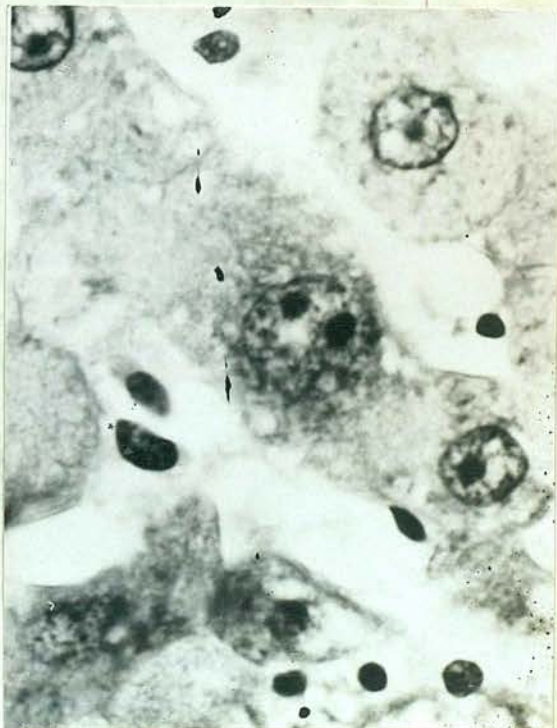


Fig. 149. (x1200)  
(Haematoxylin-eosin)

2. The other organs examined microscopically must be briefly dismissed.

The THYROID showed changes that are indicated in figures 150 & 157. The colloid vesicles were in many places reduced in size and number, and contained less colloid than in the normal gland. The epithelium lining the vesicles was often noted to be in a state of proliferation. A certain amount of interstitial change was present.

The SUPRARENAL gland did not present any unusual feature.

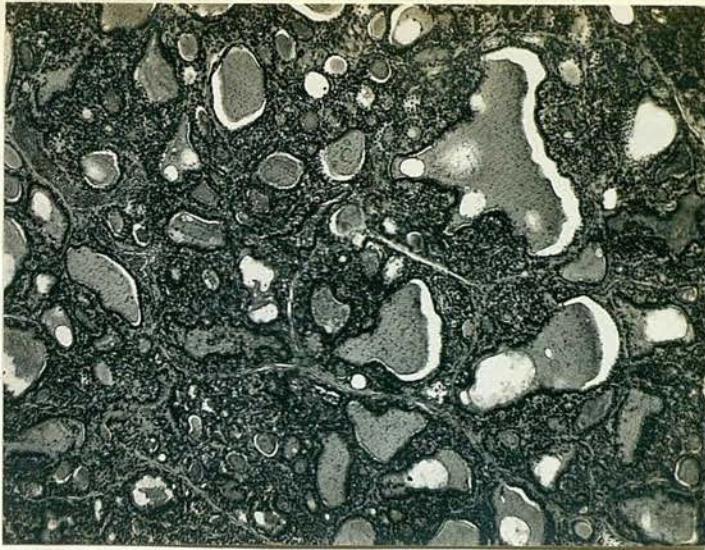
The THYMUS was of course small, but much of its tissue was persistent: it appeared to be normal.

The SPLEEN, on microscopical examination, showed little change: what change there was indicated interstitial alteration.

The KIDNEY did not present any unusual feature.

*The Pituitary was apparently normal -*

The sole remaining point in the pathology of this case of progressive lenticular degeneration is the question of a terminal infection. Scattered through the suprarenal gland, to a very much less extent in the liver, but also in the brain, cord, and kidney, clumps of bacilli were here and there to be found. Figure 152 represents one of these clumps in a minute posterior vessel in the cord: figure 153 is particularly interesting, for it represents a transverse section of a minute vessel from the degenerated area in the lenticular nucleus. Entangled in the fibrin clot will be seen a mass of bacilli, stained intensely blue-black. In view of the scattered nature of the process it is, I think, probable that its sole significance is that of a terminal infection, possibly from the alimentary canal. The bacilli resembled the bacillus coli structurally, but their staining reactions seemed in ~~one~~ one or two ways to be rather different.



X

Fig 150. Pyroid - low power - Case III  
 (haematoxylin - van Giesin)

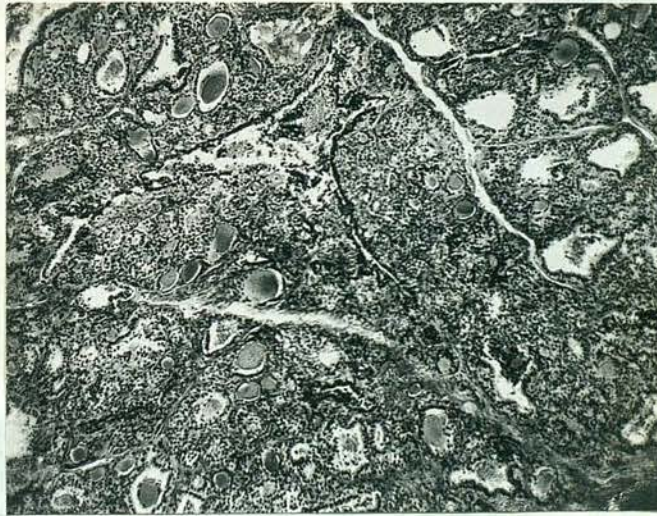


Fig 151. ditto. ditto.

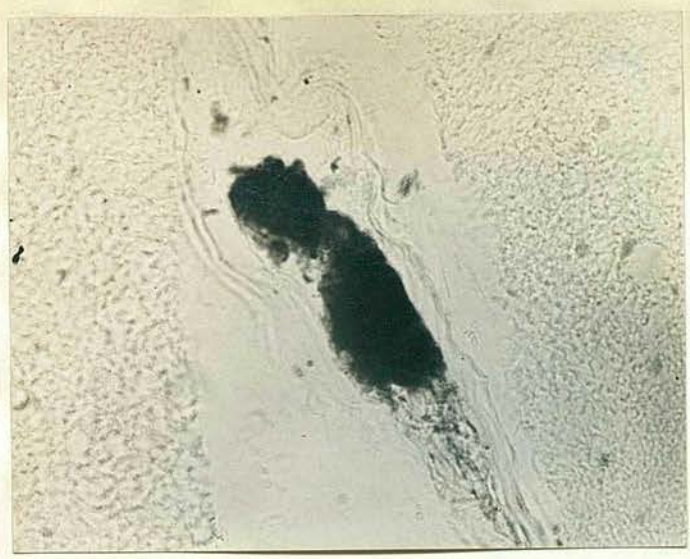


Fig 152. Plug of bacilli from vessel  
in protein column of cord -  
Case III (-Mord)

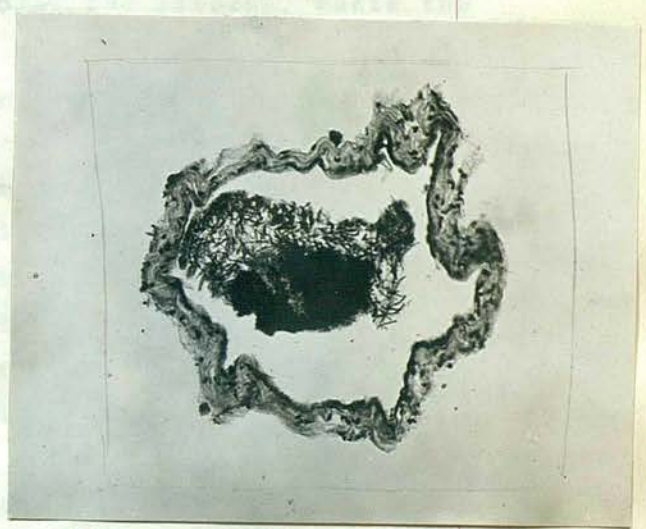


Fig 153. Minute vessel from  
degenerated putamen - clump  
of bacilli entrapped in fibrin clot  
(Haematoxylin eosin)

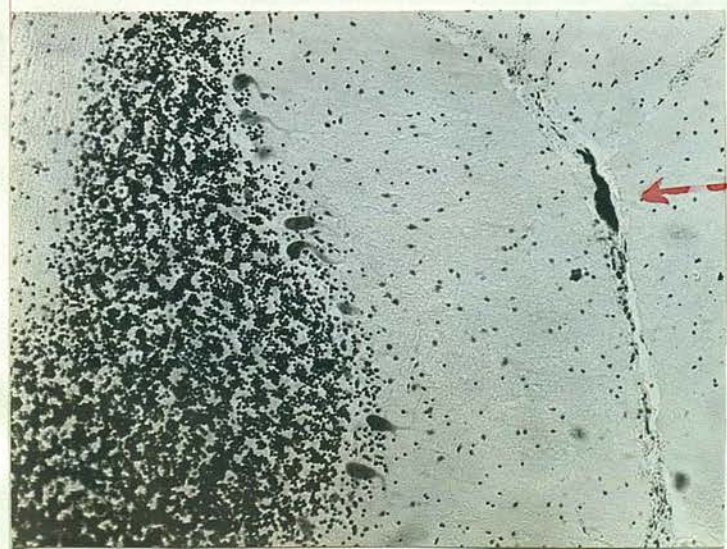


Fig 154. Cerebellar cortex - Case III  
Plug of bacilli indicated by arrow.  
(Mord)

## RESUME OF THE PATHOLOGICAL FINDINGS IN CASE III.

The brain is of good size and shape, and its convolutional pattern is normal. There is no obvious atrophy of gyri, and no definite disease of the membranes, beyond slight irregular "milky" of the arachnoid in the interpeduncular space and on the posterior aspect of the cord. The pons looks perhaps a little small in proportion.

The cerebral blood vessels are not thickened and show no patches of disease in their walls. They are all patent.

The brain is cut open by Marie's coupe d'élection and at once a bilateral and strikingly symmetrical degeneration of the lenticular nucleus, in particular the putamen, meets the eye. This structure is seen to be grossly shrunken, so that its outer margin is almost concave, instead of being rounded and convex: it is darker in colour than normal, looks friable and feels soft, is so disintegrated that a cavity formation has begun, and is perforated by minute but gaping holes in some of which the lenticulo-striate vessels, separated from the surrounding tissue are seen. The dimensions of the degenerated area average 2 by 1 centimetres. Compared with a normal brain the lenticular nucleus is in this case considerably shorter and narrower, indicating the extent of its atrophy. The globus pallidus is much less affected: the laminae and internuncial fibres between the zones of the nucleus have disappeared to a great extent in the outer section: on the inner side they are much better preserved. The caudate nucleus is perhaps a little shrunken, but the optic thalamus is normal, and the internal capsule is entirely untouched.

The softened portion of the lenticular nucleus occupies approximately the middle third of the putamen, vertically considered: below, it is apparently normal. Microscopically we find the putamen extensively sclerosed by neuroglial overgrowth, which is breaking down in the centre: the normal cells of the nucleus have to a great extent disappeared, and numerous Kornchenzellen are present: but there is no small cell infiltration whatever, to indicate an inflammatory reaction, and not the slightest sign of endarteritis in the vessels of the affected area.

Although the cortex and subjacent structures of the island of Reil have the same vascular supply, they are not involved at all, with the exception of the middle third of the external capsule, which is thinned.

The cortex in the motor area is examined from the cyto- and myelo-architectonic points of view, but it is found to be normal. The pyramidal system, from the Betz cells, through internal capsule, crus, pons, medulla, cord, anterior horn cells, to the muscles, is exhaustively examined, but no alterations of any significance are found at all, except such as can easily be accounted for by the helpless and emaciated condition of the patient.

There is degeneration in the extra-pyramidal system from the lenticular nucleus via the ansa lenticularis towards the red nucleus, but the cells of the latter structure are apparently normal.

The liver is found to be in an advanced state of cirrhosis, typically multilobular, but to some extent mixed; there is apparent increase of bile ducts in the cirrhotic tissue, great variations in the condition of the liver cells, many being in a condition of fatty degeneration, others normal, and others still actively regenerating, amitotic and less frequently mitotic division being seen in the last.

The spleen is slightly enlarged, but otherwise normal.

The thyroid shows interstitial changes chiefly, but there is also proliferation of epithelium.

The pituitary, thymus, and suprarenals do not present any special abnormality.

There are indications of a terminal infection in the presence of clumps of bacilli in some of the internal organs, as well as in the brain and cord.

CASE IV.

In case IV there was no pathological examination.

CASE V.

The autopsy was made on February 15, 1889.

"The brain tissue was soft: ? oedematous.

The membranes were healthy. On naked eye examination no obvious morbid appearance could be made out.

The spinal cord was firm: the membranes not adherent.

The liver was small, contracted. Small nodules, varying in size, many about the size of a small marble, all over surface. Section corresponds. (Extreme cirrhosis of liver).

Spleen large, fairly firm, much congested."

There is no record of any further examination, or of any microscopical investigation.

The appearance of the liver is reproduced below from the original negatives, kindly loaned me by Dr James Taylor. (Figures 155, 156.)



Fig 155.



Fig 156.

CHAPTER IV.

SYNTHETIC STUDY OF THE DISEASE.

FOR the purposes of a synthetic study of progressive lenticular degeneration we have now at our disposal 10 cases, with the inclusion of 2 less certain cases, 12 in all. Of these two Anton's is certainly more doubtful than the other (my own case V), so that we shall base this study on 11 recorded cases, in no less than 10 of which an autopsy was held. Clinically and pathologically, therefore, we have abundant material for a systematised description of the disease. Of these 11 cases, 6 date back more than 20 years, the other 5 are reported in this Thesis for the first time.

1. DEFINITION AND TERMINOLOGY.

"Progressive lenticular degeneration" is the nosological term with which I propose to characterise the disease. Of the other terms which have been proposed that devised by Gowers is the only one which has any claim to recognition. The disadvantages of "tetanoid chorea" outweigh its advantages. It was coined at a time when the pathology of the disease was utterly obscure, but pathology, where possible, in preference to clinical medicine, should be called on to supply the name for a disease: further, tetanoid chorea, even considered clinically, is misleading. The condition is not analogous to chorea at all, and "tetanoid" is not sufficiently distinctive. Anton proposed the term "dementia choreo-asthenica", which no doubt characterised his case accurately enough, but, from the point of view of the certain cases, to include "dementia" in the title gives that symptom undue prominence, even admitting that dementia is the correct term to employ. Objection, too, may be taken to the use of the epithet "asthenica". The asthenia of progressive lenticular degeneration is very different from that of neurasthenia or of Addison's disease.

It seems to me that in progressive lenticular degeneration we have a descriptive term which is brief, distinctive, based on pathological data, and at the same time non-committal, inasmuch as it says nothing as to the actual nature of

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the disease. What I have done is to select what is by far the most striking pathological feature of the disease and utilise it for purposes of nomenclature, and when we remember that twenty years ago Ormerod and Homen noted exactly the same condition I think we shall agree that the term is amply justified. In any case, it may remain till subsequent investigation find a better.

Progressive lenticular degeneration may be defined as a disease which occurs in young people, is often familial but is neither congenital nor hereditary: it is essentially and chiefly a disease of the motor system, and is characterised by tremor, dysarthria, spasticity and contractures: with these may be associated certain symptoms of a psychological nature. It is progressive and after a longer or shorter period fatal. Pathologically it is characterised predominantly by bilateral degeneration of the lenticular nucleus, and in addition cirrhosis of the liver is constantly found, the latter morbid condition rarely if ever giving rise to symptoms during the life of the patient.

## 2. ETIOLOGY.

### a. Age.

Of those whose cases have been recorded as instances of progressive lenticular degeneration, the age of the youngest, at the onset of the disease, was 10 years: of the oldest 26. The average age, calculated from the series of 11 cases, is 15. In the more acute cases the disease made its appearance at a relatively earlier age than in the more chronic cases, but that it is essentially a disease of adolescence may be definitely concluded from the material before us.

### b. Sex.

Of the 11 cases, 7 were males and 4 females. In no one of the 7 male cases was there any sign of physical infantilism, as far as one can gather from the published records and from observation in my own cases. Of the 4 female cases, one of the patients, in whom the illness began at the age of 17, had never menstruated: in the other 3 the catamenia were established before the onset of the illness: thereafter in each case menstruation became irregular or ceased.

3. Heredity.

In no one of the series is there any definite history of family nervous disease such as can be conceded to be of any significance. Such details as a neurotic temperament in a parent, or consanguinity of parents, or weakmindedness in an uncle, or alcoholism in a grandparent's old age, are etiologically negligible. They are not sufficiently precise to be of value. Nor is there a history of any special diathesis in the families concerned. Both similar and dissimilar heredity may be excluded in the case of progressive lenticular degeneration.

It is a curious fact, however, that of the 11 cases of the disease which we are using for statistical purposes, no fewer than 8 are familial cases, and it is also a curious fact that the families concerned are large ones.

In family K. (Homen) there were 11 children, and one miscarriage: the first, third, and fourth were affected and ~~two~~ died of the disease.

In family M. (Gowers, completed by Wilson) there were 14 children, and several miscarriages: the first, fifth, and eighth were affected.

In family P. (Wilson) there were 6 children, and no miscarriages: the first and second were affected:

Passing next to the families in which only one member was affected:

In family T. (Wilson) there were <sup>9</sup> children, and no miscarriages: the eighth child was the patient.

In family S. (Ormerod) there were 4 children, but it is not stated in which order they came: one child was affected: there were one or two miscarriages.

In family J. (Ormerod, Euzzard, Wilson) the patient was the only child, and there were no miscarriages.

It is possibly of some importance that in all the familial cases the eldest members were affected, and that, on the whole, the elder members suffered while the younger escaped.

The exact significance of the familial element, however, is debatable and difficult. In families M. and T. there are members living and healthy today who are older than their

brothers and sisters who suffered from the disease. All that we may conclude from the fact that the familial element does enter largely into the disease is that there must be some special predisposition which cannot as yet be expressed in more definite terms.

4. Distribution.

It is premature, of course, to generalise where there are as yet so few recorded instances of the affection. For documentary purposes, however, we may note that the K. family belonged to Finland, and lived in the country: the M. family have always lived in the east end of London: most of the P. family were born in Italy, of English parents: the T. family is English, and from the country.

5. Predisposing causes.

The generalities to which the observer in search of predisposing factors is too often driven, in ignorance or desperation, or both, need not delay us. It may once and for all be stated that in my own series of cases there is neither a subjective record nor objective evidence of syphilis as an etiological factor. Nor is there in any of the other reported cases. Homen made a most exhaustive examination of the members of his K. family but was unable to obtain any definite or unequivocal data in favour of the syphilitic hypothesis. It is true that with the Wassermann reaction to aid us opportunity should be taken to apply it in any future instances of the disease: personally I was not in a position to take advantage of it in the only one of my cases which I had the chance to examine after the test was demonstrated to be of value.

There is no evidence that alcohol may be considered as a predisposing cause. One of the M. family suffered from typhoid fever 7 years before the onset of the disease, and another had an attack of the same fever about a year before the appearance of lenticular symptoms. Yet these facts cannot be held to be of any importance.

Reference will be made in another section to the interesting circumstance that one of my patients (S.T.) had an attack of jaundice some years before the lenticular symptoms were noticed.

6. Exciting causes.

These are really conspicuous by their absence. It is noted with almost complete unanimity that the disease came on apparently without any exciting cause and in an insidious manner. Speculation therefore is otiose.

One thing is certain, however, in the midst of much that remains obscure. In my own series of cases the patients were of normal mental and physical development before the onset of the disease, and the same remark is made by other observers. If the disease represents a degenerative tendency, an abiotrophic defect--which I do not think probable at all--then it is curious that it should single out individuals who seem endowed with mental and physical gifts that are well up to the average, and who in earlier years have without exception given promise of full development.

8. SYMPTOMATOLOGY.

In progressive lenticular degeneration two clinical types may be distinguished,, one acute and the other chronic, or subacute. Symptomatologically there is little difference between the two: the former is associated with some, it may be considerable febrile disturbance, and the type of involuntary movements, which form a feature of every case of the disease, is not entirely identical with that of the more chronic cases.

Of the series of 11 cases there are 3 which may be placed in the first category: in these the duration of the illness was 4 months, 6 months, and 12 months respectively. In all, more particularly in the first, a high irregular temperature was present for a more or less lengthy period: emaciation was unusually rapid in all: the symptoms generally speaking were severe almost from the beginning, and the whole appearance of the patient suggested that he was acutely ill, as with a fever or any toxi-infective condition.

In the more chronic cases, of which there are 8, the patient's nutrition was often well maintained, sometimes for years, and he experienced a sense of wellbeing, for a long time at least, which was not belied by his looks.

In the main features of the disease, however, acute and chronic cases alike present a symptomatological aspect which is unmistakable.

If we scrutinise the record to discover the earliest clinical symptom we do not find any special distinctive feature, for in several instances more than one symptom is noted as having resulted in attention being drawn to the patient. In several, notably the K. family and the P. family, the earliest symptoms were psychical rather than physical: in the remaining 6 they were physical rather than psychical. Whatever be the first symptom to make its appearance it is not long ere the disease establishes itself by a series of symptoms which have developed with astonishing similarity in all.

Progressive lenticular degeneration is a motor disease par excellence: its most striking and characteristic symptoms are on the motor side.

a. Involuntary movements: Tremor.

Involuntary movements, and in particular tremors, form one of the outstanding features of the affection. In all my own cases tremor was one of the earliest symptoms, as it was one of the most marked: in Homen's family tremor was equally pronounced, as in at least two of the M. family, i e in 8 of the 11 cases. In the other 8 it does not appear to have been quite so prominent, although present.

