Diffuse sclerosis (encephalitis periaxialis diffusa) / by L. Bouman ; with 64 illustrations.

TWICE-TOLD TALES

N. HAWTHORNE

DIFFUSE SCLEROSIS

(ENCEPHALITIS PERIAXIALIS DIFFUSA)

BY

L. BOUMAN, M.D.

Professor of Psychiatry and Neurology, Utrecht University

WITH 64 ILLUSTRATIONS

BRISTOL: JOHN WRIGHT AND SONS LTD.
LONDON: SIMPKIN MARSHALL LTD.

1934

PRINTED IN GREAT BRITAIN BY
JOHN WRIGHT AND SONS LTD.
BRISTOL.

CONTENTS

DIFFUSE SCLEROSIS

CHAPTER I

INTRODUCTORY

THE publications concerning diffuse sclerosis or encephalitis periaxialis diffusa have been many and their dates of appearance various. It is time both to form as clear as possible a conception of the nature of the disease and to make a general survey of clinical observations and histopathological facts, even though we remain in the dark about the etiology.

The fact that during the last few years the diagnosis of diffuse periaxial encephalitis could be made during life and be verified at autopsy should stimulate the search for more positive symptoms, since at present it is often made by exclusion. It is very unsatisfactory to be limited, as we are, to the description of clinical histories and of anatomical material; and yet, for many reasons, we still cannot get beyond these limitations. When we remember that disseminated sclerosis was unknown a hundred years ago and that Valentiner in 1856 could collect only fifteen descriptions of it from medical literature, whereas we now diagnose it every week in our out-patient department, we cannot but hope that we shall in time learn more about diffuse sclerosis too. We may be the more hopeful because it shows some relationship to disseminated sclerosis both in clinical and anatomical respects. But we have great difficulties to contend with. We speak of 'diffuse sclerosis' or 'encephalitis periaxialis diffusa' when we wish to connote a certain definite anatomical substratum—one which in former days was practically never discovered except on the dissecting-table, and which in many cases even now is a surprising discovery in the post-mortem room.

Although the typical changes of this form of encephalitis had been observed by other investigators, Schilder deserves great praise, for his more minute histopathological examination, made possible by the latest methods of staining, enabled him to describe them in much more detail. They had not been generally known to the pathological anatomists. It was chiefly the neurologists interested in pathological anatomy who searched for new cases of the disease. But progress in

our knowledge of it can be but slow; many cases occurring in childhood cannot for various reasons be verified post mortem. The examination may be omitted or not permitted, or the patient may have gone home to die. With some hesitation we must add that even at the post mortem now and then, the changes are not recognized and the case never reaches the neuropathologist. The latter, moreover, is too much accustomed to give his chief attention to the cortex, although in the last few years changes in the white matter have for reasons unconnected with our subject claimed more attention than before. The cortex in this condition is often fairly free from abnormalities and the adjoining pia shows no important changes.

So this we may say is really of only secondary importance. But a more serious difficulty is this: perhaps we are not talking about a single entity at all. Globus affirms that what we are dealing with is a group of processes all leading to the same result—namely, the diffuse sclerosis of the white matter, and Weimann also says that the term 'diffuse sclerosis of the brain' covers many disease processes of types which the state of our knowledge will not let us differentiate as yet. Moreover, there are hereditary forms of the disease probably closely connected with the Pelizaeus-Merzbacher disease and with amaurotic idiocy. In separating this special hereditary group, it must be borne in mind that heredity also plays a part in disseminated sclerosis which occurs sometimes in uniovular twins, and also in the new groups of hereditary disseminated sclerosis described by Sillevis Smitt and Smit.[108]

Sometimes we come across a case of diffuse sclerosis that runs a fairly rapid course, and then one running a chronic course. Sometimes short remissions are observed. French writers have reported even long remissions and have mentioned the possibility of recovery.

The various localizations are, of course, the cause of very varied symptoms. If we compare the first case described by Schilder with cases which I shall describe here, we shall find such important differences that it is difficult to class them under the same head. And this first case, which the writer looks upon as being of inflammatory origin, which is considered by Neubürger to be of degenerative origin, and is looked upon by Lewy as neoplastic, shows how many different anatomical views are possible. This can be explained by the fact that what one person calls an inflammation is looked upon by another as the result of a degenerative process, the lymphocyte infiltration being then regarded as a mere reaction of the type known as 'symptomatic' inflammation.

If we accept the criteria of Collier and Greenfield,[32] we have the following symptomatic picture:—

"A malady usually occurring in children and young subjects

with no tangible causal factors or antecedents. The onset is a few days, the course progressive with some remissions to a fatal issue, the duration from a few months to three years.

"The chief sign is cerebral blindness which becomes complete, to which is added mental reduction and increasing spastic paralysis. Unsteadiness from parietal involvement and deafness from temporal involvement may be conspicuous. The amentia increases and passes into coma which terminates the illness. The condition, usually bilateral, may commence on one side or may be confined to one side."

The anatomical course of the disease is thought to be as follows :—

"This affection commencing bilaterally in the white matter of the occipital lobes, spreads forward through the white centres by contiguity. It spares the cortical grey matter and subsulcine arcuate fibres and the basal ganglia either completely or at least for a very long time. It advances throughout the central white matter of the hemispheres and may descend along the white matter of the capsules, crura and pons. It affects last of all the white matter of the frontal and temporal poles, and according to the stage of the disease at which death occurs these regions may be either completely spared or affected to a lesser or greater extent.

"Two-thirds of all the cases which have been reported have corresponded more or less exactly to the clinical picture which, we submit, is the usual one in this disease."

These writers say further: "The majority if not all of these cases could have been diagnosed with ease and certainty upon a recognition of the clinical type which we lay down."

They have also paid attention to the fact that "the lesion usually commences in the posterior region of the hemispheres and spreads forward thence, yet it may in fact take origin in any part of the white matter and extend sometimes narrowly and slowly, sometimes widely and quickly".

However much we may admire this description of the clinical aspect, still it has not been confirmed that "the majority of these cases could have been diagnosed with ease and certainty upon a recognition of the clinical type which we lay down." Very many who have described the disease later on will have read this publication, and one gets the impression that the diagnosis has been made with hesitation, or as a possibility.

D'Antona,[2] in discussing the symptomatology given by Collier and Greenfield, points to the fact that cortical blindness is not always present, and adds the following: "Very often a tumour or brain-softening cannot be excluded, and further visual symptoms are too often connected with cerebral conditions to be of any help in the

diagnosis of encephalitis periaxialis diffusa. The diagnosis of neuromyélite optique aiguë must also be considered."

D'Antona further remarks: "we can only presuppose an encephalitis periaxialis diffusa where we have to deal with a subacute affection which is progressive, found in young people, not accompanied by fever or in any case only slight and irregular fever, and exhibiting psychical symptoms suggesting bilateral localization. The supposition gains more probability when the focal symptoms point to an occipital localization of the process, and when the paralysis of the legs extend progressively to the arms. The condition of the fundus, the general condition of the patient, the results of examination of the cerebrospinal fluid, an investigation as to the etiology together can lead to a confirmation or negation, as the case may be, of the diagnosis."

I should like to add that I consider that Collier and Greenfield, in speaking of the differential diagnosis with regard to the presence of a tumour, put the matter rather too simply when they say:—

"But the mild nature of the optic disc changes and their non-progression to the more intense degree of papillitis in the presence of signs of rapidly increasing and widely spread cerebral destruction are important in making a distinction between the two conditions. Especially indicative in this connection is the bilateral affection of the hemispheres from the first, in so many of the cases, which in the absence of definite indications of brain-stem affection, is very much against the diagnosis of tumour."

For the rest their description is of great value, but one must be critical of these criteria, because we often have to do with important exceptions both in cases of encephalitis periaxialis diffusa and in cases of tumour. In cases of tumour we find all kinds of variations in the choked discs. And in the cases of encephalitis periaxialis diffusa there are all kinds of variations in the fundus abnormalities, as we shall see later on, quite apart from the fact that many cases cannot be examined accurately or even at all, since the psychical condition of the patient does not admit an examination.

The second criterion, "the absence of definite indications of brain-stem affections", is, as d'Antona remarked, a more valuable one, but here too there is the possibility that we may get the same symptoms when we are dealing with tumours in the mid-line or with bilateral tumours (ventricles).

Formerly a distinction was made between encephalitis periaxialis diffusa and the Pelizæus-Merzbacher disease, the 'aplasia axialis extracorticalis congenita' (e.g., Schilder and others), and then later on the connection between the two was more emphasized, on the grounds of their anatomical analogies. In some cases a connection has been sought with amaurotic idiocy because of the primary affection of the

white matter of the cerebrum and cerebellum (Globus). Krabbe has in his cases specially mentioned this connection with amaurotic idiocy.

The points of similarity to the Pelizaeus-Merzbacher disease are the occurrence in the early years of childhood, the evident destruction of the white matter, and the clinical similarity. The clinical course is somewhat different in some cases of Merzbacher which were not progressive. He showed the similarity with familial amaurotic idiocy in the progressive and fatal course of a familial degenerative affection. Globus and Strauss[49] remark that the clinical manifestations such as those described by Merzbacher and those by Schminke, who speaks of the encephalitis interstitialis Virchows with gliosis and calcification, and by others, which usually are diagnosed as encephalitis periaxialis diffusa or diffuse sclerosis, justify the creation of a new clinical group. "Thus an abrupt onset, a rather rapidly progressive course, characterized by mental deterioration, rapidly advancing spastic paralysis, epileptiform attacks, features of decerebrate rigidity, ocular palsies, and other ocular manifestations such as nystagmus, optic atrophy, and blindness without optic atrophy followed by a rapid decline with fatal issue (within two years) are features fairly typical."

After an historical description of the disease, our own cases will be described, and afterwards the pathological anatomy.

It has been difficult to collect and sift the several cases in order to give the various clinical and anatomical facts the right place in the frame in which they belong. Perhaps still more confusing is it to read these repeated enumerations. The method followed is, however, the only one possible, as we are yet searching in the dark and therefore are compelled to consider all singularities, because they may be of some future value, each in its own way.

My own cases demonstrate that it is possible to make a diagnosis. (In four other cases not yet treated in this book we have also made a correct diagnosis.) It can only be done by being quite *au fait* with, and making a survey over, the cases in the literature. The clinical symptoms and anatomical alterations treated extensively may be a guide when the diagnosis of diffuse sclerosis must be considered. It is, however, also possible that this guide may help make divisions in the probably complex framework of the so-called diffuse sclerosis, the unity of which till now is formed by the anatomical findings. When there is an increase in the appearance of the diffuse sclerosis, perhaps attended with the increase of other diseases of the central nervous system, the search for etiological and hereditary factors may eventually throw more light.

Some pathological moot points have also been treated separately—inflammation or degeneration, and the rôle of the glia tissue. Both points are worthy of description in a separate monograph. In these

questions I have also followed the method of referring briefly to the ideas of all those who have given special attention to them.

Nomenclature.—Globus and Strauss[49] say that it would be better to speak of "progressive degenerative subcortical encephalopathy." Schilder[98] came to call it "encephalitis periaxialis diffusa" by comparison with disseminated sclerosis, both the acute and chronic forms of which he found to present similarities with the encephalitis periaxialis diffusa (acute form in his first, chronic in his second case). (Marburg[80] called disseminated sclerosis an "encephalitis periaxialis scleroticans".) Marie and Foix[82] call the disease a "sclérose (intra)-cérébrale centrolobaire et symmétrique"; Flatau[39] calls it "encephalo-leucopathia scleroticans". Hermel[58] speaks of "encephalomyelomalacia chronica diffusa"; Austregesilo, Gallotti and Borges[3] speak of "leucoencephalopathia diffusa." Spielmeyer[111] speaks of "sclerosing inflammation of the white matter of the hemispheres." Patrassi[89] calls it "leukoencephalopathia myeloclastica primitiva," and d'Antona[2] "encephalopathia extracorticalis diffusa type Schilder". The familial cases of diffuse sclerosis are called "leukodystrophia cerebri progressiva hereditarea" (*see* Curtius[34])

CHAPTER II

HISTORY

Foix and Julien Marie[40] and also Guttmann[52] have tried to find publications about the disease containing descriptions of the symptomatology and pathological anatomy similar to that given by Heubner, Schilder, and Marie and Foix. Marie and Foix[82] report that what they described as "sclérose cérébrale centrolobaire" they could not find in the works of Hayem, who described the "encéphalite subaiguë hyperplastique"; nor in the works of Bourneville, who separated a new disease, the "sclérose hypertrophique tubéreuse"; nor in the various groups of encephalitis described by Chartier in his treatise; nor in the work of Babonneix on "encéphalopathies chroniques infantiles".

Guttmann quotes the description of Schmaus[101] about the "diffuser Hirnsklerose" and reminds the reader that Frankl-Hochwart[42] had collected 22 cases from literature which ought to belong to this group.

Schmaus[101] says the following: "Diffuse brain sclerosis is the word used to denote the various conditions in which the interstitial tissues of the brain are increased, this being the only or at least the most important change. Not only cases of brain hypertrophy but also certain cases of brain atrophy, in which shrinkage occurs of what was first hyperplastic connective tissue, may be classified under this head. There may be diffuse alterations of this nature following progressive paralysis and in disseminated sclerosis occurring as an extension of localized foci. In most of these cases the diffuse sclerosis is accidentally found along with other more characteristic alterations. Along with these cases there are others in which a diffuse sclerosis must be looked upon as the accidental cause of a particular symptom complex."

If one studies Frankl-Hochwart's work published in 1903, entitled *Zur Kenntnis der Pseudosklerose*, it is clear that the writer has tried to differentiate pseudo-sclerosis from diffuse sclerosis. He has given a description of 22 cases but it is clear that the disease is regarded too broadly, although a few of the cases evidently really were what we call to-day the diffuse sclerosis.

In 1897 Heubner[59] published an article: "Ueber diffuse Hirnsklerose". He quotes a remark of Leube in his *Specielle Diagnose*

innerer Krankheiten, "In diagnostischer Hinsicht können wir mit dieser Krankheit bis jetzt, offen gestanden, nichts anfangen," and says further, "Most writers look upon the disease as congenital or at least present in very early childhood". Heubner described a case to draw attention to the fact that a child may show no interference with health during the first three, four, or more years, and then develop the disease with a fairly characteristic combination of certain symptoms. In this patient the symptoms began about the age of $4\frac{1}{2}$ years. The mother attributed the change to a fall on the back of the head (the child was then $3\frac{3}{4}$ years old), and the serious bleeding which took place from the wound. Nothing special was noticed about the child before, although the fact was emphasized that the development of speech had been faulty. At the age of $4\frac{1}{2}$ he did not speak fluently, but only little and not clearly.

The boy became slow in all his movements, began to walk shakily, and was soon not able to walk at all.

He was then $5\frac{3}{4}$ years old. The legs became spastic, remaining stiffly stretched out at hip- and knee-joints, the feet being held in the equinovarus position. The arms showed tremors when trying to carry out intentional movements; later on they too were spastically contracted. Fairly early on there were difficulties in swallowing, and the speech became gradually worse, so that fairly soon after the patient was confined to bed; he could only utter inarticulate sounds. Meanwhile the child showed mental defects and became incontinent. He never complained of headache. His appetite became less, and he vomited occasionally. He began to lose weight at the beginning of his illness and this went on getting worse.

When taken notice of, the child moved his head continuously from side to side, going on doing so for some time afterwards; the upper arms were lifted up several times in succession at fairly regular intervals and then were dropped, while the fore-arms were kept in a spastic position.

While being examined after admission to the hospital the child appeared to take notice when spoken to, he laughed in a friendly way and made some grumbling sounds. When food was offered to him he opened his mouth. When hungry, thirsty, or needing to pass stools he became restless, and it was perhaps at such times one saw the above-mentioned movements of the head and upper arms; often too he cried, but in a whisper. His neurological state is described as follows:—

The upper arms lie relaxed on the thorax, the lower arms lie flexed on the upper arms, and the hands are rectangularly flexed at the wrist and usually lie on the thorax when not making the above-mentioned movements. Fingers and thumb are often flexed inwards,

there is often a slight tremor of the hands. The contractures can easily be relaxed but soon return. A certain amount of spontaneous movement is also now and then possible in the contracted parts. Both legs are a little flexed (roughly speaking at an angle of 160°) at the hip-joints. Both ankle-joints are markedly adducted and extended, the soles are concave, and the foot is shortened by strong flexion contractures. It is not possible entirely to reduce this 'club-foot' position, the foot cannot be completely abducted although the plantar flexion can be passively adjusted. There are no spontaneous movements in the legs; if one lifts the boy up and then tries to put him on his feet, the upper legs are crossed.

The boy can see. Ophthalmologic examination: Both pupils equal, react to light and accommodation. Edges of the disc are not clear. Veins thick and tortuous. Signs of congestion in the papillæ. Lumbar puncture revealed a pressure of 15 cm., cerebrospinal fluid clear.

During the first one and a half months after admission to hospital there was apparently a certain improvement, since the child put on weight; the friendly grin, and the turning of the head from side to side, became more lively, whereas the frequent movements of the head and upper arms mentioned above were less noticeable. After a diffuse bronchitis accompanied by rise of temperature there was a continued regression; the contractures in the upper arms became continuously worse, the patient became much thinner, the papillæ of the eyes passed into a state of optic atrophy.

After the disease had lasted about a year the patient died. At the autopsy it was found that the whole of the cerebrum was less in volume than normal, and there was an increase of fluid in the sub-arachnoid space. The pia was in many places opaque.

It appeared that the whole of the white matter was unusually hard and resistant, the colour was dull yellow, like old ivory. The grey matter, too, was harder than normal, although its consistency had not been so much altered as that of the white matter; its colour was pale grey and pale yellowish-grey; white and grey matter were more sharply defined in relation to each other than in the normal brain. The cerebellum, too, had become harder in consistency, as also the pedunculi cerebri, pons, and medulla oblongata. The diagnosis of tumour had been made. Heubner says that had he possessed a more accurate knowledge of the symptomatology of diffuse brain sclerosis, he would perhaps have been able to make the diagnosis during the life of the patient.

Schmaus describes a child from the Munich pædiatric clinic. It was quite healthy up to the age of $1\frac{3}{4}$ years (it had already walked

and talked), and died after the disease had lasted one and a half years. The clinical picture was similar to that described by Heubner. An accurate anatomical examination was made which led Schmaus to think there had been an inflammation. Heubner quotes a case of Bullard's[25] (13-year-old boy in whom, as in Heubner's case, there had been a preliminary head injury. Slow, dull, forgetful, clumsy with hands and feet, then demented. Paresis of cranial nerves, left-sided hemiparesis, slow speech).

Three cases in adults have been described by Erler[36] (quoted by Heubner); one was a case of Strümpell's,[117] and one of Kelp's.[65] Erler had collected a larger number of reported cases, but did not make a strict distinction between diffuse and disseminated sclerosis.

It is chiefly due to the influence of Schilder that the disease is now better understood, owing to the accurate histological examinations which have been made. We shall make a short enumeration of what he found in 1912 in his first case :—

A girl of 4 years of age had headache and vomiting, was apathetic and noisy, had a congested papilla and a limited field of vision, left abducens paresis, slight nystagmus, and anarthria; later, mutism and crying. After operation there developed a right-sided spastic hemiplegia; pressure in cerebrospinal fluid increased. The duration of the illness was four and a half months.

Histopathological: Bilateral demyelinization in the white matter of the hemispheres over large areas; cortex almost intact. Normal tissue sharply demarcated from the diseased; myelin sheaths disappeared; axis cylinders relatively intact. Atypical and degenerated glia cell-forms, fat granulation cells too, in the vessel sheaths. Infiltration of the blood-vessels with lymphocytes.

Schilder's second case (observed by Haberfeld and Spieler[54]) was that of a boy of 7 years old. Headache, incontinence of urine and fæces, disturbances of swallowing. Apathetic, noisy, crying accompanying the stretch cramps, and apart from them also, for hours at a time, grimacing. Disturbances of the ocular movements, of vision, of the gait; aphasia. Bilateral paralysis and contractures, pes equinovarus, intention tremor right and left. Babinski, tonic and clonic spasms, spontaneous chewing and swallowing movements. Fundus intact. Duration two years.

Pathological anatomy: Focus of hard consistency in the white matter of the left and right hemispheres. Demyelinization left and right; destruction of the axis cylinders, many, however, being relatively intact. The glia was changed. Strong glial fibre proliferations; many fat globule cells. Infiltration of the vessel sheaths with, chiefly, lymphocytes.

Here the symptoms could be compared with those found in Heubner's case. Schilder spoke then of encephalitis periaxialis diffusa, in the clinical sense not forming an entity : it might be like the clinical picture of cerebral tumour, disseminated sclerosis, or Heubner's diffuse sclerosis.

Hence there has been at first an odd case described, later on many more ; but we need still more to have enough data to understand the disease better. The more diagnoses are made during life, and the more accurately the post-mortem examinations are carried out, the more easily we shall be able to conquer the difficulties which doubtless still exist in the study of this disease.

CHAPTER III

PERSONAL CASES

I. ADOLESCENTS AND ADULTS

For various reasons I have thought it advisable to separate cases of diffuse sclerosis in adolescents and adults from cases of the disease observed in children. I have not made a distinction between the early infantile forms (during first three years), and the later infantile cases (after the third year), and the juvenile form (10 to 20 years).

I have made a distinction, however, between the cases occurring in children (until to 15) and those which occurred after 15 years of age. I have chosen 15 years of age because, generally speaking, in my 100 cases those under 15 years of age represent more a distinct group than those occurring after this age. One can say of this group that one is fairly sure of the diagnosis, of the course the disease will run, and the histopathological alterations which one will find post mortem. Besides, I had, as chance would have it, 50 cases of each of these two groups.

I begin with the first cases of mine published in *Brain*[21] (1924). Then follows the case of an adult diagnosed by myself during life; next I shall describe a case kindly given by Professor Tendeloo in Leiden (observed by Dr. Gans), one which had not been definitely diagnosed. I mention these *Cases III* and *IV*, following on my *Cases I* and *II*.

Are we any further forward now than a few years ago when I wrote in my article published in *Brain*, "this review clearly shows that the symptoms are so variable that it is even impossible to discover an approximate unity in the diversity"? I believe that we really have advanced, as is proved by the cases diagnosed during life by others and by myself. Even now, however, there are difficulties in the diagnosis, and still "disseminated sclerosis, brain tumour, or organic disease of the brain" are the diagnoses generally made.

CASE I

Clinical History.—Mrs. A., born on April 19, 1889, a married woman and mother of five children, was admitted into the Valeriuskliniek at Amsterdam, on Aug. 27, 1921. Her father was addicted to

drink, one sister suffered from nervous attacks, and her mother was nervous.

No particulars were known concerning the patient's youth except that she had been a good pupil at school. She had complained of a painful spot on the head for years. There had been no miscarriages; her last confinement occurred on June 28, 1921—that is, exactly two months before her admission to the hospital. After the childbirth, which was without any complications, the patient complained of dizziness: she sometimes had to catch hold of objects to prevent herself from falling, and she occasionally upset things or dropped them. She had also a peculiar way of putting things beside the table instead of on it. She occasionally felt shocks, starting from her head, which affected her whole body. She could no longer estimate distance; she would go to the door and did not know when she had reached it. Though she often felt sick she did not actually vomit; lately she had suffered from headache, and everything seemed to whirl before her eyes. She complained frequently of heaviness and loss of power in her left arm. She was constantly worrying about herself and feared she would go mad. The patient complained of being dizzy; objects she looked at did not appear to turn round, but she felt as if she herself were being moved up and down, as in a boat. On bending quickly this symptom became worse. Lately she had had a buzzing noise in her right ear and she believed she had become more deaf. She had frequent attacks of pain behind her right ear and a feeling of rigidity in her neck. Her eyesight had deteriorated and she found it more difficult to measure distance. At times she had visions of men, animals, or stars.

Somatic examination showed that the patient was anæmic and had slight albuminuria, but no casts were found in the sediment. Her blood-pressure was 120. Percussion of the skull caused no pain. There was a left-sided hemianopia; the left vision was $\frac{1}{2}$, the right 1. The optic discs on both sides were congested, particularly the left. The functions of her other cranial nerves were intact. There were no auditory disturbances. Sensibility of all qualities was unimpaired. Only an upper abdominal reflex could be obtained; it was slight but equal on the two sides.

Sept. 3.—While lying in bed quietly she felt as if she were moving, and she complained of a disagreeable feeling when sitting up, and of headache and dizziness.

Sept. 5.—More headache than before; also pain in the neck.

Sept. 9.—The patient had an epileptic fit; she made a noise, turned head and eyes to the right, moved both arms, but especially the right, drew up her legs, and ground her teeth. For a few minutes she was comatose, with a pulse-rate of 36. She lay on her left side,

and saliva dribbled from her mouth. A very doubtful Babinski reflex was present on the left side. No incontinence occurred. After this fit she was disoriented, drowsy, and amnesic for some hours. Her pulse became gradually normal. She remembered nothing of the attack.

Sept. 12.—The Wassermann reaction in her serum was 0·2. The Wassermann reaction in her cerebrospinal fluid was negative, but this was under high pressure. The Nonne reaction was slightly positive, but there was no pleocytosis.

Sept. 17.—Increasing headache, drowsiness, and a slow irregular pulse (40 to 60) varying in frequency and in volume. The cerebrospinal fluid was at a pressure of 65 cm. After lumbar puncture the pulse was quicker, though still irregular. Nonne's reaction was still slightly positive, but the Wassermann test was negative and there was no pleocytosis. After the puncture there was, for a short time, improvement in her general condition, but owing to her poor pulse, the epileptic fit, and an increasing drowsiness, trepanation was decided upon. The congestion of the optic discs and high fluid pressure gave rise to the suspicion of a tumour or cyst. The hemianopia, subjective visual perceptions in the blind parts of the visual fields, and a suspicion of an "überschüssiges Gesichtsfeld" pointed to the disease of the occipital lobe.

Sept. 20.—Operation. Neither trepanation nor puncture revealed anything abnormal in the right occipital lobe.

Sept. 27.—The patient felt better, but complained of double vision. The fundi remained unchanged.

Oct. 5.—Eyesight and hearing diminished rapidly. The patient vomited once or twice.

Oct. 12.—General condition fairly good, but the patient complained of headache.

Oct. 24.—General health satisfactory, but the patient was psychically on the decline. She no longer recognized her physician and was scarcely able to obey any order. There was perseveration of orders once given and successfully executed. Vision was so much reduced that she could no longer fix individuals in her room, and she spoke to persons who were not present. After severe attacks of frontal headache she had violent fits of screaming.

Oct. 28.—The patient returned home. Left and right vision 1/60 at the most. There were no longer any disturbances in the fundi. More accurate examination was impossible.

Feb. 8, 1923.—The patient was examined at home; naturally this examination could be only incomplete. The most striking symptoms were: paresis of both legs and of the right arm, and tenderness of the right leg. The right Achilles reflex was brisker than the

left. She had now developed cystitis and severe bed-sores, was very drowsy, and could not recognize anyone.

Feb. 28.—The patient died. The brain was removed five hours after death.

Pathological Examination.—

Macroscopical Anatomy.—By far the greater part of the hemispheres had undergone a greyish-yellow change, which was, however, limited to the white medullary matter.

Histopathology.—This revealed disappearance of the myelin sheaths with but few exceptions, and considerable changes in those which remained. The fibræ arcuatæ, however, were unaffected (*Fig.* 1).

Fig. 1.—*Case I.* Demyelinization in a large territory of the white matter of the brain. A thin layer directly under the cortex has been spared. (Weigert-Pal stain.)

The next striking feature was the dense infiltration of the adventitial coats of the vessels with lymphocytes (*Fig.* 2), a smaller number of cells similar to plasma cells, 'mast' cells, scavenger cells, oval nuclei, swollen endothelium-like nuclei and pale swollen nuclei similar to the nuclei of Nissl's 'plump' cells ("gemästete" glia cells). Many of the endothelial cells of the infiltrated vessels contained swollen nuclei. An increase of mesenchymatous tissue was observed forming nets between the vessels (*Fig.* 3).

The axons persisted, but staining revealed a considerable change in the majority of them. This explains the absence of secondary degeneration of the brain-stem. Unfortunately it was not possible to obtain the spinal cord for examination.

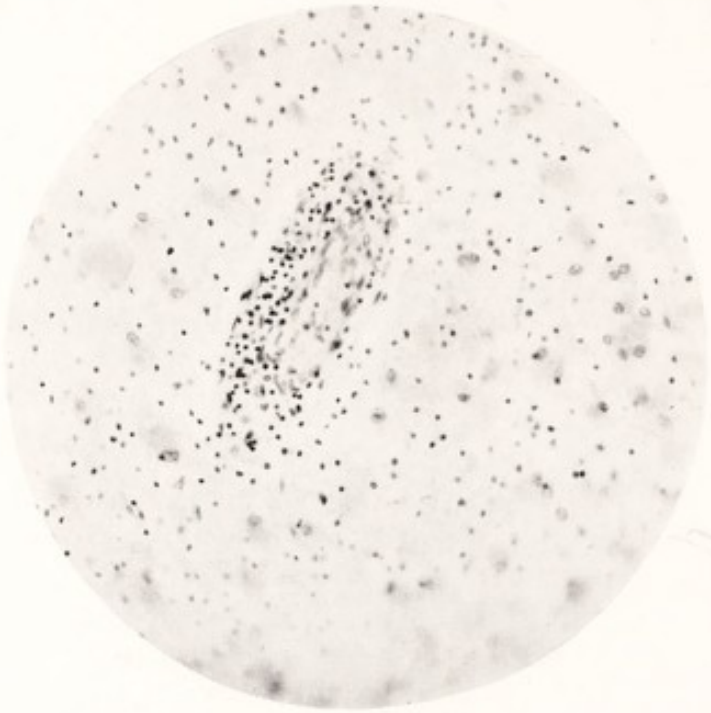


FIG. 2.—*Case I.* Perivascular infiltration and many 'plump' macroglia cells ('gemästete' glia cells). (Hematoxylin-eosin stain.)

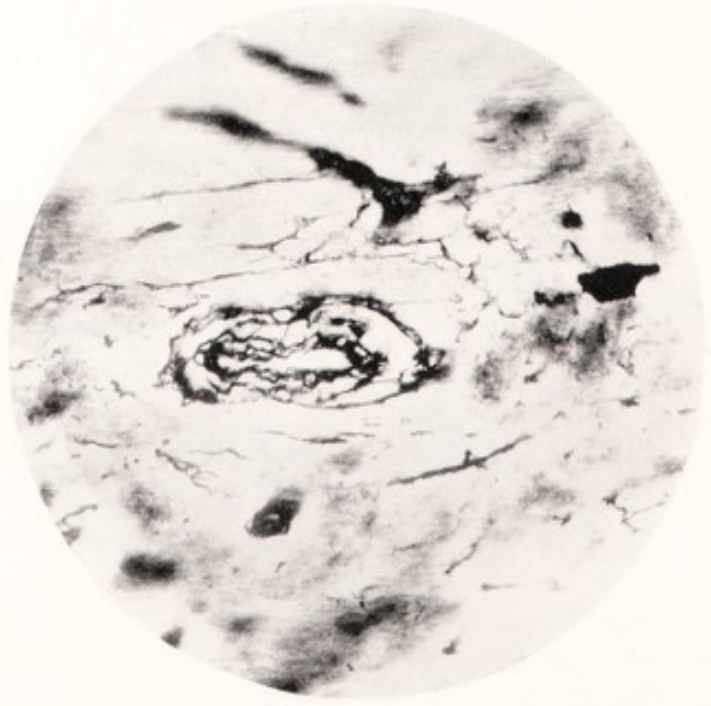


FIG. 3.—*Case I.* Hypertrophy of the reticular fibres breaking into the nerve parenchyma from the vessel wall. (Achucarro stain.)

Hæmatoxylin-eosin preparations revealed 'plump' glia cells containing one or more nuclei, which were most numerous close to the vessels. Further, many glial nuclei of irregular shape, fibre clews, monster glia cells, and an excessive development of glial fibres were present. Scavenger cells were found in relatively small numbers both around the vessels and freely scattered through the tissue. Finally, changes were observed in the brain-stem exactly similar to those which occur in patches of disseminated sclerosis (*Fig.* 4).

Fig. 4.—*Case I.* Small patches of demyelinization in the medulla oblongata as found in disseminated sclerosis. (Spielmeyer's stain.)

CASE II

Clinical History.—A young unmarried man of 20 was admitted into the asylum of Wolfheze (Jan. 15, 1919), with the following history :—

He was delivered by application of forceps, had been very backward from birth ; was long in forming clean habits, and learned to walk rather late. Until he reached the third form all went well at school, but he made no further advance. He read slowly and was scarcely able to write or cipher. He was clumsy and was inclined to make stereotyped movements with his body ; he masturbated frequently. In his youth he suffered from rickets. His sister was backward too. The diagnosis of imbecility was made. When intelligence tests were applied many defects were discovered.

June, 1920.—An ataxic gait and a tendency to fall were noted.

Aug. 4, 1921.—The patient had epileptiform attacks in which both the head and eyes turned towards the right. In addition to these fits he was subject to convulsions which involved the right half of the face and the right arm and leg, and at times spread over the whole body. During the fit the left arm was flexed in a tonic attitude close to the head; no convulsions were observed in the left arm. The left leg was also in tonic contraction, but sometimes convulsed too.

Two hours after the attacks ceased the right arm was very weak, the left spastic, and the right corner of the mouth drooped; the right leg was weak and the left spastic. The abdominal and arm reflexes could be obtained. The knee-jerks were very brisk, the left rather more so than the right, and the Achilles-jerks were also brisk. Babinski's sign was not present.

Aug. 13.—Upward and downward movements of right hand and arm occurred; the right leg was continually flexed at the knee and hip, and the head was rigidly turned towards the right. The left arm was weak and the right spastic; slight clonic movements of the right foot and calf muscles occurred, the foot being in the varus position. Babinski's sign was present on the right side. The left foot was weak and spastic, but Babinski's sign was not obtained. The knee-jerks were brisk but the Achilles-jerks were normal. The right leg was hyperalgesic. When the left leg was pricked the right was drawn up and the left moved slightly; pricks on the left foot caused dorsal flexion of all toes. Otherwise sensibility to touch and pain were not disturbed. Pricking the paralysed left arm caused abnormal movements of the right arm. The pupils were dilated and the eyes turned towards the right.

Aug. 19, *Sept.* 2, 9, 18.—Seizures, which ceased on the administration of amylene hydrate.

October.—The patient scarcely spoke and there seemed to be some disturbances of speech. He frequently moved his upper and lower limbs; the right leg was constantly kept rigidly flexed at the knee and hip.

November.—A condition of progressive dementia. The patient laughed or cried on being addressed; he answered no questions and hardly spoke, but often whined and moaned.

Jan. 2, 1922.—The patient became comatose; after about half an hour he began to vomit and developed convulsions of the whole body. Epileptiform fits occurred at irregular intervals which could not be controlled by amylene hydrate. The temperature rose to 40° C.

Jan. 3.—The left arm was in constant motion and the left corner of the mouth twitched. The left leg, which was not now paretic, was sometimes drawn up, but more commonly extended. There was no paresis of the right arm, but the right leg was very spastic and dropped

inertly when lifted up. The abdominal reflexes could not be evoked, but the tendon reflexes of the lower limbs were normal. Babinski's sign was obtained on the left side but not on the right. The head and eyes were turned towards the left, and there were slight convulsions of the left arm. The patient was very drowsy and moaned continually.

Jan. 5.—The patient had fifty-two fits.

Jan. 6.—Only two slight seizures; comatose.

Jan. 7.—Stationary coma; when the lips were touched the patient opened his mouth widely.

Jan. 9.—Died.

Pathological Examination.—

Macroscopical Anatomy.—Even to the naked eye there appeared a surprising similarity to the changes found in *Case I.* Here, too,

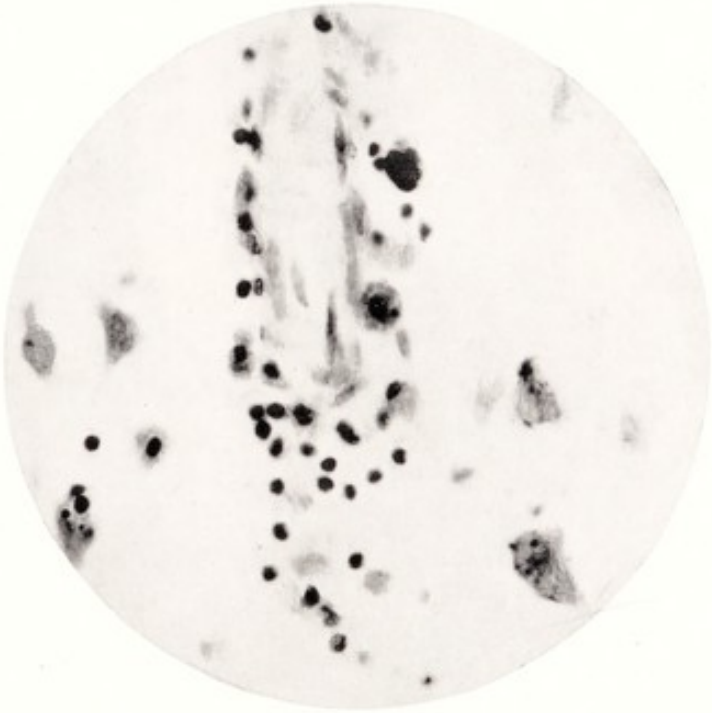


Fig. 5.—*Case II.* Slight perivascular infiltration around a vessel in the fifth layer of the cortex. (Weigert-Pal stain.)

the changes occupied almost the entire white matter of both hemispheres, and they appeared to be more severe, for the affected tissue was more gelatinous.

Histopathology.—Compared with *Case I*, a considerably larger number of myelin sheaths were preserved, and the fibræ arcuatæ were intact also. The number of vessels was not increased and they were not infiltrated, with the exception of some of the vessels on the margin of the diseased area, round which there were connective-tissue nuclei and lymphocytes (*Fig.* 5). This points to a difference between the centre and periphery of the areas of disease.

The axons were also more normal than in *Case I*, and no secondary degeneration was discovered; the spinal cord, however, was not available for examination.

The 'gemästete' glial cells which occurred here were smaller than in *Case I*. Many glial fibres, glial nuclei, and green pigmented scavenger cells were seen. This case exhibited changes in the pia, and the cortex was affected. In the outer layers of the pia a diffuse infiltration of round cells, interspersed with 'mast' cells, could be seen, and there was some perivascular infiltration by lymphocytes and large scavenger cells in the fifth cortical layer. Many ganglion cells of the fifth and sixth layers exhibited tigrolysis and were surrounded by satellites.