In the recorded cases the tremor has been a true tremor, i e it has consisted of a regular, rhythmical, alternating contraction of a given muscular group and its antagonists. The rate is variable, usually within the limits of from 4 to 8 times a second. It is increased as a rule by excitement, or if attention is drawn to it, or by voluntary effort. Thus it was always brought out well in the finger-nose test. At other times it appeared to be to a certain extent under the control of the will, for by the exercise of volition it can be somewhat diminished, though this is by no means a constant phenomenon. Thus when one of my patients grasped my hand tightly the tremor with which the effort was at first accompanied became less as the patient's grasp increased in power, but on the other hand if such was the case the tremor was likely to appear as an "overflow" in some other place, e g the leg. Sometimes when the patient was left entirely to himself a perfect riot of tremor could be observed. In most cases the tremor is more marked peripherally than proximally: i e it

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affects the fingers and hands, or the toes chiefly, and it also usually affects these segments first. Thus bad caligraphy was frequently remarked as one of the early signs of the disease.

The range of the tremor is usually fine, at least at the outset: with volitional movement the excursions become wider, and as the disease progressed the tremor, according to the experience of all the observers, becomes worse in every way. In one of Homen's cases, however, with increasing contracture the tremor rather diminished, but came in "attacks" in which the whole of the body was involved. In the later stages of the affection it is usually incessant, and involves head and trunk as well as the limbs. In one of my own cases I was able, by relaxing every joint and putting the limb into a position of complete muscular rest, to make the tremor disappear, but the moment the support was removed and the patient had to innervate his limb again the tremor reappeared and increased with great rapidity up to its maximum. As far as one can gather it usually or always disappears during sleep.

In some of the cases the tremor has been less noticeable than in others, and in one or two it is reported to have affected the lower extremities more than the upper. The tongue is often tremulous, but this is not the tremulous fibrillation of such a condition as ~~general~~<sup>bulbar</sup> paralysis: on the contrary, while the tongue is being protruded there is tremor, but when the former is fully protruded the latter disappears.

In one or two of the older cases what caught the eye of the observer was not so much tremor as what is described as "tonic" or "clonic spasms". Thus in the case of S.M. (Gowers)--one of the acute cases--both arms presented slowly changing tonic spasm, greater in the left. Sometimes the movements were quicker, and they were always increased by an attempt at volitional movement. In the legs there were similar involuntary spasmodic movements, in the trunk, and indeed in the musculature generally. There were occasionally paroxysmal exacerbations of such spasms, of a few minutes' duration. In the case of Walter S. (Ormerod)--another of the acute cases--the muscles were in a state of tonic spasm, and on the slightest forcible movement clonic spasms were produced. In the case of Alfred K. (Homen)--this was a chronic case--it is

specially noted that in addition to the tremors "during the last few weeks of life tonic and clonic cramp attacks occurred, of short duration, at the longest a minute". On the other hand, in the case of Charlotte M., the sister of Sydney M.--also an acute case--the involuntary movements were pure tremor.

It may be said, then, that in the chronic cases tremor was constantly present, was pronounced and continuous: in two of the acute cases "tonic and clonic spasms" were met with: in the other acute case the movements were those of tremor.

b. Rigidity: Spasticity.

Every one of the series of cases has been characterised by the presence of rigidity or spasticity, which has often reached an extreme degree. It has always been steadily progressive, and has resulted in the patient being reduced to a state of utter helplessness, unable to use his hands, unable to turn in bed. As a rule it has begun in the limbs, and in the cases which I have had opportunities of observing it has been more pronounced at the larger joints, possibly because here the muscles are naturally stronger and larger. The simplest way to convince oneself of the existence of this spasticity is to take one of the limbs, say the arm, and to impress on it passive movements of alternating flexion and extension at the elbow. Whether one flexes or extends one is always conscious of a considerable degree of resistance in the opposing muscles, so that quick to and fro movement of the forearm is simply an impossibility. The muscles always feel firm on palpation, and even when the limb is put into such a position as to relax any given muscle as far as possible it can always be felt to be in a state of hypertonicity. Hence ensued an extraordinary of immobility in the advanced cases: the face was fixed, expressionless or smiling stiffly, and was consequently noted as being "silly" or "idiotic". The head and neck were equally fixed: even in the recumbent position the sternomastoids did not relax. The rigidity of the trunk was such that maintenance of equilibrium became a matter of the greatest difficulty. As one of my patients was sitting on the edge of his bed he slowly fell backwards,

a helpless mass, with his legs in the air, quite unable to relax his hypertonic muscles or to use them to recover his balance.

As a rule the predominant hypertonic muscles were the flexors, though to this rule there were certain exceptions. In most instances the fingers and wrists were flexed, the elbows flexed, the arms adducted at the shoulders: the toes were curled under the feet, the feet turned in, the heels drawn up, the legs flexed at the knee and hip. In one of Gowers' cases, however, the limbs were extended at the knees, and at the elbows, and the arms were rotated inwards so that the palms looked backward outwards. It would appear that even in sleep the rigid condition of the musculature did not disappear.

It is important to note, as will already have appeared, that in these cases we are dealing with a true hypertonicity of the muscles, involving both synergic and antergic muscles simultaneously. The rigidity is not due merely to <sup>an</sup> inability to relax an antagonist, or to predominant flexor tonicity. As far as can be seen there is a generalised condition of increased tone in all the muscles indiscriminately, and the mere fact that this tonicity leads to the adoption of a flexor attitude means no more than that the latter are the stronger muscles.

The solitary muscles of the body that did not appear to be implicated in this condition were the extrinsic ocular muscles. In my own cases their volitional movements were quick and free. Gowers, however, noted that in the case of S.M. the movements of the eyes were normal, but at times the balls rolled upwards. Ormerod remarks that in his patient the right eye "worked", but possibly this means that the muscles round the right eye were involved in the spasm which implicated the right face. In the case of D.P. there were involuntary rolling movements of the eyes a few days before death. Otherwise, no voluntary muscle or group of muscles seemed to be exempt. In my opinion we must attribute the dysarthria and dysphagia if not wholly at least in great part to this rigidity. It has its most striking exemplification in the open mouth of the patient. Compare figure / taken in 1886, with figure 22, taken in ~~1888~~ 1910; and note the

indifference to the fact as expressed in the patient's face. He seems to be as unaware of the depression spasmodic of his inferior maxilla as he is indifferent to his tremor or oblivious of his sialorrhoea.

c. Contractures.

It is but a step from rigidity to contracture. Contractures are as constant a feature of progressive lenticular degeneration as the involuntary movements. It is remarked of every patient that his or her limbs were grossly contracted towards the end. As a rule the contractures begin in the distal segments of the limbs, and in various figures which have been given in the clinical section they are exemplified. As the disease progresses so do the contractures until they become extreme. It may be impossible to straighten the limbs out. We must note two stages in the process, or rather two causes for it. The first is the fixation of a limb in a particular position from hypertonicity of the muscles. This first stage is well illustrated by my case III. The patient looked as though his limbs were contracted in the attitude of double hemiplegia, or paralysis agitans, but by dint of patient passive movement it was possible to extend them almost completely. Figures 24 and 25 ought to be compared in this connection. In this first stage we are dealing with contracture-attitudes from hypertonicity, a purely nervous phenomenon. But secondly, as the result of the prolonged maintenance of fixed attitudes, myogenic contracture sets in, owing to permanent approximation of the origin and insertion of the muscles. This naturally shows itself most in the muscles which are strongest and which have caused the adoption of a given contracture-attitude: hence if this be one of flexion the flexion contracture is accentuated, and the limb gets into a distorted condition from which no amount of passive movement can correct it. Thus we read that in one case the knees were right up on the patient's abdomen: in another the lower extremities were flexed at all joints: in a third the arms were permanently contracted at the finger joints, wrists, and elbows. And so on.

It is apparent, of course, that in the matter of "tonic and clonic spasms", tremor, spasticity or rigidity, and con-

tractures, we are dealing with pathological conditions intimately allied to each other. We shall discuss their pathogenesis later, but at this point it is well to mass them together, as they may be present in varying degree in any given case, and it is desirable we should realise that this possible variability, so far from confusing the diagnosis, is really to be expected, from the nature of the disease.

d. DYSARTHRIA: Dysphagia.

Dysarthria has been present in every one of the series of 11 cases, and in all it has advanced until it has resulted in more or less complete anarthria, the patients being unable to articulate intelligibly a single word or syllable. The dysarthria is characterised by the slurring element, without the staccato element, of the speech of disseminated sclerosis: the greatest difficulty is with consonants, and there is a frequent tendency to abbreviate the ends of words. When at its worst the patient may be able to phonate when articulation is impossible, hence unintelligible sounds may issue from the throat. Homen, Gowers, and Ormerod have remarked on involuntary noises or sounds or moans escaping from the patient. In my own cases this was not perhaps quite so marked.

The defect is in no wise comparable to that of general paralysis, and so far from there being facial overaction, as in the latter condition, we find the sounds escaping from a mask-like, immobile face and mouth.

Dysphagia is as constant as dysarthria, and in a majority of the cases has come on simultaneously with it.

e. Muscular weakness and emaciation.

While progressive emaciation has marked the course of the disease both in the acute and the chronic cases there is no record of local muscular atrophy. The wasting has affected the musculature generally, and is associated, partly at least, with the contractures, and immobility of the limbs. Atrophy from disuse is a well recognised condition. At the same time, some of the emaciation must be attributed to a profound disturbance of metabolism, especially in the acuter cases, where although the duration was shorter the degree of

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wasting was if anything more profound.

In spite of the tremors, rigidity, and contractures, in the majority of the recorded cases a degree and sometimes a considerable degree, of voluntary power has remained. Several of the previous writers have been struck by the apparent incongruity between the two facts, and the significance of the contrast will be discussed in the section on the pathological physiology of progressive lenticular degeneration. It is sufficient to note at present that in the early stages, at least, considerable muscular power may be retained, and voluntary movements may be of normal range, even though the patient gives the appearance of helplessness. In each of my own three cases the patients were still able to walk at a time when their appearance suggested complete spastic paralysis.

Muscular weakness, however, is undoubtedly one of the symptoms of the disease. Volitional movements may be good in range but they are usually resisted with comparative ease. This muscular weakness, also noted by previous observers, is not to be confused with clumsiness or awkwardness from hypertonicity or tremor. There is intrinsic muscular asthenia: the patient is incapable of any sustained effort: he cannot close his eyes tightly for any length of time, cannot keep his tongue protruded, cannot maintain his grasp. It may be said, without risk of being misunderstood, that volitional innervation is defective while involuntary innervation is exaggerated.

Admitting, however, the muscular weakness, we should not use the term "paralysis" at all. Paralysis, where motion is concerned, ought to be confined to diseases of the pyramidal system. In the case of progressive lenticular degeneration the motor symptoms are foremost, but except where contractures or rigidity forbid it the patient is able to move his limbs. He is not, therefore, "paralysed". We have not got a medical term to indicate the specific motor helplessness resultant on disease of the extrapyramidal motor system.

f. Sensory.

Compared with the motor, the sensory symptoms are minimal. On the subjective side, Horen observes that his patients suffered from occasional pains in the body and limbs, more especially the legs, and mainly at the beginning of the disease. Ormerod states that his patient had at one time paroxysms of pain, evidently associated with spasmodic contractions of the muscles, skin no doubt to painful cramps. The importance of these it is difficult to gauge: in any case the symptom is far from common and may be relegated to a secondary place. Objectively no change in sensibility is discoverable. All of my cases were carefully examined from the sensory standpoint, with a negative result.

g. Reflexes.

In a pure case of the disease, such as my case III we do not find any definite alteration in the tendon reflexes: they are active, but not exaggerated. It not infrequently happens that owing to the contractures they are with difficulty elicited. There is no ankle or other clonus. From the point of view of the cutaneous reflexes the only cases which have been examined with the help which knowledge of the significance of the plantar reflex gives are my own three. Of these case I had an extensor response on one side, but in view of the undermining of the internal capsule this is easily accounted for. Nevertheless, it must be remarked that there is no descending degeneration in the pons, medulla, or cord. In case I, moreover, the abdominal reflexes were diminished on both sides. In cases II and III, which, clinically, be it observed, were just as severely affected as case I, the abdominal reflexes were normal--in case II they were readily obtained a few days before death--and there was a double flexor response. At the time when I last examined the patient whose case is no. III his condition was every whit as advanced as with case I, yet the cutaneous and deep reflexes precluded the possibility of organic disease of the pyramidal tracts. This fact is of the utmost importance from the standpoint of pathological physiology.

In every case of the series the organic reflexes are

noted as having been impaired towards the end: in fact, most of the patients have sooner or later become "wet and dirty". This is not to be taken as indicating local sphincter defect such as one meets with in disease of the lower part of the cord: on the other hand, I am not sure that it ought without further consideration to be attributed, as some would have it, to the mental deterioration of the patient, and to be interpreted as a sign of dementia. It seems to me that it may very well be due, in part at least, to increasing imperfection of voluntary control over the muscles.

#### h. Mental symptoms.

Of considerable interest are the psychical symptoms of progressive lenticular degeneration. It is a noteworthy fact that some form of mental change or impairment is specifically referred to in at least 8 of the 11 cases: its importance therefore must not be underestimated. On the other hand this mental impairment is highly variable both in degree and in kind, and therefore calls for some analysis.

Of Gowers' two patients one did not present any definite mental symptoms: at least they are not referred to as such. The other is said to have been listless, lethargic, emotional and easily excited to laughter. Ormerod's patient seemed "silly": he became noisy and apparently idiotic: "his mental condition seemed to get worse, and he lay howling all day long". Homen's 3 cases were all characterised by what he calls dementia: the symptoms he mentions may be thus generalised- listlessness, slowness of mental processes, "simple-mindedness", failure of memory and of mental powers, emotionalism, stupid and idiotic facial expression, &c. My own case I evinced a change in her disposition: she became restless and unable to settle to anything: she was easily provoked to laughter, her manners were childish, her mental powers diminished: but on the other hand her memory remained good, at least for a long time after the disease was established, and on the receptive side little defect was observable. In case II the earliest symptoms were that the patient became rather untidy in her dress, failed to obtain the same number of marks at school as formerly, later developed transient delusions, became emotional, laughing at nothing,

"her younger sister had to be a mother to her", such was her childishness. In case III the first symptoms were those of a moderately severe toxic or exhaustion psychosis, consisting in delusions, hallucinations of hearing, excitement, &c. They passed off entirely, never to ~~return~~<sup>return</sup>, but within a year the characteristic symptoms of progressive lenticular degeneration made their appearance, and in the case of this patient similar mental changes subsequently occurred to those already described in the case of his sister. He was emotional childish, docile, facile; "he looked a perfect idiot": yet here also, while undoubtedly there was impairment of mental power, to a considerable extent, on the efferent side little defect was to be seen. His memory and powers of recognition were for a long time unimpaired: his observation and perception were astonishingly quick. In the case of Christopher J. -- my case V--instead of remaining bright and intelligent, he became dull and stupid: he was very emotional, at one time laughing, at another crying: he was slow in answering questions, and in understanding everything that was said to him, but on the other hand he did everything correctly that he was asked to do.

In view of the frequency, then with which psychical symptoms are encountered in the disease, we must admit they form an integral part of the clinical picture. When we endeavour to specify the cardinal element or elements in them, or to classify them, we experience some difficulty. If we are to employ the term "dementia" to characterise them, we must remember that this dementia is limited. I examined each of my patients from the point of view of agnosia and apraxia, but in one of them were these symptoms present. Now it is in the ordinary dementia of senility, of general paralysis, and to a less extent in dementia praecox, that these symptoms are most common, especially in the first of these. Disorientation in time and space is another of the common features of dementia, but in more than one of my cases if present at all it was slight. We cannot compare the "dementia" of progressive lenticular degeneration to the steady mental involution of senile dementia or of dementia paralytica, and it can be readily distinguished from dementia praecox.

If an attempt may be made to summarise the mental defect

we may remark that there is:

1. narrowing of the mental horizon: the patient is unable to add to his store of mental images: his capacity for retaining impressions is impaired: but within his limits his powers of recognition and perception are good. In this respect the mental condition is not unlike what is found in Huntington's chorea.

2. Facility, docility, and childishness: he is easily pleased, tickled, amused: he is preternaturally cheerful, in view of the seriousness of the disease, but this is indicative of failing insight: he is unable to deliberate or pass judgment on what is presented to him: "open your mouth, Mr P." and he opens it obediently and at once, to the accompaniment of roars of laughter from himself and his fellow-patients.

3. Increase of emotionalism and of emotional reaction.

On the other hand it has been my experience in this disease that the mental symptoms are not so severe as the remarkably silly appearance of the patients might lead one to suppose, and further, they do not progress *pari passu* with the steady downward march of the other symptoms, at least not necessarily.

i. Symptoms referable to other systems.

The only system to which reference need be made is the alimentary. Hemen's patients had occasional sickness, one of them frequent vomiting. All had loss of appetite as one of the initial symptoms. Neither Gowers' nor Ormerod's patients showed any gastro-intestinal symptoms, if we except what seems to have amounted to bulimia in the latter case, at one stage of the illness. No one of my patients presented any symptoms referable to the alimentary system, except case I *sub finem*. With the exception of the case of C.J., no. V in my series, not a single one of the patients was found during life to have definite symptoms or signs of disease of the liver, i e while lenticular symptoms were present. In case I of my series it may be remembered that an attack of jaundice occurred some years before the onset of the lenticular disease, and this patient suffered from severe hæmatemesis just before death.

From every point of view the fact that ten cases show

advanced hepatic cirrhosis on postmortem examination which have never presented symptoms of it during life, is remarkable.

j. Negative symptoms.

If negative symptoms are ever of any value certain of them may be tabulated here.

In progressive lenticular degeneration:-

the optic discs are normal:

the pupillary reactions are normal (in onylone case were the pupils said to be sluggish to light):

there is no nystagmus:

the palate moves on phonation and reflexly:

there is no fibrillation or localised amyotrophy:

there are no cerebellar symptoms:

there is no impairment of sensibility:

the reflexes are not those of pyramidal disease.

There are certain general features in the symptomatology of the disease to which attention must be directed, as they help to an understanding of the condition. These are, briefly, the pronounced variability in the symptoms from time to time, and their resemblance to what is called "functional" disease. We shall discuss these points in a subsequent section.

#### 4. PATHOLOGY.

In analysing and synthetising the pathology of ten cases of progressive lenticular degeneration we are confronted with a difficulty. In 3 cases the examination of the central nervous system proved negative, viz. S.M. and C.M. (Gowers) and C.J. (Ormerod, Buzzard, Wilson). In the case of W.S. (Ormerod), Homen's 3 cases, and my 3 cases, symmetrical bilateral lenticular degeneration was found, i e in 7 out of 10 cases, a sufficiently large proportion to justify one in expressing the opinion that a minute microscopical examination of the corpus striatum in the other 3, the negative, cases, might have revealed some pathological changes. In the case of S.J. only a macroscopical examination of the brain was made, apparently, and it was negative. In the cases of S.M. and C.M. pieces of the cortex, cord, nerves and muscles,

were examined microscopically with a negative result. Now in view of the fact that in similar structures, examined in each of my 3 personal cases with modern histological methods, no definite changes of any significance could be detected, it is little wonder that the examination of 22 years ago was negative. The point is that in the acute cases it is quite possible the only lenticular change may be a microscopical one, if indeed it is to be seen at all. We have the evidence of Ormerod's case--an acute one--to show that pathological changes in the lenticular nucleus may be recognised after a few months: on the other hand, in the case of C.M. the duration was 12 months, and a priori had any obvious lenticular change been present it was sure to have been detected. We may argue by analogy from two of my series, viz case I and case III. In the former the changes were much more advanced than in the latter, yet clinically no such difference in degree obtained. Hence we must not judge of the severity of the clinical symptoms by the degree of pathological and structural change found at the autopsy. Accordingly, in the case of C. M. the function of the corpus striatum may have been profoundly disturbed without much structural change being recognisable.

In the 7 cases with positive findings in the central nervous system the appearances are so similar that they afford striking proof of the selective action of some morbid agent. In all, with the exception of my case II, where the examination was incomplete but where the assumption that the condition was analogous to the others is abundantly justifiable, there is bilateral, symmetrical, degeneration of the putamen and of the globus pallidus to a less extent. Various degrees of this degeneration are found, from discolouration and sponginess of the nucleus, through shrinkage and atrophy to complete disintegration and excavation of the ganglion. Neighbouring structures are involved to a much less extent: the caudate is often rather shrunken, but never disintegrated as is the lenticular nucleus: the optic thalamus is practically always normal, and in pure cases the internal capsule is intact from end to end. Sometimes the external capsule is somewhat degenerated; the claustrum is usually normal, and the convolutions of the island of Reil normal, though

sometimes the latter show diminution of cortical fibres. Apart from the degeneration in the lenticular nucleus the changes in the brain are insignificant. There is no evidence of established meningitis: sometimes slight leptomeningeal thickening is found, patchily distributed. The cerebral cortex offers little definite alteration: Homen found the frontal cortex possibly somewhat thinned, with slight diminution of myelinated fibres, but there is no wholesale chromatolysis by Nissl's method in any of the modern cases: on the contrary, and more particularly in the motor area of the precentral convolution the cortex is practically normal. The Betz cells are well up to normal numbers, and stain well. There is no sign in the modern cases of any small cell infiltration anywhere: Homen found slight traces of this in his cases, but remarks it is nothing like so pronounced as one meets in dementia paralytica: Ormerod found small cell infiltration in the lenticular nucleus in his acute case.

The microscopic changes in the lenticular nucleus in the chronic cases are not accompanied by small cell infiltration at all. They consist of glial overgrowth which afterwards disintegrates and breaks down: the fibres and cells of the normal nucleus disappear: <sup>n</sup>Körnchenzellen are frequently present in numbers. Even when the cavity formation is extreme there are no signs whatever of obliterative endarteritis in the blood vessels, the perforating lenticulo-striate vessels and their branches: on the contrary they are if anything thinned, and are sometimes hyaline. Occasionally their adventitia seems thickened: the intima never. Round the vessels ~~gaping~~ gaping spaces make their appearance, possibly from shrinkage of the nervous tissues, hence the nucleus gets a finely wormeaten appearance: this is a stage previous to cavitation. In Homen's cases more definite disease of the blood vessels was found than in my cases: he notes that they were irregularly sclerotic, i. e. had patches of degeneration in their walls, with small collections of granular material between the coats of the vessels; sometimes they were hyaline: sometimes the granular material bulged into the lumen of the vessel. Changes of this sort he found in all his cases, nor were they confined to the arteries of the basal ganglia.