There were many clusters of pigment granules in the sixth layer and between the fibræ arcuatæ; these were also present in the pallidum and ansa lenticularis. In my opinion these clusters were associated with scavenger cells, since it was possible to trace the gradual transition of green pigmented scavenger cells into these clusters. The cerebellum exhibited congenital anomalies.

CASE III

Clinical History.—Mrs. V., 28 years old, married, mother of three children, was admitted to hospital on Nov. 25, 1928, with the following history:—

Four weeks before admission the patient was frightened by a horse; a week later she could not see well. A week after that she remained in bed, vomited, and was paralysed on the right side. (The doctor advised a walk every day.) She walked up to five days before admission, got worse rapidly, began to vomit badly and to roll her eyes, and became very thin. According to the husband she had not been disorientated before, she slept a great deal, made sudden movements in her sleep, and gnashed her teeth. It was reported that four days before admission she had a rise of temperature up to 40° C.

On admission she appeared to be disorientated; in trying to give a hand she moved her hand above her head, left as well as right. She was incontinent, and did not recognize a few objects shown to her. Urine: albumin very weakly positive, a few hyaline cylinders.

A lumbar puncture was made and all the reactions were found to be negative. Consultation with the ear specialist excluded the possibility of an abscess. The expression on the face was all the time almost the same, more or less painfully drawn, showing great displeasure (*Fig.* 6).

Examination with the ophthalmoscope showed the edges of the papilla on both sides to be vague, especially on the left side; the pupil

reaction was slow, and there was an abducens paresis on the left side (*Fig.* 6). The head was thrown back to a slight extent in the pillows, stiffness of the neck was thought to be present; pain when the head was moved, arms in contracture.

The right tendon reflexes were diminished, the left fairly brisk. Abdomen scaphoid, abdominal reflexes absent on both sides. There were contractions in the arms, also in the right quadriceps. No pathological reflexes.

When the patient is attended to she gets contractions in arms and legs; sometimes she could not stretch her arms right away. She

FIG. 6.—*Case III.* Photograph of patient.

complains of headache and pain in the neck, seems unable to sit straight up, and she evidently cannot hold her head up. Now and then there are hemiballistic movements.

Incontinence of urine; when attended to she is stiff and makes involuntary movements. Often complains of headache; pain was caused when the head was moved.

Nov. 26.—The legs often lie over the edge of the bed, the patient suffers from contractions chiefly in the right arm, she often throws it around above her head.

Nov. 27.—Somnolent and confused, continually calls for her husband. Pupils wide, left larger than right; react well to light, but slowly. Objects shown her are often recognized (watch, pencil), but some are not recognized (key).

When asked to give a hand, aimless movements are made with both arms. One has the impression that the patient understands the request; at any rate she says "I cannot" and begins to cry. Swallows sometimes with difficulty. As soon as a glass reaches her lips she makes swallowing movements. Knee-jerks left as well as right brisk, left knee-clonus of short duration. Left Achilles-jerk difficult to elicitate, right normal. Right radius reflex very high, left absent.

Ulnar reflex depressed on both sides. Biceps reflex brisk on both sides, R > L. Triceps reflex on both sides normal; earlier on absent on both sides. Tonus: R arm > L.

Blood: 15,000 leucocytes per c.mm. Segmented nucleus, 58 per cent, rod-like nucleus 5 per cent, monocytes 1 per cent, lymphocytes 36 per cent, eosinophilocytes 0 per cent, basophilocytes 0 per cent. Slight leucocytosis without deviation to the left.

Nov. 28.—The muscle tonus of the arms and the radius reflex: R > L. In attempting to give a hand the aimless movements of both arms give the impression that the failure to do so is not only due to the paresis but that there is also an apraxia. The movements seem to be grossly ataxic. If one asks her three times running to give a hand she says, "Go away, stupid," and begins to curse; at the same time she sometimes bursts into tears. The answers to questions about objects shown are variable. When shown a watch-chain she answers when questioned that it is a watch-chain, but she perseverates when a watch is shown.

She can quite well count 1, 2, 3 fingers at 30 cm. distance. She was shown a bottle, a coin, and a pencil; then she said impatiently, "I don't know." She often held her head to the right, her body, too, often turned towards the right. Now and then swallowing was difficult.

Nov. 30.—Left disc definitely choked, right papillitis. When asked to pinch with her right hand she does so with her left; if asked to pinch with the left hand, she does it with her right and says, "I cannot." Often a sudden flushing of the face. Severe bilateral mydriasis, this having increased. Slight paresis of vertical movements of the eyes. Repeated attempts at vomiting.

Dec. 4.—The patient is evidently very easily tired. If one shows her a series of coloured skeins of wool she can tell the colour of the first three arbitrarily chosen colours all right; after that she calls every colour the same in a different way—blue, red, or yellow—as the case may be. More signs of somnolence. Pupils maximally dilated. Retention of urine. Lumbar puncture: clear, colourless, increased pressure (40 mm. Hg). Nonne negative, 13/3 cells, W.R. negative, S.G. negative.

Dec. 5.—Again continual throwing about of arms and legs, increasing somnolence.

Dec. 6.—Slight leucocytosis (13,000 leucocytes per c.mm.), no displacement to the left. Eye specialist's report: L choked disc; R papillitis. Throwing arms and legs about; becoming duller.

Dec. 10.—Difficulty in taking food, continually choking. Sometimes flow of saliva. Beating with the right hand against the bed.

Dec. 11.—Continually duller, sleeps a lot. Mydriasis has been replaced by extreme miosis during sleep. A few hours later, when the patient was awake, there was wide mydriasis again.

Dec. 13–18.—Rise of temperature and evidences of bronchopneumonia. Anisocoria constantly observed.

Dec. 18.—Patient died.

Post-mortem Report (Professor de Josselin de Jong).—Skull cavity: Dura tense, vessels well filled, left more than right. Superior longitudinal sinus contains fluid blood. Convolutions somewhat flattened.

Right transverse sinus is thrombosed, the thrombus very recent, perhaps formed a few hours before death. On the medial side of the hemisphere no impression of the falx to be seen; the tentorium on the left has left an impression on the brain. Cerebellum slightly pressed into the foramen magnum. In a number of frontal sections we see the following:

In both frontal, parietal, and temporal lobes, in the neighbourhood of the left half of the corpus callosum, and in the occipital lobes extensive soft diffuse ill-defined areas resembling a half-fluid porridge-like mass are seen, showing an evident destruction of the white matter. The cortex appears everywhere intact and forms a sharply defined wall against the soft parts. The soft areas can be seen in all the sections but not in the cerebellum.

Summary.—This patient was reported to have first complained of failing vision and paralysis on the right side, followed by the general symptoms: vomiting, incontinence of urine, difficulty in swallowing, wasting, and rolling of the eyes.

Soon there appeared to be a definite congestion of the left papilla, and a right papillitis; there was alternating anisocoria and mydriasis as well as abducens paresis. Twitchings in arms and legs were repeatedly noticed; there were swinging movements of the arms, on the right as well as on the left. There were also hemiballistic movements towards the left. Obvious psychical changes. Two weeks before death perseveration and beginning somnolence. Before admission the patient was said to have had a rise of temperature; during the stay in the hospital this was only noted when the bronchopneumonia developed. Neither the blood-pressure nor the

examination of the lumbar fluid showed anything special; there was, however, increased pressure in the lumbar fluid.

On admission the consulting doctor had thought of various possibilities, meningitis, encephalitis, abscess, and also of uræmia. All these could be excluded, and very soon the possibility of an extensive process in both hemispheres was thought of; its progressive nature soon led to the fairly confident diagnosis of encephalitis periaxialis diffusa running a subacute course. The post-mortem examination confirmed the diagnosis. The duration of the disease after it manifested definite symptoms was six weeks.

Attention must be specially directed to certain points. The movements which were made in attempting to give a hand gave the impression of an ataxia with excessive movements, the movements were more like 'schleuder'-movements; moreover, in a later period of the disease there was often, when attended to, more or less stereotyped swinging of arms and legs. The same thing was noted in my second case, and also in the cases described in children. Contractions in arms and legs were also seen when attended to.

Just as in my first case, there was much complaint of pain, and stiffness of the neck was reported. The severe psychical symptoms are of importance, being certainly much more marked than those in disseminated sclerosis or even in most of the cases where there is a 'space-encroaching process' (tumour, abscess).

The marked fundus alterations accompanied by disturbances of vision are noteworthy. Also the pressure of the cerebrospinal fluid was increased in this case, as was also evident at the post-mortem examination (cerebellum pressed into the foramen magnum).

Lastly, we must mention that the patient continually made quick to-and-fro swinging movements with the eyes, which, together with the spasms which were observed in the limbs, must be looked upon as irritation symptoms. Further, signs of apraxia, bulbar symptoms, and contractures were present.

Pathological Examination.—

Macroscopical Anatomy.—To the naked eye the cerebrum is characterized by large clearly demarcated foci in the brain. The extension of the foci is most evident from *Figs.* 7–10. *Fig.* 8 shows a frontal section through the occipital pole of the left hemisphere, in which section the myelin sheaths have been stained by Weigert-Pal's method. A large grey area shows the central focus of this section. *Fig.* 7 shows a drawing of a similar frontal section which lies rather more posteriorly (the focus is shown in black). *Fig.* 9 illustrates a frontal section through both hemispheres at the level of the corpus striatum, and *Fig.* 10 is taken from a frontal section just in front of the lateral ventricle.

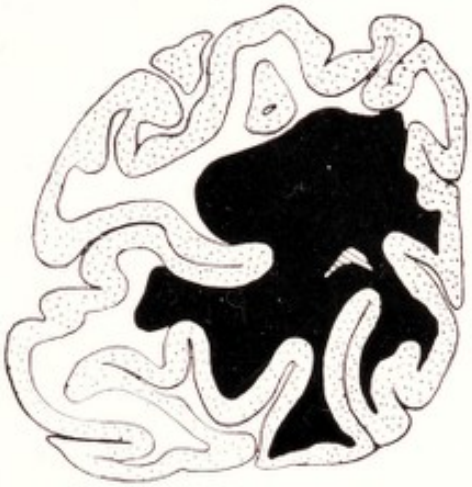


FIG. 7.—*Case III.* Frontal section through the occipital pole of the left hemisphere. Black, The patch of demyelinization; Dotted, Cortex; Striped, Posterior horn of the lateral ventricle.

FIG. 8.—*Case III.* Frontal section through the left hemisphere farther forward than *Fig.* 7. The patch of demyelinization can be seen as a light grey area with an indication of concentric layers. (Weigert-Pal stain.)

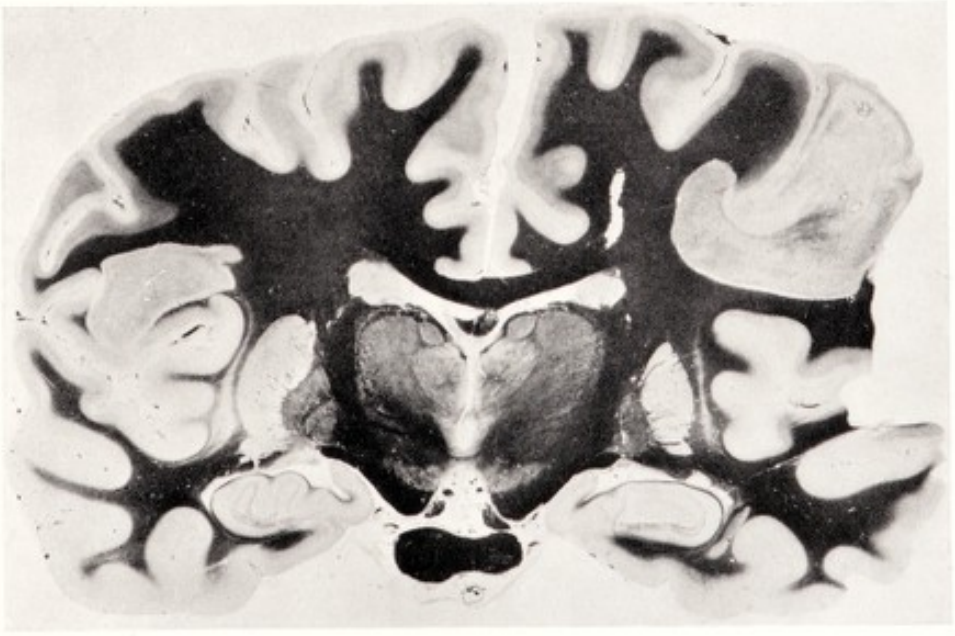


FIG. 9.—*Case III.* Frontal section through both hemispheres situated farther forward than *Fig.* 8. On the right side a fairly large section of the left patch, here impinging upon the cortex; on the left side the (smaller) patch in the right hemisphere. (Weigert-Pal stain.)

It is evident from these figures that the foci destroy a large part of the white matter in the hemispheres, but only here and there extend into the cortex and then only to a very slight extent. It is as if the process stops at the boundary line between grey and white matter; only at a very few places is there a thin layer of white matter immediately under the cortex left unaffected, as I described in the two earlier cases where this was often found (*Cases I and II*).

As to the extent of the areas on the two sides, there is a clear tendency towards symmetry, although there is no strict symmetry. Left and right areas are connected through the splenium of the corpus callosum, which is altogether demyelinated. The striatum, the globus pallidus, and the thalamus are spared on both sides.

FIG. 10.—*Case III.* Frontal section through the frontal pole of the left hemisphere. Black, Patch of demyelinization; Dotted, Cerebral cortex.

The boundary of the affected area follows to a great extent the under surface of the cerebral cortex (*Fig.* 11). Where the affected area is bounded by intact white matter, its surface has a rough knobbly character (*Fig.* 12), each protrusion being indicated by a simple and fairly smooth curve. The boundary of the area is indicated by a sharp line in all the preparations (*Fig.* 13).

HISTOPATHOLOGY.— In the white matter lying immediately outside this boundary there are many myelin sheaths, especially the thick ones, markedly and irregularly swollen, in a varix-like manner (*Fig.* 14). This swelling affects sometimes simply the myelin sheath itself in its whole circumference, but at times thick irregular myelin blisters have been formed on the clearly visible surface of the myelin tube (*Fig.* 15). These blisters sometimes lie on one side of the myelin sheath, and sometimes they are wrapped round it on all sides, forming a second myelin tube outside the first.

In the affected area itself there is an almost complete demyelinization of the sheaths. It is not everywhere equally complete or equally severe. Within each area there are some parts where scarcely any myelin sheath is left, and there are other parts where some of the myelin sheaths have been preserved. But always by far the largest

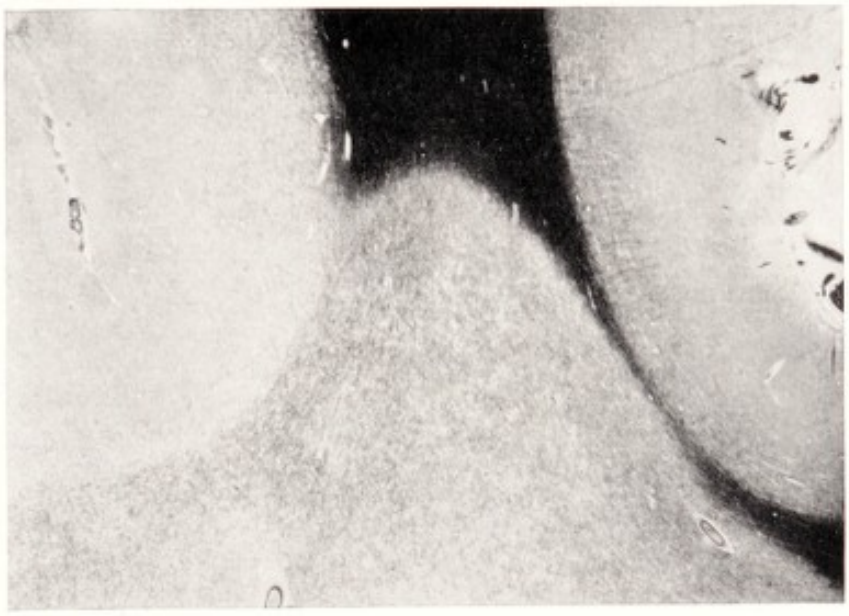


FIG. 11.—*Case III.* A patch of demyelinization (below) impinging upon the cortex (left), and on the right side separated from the cortex by a thin layer. (Weigert-Pal stain.) (× 7.)

FIG. 12.—*Case III.* A patch of demyelinization with a smooth surface to the left and a crenated surface on the right side. (Weigert-Pal stain.) (× 8.)

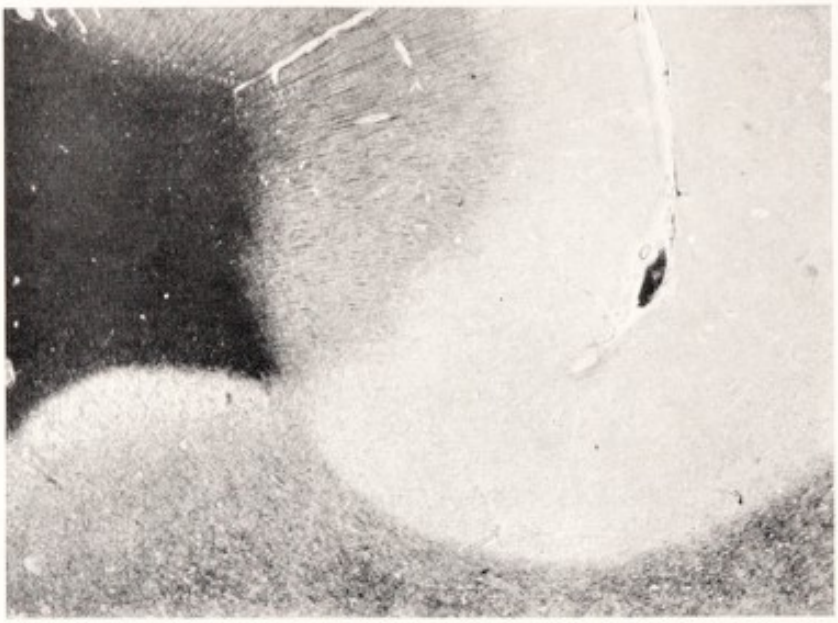


FIG. 13.—*Case III.* A patch of demyelinization (below) impinging upon the cortex. Note the sharp borderline between the patch and the surrounding tissue. (Weigert-Pal stain). (× 8.)

FIG. 14.—*Case III.* Varicose swelling of thick and thin myelin sheaths in a peripherally situated part of a patch. (Weigert-Pal stain.) (× 570.)

part of the myelin sheaths, there normally present, have disappeared, so that in a Weigert-Pal preparation even the parts last mentioned have to the naked eye only a pale-blue tint. In the parts most affected by demyelinization only very thin myelin sheaths occur, most of which show small varicose swellings (*Fig.* 16).

In the rather less severely demyelinated zones there are also several somewhat thinner myelin sheaths. The thick myelin sheaths are altogether absent in the affected area.

In several of the preparations the severely and less severely demyelinated areas may form concentric layers in the affected area, which suggest the annual rings on a tree (*Fig.* 8). In other places a more irregular and patchy distribution is found.

Immediately separating the intact surroundings there is usually a narrow boundary area in which remarkably little myelin is coloured, and beneath it a continuous broader band surrounding the whole area in which there is rather less demyelinization. In the narrow boundary area which lies directly under the affected region and which contains very few myelin sheaths, the ground tissue too shows special alterations.

In a hæmatoxylin-eosin preparation, in which the line of demarcation of the affected area may also be seen as a sharp line (*Fig.* 17), we can see the well-known thick and regular network of fine reddish trabeculæ outside the boundary line, chiefly formed by the ground reticulum. In the zone where the thick myelin sheaths show such marked varicose and bladder-like swellings the network is perhaps somewhat thicker and heavier than in the white matter farther away from the affected area.

At the boundary line this finely meshed network passes abruptly into a larger meshed network of equally fine protoplasmic trabeculæ, so that the ground tissue immediately inside the boundary of the area is of a specially light colour in these preparations. This very light stripe is fairly narrow, about 0·3 mm.

Inside it the ground tissue is again darker coloured throughout the whole area, the meshes of the network being in size between that of the normal and of the very light boundary zone, the trabeculæ being very irregular in their thickness.

In the light boundary zone the number of cells is not seriously increased, but in the deeper parts of the area their number has increased. There are numerous macroglia cells with, for the most part, very much swollen bodies, mixed up with many oligodendroglia cells and globular granular cells.

The much swollen macroglia cells look like the so-called 'gemästete' glia cells with a large egg-shaped cell-body, diffusely or very finely reticular, stained by Nissl, hæmatoxylin-eosin,

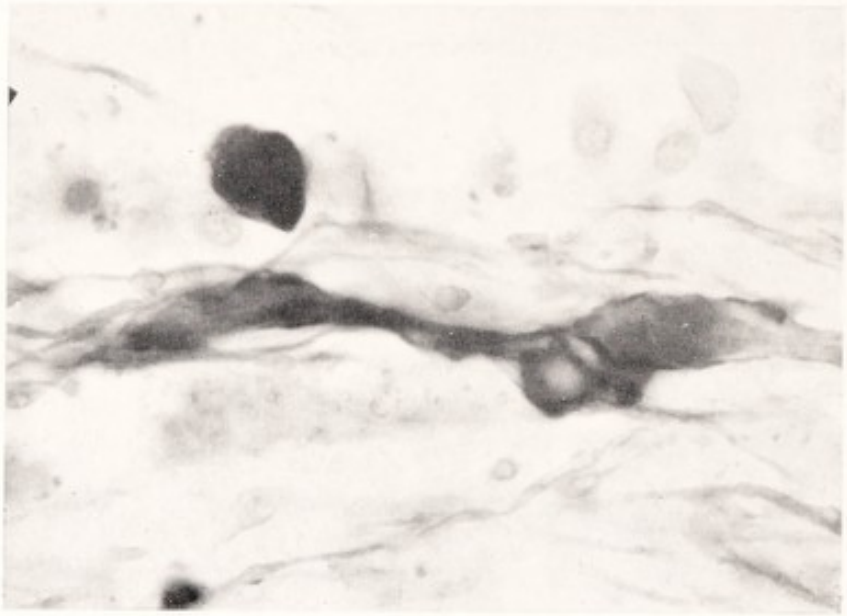


FIG. 15.—*Case III.* Varicose swelling of a thick myelin sheath in the periphery of a patch. (Weigert-Pal stain.) (× 570.)

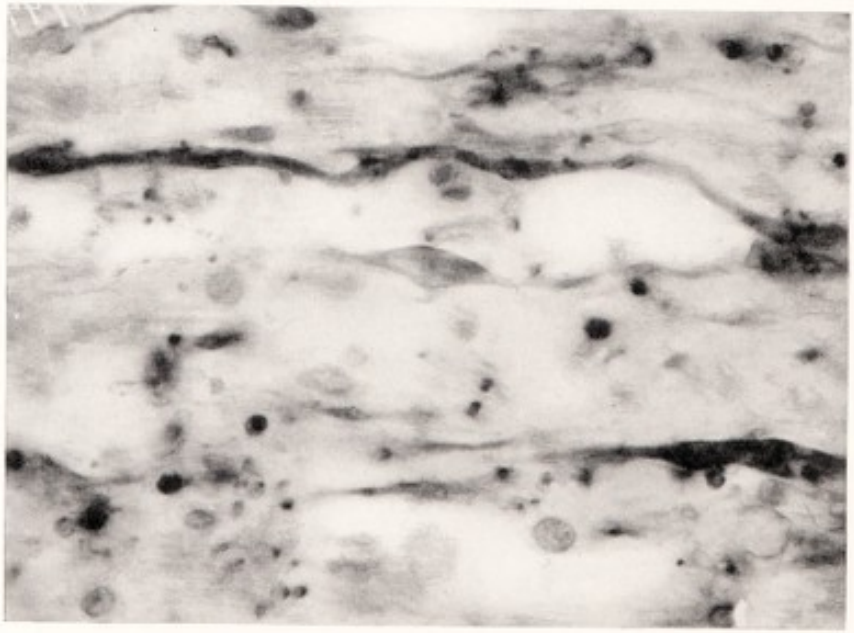


FIG. 16.—*Case III.* Part of the patch with a number of myelin sheaths. (Weigert-Pal stain.) (× 570.)

Bielschowsky, Hortega, and Holzer preparations (*Fig.* 18), with one or more large nuclei, usually lying to one side of the cell. This outer side of the cell appears strongly frayed in the Nissl and hæmatoxylin-eosin preparations; in the impregnation preparations many processes seem to sprout from it, some of which end in small feet on the outer vessel walls; and in the Holzer preparations these cells appear to be the cross-points of the much hypertrophied glial fibrils. These glial fibrils vary considerably in thickness and form extremely irregular felt-works.

The hypertrophied macroglia cells were spread through the whole area (*Fig.* 18), but are most numerous at the periphery, just in the zone which does not show the maximal degree of demyelinization, and more central than the light boundary zone described above. Then, too, these macroglia cells show the phenomenon of nuclear fragmentation much more than other cells in the area (*Figs.* 19–22).

FIG. 17.—*Case III.* The sharp borderline between the patch and the white matter. (Hematoxylin-eosin stain.) (× 38.)

In the cells in which this phenomenon occurs, the nucleus, or, rather, that which has been derived from the nucleus, is in the centre of the cell (in distinction to the other hypertrophied macroglia cells, the nuclei of which lie more peripherally). The nucleus of this special type of macroglia cell has become broken up into a large number of fragments. In some of the cells these fragments are pyknotic and irregular in form and size (*Fig.* 20), in others each fragment shows a normal nuclear structure with its own smooth oval or pear-shaped nuclear membrane, and a few small chromatin granules (*Fig.* 21). Definite nucleoli are very rare. In some of the cells these fragmented nuclei lie apart from each other; in most of them they are connected by fine processes (*Fig.* 22). Usually each fragment has one process directed to the centre of the nuclear group, meeting there the processes of the other fragments. The whole may be regularly or

irregularly disposed, forming sometimes a particular regular figure, the fragments making a perfect circle and their processes coming together at a central point like the spokes of a wheel.

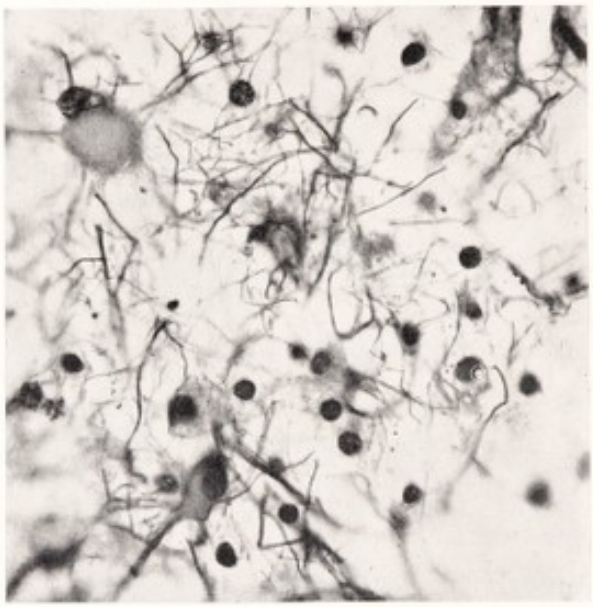


FIG. 18.—*Case III.* Proliferation of the macroglia cells and the glial fibres at the edge of a patch. (Glial fibres were stained according to Holzer.) (× 320.)

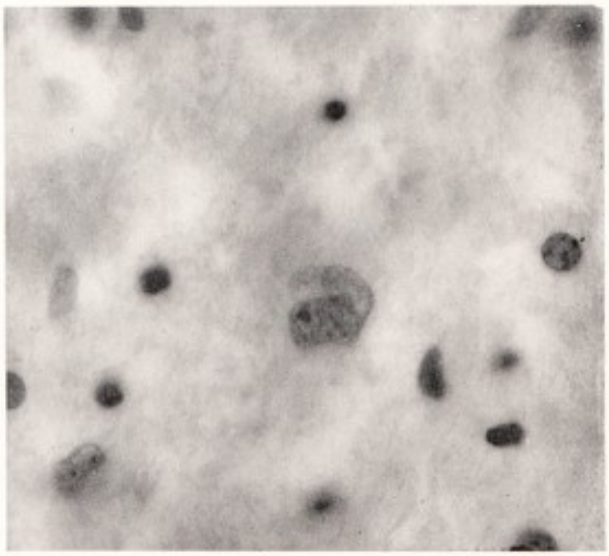


FIG. 19.—*Case III.* Monster nucleus of a macroglia cell. (Hematoxylin-eosin stain.) (× 475.)

The granular cells are spread fairly regularly throughout the whole area, but never so close together as to form compact granular cell carpets. They are round, their small nucleus lies eccentrically or

even peripherally, their protoplasm is finely vacuolized and often contains fine myelin drops which take on with Weigert-Pal's stain the blue colour of normal myelin, though at times they are darker coloured.

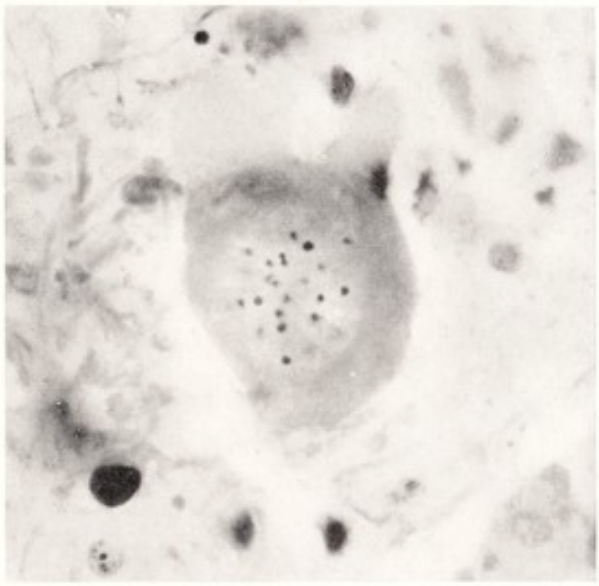


FIG. 20.—*Case III.* Macroglia cell with pyknotic nuclear granules. (Cajal-Bielschowsky stain.) (× 475.)

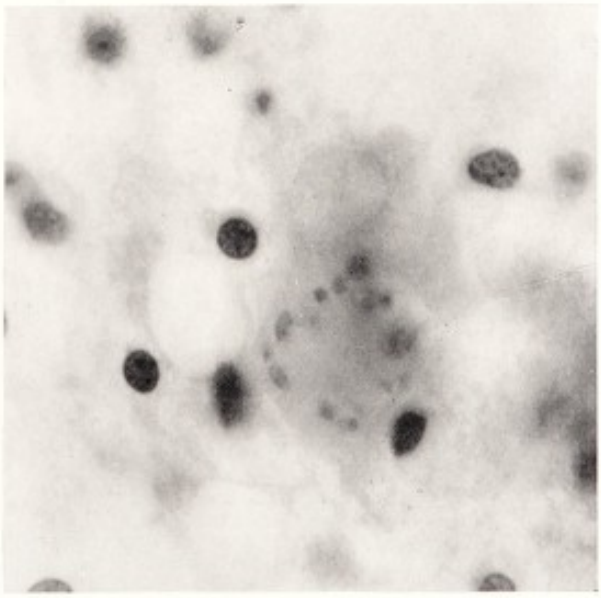


FIG. 21.—*Case III.* Macroglia cell with nuclear fragments. (Hematoxylin-eosin stain.) (× 475.)

In Sudan preparations the contents of all the granular cells take on a red colour. These granular cells, too, are most numerous in the same zone in which lie the most numerous and the most altered

macroglia cells. A few of these granular cells lie in the infiltrated vessel sheaths between the lymphocytes, plasma cells, and polyblasts. Among these granular cells there are not many which contain myelin.

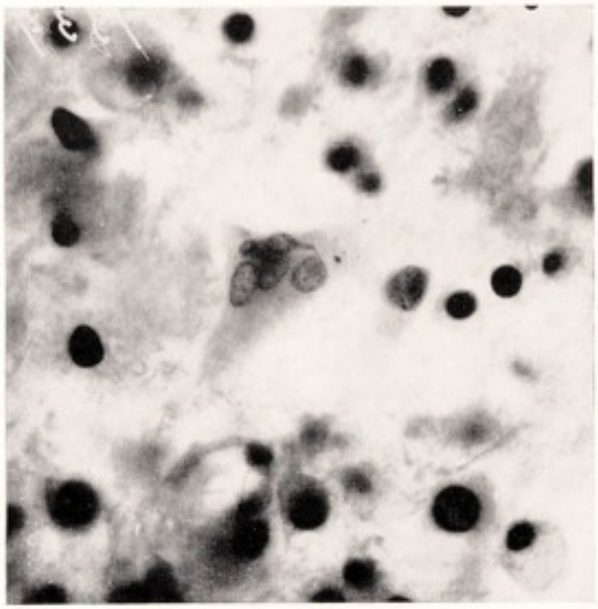


FIG. 22.—*Case III.* Macroglia cell the nucleus of which is broken up into many small nuclei, some of which are connected by thin threads. (Hematoxylin-eosin stain.) (× 475.)

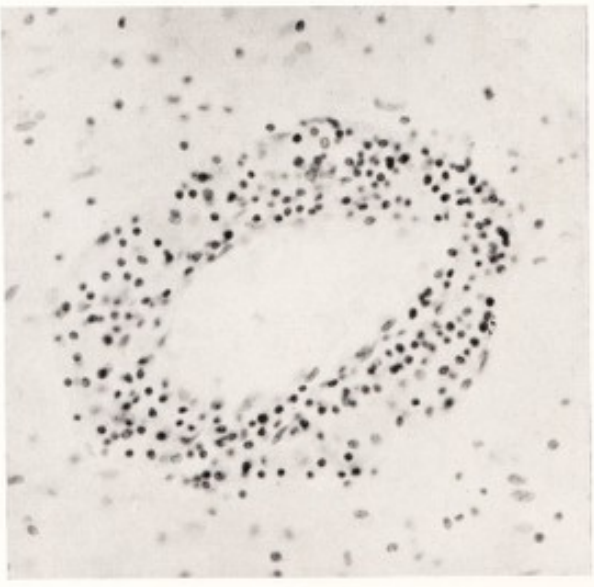


FIG. 23.—*Case III.* Perivascular infiltration in the patch of demyelinization. (Nissl stain.) (× 165.)

Perivascular Infiltration.—Everywhere throughout the affected areas the larger vessels are surrounded by a mantle of perivascular infiltration (*Fig.* 23) within the meso-ectodermal membrane, and

composed chiefly of lymphocytes. Between them we find granular cells, polyblasts, and a few plasma cells. Some of the polyblasts and plasma cells lie outside the vessel sheaths in the parenchyma itself. Outside the affected areas, e.g., in the cortex, the perivascular sheaths are by no means absent.

Axis Cylinders.—Although most of the axis cylinders have been destroyed, there appear to be still a fair number between the numerous granular cells, able to be well impregnated in the Bielschowsky preparation. Many of them show varicose swellings.

Summary.—At the autopsy we found in the white matter of both hemispheres of the cerebrum extensive more or less symmetrical and sharply demarcated areas in which the most of the myelin sheaths and neurites have disappeared. The few thin myelin sheaths and neurites still left were swollen in a varicose manner; between them were numerous round gliagenous granular cells full of 'breakdown' products. In these areas the macroglia cells were qualitatively and quantitatively hypertrophied (especially at the boundaries of the areas), having formed a feltwork of glial fibrils. The medium-sized blood-vessels were dilated, and contained in their lymph-sheaths lymphocytes, polyblasts, plasma cells, and granular cells.

CASE IV (*Fig.* 24)

Clinical History.—M., a chauffeur, 21 years of age, was admitted to Rhyngeest in Leiden on April 23, 1931. Nothing special in the heredity or in his life up till then. He had been sent by the general practitioner to the eye hospital because he had complained of a mist in front of his eyes. Nothing abnormal in his eyes had been found, and he was sent to a neurologist. He had also complained latterly of headache, situated above the eyes; he was also dizzy so that he felt as if he would fall; furthermore, he was very sleepy. During the last three to four months his character had changed; he quickly became angry, suddenly passionate, and refused to speak for four days after a quarrel about nothing. Now and then he walked as if he were drunk. He was very quiet; he could not work any more because he was too tired, and could not remember the errands he had to do; latterly he had for this reason taken someone else with him.

For a few days before admission he had been in a confused state of mind; according to the description it seems as if the state of mind had been more one of dullness. He did not know what day or which month it was; he could not well dress himself—he stood a long time with his leg in the wrong trouser leg before he realized it. During the examination he did everything very clumsily. He was disorientated, he saw badly, and was incontinent. He did not hit the

mark when he tried to take hold of something, and when attempting to look at people he could not direct his eyes on them. He talked to himself and often laughed. Paraphasia, echolalia, repetitions such as " if you please," and " at the present moment," " thank you," etc., were noticeable, and he made stupid jokes. Divergent strabismus. Absolute amaurosis; he would look alongside people. No wink reflex. Papillæ slightly congested, L > R; pupils very wide, react well to light. Forced grasping movements and forced groping in both arms, L > R. Abdomen very tense. Temperature occasionally up to 37–8° C. Possibility of encephalitis, cerebral tumour, or abscess. Gradually a papilloedema developed, L and R, of ½ D. An apraxia

Fig. 24.—*Case IV.* Photograph of patient.

of the left arm was found; spasticity of both legs, L > R; on the left absence of cremasteric reflex, also slightly positive Babinski. Nothing abnormal revealed by lumbar puncture.

Brain puncture was advised, since it was thought possible that there was a brain abscess, and the patient was removed to the surgical side on May 2, 1931. Trephined in the right frontal, the right temporal, the left frontal regions, and punctured without success. After that he moved his right arm and leg more than the left, the left arm lying almost still. The eyes remained in divergent position, moving continually to the left and to the right. The pupils were wide and reacted to light. Reflexes on the left were weak; the left arm immobile. The right hand continually grasped; this had disappeared

on the left. Abdominal reflex R +, L + (weak). Cremasteric reflex: R + L −. The left leg lay quite still. Knee-jerk on both sides positive, also the Achilles reflex. Left ankle clonus, left Babinski. The legs were not so stiff as they had been.

May 9.—High temperature (39° C.); incontinent. Now and then vomiting; perhaps a little neck stiffness. Ophthalmologist consulted. Slow to-and-fro swinging movements in the eyes. Right papilla hyperæmic, pink-coloured, misty edges, vessels outside the papilla very tortuous, swelling less than 1 D. Left papilla ill-defined edges, vessels tortuous, hyperæmia together with pallor, swelling 1 D, more aspect of a choked disc.