The pons, medulla, and cord

are uniformly negative from the pathological point of view, any changes which they may present being entirely of secondary importance. This is true also of nerves and muscles.

In the modern cases certain degenerations consecutive to the main lenticular wasting can be traced. These are, in advanced cases, degeneration of the ansa lenticularis, relative atrophy of the corpus Luysii, partial degeneration of the lenticular bundle of Forel (faisceau H) and of the strio-luysian fibres, degeneration of strio-thalamic fibres.

Two other organs are commonly affected in this disease, viz the liver and the spleen. The liver is always cirrhotic, and I do not suppose we can have a case of the disease in which the liver is not thus affected: in other words, it is essential. In several of the cases the spleen is reported as having been enlarged, but without any other change.

The cirrhosis of the liver is always advanced, and strikingly apparent. The organ is usually rather smaller than normal, but not constantly so. It is firm, hard, tends to preserve its shape, and presents the appearance of rounded nodules of tissue clustered together, of the size of hazel nuts or larger, separated by depressed cirrhotic bands. The organ is never bilestained: but is often rather lighter in colour than usual. Microscopically we find normal areas, necrosed areas, fattily degenerated areas, and actively regenerating areas, scattered irregularly through the organ. The type of cirrhosis is mixed, i e it is mostly multilobular, in some places monolobular, and occasionally there are indications of intralobular cirrhosis. So called hypertrophying bileducts are often seen in the new connective tissue formation. Finally, this cirrhotic new formation is often very narrow, and in some places is cellular, in others more fibrous.

##### 5. DIAGNOSIS.

To anyone familiar with the disease its symptomatology and course must appear so characteristic that he may well think it a morbus sui generis. It offers so many features that are almost unique that it is difficult to see how confusion might arise. The acute cases, for instance, which run a course of a few months, are in my opinion really unique. They do not offer analogies with any other nervous condition

with which I am acquainted.

Of the affections with which progressive lenticular degeneration might conceivably be confused, we may first of all mention disseminated sclerosis. Yet the resemblance is but a superficial one. In the former we do not find nystagmus, optic atrophy, amblyopia, paraesthesiae, objective changes in sensibility, absent abdominal reflexes, extensor responses and ankle clonus. The dysarthria in the two affections is not identical: the rigidity of disseminated sclerosis is rarely if ever so universal or complete as in the other: contractures do not form so essential a feature of the symptomatology. The course of disseminated sclerosis is much more variable and very often longer in duration. It is only in the early stages that confusion is possible, when there is as yet absence of organic signs, so called: a patient who suffers from intention tremor and slight dysarthria is certainly difficult to place when other signs fail.

It is scarcely worth while mentioning bulbar palsy, or pseudobulbar paralysis: the differential diagnosis should present no difficulty. Pseudobulbar paralysis is a disease of the pyramidal tracts, of that part of them which comes from the lower part of the motor area via the genu of the internal capsule to the pontine and bulbar nuclei, and if the case is a pure one, the symptoms of dysarthria which the patient presents may resemble those of progressive lenticular degeneration, and so may the dysphagia, and possibly the emotionalism, but there the resemblance ends. If, however, the patient with pseudo-bulbar palsy should also have bilateral involvement of the pyramidal paths for the limbs, that is to say if his case is one of double hemiplegia, no doubt he will present spasticity in addition, but on the other hand the signs of involvement of the pyramidal path which the reflexes furnish will reveal the nature of the condition. I do not see how the disease which forms the subject of this Thesis can possibly be confused with bulbar paralysis.

Paralysis agitans is a disease in several ways closely resembling progressive lenticular degeneration. The age of onset in the former, however, is by itself almost sufficient for differential diagnosis. The latter is a disease of youth. Paralysis agitans is very much more chronic, and speaking

generally the attitudes of that disease are just as specific, in their own way, as those of the other, from which they differ considerably.

Juvenile general paralysis may be mentioned, only to be dismissed.

#### 6. DURATION AND PROGNOSIS.

The experience of all who have had opportunities of following the course of the disease is that it is invariably fatal. We must be allowed the remark, however, that in most of the cases the diagnosis was not made till the postmortem table, and it is conceivable that cases of the disease, not being recognised, may have recovered. I do not think this in the least degree probable. The trend of the affection is always steadily downwards: remissions are so insignificant as scarcely to be worth the name. Therefore the outlook, once a sure diagnosis is made, is always serious and may soon become grave. The duration of the 3 acute cases was 4, 6, and 13 months. The shortest of the more chronic cases lasted  $2\frac{1}{2}$  years: the longest case on record is one of Homen's, which went on for 7 years. The average of my 3 cases is  $3\frac{1}{2}$  years. The average of 8 chronic cases is almost exactly 4 years.

#### 7. TREATMENT.

What can be said of the treatment of the disease? Its nature must be elicited before treatment can be lifted from the empirical to the rational level. What has been done by those who have had charge of cases has been essentially symptomatic and palliative.

## CHAPTER V.

### NATURE AND PATHOGENESIS OF THE DISEASE.

When we leave the realm of facts to face the problem of the nature and pathogenesis of progressive lenticular degeneration our difficulties commence. One's first impression of the disease is that it is so different, apparently, from most familiar morbid types, as to constitute a class by itself, and that therefore we have nothing with which to compare it. True it is that in this disease we have, I believe, the first definitely established morbid entity whose most striking characteristic is a specific association between disease of one of the viscera and of a particular part of the grey matter of the central nervous system, viz. the lenticular nucleus. But we shall find that the mystery is perhaps not so impenetrable as may appear at first. There are certain symptoms of the disease which furnish a clue to its nature, and there are certain analogies from other diseases, as we shall see, which aid us materially in the attempt to explain its pathogenesis.

We may begin by quoting the <sup>1</sup>opinions of the older writers. To the clinical acumen of Gowers, Ormerod, and Homen we owe an infinite debt, for each, recognising he was dealing with a disease sui generis, examined his cases and published the record with a fulness of detail and richness of illustration which leave nothing to be desired. Today we have entered into their labours. I count myself fortunate to be able to have access to the original notes of some of these cases, for a link is thus formed between the old and the new which materially enhances the scientific value of each.

Gowers, the observer of the first recorded case, writes as follows: -

" In the two cases I have recorded no symptom of inherited syphilis was present. The probability of inherited syphilis as the cause of the malady of the

nervous system rests entirely on the significance of the hepatic cirrhosis, whether or not syphilis is the only cause of the juvenile non-alcoholic form. Even the assumption of this causation leaves the direct pathology as mysterious as before. It is inconceivable, in the first case, and most improbable in the second, that any coarse morbid process could have existed and have escaped the careful examination to which the nerve-centres were subjected. The facts seem compatible only with a blood state as the cause of the symptoms.

But if a blood state caused the symptoms, the question arises: Were this and the cirrhosis of the liver the common effects of one cause, or can the blood state have been the effect of the hepatic disease? Anomalous as the last assumption may seem, it cannot be hastily dismissed. In connection with the difference in the character of the symptoms, there is also the association of the higher fever in the second case with a greater degree of disease of the liver. Toxic blood-states may be complex in causation: one derangement of the chemical processes of the system may induce others, the effects of which co-operate with the first."

Ormerod makes the following remarks, in addition to what has been already quoted from his paper: -

" The German cases which we shall quote presently make it probable that the softening in the neighbourhood of the lenticular nuclei had some essential connection with the disease: but it will hardly explain the whole course of symptoms.... Professor Homen apparently would explain the whole of these morbid appearances as being due to inherited syphilis, though there was no clinical evidence of this. Upon the intimate nature of the disease, however, an opinion can hardly be given till more observations have been made..... Whether it is right to put the cirrhosis of the

liver in as prominent a place as I have done in the heading of this paper, must be judged by the comparison of other similar cases, but I think it can hardly be counted as a coincidence."

Homen, in the course of his remarks on the pathogenesis of the disease, says that everything ~~suggests~~ suggests the primary lesion is the vessel degeneration, and as there is no sign of acquired syphilis, and indeed, apparently, no possibility of its having been acquired, he is driven to the conclusion that the syphilis, which he postulates for the vessel degeneration, must be congenital or hereditary. Yet he is doubtful about his own thesis. In cirrhosis of the hereditary syphilitic type the pathological picture is different from that of his cases, and clinically ascites is practically constant, whereas it was absent in all his cases. He concludes in the following guarded terms: -

"If we consider, finally, all the pros and cons, we must conclude, taking all the circumstances into account, that even though positive evidence is wanting yet in all probability we are dealing an unusually late manifestation of hereditary syphilis. This is more than a mere predisposition, and since the probability is that at the time of the begetting of the children the syphilis of the parents [there is, of course, no evidence that the parents had syphilis] had disappeared, or almost disappeared, it follows that its effect on the offspring is delayed, and not characteristic; it appears more as a special form of disease to which the syphilis bears only a remote relation.."

Apparently Homen feels that the disease ought to be considered a parasyphilitic condition, although he does not actually use the expression, for he refers both to tabes and general paralysis in this connection, viz. that of the remote action of syphilis.

If now we turn to an independent consideration of the clinical facts and pathological data which a study of all the cases affords, in particular the recent ones, what can we learn thereby as to the nature of the disease?

1. IT SEEMS CERTAIN THAT THE DISEASE IS NOT DUE TO A CON-  
GENITAL OR ABIOTROPHIC DEFECT.

Homen himself has remarked on the normal physical growth and mental development of his patients, previous to the onset of the disease. I have the evidence of the mother of the M. family that this is true also of the three members of her family who eventually succumbed to it. Neither in Ormerod's nor in my own cases was any stigma of degeneration discoverable, or any mental or physical defect noted as rendering the children in any way different from their fellows. On the contrary, they all promised exceedingly well. This point appears so well established that it is superfluous to elaborate it.

2. THE PRESUMPTION THEREFORE IS STRONG THAT THE DISEASE IS ACQUIRED.

Although of course a majority of the cases are familial we should not overlook the fact that in the T. family the sole member affected was the eighth child, whose case turned out to be, nevertheless, one of the most typical of all (my case I). This circumstance alone pleads if anything in favour of the view that the disease, whatever be the predisposition, is acquired. In this connection it might be instructive to attempt to discover whether in the familial cases the patients who suffered were placed in circumstances different from their brothers or sisters, or were in any way exposed to risks which the others did not run. We know nothing of the resistive powers of the members of the families, and speculation on such matters is at present idle.

3. THERE IS EVIDENCE TO SUGGEST THAT THE DISEASE IS TOXIC IN ORIGIN, BUT NONE TO SHOW THAT THIS TOXIN IS SYPHILITIC.

The arguments on which this statement is based are of two sorts, those one may advance from a study of the acute cases, and those which analysis of certain features of my own cases leads me to offer.

- a. All the acute cases are old ones, and we must be content with a scrutiny of the old records.

Now in Gowers' and Ormerod's cases, the duration of which was 2, 13, and 4 months respectively, we have an acute

illness, steadily and rapidly progressive, associated with high irregular fever, and with profound disturbances of general metabolism: the symptoms vary from week to week, yet no definite improvement is ever recorded: from being plump, healthy, intelligent children the patients are speedily reduced mentally almost to the level of imbecility, and physically to "skin and bone", an expression which cannot be said to be exaggerated, and all within the space of a few months. No morbid process, I submit, can be conceived so widespread in its action and so fatal in its incidence, other than a toxic or toxic-infective process.

b. Certain facts in my own cases suggest a toxic origin for the disease.

The clinical history of E.P. (case III) is particularly illuminating in this respect. His illness began rather suddenly and unexpectedly, with mental symptoms, viz. motor excitement, disorientation, auditory hallucinations, /c, symptoms which are strongly indicative of a toxic psychosis. In other words, they are the symptoms which commonly appear when the cerebral cortex is thrown out of gear as the result of toxic action, whatever that toxin be, and whatever its origin. From this typical toxic psychosis the patient made a good recovery, yet within a few months of his discharge from the hospital the physical symptoms of progressive lenticular degeneration made their appearance. This is surely at least suggestive of the continuance of the action of some toxin on the nervous system.

Again, the transient mental symptoms which his sister showed in the early part of her illness--as distinct from the general mental deterioration, such as it is, which practically all patients with progressive lenticular degeneration present--suggest an intoxication of some sort. I do not think the argument is invalidated by the objection that in neither case were these symptoms persistent. Considering the variability of action of toxins, and the fact that another part of the brain than the cortex is much more profoundly affected, so that other nervous symptoms are much more in the clinical picture, it is

not remarkable that this should be so.

c. The variability of many of the symptoms from time to time suggests a "functional" or "nutritional" rather than a structural change.

Ormerod, Gowers, Homen, and myself have in turn been struck by the extraordinary way in which the patients, seemingly so inarticulate, have occasionally been able to utter words or phrases with comparative ease and distinctness. Similarly, notwithstanding their appearance of helplessness, yet in the early stages of the disease their voluntary movements and their muscular control and power have all varied so from time to time that the suspicion has crossed the mind of more than one observer that the condition was "functional". This being so, and in the absence of so called "organic" signs, it is natural to suppose that some morbid agent is at work producing varying functional effects so long as structural change is as yet slight, and equally natural to imagine that this agent is or may be some form of toxin, autogenous or otherwise.

As far as the second part of statement 3 is concerned, the whole weight of the pathological evidence in my cases is against the syphilitic hypothesis, even if we ignore the fact that clinically there is no more reason why syphilis should be proposed as a possible explanation of the disease than, say, malaria. Further, the pathological evidence of Homen's cases cannot in my opinion be taken to support a syphilitic hypothesis. The sentences already quoted from Homen show his attitude to be one of faute de mieux. Finally, although acute syphilitic meningitis is a recognised clinical and pathological entity it is nosologically irrational to conceive of syphilis hereditaria tarda causing an acute and rapidly fatal illness after ten years of healthy mental and physical development.

#### 4. IT IS POSSIBLE THIS TOXIN MAY BE ELABORATED IN THE LIVER.

Cirrhosis of the liver is an absolutely constant feature of the disease, and the opinion therefore is not unwarranted that it must be integrally associated with the pathogenesis of the condition the more so because it is the sole visceral change which is <sup>always</sup> ~~always~~ found post-mortem. The question is,

is the cirrhosis primary and the lenticular degeneration secondary, or are both the effect of the action of some morbid agent? We have already seen reason to believe that the disease is of toxic origin: the problem, then, may be stated in another way. Is a toxin liberated or elaborated in the liver which has a double action, on the liver itself and on certain nervous tissues? Or is it produced elsewhere, and has it a simultaneous incidence on the liver, producing cirrhosis, and on the lenticular nucleus, causing the latter to degenerate? Or does some morbid process act on the liver which is thus made to produce a poison that affects the corpus striatum? How does the presumed toxin act, and what is its nature?

It is obvious, of course, that such questions are more easily posed than answered. One or two points, however, may be alluded to.

While all previous writers on the subject have remarked on the absence of hepatic symptoms during life--in this connection the loss of appetite and occasional vomiting of Homen's patients are not specific--there are two cases in the series in which certain liver symptoms were present at one time or another, and it is to these that attention must now be drawn.

At the age of 21 S.T., my case I, had an attack of jaundice of five weeks' duration, and for several years thereafter she showed at intervals definite signs of persisting liver disease in the form more particularly of oedema of the legs and feet. Four years after this attack, and therefore at a time when the liver disease could not have been long in abeyance, the earliest symptoms of progressive lenticular degeneration made their appearance, in the shape of bilateral tremor. Such a sequence of events is exceedingly suggestive, although I admit, as far as the series goes, it is unique. It may be taken to show that where liver symptoms are present at all they antedate the lenticular symptoms.

C.J., my case V, had unmistakable liver symptoms during life in the form of ascites and oedema, and in this respect the case is unique, too: none of the others has presented the combination of liver and of lenticular symptoms at one and the same time. From the clinical record, it would appear that the two ran a course *pari passu*. What importance to attach to these facts it is difficult to determine. Cases both more acute

and more chronic than this one have not shown any liver symptoms at all. There may have been some complication or pathological complication which produced them in the case of C.J.

If we suppose the condition to be of toxic origin, we have to account for the continued action of the morbid agent, as it is unlikely that once lenticular degeneration commences it must proceed inevitably without further ado. Now when we remember that the disease of the liver is a universal feature, that it is always advanced, even in the acute cases, and that no other viscus shows a constant change, it is natural to suggest that this disease has to do with the continuance of action of the toxin. Further, the microscopical evidence furnished by examination of the liver proves that the changes in it are always active and some of them recent, for necrosis and regeneration proceed side by side. This may, I think, be taken to suggest that the morbid process is never in abeyance, as far as the liver is concerned, <sup>but</sup> that fresh areas of that organ are attacked while others recuperate. On the other hand, as Homen's and my own cases conclusively demonstrate, the longer the duration of the disease the greater the disintegration of the lenticular nucleus. Hence we are justified in advancing the hypothesis that disease of the liver is in some way the cause of the lenticular disease. Beyond this speculation is at present undesirable.

While perhaps it may be a little difficult to conceive of prolonged toxic action such as one or two of the cases are presumed to show, we should remember that between the acute and the chronic cases there is no violent distinction, as far as duration goes. The exact duration of the series of cases, in order, is as follows: 4 months, 6 months, 12 months, 2 years, 2½ years, 3 years (two), 4 years, 4½ years, 6 years, 7 years. This fact alone is in accord with the hypothesis here offered.

##### 5. THE TOXIN HAS A SPECIFIC ACTION ON THE LENTICULAR NUCLEUS.

When we talk of a toxic condition we invariably think of a generalised condition, but many toxins have a specific action, instances of which readily suggest themselves. In progressive lenticular degeneration

the action of the toxin is both general and local. Among the effects of the former process are the disturbances of metabolism, more particularly in the acute cases, the mental signs of toxæmia, and so on. The local effects of the toxin are seen in the degeneration of the lenticular nucleus on both sides. In this respect my case III is particularly instructive, for the disease has not progressed too far: we can see, as it were, degeneration in the making: we can follow the steps in its establishment. It is unnecessary to repeat what has often already been noted, that the selective action of the morbid agent is by far the most striking characteristic of the disease--optic thalamus, internal capsule, and caudate nucleus intact, lenticular nucleus ~~shrunken~~ shrunken, atrophic, crumbling. Let it not be supposed that this selective action is merely a question of vascular distribution: a glance at the accompanying diagrams will dispel the idea. Fig 177 - 50 According to the latest and most accurate researches the lenticular nucleus has two, if not three, main sources of vascular supply, distinct from each other. Were we dealing with disease in a particular vascular distribution the structural changes would be quite different. Look at the cavitation of the right lenticular nucleus in figure <sup>50</sup><sub>A</sub> and observe how well preserved all the tissues are round it. It is abundantly clear that no vascular supply will account for the steady disintegration of a collection of grey matter in one place while other collections of grey matter, all round it, are entirely unaffected. Further, there are no changes in the blood vessels such as one usually associates with vascular disease, and it is in my opinion quite possible that in the affected areas the degeneration of the vessels--their fragility and thinning--is the result of the degeneration round them. This would certainly seem to be the case with the vessels round the cavities in case I. There is no direct evidence that the toxin, whatever it be, acts on the nuclei via the blood-stream. It may be a matter of lymphatic spread.

How, then, are we to explain the facts? Is there a direct chemical or structural affinity between the nerve elements of the lenticular nucleus and the presumed toxin? We cannot gainsay the fact of the restriction of the process to that

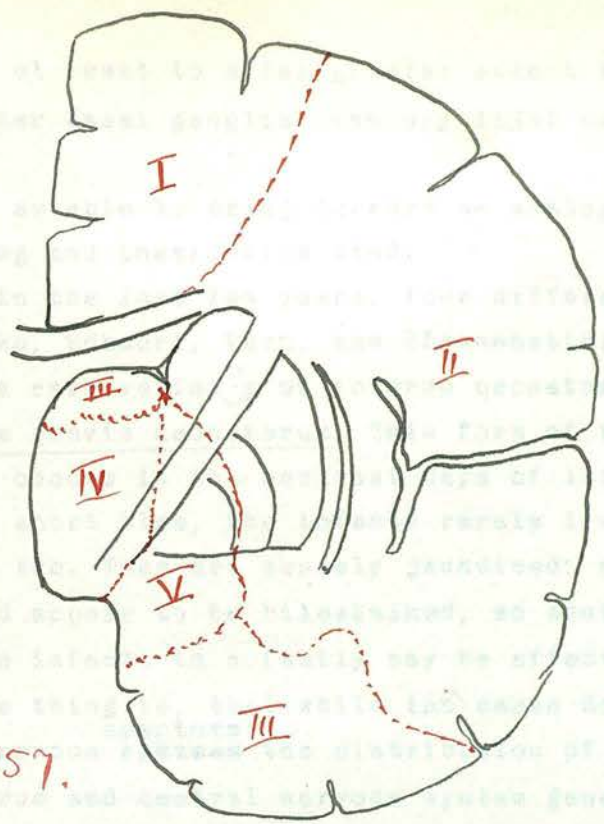


Fig 157.

- I. Anterior cerebral
- II Middle cerebral
- III Posterior cerebral
- IV Posterior communicating
- V Anterior choroid.