May 11.—Sudden rise of temperature to 40° C.

May 12.—Died.

Post-mortem Examination (Professor Tendeloo).—Encephalitis periaxialis diffusa. Congestion in all organs, chronic splenitis (?), habitus asthenicus, hypoplastic kidneys. After making a frontal section of the brain, no doubt as to the diagnosis was possible.

Summary.—In this case we have the following symptoms: cerebral blindness, mental deterioration, spastic paralysis, tottering gait, which—except for deafness—were the chief symptoms of the disease mentioned by Collier and Greenfield. Along with them there is a series of other symptoms which must be considered of importance. Headache was complained of early, and vomiting was noted a few days before death. A choked disc, though not very marked, developed in the papillæ, L > R, with some indication of optic neuritis. Of the cranial nerves, the VIth was affected on both sides; there was mydriasis. From the clinical symptoms one can take for granted that there was a hemianopia. Express mention is made of the to-and-fro swinging movements of the eyes; mention is made of apraxia, certainly in the left arm. In the stage of spastic paralysis there was a Babinski reflex on the left side, whereas the cremasteric reflex had disappeared. Mention is made of paraphasia, echolalia, repetition of the same expressions, the presence of moria, an increasing dementia, and incontinence. The sleepiness which the family spoke of must probably be looked upon as a dullness of mind. At first there was a slight rise of temperature, and some symptoms varied in degree (e.g., the spastic paralysis). Other symptoms worthy of note were: loss of wink reflex and the forced grasping and groping in both hands which later on disappeared from the left hand.

Although the observation was comparatively short, from April 23 to May 12, 1931, it was three to four months before this that his character had changed, so we can say that the disease had lasted three and a half to four and a half months, although manifest symptoms had lasted for a much shorter period.

In this case the symptom which was present in my first case is noticeable—namely, that the patient continually missed the object he tried to get hold of. Moreover, the symptom of the to-and-fro swinging movements of the eyes is present in this case. The mental symptoms were very evident here, and there was a slight rise of temperature at times.

Pathological Examination.—

Macroscopical Anatomy.—At the autopsy abnormalities were found which may be described in the same words as in *Case* III (*see* p. 24). After being fixed a short time in formol, the cerebrum was divided up into frontal sections. On these the foci are conspicuous as large areas which are less white than the white matter outside the foci, and which are bounded by a narrow (about 1 mm. wide) darker area, the outside layer of which is tinted a somewhat reddish colour. At those places where such an area reaches the cortex, this latter layer is less evident. These areas feel softer than the rest of the white matter.

The shape of the areas is, speaking generally, capricious, as is illustrated in the accompanying drawings, in which the foci are

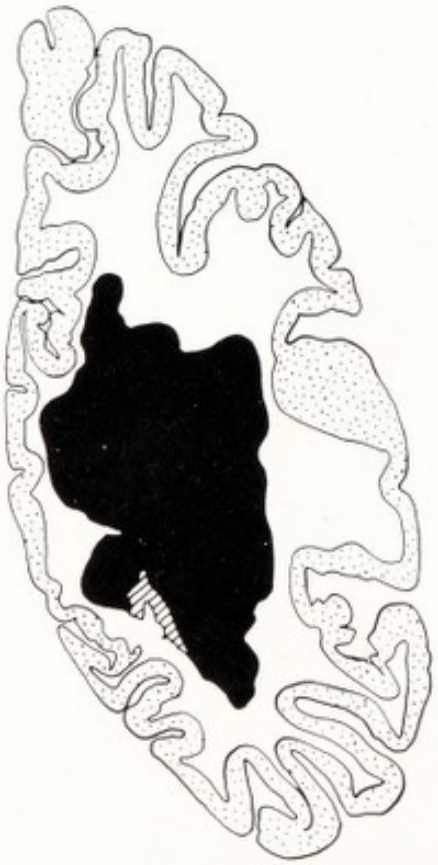


Fig. 25.—*Case IV.* Patch of demyelinization in the right hemisphere. Section through the posterior pole of the lateral ventricle. Black, Patch; Dotted, Cortex; Striped, Ventricle.

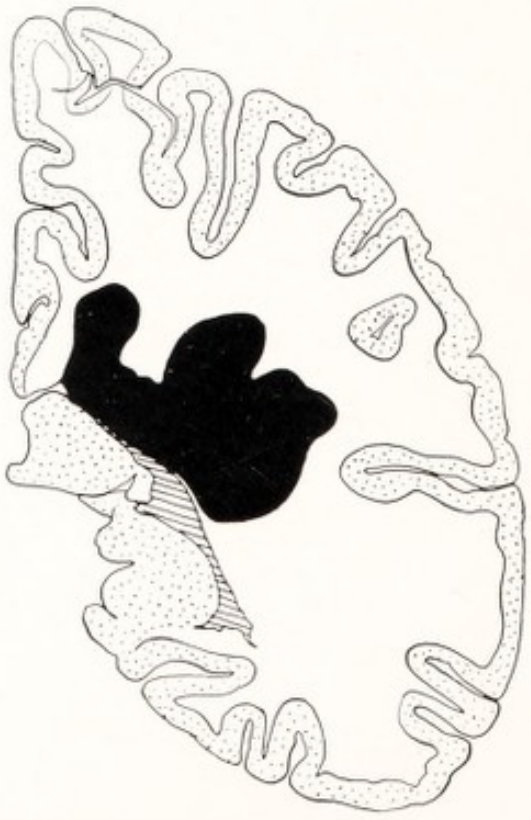


Fig. 26.—*Case IV.* Patch of demyelinization in the left hemisphere. Section through the posterior pole of the lateral ventricle. Black, Patch; Dotted, Cortex; Striped, Ventricle.

darkened (*Figs.* 25–28). In the occipital specimens there is one section in each of the two hemispheres through one such area (*Figs.* 25, 26), which has proceeded in a forward direction through a number of

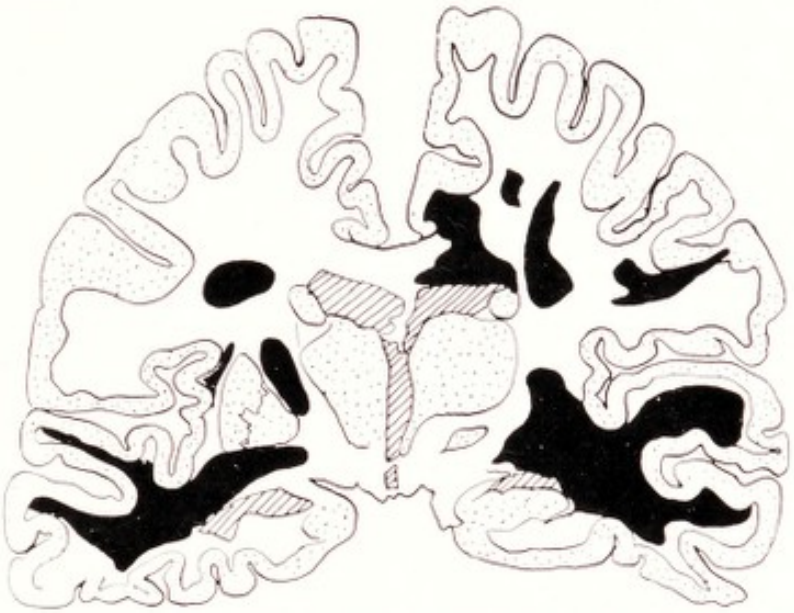


FIG. 27.—*Case IV.* Patches of demyelinization in the brain. Section through the thalamus. Black, Patches; Dotted, Grey matter; Striped, Ventricles.

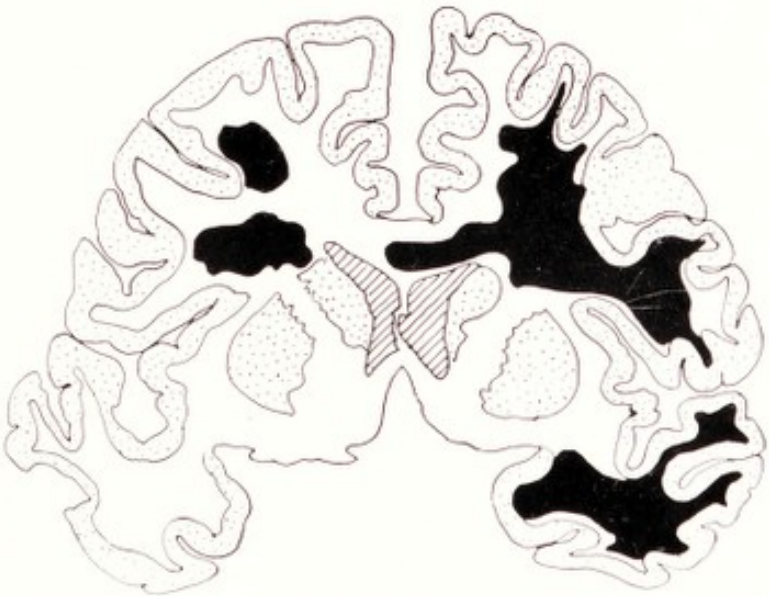


FIG. 28.—*Case IV.* Patches of demyelinization in the brain. Section through the corpora striata. Black, Patches; Dotted, Grey matter; Striped, Ventricles.

processes, becoming gradually smaller and more numerous as they branch off (*Figs.* 27, 28). Besides that, these areas prove on section to be distinctly bounded by a definite wavy line. The undulations

are fairly large and smooth in surface; inside the waves, which can be easily seen on the drawings, the areas do not show finer ripples, nor an irregular line with lumps here and there, so that seen through the microscope the boundaries of the area are only slightly curved, and for the rest form simply a straight line. Everywhere the extent of the abnormal areas is greater in the right hemisphere than in the left, but in their general outline they are symmetrical, except for the capricious character of the forward-protruding extension processes.

The compact parts of the areas situated in the occipital lobes lie latero-dorsally to the posterior horns of the lateral ventricle and extend on both sides backwards from this. They lie directly against this posterior horn, the right one touching a larger part of the ventricle wall than the left. The right area covers the whole of the lateral as well as almost the whole of the medial wall of the ventricle, so that only the ventral wall remains free. (But this is altogether free: even farther away from it there is no part of such an area on the ventral side of the ventricle.) The affected area on the left side, however, lies against the most dorsal part only of the lateral wall of the posterior horn of the lateral ventricle, covering only the middle third of the lateral wall of the posterior horn for a small part and leaving the lower third of the lateral wall as well as the medial and ventral ventricle walls quite free.

The same difference in degree between left and right is found with regard to the forward-directed processes of the affected area in relation to the lateral ventricles. The lower horn of the lateral ventricle is touched on both sides dorso-laterally by a large process of the patch in the temporal lobe, on the right over a larger area than on the left. And the roof of that part of the lateral ventricle that joins the foramen of Monro is altogether and immediately covered by a process of the patch beyond the level of the anterior commissure and on the left this part is not at all affected.

Again, the number of frontally directed processes is greater on the right side than on the left. In the drawing made at the level of the third ventricle we can count four on the left side and five on the right (*Fig.* 27). The difference is remarkably small, and still further frontally the number on the left and right sides is again the same—namely, two in each hemisphere. Possibly this is the result of a joining up of some of the processes on the right side, a compact part of the area lying centro-frontally being formed.

Without exception, the extent of the area and of the processes of the patches is greater on the right than on the left side. This is most noticeable in the contact of the areas with the cortex of the brain, which contact is much more extensive on the right side than on the left.

The compact areas in the occipital parts do not touch the cortex. They only get near to it in the cuneus around the deepest parts of the calcarine fissure, especially on the right side. On the right side the lateral boundary of the area has approached nearer to the lateral cortex and over a larger area than on the left side, but immediate contact has nowhere been reached. Many of the frontally directed processes lie against the cortex, some of them over large areas.

The most definitely developed frontally directed processes are the two which penetrate into the right and left temporal lobes, where they have destroyed almost all the white matter, except for a few thin strips situated immediately under the cortex, and for the white matter of the left temporal pole, here again showing less penetration forwards on the left side of these otherwise symmetrical processes. The right temporal process has also destroyed a large part of the right corpus striatum, whereas the left corpus striatum has remained outside the areas; in its immediate vicinity we can only find a fairly thin process lying in the internal capsule and a still thinner one which has destroyed the back part of the claustrum and the parts of the capsula extrema lying next to it. (The caudate nucleus has been altogether spared on both sides.)

In the white matter dorsal to the corpus striatum one finds processes of the occipitally affected areas both on the right and on the left sides, which extend on both sides up to the sulcus centralis.

In the drawing of the most frontal of the areas which have been sketched, it is difficult to say whether the area lying most dorsally in the drawing is connected with the rest of the processes (which is certainly probable), or whether it is an area separate from the other affected areas, since intervening parts have been lost in making the microscopic preparations.

It can be said of these frontal lesions, too, that they are more extensive on the right side than on the left. On both sides they reach the cortex, on the left side only just, on the right side over a large area round about the sulcus centralis and annectant gyri. Where the affected parts touch the cortex of the cerebrum they do not as a rule penetrate into it, or, if they do, then only half way through the thickness of the layer.

The difference in degree of the extent of the disease on the right and left sides is shown lastly by the fact that only on the right side a process of the patches penetrates into the corpus callosum, up to a little way over the median section in the left half.

Histopathology.—In the slides in which the myelin sheaths are stained by the Weigert-Pal method, the foci are characterized by an intense demyelinization.

In every focus two different types of areas can be demonstrated: areas in which in Weigert-Pal preparations no fibres at all are stained, and areas in which many fine myelin sheaths are stained, and fine

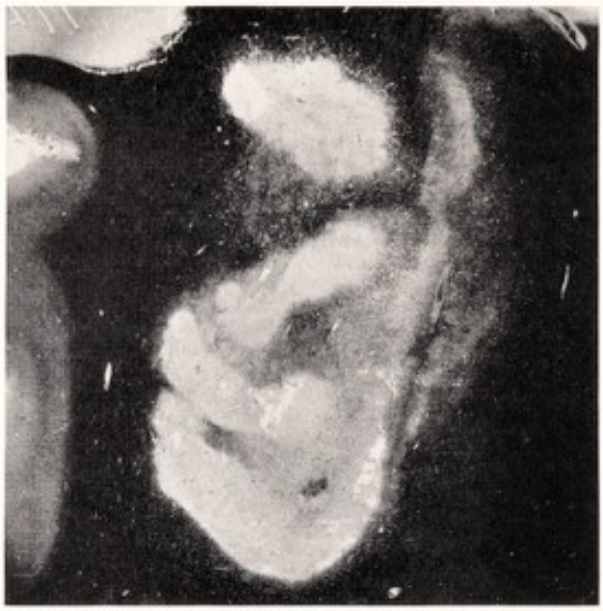


FIG. 29.—*Case IV.* Survey photograph of one of the patches of demyelinization. Notice the regions with alternating severe demyelinization. A tendeney towards a concentric structure can be seen in their arrangement. (Weigert-Pal stain.) (× 2.)

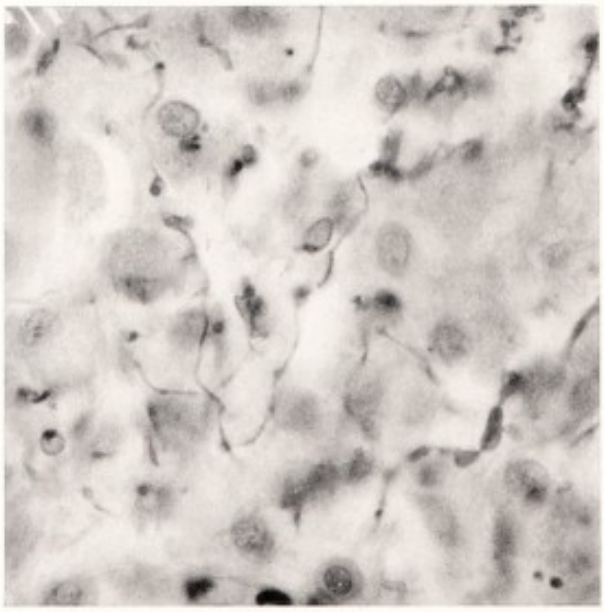


FIG. 30.—*Case IV.* In the patch only a few fine myelin-sheaths remain, showing varicose swellings. (Weigert-Pal stain.) (× 475.)

myelin droplets are present (*Fig.* 29). Macroscopically areas with complete demyelinization are colourless; the ones with incomplete demyelinization show a slight blue staining. As a rule, the colourless

areas are situated centrally in the focus and those which are slightly stained are found peripherally, greatly varying in their extent; or they may form bands across the focus between the colourless areas.

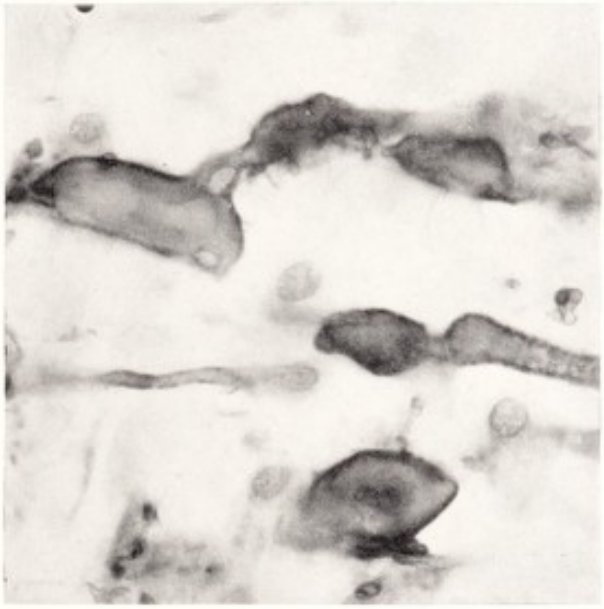


FIG. 31.—*Case IV.* Varicose swollen myelin-sheaths in the periphery of the patch. (Weigert-Pal stain.) (× 475.)

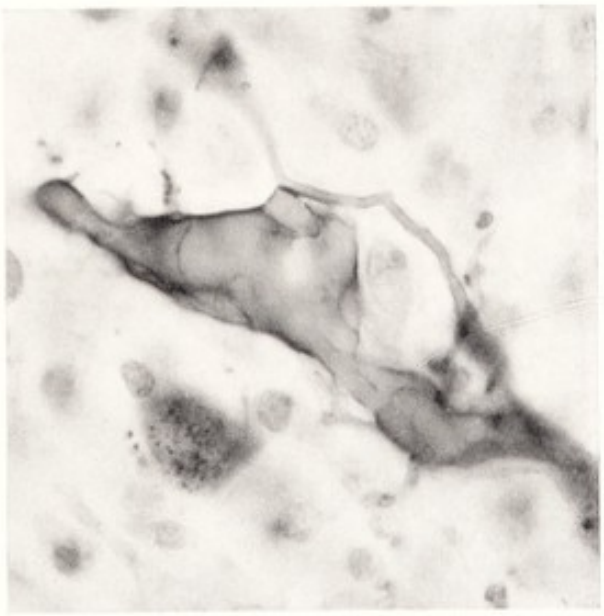


FIG. 32.—*Case IV.* Intensely varicose swollen myelin-sheaths in the periphery of the patch. (Weigert-Pal stain.) (× 475.)

In the slightly coloured areas all the thick myelin sheaths have been destroyed, whereas only some of the thin myelin sheaths are still demonstrable, their number varying. They show numerous though

small varicose swellings (*Fig.* 30). Between them many globular cells with a small nucleus are present, containing a large number of fine droplets of blue-stained myelin. The areas with complete

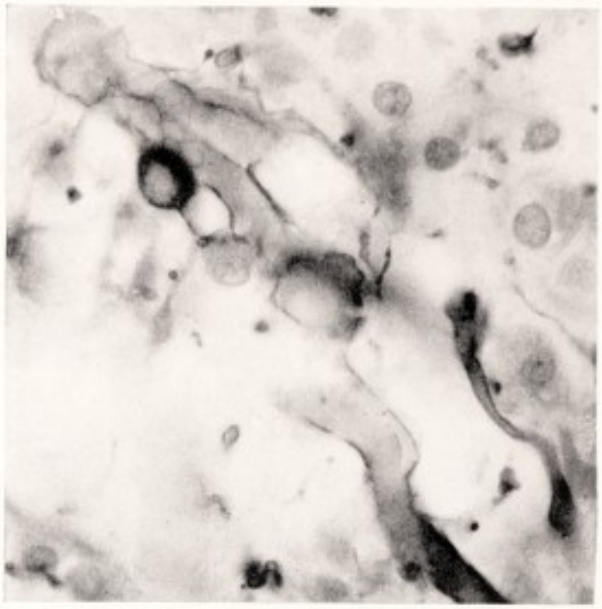


FIG. 33.—*Case IV.* Diffuse swollen myelin-sheath in the periphery of the patch. (Weigert-Pal stain.) (× 475.)

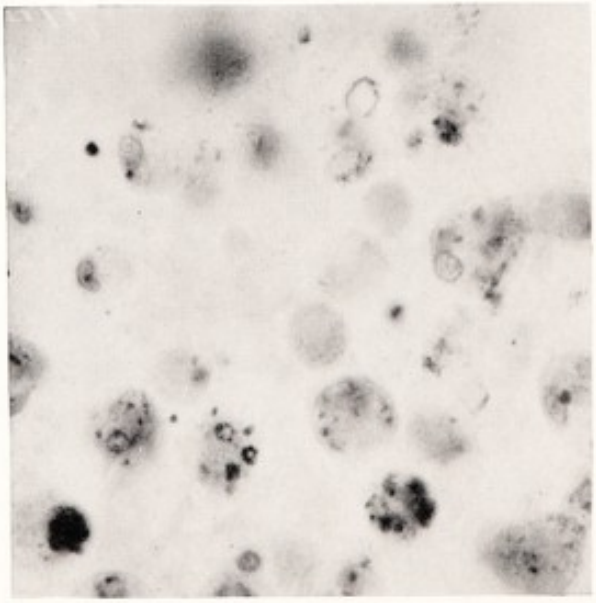


FIG. 34.—*Case IV.* Scavenger cells in the centre of a patch. Most of them contain 'breakdown' products, showing the changes by the staining method for myelin. (Weigert-Pal stain.) (× 400.)

demyelinization and those with incomplete demyelinization are bounded by a sharp line.

In a narrow transitional zone situated just outside the focus,

numerous myelin sheaths are swollen or varicosely distended to a very great degree (*Figs.* 31–33). These alterations are found chiefly in the thick myelin sheaths. Sometimes the whole myelin sheath is

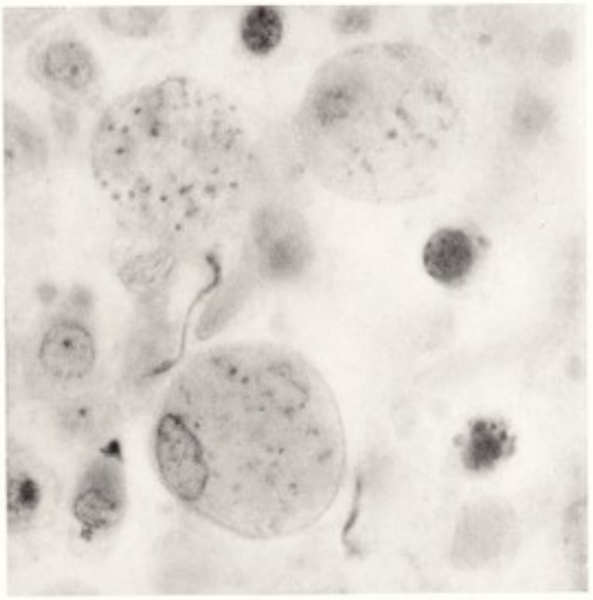


FIG. 35.—*Case IV.* Scavenger cells in the periphery of a patch. Most of them contain 'breakdown' products showing the changes by the staining method for myelin. (Weigert-Pal stain.) (× 580.)

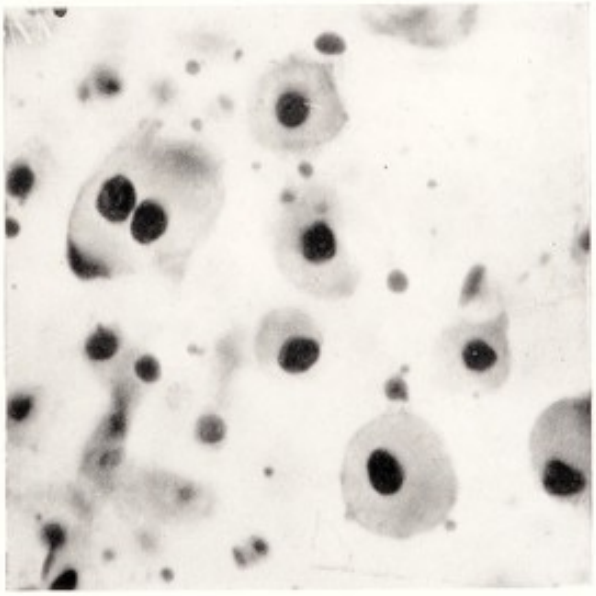


FIG. 36.—*Case IV.* Scavenger cells in the edge of the patch. (Hortega's microglia method.) (× 425).

swollen, then there are other only slightly swollen myelin sheaths; some thick bubbles of myelin may be seen, some of which seem to have burst.

The foci are filled up with a large number of scavenger cells. At the periphery (where the Weigert-Pal stain has given a slight colouring) these scavenger cells contain many fat droplets, coloured a glaring

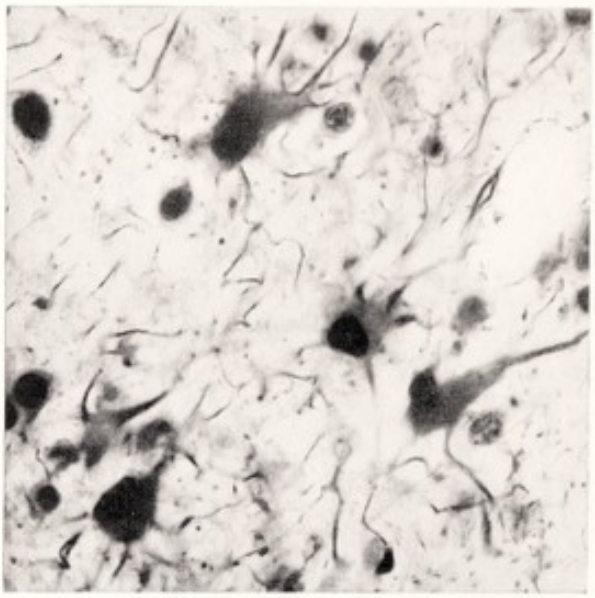


FIG. 37.—*Case IV.* Proliferation of the macroglia cells in a patch. (Cajal-Bielschowsky stain.) (× 350.)

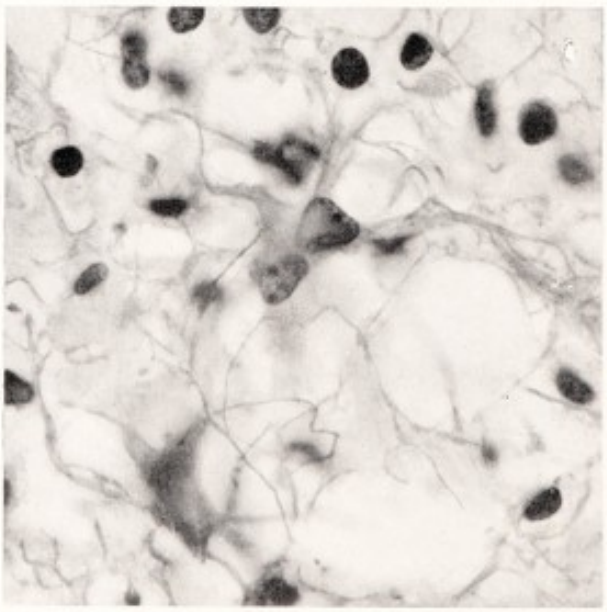


FIG. 38.—*Case IV.* Glial fibres in a patch. (Holzer stain.) (× 425.)

red by the Sudan stain. The same droplets are found to a smaller extent in the ground tissue between the scavenger cells. The scavenger cells contain also very fine granules stained blue or black

by the Weigert-Pal stain (*Figs.* 34, 35). They vary greatly in number and size.

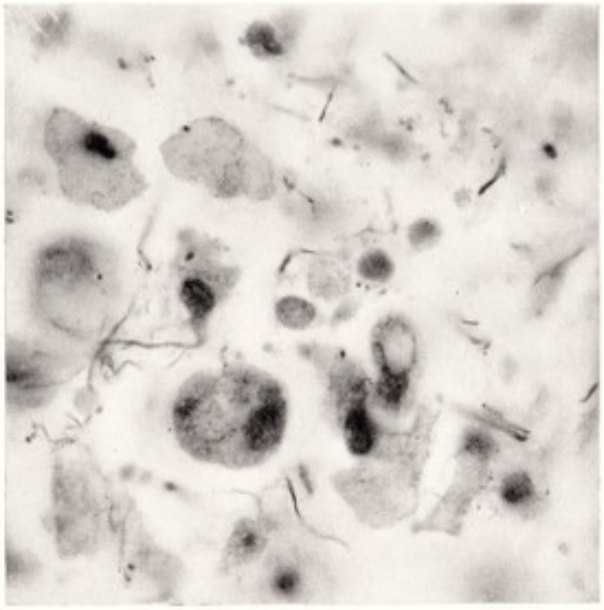


FIG. 39.—*Case IV.* In the patches a few thin neurites between the scavenger cells still remain. (Bielschowsky stain.) (× 425.)

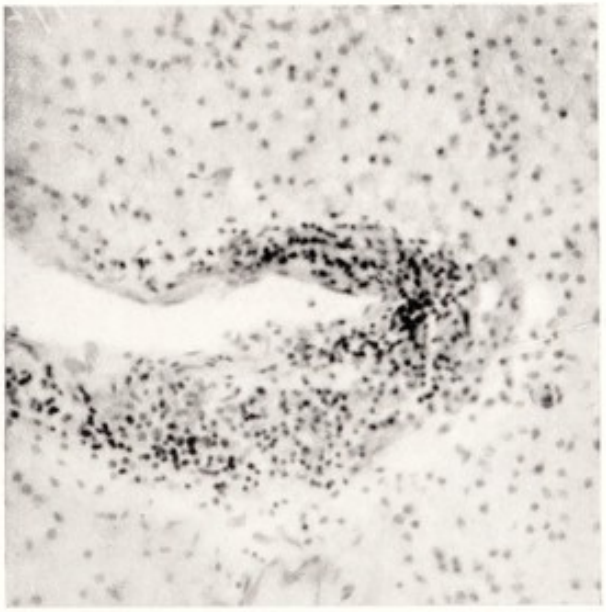


FIG. 40.—*Case IV.* Perivascular infiltration in a patch. (Hematoxylin-eosin stain.) (× 135.)

The nucleus of the spherical scavenger cells is sometimes situated peripherally, sometimes centrally. Mitosis could frequently be found; sometimes two nuclei were lying in one cell (*Fig.* 36). The boundary

of the focus shows various transitions of the normal microglial cells into scavenger cells.

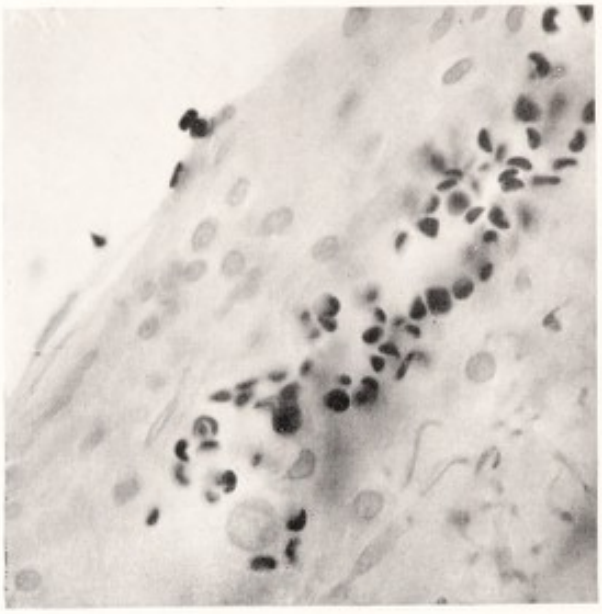


FIG. 41.—*Case IV.* Perivascular infiltration (cell-nuclei light) and perivascular hæmorrhage (erythrocytes dark) in a patch. (Weigert-Pal stain, afterwards carmine stain.) (× 350.)

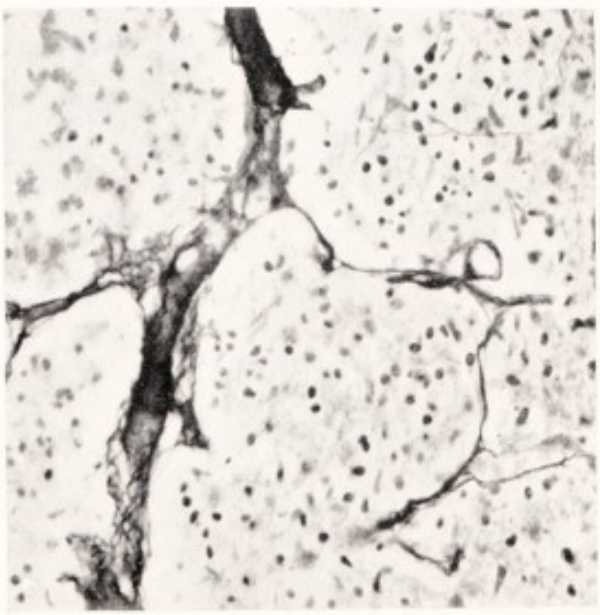


FIG. 42.—*Case IV.* Hypertrophic reticular nets at the edge of a patch. These nets go out from a blood-vessel and are situated in the nerve parenchyma. (Perdrau stain.) (× 135.)

The periphery of the area contains a number of hypertrophic macroglial cells (*Fig.* 37), but only a relatively small quantity of

glial fibres (*Fig.* 38). The hypertrophic macroglial cells are large with many and long processes. They are hyper-stainable: the Bielschowsky stain as well as the hæmatoxylin-eosin stain and the Nissl stain showed 'gemästete' glial cells.

The nuclei of the hypertrophic macroglia cells show many peculiarities. Some of them display the lobate form resembling the Alzheimer's glia cells. Others are broken into pieces forming crumbs which are sometimes connected by fine threads. Such a broken-up nucleus is always situated in the centre of the cell.

Axis Cylinders.—In the centre of the focus the axons cannot be stained adequately by the Bielschowsky stain. We have the impression that the axons have disappeared there (*Fig.* 39). In the peripheral parts of the focus most of them have disappeared, only a few can be found which were well impregnated, whereas a larger number was only slightly impregnated.

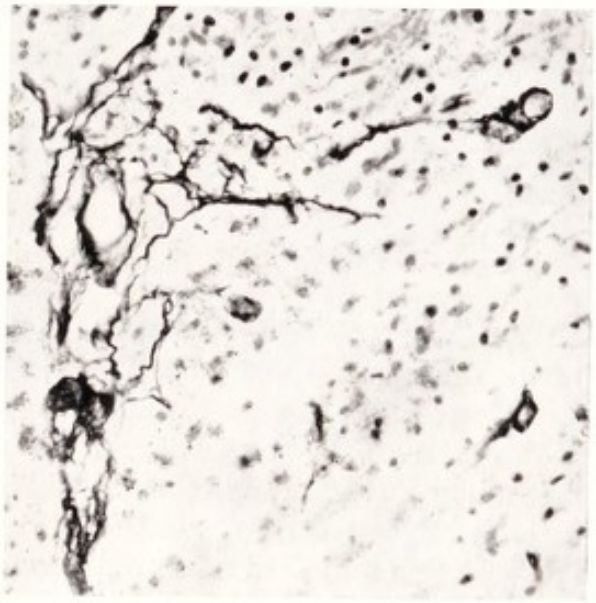


Fig. 43.—*Case IV.* Intensely hypertrophic reticular nets at the edge of a patch. (Perdrau stain.) (× 135.)

The majority of the impregnated axis cylinders show varicose swellings such as are described above with regard to the myelin sheaths, only these varicose swellings of the axons are longer and have a drawn-out appearance. Perhaps the axons were a little more resistant, but, generally speaking, the changes of the axons correspond with those of the myelin sheaths.

Perivascular Infiltration.—In most of the areas the adventitial sheaths of the larger vessels contain dense infiltrations (*Fig.* 40). In these infiltrations the majority of the cells are lymphocytes, being intermingled with a fairly large number of scavenger cells, polyblasts, and plasma cells. The infiltration coats are sharply limited by the meso-ectodermal membrane; some infiltration cells, however, are situated outside this membrane, i.e., in the nervous parenchyma itself.

Hæmorrhages.—Perivascular hæmorrhages can be found around some of the large vessels, both those which are centrally as also those which are peripherally situated. These extravasations are usually situated outside the infiltration coats immediately under the meso-ectodermal membrane (*Fig.* 41).

Reticular Nets.—Perdrau stain shows a pronounced increase of 'mesenchymatous' tissues (reticular nets) penetrating into the nervous parenchyma (*Figs.* 42, 43). This can be seen chiefly at the boundary of the foci.

SUMMARY.—The extent of the areas of demyelinization on the two sides is different ; on the right side the patches are more extended. This is also noticeable in the contact of the areas with the cortex. The areas with complete demyelinization are bounded by a sharp line. The foci are filled with a large number of scavenger cells. The periphery of the area contains a number of hypertrophic macroglial cells, many axons have disappeared, and many have varicose swellings. Generally speaking, the changes of the axons correspond with those of the myelin sheaths. There is perivascular infiltration, most of the infiltration cells being lymphocytes. Hæmorrhages (perivascular) and reticular nets are found.

II. CHILDREN

CASE V

Clinical History.—The boy, A., born August 3, 1925, was admitted into hospital with the following history (Dr. Engelman).

The father and mother of the child are first cousins (the father of the father and the father of the mother were brothers). The first pregnancy of the mother, which was conceived before marriage, ended in the birth of a stillborn child. The two following children only lived a day or two and died of convulsions. The fourth child is our patient. I saw the fifth child to-day. It is a year old, can walk already and say a few words, looks healthy, but has a trace of hydrocephalus. The father of the patient did not appear normal to me. I had not the opportunity of examining him, but he clearly had a right-sided facial paresis. He denies having suffered from any venereal disease. He was not passed for military service because of defective eyesight on one side. The mother of the child declares herself to be healthy, though she looked very delicate and apathetic. Further family history : father of the father died at the age of 42, cause unknown. Mother of the father died of consumption at the age of 38. Father of the mother died at the age of 59 from an internal disease. Mother of the mother died at 72 of old age. The mother has a sister who bore a seven-months' child twice in succession, both dying, and then a child that died at the age of three of convulsions.