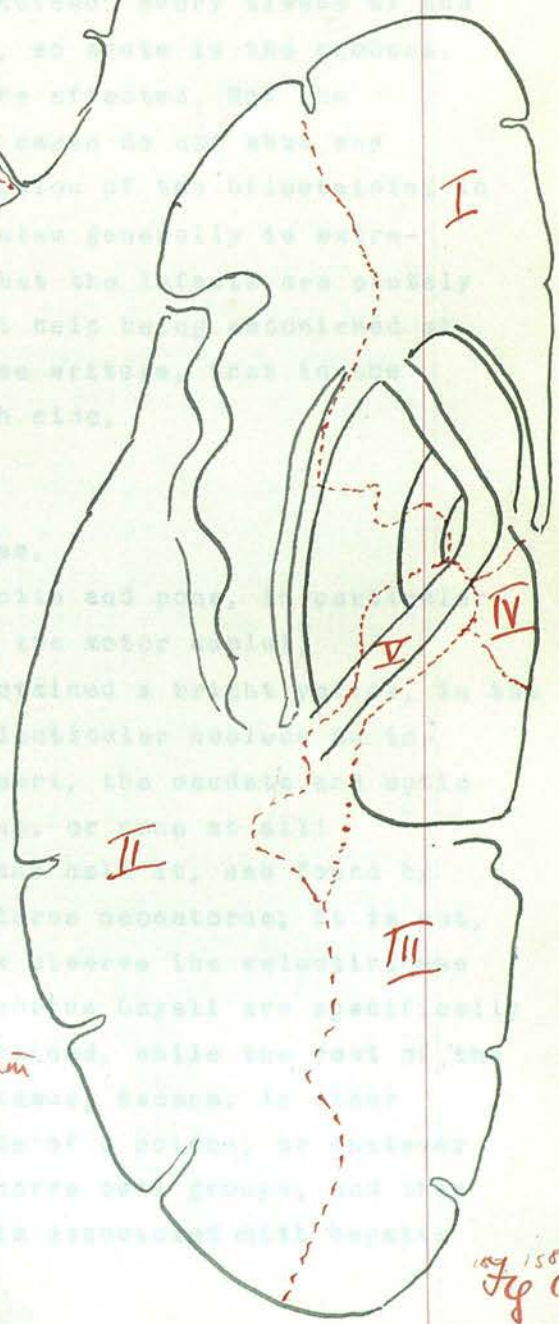


Fig 158.

Copied from Bevon's communication  
 in the *Institution of the Cerebral*  
*Arteries* (Phil: Trans.)

nucleus at least to a far greater extent than in the case of the other basal ganglia. Can any light be thrown on the subject?

I am able to bring forward an analogy of an exceedingly interesting and instructive kind.

Within the last few years, four different German authors, viz. Beneke, Schmorl, Esch, and Pfannenstiel, have described cases of a rare variety of icterus neonatorum, distinguished as icterus gravis neonatorum. This form of the disease is familial, occurs in the earliest days of life, and is fatal in a very short time, the infants rarely living longer than a week or two. They are acutely jaundiced: every tissue of the body would appear to be bilestained, so acute is the process. Successive infants in a family may be affected. Now the remarkable thing is, that while the cases do not show any special nervous <sup>symptoms</sup> ~~systems~~ the distribution of the bilestaining in the cerebrum and central nervous system generally is extraordinarily selective. Remembering that the infants are acutely and universally jaundiced, we cannot help being astonished at the fact, as established by all these writers, that in the brain the lenticular nucleus on each side,

- the corpus Luysii,
- the cornu Ammonis,
- the nucleus dentatus and olives,
- the sensory nuclei of the medulla and pons, in particular the eighth and tenth, and not the motor nuclei,

are specially singled out and are stained a bright yellow, in the case of the corpus Luysii and the lenticular nucleus an intense yellow, while the cortex cerebri, the caudate and optic thalamus show only the faintest tint, or none at all!

This "Kernicterus" as the Germans call it, was found by Schmorl 6 times in 120 cases of icterus neonatorum; it is not, therefore, so exceedingly rare. Now observe the selectiveness of it. The lenticular nucleus and corpus Luysii are specifically mentioned by all as being deeply stained, while the rest of the corpus striatum, and the optic thalamus, escape. In other words, we have a localised incidence of a poison, or whatever we like to call it, on particular nerve cell groups, and this poison circulating in the system, is associated with hepatic

disease. In these cases there is no evidence of infection of any ordinary type: the liver cells are swollen and some are necrosed: syphilis can be excluded. This disease, whatever be its origin, occurs in families, is fatal during the first few weeks of life, and is characterised by profound and generalised icterus: yet in the brain certain cell groups are singled out, others are untouched. Microscopically the bile pigment is found in the nerve cell bodies, and in their immediate neighbourhood masses of pigment may be deposited.

Now in ordinary cases of jaundice in older people, from whatever cause arising, and in the jaundice of congenital bileduct obliteration no such selective staining of grey matter has ever been found, as far as I have been able to discover. We cannot, I hold, resist the conclusion that in familial icterus gravis neonatorum, of the Kernicterus type, we are dealing with a highly specialised disease where a toxin presumably of hepatic origin exhibits an affinity for the lenticular nucleus and corpus Luysii, in addition to other smaller collections of grey matter, while it leaves the optic thalamus and caudate nucleus untouched, or practically so.

The analogy Kernicterus offers to progressive lenticular degeneration is therefore profoundly suggestive. A whole field for research seems to be opening up as we study these two diseases more closely, but in pointing out the analogies between them enough has been said at present.

6. THE NATURE OF THE TOXIN IS SPECULATIVE: IT IS PROBABLY NOT MICROBIAL.

There is no evidence that progressive lenticular degeneration is microbial in origin. Only the modern cases have been examined from this point of view. In two of my cases there was abundant trace of infection of bacterial type, but every reason to suppose, at the same time, that this infection was terminal, and therefore of no pathogenic significance. The third case, although examined just as minutely for signs of bacterial invasion, was negative. Hence we may dismiss this idea. Possibly the toxin is of the nature of a hypoid.

CHAPTER VI.

P A T H O L O G I C A L P H Y S I O L O G Y O F  
T H E M O R E I M P O R T A N T S Y M P T O M S.

The symptoms which stand out conspicuously in the syndrome of progressive lenticular degeneration are tremor, muscular rigidity and contracture, dysarthria, and emotion-  
alism, and these we shall consider briefly, in turn.

1. TREMOR.

In at least 8 of the series of 11 cases tremor was an early, a prominent, and a progressive symptom: in two others it was not quite so noteworthy, clonic and tonic spasms being specified as the type of involuntary movement present. For practical purposes, however, tremor, of a more or less regular rhythmical sort, is in the very foreground of the clinical picture. Whence does it arise?

The idea which was formerly held widely--see, for instance, Sharkey's Goulstonian Lectures for 1886--that tremor was of cortical origin, and due to "cortical irritation" whatever that may mean, must be given up. Homen's remark that in his tremor cases it is to be regarded as "Ausdruck einer Corticalreizung" will not suffice, indeed only leads to confusion. It appears to be clear that for tremor we must have integrity of the cortico-spinal paths. In favour of this view are the facts, which hold good in my own cases, that with excitement, or with volitional effort, the tremor usually increases. It has long been recognised, in fact since the days of Benedict, that tremor is of frequent occurrence in lesions of the basal ganglia and midbrain, and that while it frequently comes on after an attack of hemiplegia--so called post-hemiplegic hemitremor--the slighter the paralysis the more likely is the tremor to be conspicuous. A large number of tremor cases have been collected by Holmes (Brain, 1904) as a result of the analysis of which it appears that tremor is more constantly associated with lesions of the tegmentum than with any other part, whereas athetosis and posthemiplegic chorea--so called--are associated rather

with lesions of the optic thalamus. A certain number of cases of true tremor, however, have been noted with lesions more particularly of the lenticular nucleus. There is increasing clinical and experimental evidence, which it would be undesirable to enter into fully in this place, to show that with lesions of the nucleus ruber and the descending rubro-spinal tract of Monakow tremor is prone to make its appearance. It may, in fact, be taken as established, and I have personally seen numerous midbrain cases to corroborate the contention, that lesions of the cerebello-rubro-spinal system are associated with tremor. The rubro-spinal system is part of the extrapyramidal motor system, and the more intact the cortico-spinal paths are, the more likely is tremor to develop with lesions of the former.

We cannot, however, suppose that a positive symptom, as tremor is, can arise from a negative lesion. Degeneration of Monakow's bundle cannot cause tremor: it may allow it. The presumption therefore is that with impairment of the rubro-spinal system some influence of an inhibitory or steadying nature is removed, and tremor becomes possible.

The next point is, that we cannot imagine the nucleus ruber to be isolated from above. In other words, what are its central connections? Can we not have impairment of the system's function by lesions central of the nucleus ruber? There is increasing evidence to support this contention, and I hold that the disease known as progressive lenticular degeneration is conclusive proof of it. I have shown that in my cases the ansa lenticularis is degenerated, as well as certain systems connected with the corpus Luysii, as a result of disease of the globus pallidus. Dejerine has traced degeneration descending from the globus pallidus via the ansa to the capsule of the red nucleus. In my experiments I have traced descending degeneration from the globus pallidus to the red nucleus on the same side. Thus the rubro-spinal system is directly linked with the lenticular nucleus: in fact the latter may be said to form its central station. We may expect, therefore, that lesions of an extrapyramidal system, from lenticular nucleus via ansa and nucleus ruber to spinal

cord, will be associated clinically with tremor. Let it not be supposed that only in lenticular degeneration of the type here discussed is tremor found. Rhein of Philadelphia has recently published a beautiful <sup>case</sup> of posthemiplegic tremor from a bilateral lesion of the lenticular nucleus, and there are others on record.

A further point, however, is as to the production of the tremor. We have seen reason to believe that impairment of the steadying action of the lenticulo-rubro-spinal system allows tremor to supervene. Does this system act upwards, or downwards? In other words, is it because of defect of action of the rubro-spinal system on the anterior horns of the cord, or because of removal of influences passing upwards to the cortex?

The connection of the lenticular nucleus with the cortex, according to my experimental evidence, is almost entirely indirect, via the optic thalamus. Of the degenerating fibres from lesions of the nucleus an immense number pass across the internal capsule to the outer, posterior, and inferior parts of the thalamus. The linkage of the thalamus with the cortex is very intimate, not merely with so called <sup>sensory</sup> ~~sensory~~ areas, but as Sachs has shown experimentally, with the motor area. On the other hand, direct implication of cortical fibres from lesions of the lenticular nucleus is minimal. The nucleus is practically autogenous. Hence in disease of the lenticular nucleus, if at all widespread, we should expect considerable functional defect via the thalamus on the cortex.

Which of the two paths is responsible for the tremor is difficult to decide. In view of the fact that tremor is more common in lesions below the nucleus ruber, and implicating it, than in lesions of the lenticulo-rubro-spinal system above the red nucleus, I think probably it is the downward connections of the lenticular nucleus that should be associated with the tremor, whereas the upward connections, as we shall see immediately, may be connected with the rigidity.

2. RIGIDITY AND CONTRACTURE.

All of the series of 11 cases showed rigidity and contracture in greater or less degree. Rigidity, therefore, may be taken as a cardinal feature of the disease. We have already seen that this rigidity, or rather hypertonicity, is different from the ordinary spasticity following on lesions of the cortico-spinal system. In an ordinary case of spastic paraplegia it is often found that when the limbs are put into such a position as to relax the muscles the latter are not really hypertonic: consequently the stiffness and dragging of the feet are the result rather of weakness of the flexors, their antagonists being by contrast hyperactive. In progressive lenticular degeneration, however, if we take a limb and move it passively, we are conscious all the time of an sense of increased resistance, both in flexors and extensors, and though we relax the muscles as far as possible they feel firm and hypertonic on palpation. Besides, from the pathological standpoint, there is absolutely no degeneration in the cortico-spinal or pyramidal system: hence the presumption is strong that the rigidity is of extrapyramidal origin.

It is true, of course, that the question of muscle tone is far from being settled, and much of the evidence on the subject is rather conflicting. In the present series of cases, however, we have no reason to suppose that the hypertonicity of the musculature is myogenic. The clinical history especially of my case III suggests that the contracture of the muscles is entirely secondary to the rigidity and immobility of nervous origin. We have seen how contracture-attitudes precede the permanent establishment of contractures. There is no pathological evidence of such changes in the muscles as to suggest a primary muscular inflammation or other process to produce rigidity. We conclude, therefore, in all probability, that the rigidity is neither myogenic nor pyramidal.

Now the next point is that this rigidity is closely associated with the tremor, proceeds pari passu, varies from time to time as does the latter, comes in "attacks" of slow spasmodic tightening and relaxing of the muscles sometimes,

specially in the acute cases, and the tremor too is occasionally noted to come in "attacks". It has been suggested by Dr Hughlings Jackson, in regard to paralysis agitans, that tremor is rigidity "spread out thin", and conversely, rigidity is tremor "run together". The idea is illuminating. It may be that in progressive lenticular degeneration such an explanation is more than probable. In any case the association of the two, in varying degree, is as characteristic of the disease as of paralysis agitans.

The suggestion which I offer, then, may be expressed in the following way. Disease of the corpus striatum, and in particular of the lenticular nucleus, especially if it is bilateral, removes an inhibitory influence, a steadying influence, on the innervation of the corticospinal paths. Presumably this influence is exerted via the thalamus, at least in part: perhaps also via the rubro-spinal descending system to the anterior horn of the cord. In the absence of this influence, this "Hemmung", the pyramidal system gets out of hand, and there is increase of tonicity in all the skeletal muscles reached by the system, as well as tremor which is aggravated by voluntary movement. There is no true paralysis, for the system is intact from Betz cells to muscles, but its function is weak and greatly interfered with.

It may be that the afferent impulses to the motor and sensory cortex from the thalamus are altered as a result of the disease of strio-thalamic paths: in any case we must postulate an indirect causation of the rigidity, for, as has been said, the lenticular nucleus is practically autogenous.

The presence of contractures in extrapyramidal disease is of interest and importance. With the exception of paralysis agitans the disease which is here described is the first, apparently, in which contracture has been shown to occur with an intact pyramidal system. The fact brings paralysis agitans and progressive lenticular degeneration even closer together.

S. DYSARTHRIA.

It seems most natural to associate the dysarthria which all the cases have shown, with the rigidity of the musculature. The late Professor Brissaud was the apostle of the theory which placed subsidiary centres for articulation and deglutition in the putamen. According to this view, the dysarthria that is so common a feature of pseudobulbar paralysis is not due to impairment of the capsule functions, i e to involvement of true pyramidal fibres, but to implication of these secondary centres in the putamen, or of the fibres coming from them. But the researches more especially of Comte (Thèse de Paris, 1900) have demonstrated the erroneousness of this theory. In pseudobulbar cases the cause of dysarthria and dysphagia is involvement of the fibres from the lower part of the motor cortex, via the genu of the capsule, to the nuclei of the pons and medulla, somewhere in their course.

Now in my case I it is true that the genu fibres are implicated, on one side, at least. But it is fortunate that in case III an equal degree of dysarthria and dysphagia is not associated with any pyramidal lesion whatsoever. We must assume, therefore, that these symptoms have another explanation than that of pseudobulbar palsy. The most natural explanation to give is that the muscles of the throat, palate, and tongue, ~~were~~<sup>are</sup> just as involved in the overaction of the pyramidal system as any of the other muscles of the body. Accordingly their volitional control ~~was~~<sup>is</sup> just as feeble, and just as imperfect. This view, moreover, brings these symptoms entirely into line with the others, for in the clinical histories it will be remembered that the dysarthria and the dysphagia were both characterised by variability. Were they due to structural defects of their innervating nervous paths I do not see how this variability could be explained satisfactorily. If we think of it, however, as due to variable disturbance of a controlling, steadying, inhibitory influence exercised by a large ganglion that is slowly degenerating, it will I think be agreed that the suggestion is eminently feasible.

#### 4. EMOTIONALISM.

We cannot delay over a consideration of this symptom, so prominent a feature of progressive lenticular degeneration, mainly because the association of rire and pleurer spasmodique with disease of the basal ganglia has long been recognised. The emotional reaction of all of the cases I have personally observed was excessive: in by far the greater majority of the reported cases the tendency was to laugh, and not to cry. I could not determine that the spasmodic laughing was associated with any definite affective tone: if anything, I should say that the patients did not experience the emotion which their musculature seemed to express.

The exact nature of the association, however, between the disturbance of this function and the structural regions concerned is not elucidated with completeness. Following Nothnagel it has been commonly taught that it is in disease of the thalamus par excellence that involuntary emotionalism occurs, and there is much evidence to support this hypothesis. But how this disease causes, or allows, the symptom, is another matter. In my cases the main lesion was lenticular; the thalamus was involved, if at all, only secondarily, and presumably mainly in a functional way. We may suppose that the involuntary laughing is on a par with the other symptoms which indicate defect of cortical control, however arising; it is a positive symptom, requiring for its manifestation an unparalysed pyramidal system, at least of the lower motor neurone.

## CHAPTER VII.

## SYNDROME OF THE CORPUS STRIATUM.

After the full discussion of the pathological physiology of the more important symptoms of progressive lenticular degeneration it is unnecessary to cover the ground again from another standpoint. While it is desirable to crystallise our ideas on the symptomatology of disease of the corpus striatum I cannot do more at present than give a brief revue d'ensemble of what we have learned from a study of the affection which forms the subject of this Thesis.

I shall not attempt to sift the voluminous literature on the physiology and pathology of the lenticular nucleus and corpus striatum generally. Only those who have had occasion to work through it, as has been my lot for the last year, can realise how conflicting and how scattered the evidence is. It would take up too much space to refer to the more important papers only: but in order to defend the statement that hitherto our knowledge of the functions and pathology of the corpus striatum has been notoriously indefinite I shall content myself at present with one or two quotations.

In the first place it is well known that small lesions of the corpus striatum may be entirely ~~be~~ latent, giving rise to no discoverable symptoms during life.

It is also known that while lesions of the lenticular nucleus are often associated with hemiplegia on the opposite side, most of the evidence goes to suggest that the paralysis is due to capsular involvement. In fact the great difficulty in ordinary cases of haemorrhage, thrombosis, and so on has always been that the internal capsule is liable to be implicated. In the last edition of his "Gehirnpathologie" Monakow is forced to adopt a negative attitude. "In spite of the investigations of numerous experimenters, we know as little of the clinical effects of lesions of the lenticular and caudate nuclei, or as much, as Nothnagel did 25 years ago". What is wanted, then, is a series of cases of uncomplicated lesions of the nuclei, large enough to produce effects, but

not so large as to invade the capsule. If the cortico-spinal paths are invaded, then the clinical picture changes at once.

If Monakow's attitude is negative, others have been more bold. Within recent years one or two contributions to the subject have emanated from American authors. To show, however, how essentially speculative and practically useless such positive statements have been, I may be allowed to quote one of them. Dana, Journal of nervous and mental disease, 1908, writes as follows:-

"The corpus striatum has not any independent or specific motor function. It probably has some supplementary motor function, especially in connection with articulation. It may have some control over the bladder (double lesions). It seems to have some control over vasomotor and trophic conditions of the skin. It has no thermic centre. It may have some supplementary and associative psychic function, so that lesions affect memory and initiative. In severe gas poisoning there is a double softening of the lenticular nuclei, due to thrombosis of "the artery of cerebral thrombosis", and there result vasomotor and gangrenous conditions of the skin, so that these conditions in connection with a history of coma from gas poisoning form a group of symptoms called "the syndrome of the corpus striatum". "

Anything more unsatisfactory it would be impossible to conceive. Why coma, vasomotor palsy and gangrene, the result of gas poisoning, should be dignified with a title such as "syndrome of the corpus striatum", I utterly fail to apprehend. In these patients who die of gas poisoning it is true that sometimes the lenticular nucleus is acutely softened on both sides, but these are not the sort of case in which to differentiate corpus striatum symptoms. In acute gas poisoning the futility of attempting to localise seems obvious.

I venture to assert confidently that in the disease which I call progressive lenticular degeneration we have a better opportunity than has ever offered itself before, of differentiating lenticular from cortico-spinal symptoms.

I consider that in this respect my case III is most valuable. Here, with perfect integrity of the capsule, and pyramidal paths generally, there is atrophy of the lenticular nucleus on both sides, and there follows a train of clinical symptoms corroborated by the results of a number of other cases all collected here so that a revue d'ensemble provides a striking confirmation of the general statement.

The SYNDROME OF THE CORPUS STRIATUM, therefore, which I put forward may be expressed as follows.

IN PURE UNCOMPLICATED BILATERAL LESIONS OF THE LENTICULAR NUCLEUS, AND CORPUS STRIATUM GENERALLY, PROVIDED THEY ARE OF SUFFICIENT SIZE, THE SYMPTOMS ARE BILATERAL TREMOR, RIGIDITY, AND EVENTUALLY CONTRACTURE OF THE MUSCULATURE OF ALL THE BODY, WITH DYSPHAGIA AND EMOTIONALISM, BUT WITHOUT ANY SENSORY DISTURBANCE, WITHOUT ANY TRUE PARALYSIS, AND WITHOUT ANY ALTERATION IN THE CUTANEOUS REFLEXES.

IF THE ABDOMINAL REFLEXES ARE ABSENT, OR THE PLANTARS OF EXTENSOR TYPE, THEN THE SYNDROME IS NO LONGER PURE.

In view of this syndrome, thus differentiated for the first time, we must give up the loose way we have adopted of referring to "organic" and "functional" disease of the nervous system. We talk of a patient "having no organic signs". My cases of progressive lenticular degeneration had "no organic signs", yet a more serious and grave organic disease of the nervous system it would be impossible to imagine. We must distinguish between pyramidal and extrapyramidal motor disease hence forward, otherwise we shall do what was done to the poor creature that forms case III in the historical survey (Ormerod's ) and put him into a bath by way of correction, half killing him as a result.

It must strike all who are familiar with nervous disease that the simplest way to describe paralysis agitans is that it is an "extrapyramidal motor disease". I am convinced that the key to its mystery is to be found in defect or

impairment of function of the corpus striatum. In this connection it is most instructive to learn that in a recent paper Jelgersma has found bilateral degeneration of strio-thalamic fibres and of the lenticular bundle of Forel in that disease. This is the right track, and ere long we shall be able to cry "Eureka" to another of the common diseases whose incidence is as frequent as their explanation has been elusive.

The whole study of the syndrome of the corpus striatum would require a monograph for itself. But enough has been said, I hope, to indicate the lines for further research.

paper sent here  
2 copies for the new case  
[Charlotte T.]

CHAPTER VIII.

EXPERIMENTAL RESEARCH ON THE ANATOMY AND PHYSIOLOGY OF THE LENTICULAR NUCLEUS.

With a view to elucidating some of the vexed questions in regard to the corpus striatum and its connections, and in the hope of learning something definite as to its physiology I commenced a series of experiments under the aegis of Sir Victor Horsley, in his laboratory at University College, London. These experiments were begun rather more than a year ago, but owing to the time taken up by hospital duties they have progressed less rapidly than I should have liked, and they are not yet completed. Nevertheless I have obtained a number of positive results, which will be duly set forth in the subsequent pages. It will, I hope, be understood that I do not attach finality to these results, for in a matter of this kind it is desirable one should prove all things by abundant repetition of experiments. But at the same time in the animals we have experimented on I have obtained results so identical that the conclusions I shall draw are justified amply, and may be taken as proven, as far as I have yet gone.

MATERIAL.

For the purposes of this experimental research I have used cats and monkeys: the latter usually either the ordinary rhesus monkey, or the bonnet monkey. I shall quote the results of the complete examination of the brain of 10 monkeys, after experimental lesions. The cats I shall not refer to, as I have not done so many of them, and their corpus striatum differs in some ways from that of animals higher in the vertebrate series.

METHODS.

All the lesions have been made by means of the Stereotaxic Instrument of Horsley and Clarke, which is fully described in BRAIN, vol 31, and therefore need not be further specified. Very briefly, this is an instrument for directing a needle in any one of three planes. The average size of rhesus heads

varying very slightly within certain limits, a brass cage is devised inside which the animal's head is fixed. The vertico-transverse plane which passes through the external auditory plane on either side, and known as the interaural plane, is taken as the zero plane. On the brain it passes almost constantly just behind the upper limit of the fissure of Rolando. A horizontal plane passing through the inferior margin of the bony orbits and the auditory meati, known as the basal plane, is taken as zero for up and down measurements.

(Fig 159, 160)

The needle which is employed consists of a fine double capillary glass tube, inside which are two fine platinum wires. At the end of the needle they are exposed for about half a millimetre, and when they are connected up by the wires from the other end, and a constant current allowed to pass, a beautifully limited electrolytic lesion is readily obtained, passing in circles from the points of the wires. In my experiments most of the electrolytic lesions were made by a current of 3-5 milliamperes running for 5-15 minutes. The damage made by the passing of the needle through the cerebral tissues is astonishingly slight, as I have seen again and again.

(Fig 161)  
162

The next point is to know where to go. We have used for this purpose a series of photographs of the vertico-transverse sections of a frozen rhesus head, cut two millimetres thick and numbered from the interaural plane forwards. A plane about 12 millimetres in front of the interaural plane cuts through the three segments of the lenticular nucleus. Accordingly we move our needle carrier 12 millimetres along an antero-posterior brass bar, which brings the point of the needle opposite this desired plane. Then the depth of the area we wish to reach from the surface is measured on the photographs, and found to be say 16 millimetres. We therefore move the needle in 16 millimetres from the cortex, and know for a certainty, if we are the correct height above the basal plane, that the point of the needle is somewhere in the globus pallidus. The precision of the instrument is admirable, and from the very first animal experimented on I began to get positive results.

In the experiments for which the instrument was used first,

Fig. 159.

Clarke & Husley's  
stereotaxic instrument in  
position.

Specialy photographed  
for this thesis to show  
the lateral bar  
attachment, used for  
the first time in this  
research.



Posterior view:  
lateral bar to right hand.  
The needle can be seen.

Fig. 160.



by Clarke and Hobsley, the instrument was employed so that the needle entered by the posterior aspect of the brain. For my purposes it became necessary to enter it from the side, and accordingly a lateral bar attachment was devised, which is seen in the accompanying photographs. The needle can thus be entered from the side, and the attachment has proved satisfactory in every way. It does not take long before one learns where the projection of the corpus striatum on the lateral aspect of the hemisphere is to be found. Speaking generally, if the needle be introduced through the operculum, through the extreme lower end of the third frontal convolution, through the upper or middle part of the superior temporal gyrus, one is certain to strike the lenticular nucleus, at a depth of 12-16 millimetres. In order, however, to make sure, we stimulated at intervals as the needle was moved inwards.

RESULTS OF STIMULATION EXPERIMENTS.

Although the lenticular nucleus in various sections was stimulated frequently, I never obtained any definite motor phenomena that could be attributed to its stimulation. On several occasions the animal opened its eyes, "woke up", as it were, from the anaesthetic, but this cannot be considered a local phenomenon. On several other occasions I saw the eyes jerk a little to one or other side, usually the opposite side, and then "fix", but this too cannot be held as a pure lenticular stimulation result. Other movements sometimes obtained were unmistakably of capsular origin.

It may be said, then, from numerous experiments on macacus rhesus, and macacus siniticus, that the putamen and globus pallidus are electrically inexcitable.

RESULTS OF ELECTROLYTIC EXPERIMENTS.

I. Rhesus 248.

The lesion is a small electrolytic one in the upper and anterior portion of the right putamen.

The area of the putamen affected by the lesion is almost exactly one quarter of its vertical height and one half of its breadth. The lesion extends from the anterior limit of the putamen backwards to where the middle zone



Fig 162. Low power view of gliotic brain  
in Putamen.

Fig 163. Lesion in Rh: 248.

begins, i e it involves about a quarter of the putamen from before back, as seen on horizontal section. The site of the lesion is seen in the accompanying photograph.

Degenerations.

[Figures 164, 165]

- a. There is very slight descending degeneration from the needle track downwards round the capsule of the putamen.
- b. The slight degeneration of scattered cortical fibres from the needle track need not be further specified.
- c. From the site of the lesion there is very well marked and easily followed fine degeneration in numerous bundles of fibres of the putamen, all, without a single exception, degenerating downwards, backwards, and inwards, towards the mesial plane. It is strictly confined to these pencils of fibres on the mesial side: i e there is no degeneration outwards or upwards.

As one goes back the degenerated bundles gradually converge as they go downwards, and fresh "pencils" of fine normal fibres make their appearance to take the place of the former.

By the time the external medullary lamina is reached the degenerated bundles have converged towards its upper and middle thirds. There are practically no degenerated fibres to be seen leaving the bundles to enter the lamina. By far the greater number of them pass directly across the lamina. In the middle zone the degenerated bundles have converged still more, and the degeneration becomes a little diffused. Some of the fibres keep closely together, however, and can be traced as a narrowing pencil, gradually losing its degeneration, across the middle zone, across the internal lamina, to end by diffusing out in the centre of the inner zone of the globus pallidus. By this time complete new bundles have taken their place in the putamen and in the middle zone.

None of the degenerated fibres that reach the inner zone pass either up or down in the internal lamina.

As the degenerated bundles travel down and back they slowly diminish in quantity, particularly after reaching the

248.5.9



Fig 164 - Rh 248.

248.7.3.



Degeneration in RED

Fig 165. outo.

middle zone.

There is no evidence of any fibres reaching the thalamus.

There is no evidence of any of the degenerated putamen fibres entering the internal capsule.

There is no degeneration in the ansa lenticularis.

II. Rhesus 280. 1

The lesion is a large one, and as it were double. The main part of it is indicated in the drawings. It occupies the whole of the outer portion of the putamen, extends mesially half way across the nucleus, and vertically destroys at least a third of it. Only the anterior portion of the putamen, however, is directly involved in the lesion. In addition, the bubbles of gas have made their way upwards and forwards, round the capsule of the putamen, separating the latter from the white matter adjacent, and destroying its outer margin. The lesion has completely cut across a great portion of the fibres entering the internal capsule on the anterior side.

Degenerations. [Figures 166-169]

- a. There is descending degeneration, not so much as might be expected considering the degree of destruction, from the lesion along the capsule of the putamen. It soon disappears.
- b. There is marked degeneration of cortical fibres from the upper aspect of the lesion, outwards to the cortex and also turning across the corpus callosum.
- c. There is abundant degeneration of putamen fibres, in bundles all passing mesially, and at the same time down and back. The amount of degeneration from the lesion is exactly proportional to the size of the lesion, as in Rhesus 248, which shows that the degeneration originates in the putamen. The degenerated bundles occupy at least one third of the vertical height of the putamen. They can be traced easily across the outer medullary lamina, across the middle zone, across the internal lamina, right into the centre of the inner zone of the globus pallidus. As they traverse the nucleus they converge, gradually diminish in quantity of degenerated fibres, and in the middle and more particularly

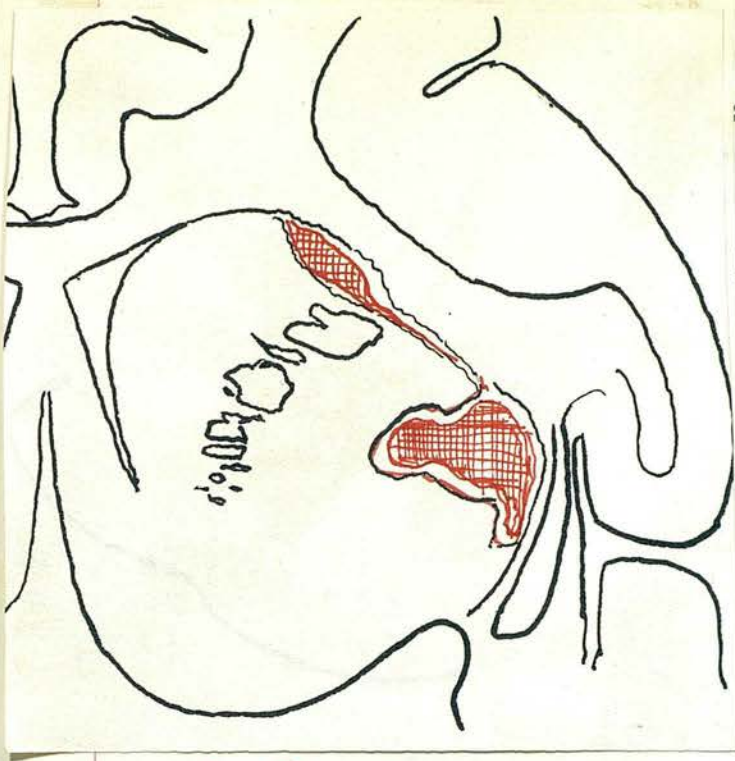


Fig 166 Rh. 280.



Fig 167. Rh. 280

280.12.3.

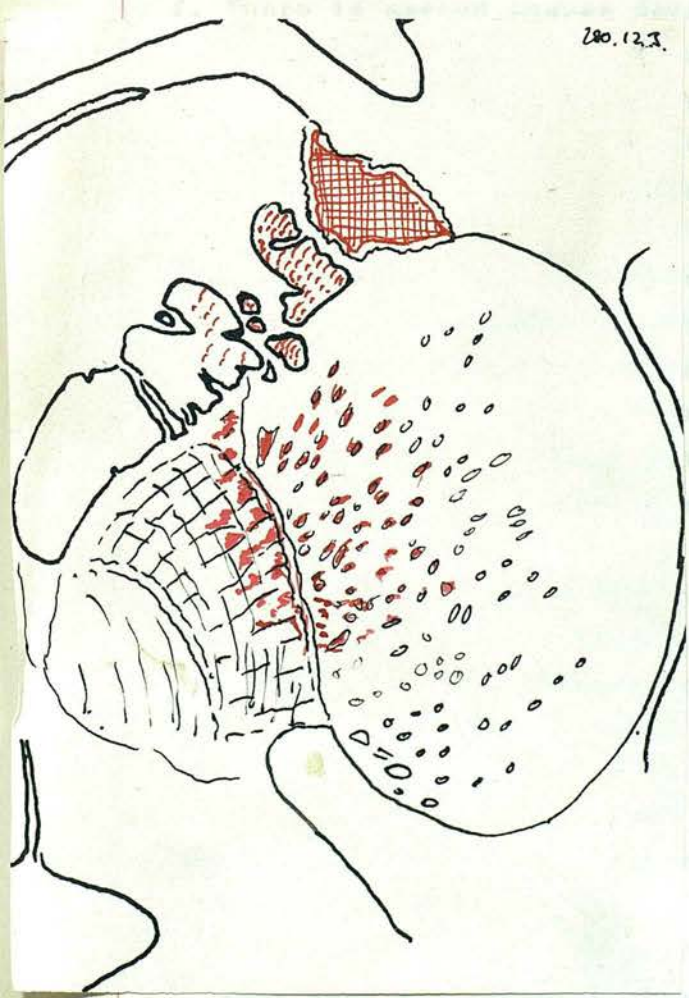
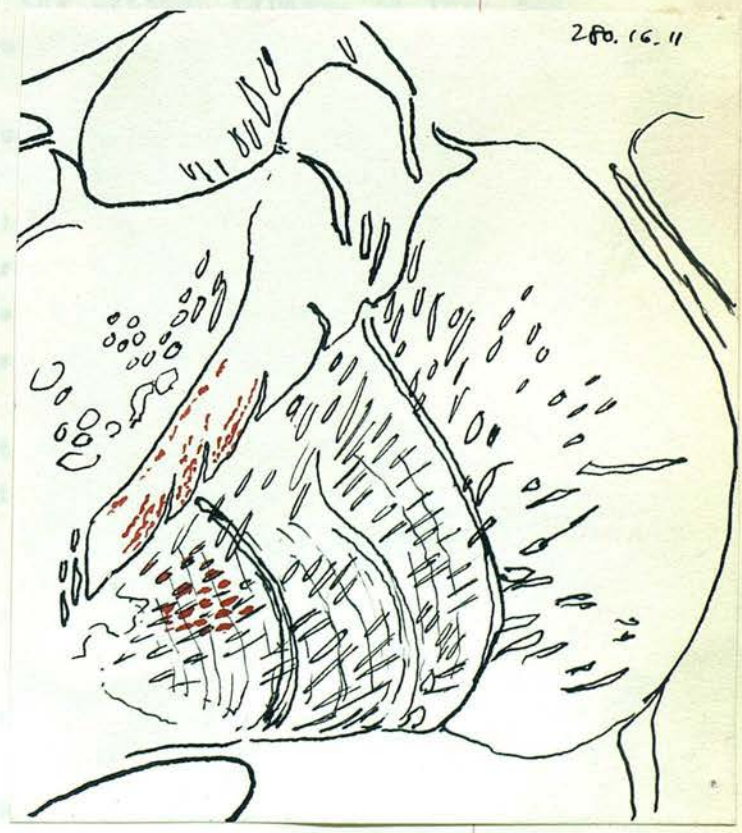


Fig 168. Rh. 280



280.16.11

Fig 169. Rh. 280.

the inner zone, diffuse out.

They give off a very few degenerated fibres to the outer lamina--only a very small proportion of the total number of degenerated fibres--and an equally small amount to the inner lamina.

They cannot be traced beyond the globus pallidus: they do not enter the ansa lenticularis.

- d. There is very little degeneration from the putamen into the caudate across the upper third of the internal capsule: in ~~fact~~ fact this degeneration is questionable. But numbers of healthy fibres come in the reverse direction.
- e. There is some degeneration across the internal capsule from the putamen or rather from the upper and anterior part of the middle zone into the lateral aspect of the optic thalamus. This degeneration, however, is much better seen in some instances to be described below.
- f. There is marked coarse degeneration of a large quantity of the fibres of the internal capsule. This of course is traceable with the greatest ease, and affords a striking contrast with the fine degeneration of the putamen fibres. As they run side by side downwards and backwards they can readily be distinguished.

The degenerated capsular fibres do not give off any to enter either the outer or the inner laminae. A few which pass laterally from the capsule at these points are found on serial sections to be aberrant bundles which converge on the main body of degenerated fibres a little lower. There are no degenerated fibres entering the globus pallidus from the capsule.

It is, however, more difficult to say whether any of the degenerated putamen fibres which reach the inner globus pallidus pass on to mingle in the capsule. As far as I can determine, they do not.

III. Rhesus 292.

The lesion is almost identical with that of Rh. 248. Degenerations. (Sp 170, 171)

- a. The usual putamen degeneration is got. The fibres all pass back and mesially. There are no fibres which degenerate

outwards, upwards, or forwards from the lesion.

The degenerate pencils can be traced to the inner zone of the globus pallidus. They give off practically no fibres to pass up or down in either of the laminae. They thin off comparatively quickly in this case.

There is no trace of degeneration into either the caudate nucleus or the optic thalamus. There is no degeneration of the ansa lenticularis.

b. There is some degeneration of fibres round the outer capsule of the putamen, from the needle track.

In this connection it is important to note that there are a few fine bundles of degenerated delicate fibres which apparently enter the putamen in its upper and anterior portion from the outer side. The presumption is they have degenerated from the needle track, for they are beyond the degenerated putamen area. These fibres are particularly interesting, as they are the only evidence I have obtained of fibres entering the putamen from without. They pass downwards and mesially, skirting the internal capsule, and can be traced for a short distance only. As already remarked, there are at the most about three or four such bundles, and they are very small.

The amount of degeneration from the putamen lesion is exactly proportional to its size.

IV. Bonnet 216.

The lesion is rather further back in the putamen, and though smaller is of interest because it is just in front of and above the middle zone and outer medullary lamina.

Degenerations.

a. As the lesion is smaller the degenerated putamen bundles of internuncial fibres cannot be traced so far. On the other hand, the importance of this case lies in the point that the lesion is close to the outer lamina. Hence the degenerated bundles are at their maximum when they cross it, and it can be readily determined that no fibres of these bundles leave the latter to pass up

292.24

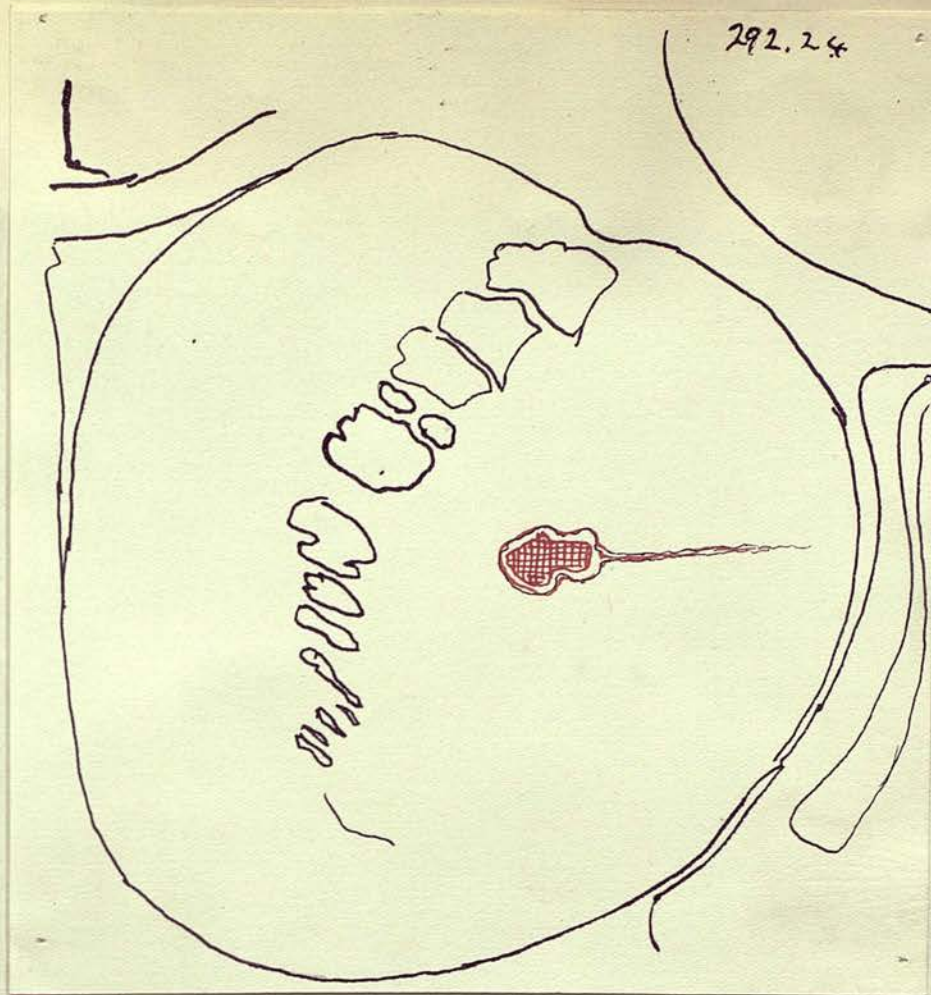


Fig. 170 Rh 192.