Our patient developed normally at first ; he walked at the age of 14 months, learnt to say several words at the age of 1½ years, such as 'father', 'mother', 'horse', 'cow', 'cart', etc. (in Dutch). Talking did not develop further than making short sentences because the child

contracted the disease at the age of $3\frac{1}{2}$ years. Although he had not learnt to be quite clean, still one can say that he had developed as an ordinary farmer's child up to the outbreak of the disease. Then suddenly in February, 1929, epileptiform symptoms manifested themselves, which were described by the father as follows :—

The child suddenly became weak in the legs, dropped down, lisped a few ordinary words, then became irregularly coloured (blue-purple spots), turned the eyes to the left, developed tremors in the tongue, kept the mouth open, and became unconscious. After that clonic cramps developed in the arm (which arm they could not say, but in following convulsions both arms were involved), not definitely incontinent, did not bite the tongue. The fit lasted a few minutes, after which the child became still and fell asleep. After that these epileptiform attacks were repeated almost every week. Occasionally they were absent for a fortnight. There were never spasms in the legs. Sometimes the fits were very slight without spasms, in which the child was not, or only just, unconscious, and the colour of the face hardly changed. It appears that the child also had 'absences'. After the middle of June there were no more fits. The legs remained stiff after each fit. After the fits had begun the child remained healthy bodily, but he often displayed less interest than before. However, he recognized almost everybody up to a short time ago, such as members of the family, the milkman, and the grocer. He talked gradually less and stammered in speaking. At the same time he became weaker on his legs ; he could walk 300 metres, but soon dropped down. In October last he continually fell. Speaking has become much worse, he says little, being practically mute.

On admission to our clinic (Dec. 2, 1929) the child catches at everything within its reach, forced grasping with the fingers and also with the mouth. The ataxia is the chief symptom. Disturbance of speech. Sucking reflex. Strong alteration of tonus in the extremities. Pathological reflexes : Babinski and Oppenheim L and R. Legs are usually flexed and crossed. Child lies continually, shouting and crying, pulls strange faces, and is restless. Marked spastic reflexes in the arms and particularly in the legs. Cannot stand or sit properly without support. Fundus normal. Sometimes incontinent, apathetic. Child understands when spoken to. Now and then plays with toys. Sensibility intact. Lumbar puncture showed clear colourless fluid, high pressure and negative Nonne, no cells. Wassermann and Sachs-Georgi reactions negative. Wa. and S.G. reactions of the father also negative.

Dec. 10.—Fit : eyes turned to the left and upwards ; left pupil much smaller than right. Duration ten minutes. Two and a half hours later there were again convulsions in both arms—right bent,

left stretched. After two and a half hours another fit, right leg drawn up, left leg stretched stiffly. A little later the right leg also drawn up, and clonic spasms in both, also in left arm, tongue bitten, cyanosed. Three hours later patient suddenly looked very pale and fell at once asleep. Calling did not waken him.

Dec. 20.—After a lumbar puncture a very deep sleep. Fidgetiness changeable, sometimes very marked. Patient makes suddenly a strong opisthotonos, he thrusts his head back in the pillows and falls to the side; duration a few seconds. Often rotating movements made with the head as if he continually looked from left to right and from right to left. His gaze wanders from one object to another. The mouth is usually opened, the patient sometimes making smacking sounds with it or pouting with his lips. If an object is brought near to his mouth, he bites at it and licks it with his lips. It seems as if he sometimes makes an effort to say something, but one seldom hears a sound. When in this stage the patient seldom keeps his arms still. He is very ataxic in his movements. When he sits up there appears to be marked ataxia of the trunk. The legs are usually crossed, and make many jerking irregular movements. When he tries to walk, which he is quite unable to do, he puts his legs in front of and over each other. When passively moved the tonus is increased. Fundus normal. Absolute incontinence. Temperature usually normal: lowest, 34·6° C., with a pulse of 48; highest, 38° C. pulse 80 (Dec. 10). Pulse: lowest frequency 48 (Dec. 20), highest frequency 132, sometimes irregular.

Feb. 14, 1930.—Discharged.

June 18.—Admitted for the second time. Since leaving hospital the patient has gradually deteriorated mentally, latterly more rapidly. Since the beginning of April he has become much more nervous, and very fidgety; he was at first able to lift himself up in bed to a certain extent, but that is no longer possible. Four weeks ago he was troubled with jerking movements and muscular contractions, crying out every time they took place. After he had slept, which he did quietly, he was less troubled with them.

During the last three weeks he has kept his right arm and hand in a fixed position: adduction, flexion at the elbow and wrist. The left arm is also somewhat affected. When walking, he lifts up his legs much too high and is very unsteady. Arms begin to be ataxic and move with uncertainty. Sleeps well usually, eats well. Has to be fed, tongue is ataxic. Incontinent.

June 20.—Great fidgetiness; face, arms, and legs in continual movement, sometimes hemiballistic; lies with legs drawn up, flexed at the knees. Ataxia very marked. Does not react at all to his surroundings. Often screams and cries out a great deal. Strong

sucking reflex left and right of the mouth. Tremor of the lips when eating and drinking. Becoming much worse. 12 o'clock: in a deep sleep out of which he could not be wakened. 1.20: awake. 3 o'clock: again in sleep, out of which he was awaked with difficulty at 4.30.

July 15.—Patient recognized his surroundings, reacts when spoken to, is still very ataxic.

July 21.—Much less stiff in his movements. General condition much better. Ventriculography: 20 c.c. liquid withdrawn, 20 c.c. air introduced. Patient very restless in spite of being firmly tied down. X-ray: no air to be seen in the ventricles.

July 23–28.—Slight rise of temperature. Athetoid movements are much diminished. Patient now lies in a different position to that described on June 20, 1930. Both arms are extended, both lower arms strongly pronated, the hands closed into fists, the thumb inside the fist. The legs are far less often kept drawn up. General condition somewhat improving.

Aug. 1.—Afternoon temperature 38° C. Evening temperature 39·2° C.

Aug. 2.—Morning temperature 37·8° C.

Aug. 5.—Report: "In the afternoon the patient screamed a great deal, every time just for a moment and then he lay quietly looking out. Patient has sometimes muscular contractions and he shakes all over. The eyes turn upward for a moment and then shut for a moment. It is always very quickly over, but patient cries a moment directly afterwards."

Aug. 9.—Temperature 36·7°; 37·6°; 37·5° C. Cried out a lot, vomited.

Aug. 13.—Condition the same as on Aug. 5.

Aug. 18.—Had some muscular contractions, which shook his whole body; after they had passed he shut his eyes tightly a moment and then cried a little.

Aug. 22.—Was extremely sleepy at night, very deep sleep, though he has not had any medicine, looked pale, almost leaden grey at times. Pulse: 56 and irregular. In the afternoon the patient was very restless, ataxic movements. Arms kept rotated outwards, left in flexed attitude at the elbow, right stretched. Legs drawn up, lower legs crossed over each other, spastic.

Aug. 30.—Repeated shaking of his whole body; at such times he kept the mouth shut in a spasm, and then opened with a smacking noise. The eyes turned momentarily upwards and were then shut. After every shaking the patient cried as if it hurt him. These shaking movements of the body were observed in the daytime also.

Aug. 31.—Muscular contractions in face, and in the left arm and left leg, give the impression of being ataxic, large tremors, which

come in attacks. At night the same sort of tremors were observed in the right arm.

Sept. 2.—At night, muscular shocks as were observed on Aug. 30; after they had passed, a loud cry. Adductor spasm.

Sept. 7.—*In statu quo*; still small contractions.

Sept. 9.—Patient lies in the most strange positions in bed. As well as a continual choreiform restlessness of the limbs and the head, there is an almost constant tremor especially in the legs. The forehead remains restlessly frowned. The eyes are expressionless, move irregularly but slowly, and the gaze is fixed only for a moment now and then. The mouth is half opened and the tongue is only just visible between the teeth. He makes irregular smacking movements and sounds, and utters occasionally, without an outward cause, an inarticulate scream. He scarcely reacts when spoken to or when pictures are shown him. After being pricked with a pin he seems for a moment to be on the point of crying. Emotion and intention movements increase the motor agitation, but not to a great extent. There are exaggerated stretchings, torsions, etc., in the arms and legs which point to hypotonus. On palpation, all the muscles which are not being contracted feel very flabby. Passive flexion of the arm clearly reveals the cog-wheel phenomenon. The boy does not attempt to speak or to make gestures. Hands and feet are noticeably cold and damp. Lips somewhat anæmic.

Movements much resembling associated movements, e.g., in the facialis. Leg reflexes: Achilles- and knee-jerk are spastic; knee clonus ?; ankle clonus R −, L +; Babinski R −, L +; Oppenheim +; Rossolimo ?; Mendel-Bechterew ?; Gordon +; Chaddock +; Puussepp +. Arm reflexes: Mayer −; Léri −. Pulse: 120, irregular. Scarcely responds on being spoken to. Breathing irregular.

Sept. 12.—Large athetoid movements, clonus of the feet, sucking reflex and two slight contractions were filmed.

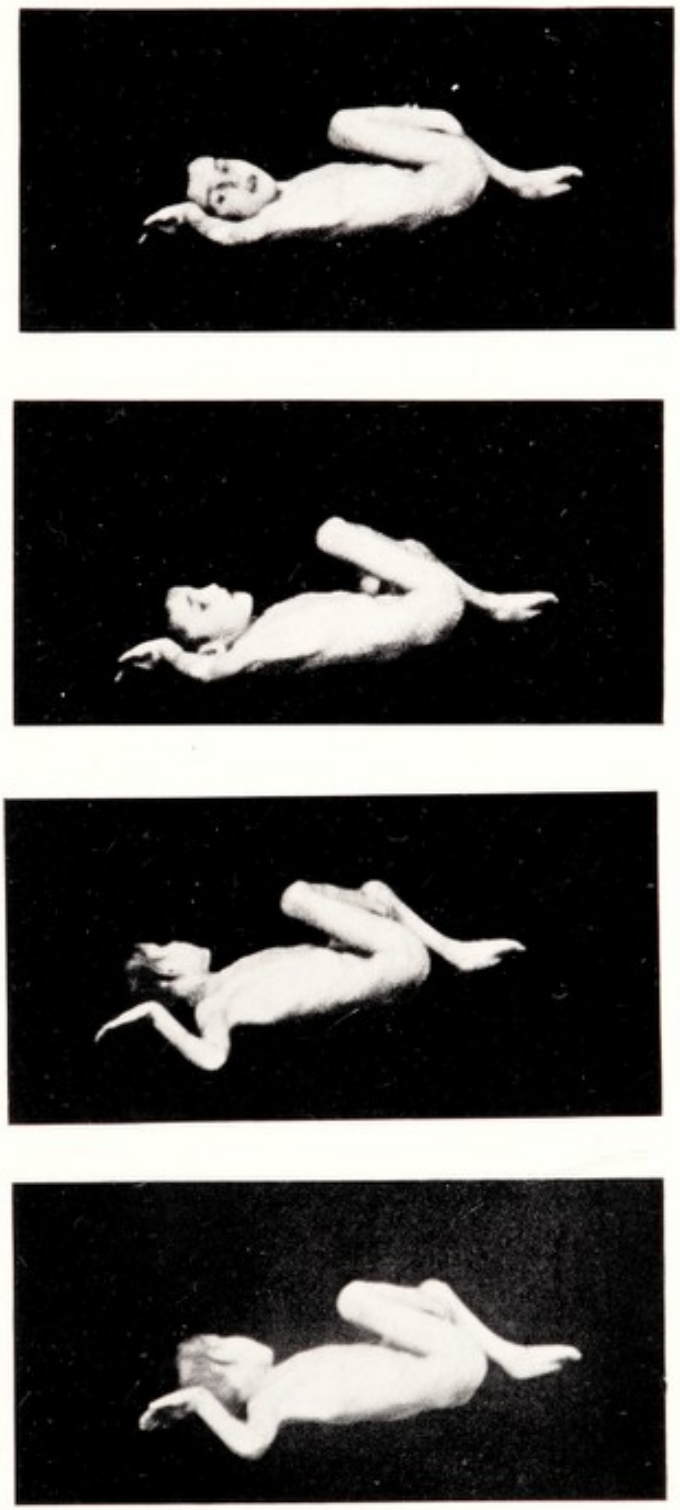
Sept. 16.—*In statu quo.*

Sept. 18.—Returned home. According to the father the journey went off satisfactorily; at home the child was nervous, went to sleep normally.

Sept. 20.—He was calm and ate with appetite.

Sept. 30.—Was very 'nervous'. Died in the evening.

Description of the Film taken Sept. 12, 1930 (*Figs.* 44–50) (The pictures are reversed).—The first part gives a picture of successive positions of the head and the corresponding positions of the arm: head and trunk moving afterwards slightly to and fro; the left arm is extended at the shoulder, and flexed and maximally pronated at the elbow, the wrist is bent and the fingers are spread. The right arm is extended, the forearm is in a supinated position,



FIGS. 44–50.—*Case V.* SERIES FROM A FILM.

FIG. 44.—*First and second pictures*: Head to the left, left arm extended at the shoulder. *Third and fourth pictures*: Head to the right, left arm flexed and maximally pronated at the elbow; the wrist is bent and the fingers spread.

the hand being stretched. The legs are drawn up, lying usually crossed (spastically) over each other (*Fig.* 44).

A stereotyped movement is noticeable: he continually catches at his left foot with his right hand (*Fig.* 45).

A series of photographs shows how the patient catches at the end of a stethoscope which is moved to and fro by the indiarubber tubes.

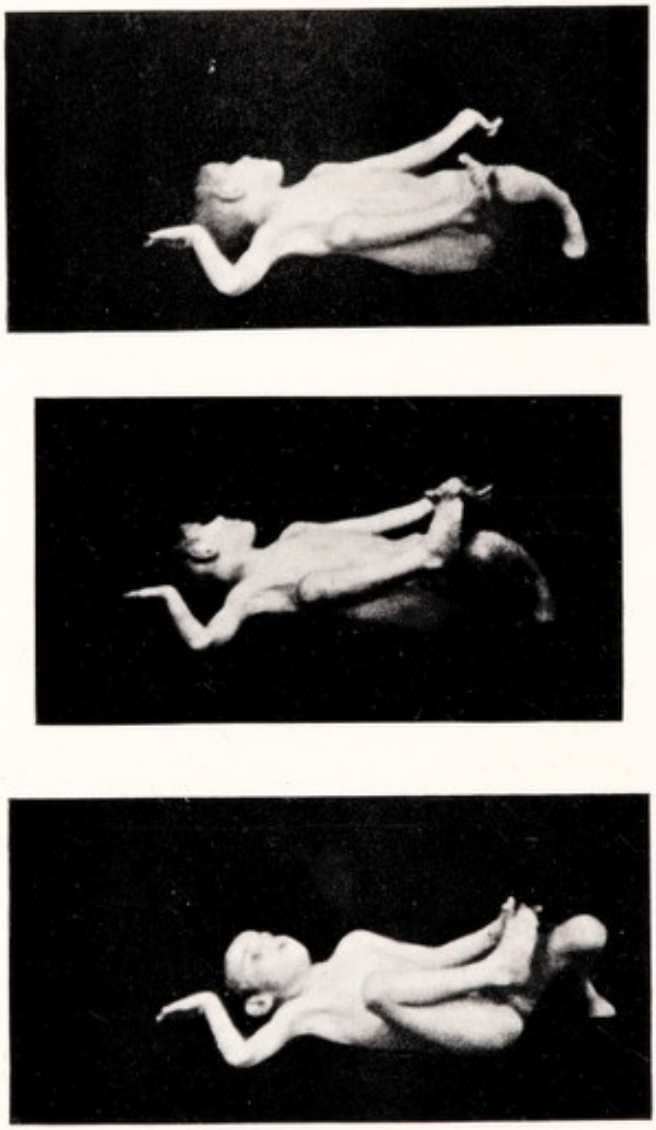


FIG. 45.—The left foot is continually caught with the right hand.

The left arm remains in the same stereotyped position, whereas the right arm makes very inco-ordinate movements. The more marked simultaneous movement of the trunk, which rolls continually backwards and forwards, is very conspicuous. Now and then the mouth opens and grunting sounds are made. If the stethoscope is put into his hand, he is not able to close the hand over it (*Fig.* 46).

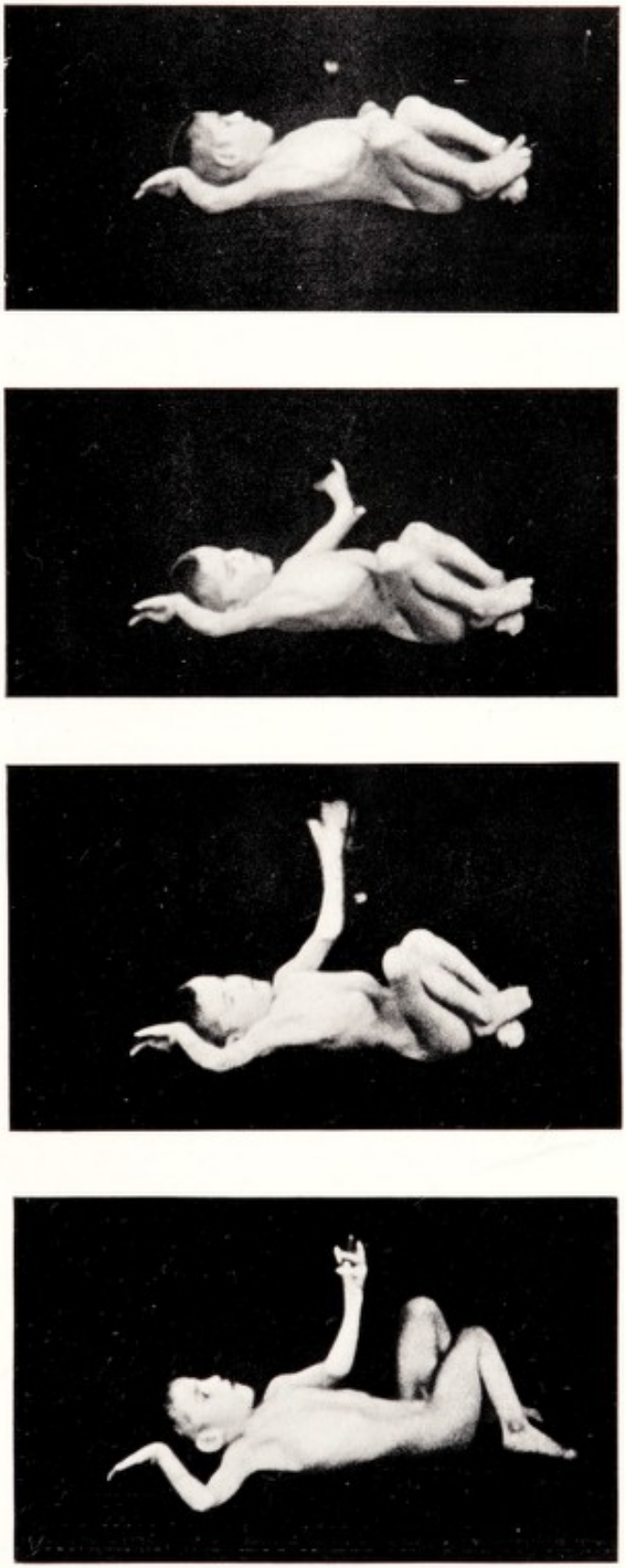
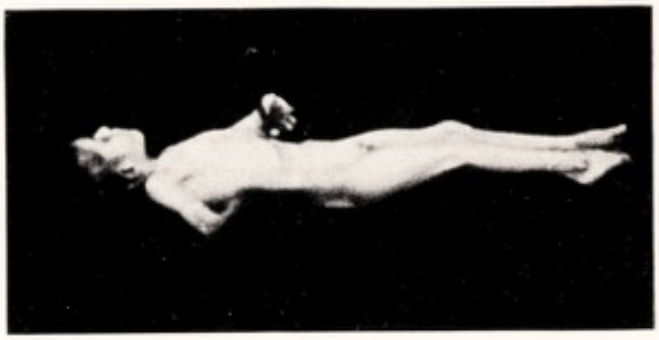


FIG. 46.—The right arm makes inco-ordinate movements to catch the end of a moving stethoscope.

To show that there were no contractures in the above-described position of the body, the patient was laid in an extended position. The following was then noticed: slight lordosis of the loins, slight flexion of the legs at the knee-joints. The left arm could be laid along the body but could not be altogether extended, whereas the



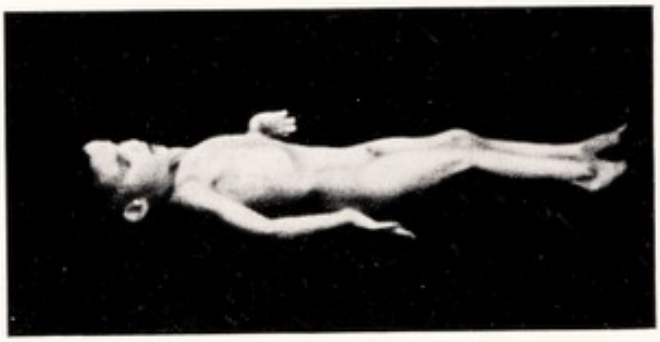


FIG. 47.—*First picture*: Laid in an extended position, slight lordosis of the loins, slight flexion of the legs at knee-joint is seen. *Second picture*: Left arm laid along the body could not be extended, the hand being kept in slight hyperextension at the wrist. *Third picture*: Carrying out grasp-movement the forced position of the left arm and in the legs returns.

hand was kept in a position of slight hyperextension at the wrist. The right forearm lies in a position of abduction and supination. As soon as the patient begins to carry out grasp-movements, the forced position returns at once, beginning in the left arm and following in the legs (*Fig.* 47).

An order to get up cannot be carried out properly by the patient; first he rolls excessively to and fro in strong opisthotonos, the right arm making strong swaying movements, whereas the left remains fixed in a forced position, and definite adduction spasms occur in

FIG. 48.—Grasp movements with the right arm, forced position of the left arm.

the legs. The next part of the film shows the grasp movements and forced position from another point of view (*Fig.* 48). Then comes a part showing the movements which occur when the patient is lifted up. The left arm remains continually fixed, the opisthotonos becomes very evident, and the movements are very inco-ordinated (*Fig.* 49).

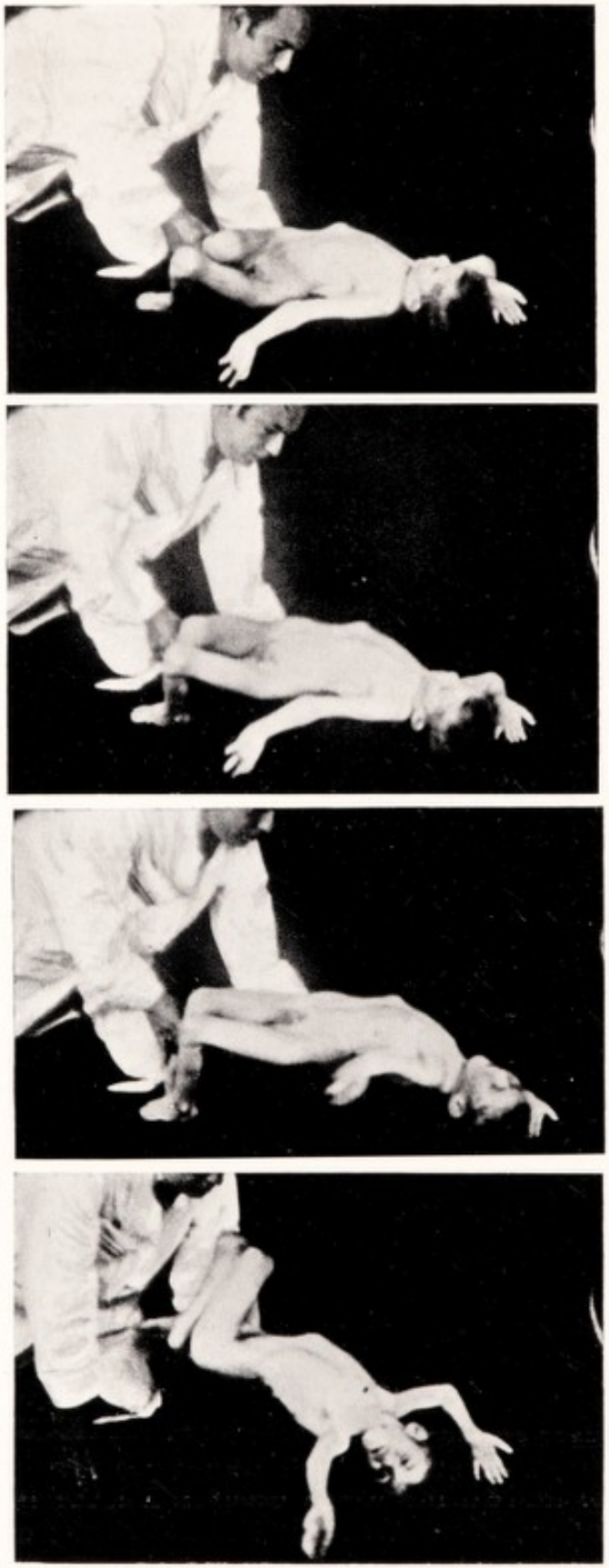


FIG. 49.—When the child is lifted up the left arm remains continually fixed at the elbow; opisthotonos.

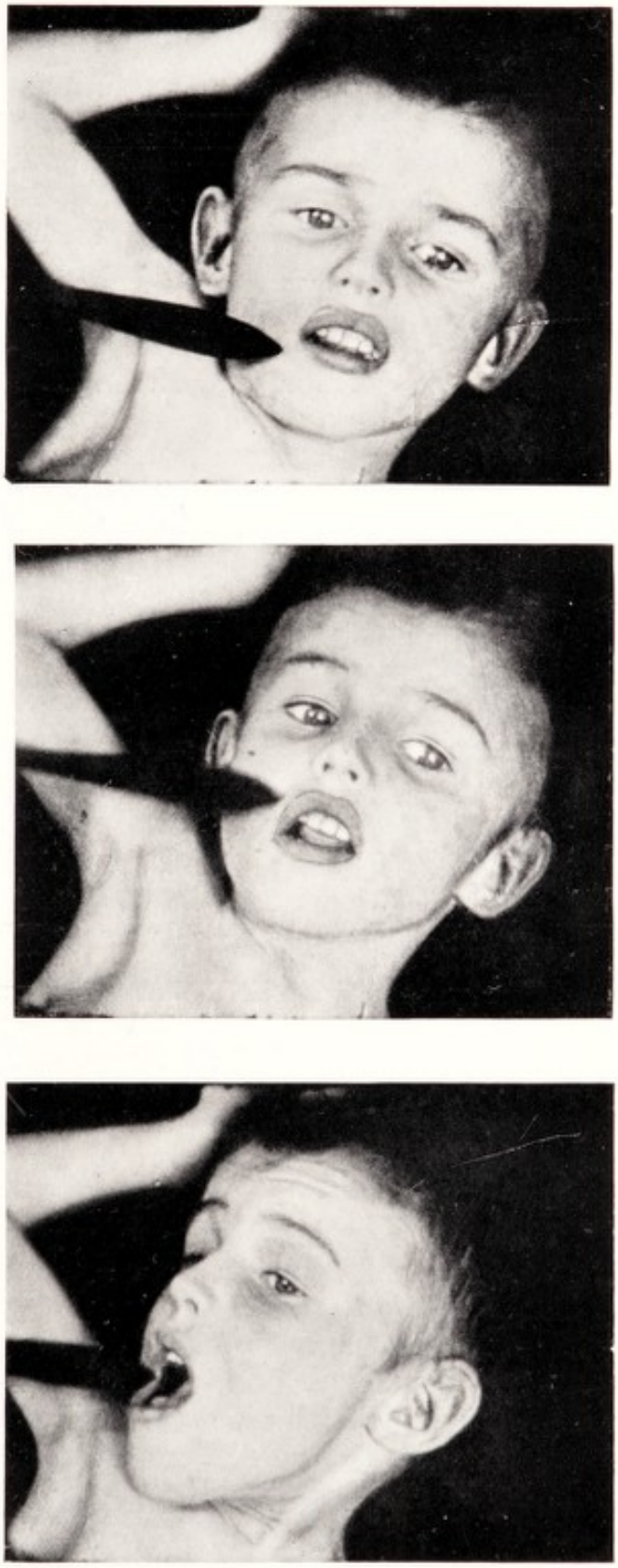


FIG. 50.—Sucking reflex.

An enlarged photograph (not reproduced here) of the left foot placed on the right knee shows the occurrence of spontaneous clonus in the left foot, whereas a photograph of the face shows the sucking reflex (*Fig.* 50) and the facialis-phenomenon (the last not reproduced).

SUMMARY.—In this case of a child who had developed normally up to the age of 3½ years and then had an epileptic fit, it was noticed that after the fit the speech became worse, and the legs became weak. There gradually developed a severe ataxia, the sucking reflex, involuntary grasping and swallowing movements, pathological reflexes, mutism, and incontinence. The fundus did not show any abnormalities. Later: more mental deterioration, continued convulsions, and specially loud crying. Left arm fixed in a forced position. Hemiballistic movements, now and then also athetoid movements. Slight fever. Symptoms variable, general condition showing now and then slight improvement. A lumbar puncture showed the presence of high pressure. Now and then the child fell into a deep sleep, out of which it could not be wakened. Several times during a clinical examination epileptic attacks were observed. Along with them sudden clonic spasms were elicited. The child died after 1½ years. There can be no doubt about the diagnosis, although there was no post-mortem examination.

CASE VI (*Fig.* 51)

Clinical History.—Schm, female, born Feb. 5, 1920. Admitted into hospital, April 22, 1932, with the following history:—

The patient was the fourth of five children, had rickets in the first two years of life, was for that reason not so quick at walking, backward too at talking. At the age of 2 years she was up to other children of that age; she did not have other illnesses after that except measles at the age of 3 years. She went to school and was able to keep up with her class; she was even ahead in sewing, although she often missed school because she lived with her parents on a ship.

Whitsuntide, 1930.—The patient had headache for half a day (without vomiting or eye complaints) and began to walk as if her legs were tired, "as if affected by the weather"; she stumbled over her legs, fell to the left side, and the body made jerky movements. The father did not dare let her walk over the plank alone. As the family feared it was poliomyelitis, of which several cases had occurred in the neighbourhood, and the doctor thought it was Little's disease, he sent her to bed for eight days; when she got up she could not walk without support.

September, 1930.—She was troubled with jerking movements in her arms, legs, and trunk, and also in her face, the left side being

worse; the left foot took on a crooked position. She could speak quite well then, and was mentally sound.

Winter, 1930–31.—She sustained a fit for the first time: the head moved quickly to and fro, and the eyes too, there was a short tonic cramp followed by clonic cramps, and also incontinence. Both sides were equally affected. The fit lasted a few minutes. She had amnesia for the fit. The fits occurred on the first occasion four times in twenty-four hours, after six days again, and then once in six to eight weeks. During that time she vomited occasionally. She also made jerky movements in her sleep like one stretching oneself, laying the hands flat on the clothes, and throwing back the arms.

FIG. 51.—*Case VI.* Photograph of patient.

Spring, 1931.—The patient began to get speech disturbances; at the same time the left arm and hand came to lie in a forced position. She could then still grasp with the right hand and throw a ball away with it. At that time she became mentally less alert; at first she wrote occasionally in an exercise book and read, but she gradually gave up doing so.

Autumn, 1931.—The head and eyes were turned to the right side; the speech disturbances increased and at the end of 1931 her speech was incomprehensible.

Early in 1932 the speech became clearer; the patient was occasionally incontinent of urine, but when admitted to hospital in April, 1932, she was not so; she recognized the children on the ship by their

voices, was latterly mentally clearer. She had no headache, and no visual disorder; hearing was good. She had no appetite for her food, was thirsty, no definite sleep disturbances, difficult defæcation, difficulty with swallowing (food had to be softened first), complaints latterly of pains in the legs. Gnashing of teeth, laughing spasms. She gets crying fits when she is not helped at once.

Heredity: the parents and grandparents come from large families, nothing special about them. One sister only of the patient has had convulsions and cannot speak properly.

April 22, 1932.—When admitted to hospital the patient lay passively in bed, head mostly turned to the left, eyes to the right. Right arm and hand in flexed contracture at all the joints except the thumb, which was kept stretched; left arm in the same position but rather more flexed; left leg spastic and in extension; right leg slightly bent at the knee and stretched at the ankle-joint. The patient continually made at intervals of ten to twenty seconds abduction movements with the left arm, lifting up and adducting the right upper arm, and at the same time lifting up the right thigh and bending it at the knee; on the left side a wave-like motion of the quadriceps was visible; adduction of the foot on the left side (*Fig.* 52).

Every now and then after an external stimulus, there would develop a fit in which the eyes turned first to the left and then upwards, and lastly to the right, showing nystagmus; the face showed a forced laugh; the right upper arm and the left lower arm were slightly raised.

Examination: the patient had circular pupils, equal in size, reacting slowly to light. The vertebral column showed a lumbar scoliosis to the left; abdominal reflexes were absent; arm reflexes—on both sides the triceps sluggish, biceps brisk, radialis and ulnaris fairly active. Mayer's reflex could not be elicited. The tendon reflexes in the legs as far as they could be elicited were brisk, with a tendency to clonus; there were various pathological reflexes. Hearing and sight appeared to be normal. The eye specialist could not find any abnormalities in the fundus. According to the examining ear specialist the drums and the caloric reaction in the labyrinth were normal. The patient showed the following, examining the Magnus de Kleijn reflexes: turning the chin to the left and the back of the head to the right: less flexion in the left elbow-joint; chin turned to the right, back of the head turned to the left: strong flexion in the left arm. In the right arm one only notices an increase and decrease of the flexion tonus, no visible movements. When lying on the back, chin on the chest: decrease of the flexion tonus in the left arm. When lying on the back, with the head thrown backwards: increase of the flexion tonus in the left arm. When the head is turned there is nothing

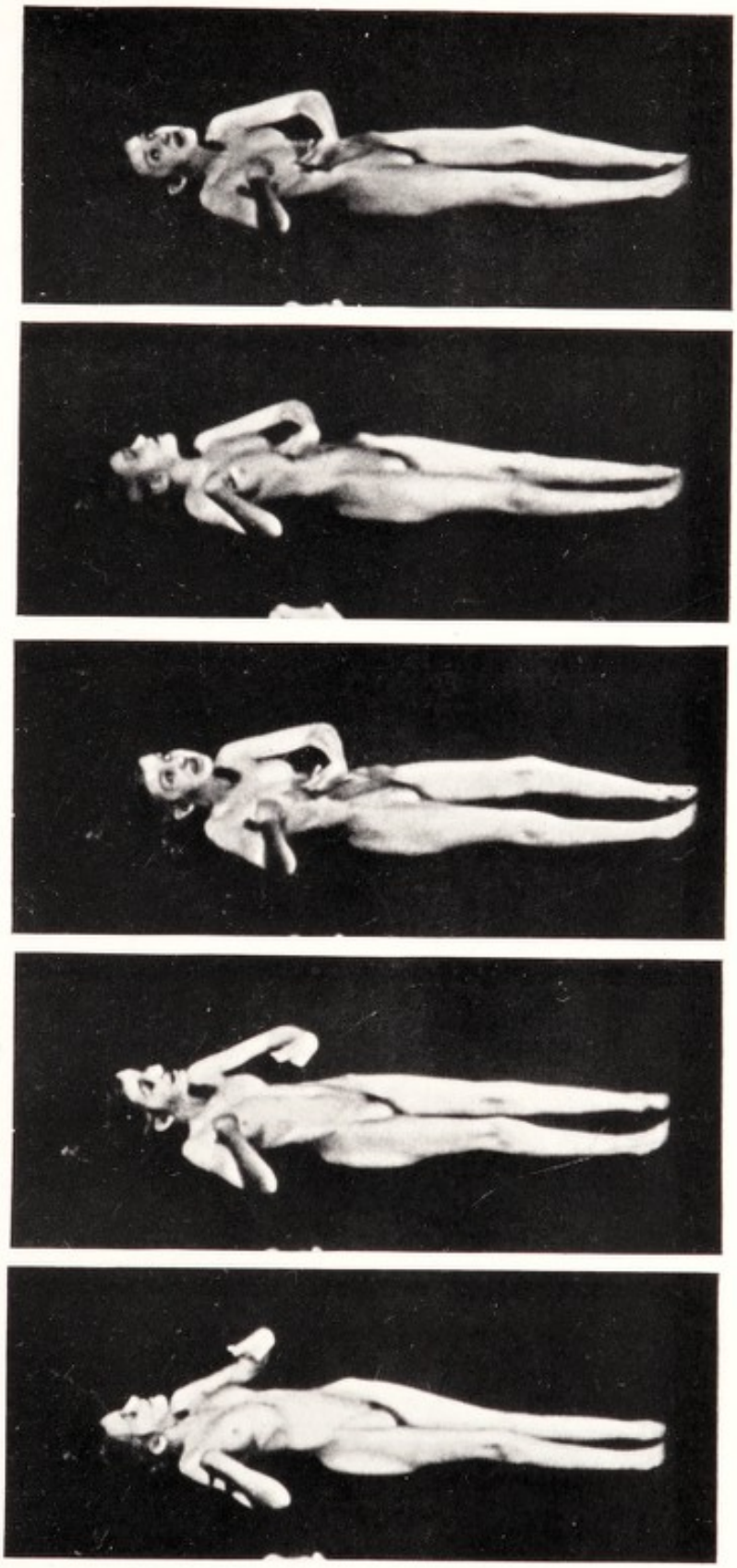


FIG. 52.—*Case VI.* Series from a film showing spontaneous movements (see text). (The pictures are reversed.)

special to notice in the legs, only now and then some twitchings in the right leg are seen (*Fig.* 53).

Lumbar puncture: Clear colourless liquid. Nonne, a trace. Pressure 12 mm. Hg; 5/3 cell. Pandy +. Mastix 5 5 4 3 2½ 2 1½ 0 0. Gold sol 5 5 5 5 5 4 3 2 1 0 0. Colloidal benzoin reaction +. In blood and C.S.F. Wassermann and Sachs-Georgi reactions negative.

During her stay the condition of the patient changed very little and it was possible to make some contact with her. She reacted to unpleasant sensations with crying, to pleasant ones with laughter, which now and then gave the impression of being without a reason. She seemed to recognize her surroundings, cried when her visitors left, followed with her eyes whatever took place in the ward, appeared able to understand simple questions but seldom answered more than 'yes' or 'no'.

July 4, 1932.—The patient contracted pneumonia, to which she succumbed.