292.4.10

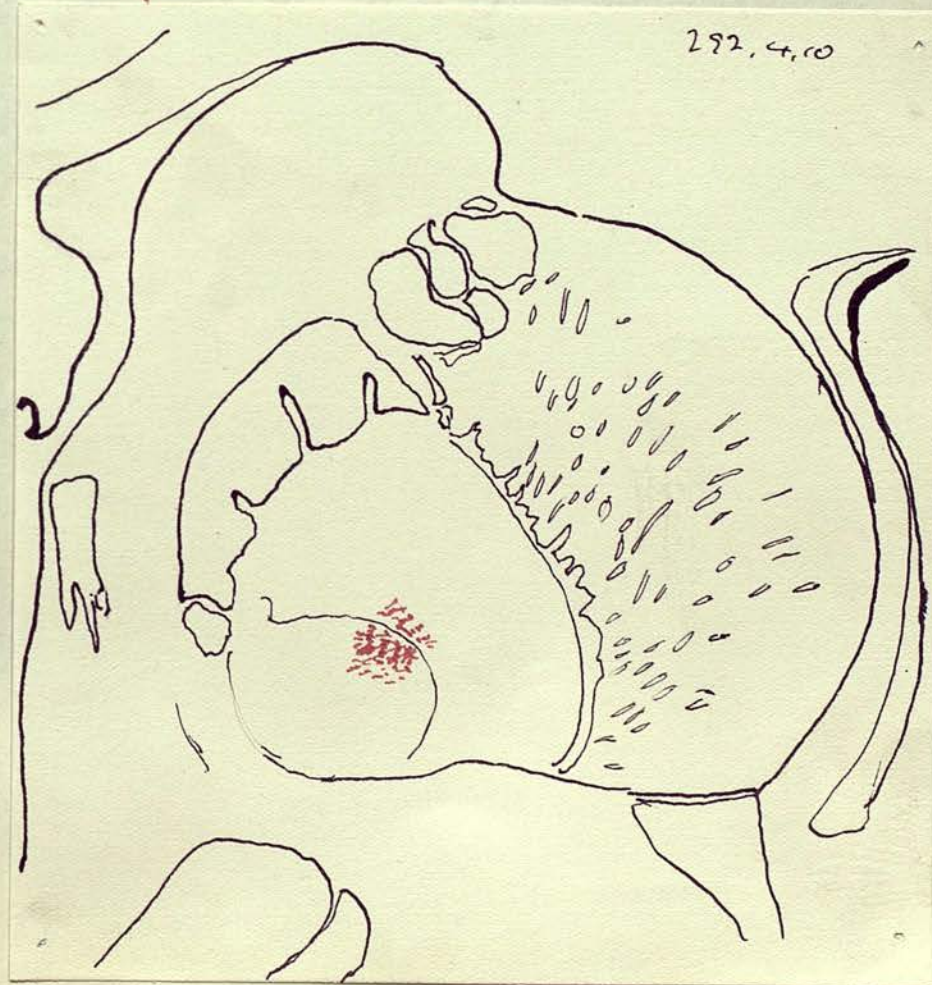
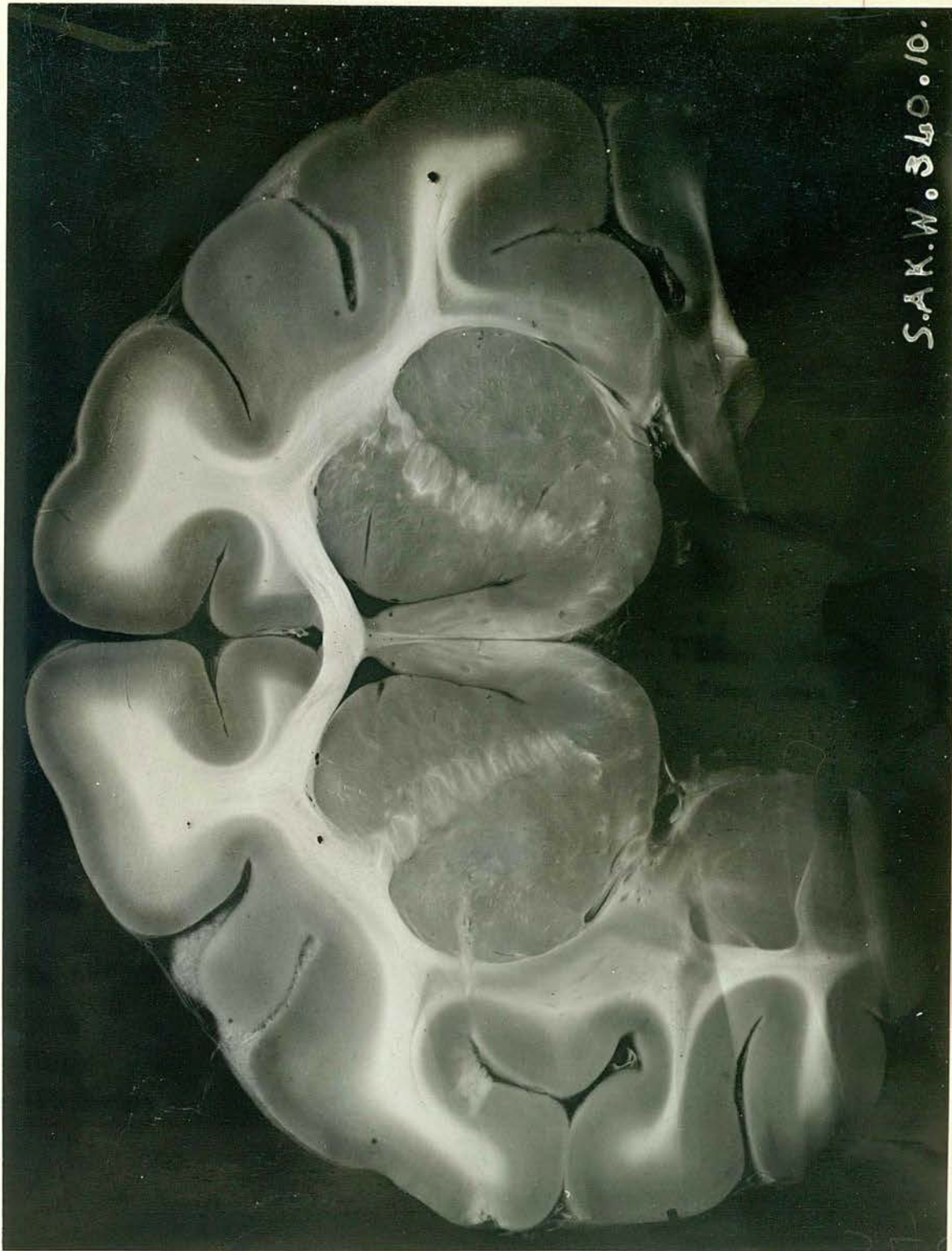


Fig 171. Rh. 192



S.A.K.W. 340.10.

↑ needle track.  
Fig 172. Rh 340.

or down in the outer lamina. All cross it without apparent diminution in the number of degenerated fibres. In fact, the healthy laminal fibres can be seen passing right through some of the degenerated pencils.

V. RHESUS 840.

In this animal the lesion is too small to be of value, but the accompanying photograph is given to show the very slight trace of the needle track, and its relative insignificance. [Figure 172]

VI. Rhesus 844.

The lesion was made well to the mesial side of the putamen, in order to determine whether many or any fibres passed round the internal capsule from caudate to lenticular or vice versa. It is in front of the middle zone of the latter. As a matter of fact the result is almost entirely negative. [Figure 173]

Degenerations.

There is slight degeneration in the internal capsule, descending. There is also very slight degeneration of a few fine fibres from the caudate through the internal capsule into the putamen, but they are so few in number as to be impossible to trace.

VII. Rhesus 848.

The lesion was made in the corona radiata just above the anterior end of the internal capsule for the express purpose of determining whether any fibres entered the putamen. It can be seen in the photograph to occupy an area just above the putamen anteriorly, which it is implicating in no way, while it has caught a great number of capsular fibres from the operculum and lower motor and frontal area. [Figure 174]

Degenerations.

a. There is gross capsular degeneration, not of course

Fig 173. Rh 344.

lesim.

Figure 174. Ph 348.

anything like complete. The degenerated fibres are coarse, and readily followed. In this case it is clear that none of the degenerated fibres enter either the upper or the lower laminae.

None of the degenerated fibres enter either the middle or the inner lenticular zones.

None of the degenerated fibres can be seen to cross the capsule of the putamen to enter it from the outer side.

- b. There is marked degeneration of associational cortical fibres in various directions.
- c. There is only a slight descending degeneration in the external capsule, which cannot be traced far.
- d. There is a beautiful and marked degeneration across the corpus callosum, in regard to which the following interesting point must be mentioned. While most of the degenerated fibres make their way to the opposite cortex, a number of them turn round to enter the opposite internal capsule ( as was shown long ago by Hamilton). The fibres which thus enter the opposite internal capsule can be traced as far as its basal third, on vertico-transverse section, i e to about the level of the subthalamic region.

An experiment such as this goes far to show that the putamen is practically autogenous, as far as its main bulk of fibres is concerned.

VII. Rhesus 484.

The lesion is well seen in the figure. (Fig 175)

It occupies the upper and anterior portion of the middle zone, in its whole transverse extent, as well as the neighbouring inner part of the putamen and outer part of the inner zone, this latter, however, only slightly. It has completely destroyed the upper half of the outer lamina, and impinges on the internal capsule about the junction of its upper and middle thirds.

Degenerations. (Figs 176-8)

- a. There is very slight but definite degeneration of some fine strands of fibres from the outer part of the globus

Lj 175. Rh 434.

pallidus, i e the middle lenticular zone, across the internal capsule, to the caudate. A far greater number of healthy fibres are coming in the converse direction.

b. There is degeneration, finely granular, down the crescentic outer lamina, but it is not much in quantity, and once we get behind the actual lesion fresh and healthy fibres at once appear in the lamina. In any case, even at the maximum of the lesion or a little posterior, not all the laminal fibres are degenerated.

A large number of fine fibres, however, which enter the nucleus by the lamina, are degenerated: they, however, do not follow the lamina downwards, but leave it almost at its upper third, and pass into the putamen. There is every reason to suppose these are inter-nuclear fibres from the caudate.

c. There is very well marked degeneration of bundles of fibres crossing the middle zone radially, below and behind the level of the lesion, and running mesially into the inner zone. As we follow this degeneration backwards we notice that these degenerated bundles edge towards the capsule and cross it obliquely, but they have reached the level of the inner zone before they start to cross.

The fibres can be followed between the bundles of descending capsular fibres into the lateral and inferior part of the optic thalamus.

The type of this degeneration is rather different from that of the pure putamen degenerations: the granulation is distinctly coarser.

It is noteworthy, however, that considering the extent of the lesion none of the affected fibres seem to travel far. They are all on the short side: the longest are those into the thalamus.

A number of the radial degenerated bundles, those more towards the centre, do not appear to go further than the inner zone: they diffuse out, as the putamen bundles, and cannot be traced beyond.

d. In addition to the radial degeneration there is well marked degeneration of transverse bundles in the middle zone, i e

434.2.8

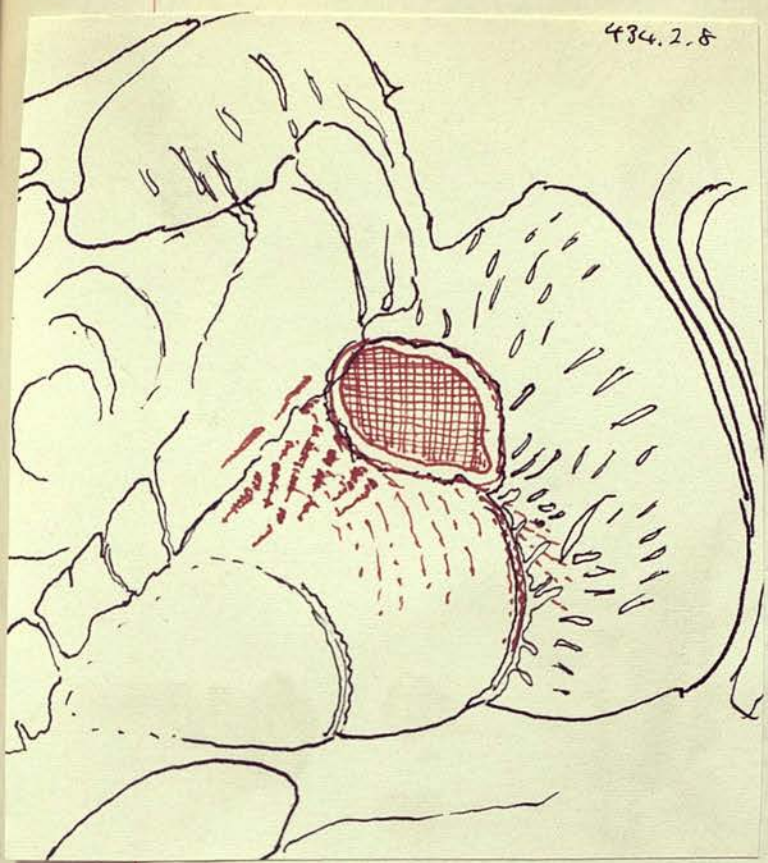


Fig 176.

434.4.9

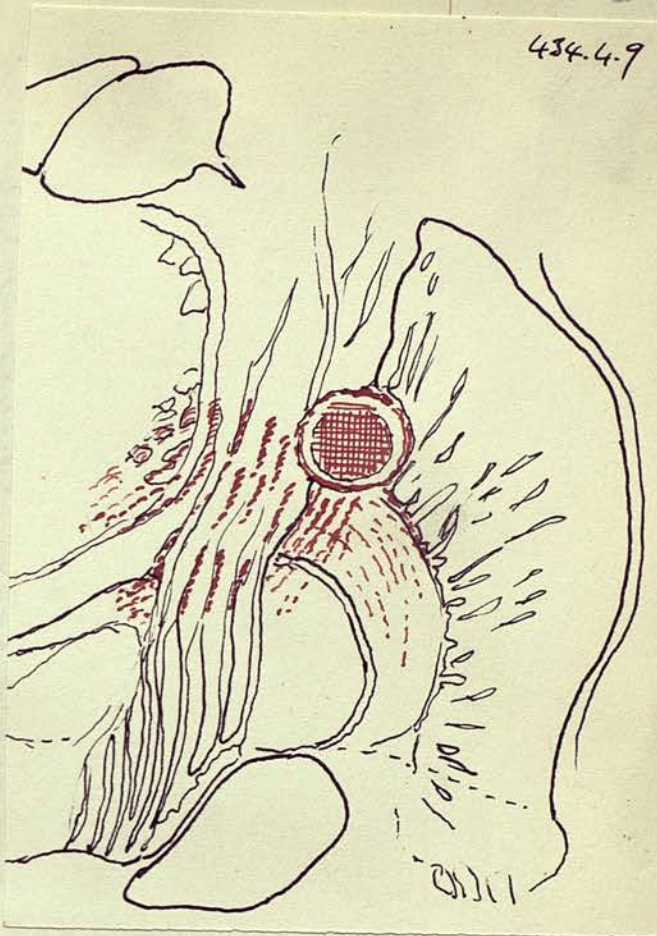


Fig 177.

434.4.13

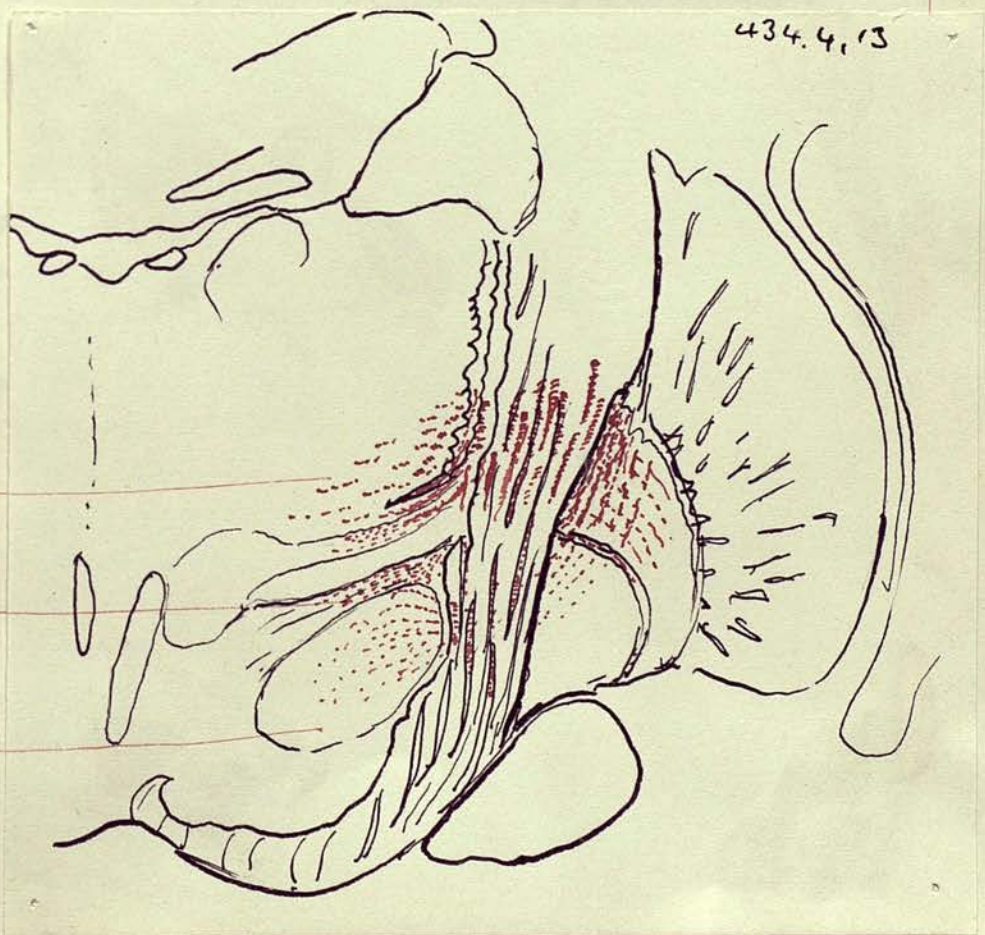


Fig 178.

To avoid confusion the capsule designation is not indicated

Chondrum  
(strio. chondrum)

Ind.

Capsum  
Ligum.

bundles which are more or less parallel to the course of the outer medullary lamina. They consist of somewhat coarser fibres, but the degeneration in them is more scattered or diffused. They can be traced down and back towards the lower part of the middle zone, but only a few of them seem to enter the ansa.

The degeneration of these transverse fibres is just as marked as the degeneration of the radial fibres, but it does not extend so far.

There is the slightest degeneration of a few fibres in the inner lamina, from above down, but the ansa lenticularis contains far more healthy than degenerated fibres.

e. It is interesting to note that as we get further back and down some of the radial fibres which cross the capsule obliquely are making their way into Forel's field, and others certainly end in the corpus Luysii.

f. It is difficult to say whether a few of these radial fibres do not pass into the internal capsule in its basal third.

VIII. Rhesus 450.

The lesion is well seen in the photograph. [Fig 179]

Its situation is almost identical with that in Rhesus 484, but it has invaded the internal capsule more, and also the inner lamina more.

Degenerations.

a. The main degenerations are identical with those obtained in the preceding animal.

There is marked degeneration of strio-thalamic fibres, easily traceable across the capsule to the lateral part of the thalamus. In subsequent sections they can be followed far into that nucleus, towards its mesial zone, as little bundles of degenerated fibres keeping closely together until they diffuse out.

The radial and transverse degenerations are as before. Rather more degenerated fibres appear to enter the ansa, but the latter structure is still nearly normal. The degeneration in the outer lamina soon ceases.



*[The text in this section is extremely faint and illegible, appearing as a series of light grey smudges and ghosting of characters.]*



Fig 179. RL 450

b. As we go down and back, the radial bundles which have edged across the capsule obliquely are divisible into two groups. Some enter Forel's field, passing more mesially. Others still run obliquely and enter the corpus Luysii in part. Others belonging apparently to this group can be traced mesially and inferiorly to the red nucleus, in its anterior part.

IX. Rhesus 488.

[Figures 180, 181]

This experiment, and the following one, were made to determine whether any fibres entered the putamen from behind and below. The lesion is seen in the photographs, which are taken from consecutive slabs 2 millimetres thick. The needle has passed through the middle of the superior temporal gyrus, and the lesion is situated in the claustrum and external capsule at the lower and posterior extremity of the putamen. It nowhere actually invades the latter.

Degenerations.

- a. There are no degenerated fibres whatever to be traced entering the putamen from its outer side. All the degenerated fibres skirt the nucleus without entering.
- b. There is well marked degeneration upwards along the external capsule, more than in the other animals where the degeneration travelled downwards.
- c. Various degenerations of cortical associational fibres need not be further specified.
- d. The temporo-pontine fibres and Turck's bundle are caught only very slightly. Had the lesion been 2 millimetres deeper the degeneration would have been more noticeable.

XI. Rhesus 502.

The lesion is well seen in the figure.

[Figure 182]

It occupies the lower portions of the putamen and middle zone of the lenticular nucleus, has not actually invaded the inner segment, and is entirely free from capsular implication. It has caught the lower end of the outer lamina, and a great number of fibres just

← lesion.

Fig 180. R. 488

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←  
lesim

Fig 181. Rh. 458

before they unite more definitely to form the ansa.

As at the moment of writing (April 22nd, 1911) I am not yet quite finished with my examination of the serial sections of this Rhesus brain, it is preferable not to enter on a description of it.

I may say, however, that degeneration can be traced along the ansa as it skirts the foot of the capsule, and that there is degeneration passing mesially across the capsular fibres to the immediate neighbourhood of the corpus Luysii and below and beyond it.

PHYSIOLOGICAL RESULTS.

All the animals were allowed to live from two to three weeks after the experiments. In every case uninterrupted recovery, uncomplicated in any way, was made. During these weeks they were tested in all sorts of ways, allowed to climb about the room used as a monkey-house, tried with the use they made of objects, their reflexes tested, &c.

I do not think a more negative set of monkeys could have been found!

The first point to remember is that the lesions have all intentionally been small ones. In the case of such complicated fibrous areas as the globus pallidus it is absolutely essential to make small lesions to begin with. No method other than that which I have had the privilege of utilising can possibly be of service. By tracing minute degenerations to begin with we can unravel the large ones when I come to make big lesions, as I am now doing. Thus while the research has been fruitful anatomically the lesions have been too small, I think, for them to produce any physiological changes.