Post-mortem Report (Prof. de Josselin de Jong): encephalitis pneumonia duplex, hyperæmia et œdema cerebri.

Summary.—In a child who had suffered from rickets, the first symptoms of the disease began at the age of 10 years. First there was interference with walking and contractures in the beginning at the left side, soon followed by jerking movements. After about six months fits commenced. Later on difficulty with the speech began, which, however, had a tendency to improve on occasions. Then the arms were kept in forced positions. Gradually difficulties with swallowing developed, and the patient deteriorated mentally. When admitted to hospital the diagnosis of encephalitis periaxialis diffusa was soon made. The child often showed jerking movements, myo-acoustic reflexes, and the Magnus de Kleijn reflexes could partly be elicited. The fundus and the hearing remained intact. Examination of the spinal fluid revealed a positive Pandy, whereas the mastix and gold sol reactions pointed to the presence of an inflammation accompanied by degeneration. The colloidal benzoin reaction was also positive. The child continued to regress mentally, and died from an intercurrent disease two years after the first symptoms had appeared.

Pathological Examination.—

Macroscopical Anatomy.—A number of areas are scattered throughout the white matter of both hemispheres in which almost all the myelin sheaths have disappeared. The size of these areas is fairly constant, the largest (*Fig.* 54) measured lineally being not much more than twice as large as one of average size, of which an example is given in *Fig.* 55.

As we have said, these foci lie in the white matter, although some of them just impinge on the cortex. Usually the foci lying near the

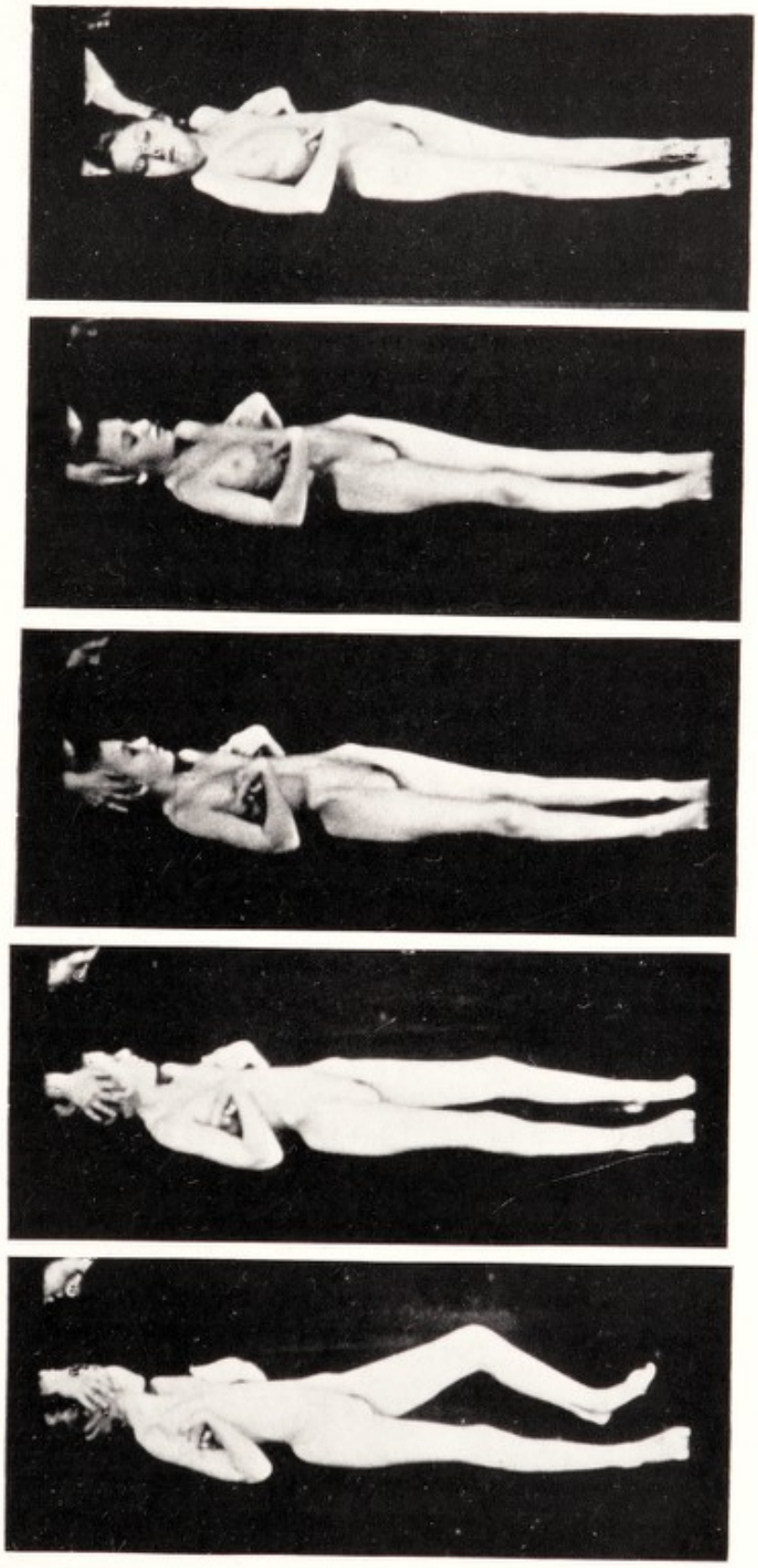


FIG. 53.—*Case VI.* Series from a film (Magnus de Kleijn reflexes) (*see* text). (The pictures are reversed.)

periphery are separated by a small band of white matter from the cortex, this band containing a layer of fibres which, although not containing the normal number of myelin sheaths, still in the preparations stained by the Weigert-Pal method were macroscopically very evident as a band containing myelin sheaths. The area seen in *Fig.* 55 shows this narrow subcortical band of myelin sheaths between the focus and the cortex, and also at one place the impingement of such a focus on to the cortex.

We wish specially to point out that these demyelinated foci can scarcely or not at all be seen on the surface of a fresh section; hence on an unstained section they are almost or altogether invisible, so that the diagnosis cannot really be made without the help of specially prepared microscopical specimens. Even when the clinical disease has led to a strong suspicion of this diagnosis, or when the diagnosis has actually been made during life, the pathological anatomist will still be inclined in some cases after seeing the fresh section of the brain to doubt the correctness of the diagnosis, not being able to see anything abnormal in the fresh section with the naked eye.

Even after the brain has been hardened, or after it has been kept whole or cut for some time in a solution of formalin, the foci are scarcely more visible.

Histopathology.—The demyelinated foci show no sharp boundaries against the surrounding white matter. They are surrounded by a transition zone, in which the amount of myelin gradually changes. The breadth of this transition zone is very varied, as will be seen in *Fig.* 55. The demyelinization is never absolute in the foci. A few myelin sheaths may be found in almost every focus whatever their situation. Apart from the above-mentioned transitional boundary-zones, in the focus itself only the finest myelin sheaths remain intact, and these show many small varicose swellings. All the thick and moderately thick myelin sheaths in the foci themselves have disappeared.

In the transition zones where the focus reaches the surrounding white matter and where already many myelin sheaths have been destroyed (especially the thick ones), a number of the intact myelin sheaths exhibit marked abnormalities: either diffuse swellings, so making the myelin sheaths thicker, which in such cases take on a lighter colour than normal, or local swellings; also varicose swellings (*Fig.* 56). These last-mentioned varicose swellings may take on large proportions, the protruding myelin blister either forming the whole thickness of the myelin sheaths and making an impression of a homogeneous structure, or this swelling seems to lie outside the myelin sheath, but close against it, there being a sharp dark-coloured line separating the actual myelin tube from the blister.

FIG. 54.—*Case VI.* Demyelinization patch in the frontal part of the brain. (Weigert-Pal stain.) (× 2·75.)

FIG. 55.—*Case VI.* Patch of demyelinization in the gyrus præcentralis and the gyrus frontalis primus. (Weigert-Pal stain.) (× 3.)

In this case such a blister may lie on one side of the myelin sheath, or it may lie round it so as to enclose it (*see* these varying conditions in *Fig.* 56). Myelin blisters are fairly often found divided

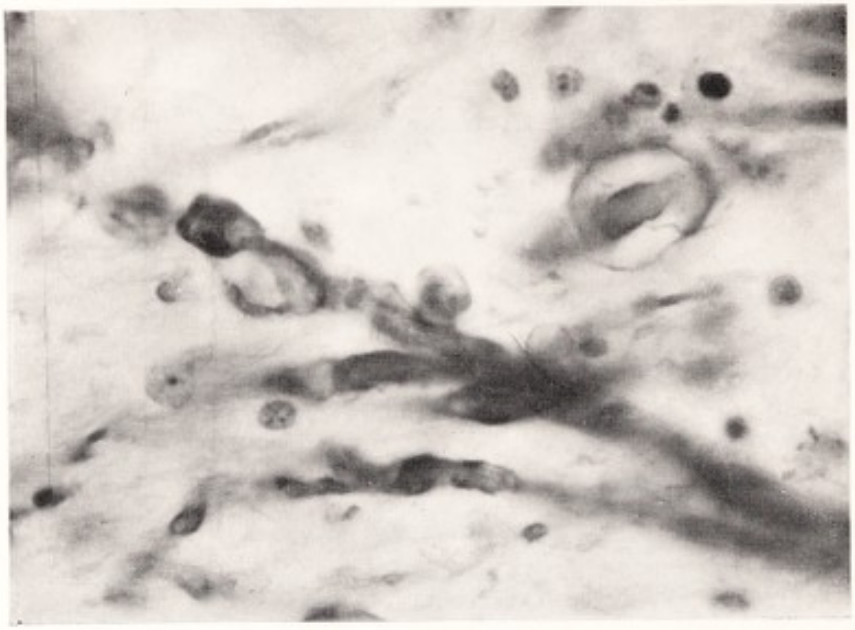


FIG. 56.—*Case VI.* Intense swelling of the myelin sheaths at the edge of a patch. (Weigert-Pal stain.) (× 535.)

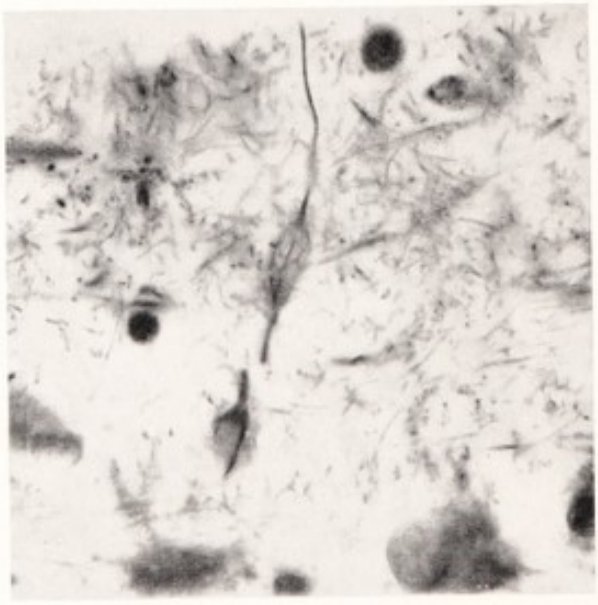


FIG. 57.—*Case VI.* 'Entbündelung' of a neurite in a patch. (Bielschowsky stain.) (× 610.)

by thick myelin divisions into a few irregular blisters, which lie sometimes somewhat concentrically arranged round about each other.

After the histopathological description of the foregoing cases

(adults), we can describe the pathological character of the foci which is found in this case quite briefly.

The axis cylinder impregnations (Bielschowsky) show that only

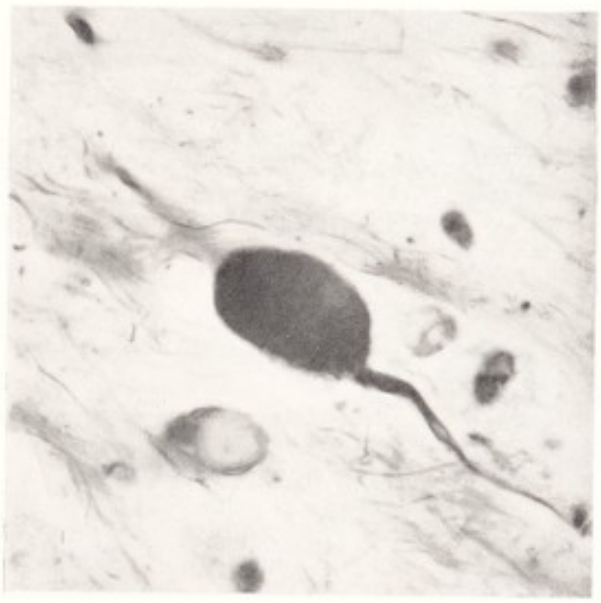


FIG. 58.—*Case VI.* Torpedo (axon-swelling) in a patch in the brain. (Bielschowsky stain.) (× 610.)

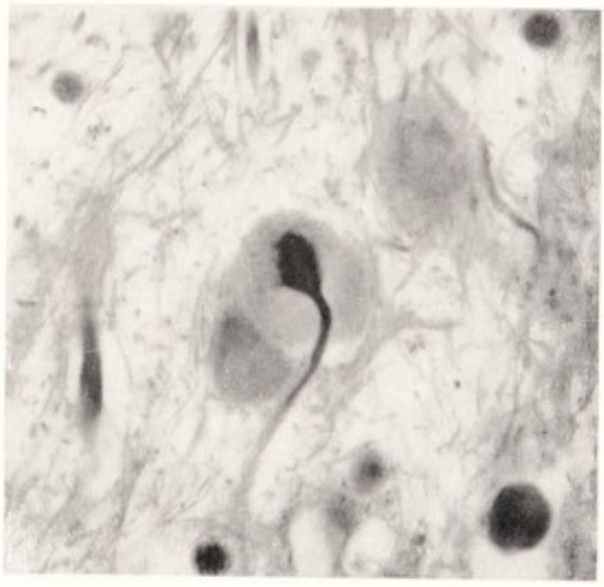


FIG. 59.—*Case VI.* Torpedo in homogeneous pellicle (cerebral patch). (Bielschowsky stain.) (× 610.)

a few neurites are normally impregnable in the foci. Between the few black-stained neurites there are numerous light grey lines to be seen, of which we cannot say whether they are neurites which have

been so much altered physico-chemically that they cannot be normally impregnated again, or whether we are dealing with threads of the glia-reticulum which have become thicker than normal.

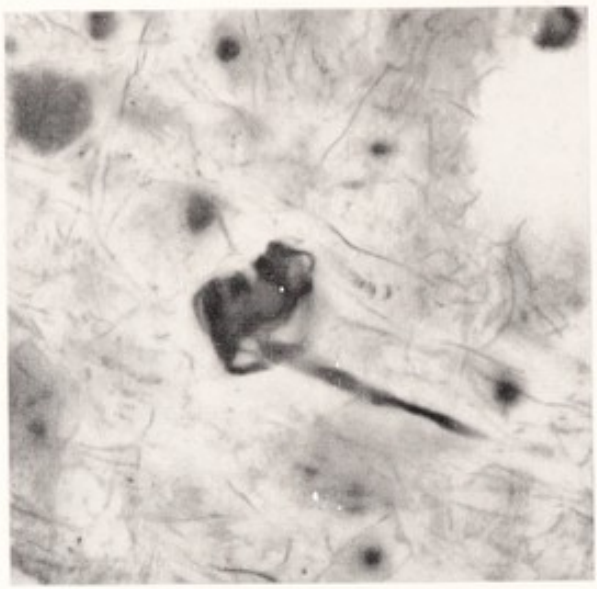


FIG. 60.—*Case VI.* Cerebral torpedo, the structure of which resembles Alzheimer's fibrillary changes. (Bielschowsky stain.) (× 610.)

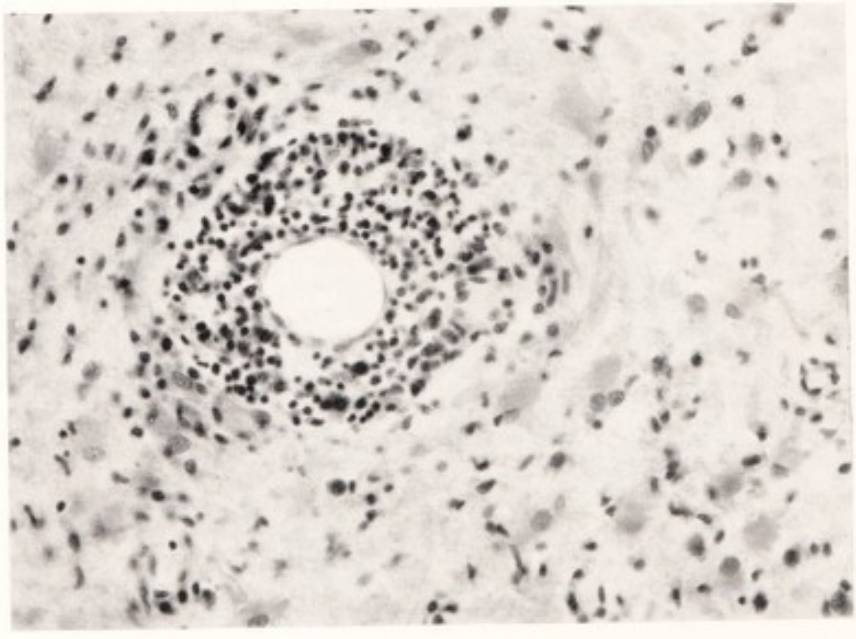


FIG. 61.—*Case VI.* Perivascular infiltration and 'gemästete' macroglia cells ('plump' cells) in a patch. (Hematoxylin-eosin stain.) (× 180.)

The few still well-impregnated neurites show many swellings of all kinds. Usually small varicose swellings are found, sometimes a filiform swelling, sometimes 'Entbündelung' (*Fig* 57). The large

round bullet-like swellings passing suddenly or gradually into the unswollen neurite parts (*Fig.* 58) resemble in their form, structure, and size the 'torpedoes' which are so often found in the cerebellum—(e.g., in practically all patients with senile dementia), but extremely seldom in the cerebrum. Some of these cerebral torpedoes are wrapped in a homogeneous pale grey spherical mass (*Fig.* 59), sometimes we find such a homogeneous mass on one side against the torpedo. Some torpedoes resemble in their structure the Alzheimer fibrillary changes (*Fig.* 60).

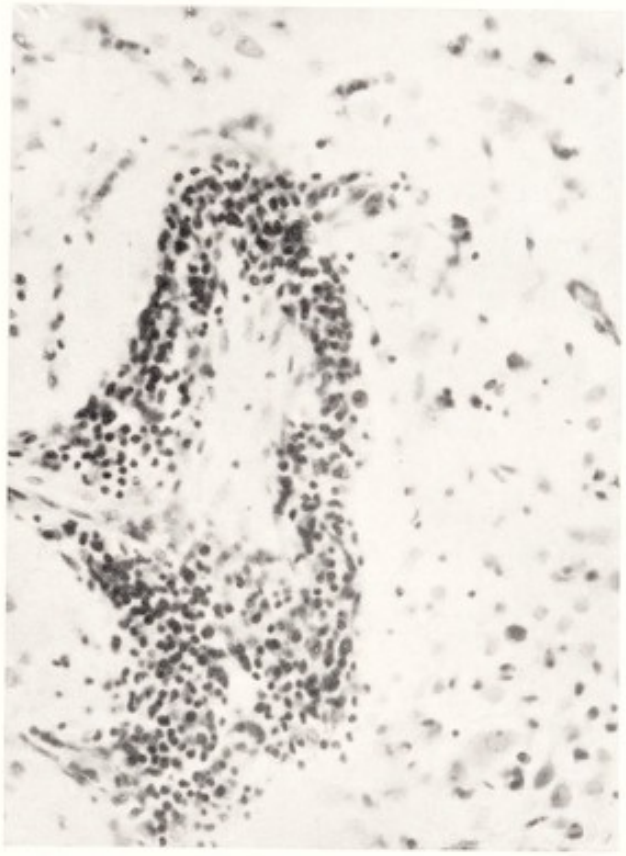


FIG. 62.—*Case VI.* Perivascular infiltration in the cerebral cortex. (Nissl stain.) (× 180.)

In this case too there are many blood-vessels in the foci which have a definite cuff of perivascular infiltration cells (*Figs.* 61, 62). In the majority of the foci the most strongly infiltrated and largest vessel lies in the axis of the oblong focus. The infiltration cuffs consist of lymphocytes with polyblasts, plasma-cells, and a few 'mast' cells and spherical granular cells scattered amongst them. This mantle is sharply limited on its outer side by the meso-ectodermal membrane between the glia and the connective tissue. A few of the above-mentioned infiltration cells lie outside this membrane. Definite extravasations of blood are not found.

Immediately outside the meso-ectodermal membrane the above-mentioned granular cells lie closer together than inside it; further away from the vessel they become less concentrated, and then in the boundary zone more concentrated again. Outside the foci they are less numerous than in the foci. In the case of adults, as described above, many of them are found throughout the whole of the white matter, whether demyelinated or not.

When fat stains are used (e.g., Sudan) all the granular cells take on the same red colour. Hence in this case there seemed to be no question of an insufficiency of the function of the glia, such as Bielschowsky and Henneberg, and van Bogaert and Scholz have described in cases in which only the granular cells in the blood-vessel walls took on with fat stains the typical red colour, whereas the granular cells in the nervous parenchyma itself were only lightly stained, a slight pinkish-brown. In this case we do not find that difference; the granular cells seem to reach the final lipoid stage right away, after absorbing the products of disintegration, also reaching the blood in this form. (The Scharlach staining method, when used, gave other results, however.)

These granular cells are evidently for the most part gliogenous, being derived from the microglia cells and possibly too from the oligodendroglia cells. In the Nissl preparations the large number of glia cells inside the foci is very noticeable, and a remarkable number of these glia cells have taken on the Nissl stain in their cell bodies. In these preparations it is noticeable that very many of the overstained glia cells have taken on the form of the microglia cells in the most varied degrees of swelling, so that we see a large number of all kinds of transition stages between the normal glia cell and the round ball-like granular cells without processes. These developmental stages of the above-mentioned cells which can be stained by Nissl stain are much more numerous than in the first described cases of adult patients. The Nissl preparation of this child reminds us in this respect of the foci in post-vaccinal encephalitis, although in the latter the foci are many times smaller and contain many more transitional cells which can be stained by Nissl stain, although the perivascular infiltration is not so marked as in this case.

Some granular cells contain granules which can be stained in the same way as myelin. They do not occur in the vessel sheaths. They are probably granular cells which have taken up free myelin shortly before, which they will disintegrate before reaching the vessel wall.

Irregularly distributed through the foci there are collections of 'gemästete' macroglia cells with a large more or less egg-shaped and fairly equally stained cell body, in which the nucleus lies as a rule eccentrically (*Fig.* 63). In the preparations stained by Holzer's

method the focus seems to be filled with a thick felt-work of glial fibres, in patches more or less dense (*Fig.* 64). Only towards the boundary of the focus do we find 'gemästete' macroglia cells in this

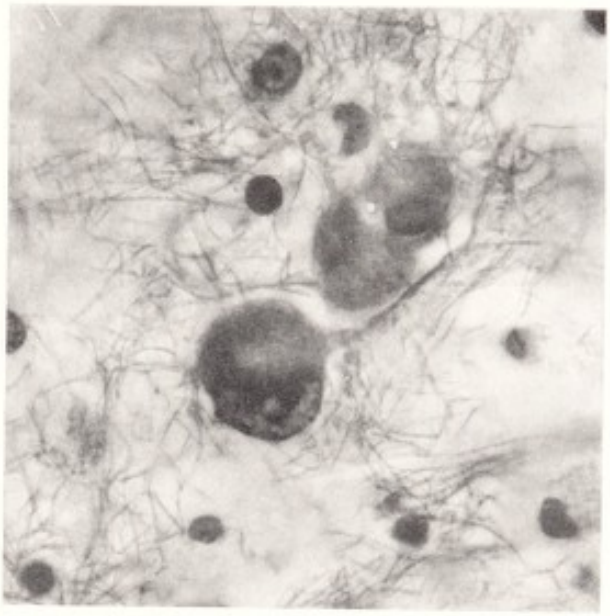


FIG. 63.—*Case VI.* Swollen macroglia cell. (Holzer stain.) (× 570.)

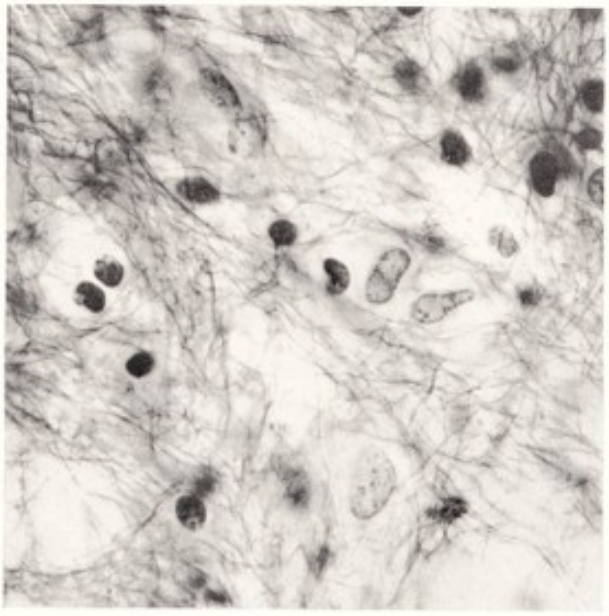


FIG. 64.—*Case VI.* Glia felt-work (and glia-nuclei) in a patch. (Holzer stain.) (× 455.)

felt-work of fibres (*Fig.* 63); in the focus itself we do not find the macroglia cell bodies stained round about the nuclei. The glia reticulum is very wide-meshed in the foci (*Fig.* 64).

Another peculiarity of the case here described is the fact that evidences of inflammation are found in so many places of the cerebral cortex too (*see Fig.* 62). The inflammation mantles found in the cortex are often thicker than those in the white matter.

SUMMARY.—In this case a great many foci were found which could be diagnosed only after microscopic examination. There is no sharp boundary to the foci, there being a transition zone between them and the surrounding white matter.

Generally speaking, the findings do not differ much from those in adults (*Cases I–IV*). We remind our readers of the swollen neurites, taking on the round bullet form and the filiform swellings similar to the torpedoes we have described in the cortex of the cerebellum in various degenerative conditions, especially senile dementia. Many vessels in the foci are surrounded by infiltration mantles containing lymphocytes, polyblasts, plasma cells, mast cells, and granular cells. The glia tissue shows a marked hypertrophy; many microglia cells are swollen, hypertrophied macroglia cells have built up a glial felt. The granular cells outside the meso-ectodermal membrane are stained red by the Sudan method, hence differing from what Bielschowsky and Henneberg and also Scholz described in the hereditary cases where the granular cells in the nervous parenchyma did not show this red colour. (*See* p. 74, however.)

In the Nissl preparations the glia cell alterations are similar to what we find in post-vaccinal encephalitis, although the foci are much smaller in that condition and contain many more developmental stages, which can be stained by the Nissl method. In the cerebral cortex are various evidences of inflammation.

In the tables on p. 150 containing the clinical symptoms an artificial separation has been made by dividing the cases into two groups according to whether the onset is before or after the fifteenth year. The anatomical alterations are the same in the two groups. Usually the children come into other hands than the adults, especially when they show psychical symptoms in the beginning, as is so often the case. It cannot, however, be denied that, generally speaking, the children give other reactions than the adults, although analogous symptoms are found in both groups. Clinically it is now a question whether we are able to diagnose diffuse sclerosis during life. In the tables much variety is still visible, but according to our experience many more points of contact than before are now present. Several cases could then be diagnosed which were afterwards confirmed by post-mortem examination.

CHAPTER IV

CLINICAL ASPECT

I. THE CLINICAL PICTURE IN ADOLESCENTS AND ADULTS

Initial Symptoms.—Whereas convulsions and disorders of gait predominate in children, *disorders of vision* are predominant in adolescents and adults. *Acute blindness* is found in several cases (*see* the table on p. 150), sometimes beginning in one eye and later on occurring in the other one. Disorders of vision are often observed. The patients may have a mist before their eyes, central scotoma for colours, or diplopia, or complain of photophobia or pains in the eyes. Sometimes a hemianopia, now and then quadrantic, occurs at the outset.

Corresponding in frequency with the visual defects are the *psychical disorders*—in many cases, however, rather vague. In this regard forgetfulness and dullness have to be mentioned in the first place, then irritability and confusion; further, 'läppisch' cheerfulness, dementia, euphoria, foolish laughter, puerility, changes of character, disinclination to work. Sometimes as an initial symptom there is already disorientation.

The *one-sidedness* of the symptoms is more often found in adolescents and adults than in children, mostly as hemiplegia or monoplegia, anæsthesia, paræsthesia, or ataxia; aphasia and apraxia may also be present. Sometimes a transitory hemiparesis is found, followed by psychical disorders.

Paræsthesias occurred four times, three times without distinct information as to the localization. Symptoms of severe *ataxia*, as in two of my cases, are worth mentioning. *Hemicerebellar symptoms* are also present as initial symptoms. *Disturbances of sensibility* in arms and legs are found in the case of Kraus and Weil.

Pains are mentioned in neck and arm, forehead and legs, and twice are described as lancinating pains. In the older patients with arteriosclerosis, *pseudobulbar paralytic symptoms* occur with bulbar speech and forced crying.

Apoplectiform attacks are four times mentioned, besides apoplectiform *and* epileptiform attacks (once), and without distinct information about the localization (once).

Epileptiform attacks are much less numerous in adults than in children, which can be easily comprehended. They are mentioned four times as initial symptoms, once preceded by a tired sensation and paræsthesia. Kraus and Weil[73] mention sudden falling without convulsions and unconsciousness, complete powerlessness, the legs as well as the arms being affected.

Disorders of gait are also less numerous in adults than in children; however, they are mentioned eleven times. In the case of Foix and Jul. Marie[40] the patient developed a progressive weakness of the legs in a fortnight; the legs were stiff 'as wood', the arms were also stiff, speech was impossible (it could not be determined whether aphasia was present). Here was a slowly progressing amelioration. Gans[45] speaks of disorders of movement as in disseminated sclerosis. The uncertain gait, the tottering gait, and also the ataxic gait mentioned above, belong to this group.

The disease may begin in a gradually progressive manner, but there are also acute or 'foudroyant' cases developing in a few hours (acute blindness), or an apoplectiform attack is the initial symptom.

Consideration of the Symptoms in Detail.—In the apparently acute cases, as in the case of Shelden et al., after an *acutely appearing blindness*, the patient soon became stuporous, and had nausea, involuntary micturition and defæcation, grimaced frequently as if in pain, and showed partial paralysis of the left side and optic neuritis.

Something analogous is found in the case of Rochon-Duvignaud et al.,[92] where an acute blindness occurred, though later on the choked discs diminished. The general symptoms in this case were scanty: headache, but no vertigo or vomiting. Afterwards there were tonic convulsions on the right side and then somnolence and vomiting, slow irregular pulse, slight irritation of the meninges, blinking of the eyelids, paresis of the right arm, progressive emaciation, extension-contracture of the legs, flexion of the arm, Babinski on the left and right side, contraction of the abdomen, and stiffness of the neck. Later, legs in flexion, attitude 'chien de fusil', arms in flexion, optic atrophy.

In the case of Shelden et al.[106] a confinement, in that of Rochon-Duvignaud an abortion, preceded the illness.

In my *Cases III and IV*, acute or subacute (three months) eye symptoms also were present directly or after a relatively short time (*see also* Coenen and Mir's[31] case).

The fundus is *normal* in many cases (Klarfeld,[67] Weimann,[125] Henneberg II,[57] Austregesilo et al.,[3] Wertham I,[127] Claude and Lhermitte[30]); disorders of vision may be present together with a normal fundus oculi. *Choked disc* (*see* table on p. 150) is mentioned in many cases, also papillitis, optic neuritis, and optic atrophy.

Temporal atrophy is mentioned in the cases of Stauffenberg[112] (at the left side), Ferraro I and II,[38] Gozzano and Vizioli,[50] Bielschowsky and Maas,[13] and Benoit I.[9]

To-and-fro swinging movements of the eyes are seen in Bouman III and IV, also in the case of Gozzano-Vizioli.[50] *Hemianopia* is very often present (*see* table on p. 150). *External ophthalmoplegia* also occurs (paresis of the IIIrd cranial nerve 16 times; and of the VIth 6 times). There was paresis of conjugate lateral deviation in the case of Kraus and Weil, and hemispasm of the eyelids in that of Klarfeld.[67]

In a very great number of cases an *internal ophthalmoplegia* was found, mydriasis (maximal wide, without reaction, Kogerer,[68] hardly any reaction, Austregesilo et al.), sluggish reaction to light (Ferraro I), absent reaction to light (Rochon-Duvignaud et al.).

For the rest, in many cases anisocoria, sluggish reaction to light, and irregularity of outline are found.

Although complete *deafness* is not so frequent, complaints of hearing buzzing (Bouman I) or hissing noises (later on actual voices, Ferraro II) are often found.

Trismus is mentioned in Baló's[4] case; absence of the corneal reflex, and trigeminus analgesia in the case of Kraus and Weil. Unilateral paresis of the tongue has also been mentioned.

There was *disturbance of smell* in Kraus and Weil's case.

Psychical symptoms are also of great importance, because they are often initial symptoms, and so a psychosis is more taken into consideration than a cerebral disease *proprio sensu*.

The great number of these symptoms is clearly shown in the table on p. 150. An extraordinary variety may be found corresponding with the extensive alterations in the brain. It goes without saying that vague symptoms are predominant. The same is true in large gliomas of the brain, which have mostly nothing characteristic. A slowly increasing progression gives a progressive dementia (Claude-Lhermitte, Klarfeld). This is the less important, as in such cases it is clear that a serious cerebral process is developing. Further, patients at a higher age must be taken into consideration, e.g., Guttmann[52]—euphoria, disorientation, dement delusions, confabulation, echolalia; Kufs—often ictus, disturbed 'Merkfähigkeit'.

To evaluate the psychical symptoms it is important to know the psychical reaction at the beginning of the illness and in subacute cases. In some cases psychopathic signs had already been observed before. Gans: ethical defects. Weimann: psychopathic irritability, 'affektabil', later on 'ratlosig', 'Denkhemmung', disorientation, forgetfulness. Wertham: drank a good deal, was observed accosting girls, showing a tendency to homosexual advances. In the cases of

Ferraro with marked hereditary predisposition, there is a resemblance to the psychical symptoms in disseminated sclerosis.

No psychical symptoms were found in Henneberg II, Benoit II, both with remissions, or only euphoria (Benoit I), or euphoria and depression (Benoit III). The patient described by Stewart, Greenfield, and Blandy[114] was noted to be dull, but not confused. In the special case of Fr. Bielschowsky[19] with remissions and exacerbations combined with rise of temperature, psychical symptoms were more than once present.

Important *remissions* were found in the case of Kraus and Weil and slight psychical symptoms resembling neuropathy or hysteria. Sometimes the illness is of long duration and no psychical symptoms appear (Foix-Marie, Kraus and Weil). In the case of Cassirer-Lewy[28] the patient was 'unbesinnlich'.

One must also consider a reaction to a somatic illness, as in encephalomyelitis, e.g., hypochondria (Urechia-Mihalescu[121]).

In other cases, where depressions are mentioned, depression has sometimes been present previously (f.i. Henneberg I).

In some cases the patient entered the hospital in a confused state, considered as a hysterical reaction, e.g., that of d'Antona, where disorientation, visual and acoustic hallucinations, and later on progressive dementia were subsequently observed. In the case of Rustrich-Krylov[94], following a transitory hemiplegia, exaltation, impulsiveness, obstinacy, refusal of food, poverty of ideas, foolish repetition of words, with intact orientation, were noted. Here a schizophrenic process must probably be accepted. In Braun's case[23] there were delusions, refusal of food, hallucinations, irritability, without interest. These latter cases have also a relatively rapid course.

Often the diagnosis of dementia paralytica has been considered, on account of the demential euphoria (Walter[123]) which occurred as an initial symptom. Symptoms of moria, foolish cheerfulness, 'läppische Witze', afterwards crying, combined with abnormal default of inhibition, labile psychical conduct, marked disturbances of 'Merkfähigkeit', and later on cerebral screaming, were described in the case of Stauffenberg. The case of Kogerer (also with moria) demonstrates that in such cases a localization in the frontal lobe has been considered: excessive laughter, obscene language, defective orientation were observed. In the last two cases disturbances of vision had preceded.

In the case of Austregesilo et al. a childish euphoria, disorientation, and defects of memory were present. In this and the former two cases remissions were seen, in Kogerer's case especially in regard to the paresis of one leg.

Changes in character were observed in Bouman IV (together

with disturbances of vision); disordered conduct by Bodechtel and Guttmann[15] (bit the nurse in the arm, was temporarily passive while being fed, although he could eat without help). Forgetfulness is mentioned in the beginning of the illness (Klarfeld); disorientation in the case of d'Antona, Casper,[27] Jakob,[63] and Henneberg I, and in a later period in many other cases before or after an apoplexy. Later on disturbances of 'Merkfähigkeit' (Henneberg I), diminution of intellect, and dementia occur (sometimes with restlessness, Rossolimo[93]). In many cases incontinence of urine, sometimes of psychical origin, is present; mostly, this symptom appears in the course of the illness.

Some of the psychical symptoms are well known from cerebral lesions: cerebral screaming, forced laughter (Bielschowsky and Maas, Stauffenberg); crying without cause, associated with turning of the head to the left (Barré); involuntary laughter (Ferraro II and III), repeated laughter (Kogerer); forced crying (Matzdorff[84]); screaming of words impulsively (Austregesilo et al.[3]); cerebral screaming (Bouman III). The last-mentioned symptoms are much commoner in children; also the bulbar or pseudobulbar symptoms are less represented in adults.

Difficulty of swallowing (Bouman I, Matzdorff, Gozzano and Vizioli, Henneberg II—pseudobulbar symptoms in the case of Matzdorff at older age) of cerebral origin is certainly to be included here; also the grimacing expression of the face in Bouman III (*see Fig.* 6) and in Shelden's[13] patient, who grimaced frequently as if in pain; and the mask-like face, as in Bodechtel-Guttmann's case.

It must be remembered that apraxia and agnosia can often simulate psychical disturbances.

Apraxia of the upper half of the face and of the eyelids is mentioned by Schilder[100]. Further, apraxia is mentioned in the cases of Walter, Bouman III, Barré[6] (with alexia), Bielschowsky and Maas, Klarfeld, Claude-Lhermitte (also alexia), Baló (combined with aphasia), Fr. Bielschowsky (combined with aphasia—temporary). Optic agnosia and apraxia are recorded in Weimann's and Kogerer's case; amnesic aphasia in those of Cassirer-Lewy, Walter, Klarfeld, and Kraus and Weil. Aphasia without foregoing apoplexy, epilepsy, or trephining are mentioned by Benoit II, Walter (also agraphia), Bodechtel and Guttmann, and Cassirer and Lewy.

Articulatory symptoms were noted by Casper, Henneberg II, Benoit III, van Londen and Frets,[77] Rossolimo, and Barré. *Scanning speech* by Ferraro III (Ferraro I and II: speech ataxia), Gozzano and Vizioli, Kraus and Weil, Gans, Benoit I, Austregesilo, Bielschowsky and Maas, and Kaltenbach. *Speech slow but distinct* is recorded by Stewart et al.

The *motor symptoms* express themselves at the beginning of the illness by a slight paresis on one side, as monoplegia, hemiplegia, facial paresis; often, however, by disturbances in gait or slight ataxia in the arms or a feeling of heaviness in one of the arms (Barré et al., Bouman I). In some cases the one-sidedness is apparently permanent (comprehensible in a subacute type of the illness); in other cases the paralysis of one side may be predominant later, the other side being paralysed to a slight degree only. In Benoit II is noted: first a right-sided paresis, then, after influenza, an acute paralysis of the left side, which improved. There is a progression in the motor disturbances not only in extension but also in intensity.

We do not find so many quadriplegias or triplegias in adolescents and adults as in children. What we have described later in the tetraplegias in children—viz., extension contractures of the legs, flexion contractures of the arms—is also to be found in adults (e.g., Rochon-Duvignaud), mostly, however, in the older children. The pyramidal rigidity is more severe in children.

In most cases we have *spastic symptoms*, and it is superfluous to say that exaggeration of the reflexes, clonus, pathological reflexes, absence of abdominal reflexes, sometimes defence reflexes are found. In Cassirer and Lewy's case no symptoms of paralysis or contractures are mentioned. In Ferraro II all muscular movements were clumsily performed, although the sense of position was not lost. Ferraro I and II and others mention no Babinski reflexes; certainly an extensor plantar response is less frequent in adults than in children. Now and then they are alternately present or absent.

Sometimes a *flaccid paralysis* (Henneberg II) is noted. Hypotonia is found in Henneberg I, Kogerer, and in Ferraro I it is noted no spasticity is present. 'Schleuder' movements of the arms are recorded in Bouman III, also hemiballismus, athetoid movements in some cases (*see* table, p. 150); grasping and groping movements in Bouman IV, and reeling as if drunk in Bouman IV and many other cases. Remissions of the paralysed extremities are noted, especially in the cases resembling disseminated sclerosis.

Rolling of the eyeballs or pendulum movements are described in Bouman III and IV and in the case of Gozzano-Vizioli, and in many cases conjugate deviation of the head and eyes.

Van Londen and Frets mention an *atrophy* of the tongue muscles; Gozzano and Vizioli of the interossei, and Barré has found atrophy of the left arm. In some cases Charcot's triad is present; as a rule intention tremor is not often observed (*see* table p. 150). It is the same in regard to nystagmus. As to cerebellar disturbances, there is the case of Braun: slow and awkward movements, and adiadokokinesis on one side.

Tremor is more often mentioned—of hand and fingers (Kraus and Weil), atypical tremor of the hands (Shelden et al., Ferraro II): tremor of the tongue and face, Wertham II: tremor of the extremities (also intention tremor), Kaltenbach: fine tremor of the hands.

It is understandable that *epileptic convulsions* should not occu as often in adults as in children. Exceptionally an increase of rigidity is observed spontaneously or after a noise or touch, or after speaking to the patient (Bouman III). Barré mentions painful contraction, especially when speaking to the patient and when she tries to answer. These subcortical tonic fits occur much more often in children than in adults. There were clonic convulsions in the muscles supplied by the right spinal accessory nerve in Klarfeld's case.

Sometimes there is staring to one side and unconsciousness without convulsions, as in Stauffenberg's case, starting with turning of the head to the left; later on tonic convulsions of the whole body appear, with head and eyes turned to the extreme left. Occasionally spontaneous twitchings occurred in hand and arm of one side in Wertham I. The epileptiform convulsions are of the Jacksonian type (Fr. Bielschowsky, Rossolimo, and others) or more generalized (Jakob, Cassirer and Lewy).

Wertham mentions in his first case '*fugues*'.

Stiffness of the neck and symptoms of *meningitis* are mentioned by Rochon-Duvignaud et al. (also contraction of the abdomen); cervical pain in Bouman III, and stiff feeling in the neck in Bouman I.

Increased pressure in the cerebrospinal fluid is mentioned in Bouman I, Bouman III, Sheldon et al.; independently, however, headache, vomiting, and vertigo are found.

Headache: 17 times, vertigo 8 times, vomiting 14 times; all three together 5 times, headache and vomiting 5 times, headaches and vertigo twice.

Rise of temperature is often mentioned; the most curious case is that of Fr. Bielschowsky, where each bout of fever was followed by an exaggeration of the cerebral symptoms. In Bouman III the beginning of the illness was associated with a rather high temperature; in Coenen and Mir's case slight rises of temperature were noted. Casper and Claude-Lhermitte also mention rise of temperature; in the last case there followed an exacerbation of the illness.

Positive globulin reactions are mentioned in the cases of Jakob, Stauffenberg, Bouman I, Shelden, Stewart et al. (Schilder post operationem). The colloidal reactions are only rarely done. There was an increase of cells in the case Stauffenberg (20 cells, second examination 44 cells).

The cases of Ferraro may be reckoned among the *heredo-degenerative* cases. To the *infantile* and *juvenile* type of the heredo-degenerative forms belong the cases of Krabbe, Scholz and v. Bogaert[18], and others.

Principally in adolescents and adults many cases often show important *remissions*, reminiscent of disseminated sclerosis. With the exception of the case reported by Foix-Marie as "sclérose centro-lobaire, une forme chronique cicatricielle, fixée, dont les séquelles peuvent être importantes, massives, bilatérales ou au contraire partielles, mais de tout façon compatibles avec l'existence", the disease is progressive but of varying duration (*see* the table on p. 150); the course is a year or less in nearly one-half of the cases.

II. THE CLINICAL PICTURE IN CHILDREN*

Initial Symptoms.—In the initial stage *convulsions* and *disorders of gait* are predominant, statistically in an equal number. (Five children had not yet learned to walk when the initial symptoms were observed).

Psychical symptoms, such as apathy (the children are too quiet, no longer play), irritability and restlessness, alteration of character, and falling off of school-work, are found in about 30 per cent.

Disorders of vision of central type are noted in 12 per cent; a combination of disorders of vision and hearing in 6 per cent. Disorders of hearing were present in 4 per cent.

The *general symptoms* (headache, vomiting, vertigo) were commoner in children than in adults, but not so frequently as to constitute predominant symptoms in the initial stage.

Hemiplegias are reported more (twice) in adults, monoplegia just as often in children as in adults, while paræsthesias and pains are not noted in children though they occur in adults relatively often. The last has probably to be connected with the fact that children do not so easily give expression to their feelings, or—and this I say with some reserve—because more than one of the cases in adults is a transition to disseminated sclerosis, especially with regard to the paræsthesias observed over the well-known areas.

The symptoms mentioned above, namely, psychical symptoms and gait disorders, are initial symptoms; disturbances of vision are much more frequent in later stages of the disease.

For a great part we derive our history from the family; only a few of the children were directly observed by competent doctors.

Consideration of the Symptoms in Detail.—Giving in detail the description of the complete picture of the disease, it is impossible to avoid repetition of what has been noted above.

* Up to 15 years.

A child, healthy up to the onset of the first symptoms, begins to show *gait disorders* and *fits*—severe attacks resembling epileptic fits or slight ones manifesting themselves as twitchings. Opisthotonos is often mentioned—certainly not restricted to the familial cases of Krabbe. Sometimes the fits are not observed, because they occur in the night.

In the meantime, *psychical disorders* of a great variety are noticed: apathy, restlessness, exaltation without restraint, irritability, bitterness, depression, slovenliness, inertness, shyness, and now and then disorientation.

In a great many cases *crying* and *screaming* are noted, with various characteristics: yelping cries, often observed in cerebral lesions during the terminal stages; this symptom, however, can certainly not be explained as a reaction to a feeling of discomfort, but has to be considered as a symptom of irritation. There may also occur fits of convulsive crying, in which some rhythm may be observed (rhythmical chewing and sucking are also mentioned); during the screaming the spastic flexions are sometimes increased and jerking movements occur. Now and then purposeless laughter and screaming are noted; sometimes grinning is present, accompanied by grunting sounds.

The succession of the predominant symptoms or disorders of gait, fits, psychical symptoms, is not always the same. As in my fifth case and in many others, epileptic symptoms can be observed at the outset, and only afterwards psychical symptoms and disorders of gait. It is also possible that children, hitherto sane, change in a pathological sense with regard to the character. In time the child *deteriorates with regard to his intellect and general behaviour*. This change, variable in duration, is always present.

General disorders of 'Leistung' are observed: forgetfulness, difficulty in thinking and in comprehension, as well as want of interest in the games of comrades or want of initiative in their own games. Sometimes reading and writing are still performed by children of school age, but that also comes to an end. With the aid of experiments it is possible to control these disorders of 'Leistung'. Heubner[59] gives a description of this stage, characteristic of the time in which he wrote it: "Man kann sich überzeugen, wie diese (allmählig fortschreitende allgemeine Verblödung) herbeigeführt wird durch eine schrittweise zunehmende Lösung aller Fäden, welche das Grosshirn mit der Aussenwelt in Beziehung setzen, ebenso auch derer, welche die einzelnen Regionen des Grosshirns mit einander verbinden. So geht gleichzeitig die Zufuhr von Eindrücken zur Bildung neuer Vorstellungen, wie die Fähigkeit die gewonnenen Anschauungen und Erinnerungsbilder nach Willkür zu benützen, verloren. Der geistige Inhalt der Seele versinkt in Nichts."

Together with the psychical deterioration, *incontinence of urine* repeatedly occurs, sometimes, however, only combined with epileptic attacks. Meanwhile *spastic contractures of the legs* have developed, very often followed by paralyses and afterwards also by *contractures of the arms.*

It goes without saying that many variations can be observed under these circumstances: paraplegia, triplegia, quadriplegia, often with extension contractures. In the majority there are to be found exaggerated tendon reflexes and clonus, pathological reflexes on the left and the right side as far as can be elicited. In some cases the bilateral pathological reflexes are present only in a later stage of the process, a hemiplegia having preceded. A pes equinovarus is not rare; contractures of the adductor muscles are often very strong. The arms—especially in the case of children—are extremely flexed at the elbow- and hand-joints, the arms firmly pressed against the chest, the fingers bent into a fist. Now and then an alternate hyper- and hypotonus is found, probably in connection with the Magnus de Kleijn reflexes, which in several of my cases could be elicited very well. In the same case clonic twitches of the head and tonic deviation of head and eyes to one side were present.

Ataxia with intention tremor of the arms is not rare. Moreover, tremors are often described, as well as hemiballistic, athetoid, and choreiform movements, as clearly exemplified in a film taken of one of our patients. Movements of lightning speed over the whole body are also noted. The lightest touch of the limbs often causes an increase in contractures (pressing on the muscles, scratching with a pin).

In many cases the child who hitherto has spoken very well gradually begins to *speak in an indistinct and lalling fashion.* Finally it is no longer possible to understand the child; only the mother, who is daily in contact with it, may still comprehend a little of what is spoken. This stage also passes and the child no longer produces a single word. Now and then motor aphasia is noted, sometimes motor and sensory aphasia. But apart from the difficulties connected with the examination of the aphasias in these cases, in many instances it is still necessary to think of a disorder of speech of *articulatory character* (as the disturbances of swallowing of pseudobulbar character).

For rather a long time it is possible for the parents to retain some contact with the child, and questions and requests may be comprehended. Reading and writing are also given up, partly because of lack of interest.

It is of some importance to state that *disturbances of swallowing* are particularly often observed in many of the cases; in 38 per cent

they are emphatically noted. Headache, vertigo, and vomiting are also observed in a *later* period of the disease, but not so often as in adults.

It is necessary to emphasize that in a series of cases examined minutely and controlled by the ophthalmologists, the *fundus* was found normal (noted in 32 per cent). However, a *bilateral neuritis* was often noted, and repeatedly an *atrophy of the optic nerve*; a *choked disc* was very exceptionally found. In some cases *temporal pallor* is mentioned. Only in a very small number hæmorrhages in the retina occur. *Cerebral blindness* as well as *hemianopia* have been noted, but only rarely. When a homonymous hemianopia is found, then it is possible that first the left side and afterwards the right side is affected, followed by blindness. Now and then blindness is combined with deafness, and then sometimes deafness precedes the blindness.

With regard to the other cranial nerves, in some cases an *abducens paresis* is present. In cases beginning unilaterally a facial paresis is often mentioned; now and then unilateral ptosis. *Nystagmus* may be present. In many cases the *pupillary reactions* are normal; sometimes a sluggish reaction is found, or the light reaction may be completely absent. Sometimes the pupils are wide; small and unequal pupils are also noted at times.

Reliable data as to *sensation* are mostly lacking. Sometimes a disorder in the perception of touch is mentioned. The *abdominal reflexes* are absent in some cases. Now and then there is question of *deviation of the head to one side with deviation of the eyes to the same side*. *Disorders of smell* are mentioned by Schilder and Schaltenbrand.

The *cerebrospinal fluid* is in almost all cases unaltered; in a few cases the globulin reaction is positive. The same holds true for the cellular increase. The colloidal reactions have been insufficiently investigated (in my *Case VI* positive).

Rise of temperature is noted in some cases, as in one of mine.

Can the cases described as *heredo-degenerative forms* be isolated clinically from what has been mentioned above as characteristic of the restricted group of diffuse sclerosis in children? According to the Cases I and II described by Bielschowsky and Henneberg, it is not possible to differentiate them clinically as a special group. The same holds good for the cases of Scholz and van Bogaert and Scholz. The cases of Krabbe[69, 70] are regarded by Ibrahim[62] as the acute infantile form; those of Scholz[102] as the subacute juvenile form; those of Pelizaeus-Merzbacher are supposed to be the chronic variety. Schilder, referring to the cases of Krabbe, thinks it probable they may be non-inflammatory, partly endogenous, partly (non-familial) exogenous.

These, too, may not be regarded as a special group. Here the outset occurred at a very early age. The children, at first totally without any symptoms, contracted an acute illness, lasting five to six months, combined with general muscle stiffness, most prominent in the legs, with severe convulsions, precipitated by touch or by noise (myo-acoustic reflexes) or by glaring light ; furthermore there was nystagmus, and in later stages optic atrophy. Krabbe especially mentions periodical rises of temperature, without demonstrable cause outside the central nervous system. The attacks were described as follows : head bent backward, opisthotonos (in one case only lumbar lordosis with marked dorsal kyphosis was present) ; the arms flexed and fixed at the elbow-joint, hands sometimes clenched into a fist, in other cases in obstetrical posture, the legs in extension at the hip-, knee-, and foot-joints, often adducted till the legs are crossed.

In the cases of Scholz, the onset of which was in infancy, progressive psychical deterioration, spastic paralysis of all extremities, deafness, and blindness were noticed.

The similarity in the *last stages of the illness* in various cases is remarkable. The face, as it appears in *Figs.* 52, 53, taken from a film, has a grinning expression, the eyes wide open. There are contractures at the elbow-joint and the wrist ; the hands are rolled around (often also adducted) ; the legs are stiff in extension (often also strong adduction) ; the feet are turned downward and inward. Psychically the patients are deteriorating, going on to a terminal dementia, combined with severe cachexia. As a rule death follows after an intercurrent illness.

III. DIFFERENTIAL DIAGNOSIS IN ADOLESCENTS AND ADULTS

The differential diagnosis in these cases is very difficult. Differentiation from Pelizaeus-Merzbacher disease, amaurotic idiocy, and other diseases of childhood is described later.

In 1925 Guttmann[53] gave the following clinical picture : Diffuse sclerosis is an organic disease of the brain, rapidly progressive, appearing at any age, but with definite times of predilection—viz., in early childhood and around the twentieth and fortieth years of life.

The psychical picture of the disease is not characteristic, but it is defined by the diseased brain. If the disease affects children, there is a change of character ; finally there are also simple processes of dementia. Even in adolescents and adults there are psychical symptoms ; they are, however, more often the exogeneous reaction-forms of Bonhoeffer. In connection with them, but differing in time, there appear epileptic attacks, spastic hemi- or tetrapareses, eventually

symptoms, showing themselves at the same time, which point to more or less extensive foci in the cortex.

From the standpoint of differential diagnosis we must exclude a series of congenital defects, processes of dementia in adolescents, in adults cerebral arteriosclerosis, and in both the symptoms of cerebral tumour and disseminated sclerosis. Increased intracranial pressure suggests tumour; now and then the dullness will be characteristic of tumour and plead against the other exogenous reactions. Remissions as well as spinal, pontine, and medullary symptoms would suggest rather a disseminated sclerosis, though they are also observed in diffuse sclerosis. A positive finding in the cerebrospinal fluid argues in favour of disseminated sclerosis. Against arteriosclerosis will speak the age, the lack of peripheral and cardiac arteriosclerosis, the disturbances of 'Merkfähigkeit' and sleep.

Brain processes, such as, for example, Pick's disease, more rarely have a chronic course.

Collier and Greenfield gave, divested of minute details, the following clinical aspect: a malady usually occurring in children and young subjects with no tangible causal factors as antecedents. The onset is over a few days, the course progressive, with some remissions, to a fatal issue; the duration from a few months to three years. The chief early sign is cerebral blindness, which becomes complete, to which is added mental reduction and increasing spastic paralysis. Unsteadiness from parietal involvement and deafness from temporal involvement may be conspicuous. The amentia increases and passes into coma which terminates the illness. The condition is usually bilateral, but may commence on one side or may be confined to one side.

When there is headache, vomiting, and papillœdema, the question of a cerebral tumour arises. But the mild nature of the optic disc changes and their non-progression to the more intense degree of papillitis in the presence of signs of rapidly increasing and widely spread cerebral destruction are important in making a distinction between the two conditions. Especially indicative in this connection is the bilateral affection of the hemispheres from the first in so many of the cases, which in the absence of definite indications of brain-stem affection is very much against the diagnosis of tumour.

When we compare the descriptions of Guttmann and Collier and Greenfield it is conceivable that I was justified in writing in this manner in 1924: "This review [of the different symptoms and the diagnoses arrived at] clearly shows that the symptoms are so variable, that it may be impossible to discover an approximate unity in the diversity. A glance at the different localizations which have been

made is quite sufficient to show that we pass the limits of diagnostic possibility in this very characteristic structural disease."

The chief early symptoms of Collier and Greenfield—cerebral blindness, which becomes complete, to which is added mental reduction and increasing mental spastic paralysis, or, according to Coenen and Mir, symptoms of apathy and blindness under the form of hemianopia—may be found in some cases; they are, however, not present in many others that have been published. The same is applicable to what Schilder[98] had mentioned: "optic neuritis and atrophy together with 'a diffuse symptomatology of the hemispheres' speaks decidedly in favour of encephalitis periaxialis diffusa." More generally, but also more in accordance with the facts, is what d'Antona[2] gives: "A suspicion of encephalitis periaxialis diffusa is then present, when there is a subacute affection with progressive evolution in young people without fever or with a slight fever with irregular course, psychical symptoms, and neurological symptoms of bilateral character. The probability is greater when the symptoms point to an occipital localization of the process or when there is motor paralysis ascendant from the legs to the arms. The fundus can give assistance in differential diagnosis. General condition, cerebrospinal fluid, etiology can be of further value."

The diversity of symptoms causes great difficulties, and that is why it is of the utmost importance to give the differential diagnosis from those diseases which show many analogies in their symptoms.

Disseminated Sclerosis.—First of all stands this disease. In my first case I found plaques of disseminated sclerosis, as already described by Jakob, Stauffenberg, and Rossolimo. Since then many examples have been given, and now and then transitions between diffuse and disseminated sclerosis were described. Kufs[74] spoke of gradual transitions between the mildest forms of disseminated sclerosis and the most severe forms of diffuse sclerosis. One of the cases registered in the statistics—that of Urechia and others—should rather be considered as being disseminated sclerosis. The third case of Benoit,[9] recently published, is interpreted by the author as a simultaneously existing disseminated and diffuse sclerosis; contrary to Kufs, he does not choose to speak of a transition from one form into another. Later, I shall discuss whether it is possible, as Benoit says, to diagnose disseminated sclerosis by the presence of the argyrophil cells of Steiner.

Collier and Greenfield have said that "on the clinical side there seems to be little or nothing which is common to the two maladies except the occasional signs of the existence of more than one lesion."

Schilder pointed out the close connection with the acute variety of disseminated sclerosis, and he discussed the question whether there were two forms of the same disease.

In his case Gans[45] spoke of symptoms of disseminated sclerosis: nystagmus, scanning speech, intention tremor, exaggerated reflexes, spastic paretic symptoms, bilateral Babinski responses; moreover the patient had psychical symptoms, was shameless, erotic, but without intellectual defect. Casper[27] had also diagnosed disseminated sclerosis in his case: nystagmus, lalling speech, Babinski responses, and absence of the abdominal reflex on one side.

In the first case of Benoit, where he found the Steiner cells, the spinal cord showed alterations corresponding in all parts with those found in disseminated sclerosis, and he speaks here of a combination of disseminated and diffuse sclerosis. In this case the remissions were manifest, there was also nystagmus, scanning speech, abdominal reflexes absent, temporal atrophy of the optic discs, R > L, euphoria.

In considering the different cases in adults, it struck me here, too, that the *psychical symptoms in diffuse sclerosis* were often preponderant and that they can develop in a relatively short time (my *Cases III* and *IV*). Sooner or later there is the question of disorientation and forgetfulness, changes of character, surliness (my *Case III*) or eagerness, and passionate temper, strong 'Secundarfunction', and affectivity. There also occurs depression with tendency to suicide; further, there are deliriant exaltation states, emotional incontinence, euphoria, moria, aggressiveness, ethical defects, defective judgement, progressive dementia, and psychopathy.[127] Wertham mentions many psychopathic traits in his Case II: inebriety, attacks on women, stealing, begging, and homosexuality. D'Antona mentions hallucinations only. Screaming is mentioned in a very few cases—Kogerer, Coenen and Mir, Austregesilo et al. ("the words are uttered screamingly"). In my *Case I* I spoke of fits of screaming and in my *Case II* of continual moaning (*see also* my *Cases III* and *IV*).

Generally speaking, we can say that, in contrast with the foregoing, the *psychical symptoms in disseminated sclerosis* are not very prominent. In experimental investigations alterations were found, and there are investigators of the opinion that they are nearly always present: memory defects, difficulty in carrying out simple arithmetical sums, stupidity, euphoria, and now and then exaggerated irritability. In the well-known report of Guillain[51] (Société de Neurologie, May 30 and 31, 1924) he mentions that the psychical disturbances in disseminated sclerosis are of secondary importance. The investigation of the American Association for Research in Nervous and Mental Diseases had stated: "there are no special psychical disturbances which are typical of disseminated sclerosis; the development of the plaques in the brain does not manifest itself in one of the well-known psychoses."

Only in a single case of disseminated sclerosis we observed, before the manifestation of clear physical symptoms, depression, uneasiness, and being easily frightened, with transitory delirious hysteriform states —but these are rather exceptional. When there are states of manic-depressive insanity, or those which have many analogies with schizophrenia, it is necessary to attach great significance to the endogenous factor. In this way the 'syndrome psycho-encéphalitique' of Ombredane[87] must be considered, which can also be found in encephalitis lethargica, encephalitis postvaccinalis, and in acute articular rheumatism. Here a recurrent anxiety is the pivotal symptom. All these symptoms, after a time, may or may not improve, and in the last case are followed by symptoms of schizophrenia. There is, however, no question of considering these symptoms as typical ones.

Comparing the processes in diffuse and disseminated sclerosis one can say that where endogenous factors are not responsible in the first place, *psychical disturbances are more severe in diffuse than in disseminated sclerosis*. The resulting dementia if observed in disseminated sclerosis is in most cases not so important as in diffuse sclerosis, and the psychical symptoms develop quicker in diffuse sclerosis. Kraepelin mentions that in about 10 to 30 per cent of disseminated sclerosis there is a distinct state of mental deterioration, seldom in high grades; the judgement now and then proves to be surprisingly good, and, contrary to expectation, a fair amount of intelligence remains, in contrast with dementia paralytica.

Euphoria and *hysterical symptoms* are more frequent in disseminated sclerosis. There will certainly be some difficulties—e.g., in the case of Gans—where nymphomania preponderated, already described by Redlich in disseminated sclerosis.

Remissions, so rare and often of very short duration in diffuse sclerosis (Austregesilo et al., Sheldon et al. saw remissions in the disturbances of vision, etc.), are very often observed in disseminated sclerosis. Headache, vertigo, and vomiting, so often suggestive of a tumour of the brain, are certainly commoner in diffuse than in disseminated sclerosis, although there, too, are some symptoms of severe headache and also often of vertigo.

The *fundus in diffuse sclerosis often shows a bilateral neuritis and bilateral atrophy*, now and then also bitemporal atrophy.

Occasionally optic neuritis may also be seen in disseminated sclerosis. Choked disc is certainly relatively commoner in diffuse sclerosis than in disseminated sclerosis, where it is very exceptional. Besides, one must mention that many cases of diffuse sclerosis are described *without alterations* in the fundus.

On the other hand, *persistent blindness* as opposed to transitory amaurosis, which rather often occurs even without alterations in

the fundus, is seen very seldom in disseminated sclerosis, but occurs in diffuse sclerosis in adults, as well as in children. Gozzano and Vizioli alone mention an amaurosis of short duration in diffuse sclerosis. Rochon-Duvignaud et al. have described a case in which they were surprised by the sudden onset of blindness as there were only very moderate and recent choked discs. Occasionally there is hemianopia in diffuse sclerosis; (e.g., my *Case I*). Transitory deafness now and then occurs in disseminated sclerosis; *persistent deafness as in children* is not found in adults, or only very exceptionally. At times, however, tingling in the ears and slight deafness may occur. Disappearance of the vestibular function, described by Beck as 'transitorische Octavus-Ausschaltung', was in no case observed.

With respect to *articulatory speech disturbances*, there is no difference between diffuse and disseminated sclerosis. In diffuse sclerosis we find scanning speech, aphasia (also agraphia and alexia), and now and then apraxia (despite the difficulty in investigation). Intention tremor is often observed, although not so frequently as in disseminated sclerosis. In two of my cases there was a very marked ataxia with hemiballismus.

Pupils as a rule react well, but in some cases sluggish reactions are found; sometimes the reaction to light is abolished and there is the Argyll-Robertson phenomenon, also described in disseminated sclerosis, though very exceptionally. The pupils are sometimes not quite circular and anisocoria may be found in diffuse sclerosis.

Abdominal reflexes are often absent in diffuse sclerosis, though less than in disseminated sclerosis according to the description of the cases (of which many had not completely been examined). The well-known *paræsthesia* at the tips of the fingers, so common in disseminated sclerosis and other paræsthesias, is rare in diffuse sclerosis (in van Londen and Frets' case). Coenen and Mir mentioned irritation and velvety feeling around the chest, one side of the body being insensible.

Besides headache there are often, in my *Cases I* and *IV* too, complaints of 'pain and rigidity in the neck'. Gozzano and Vizioli mentioned disturbances in general sensibility.

In a great many cases of diffuse sclerosis there is a *Babinski reflex*, usually bilateral, though sometimes unilateral. This sign is probably not as common as in disseminated sclerosis, though it is perhaps necessary to take into account the psychical state of the patients, which sometimes renders examination difficult or impossible. *Knee-jerks and ankle-jerks are strongly exaggerated* just as in disseminated sclerosis; clonus is also mentioned, not so often, however, as in disseminated sclerosis, probably because of the spastic symptoms. Only in the case of Matzdorff, to be reckoned among the blastomatoses, were the ankle reflexes diminished.

Nystagmus is often mentioned in diffuse sclerosis. In those cases which are to be considered as transitional (Gans, Kufs, Benoit) it was never lacking; in the other cases it occurred less often than in disseminated sclerosis.

The *slight tremors* found in head and trunk in disseminated sclerosis are not mentioned in diffuse sclerosis; sometimes there is a slight tremor of the hands in the latter disease; Shelden et al. mention a generalized tremor.

Abducens paresis is often mentioned in diffuse sclerosis, mostly unilateral, sometimes bilateral. The typical alternate coming and going as in disseminated sclerosis is only very exceptionally seen in diffuse sclerosis (Austregesilo et al.).

To-and-fro swinging of the eyes, which I have also occasionally found in tumour of the brain, occurred in my *Cases III* and *IV*, and was also observed by Gozzana and Vizioli. They, too, speak of instability; this is looked upon by them as related to nystagmus.

As for semeiological interpretation and the physiopathological mechanism, Gozzano and Vizioli found in their case that nothing occurred when the head was lifted up from the pillow, but afterwards a rhythmical tremor with slow jerks occurred regularly, partly communicated to the trunk, but more especially to the neck muscles by which the head continually was moved.

Sometimes *facial paralyses* were found, always of central type. *Disturbances of swallowing* have been rarely noted in adults (Bouman III, Matzdorff). Van Londen and Frets describe a right-sided *atrophy of the tongue muscles* without degeneration; Schnitzler has found the same in disseminated sclerosis (Case V), there, however, with reaction of degeneration. I also have seen the same in disseminated sclerosis. Gozzano and Vizioli found *atrophy of the thenar eminence and interossei*, but there the faradic irritability had disappeared and with the galvanic current a distinct reaction of degeneration could be shown.

Tottering gait, exceptional in disseminated sclerosis, is rare also in diffuse sclerosis (Guttmann, Bouman IV, Ferraro, Benoit; in the last case only transitorily). Unilateral paresis and paralysis are often mentioned, nearly always spastic in type; often in connection with apoplectiform and epileptiform attacks. This and the spastic paraplegia remind us of what commonly occurs in disseminated sclerosis. Contractures, so important in children, are certainly less often observed in adults (Guillain mentions three cases of disseminated sclerosis with flexion contracture). This is especially applicable to the *flexion contracture of the arms*. This is exceptional in disseminated sclerosis and also in diffuse sclerosis in adults (though common in children).

The same can be said of *epileptiform attacks* ; these too are not so frequent in adults, though not exceptional. D'Antona mentions Jacksonian attacks with deviation of head and eyes. I found the same in one of my cases. Curschmann has described the same in disseminated sclerosis.

The *cerebrospinal fluid* gave negative results in most cases of adults ; Gozzano and Vizioli mention a positive Wassermann reaction in the spinal fluid and a negative one in the serum. For the globulin-reaction see the table, p. 150 ; only a few cases gave a positive globulin-reaction. Nearly always a lymphocytosis is lacking (positive in Wertham's Case II, Stauffenberg). As to the colloidal reactions (often characteristic in disseminated sclerosis) there are very few reports ; if they were mentioned in diffuse sclerosis, they were negative (only my Case VI is positive). The same can be said of the benzoin reaction. Here later reports must be awaited. Sometimes there was a high pressure in the cerebrospinal fluid.

Elevation of temperature is mentioned by Schilder, Klarfeld, Stauffenberg, Casper, Fr. Bielschowsky. In the last case and in Bouman III, Weimann, elevations of temperature were present before the outbreak of the disease. Now and then they are also found in disseminated sclerosis.

Taking into consideration the many analogies between diffuse and disseminated sclerosis, apart from those cases where a so-called combination is present, it is easy to understand that the diagnosis of disseminated sclerosis is often made in cases of diffuse sclerosis. Schilder has asked himself whether diffuse sclerosis is really a form of acute disseminated sclerosis, especially incident in childhood.

Anatomically Spatz[109] has already observed that there is a central type of diffuse sclerosis in which the inflammatory changes play a great part and certainly are greatly related to disseminated sclerosis (Gans, Gagel,[44] Jakob, Braun).

Marburg,[81] too, accepts the opinion that a great many of the cases of diffuse sclerosis are really instances of disseminated sclerosis. From what has been said, it must be conceded that many arguments for this conception are present. Practically, however, it is preferable to distinguish the two forms, though there are so many connections, because the combination of symptoms on the one side and the intensity of special symptoms on the other side offer differences.

Cerebral Tumour.—The diagnosis of tumour of the brain has often been made in cases of diffuse sclerosis. Collier and Greenfield say that headache, vomiting, and papilloedema point to this diagnosis. We mentioned before that the general symptoms of brain tumour are often observed in diffuse sclerosis.

In many cases of diffuse sclerosis, in the beginning at least, the *paresis* is unilateral, which may be a source of error. As for the *fundus* symptoms, there are also variations of all kinds in a tumour. Without doubt choked discs also occur in our cases. In my *Case III* there was a papillœdema on the left side and a papillitis on the right side; in *Case IV* papillœdema of no great intensity, L > R, with indication of optic neuritis; also in Schilder III there was a bilateral choked disc. In the first case of Schilder a temporary atrophy in the right eye was present, blurred papilla (3 D), and in the left a hyperæmic papilla (3 D), afterwards papillœdema 5 D on the right side and 6 D on the left side; in the meantime there was a period in which the ophthalmoscopic investigation indicated neither neuritis nor papillœdema. In a yet later period there was 4 – 5 D on the left side and 2 – 3 D on the right side. Barré et al. also found a choked disc; Rochon-Duvignaud et al. slight papillœdema with regression and rapid transition into atrophy, certainly not unlike that in tumour of the brain (Sachs[95]). The slight papillœdema and rapidly developing blindness is in some cases characteristic in diffuse sclerosis; therefore one is compelled to admit other lesions on the side of the visual paths. Notwithstanding the great extension of the syndrome there is no increase of papillœdema (Foix and Marie[49]). Moreover, there are many cases of tumour of the brain never showing papillœdema, either in the beginning or later on; hence no weight should be laid on its absence, if other signs point to intracranial growth (Purves-Stewart[116]).

"Early transient blindness, sometimes momentary, sometimes lasting a few hours or days at a time in one or both eyes," as we saw before, is not mentioned in any of the cases.

Admitting with reason that increased intracranial pressure is the cause of the choked disc, we have already seen that very rarely high pressure was present in those cases where lumbar puncture was done. Some ophthalmologists and neurologists, especially in America, use the term 'optic neuritis' to designate a swelling of the nerve-head which measures less than two diopters (Sachs). In this manner confusion might arise; practically, however, it is of no importance. (*See* the table on p. 150, where the English and American authors are named.)

Victor Horsley[61] said that " the emphasis should be placed upon the age of the process, as determined by the hæmorrhages, their extent, and the appearance of the exudate, and not upon the number of diopters of swelling."

It would be possible to adopt choked discs with hæmorrhages as a point in differential diagnosis from cerebral tumour, but this does not quite correspond with the facts. Schilder I, for example, showed in a certain period of the disease retinal hæmorrhages. In

this respect we can, however, support the remarks of Collier and Greenfield about the differential diagnosis from tumour, but it is of minor importance for the early phase of the two diseases. There are indeed many more inflammatory changes in diffuse sclerosis than are ordinarily found in tumour of the brain, as is clearly shown by the table on p. 150 and by what has already been reported above.

When there is no clear indication of brain-stem affection, the *bilaterality of the symptoms* is no doubt rather suggestive of diffuse sclerosis; crossed paralysis—e.g., as in pontine affections—I have found nowhere.

Symmetrically placed tumours of the brain are rare; bilateral gliomata, bilateral abscesses are now and then found; encephalomalacia on both sides in advanced age cause the syndrome of pseudobulbar paralysis. Tumours of the paracentral lobules may give bilateral affections. In the beginning, as is well known, the general tumour symptoms are mostly totally lacking or in any case inconspicuous. So the general symptoms come afterwards, and only in advanced stages do the symptoms of very high pressure finally show themselves.

Examination of the *cerebrospinal fluid* in some cases gives indications of a tumour, sometimes by tumour cells, sometimes a positive Nonne reaction, lymphocytosis, as well as blood pigment, hæmorrhagic fluid, and xanthochromia.

The *psychical symptoms* are of more importance. Besides the well-known symptoms in tumours of the corpus callosum, always combined with psychical disturbances, moria may appear with tumours of the frontal lobes, social and ethical disorders, the misunderstanding of the point of what is read or heard, often also emotional incontinence. In diffuse sclerosis they are usually qualitatively different. In my *Case III* the diagnosis during life was also based on psychical symptoms. Disorientation and affective lability were especially prominent and early, afterwards followed by bilateral cerebral affections. In my *Case IV*, too, the diagnosis might be made, where character changes were very prominent and early; later disturbances of 'Merkfähigkeit' were found and dullness and perseveration were present—in this case also combined with bilateral cerebral affections.

Notwithstanding these remarks, in adults the differential diagnosis from tumour of the brain is always difficult, though the psychical symptoms are often more rapid in development. The general psychical symptoms in larger tumours and those in diffuse sclerosis—dullness, apathy, slow conception, perseveration (Bouman IV)—will give few differences. Those just mentioned, occurring in tumours of the frontal lobe, may also of course be observed in those cases of diffuse sclerosis which begin in the frontal lobes. Tumours of the occipital lobe do not give special psychical symptoms.

Especially in malignant tumours with their rapid growth psychical symptoms are present in an early stage and to very high degree. The discrepancy between the mental changes and the duration and intensity of the general symptoms of tumour are sometimes conspicuous.

According to d'Antona, it is not quite improbable that among the cases diagnosed as pseudo-tumour there are some cases which belong to the group of diffuse sclerosis, especially if the opinion of a few French authors is accepted, that encephalitis periaxialis diffusa does not necessarily end in death.

IV. DIFFERENTIAL DIAGNOSIS IN CHILDREN

In order to distinguish the cases of diffuse sclerosis in children, other diseases must be considered.

Pelizaeus-Merzbacher Disease. — Pelizaeus-Merzbacher disease (aplasia axialis extracorticalis congenita) was formerly not considered in differential diagnosis, because it is an exclusively heredo-familial disease, but this criterion is no longer valid, since many cases of familial diffuse sclerosis have been described. Taking into account the alterations in the white matter, though they may be different from those observed in diffuse sclerosis, because greater and smaller insulæ of myelin are spared, it is easy to comprehend that parallel symptoms must be present.