In one or two animals preference was shown, in the taking of nuts, &c, for the homolateral limb. Others, again, were a little clumsy, just a little awkward, with their use of the limb opposite to the side of the lesion, when they were climbing about the bars of the monkey-house. Yet nothing approaching to paralysis or paresis was ever seen. I could

Fig 182. Pl. 502 -

not satisfy myself that there was any alteration in the tone of the muscles of the limb opposite to the lesion. From the point of view of the tendon reflexes, I could not establish any certain alteration. Once or twice, perhaps, the knee jerk appeared a little more active on the contralateral side, which may be taken for what it is worth. I never saw any tremor.

We must not forget, secondly, that the lesions were unilateral to begin with, and until bilateral destruction of the lenticular nucleus is essayed it is premature to speculate.

Thirdly, it is precarious to argue physiologically from the corpus striatum of animals to that of man, for several reasons.

CHAPTER IX.

CLINICAL CONCLUSIONS.

1. PROGRESSIVE LENTICULAR DEGENERATION is a motor nervous disease, which occurs in young people and very often is familial. It is not congenital or hereditary.
2. It is progressive and fatal within a varying period: acute cases may last only a few months: chronic cases have as a maximum lasted 7 years.
3. It is characterised by a definite symptom-complex, whose chief features are:- generalised tremor, dysarthria and dysphagia, muscular rigidity and hypertonicity, contractures, emotionalism: also certain mental symptoms, either transient and such as one sees in a toxic psychosis, but not severe, or more chronic, consisting in a general restriction of the mental horizon, without delusions or hallucinations, and not necessarily as progressive as the somatic symptoms. While the somatic symptoms are invariable the mental symptoms may be very slight indeed.
4. In pure cases the disease is a perfect example of extra-pyramidal motor disease, for the reflexes are normal from the point of view of the function of the pyramidal tracts.
5. The symptoms constitute a syndrome of the corpus striatum, which has not hitherto been thus differentiated.
6. In many ways the disease bears a resemblance to paralysis agitans, and throws light on the problem of that affection, which has hitherto not been satisfactorily solved.
7. Although cirrhosis of the liver is constantly found in this disease, and is an essential feature of it, there are no signs of liver disease during life.

PATHOLOGICAL CONCLUSIONS.

1. Progressive lenticular degeneration is due to bilateral symmetrical degeneration of the putamen and globus pallidus, in particular the former.
2. This degeneration is the sequel to the selective operation of some morbid agent on the cells and fibres of the putamen and lenticular nucleus generally. Other large collections of grey matter in the immediate neighbourhood of the lenticular nucleus, and with the same blood supply, are not affected at all, in a pure case, and even in the most advanced cases can be described as being intact, for all practical purposes.
3. The morbid agent is probably of the nature of a toxin.
4. A constant and essential and perhaps primary feature of the pathology of the disease is cirrhosis of the liver, not syphilitic or alcoholic: it is multilobular or mixed in type, always pronounced, but presenting a varying pathological picture of degeneration and regeneration.
5. It is probable that the toxin is associated with the hepatic cirrhosis, and may be generated in connection therewith. An important analogy is drawn from the occurrence of "Kernicterus" in certain cases of familial icterus gravis neonatorum, where in spite of the universal bile-staining of the tissues of the body certain collections of grey matter in the brain show a marked affinity for the circulating poison, while others do not. The parts that are stained profoundly are in particular the nucleus lenticularis and the corpus Luysii (among others), while the optic thalamus, for instance, is not stained at all.
6. The pyramidal tracts are intact from Betz cells to muscles, except for certain secondary changes of little significance.
7. Certain secondary degenerations in the subthalamie region of physiological importance, follow on the lenticular disease.

PHYSIOLOGICAL CONCLUSIONS.

1. The corpus striatum exercises a steadying effect on the action of the cortico-spinal system.
2. This is effected either by the lenticulo-rubro-spinal system, or more indirectly via the optic thalamus and its cortical connections.
3. When this influence is impaired, pyramidal overaction results, and is seen in hypertonicity or rigidity, as well as in tremor on voluntary movement.
4. There is not, however, any paralysis in the strict sense.
5. The direct connection of the corpus striatum with the cortex is minimal.
6. There is no reason to postulate articulatory "centres" in the putamen or globus pallidus.
7. Dysarthria may result without any pyramidal involvement of genu fibres, and with intact cranial nuclei, from hypertonicity of the musculature concerned.
8. Tremor is due more particularly to failure of function of the lenticulo-rubro-spinal system.
9. Hypertonicity or rigidity of the musculature from defect of corpus striatum "Hemmung" is probably associated with impairment of impulses from that body via the optic thalamus to the cerebral cortex.

EXPERIMENTAL CONCLUSIONS.

1. The putamen is practically autogenous as far as its fibres are concerned. While it receives many from the caudate nucleus it gets none, or practically none, from the cortex.
2. The vast majority of the putamen fibres arise from putamen cells and pass down, back and mesially, in bundles, of short internuncial fibres, most of which cannot be traced beyond the globus pallidus, inner zone.
3. These do not form any integral part of the laminae medullares.
4. A large proportion of the radial fibres of the inner sections of the lenticular nucleus edge obliquely across the internal capsule. Some go into the lateral and inferior part of the optic thalamus: others end in and round the corpus Luysii: others can be traced into the anterior part of the nucleus ruber on the same side.
5. A number of transverse fibres of the inner sections, but more particularly those of the inner zone, help to form the ansa lenticularis. The ansa does not degenerate from lesions of the putamen, nor from lesions of the middle zone, to any extent.
6. There is little evidence of capsular fibres entering the laminae or the globus pallidus.
7. It is not certain that any fibres from the globus pallidus mingle with those of the capsule.
8. Degeneration in Forel's field is associated with lesions of the inner segment of the globus pallidus.
9. Small unilateral lesions of the lenticular nucleus do not give rise to any definite symptoms whatever.

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A P P E N D I X.

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C A S E 1.

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The patient was a boy, Sydney W., aged 10, who was admitted to the National Hospital for the Paralysed and Epileptic on October 5th, 1886. His father's brother is said to have suffered from a similar affection at the age of 16, and to have recovered after an illness lasting 12 months; a sister of his father also had "St Vitus' Dance" at the age of 16, which lasted 3 months; two children of another sister also apparently suffered from some form of chorea and recovered. The patient was the eighth of 16 children, of whom 11 were dead, one from consumption the others, it was said, from bronchitis; his eldest brother was in the National Hospital six or seven years before, and died from some form of paralysis at the age of 15. The patient had never suffered from rheumatism. His symptoms began three months before admission, without any exciting cause. Clumsiness with his knife and fork first attracted attention, and the awkwardness in moving the hands gradually increased; spontaneous movement developed and affected the legs as well as the arms.

On admission he was found well nourished. His heart was normal. Constant, slowly changing movements in the limbs and arms at once attracted attention. A contraction of the zygomatic muscles caused a continuous smile, now greater on one side, now on the other. The mouth was usually wide open and the tongue retracted, but sometimes, by an effort, he could slowly protrude it. The open mouth was due to spasm in the depressors of the lower jaw. If told to shut his mouth he pressed the lower jaw up with his hand beneath the chin, and after a moment or two the spasm seemed to give way and he closed the mouth easily, but in about a minute the spasm came on again and lowered the jaw. The strong retraction of the tongue interfered much with swallowing, because the tongue was pressed up against the hard palate; liquids taken into the mouth ran out again, unless the jaw were raised up; as the jaw began to descend

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again, he was able to flatten his tongue sufficiently to allow the liquid to pass into his throat, but the tongue immediately resumed its rigid position. This process had to be repeated with each mouthful. He seldom tried to speak, but occasionally managed to utter a sentence which could be understood, especially in the morning. The spasm was always less after sleep, and worse as the day went on. He almost constantly made a low whining sound.

The movements of the eyes were normal, but at times the balls were rolled upwards. There was much spasm in the neck muscles, especially at the back, so that the head was almost constantly bent backwards; there was also strong spasm in the sterno-mastoids. Occasionally, however, when he sat up in bed, his back and neck were arched forwards so that his head was between his knees.

Both arms presented slowly changing tonic spasm, greater in the left. The forearms were usually pronated; the fingers half flexed at all joints, and the thumb also flexed. From time to time the spasm increased, and then the elbows became strongly extended, the arms adducted at the shoulder. Voluntary movement was interfered with by the spasm to a less extent than might be anticipated; he could take hold of any object with a little difficulty. At times the spasm changed so that the fingers were spasmodically extended; occasionally they were spread out and moved irregularly in a manner resembling athetosis, now and then more quickly, but the constant tonic spasm prevented any actual resemblance to ordinary chorea. It was always increased by an attempt at voluntary movement, even when this could be effected.

In the legs there was similar spasm, also a little greater on the left side. The left foot was in constant strong extension at the ankle, and inverted; the spasm could not be completely overcome by passive force. It varied less than in the arms, but occasionally passed off entirely for a short time. The right foot presented very little spasm, but at times the leg was extended at the hip and knee by spasm which came on gradually and slowly passed away. At the hips the spasm occasionally changed to flexion, and the leg, still extended, became flexed on the trunk at an

angle of about 60°. The boy was able to walk; the spasm in the left foot generally prevented the left heel from reaching the ground, but now and then relaxation of the calf muscles permitted him to walk naturally. The abdomen was generally retracted by spasm in the abdominal muscles, distinctly greater on the left side.

When the body was spasmodically bent forwards the spine presented one long curve, with a slight lateral deviation in consequence of the stronger action of the muscles on the left side. The knee-jerk could be obtained on each side, but was slight, apparently from the interference of the spasm. There was no foot clonus. The plantar reflex was slight, the cremasteric active; no abdominal reflex could be elicited. Mechanical irritability of the nerves was repeatedly searched for in the limbs, but could not be found. Sensation was everywhere normal. He complained of some pain in the dorsum of the left foot. His optic discs were normal. His mind seemed unaffected. When the spasm in the tongue prevented him speaking he would write down the word he wanted to say, and evidently understood everything that was said to him. His urine was normal, and so, at first, was his temperature. When he was asleep the spasm passed away entirely, except in the calf muscles of the left leg; the mouth was closed.

During the first few days after admission a distinct improvement occurred, but after the first week he became rapidly worse. His temperature rose to 100° and 101°; the spasm had the same character but was greater, and became as severe on the right side as on the left. He ceased to speak intelligibly and became drowsy, and began to pass his urine and stools into the bed.

On October 16th, attacks of spasmodic difficulty of breathing came on. When lying moderately quiet, with the usual spasm of the arms and hands, this would suddenly increase; the mouth opened so widely that the jaw seemed subluxated, and went back with a snap when the mouth closed. As the jaw descended the breathing became quicker, and it was seen that the tongue seemed to be drawn up almost into the throat, so as to impede the breathing, until relieved by drawing the tongue forward and forcibly closing the jaw. During the attack the face was flushed but not livid. Such

an attack, lasting half a minute, would recur every four or five minutes. His temperature rose to 101.6° and his pulse to 168. The attacks ceased on the application of a spinal ice bag. Next day he was much quieter, the pulse fell, but the temperature rose to 102.6°; in the evening the spasms became very violent.

For the next fortnight the condition continued nearly the same, in spite of varied treatment. The temperature continued between 100° and 102°, and he rapidly lost flesh. Severe paroxysms occurred, in which his respirations were 60 to 80 a minute. The general spasm continued the same in general character, but that in the hands became very uniform. Both were generally strongly flexed at the wrist, the fingers semi-flexed but not forced into the palm, the thumb adducted, the forearm supinated to its full degree so that the back of the hand was downwards. The face presented little spasm, except during the paroxysmal increase, when his features were distorted. These attacks did not seem to involve the legs, but the extreme extension of the feet continued. The spasm no longer ceased during sleep, but continued much as when he was awake; it seemed to cause little suffering.

A month after admission, some improvement occurred; he became able to speak a little. The temperature was generally about a hundred degrees. Emaciation continued; the muscles wasted, but presented no change of electrical or mechanical excitability. In the middle of November there was again an increase in the spasm. The feet were strongly extended at the ankles and the toes were strongly flexed. The spasm of the trunk was still flexor; the body bent forwards, and the thighs flexed at the hip, raising the legs off the bed, so that the patient seemed balanced on the gluteal region. But after two weeks the spasm again lessened, and such flexion of the trunk became rare, but the plantar flexion of the feet and toes increased, so that the sole became arched. The spasm in the arms continued but the flexion of the left wrist became less than that of the right. During November the temperature varied, sometimes normal for a day or two, then rising to 102°, 103° or 104°. The wasting

steadily increased, so that the child was reduced "almost to a skeleton", although a fair amount of nourishment was taken. During the first fortnight of December the spasm was definitely less and the temperature was lower, varying from a little below to a little above normal; occasionally he would talk a little. On December 17th his cheeks and supramaxillary regions were found to be swollen and crepitated on pressure, evidently from air in the cellular tissue. This condition spread down the left side of the neck to the left axilla and left side of the chest but rapidly lessened in the next few days. The evening temperature was generally 100° or 101°. The boy became weaker, ceased to swallow, mucus accumulated in the chest. On December the 22nd the temperature rose to 104° and he died, eleven weeks after admission, and about six months after the commencement of the symptoms. Throughout, his heart presented no murmur and the urine no albumen. The position of the legs and arms produced by the spasm during life continued after death.

A careful post-mortem examination was made, and a thorough naked-eye examination of the brain, spinal cord, and membranes revealed nothing abnormal. The heart was healthy. The cellular tissue of the anterior mediastinum contained air, which extended in front of the trachea, and down to the subpleural tissue of the left lung near its root, whence it had evidently escaped. The liver was noted to be "firm, hard, lobular, light in colour, not greasy, and not staining with iodine." (It was evidently cirrhotic, although the significance of this was not realised at the time.) There had been no jaundice.

Portions of the cortex of the brain, of the spinal cord, peripheral nerves and muscles, were hardened and examined microscopically by Dr. Wilson, but no deviation from the normal could be discovered.

CASE 11.  
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Two years later, August 28th, 1888, the boy's sister, Charlotte M., aged 15, was admitted, because for nine months

she had been restless and lethargic, with some thickness of speech and tendency for saliva to flow from the mouth. At the onset the cataplexia, established for eighteen months, had ceased. She was a heavy-looking girl, with mouth generally open and lower lip hanging down, easily excited to laughter. The tongue was rather large, and when protruded had a slight tremulous movement. There was nothing abnormal in the throat except some congestion. She was able to walk well, the knee-jerks were normal; there was no foot clonus, the optic discs were normal, and no other symptoms were found. At the end of six weeks she was sent to the Country Branch. But six weeks later, "choreic movements" commenced in the right leg, and extended to the other leg and to both arms in a fortnight. She was readmitted on January 2nd, 1889. The movements increased during the month before admission, and for a few days the legs had been drawn up, flexed at the hip and knee, while her arms were extended and raised above her head. Lying thus, there was constant regular movement of the feet, the heels resting on the bed and the toes sharply depressed and then raised; at the knees and hips there were also slight flexor and extensor movements, moving the heels up and down the bed for an inch or two. Similar rhythmical movements occurred in the arms at the elbows. The trunk muscles and those of the neck and head were free, and the face was still. The tongue now presented no tremor or spasm, and could be voluntarily protruded.

The movements varied in degree, and could be occasionally stopped for a few seconds by voluntary effort. There was no tenderness of the muscles or wasting. Passive movements caused some pain, especially attempts to extend the legs. The knee-jerks could not be obtained (perhaps from the spasm); there was no foot clonus.

No derangement could be found in any cranial nerve, pupils, eye movements, or optic discs. The heart was healthy. The urine contained  $\frac{1}{6}$ th albumen (casts are not mentioned). The temperature was raised, and during the first three weeks it frequently reached in the evening 103° or 104°. She steadily lost flesh and became thinner and more feeble. The movements continued, varying much in degree.

At times the forearms were brought in front of the chest, and moved rapidly in flexion and extension.

The only medicine which had a marked effect on the movement was the hydrobromate of hyoscin, but toxic effects prevented its continuance. On the evening of January 23rd her temperature was 106.2° (verified by several thermometers) reduced to 100° by cold sponging. There was no delirium or headache, the pulse was 180 and respirations 68, although no morbid sign was presented by the lungs. The patient became much more excited, and, apparently in consequence of this, the movements became less violent. The heart sounds continued normal, but bronchitic râles appeared. The albuminuria continued. Twice again the temperature rose to 106°. Evacuations were passed into the bed. She died on January 30th, the temperature rising just before death to 108.4°.

Post-mortem examination revealed no morbid appearance in the membranes of the brain; no sign of tubercle could be discerned in them. The white substance of the hemispheres was studded with minute "pits" the size of a pin's head (the significance of which is probably small). No other morbid state could be discovered in the brain. The spinal dura mater was, in places, adherent to the bone, but was not thickened, and presented no other morbid appearance, in the lower dorsal region there was a small extravasation outside the dura mater, but there was no morbid appearance on its inner surface. The spinal cord and sections of this in all parts appeared perfectly normal to the naked eye. The heart was healthy. No sign of tubercle could be found anywhere. In the lungs there was very slight hypostatic congestion.

The liver, of normal size, presented the typical appearance of cirrhosis. Strands of connective tissue enclosed yellow lobules of various sizes rising above the level of the section. The tint was found to be due to fatty and granular degeneration of the cells. The condition of the liver led to careful inquiry regarding alcohol, but it was found she had never taken it. There is no record of a microscopical examination.

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C A S E I I I.

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Walter William S., aet. 10. Admitted to Luke Ward, under care of Dr. Gee, September 20, 1889. Transferred to Casualty Ward, October 22, 1889. Died January 21, 1890.

*NOTE ON ADMISSION* - Three or four months ago right arm and hand noticed to be weak, and fingers to be kept in cramped position. Speech affected soon after arm; could not pronounce his words intelligibly. Speech got a good deal worse about a month ago; has since been scarcely able to speak at all. Not walked quite naturally for two or three months, but this has got much worse during the last fortnight. No difference noticed in the two legs. For about the same time the left arm and hand have "not been right". No trouble with micturition or defaecation. Some drawing of the face has been noticed from the beginning, but only occasionally and usually to the L. No squint. Has seemed silly (laughing unnecessarily, &c.) for a month or two. Never had fits.

For about a month has had some difficulty in swallowing; food does not come back through nose, but returns through mouth. Lately saliva has run from mouth. During three or four months some bleeding from ears and mouth, never pus; never headache or giddiness. No vomiting.

Always fairly healthy; got on fairly at school, though never very sharp (in Second Standard).

Three other children in family - these died young; one with "rheumatism of the heart", two with whooping cough and fits.

Mother dead; had one or two miscarriages. No family history of consumption or insanity. Maternal uncle subject to fits. A further note, October 31, states: - He comes of a neurotic stock. His father frequently weeps; his aunt is said to have had the shaking palsy, and to have recovered from it after eighteen months.

*PRESENT CONDITION* - Has rather an idiotic look.

*EYES* - Pupils widely dilated, act well to light and

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accommodation. Movement of eyeballs good in every direction; no squint nor nystagmus. Sight appears good; optic discs natural.

*EARS* - Some dried blood in each; no deafness, perosseous or otherwise.

*FACE* - No very manifest paralysis. Eyes can be closed tightly. On laughing both sides of face move well. Mouth is kept open; it is sometimes drawn a little to R. sometimes to L. He can open it widely; the jaw muscles can be felt to contract well on closing it.

*TONGUE* - Furred, protrudes it a little way only beyond lips; irregular movements as he does so.

No power of *speech*; can't say "yes" or "no", but makes the same sound whatever he tries to say.

*THROAT* natural; normal movement of soft palate.

*ARMS* - No actual paralysis of either arm. R. thumb is kept more or less flexed into palm; is unable to close fist without first drawing out thumb with other hand. Grasp of R. weaker than L. Slightly rigidity sometimes at wrist and elbow; no increased reflexes. No manifest wasting anywhere, but perhaps a little about thenar eminence. All movements of hands and arms performed fairly, but he can't pick up pin with R. hand. No anaesthesia.

*LEGS* - Perhaps some rigidity at knees; knee-jerks marked, + R; no ankle-clonus.

*GAIT* rather uncertain and stiff; stands well with feet together and eyes shut.

*PULSE* 80, good strength. *Respiration* quiet. *Temperature* normal.

*CHEST* - Heart and lungs normal. *Abdomen* normal; skin-reflexes marked.

*SPINE* - No tenderness or curvature of spine.

*MENTAL CONDITION* is perfectly clear; does everything he is told at once.

September 21 - *Urine*, alkaline, 1014, no albumen or sugar.

September 22 - As to swallowing, nothing very remarkable has been noticed; he eats and swallows mince without any difficulty; he moves his lips well. In drinking he has rather more difficulty, letting come back from mouth into

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cup; chokes a little sometimes. Feeds himself quite well; spoon held in R. hand, but very awkwardly.

September 23 - Electrical reactions quite natural.

September 24 - R. tympanic membrane seen; looks natural.

September 25 - He can write his name (a specimen appears in the original notes; nothing can be said about it except that it is clumsy, the letters of different sizes and the upstrokes a little shaky); sometimes will mention a letter pointed out to him, but never pronounces them distinctly; evidently knows the letters well. Sometimes asks for what he wants.

September 26 - Spoke distinctly this morning; referring to his medicine, said "That is water;" but when asked to say anything does not seem able to.

September 29 - Always talks best first thing in the morning.

October 3 - Last night L. side of face was much drawn down. Can protrude tongue better. Cannot use hands at all, but is willing to try.

October 11 - Is now frequently suffering severe paroxysms of pain in the L. hand. The contractions are then more rigid.