In the recent publication of Friedmann and Scheinker[43] the following symptomatology of the Pelizaeus-Merzbacher is given : In the first months of life the symptoms manifest themselves in nystagmus, tremor of the head (Kraepelin[71] : " können ihren Kopf nicht tragen ") ; oscillations of the eyes ; not being able to sit and stand erectly, without manifest pareses ; disturbances of co-ordination of the limbs, illustrated by grasping, etc. ; sometimes 'Mitbewegungen' (associated movements) and choreiform movements, mask-like expression of the face, often also grinning. There follow gradual development of spastic pareses, chiefly in the legs ; adductor spasms ; and disturbances of speech bradylalia, scanning, monotonous, indistinct speech, difficult to understand. Early disturbances of vision seem already to be present, apparently not only caused by nystagmus, but often also by affection of the optic nerve. Walking is, if ever, very slowly learned ; this also disappears when contractures arise. Further are mentioned as typical symptoms : vasomotor trophic disturbances of the feet (coldness and cyanosis), then partly rachitic, partly osteoporotic, partly osteomalacic alterations of the bones. The mental symptoms are : persistance of a low grade of development ; exceptionally a good 'geistige Regsamkeit' is found. Up to the sixth year the illness is much more progressive than later.

As for heredity, this special fact can be recalled that in all cases the patients are direct descendants of healthy mothers ("the disease passes through the mother, she herself remains free," Pelizaeus). Most patients by far belong to the male sex.

There are no disturbances of sensation, nor of the uropoietic system, and no cranial nerve palsies, muscle atrophy, or degenerative reactions of the muscles.

Though many points of similarity with diffuse sclerosis are present, the following is of importance in differential diagnosis. In diffuse sclerosis a long duration of the disease is very exceptional; feeling and intellect are relatively little disturbed in Pelizaeus-Merzbacher disease, contrasting with diffuse sclerosis, where the psychical symptoms are early and very prominent, leading to total dementia.

Generally speaking, Pelizaeus-Merzbacher disease begins at a younger age than diffuse sclerosis. Disturbances of vision, speech, and hearing are often found in diffuse sclerosis, as well as alterations of other cranial nerves; furthermore, disturbances of swallowing and incontinence of urine are found.

Bielschowsky and Henneberg have described a transitional form. A difference in intensity and rate of progression of the process can be taken into consideration.

Globus[48] pointed out a progressive affection of the white matter in infantile and late infantile cases of amaurotic idiocy (in the cerebrum and the cerebellum). In some regions patches are even found partly combined with marked fragmentation of axis cylinders and peculiar swellings of the axis cylinders. According to Globus there may be a connecting link with Pelizaeus-Merzbacher disease.

Amaurotic Idiocy.—In the differential diagnosis from amaurotic idiocy difficulties can occur. The well-known triad of Sachs in the infantile form (Tay-Sachs) is characteristic:—

1. Continually progressive weakness of the limbs and finally of all the muscles, going on to total paralysis, often with exaggerated reflexes and spastic symptoms.

2. Decrease of vision, proceeding to total blindness with the well-known macula spot.

3. Rapidly progressive dementia; furthermore, strong predominance of the Jewish race and exclusively familial heredity.

In the juvenile form the triad—blindness, paralysis, and progressive dementia—is also present, but the macula is here not affected, though there is usually atrophy of the optic nerve (sometimes also retinitis pigmentosa), and no racial disposition. In the late infantile form atrophy of the optic nerve without typical macula changes is present.

The duration of the disease is three to four years. Here the familial character is of importance for the differential diagnosis from

diffuse sclerosis (though now and then it is lacking), also the constantly present triad. Nevertheless, difficulties may arise, only to be solved post mortem by the typical histopathological changes (general swellings of the ganglion cells with the inclusion of singular products with fragmentation of the central intracellular fibrils) occurring in all forms of amaurotic idiocy.

Tuberous Sclerosis.—Here again a familial occurrence is sometimes present (van der Hoeve[60]). A gradually progressive dementia mostly combined with epileptic convulsions is found. The onset is in early youth, mostly in the first year, now and then after the sixth year, introduced by epileptic convulsions. Some children show from the start profound idiocy (most of them were idiots), in others the intellectual development, progressing fairly well at first, is more or less rapidly stopped. No development of speech is present in those patients who are already idiots; in many of those who afterwards become demented speech becomes again totally lost, after having been indistinct and monotonous; the development of speech is a good indication of the disease process.[11]

Now and then the patients are restless, generally speaking showing symptoms which can be observed in idiots. In many cases epilepsy and psychical decline run parallel, though not always; psychical decline may also be found without epileptic convulsions. Some children are intellectually not endowed, but are further not outstanding, others are morally defective. Delusions and now and then acoustic hallucinations are sometimes found.[71]

The development of the epilepsy is ordinarily free from remissions and often shows the distinct progressive organic character. Movements in the face and the eye muscles are very often marked in the attacks; a tendency to serial attacks is found. Often focal symptoms develop in the course of the disease; as a rule a Babinski reflex and foot clonus are not present in these circumstances.

Progression can be very slow, extending over many years; apparently no improvement is possible, but remissions may occur.

Diffuse sclerosis is, generally speaking, quicker in progression, and while most patients suffering from tuberous sclerosis are idiots from birth, this is not the case in diffuse sclerosis. It must be granted that in diffuse sclerosis also epileptiform attacks often occur, but they are not as common as in tuberous sclerosis. The severe spasms and contractures so often observed in diffuse sclerosis in children are only exceptionally found in tuberous sclerosis.

Of great importance in differential diagnosis is the fact that tuberous sclerosis is a developmental defect, and elsewhere in the body signs of faulty development are also present (stigmata of degeneration and malformations). The tumours of the brain, skin, and

kidney are well-known (out of 78 cases collected by Bielschowsky and Gallus[11] tumours of the kidney occurred 41 times, adenoma sebaceum 28 times—rising to 35 times, when other tumours of the skin are reckoned to belong to this category—tumours of the heart 11 times.) When these are present, isolated or combined, the diagnosis of tuberous sclerosis can easily be made.

Only very exceptionally in tuberous sclerosis disturbances of the optic nerves are found, though often observed in diffuse sclerosis; certainly central blindness and deafness are not found as in diffuse sclerosis, either separately or combined.

Atrophic Lobar Sclerosis.—Flatau[39] calls attention to this rare condition. According to Zingerle it is primarily a destructive process with secondary glia-proliferation, caused by syphilis, trauma, inflammation, or encephalomalacia. Possibly the process is quite the opposite—that is, the glia-proliferation may be primary and the changes of the brain secondary. Following epileptic attacks the intellect gradually declines, afterwards the transient foci produce new symptoms.

Encephalitis and Meningo-encephalitis.—The encephalitis and meningo-encephalitis of children has a fairly typical course with convulsions and fever; later motor symptoms corresponding with the foci occur, also motor aphasia, disturbances of sensibility, and hemianopia. Later still, disturbances of the psychical functions are seen, and some of the cases become epileptic.[122]

Cerebral Palsy.—Cerebral palsy of children is a diagnosis of purely clinical character, with the most divergent etiology and pathological-anatomical changes. Here, too, atrophy of the optic nerves, disturbances of speech, and psychical disturbances may be found. In this regard, however, there will be as a rule no difficulty in the differentiation from diffuse sclerosis.

Familial Infantile Diplegia.—This begins in the ninth to twelfth year; it differs, however, psychically from diffuse sclerosis. Though in a great many cases the intellect is declining, in many others it remains intact.

Little's Disease.—Here premature birth is accepted as an etiological factor, in particular birth-trauma must be taken into consideration as a cause of the rigidity and the motor weakness of the legs. Disturbances of speech, strabismus, psychical defects, epilepsy, and choreo-athetotic symptoms are observed.

Neuromyelitis Optica Acuta.—Retrobulbar neuritis together with papillitis and paraplegia remind us of 'neuro-myélite optique' or 'Devic's disease'. In this, however, important changes in the cerebrospinal fluid are present; in the progressive form the development of the disease is quite different from that of diffuse sclerosis and it ends with multiple bulbar symptoms.

Encephalomyelitis Disseminata Acuta.—Many points of contact with diffuse sclerosis are present. The development of encephalomyelitis disseminata acuta is, however, quite different, and psychical symptoms are, as a rule, lacking.

Congenital General Paralysis.—This will not give many difficulties, though a positive Wassermann reaction in blood serum and cerebrospinal fluid may be absent. Pareses and also contractures are found here, mostly, however, not so prominent as in diffuse sclerosis; other focal symptoms and epileptiform attacks are noted. Often optic atrophy is present. Absolute immobility of the pupils is far commoner than the Argyll-Robertson phenomenon. The last symptom is only very exceptionally found in diffuse sclerosis; real 'Silbenstolpern' has not been found. The mental disturbances are also different: in diffuse sclerosis a gradually increasing dementia, in juvenile general paralysis often periodic states of exaltation. Positive reactions in serum and cerebrospinal fluid and colloid reactions pointing to progressive paralysis clinch the diagnosis (Schilder and Gozzano and Vizioli alone have found positive serum reactions in diffuse sclerosis).

Meningitis and Hydrocephalus.—The various forms of meningitis and hydrocephalus give totally different symptoms, so confusion with diffuse sclerosis is not possible.

V. ETIOLOGY, PROGNOSIS, AND THERAPY

Etiology.—As to the etiology of diffuse sclerosis we are almost entirely in the dark. Cerebral trauma, burns, influenza, varicella, typhus, measles, scarlet fever, whooping-cough, mumps, and repeated tonsillitis are cited as causes. Sometimes there is connection with one of these diseases in regard to time; sometimes, however, a long interval between them and the onset of diffuse sclerosis is noted. 'Endocarditis verrucosa' is also cited. Fr. Bielschowsky in particular points to the importance of infection in diffuse sclerosis.

In my first case the onset of the disease occurred two months before a childbirth took place, while the patient of Gozzano and Vizioli came under treatment while pregnant, and deteriorated rapidly after the confinement. Shelden et al. mention a puerperal fever; now and then rises of temperature were present, occurring at irregular intervals; after that deterioration took place (Stauffenberg, Bielschowsky). In Bouman III, also in Patrassi, the beginning was with febrile symptoms. In an unpublished case of mine fever was present in the last few days of life, without post mortem changes in the internal organs which might explain the rise of temperature; also to be considered as fever of central origin.

The presence of products found by Steiner in disseminated sclerosis and considered by him as spirochætes, and of argyrophil cells (found by Benoit), are only of importance if they have the significance attached to them by Steiner. In this regard it is well to keep an open mind. In my *Case VI* products were found (stained by Steiner method) certainly in many respects resembling those found by Steiner in disseminated sclerosis.

In several cases hereditary and constitutional factors must be considered as important. Familial forms have been described by

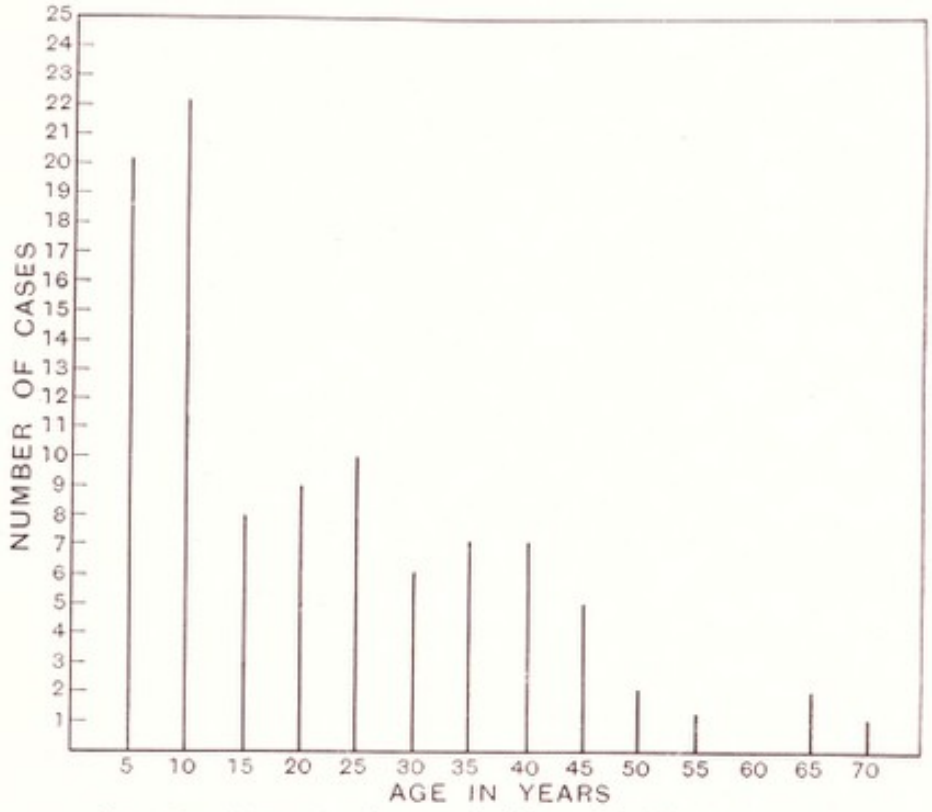


FIG. 65.—Chart showing age incidence of diffuse sclerosis.
Sex incidence in 100 cases: Children—girls 15, boys 35; Adolescents and Adults—females 25, males 25.

Krabbe, Scholz, Haberfeld and Spieler, Ferraro, Bielschowsky and Henneberg, Symonds,[119,120] v. Bogaert and Scholz. In the first familial cases of Scholz, among other affections of the central nervous system in the family there were cases of progressive paraplegia of very slow development. Together with diffuse sclerosis and spastic spinal paralysis other nervous affections and cases of still-born children were found.

In the recent case of van Bogaert and Scholz many cases of tuberculosis were in the family; one member had died of progressive nervous disease and several of convulsions. In my *Case I* the father was addicted to drink, one sister suffered from nervous attacks, and the mother was 'nervous'. In Schilder III the father committed

suicide. In Schaltenbrand's case the mother and grandmother were psychotic, in Weimann's case the father probably had syphilis, the mother had arteriosclerotic dementia, and the sister dementia præcox. In a case of Bodechtel and Guttmann the father was addicted to drink, in another of their cases there was a nervous affection in the family; an uncle had an organic affection. In Patrassi's case the mother was nervous and irritable. In Kaltenbach's case alcoholism is mentioned. In the case of Gozzano and Vizioli the father had syphilis and was addicted to drink, and the mother was a psychotic. In Bielschowsky and Henneberg I and in Bouman VI there was dyspinealismus. Feeble-mindedness or imbecility was mentioned in the cases of Bodechtel and Guttmann, Bouman II, Gagel, and Ferraro, and psychopathy in Weimann's case. In Bouman V the father and mother were cousins; in Ferraro's case the grandmother (on mother's side) suffered from insanity.

On the whole, we may say that the etiology is fairly unknown. Instances of familial character are continually increasing, so exact examination in this direction is necessary. The possibility of infection is not excluded on that account in other cases; a special disposition must then be reckoned with.

Fig. 65 shows the predominance of the younger age. Many more boys than girls have been observed; the number of male and female adolescents and adults is equal.

Prognosis.—Generally speaking the prognosis is fatal. The duration of the disease is from some months to some years. Marie and Foix have described cases with remissions in which return of speech was mentioned, also regression of the paralysis confined to one limb.

Foix and Jul. Marie distinguish three periods of the 'sclérose centrolobaire': (1) 'Phase d'attaque'; (2) 'Phase de régression'; and (3) 'Phase de séquelles'. This last period is said to appear twelve to eighteen months after the beginning of the disease; in this third period a manifest regression of the symptoms could be excluded, the cicatrix was then present, and mostly contractures occurred (an invariable neurological syndrome).

It is certainly of importance to distinguish between the affection in adolescents and adults and in children (up to the age of 15). Generally speaking there are obvious differences. It is, however, not possible to say why one case lasts so much longer than another; intensity of the noxious agent (when this can be accepted), the time factor, individual reaction, as well as other affections, must be considered.

Therapy.—It is easy to understand that we cannot speak of a rational therapy while there is so much uncertainty about the genesis of the disease or diseases described under the general name of 'diffuse sclerosis'.

CHAPTER V

PATHOLOGICAL ANATOMY

I. MACROSCOPICAL ANATOMY

For the description of the anatomy of diffuse sclerosis I have made use of the cases observed by myself (5 out of 6) and further of those which have been published in the literature.

The external surface of the brain as a rule shows a normal configuration. On dissecting the brains of diffuse sclerosis patients soon after the autopsy, manifest alterations can often be found. Especially after having passed some days in formalin, many patches are seen, often caved in, or less often rising in relief. The patches are often of a grey colour, sometimes bluish, gelatinous, though also at times looking or feeling tough and hard. My *Case VI* demonstrates that sometimes nothing conspicuous is observed. In some cases atrophy of the brain is described (Schaltenbrand,[86] Max Bielschowsky and Maas,[13] also Davison-Schick[35] rather strongly); in these cases dilatations of the ventricle are mentioned, but even when atrophy is absent, dilatations of the ventricle may be found. Shrinkage in other territories is found (Wertham I, e.g., atrophy of the thalamus; in the case of Shelden et al. the distal optic nerves were slightly shrunken).

Distribution of the Abnormalities.—From an examination of large sections stained by the Weigert-Pal method, demyelinization of the white matter of the brain is found in many regions, here more, there less, now exposing itself in one, now in some other territory. The demyelinization can sometimes be seen extending from the frontal to the occipital pole and more or less symmetrical alterations in the hemispheres are found. This, however, is by no means always the case; it may happen that definite parts are much altered and others either not at all or little; or one hemisphere can be altered markedly, whereas in another only a few scattered patches are found (e.g., the case of Pátrassi). Finally, it is possible that the hemispheres may differ in that while symmetrical patches are found on both the left and the right side, they are more intense in one hemisphere (the cases of Casper and Kufs II, etc.).

When I compare my experiences of the last few years with those of some years before (1924), I still find that in the majority

of the cases the alteration of the occipital lobe is greater than that of the frontal lobe; but the contrary is by no means rare. Often the demyelinization is principally around the posterior horn of the ventricle (Weimann's case), or around the lateral ventricles (Gans, Kufs I). In some cases (as in my *Case III*) concentrically arranged rings of demyelinization are found, between them lying strips of white matter which are in relatively good condition. Many years ago Marburg had already described this concentric formation in acute disseminated sclerosis and he called it 'Landkartenherde'. Very explicitly this is seen in the paper of Baló.[4] Here in the front part of the anterior horn of the right lateral ventricle strips of alternately white and grey substance could be seen; the white strips were the same colour as the white matter, the grey ones were caved in. Baló spoke of 'grey softening'. I shall discuss these peculiarities later; it is only of interest to mention that the concentric rings are conspicuous principally in the right occipital lobe (*Figs.* 2 and 3 of his paper).

Barré, Morin, Draganesco, and Reys[5] had already mentioned a characteristic concentric demyelinization in the white matter of the superior frontal gyrus (it made them think of a toxin), whereas Baló, just as Marburg, sought the cause in a lecithinolytic ferment, attacking various regions of the hemispheres at different times. Meanwhile Patrassi had also found these patches, and in particular Hallervorden and Spatz[56] had paid attention to them. Casper also found similar figures.

The U-fibres are often free in several spots, but it is by no means a hard and fast rule. Many times I myself found, just as in the cases in the literature, that the U-fibres were altered. In many cases the cortex, and within the cortex the fibres, were also altered. A great variety is shown in regard to the alterations of the other parts of the brain.

In my former paper I indicated that in some cases the subcortical parts were altered, capsula externa and interna, anterior commissure, chiasma, pes pedunculi, pons, medulla oblongata, and the cerebellum, together with the corpus callosum. In the cases afterwards published these parts are repeatedly cited as diseased, only exceptionally are they totally intact (e.g., the cases van Londen and Frets, Weimann).

In my first case I have already pointed out the numerous small, sharply limited, demyelinizated spots in the brain-stem, which were exactly similar to those found in patches of early disseminated sclerosis (*see Fig.* 4, p. 17); in the cases published afterwards this combination of diffuse and disseminated sclerosis is often cited. Kufs, for instance (Case I) found a patch of disseminated sclerosis in the left thalamus. The myelin sheaths in the patch were absent,

but the axis cylinders were fairly intact without being deformed. He speaks of a transitional form between diffuse and disseminated sclerosis. In Gagel's case insular patches were found reminiscent of disseminated sclerosis. Schaltenbrand also mentions "patches like foci of disseminated sclerosis in the chiasma and optic tracts" (*Fig.* 18 of his paper). In Beneke's[8] case patches in the spinal cord strongly resembling those of disseminated sclerosis were present. Without doubt secondary degeneration must be admitted in this case, but in addition patches could not be excluded. Jakob described numerous small demyelinated patches (together with secondary degeneration of the pyramidal tracts) in pons, medulla oblongata, and medulla spinalis. Hints in this direction are to be found in the older publications of Rossolimo, Stauffenberg, and others.

Looking at the spinal cord sections of Wertham in his paper on "small foci of demyelinization in the cortex and spinal cord in diffuse sclerosis" (e.g., *Fig.* 3 from the cervical part of the spinal cord), we get the impression of a case of disseminated sclerosis. In addition, many small areas of demyelinization were found diffusely distributed over the cortex. They were visible to the naked eye in stained preparations. They usually lay in the cortex, but sometimes extended into the subcortical white matter. Notwithstanding, Wertham, rightly in my opinion, allots his *Case I* to diffuse sclerosis because there were such large continuous lesions involving a good part of the central white matter of several lobes, not usually observed in disseminated sclerosis. In his second case also a great similarity with forms of disseminated sclerosis was found. A pallor in the posterior columns of the cervical part of the spinal cord was present, a marked fibrous gliosis had replaced the myelin-sheaths. Besides this there were in the lateral parts of the posterior column two small round lesions with well-defined borders in which no myelin-sheaths were stained and in which fibrous gliosis occurred. In this *Case II* patches in cerebellum, pons, tegmentum, and medulla oblongata were found. Here may be considered the case of Gans which is connected by Wertham himself with his own cases. One might think of a special form of diffuse sclerosis which is, as it were, complicated by such smaller lesions. Gans spoke of disseminated sclerosis as it macroscopically occurred, which was corroborated by histopathological examination. He, too, mentions large symmetrical patches extending from the frontal to the occipital pole, and numerous patches of sclerosis in the brain and the spinal cord as well.

Bielschowsky and Maas also mention many small scattered patches. Here again sharply limited patches are present with the typical characteristics of polysclerotic plaques and by the side of those diffuse alterations, thus presenting a sclerosis of nearly the

whole of the white matter of the hemispheres and the processes extending from it. "Als Bindeglied zwischen beiden Arten von Veränderung können diejenigen in Thalamus gelten, die den Eindruck erwecken, dass kleinere Foci zu grösseren, stark schrumpfenden Herden confluieren."[13] Such is the histopathological description of their case. From the striatum up to the sacral part of the spinal cord the patches often have the appearance of old polysclerotic plaques; they have sharp edges, are demyelinated, the axis-cylinders being nearly totally spared. There were not only glial elements replacing the degenerated tissue, but yet more glia, isomorphical however, was present.

By the side of these multiple patches Bielschowsky and Maas found still other foci. In the spinal cord as well as in the more central territories there were foci deviating from the ordinary type by no sharp limitation. Here they were surrounded by 'Markschattenhöfen', representing a slow transition into the normal surroundings ("in den Höfen eine Verdünnung der quantitiv nur wenig reduzierten Myelinscheiden"). Many of these patches in the spinal cord and also in the pes pedunculi were totally independent of typical plaques. In regard to the extension in length, these 'Markschattenherde' surpass the typical plaques considerably and become 'diffuse'. In this respect they approximate to what was observed in the white matter of the hemispheres. Stripe-formed 'Markschatten' were present in the white matter of the cerebellar lobules with this peculiarity, that they demonstrated a slow transition to completely myelin-free 'Markblätter' in secondary lamellæ.

II. MICROSCOPICAL ANATOMY OF THE PATCHES IN THE WHITE MATTER OF THE BRAIN

Myelin-sheaths.—As a general rule in all publications a demyelinization in the centre of the large patches is described, though here also exceptions occur now and then. We have already spoken of cases with alternate destruction and retention of the myelin-sheaths.

When many myelinated fibres have been retained, they are often of small diameter. Bielschowsky and Maas were able to follow them into the deep layers of the cortex and to recognize there the myeloarchitectonic ground-plan as thin and 'aufgelockerte' radiate bundles ("wie eine diffuse Markschattenbildung, aber nicht eine Demyelinisation von gewöhnlicher Intensität"). In my first paper I called attention to the cases of Marie-Foix and Walter, where the fasciculus longitudinalis inferior was not altered although the fibres passed through the focus. In my *Case I* some thin fibres of the 'radiation thalamique' passed through the altered area, and conversely

in the case Rochon-Duvignaud et al. the 'radiation thalamique' was not so well coloured as the surrounding tissue.

Nearly always where myelin-sheaths had totally disappeared in the centre of the patch, the myelin sheaths in the immediate surroundings of the patches were altered, being rosary-like, tortuous, and showing swollen lumps like bullets (Kaltenbach); in part these were included in cells (case Weimann).

Rossolimo describes a thin layer at the edge of the ventricle with totally intact myelin-fibres. There are differences in regard to the ventricles; in the case of Casper the subependymal fibres around the posterior horn are totally free, and in Schilder I numerous rests of myelin-sheaths were found in the surroundings of the ventricles. In Fr. Bielschowsky's case the periventricular white matter of the inferior horn was nearly intact, and he distinguishes two histological forms of demyelinization: (1) a complete, and (2) a partial and discontinuous form; at the same time, however, a diffuse form occurs where the myelin-sheaths become less numerous, are irregularly coloured, balloon-like, and swollen. From a wide experience with Weigert-Pal's stain it is well known that it is necessary to be cautious; we need only think of the edges of preparations of the spinal cord; so too artefacts must be considered, as well as other causes for alterations (agonal changes, for instance). Sometimes the arcuate fibres (U-fibres) were well-preserved, but in many other cases these too have disappeared now and then, even where the cortex is not altered, as in my *Case IV*. Sometimes again the arcuate fibres are present but thinner than normal (Stewart, Greenfield, and Blandy I, paler and very many compound granular corpuscles).

Axis-Cylinders. — In regard to the axis-cylinders there are numerous variations. It is difficult to perform the Bielschowsky staining of the centre of the patch, because disintegration is seen, which I have observed to some extent in all my cases. In my *Case I* probably all axis-cylinders were retained, but the greater part was faintly coloured by Bielschowsky stain. Some were better impregnated and irregularly formed, now and then varicose. The same thing was seen in Stewart, Greenfield, and Blandy's case. In my *Case II* many axons stained faintly, but a vastly greater number than in my first case stained well, though some had varicose distensions. Jakob records that in his case axons could be seen only here and there in the vicinity of intensely infiltrated vessels; those present were thin and showed evidences of degenerative changes. In areas of acute disease most of them as a rule had disappeared, and in the more chronic patches hardly any traces of nerve-fibres were left. Here too the disappearance of myelin-sheaths was on the whole greater than that of nerve-fibres.

In the heredo-degenerative form described by Scholz the axons were destroyed together with the myelin-sheaths. This has been noted over and over again in the literature. There is also mentioned partial integrity of the axis-cylinders in the initial phase, and afterwards destruction (d'Antona). Sometimes, at the periphery of the patch, the axis-cylinders are much better retained than the myelin-sheaths, while in the centre they show swelling, 'Auffaserung', laceration, and 'boules terminales' (Weimann). Sometimes (Shelden et al.) there is mention of fragmentary and tortuous axis-cylinders, most of which are swollen and beaded; without doubt they had been retained longer than the myelin-sheaths, and some of them proceeded for a considerable distance into the degenerated area, but none were preserved intact; often they had a granular appearance; this was in the edge of the degenerated area. In Bielschowsky-Henneberg's[12] Case II it is also mentioned that around the ventricles the axis-cylinders had disappeared.

Now and then a local variety appeared. Gagel, for instance, mentions that the axis-cylinders have diminished in number, and when present they are degenerated; in a slighter form this was also found in the cerebellum.

With regard to the secondary degeneration in the first case of Schilder, a degeneration of the right fasciculus cerebrospinalis and of the left fasciculus cerebrospinalis anterior, not visible in Weigert-Pal preparations, was found in the Marchi preparations. Marchi's method also showed degeneration in the posterior roots, and in the second case of Schilder a secondary degeneration of the fasciculi cerebrospinales laterales and anteriores. Secondary degeneration was also present in the cases recorded by Jakob, Marie and Foix, Rossolimo, Siemerling and Creutzfeldt, and to some extent in Schröder's first case (Weigert-Pal preparations).

In Schröder's[104] second case there was secondary degeneration of the pyramidal tract in the pons and spinal cord, and in the pes pedunculi there was a band of secondary degeneration more mesially situated. Austregesilo et al. found secondary degeneration up to the lumbar enlargement. One of Foix and Julien Marie's cases (a child, aged $4\frac{1}{2}$) had secondary degeneration in the pyramidal tracts; in Schaltenbrand's[96] case the pyramidal tracts in the pons were pale and shrunken, especially on the left. Of the first case of Shelden et al. it is stated "secondary degeneration was not so abundant as might be expected. The outstanding examples were shown in the corticospinal tract." "The pyramidal degenerations were undoubtedly secondary as they could be traced from above downward, and in the cervical cord the corticospinal tracts were the only ones involved."

Gagel's case showed secondary degeneration of the pyramidal tracts in the medulla oblongata and spinal cord dependent on foci in the internal capsule and pes mesencephali. In the first case of Bielschowsky and Henneberg there was secondary degeneration in the corticofugal tracts: the pyramidal tracts, and the corticopontine tracts. The degeneration of the pyramidal tract was present throughout the whole cord. (The same could be demonstrated in my *Case VI.*) In their second case there was also a degeneration of the corticofugal tracts, only in the medial part—belonging to the frontopontine tract—portions remained. Down to the first cervical segment there was a degeneration of the pyramidal tracts (L and R); the spinal cord was not available for examination.

In one of Henneberg's cases many ganglion cells in the ventral horns showed chronic Nissl changes. There was degeneration of the pyramidal tracts, but it resembled that found in funicular myelitis. In my former publication I mentioned that this case leaves room for doubt. It is not without interest that Kraus and Weil also found early degeneration of the cells of the anterior horns.

Bielschowsky and Henneberg found cell defects in the third and fifth layer of the parietal and occipital lobes. They estimate this as a secondary degeneration of the destroyed axons in the central white matter of the hemispheres. The same explanation may apply to the cell defects in the pulvinar and the lateral, medial, and anterior parts of the thalamus by a lesion of the thalamo-cortical tracts. According to these authors the separation of primary and secondary degeneration of the lateral tracts in the spinal cord is very difficult, and they think that here a combination of primary myelin destruction and a severe descending degeneration is perhaps present. The number of the fibres persisting in the pyramidal tracts is smaller than is usually seen in the ordinary secondary degeneration, for the area of the pyramidal tracts 'überschneidet sich' with those of the cerebrospinal tracts and has also short neurons in its medial part.

Blood-vessels. — My first two cases illustrate the contradictory statements made about the blood-vessels. In my first case the vessels were increased in number and in size. Their adventitial sheaths were densely infiltrated by cells, especially by lymphocytes, as well as by cells resembling degenerated plasma cells, a few 'mast' cells, and finally scavenger cells, which were scarce in some places and abundant in others. Furthermore, in the sheaths of the vessels oval nuclei similar to swollen endothelial nuclei, and large pale nuclei closely resembling those of 'gemästete' glia cells were found. The reticular fibres of the connective tissue round the vessels ('mesenchymal' nets) had also increased. On the other hand, my second case showed no increase of vessels in the diseased area, and those present

were not infiltrated, except close to the periphery of the lesion where a few connective-tissue elements and some scattered lymphocytes were present in the wide-meshed perivascular lymph space.

Jakob's case corresponds to my first case, the infiltration of the vessels consisting of lymphocytes, plasma cells, and polyblasts; plasma cells were also found outside the vessels, and there were many small scavenger cells, partly of mesodermal, partly of glial origin. Every focus of diseased myelin-sheaths, whether acute or chronic, contained 'mesenchymal' tissue, and there was severe endarteritis of the capillaries in the rare cortical patches. The same occurred in Braun's case, where lymphocytes, scavenger cells, and a few leucocytes, but no plasma cells, lay in the perivascular spaces, while in the apparently unaffected surrounding tissue the smaller vessels showed some infiltration, hæmorrhage, and an increase of endothelial cells. He found proliferated glial fibres around the vessels. In Stauffenberg's case dense collections of cells were present in the sheaths of the vessels, even in apparently normal tissue. Here there was occasional fever and lymphocytosis in the cerebrospinal fluid. Siemerling and Creutzfeld described a marked infiltration with plasma cells and lymphocytes in the adventitial spaces, and plasma cells freely scattered throughout the tissue close to the vessels, as well as scavenger cells and epithelioid elements rich in protoplasm (macrophages) in the sheaths of the precapillaries and veins; there was also an apparent increase of vessels, which is probably to be explained by the increase of cells in the walls of the veins and capillaries. In Neubürger's case there was also vascular infiltration by scavenger cells, plasma cells and lymphocytes, and fat-granule cells, often arranged in circles, were seen in the walls of the vessels. Plasma cells, 'mast' cells, fat-granule cells, and 'gemästete' glial cells also lay in the very cellular tissue between the vessels. When the products of degeneration had disappeared the vessels were infiltrated and the mesenchyma had increased. In the centre of the patches alternate masses of glial fibres and mesenchymal fibres were found.

Schröder's cases and Henneberg's second case may be included in the so-called inflammatory type. Schilder's second case also belongs to this group since it showed chiefly lymphocytic infiltration of the vessel sheaths, but no plasma cells, polyblasts, or scavenger cells peripheral to the lymphocytes; the vessels in the neighbourhood of the diseased areas were infiltrated, and there was congestion of the lymph spaces around many vessels. In Schilder's first case the process was purely degenerative, but there was an infiltration by scavenger cells, lymphocytes, or the small lymphocytes of Held, and occasionally a slight proliferation of the intima and adventitia of the vessels. The disease was similar in Marie and Foix's case,

but there was no perivascular infiltration; the same is true of Stewart's second case, where only slight proliferation of the sheaths of the vessels was present. Hermel's[58] case did not show infiltration, although there were scavenger cells in the vessel walls, accumulations of small glial elements, an increase of vessels, new capillary formations, and fresh hæmorrhages. In both the cases of Klarfeld and Kaltenbach it is stated that there was hardly any vascular infiltration. Krabbe's case exhibited dense masses of cells around the vessels, it is true, but they consisted of glial elements, some being rich in protoplasm, others granular and without formed fibres.

In some cases there was swelling or proliferation of endothelial cells (Flatau,[39] Shelden et al. I and II, Baló), Weimann mentions proliferation of the intima, and Bielschowsky and Henneberg I lipoid substances in the endothelial cells and intimal cells.

Often there are seen thick rings of glia concentrically around the vessels (Foix and J. Marie). In Bielschowsky and Henneberg's first case there was a glia felt-work around the vessels. Fra. Bielschowsky[10] found perivascular glial patches at the border of the white matter and the cortex, while Flatau noted scavenger cells and glial cells around the vessels. Later I shall discuss the inflammatory nature of the histopathological process.

In the recently published cases fat stainings have been made, and it is very common to find that the vessels are surrounded by fat-containing cells. There are progressive and regressive changes in the cells of the vessel walls. Tightly filled capillaries are often seen (Casper, Kogerer, Baló—hyperæmia, Schlatenbrand). There are sometimes blood-vessels with proliferation of adventitial meshwork (Gasul[46]). In this case there are also 'gemästete' glial cells (in the English literature often named 'globoid cell') in the adventitial lymph-sheaths. Collier and Greenfield found perivascular compound corpuscles and in their second case small uni- or multinuclear granular corpuscles, and the perivascular spaces were filled with these and small granular cells. Sometimes there are 'Gliarasen' in the neighbourhood of vessels. There are also neoformations of capillaries and lymph-accumulation (Schilder III). Kogerer also found an increase of capillaries, and Foix and Julien Marie found the capillaries hypertrophied and in the third case (65 years old) noted a sclerotic reaction around the vessels and thick walls and an increase only through retraction. Now and then the infiltration-cells (lymphocytes and plasma cells) are outside the adventitial sheaths in the parenchyma (Kogerer).

The 'mesenchyma' had increased in Neubürger's[85] case. In Klarfeld's case mesenchymal production also occurred; Weimann speaks of mesenchymal structures, and Patrassi of mesenchymal

reaction. In the second case of Bielschowsky-Henneberg mesenchymal fibres originated from the vessels, which here had thick walls; principally dependent on a proliferation of the connective-tissue elements of the adventitia. Gagel found a slight increase of vessels and proliferation of the mesenchyma. Scholz mentions that he has not seen any mesodermal tissue. In our first case we saw a pronounced increase of mesenchyma forming nets between the vessels (*see Fig.* 3). In our fourth case the mesenchyma tissue (*see Fig.* 42) was also increased. Bielschowsky and Maas found special foci in the cerebellum, with great loss of substance. Here the tendency to reaction of the glia had strongly suffered. This was taken over by the mesenchymal proliferation.

Hæmorrhages.—When hæmorrhages are found, it is not easy to decide whether or not they are agonal in nature. Without doubt many hæmorrhages of this type are found. Hermel found fresh, often rather extensive, hæmorrhages. Gagel, who found a small fresh hæmorrhage in the anterior commisure, also asks whether this fresh hæmorrhage is perhaps agonal. Stewart, Greenfield, and Blandy in their third case have also seen hæmorrhages, but they have demonstrated that they were not fresh, agonal hæmorrhages. In the anterior horn cells of the cervical cord they found, for instance, pigment. According to the findings of Claude and Lhermitte, its appearance in their case indicates that the minute hæmorrhages in the pons and the cervical cord were at least forty-eight hours old, or at any rate that they did not occur immediately before death.

Schaltenbrand describes a dark-looking focus around the left claustrum, of which the perivascular spaces contained masses of hemosiderin indicating earlier hæmorrhages. Shelden et al. II, Stewart et al. III, Weimann and Gagel, as well as Flatau and Kraus and Weil, have also seen hæmorrhages; Flatau in the grey matter of the lumbar enlargement (especially the anterior horns, but also in the intermediate layer and at the basis of the posterior horns and in the lateral columns in the neighbourhood of the grey matter). Kraus and Weil found them specially in the corpus striatum. In Schröder's first case hæmorrhages also occurred. In my *Case IV* perivascular hæmorrhages around some large vessels were found.

Glia.—In discussing the glia distinction must be made between the central parts of the patch, the periphery, and often also the parts remote from the patch.