October 15 - Every day has attacks of pain in L. hand, and shrieks; lower part of face (not upper) drawn to L. Seems more placid when asleep; and can draw down the mouth at will. L. hand continues flexed and in a condition like tetany, even when asleep. Can talk plainly sometimes.

October 22 - Very noisy and quite a nuisance (had to be transferred to Casualty). Behaves in an idiotic manner. Is able to relax his facial muscles at will.

October 31 - His condition is investigated and described as follows:- Thin and emaciated. Pupils dilated; fundi natural. Mouth drawn to L; L. side of nose drawn down, and L. nostril dilated; but these distortions seem to be voluntary. Can protrude tongue but not at once, and creates some trouble over it. Is unable to talk. Does not seem to be paralysed at all. L. arm is kept contracted at elbow; straightened when he likes. L. wrist and fingers

flexed; can also be straightened. R. arm and hand fairly normal but some approximation of thumb to palm. Prefers to lie with his thighs and knees flexed and feet *en griffe*; But on the application of the needle will put every joint in its ordinary position. Muscles react well to faradism; no R.D. Can walk when he chooses. When he falls about he bruises himself, but not seriously.

November 3 - His temperature, hitherto normal, rises: *vide* table.

November 4 - Last night had a hot bath; with a view of seeing what he really could do, he was allowed to go under the water. He seemed to realise his position, but made no effort to help himself; swallowed enough warm water to make him sick. Sweated much after the warm bath. Thirsty and feverish this morning. Pain in belly over region of liver.

November 5 - Bit his lower lip slightly. Tongue dry and coated with blood.

November 7 - Dr. Gee can find no signs of local disease to explain the fever. Ophthalmic examination gave no results. After examination he lay and yelled lustily. 4. p.m. sweating profusely. Looks as idiotic as ever.

November 8 - Profuse sweats. Heart beats 226. Respiration 40. Temperature fluctuates, *vide* table (rose to 103.6° to-day). Takes well.

November 9 - Improvement. Anaesthetic given and splints applied to straighten the legs; respiration became slower and more regular under the anaesthetic.

November 10 - L. arm much better, uses it volitionally; but R. hand appears to be gradually taking on the same characteristics as L; the thumb is adducted and the fingers are beginning to be flexed. He likes the splints. Distinctly said "no" in answer to a question from the house-physician. Has paraldehyde to procure quiet nights.

November 13 - Bedsore appeared on sacrum since yesterday (the splint has been removed).

November 14 - More feverish again. Much flexion of R. little toe. Less flexion of legs. Howls vehemently.

November 16 - Cries when he wants anything; but does not speak. Swallows everything that is given him, but does not masticate. Is quite anaesthetic over the bed sore.

November 18 - Temperature reached 105° to-day. Another bed sore, character like the last. Urine very offensive, alkaline and phosphatic.

November 21 - Face bluish. Still lies drawn up. Never asks for anything. Still yells.

November 22 - Fever abated (*vide table*); and seems better, excepting the bed sore, which is worse. Marked spasm of R. facial muscles when he attempts to speak.

November 23 - Less rigidity of arms; legs still contracted; looks more cheerful. The improvements seems to have been maintained till December 7, when the constant yelling recommenced. Still lies in fantastic attitude. Understands, but cannot formulate words.

December 10 - Howls dismally about 16 out of the 24 hours. Takes well; can appreciate when his meal times come but does not speak. Fundus of eyes rather hazy. Bed sore better. As to the contractions, knees flexed; feet extended. Face now drawn to R; constant movement of R. facial muscle.

December 13 - Hard places on lower lip and L. cheek, apparently where rubbed by the teeth.

December 30 - Temperature, which has lately been nearly normal, begins to mount again in an irregular fashion (*vide table*).

January 1, 1890 - His condition is again described thus:- He has no appreciation of time or season now; the only thing he can do, and that not humanly, is to devour food ravenously when put into his mouth; he does not chew it, and is therefore fed on slops. His posture is as follows:- Kneews drawn up one on either side of chin, so that thighs are flexed on abdomen and legs on thighs. Feet extended and toes flexed. L. arm flexed to a right angle at elbow, forearm across chest. L. hand flexed at rist, thumb adducted, and finger adducted and flexed. R. arm generally extended by side, forearm pronated as far as

possible; thumb adducted, fingers adducted and a little flexed. In this position he lies, usually howling dismally, so that a half grain of morphia is given daily. The perverted action of his muscles is intensified, and on the slightest forcible action clonic spasms can be produced. His R. eye works now, and the R. side of his face. His mouth is not sore, but he has neither the volition nor the power to put out his tongue. He passes everything under him. He sweats profusely. Fundus of eyes natural. Electric reactions natural.

January 15 - The fever, which had abated somewhat since the 4th. is again increasing. Breaths very rapidly. Does not howl so much, sleep induced by morphia. But is in a most deplorable condition; passing everything under him, and lying like a log unless turned over. Bedsore healed.

January 19 - Much worse; breathes very infrequently, usually four times to the minute.

January 21 - Died.

I made the *post-mortem* the day after his death. The following is a record from the P.M. book:-

*External appearances* - extreme emaciation. Bedsores on sacrum, trochanter, and R. elbow. Legs tightly flexed upon his hips and hips on thighs; they could not be straightened out.

*HEAD* - Cranial bones very thin. Dura mater and sinuses normal. Arachnoid and pia mater rather watery looking, otherwise normal. Arteries normal at the base. Brains: convolutions perfectly normal in appearance and to touch. Spinal cord normal to naked eye.

The brain and cord were put in spirits and water till next day.

*EYE AND EAR* - Not examined.

*NECK* - Not examined.

*CHEST* - Lungs dirty and flabby-looking, and smelling badly, but no definite disease.

*HEART* - Normal.

*AORTA AND VESSELS* - normal.

*ABDOMEN* - Peritoneum normal. Stomach normal.

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Intestines discoloured. Liver in an extreme state of cirrhosis; weight 16 oz. In size, uniformly small. Surface covered with small rounded elevations. Section firm, and showing bands of connected tissue, enclosing degenerating lobules. Some few of these lobules were yellowish, and so disintegrated that could be pressed out of the section. General colour of the organ a sort of pinkish brown.

It was sent to the Museum as a specimen of typical hob-nailed liver in a child.

(In order to meet the wishes of the friends, the examination was <sup>to</sup> a certain degree limited, so that the nerves of the limbs were not removed, nor the joints opened).

Vertical sections were made through the brain next day. In a section at the level of the optic commissure (practically equivalent to the frontal section of Pitres), a small patch of softening was noticed, having the shape and position indicated in the diagram, i.e., involving the outer layer of the left lenticular nucleus. On a section about 1 1/2 inches further forward (pediculo-frontal) and on the next section behind (viz, through anterior border of pons=parietal section,) this softened patch could no longer be seen. Dr. Gee examined the sections after they had been two days in Muller's fluid. He noticed another similar but smaller streak, symmetrically placed upon the right side. He pointed out that these alone could not explain the whole of the symptoms.

The brain, pons, medulla, and cord were hardened in Muller's fluid, and then further examined. The streak of disease by the left lenticular nucleus was then found to extend backwards and forwards for about an inch, tailing off, and gradually disappearing within these limits, but preserving the same position in relation to the adjacent parts of the brain. Thus it formed a small flat area, covering a considerable part of the external aspect of the nucleus, between this and the claustrum. The tract of disease on the right side was in every way symmetrical to the left, except that it was smaller in extent.

Microscopically these tracts of disease were found to consist of closely packed lymphoid cells, in which a few vessels ran. They were, I presume inflammatory.

In the upper part of the pons were some tiny patches, apparently of softening, placed as follows:-

(1). In a section just below the superficial origin of the fourth nerve were two narrow patches, one on each side of the mesial raphe about  $\frac{1}{4}$  inch from it. They were in the dorsal part of the transverse fibres of the pons, lying in the direction of these transverse fibres, and measuring at most  $\frac{1}{8}$  inch in length.

(2). In a section about half-way between the superficial origins of the fourth and fifth nerves were two little patches corresponding in position to those just described, but smaller; and two other points, size of pin-heads, lying still more dorsally, i.e., in the fillet

Microscopical examination was made of many parts of the motor area of the cortex cerebri and of the cortex cerebelli. I could not make out any disease here. The spinal cord also was perfectly normal; there was no trace of descending degeneration to account for the contractures. In the liver was found what was expected from the naked-eye appearances, viz., large bands of connective tissue occupying the periphery of the lobules. In the sections I have, the cells of the lobules are less degenerate than I should have expected. Moreover, amid the connective tissue growth, bile-ducts are very numerous, and very prominent objects.

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C A S E 4.

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Alfred K. was born of the 1st. December 1866, and was the third member of the family. During his boyhood he had been perfectly healthy, and suffered in any way. At the age of 20, he was working as a carpenter, Not long thereafter, in the spring of 1887, he began to suffer from headache, and general listlessness, and about the same time his mother noticed that he seemed to become more "simple", and in a general way "fail" (expression of his mother). At the same time his memory became impaired, but at this time no other symptoms were present.

After about a year of this or rather less, during which time the symptoms were slowly increasing, the patient began to walk in an irregular and uncertain fashion. He also complained of occasional pains in his legs.

At the beginning of 1888, that is to say about a year after the onset of the illness, he began to have difficulty in articulation. At the same time or perhaps a little later, a certain stiffness of the whole body was noticed, especially in the lower extremities, which began to contract slightly at the knees and hips. Slight but definite tremor made its appearance in the arm and hands, and gradually increased. All these symptoms gradually became more intense with the result that the patient became more and more helpless. Occasionally there was vomiting. From December 1888, the patient was bedridden, and unable to feed himself.

On the 6th. May 1889, he came under the observation of Prof. Homen who made the following examination:-

The patient is rather small and delicate looking, but his nutrition is good. The expression of his face is childish, stupid and half idiotic, and somewhat staring. Speaking generally he seems to take in what goes on round about him, answers simple questions slowly, as if he were thinking about them, but sometimes he does not respond at all. Speech is slurring and difficult, and restricted to a few words or to a short sentence; on the other hand

he does not miss his letters or make mistakes in his words. Movement of the tongue appears somewhat difficult, but there is no fibrillation. The pupils are of medium size and react alike although a little slowly. Vision is normal, and the other organs of special sense are also normal.

The customary attitude of the patient is as follows:-

He usually lies on his side with his head drawn a little back, although the neck muscles are markedly contracted. When he sits up his head usually moves to and fro in a fine tremor. His mouth is often held open and there are occasionally slight tremors of the lower jaw. Both arm, especially the L. are somewhat flexed, and cannot be straightened beyond an angle of 150°. At the wrist the left hand can be drawn into a line with the forearm, but cannot be dorsally flexed; the first and second phalanges are flexed to a right angle, the third phalanx is in slight dorsal flexion; the fore finger is not so flexed as the others. It is almost impossible to straighten the other fingers. The thumb is contracted, and its movements are very imperfect. The right hand and its fingers is much less contracted and more moveable. Almost always a slight slow tremor of the hand is present mostly from side to side, but occasionally also rotatory. The forearms when they are held free also show a tremor of alternating flexion and extension.

The lower extremities are also contracted, especially at the knee and hip. The knee cannot be extended beyond 150°. Both legs show very definite tremors, especially when the patient tries to straighten them. These consist of alternating movements of the knees and toes.

The musculature is slightly atrophic. The cutaneous reflexes are "weak"; the tendon reflexes cannot be tested well, because of the contractures. There is no obvious disturbance of sensibility and the electrical reactions of the nerves and muscles are normal. The left hand is so tightly closed that it cannot be opened, but the power of the right grasp is 15 on the dynamometer. During this test a wide course tremore becomes manifest.

During his stay in the hospital the patient's condition

gradually became worse in every respect. His perceptive powers seemed to become more feeble, and during the last weeks he never spoke at all, apparently from failure of perception, than from inability to articulate, since even to the end. He could occasionally articulate a few words correctly. As a rule it was more or less unintelligible sounds that escaped from him.

The contractures were intensified, but the tremor became rather less; towards the end it came in attacks, which spread over the whole body and lasted from five to ten minutes. Saliva escaped from his constantly open mouth. During the last few weeks of his life, tonic and clonic attacks of cramp lasting about a minute were sometimes noticed. During his stay in the hospital he had steadily emaciated, and a few slight bedsores made their appearance; On the first of September 1890 his temperature began to rise, and his tonsils became inflamed and swollen. He gradually sank, and on the evening of September 13th, 1890, he died, being scarcely 24 years old.

The post-mortem was held the next day, and of the long description which the author gives, the following are the essential points:-

The contractures are extreme. It is quite impossible to straighten the arms and legs. The cranium is thickened. The dura mater is slightly thickened also; the pia mater is somewhat oedematous, and in one or two places slightly adherent to the cortex underneath.

The weight of the brain (including the cerebellum and the abdulla) is 1060 grams. The convolutions of the frontal lobes appears slightly atrophic, but both halves of the brain are symmetrical, and the convolutional pattern is normal. On transverse section the grey matter of the cortex, especially the frontal lobes seems a little thin. By a section across the basal ganglia it was seen that the middle division of the lenticular nucleus on both sides was softened and discoloured, over an area about 1 cm. long and broad. The other basal ganglia, and the internal capsule were perfectly normal.

There were slight sclerotic patches in the aorta.

The liver weighed 1160 grammes, was of firm consistence, and had a knotty, granular surface. Its capsule was slightly thickened in places. On transverse section, it was seemed to be typically cirrlosed, with numerous nodules of liver tissue, separated by abundant, small, grey-white bands of connective tissue formation.

The spleen was of normal consistence and its capsules smooth. It was not obviously enlarged.

Microscopical eximination.

BRAIN - Nowhere is there any obvious diminution of the medullated fibres, although in a few places in the frontal lobes there may be slight diminution, but it is nothing like so marked as in a case of general paralysis. Where it was present it concerned chiefly the tangential fibres, and the supraradiary network. Over the frontal lobes the pia mater is thickened in places and a little infiltrated with round cells. The neuroglia also appears a little thickened, especially in the tangential layer, but in any case the changes are not nearly so marked as in a case of general paralysis.

The blood vessels are distended with blood, and in some places appear to be widened. The walls of the vessels and of the smallest capillaries are here and there thickened and have a sclerotic or hyaline appearance. In the walls of the vessels are small connections of fine fatty granules, which sometimes bulge into the lumen of the vessel. Very occasionally there are found a few round cells in the adventitial lymph-sheaths. Occasionally also in the blood vessels or rather in the perivascular spaces are yellow coloured refractile pigment granules. There are perhaps slight changes in the large pyramidal cells of the cortex; some of them are normal, others seem small and shrunken or sclerosed with diminution of their processes and with pigmentary degeneration.

In the vessels which leave the middle cerebral artery to supply the basal ganglia the changes which have been already described were more marked than elsewhere. In one

or two places there were very small cellular masses, which looked like thrombi which were commencing to organise.

The pons and the medulla are normal.

SPINAL CORD - The spinal cord, examined at various levels is perfectly normal.

NERVES - The nerves show no changes that can be considered of any significance.

MUSCLES - The muscles appear normal, perhaps here and there a little atrophic, but without further degenerative changes.

LIVER - The nodules of cirrhotic tissue contain as a rule from 3 to 5 lobules, but sometimes more, and occasionally only one. In the strands of cirrhotic tissue are numerous bileducts. Occasionally also there<sup>are</sup> very fine strands of connective tissue between the columns of liver cells and sometimes also between individual cells. In these lobules the liver cells are often quite normal, but others show fatty degeneration. The whole liver picture bears a marked resemblance to that of "cirrhosis hypertrophica adiposa".

C A S E 5.

Wilhelm K. Was born of the 8th. August 1870, Up to the age of three he suffered from slight attacks, the nature of which is not very definite; apparently they were like petit mal. He developed perfectly normally, and up to the age of twelve was "fat and well". In the Autumn of 1882 for no apparent reason he began to suffer from slight attacks of giddiness. At the same time he complained of head-ache, of pains in his limbs, and of a general feeling of tiredness. About the same time his understanding and his memory seemed to fail. Almost from the outset it was noticed that his gait was somewhat uncertain.

After these symptoms had continued for about a year, it was noticed that the patient's speech was becoming

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defective, and at about the same time his arms became stiff so that he could not use them properly. Tremor made its appearance in the upper extremities while the legs also began to get stiff. As a result the latter soon became flexed at the knees and hips.

All these symptoms steadily increased so that after three or four years the patient became bedridden and had to be fed by others. His speech was limited to a very great extent; it was only rarely that he spoke at all, and then with great difficulty. Saliva constantly escaped from his half open mouth. Occasionally he had attacks of vomiting.

On the 11th. December 1888, he was taken to the hospital to be under the care of Prof. Homen it was then remarked that his general look and appearance suggested complete dementia. He did not appear to understand what was said to him or to pay much attention to what was going on around him. He never spoke at all but occasionally unintelligibly sounds escaped from him, and yet if he were disturbed or aroused he could articulate a few words well enough, and even make use of short phrases, of course with difficulty.

The pupils were of medium size and reacted alike slowly to light. Contractures were very pronounced, so much so that the knees were flexed over the abdomen. The arms were flexed. It was possible however to straighten the limbs by a passive movement though not to their full extent. As a result of the contractures and of the patient's mental condition he was reduced to utter helplessness. Tremor was almost constantly observable in the hands and arms, occasionally also in the head and in the legs. The musculature was slightly atrophic, and the patient generally much emaciated. The cutaneous reflexes were "weak". The tendon reflexes could not be tested because of the contractures. The patient's condition steadily deteriorated and he died on 17th. October 1889, being then 19 years old.

The post-mortem examination was held the next day. The contractures of the limbs more especially of the legs were extreme. There were bedsores on the trochanters, and elsewhere.

The cranium was thickened, the dura mater was somewhat thickened. The pia mater was oedematous and in one or two places adherent to the under lying cortex. The weight of the brain was 1160 grammes; this included the cerebellum. The cerebellum, pons, and medulla weighed together 130 grammes. The convolutions of the brain appeared normal with the possible exception of very slight atrophy of the frontal and central gyri. On transverse section the cortex was possibly somewhat thin in the frontal and central regions. On horizontal section through the basil ganglia, the optic thalamus, internal capsule, and the caudate nucleus were perfectly normal. On the other hand, in the middle of each lenticular nucleus, and symmetrical on the two sides was a cavity which began about half a cm. from the upper surface of the nucleus and was 3 cm. long. More than half of the lenticular nucleus was completely destroyed in breadth, and the cavity which was left, contained some serous fluid. The cavity extended to the posterior and inferior end of the nucleus. Round the cavity the tissues were softened for an extent of several millimetres, otherwise the brain seemed perfectly normal.

There were a few sclerotic patches in the aorta.

The spleen was 17cm. long by 11cm. broad, and of firm consistence.

The liver was 21 1/2 cm. long, 13cm. broad, 7 1/2 cm. high. Its surface was markedly cirrhotic. The capsule was in one or two places thickened. On section, the liver was seen to be composed of nodules about the size of lentils or larger, surrounded by strands of connective tissue.

Microscopical examination.

The fine fibres of the cortex, especially in the tangential and supraradiary layers were slightly diminished, and the neuroglia was slightly thickened. In the blood

vessels there were here and there small localised endarteritic changes, consisting of minute granular more or less homogeneous masses, which often bulge into the lumen of the vessel. These masses lay between the intima and the fenestrated membrane, and occasionally seem to brake through the latter. The changes were most commonly seen in the perforating arteries coming off the middle cerebral artery.

The tissue round the cavity in the lenticular nucleus was softened crumbling, and infiltrated with cells, but under the microscope no further changes could be seen in the basal ganglia or internal capsule.

The pons, medulla and spinal cord were entirely normal.

Sections of the liver, as in the first case showed a mixed type of cirrhosis, which was partly multilobular, partly interlobular, partly intralobular. There was marked fatty degeneration of much of the liver tissue; in the cirrhotic tissue bileducts were abundant.

C A S E 6.

Anna K. The eldest member of the family, was born on July 6th. 1862. Her mental and physical developement was perfectly good. In her 20 year towards the end of 1882, exactly the same symptoms as in the case of her brothers, made their appearance. She complained of giddiness, head-ache, general tiredness, and loss of appetite, and at the same time her memory became less good. After about six months or more it was noticed that her walking was a little irregular; at the same time she complained of occasional pains in her legs.

At the age of 22 the muscles began to get stiff and not long after contractures set in at knees, hips and elbows. Articulation became more and more difficult. At this time or a little later tremor appeared, most marked in the arms and hands. All these symptoms steadily increased, so that

the patient was helpless and bedridden. She had considerable difficulty in swallowing, and the saliva escaped from her open mouth.

The patient entered the hospital on August 29th. 1888. She was completely helpless, looked demented, lay apathetic in bed, did not speak at all, and paid no attention to what was going on around her. occasionally she gave vent to a few inarticulate sounds, and yet sometimes she could articulate a few words distinctly though with difficulty. She died from inflammation of the lungs on October 19th. 1888, at the age of 26.

The post-mortem examination was held the next day.

The cranium was thickened, as was the dura mater. The pia mater was slightly adherent in one or two places to the cortex underneath-

The frontal convolutions appeared a little shrunken. On section, both lenticular nuclei were softened in their central part, and coloured a patchy grey-yellow. The brain with the cerebellum, and medulla weighed 1180 grammes.

There were a few sclerotic patches in the aorta.

The spleen measured 12x7 cm. The liver measured 25x14x8 cm. it was obviously cirrlosed, and on section the nodules of liver tissue were seen to be about the size of hazel nuts, though they varied considerably. They were surrounded by firm grey fibrous bands.

Microscopical examination of the basal ganglia showed that in the degenerated area of the lenticular nucleus on each side. There was commencing softening, with degeneration of nerve cells and fibres.

In the blood vessels there were a few circumscribed endarteritic changes. Here and there in the degenerated area slight small cell infiltration was noticed.

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