In my first publication I wrote the following (p. 983): "Particularly characteristic in the histopathological examination are the 'gemästete' glial cells surrounded by elements which are probably of a phagocytic nature." In the article of Collier and Greenfield it is also mentioned that where myelin destruction was active, particularly

in those regions where it appeared to be of "more recent date, there were large globoid cells of a peculiar character." In the description and in the figure (*Fig.* 9) which the authors gave it is clear that the 'gemästete' glial cells and the large globoid cells are the same products. The 'gemästete' glial cells were often surrounded by smaller ones. They are enclosed in a dense fibrillar neuroglial network and form a glial feltwork. Many macroglial nuclei have fallen into small pieces; others are abnormally large, and have a diameter five times as large as the normal ones. The central portions of the diseased areas were occupied by proliferating glial fibrils, the younger parts of these areas containing numerous astrocytes and firm but not very dense masses of fibrils, whereas the older areas were poor in nuclei and contained compact bands of more delicate fibrils. In many regards this resembles my first case (also Siemerling and Creutzfeld's case and Schilder's second case).

Stewart, Greenfield, and Blandy I shows the same: dense felt-work with many large cell bodies, mostly with many nuclei and globoid cells (according to them an evidence of recent sclerosis). At a later stage spider cells and particularly dense felt-work were present. A great difference from this has been just described in Stewart, Greenfield, and Blandy's second case. There was no overgrowth of fibres nor enlargement of cell bodies, comparatively few typical compound granular corpuscles, complete absence of enlarged or multinucleated neuroglial astrocytes or of spider cells. Further, the nuclei of the interfascicular glial cells were greatly multiplied.

In the third case of Stewart et al. were many granular corpuscles and rod cells. There was an increase in the numbers of small round nuclei belonging either to the microglia or more probably to the oligodendroglia (interfascicular glia). The changes in the fibrous neuroglia were more often degenerative than reparative; the most frequent change was swelling of the cell body without formation of new fibres; moreover, there were degenerative changes in the nucleus, either swelling or karyorrhexis, the first being commoner (Braun[23] also found an abundance of great glial cells, karyorrhexis intermingled with glial nuclei).

Coenen and Mir have also found granular corpuscles, astrocytes, the globular form of the microglia, and swelling of the oligodendroglia.

Fr. Bielschowsky speaks of typical mitosis, not easily to be distinguished from karyorrhexis. In the case described by Gagel there was much glia proliferation and in the periphery a great number of 'gemästete' glia cells, and great glial forms with nuclei with spoon or bowl form. In the periphery there were further numerous gliogenous scavenger cells (typical fat granular cells). In the centre of the patches there generally were more small nucleated glia-forms.

Gagel saw no giant cells or cells with atypical nuclear forms. Schilder also found 'gemästete' glia cells in his Case I, swollen oligodendroglia, astrocytes in the demarcation zone, and almost the same in his second case. In Marie and Foix's case of 1914 there were more fibrils than cells in the old sclerotic areas, and close to their centres hardly anything but delicate fibrils. In my second case the glial cells were smaller than in my first case, and there were scavenger cells with few fat and many glial fibres.

In the central part of the patches Casper found glial cells with very small fat droplets, the edge of the demyelinization contained no fat granule cells, and no glial fibres were present. In Braun's case there was an increase of fat granule cells towards the centre of the lesion; in the periphery the development of scavenger cells could be traced from proliferating glial elements. There were probably fat droplets in the processes of the glial elements. In Weimann's case there were also many 'gemästete' glial cells with much fat, typical fat granule cells in the centre, very dense at the edge, and around the capillaries there were broad cuffs. In the cases of Bielschowsky and Henneberg there were also many fat granule cells, in the second case especially at the edge and in the centre around the vessels and also but rarely free in the parenchyma. In Kufs II there were compact glia fibre bundles, mobile scavenger cells, and fat granule cells also around the vessels.

Bielschowsky-Maas[13] in their case with relatively acute changes in the left frontal lobe, found neither in the periventricular white matter, nor in the border of the cortex and the white matter, fat-granule cells or scavenger cells. Only in the immobile elements of the glia, especially in the perinuclear plasma of the astrocytes, there were everywhere granules which could be stained by the Scharlach method. In the adventitia of the vessels here and there lipoid material was present in the connective-tissue cells. Typical Hortega cells, glial elements as intermediary between microglia elements and scavenger cells, were nowhere present here.

In the border of cortex and the diseased white matter (left postcentral gyrus) the authors found an important production of 'plasmareiche' astrocytes and 'gemästete' glia cells. Besides there were numerous rough glial fibres already liberated from their 'Bildungszellen'. Specimens stained by Sudan showed fat in the plasma of proliferated astrocytes and in the connective-tissue cells of the vessels. Here too were no fat granule cells or Hortega cells or transitions.

The hypertrophic elements from the immobile plasmatic glia have the chief rôle in the 'breakdown' of the parenchyma. There are often 'plasmareiche' glial cells burdened with fat granules without the shape and structure of typical fat granule cells.

In the right thalamus, where a severe lesion was found, there were everywhere glial scars replacing the ganglion cells (satellites). These elements belong chiefly to the oligodendroglia ; now and then there are Hortega glia-cells, everywhere iron-free pigment. Here too the fat-granule cells are missing, but 'gemästete' glial cells are present, containing iron-free pigment.

Examination of many areas, apparently unaffected, shows microscopical changes. In the white matter of the left frontal lobe, apparently of good structure, Bielschowsky and Maas found an excess of glial fibres.

There is a tendency to distinguish several stages in connection with the special glia production. In the transitional zone Schaltenbrand found all phases of development of the microglia cells into 'rod' cells, from these to scavenger cells with prolongations and irregular outline, and finally to round scavenger cells without prolongations. In areas of severe degeneration the round scavenger cells were abundant. The large astrocytes, some with two nuclei, were situated at regular distances and had produced a strong network of glial fibres (in the spaces were fat-laden scavenger cells). No oligodendroglia.

In the centre of severe degeneration the nuclei of the scavenger cells became pyknotic and their plasma disintegrated into a granulated mass. The bodies of the big astrocytes showed definite accumulation of fat. They form plump cells—the 'gemästete' glia cells. In the grey substance there was swelling of the oligodendroglia, slight increase of neuroglia, and the microglia in places had begun to change into scavenger cells.

In his first case Wertham saw : (1) Lipoids everywhere in the adventitial sheaths, but they were only in small quantities ; (2) A great deal of fat in compound granular corpuscles ; (3) Only in the thalamus much lipoid material in the glia cells (not staining bright red with Herxheimer fat stain). With Holzer stain wheresoever lesions were found in the myelin-sheath stain there was an enormous fibrous gliosis. A wealth of fibrous astrocytes was seen in the pulvinar and in the lateral and mesial geniculate bodies, as well as in all those places where the lesions extended into the cortex.

In the second case no signs of fat ' breakdown ' were seen, only in one place a few compound granular corpuscles laden with fat were present around a vessel. The gliosis extended much farther than the demyelinization in the myelin-sheath preparations. The white matter was filled with dense fibres, and where the process reached into the cortex fibroblastic astrocytes were found among the deeper layers.

As for the spinal cord, a recent ' breakdown ' was found in the first case. There was a fair amount of lipoid material, breakdown phenomena still continuing. In the same area enormous fibrous gliosis

was present (a strong proliferation of fibrous glia may also occur early, e.g., even in the acute or subacute stage).

The rôle of the glia tissue in the familial cases is treated separately (*see* THE ROLE OF THE GLIA TISSUE, p. 130).

In the interesting paper on the pathology and symptomatology of diffuse lesions of the white matter Bodechtel and Guttmann mention that in very fresh processes, not only the proliferation of macroglia ('gemästete' glia cells and monster glia cells) but also the reaction of microglia elements, especially functionating in the breakdown, take a leading part. Besides the time-factor the glial reaction will be dependent on the age of the patient and on constitutional factors. There is no decisive criterion in regard to the relation of the glial reaction to the causal agent and to the demyelinization. There are cases where the glial reaction is locally more extensive than the areas of demyelinization (relatively slight), and on the other hand there are instances where local scar formation represents a substitution of the parenchyma.

The authors direct special attention to the gliosis in the thalamus. In one case there was rather slight gliosis of the white matter without cortical changes, with strong gliosis in the thalamus. Taking account of the fact that most intense gliosis is often found where normally there is already much glia, the authors believe that in many processes of diffuse change of the white matter the glia is in a certain state of irritation, by which it is compelled to react also in regions where there is no widespread disappearance of parenchyma.

These fibre-formations occur chiefly independently, and not only in the sense of substance replacing the defect. In encephalomyelitis, Gerstmann and Sträussler have also laid stress on the *independent* glial proliferation. When the process lasts longer, then there is a regression of the infiltration symptoms, also of the intensive fat breakdown, and at last demyelinization and intensive gliosis (scar).

Mucin. — Many examples of mucinoid degeneration have been described (Schaltenbrand, Shelden et al. I, Stewart I, II, III, Gasul,[46] Coenen and Mir, Bouman.)

Schaltenbrand[96] found the most striking appearances of the early degeneration to be the large number of round or mulberry-shaped holes which were everywhere equally distributed. These holes contained a substance which could be stained by special methods. In many of the round glial cells in the white matter the protoplasm had begun to swell to enormous dimensions and the cells stained red with mucicarmine. Finally, the cell membranes disappeared and the mucicarmine-stained masses entered the surrounding tissue diffusely. When adjacent groups of these cells degenerated and became fused, a mulberry or grape-shaped form of the patches was seen.

Afterwards the glia nuclei disappeared. The degenerated cells proved to be oligodendroglia, and corresponded exactly with what Penfield and Cone have described as "acute swelling of the oligodendroglia."

Coenen and Mir also found round holes everywhere in the brain. Numerous oligodendroglia cells were swollen and stained by mucicarmine.

In the first case of Shelden et al. there was a large amount of mucus in the degenerated area and there it was almost entirely contained in the scavenger cells when present in the perivascular spaces (occasionally in an astrocyte as well). Collections of mucus were scattered throughout and in the edge of the degenerated tissue, sometimes even small amounts could be seen in the normal tissue near the edge of the degeneration, and these masses were not intracellular. In their second case there was mucus in the scavenger cells throughout the areas of degeneration (also in some of the perivascular spaces). Mucus was present in greater abundance in the centre of the degenerated area than near the edge, but in the case of fat the reverse was true. I have seen the same in my *Case IV*, where the mucicarmine stain was positive.

Iron and Pigment.—Barré et al. found numerous siderophil cells and a strong iron-reaction in the sclerotic area around the vessels. There was also iron in the glial cells around the vessels. The same was found in the case of Guttmann, where iron-containing pigment was found accompanying the vascular infiltrations as in progressive paralysis, being unknown in all other processes of inflammation (except trypanosomiasis).

In the third case of Stewart et al. there was pigment in the nerve cells, black or dark-brown, and double-refractile, dependent on hæmorrhages. Bielschowsky and Maas have found pigment free from iron in the cells of the glial nets.

Cysts.—In his first case Schilder speaks of cystic hole-formation, and he recalls the case of Rossolimo, with cyst-formation together with a patch of disseminated sclerosis. He also gives a citation of Lüttge, a case of acute disseminated sclerosis with cysts. In my first case there was a large cystic distension towards the occipital pole in the posterior horn of the right ventricle; in consequence of this the posterior part of the occipital pole was formed only by a membrane about 2 mm. thick, the inner wall of which was continuous without any sharp demarcation with the ventricular lining. The cyst in Rossolimo's case was not continuous with the lateral ventricle.

In the white matter on the level of the calcarine region rather far from the ependyma, Barré et al. found a series of cysts of various dimensions macroscopically visible; sometimes they were surrounded by several layers of cylindrical cells, giving the impression of small

gliomas. The authors considered that they probably originated from the ependyma. Bodechtel and Guttmann found in their fourth case a cyst the size of a plum at the right operculum. In histological sections through the frontal area the cystic degeneration of the operculum is seen more clearly. The cyst has reached the white matter. Here the cyst is a post-traumatic reaction. In addition a large gliosis of the white matter without fresh or past inflammation was found. Here both cyst and gliosis are of the same origin : trauma dependent on an individual disposition (sometimes the brain reacts by blastomatosis). In the original trauma large parts of the brain white matter and cortex have probably sustained such large lesions that they are pushed on to this extreme gliosis.

In the cortex of the middle temporal gyri, Braun found a cyst with thick walls, but the tissue around it was normal with smooth base and its wall white and firm.

In their first case Shelden et al. describe one cystic area supralateral to the anterior commissure and the tail of the caudate nucleus.

In the second case of Schilder he found 'Lichtungsbezirke', described by Borst in disseminated sclerosis. He speaks of perivascular lymph accumulation.

Corpora Amylacea.—Corpora amylacea occur in some cases, for instance that of Austregesilo et al., mostly of the versicolor type, several of the flava type. The mucin reaction was negative.

In Schilder I corpora amylacea were mentioned. Formations which resembled them were mostly found in the neighbourhood of the focus of severe degeneration and in the internal capsule. " According to Stanley Cobb, the possibility exists that mucin indeed may change into corpora amylacea " (Schaltenbrand). Kaltenbach has paid attention to the metachromic 'protagonoide Abbaukugeln' in the areas of beginning degeneration, and I myself have probably seen the same products (*see Fig.* 15, *Brain*, 1924).[21]

A large amount of amyloid was seen in Kraus-Weil's case in the form of small globules which were closely packed in the subarachnoid region and around the ependymal layer of the ventricles. In this last region corpora amylacea are very often seen in older patients ; in their case it was an elderly man.

III. MICROSCOPICAL ANATOMY OF THE CEREBRAL CORTEX

In several instances the *cerebral cortex* was entirely normal, in other cases there were more or less severe changes. In my first case I did not find the cortex altered (the same : Marie and Foix, Kaltenbach, Krabbe, Rossolimo, Henneberg I, Henneberg II, Claude and Lhermitte, Siemerling and Creutzfeld, Schröder II, Schröder III,

Rochon-Duvignaud et al., Gans, Casper, Patrassi, Kogerer, Baló, Stewart II). Slight changes occurred in the cases of Austregesilo, Coenen and Mir (ganglion cells without prolongations, badly stained Nissl bodies, sometimes complete tigrolysis, changes in oligodendro-, macro-, and microglia); Shelden et al. I, only the deep fibres were destroyed; Gagel, ganglion cells destroyed. Stewart et al. I, astrocytes in the deepest layers, some vessels with compound granular corpuscles. Weimann: slight changes in the supraradial area, sometimes changes up to the fifth layer. Severer changes, Klarfeld: changes in the ganglion cells, proliferation of large glial cells, and fibrous glia. Bouman II: fifth and sixth layers tigrolysis of many ganglion cells surrounded by satellites, also some perivascular infiltration. Schröder I: occasional disappearance of myelin-sheaths in the deepest cortical layer. Neubürger: at the bottom of the sulci disturbances in the deepest cortical layer, similar to those in the white matter; alterations in ganglion cells. Walter: the architectonic structure of the cortex was scarcely disturbed, but in some places it was thinned and the number of the ganglion cells reduced. Similar changes to those just described were found in the cases of Bielschowsky and Maas, van Londen and Frets, Kufs I and II, Bielschowsky and Henneberg I and II, Franz Bielschowsky, Shelden et al. II, Schaltenbrand (cortex thinned and paler above chief lesions), Kraus and Weil, Wertham I and II, and also in Bouman III, IV, and VI. The last cases of Foix and Marie: II, badly stained, relatively free; III, slight destructive lesions, a small patch of necrosis.

In the third case of Schilder there were no structural changes, but chronic ganglion cell changes; in the deepest cortical layers abundant fat in the cells; and the vessels were partly infiltrated by lymphocytes; in the insula the upper layers were changed.

In Jakob's case there were areas of chronic degeneration and loss of ganglion cells, and progressive glial changes in the deeper cortical layers. In some places, where the cortex was damaged, there were endarteritic changes in the capillaries, a new formation and budding of vessels and emigration of lymphocytes, especially of plasma cells. The ganglion cells appeared as though torn, the nuclear membrane being no longer visible. There were scavenger cells also around the atrophic ganglion cells. Many cortical cells and some cells in the head of the caudate nuclei showed acute cloudy swelling. The glial elements were proliferated and rod cells were present.

In Hermel's case there were disturbances in the structure of the cortex; where the lesions were more severe, these consisted of acute ganglion cell changes.

In Braun's case the cortex of the left middle temporal gyrus contained a thick-walled cyst the size of a pea, but the tissue around

it was normal, its base was smooth, and its wall white and firm (the cortex contained 'monster' glia cells and sausage- and crescent-shaped fat-granule cells around the vessels, even where no lesion existed).

In the second case of Shelden et al. it is mentioned that the fibræ arcuatæ were destroyed, the cortex being free in most cases. They found, however, the fibræ arcuatæ and the deep layer of the cortex destroyed together.

Is it permissible to admit that demyelinization may depend on cortical alterations ? Bodechtel and Guttmann[16] (1932) deny this conception. In their first case intensive gliosis together with relatively intact myelin sheaths were present and the whole cortex was altered. In many cases there was a shrinking of the cortex as in the first case of Collier and Greenfield, especially in the cunei and occipital regions. In Brock's case there was a thinning of the cortex above the lesion. Kuf's second case showed thinning of the cortex in some territories. In Bielschowsky and Maas' cases there was a shrinkage in both hemispheres, the temporal lobe and the insula being especially affected ; the cyto-architectonic structure was also partly changed. Van Londen and Frets mentioned an excavation of the temporal lobe, the cortex being there destroyed and the lesion reaching the surface. In the case of Barré et al. there was a global shrinkage with reduction in size of the gyri.

Wertham found the left parietal lobe atrophied in his first case. In his second case Scholz found a general atrophy of the cerebrum with external hydrocephalus. This atrophy extended to the corpus callosum and thalamus. Schaltenbrand found atrophy on the right side of the frontal lobe ; there was also a shrinking of the left side.

Where there was an important shrinkage there was also a dilatation of the lateral ventricle, already mentioned in Collier and Greenfield's first case, but also in Bielschowsky and Maas' and many other cases, among which I would draw special attention to the hereditary case of Scholz.

The supracortical *pia* has often been reported as normal. At times there are various changes, such as simple thickening (Austregesilo, Rochon-Duvignaud et al., Neubürger, Kaltenbach, Bouman II) or the finding of severe lymphocytic infiltrations. In Schilder III there were also lesions of the upper layers of the cortex of the insula ; in Braun's case there was thickening and infiltration by lymphocytes, or slight proliferation of cells (Flatau), fat-granule cells and proliferated glial fibres, or only small fat-drops with slight œdema of the meninges (Kraus and Weil) or slight infiltration with scavenger cells (Schaltenbrand). In Siemerling and Creutzfeld's case there was found in the pia a patch of dense infiltration by macrophages—some of which had become scavenger cells—as well as by polyblasts and by lymphocytes.

Franz Bielschowsky found the pia in many territories intact, but over the whole fore-brain there were patches of cell infiltration more or less intense and widespread, especially where a pia-lamella separates two gyri. Over the surface of the brain also were dispersed very small patches, analogous in structure to the larger ones. These meningeal infiltrations consisted of macrophages, plasma cells, lymphocytes, and cells intermediate between both these types. Furthermore, there were elements with oblong structure of vessel-wall origin and 'mast' cells in various numbers. In the diseased territories there are proliferated cell-forms taking their origin from immobile conjunctive tissue cells of the leptomeninges.

The macrophages are found especially in the pial meshes, and the lymphocytic elements especially in the adventitial spaces and the immediate surroundings of the vessels. The macrophages are filled with a lipoid 'breakdown' product. This is a very special case, because Franz Bielschowsky found bacteria in the pial lamellæ. They were mostly situated in the adventitia of the vessels, but also in the territory of the 'Zelleinwanderung', and now and then in the macrophages.

IV. MICROSCOPICAL ANATOMY OF THE SPINAL CORD

In recent years the spinal cord has been more often examined than formerly. We have seen that in several cases there has been a secondary degeneration. Bielschowsky and Maas found, throughout the cord generally, patches for a great part analogous to those of disseminated sclerosis. Besides these there were 'Markschattenherde' of varying size in the white and grey matter. There were no fresh patches, and scarcely any fresh 'breakdown' products were stained with Herxheimer fat stain. In almost all patches the cells of the vessel sheaths contained lipoid material.

In Stewart et al. III the cervical region of the spinal cord was swollen and rather softened in its right half. This swelling extended almost throughout the cervical region and in some segments involved the whole area of the cord. Below it, the white matter immediately around the horns was acutely congested, the horns themselves looking healthy. The diffuse pallor and swelling disappeared in the sixth, but reappeared in the seventh and eighth cervical segments. Microscopical examination showed the myelin-sheaths in the damaged areas swollen and broken up and many compound granular corpuscles containing fatty material were scattered throughout the tissue or collected around the vessels. Flatau saw changes, already described above (hæmorrhages). In addition there were infiltrations by small cells, chiefly in the neighbourhood of the pyramidal tracts in the

vessels from the periphery to the centre of the postero-lateral tracts. Possibly there was some slight increase of glial cells in the grey matter, and now and then granular cells were seen.

In his first case Wertham found a focal area of demyelinization in the cervical part of the cord. In the cord was a dense fibrous gliosis. There was much more fat near the margin of the focus, and here it occurred in scavenger cells as well as in immobile glial cells. The vessel sheaths in the centre of the lesion and at the periphery contained a considerable amount of lipoid material in scavenger cells. In his second case there was a pallor in the posterior tracts in the cervical cord (*see above*).

V. DEBATABLE PATHOLOGICAL POINTS

Inflammation or Degeneration? — In the past the problem of inflammation as opposed to sclerosis has been much discussed; according to Guttmann and others, the answer depends chiefly on the intensity, progression, and duration of the disease, and the individual resistance of the patient. Considering the cases of long duration first, the case described by Marie and Foix as centrolobar intracerebral symmetrical sclerosis lasted ten years and there were more fibrils than cells in the old sclerotic areas, and close to their centres hardly anything but delicate fibrils. In the case of Kraus and Weil of thirteen years' duration there was a marked increase of glia tissue; the blood-vessels, however, showed a perivascular infiltration, especially in the region of the corpus striatum. Hermel found no cellular infiltration at all. Kaltenbach found only a few lymphocytes and no plasma cells. In Ferraro's cases, of six, five, and ten years' duration respectively (familial form of encephalitis periaxialis diffusa) no inflammatory lesions were present, with the exception of localized perivascular infiltration in which 'breakdown' cells and lymphocytes were collected (here, according to the author, the picture of a symptomatic inflammation of Spielmeyer). In Walter's case (a rather dubious case of three and a half years' duration) only large scavenger cells, astrocytes, and an increase of glial fibrils were found in all sections.

My second case, formerly distributed among the so-called degenerative cases, had probably also a long course; already three years before his death the patient had been admitted to the asylum (in my first article I noted a five months' duration—viz., the onset with epileptiform attacks). In this case many glial fibres, glial nuclei, and green pigmented scavenger cells were seen. This case exhibited changes in the pia, and the cortex was also affected. In the outer layers of the pia a diffuse infiltration of round cells interspersed with

'mast' cells could be seen and there was some perivascular infiltration by lymphocytes and large scavenger cells in the fifth cortical layer.

Kogerer (two years' duration) found an increase in glial fibres, small and large cells, and fat granule cells.

Wertham's first case, a woman aged 53 (eight years' duration) showed, according to the author, in the main a chronic process. There was absence of fat within the lesion, and only in two spots fresh 'breakdown' of lipoid material was found.

In his second case admitted to the hospital at the age of 30, the disease lasted from eleven to twelve years at least. The whole picture was here also a chronic one, even like that of a scar; there was no evidence of acute 'breakdown' phenomena. With Holzer stain a diffuse fibrosis was present, even in places where the demyelinization could not be indicated by the myelin-sheath preparations. Klarfeld's case showed the vessels almost entirely free from infiltration, now and then some lymphocytes in a regressive stage, no plasma cells; endothelium intact.

In Krabbe's cases of the so-called heredo-degenerative form, although of short duration, sclerosis of the white matter was present. The loss of substance was filled by proliferated glia, a dense net of fibrous glia, and atypical forms of protoplasmatic glial cells.

Scholz also described heredo-degenerative cases with a duration of from one and a half to nearly five years, with the onset of the disease at seven and a half to eight and a half years. He found an intense glia proliferation. The mesenchyma had not taken part in the process. The adventitial sheaths of the vessels were dilated and a varying number of typical scavenger cells was present. At the edge of the degenerated area here and there larger vessels with infiltration by lymphocytes were found.

In the first case of Bielschowsky and Henneberg there was also a glial 'Ersatzmasse', having the well-known features of a spongy glia scar, and the adventitial lymph sheaths of the vessels were filled by lymphocytes, where a fresh degeneration occurred.

In the second case also a glious scar was found. Only at one place did 'mesenchymal' elements contribute to the scar formation. The authors suppose that the beginning stage of the disease was especially intensive. It is also possible that a great part of the glia was destroyed with the disappearance of the myelin-sheaths and the blood-vessel–connective-tissue apparatus had contributed to the filling-up of the defect. But another possibility must be borne in mind as in the first case: the scar was originally purely glial, but the glial material had not sufficient stability for filling up the defect continually alone, and then in a later stage of the disease a mobilization of the blood-vessel–connective-tissue occurred (*see later*).

In the first case of Kufs', a man of 63 years with a chronic type of process, there were found in the deep white matter of the hemispheres around many vessels infiltrations containing numerous lymphocytoid elements. In the periventricular parts the sclerosis was densest; more in the direction of the cortex the sclerosis has fewer fibres; and at last delicate fibres between the bundles of myelin-sheaths were present.

Again, in the second case, a boy of 4 years, patches of complete sclerosis were found. The adventitial lymph-sheaths of the blood-vessels of the white matter contained many lymphocytic elements and also some plasma cells.

Guttmann found in a man of 71 years not only arteriosclerotic changes but also clear signs of inflammation, very extensive infiltrations with lymphocytes and plasma cells. The plasma cells are widely spread abroad in the surroundings of the vessels. It is important, as Guttmann emphatically says, that here there is no question of 'symptomatic' inflammation (as found in tumour and 'breakdown' processes, Spielmeyer). What is especially striking is the proliferative component, large proliferation of glial cells and fibres. Especially in the centre there takes place a proliferation of mesenchyma fibres which are very intimately intermingled with glial fibres. The author considers this point as one of differentiation from the typical patches of disseminated sclerosis. In this case a combination was found with patches which were most probably senile plaques. The Neubürger case can be compared with the Guttmann case: mesenchymal and glial proliferations were also present.

Also in the case of Bielschowsky-Maas there were found a gliafelt, astrocytes with much plasma, and 'gemästete' glial cells, but no fat granule cells or typical Hortega cells or intermediate forms. In all parts of the central nervous system which were examined, however, inflammatory symptoms of reaction were present, though very limited.

There occur many instances where previous inflammatory processes are supposed to exist. Weimann, generally accepting a symptomatic inflammation, notwithstanding a very large infiltration of lymphocytes in his own case, admits that cases with a clear inflammatory character are not uncommon—for instance, the cases of Neubürger and Guttmann, where at the edge of the area an extensive plasma-cell infiltration, and especially a removal of the infiltration cells from the diseased tissue, was found.

In my first case the vessels contained dense infiltration of cells. The majority were lymphocytes, but there were also elements resembling degenerated plasma cells which stained metachromatically, were angular in outline, and contained vacuoles. The same was found in my *Cases III* and *IV* (subacute cases) and especially in *Case VI*.

Stauffenberg found dense cell accumulations in the lymph-sheaths of vessels, and also in apparently normal tissue. Schröder found in his fourth case diffuse and perivascular infiltrations, with very dense cuffs, mostly of lymphocytes, but now and then also of large plasma cells.

Siemerling and Creutzfeld[107] discussed the question of inflammation and mentioned that as 'alteratio', 'proliferatio', and 'infiltratio' occurred in their case, it must be answered in the affirmative. Excepting areas poor in cells and rich in glial fibres in the centre of the large area in the hemispheres, as well as in an area in the upper part of the corpus callosum, the pons, and the middle of the cerebellum, there was everywhere a severe non-purulent inflammation; therefore it would be of no value to speak of young or fresh patches—at the utmost some small ones in the internal capsule and a subcortical one in the gyrus lingualis can be reckoned to them. In all regions there was a clear dependence upon vascular distribution, which was especially distinct in the cerebral peduncles and pons; small off-shoots from the end of the basilar artery, perhaps also from the posterior cerebral artery and the posterior communicating ramus, for the cerebral peduncles; the lateral pontine vessels for the pons, for a large part having their origin in the superior cerebellar artery. The large patch could not so easily be referred to one vessel territory; the possibility of confluence of several patches or the presence of secondary degeneration of the white matter in the neighbourhood of the patch not being acceptable (the severe symptoms of inflammation in these territories of the cortex present difficulties). Most probably, however, there was a progression of the toxin, causing the process, in the glial ground-tissue, and together also in the myelin-sheaths, and thus the progression of the patch could be explained. So there would develop an extension of the patch to the convexity, limited by the fibræ arcuatæ, which derive their blood-supply from the cortex and which have a direction and tectonic structure entirely different from the other fibres. There is also, however, a secondary degeneration in the strict sense in the centrum semiovale, which could be shown by Weigert-Pal stain in the pallor of the deep temporal white matter and in the white matter of the frontal lobe. A progression of the toxin as a possibility of explanation is demonstrated by the alteration of the pyramidal tracts, which is morphologically of inflammatory nature. This alteration extended from the pons to the upper cervical part of the cord and was exactly limited to the pyramidal tracts; the authors consider this as a proper system-disease; in regard to the lower parts of the spinal cord there is a purely secondary degeneration of the corticospinal tract.

Schröder found in his first case around the vessels in the edge of the area scavenger cells (also in the deeper parts of the large

area) and also typical plasma cells and lymphocytes. The author thinks that these cells play only a subordinate rôle, confined to the boundary territories. He discusses the significance of lymphocytes and plasma cells around the vessels and in the tissue. Must all these pathological processes, however various they may be, where these elements are present, therefore be summarized and interpreted as 'inflammatory'? His opinion is that it is dubious; they might be subordinate or secondary processes, and the cases of so-called diffuse sclerosis are not decisive, so long as our knowledge of these special processes is insufficient.

Walter,[123] impressed with a striking analogy with disseminated sclerosis, recalls the remarks of Anton and Wohlwill.[1] These authors consider the possibility that the perivascular infiltration might be merely secondary to the 'breakdown' of the parenchyma. This, according to Walter, is totally consistent with his case. It is difficult to conceive that the basis of the severe degenerative process would be an inflammatory one, when the perivascular elements are relatively slight.

Jakob found in his case very distinct exudative and infiltrative changes with the character of chronic inflammation in the areas of degeneration and often also in the localized processes. There was, however, no direct dependence between severity of the infiltration processes and the intensity of the degenerative parenchymatous lesions; areas with very regressive and progressive tissue processes had sometimes only a little vessel infiltration, and vice versa. It would be possible to explain these facts by the casual acuity of the process, but the degenerative and proliferative processes are often far more extensive than the slightly infiltrated vessels—that is, the glia proliferations are often widely exceeding the limits of the areas (cf. Anton and Wohlwill in a case of acute disseminated sclerosis).

According to Jakob, there is 'alteratio', 'exudatio', 'proliferatio'; there is inflammation, exogenous in type. The severity of the exudative-infiltrative processes in the areas, the severity of the myelitic processes with abundant emigration of the mesodermal cells, the endarteritic processes, and especially the infiltration outside the areas, contribute to this conception.

In my opinion we cannot yet decide as to the problem of inflammation or degeneration. Certainly there are cases where there is no evidence at all of inflammation—for example, the heredo-degenerative cases of Krabbe, the fourth case of Globus and Strauss, the cases of Scholz, etc.—but we cannot always deny the possibility of pure reactive infiltration in the sense of a symptomatic inflammation (Spielmeyer, *Histopathologie des Nervensystems*) as might accompany an encephalomalacia (Aschoff speaks of 'reparative'). Spielmeyer

himself indicates the difficulties, especially in his so-called "sklerosierende Entzündung des Hemisphärenmarks". He himself was often in doubt whether the exudative infiltrative infiltrations of the vessel sheaths and the free cells were exudative and proliferative reactions on the necrotic degeneration. Are they in relation to the reaction of the 'breakdown' products, or is there an independent inflammation? Spielmeyer admits inflammations (thus also 'sklerosierende Entzündung') and secondary reactions. According to him, it is a very important point whether or not there are neoformation of vessels and mesenchymal nets; moreover, the behaviour of the mesodermal parts is important. They are almost never missed in the destructive inflammation of pathological form, but they do not belong to the autonomic degenerative processes.

It is very curious that the opinions of the different authors on some cases from the literature are totally contrary—for example, the case of Stauffenberg is relegated by Weimann to the degenerative group and by Steiner to the inflammatory group, demonstrable already by the clinical symptoms. In the same way Weimann referred my first case to the degenerative group, while I myself considered it, because of apparent inflammatory symptoms, as belonging to the inflammatory group. There is also difference of opinion as to Schilder's first case. Steiner[113] cites the case of Fr. Bielschowsky as strongly indicating an inflammatory character.

I have tried to divide the several cases in connection with the severity of the inflammation—that is, the severe cuffs around the vessels—and further in connection with the criteria given by Spielmeyer. Thus we have, for instance, Gagel's case, where a slight newformation of vessels and proliferation of the mesenchyma were found, while there were in the patches frequent plasma cells, a small quantity of lymphocytes, and 'mast' cells. In this case there was an etiological factor in an attack of measles.

In Klarfeld's case there was a history of influenza. Klarfeld himself considers his case as a degenerative one, with this remark: that, by analogy with his findings in encephalitis epidemica, there is clinically no difference between those two but only morphological differences—that is, no difference clinically between 'itis' and 'osis' (Klarfeld,[66] 1922). In this case a mesenchymal proliferation was present, but almost no vessel-infiltration; now and then a lymphocyte in a regressive stage could be seen, but no plasma cells at all. He finds resemblances with Hermel's case, where infiltration-processes were totally wanting, but on the other hand new formation and sprout formation of the capillaries were found. Here a complete disappearance of axis cylinders was present.

Schilder's third case began also with influenza, and in connection

with this disease the first neurological symptoms were seen. At post mortem thick cuffs of lymphocytes and now and then a plasma cell were found. Besides, there was infiltration also free in the tissue and mesenchymal nets containing fat granule cells and glial cells. In the immediate surroundings of the demyelinization-area vessel proliferation and lymph-accumulation were found, and also vessel-sprouts and new formation of capillaries. In this case there was an 'endocarditis verrucosa' of the mitral valve as an old process.

The same was found in Braun's case, where slight traces of an old 'endocarditis verrucosa' of the aortic valve were present. Here the perivascular lymph sheaths were intensely dilated and filled with lymphocytes and scavenger cells; only very rarely leucocytes, and no plasma cells. There was also infiltration in the apparently healthy surroundings. In the small vessels an important increase of vessels with conspicuously large and pale nuclei was found. No increase of vessels was visible. Achucarro stain failed. There were no demonstrable examples of vessel-sprouts. Braun himself considers his case as allied to Jakob's case and representing an earlier stage.

In Stauffenberg's case, in addition to the large demyelinated areas, a patch in the chiasma occurred, very much resembling a plaque of disseminated sclerosis. In this case there was a slight increase of temperature and lymphocytosis in the cerebrospinal fluid (but there was meningitis), and clinically an inflammatory disease was suspected.

In my third case an increase of temperature was noted in the beginning of the disease and also some days before death. In my *Case VI* many vessels in the foci were surrounded by infiltration cuffs, containing lymphocytes, polyblasts, 'mast' cells, and granular cells. Examination of the cerebrospinal fluid revealed positive Pandy and positive colloidal reactions.

There are therefore cases which are *certainly inflammatory processes*. The examples given above also appear to indicate an infective origin (measles, influenza), although this could be demonstrated only now and then clinically. There are *also degenerative forms* (Haberfeld-Spieler, Krabbe, Scholz, Ferraro, Bielschowsky and Henneberg). In other cases it is not possible to give a decisive opinion.

The Rôle of the Glia Tissue.—Now we return to the interesting remarks of Scholz[102] on the lipoids and the dystrophic glia processes. He has laid much stress on the study of the Sudan-stained preparations. There were in his *heredo-degenerative* case at the edge of the diseased area scavenger cells in the lymph-sheaths of the vessels, filled up by glaring red masses. The gliogenous scavenger cells free in the tissue, however, had a pale pink ground-colour and were lightly covered with finest red granules. Many of the progressively changed

immobile glial cells contain the same inclusions. The scavenger cells nearest the edge of the area do not contain elements coloured red with Scharlach or Sudan, but they have inclusions varying from yellow-red and palest yellow—at times granular, at times homogeneous. Lorrain Smith staining (Nile blue sulphate) shows a difference between vascular scavenger cells and those which are free in the tissue. The inclusa of the latter are pale blue, of the former red. We can expect a chronic process, because the number of the mobilized gliogenous 'breakdown' cells is relatively slight, therefore the number of elements which must be disintegrated is not very large. The glia cells have lost (totally or partially) their function of the transformation of the disintegrative products into transportable substances. There are not ordinary lipoids, but instead of those, substances with affinity to hæmatoxylin and secondly with defective reaction on fat stains; therefore there is reason to suppose that the change of the disintegrative products in the glia cells remains at an intermediary stage. *The glial cells have also been deficient in the function assigned to them.*

Those intermediary products in many regards resemble the prelipoid products of Alzheimer in amaurotic idiocy (in the ganglion cells; often, however, also in the glia cells).

Scholz mentions Bielschowsky in connection with his investigations on amaurotic idiocy. Probably the trophic function of the glia, especially the participation in the myelin building and in the lipoid metabolism, is severely damaged in this disease. The atypical products in the large glia cells demonstrate perhaps a trophic insufficiency. The origin of the characteristic inclusions in the ganglion cells is similar. Bielschowsky adopts the conceptions of Parhon, Goldstein, and Benders[7] and sees the fundamental lesion in the absence or diminution of special ferments necessary for normal metabolism.

According to Scholz there are, however, important differences from amaurotic idiocy. In familial diffuse sclerosis there is no *independent* participation of the specific elements of the nervous tissue in the lesion of the metabolism. The proper nutritive or trophic function of the nerve-fibre belongs to the glia cells in the direct surroundings. They care for the supply of the necessary nutritive elements and also for the transport of the elements which can no longer be used after their transformation in the nerve-fibre; in this manner the metabolism is in equilibrium. The glia offers also the elements necessary for the metabolism of the fibres in an entirely definite chemical composition. The nutritive or trophic function of the glia is perhaps in a different manner, and perhaps also in a different degree, disturbed in both diseases, the effect on the nerve-fibre is in both cases the same. The fundamental pathogenic lesion of the processes in the familial diffuse sclerosis in the infantile cases is very probably a

nutritive or trophic dysfunction of the glial tissue, a vegetative insufficiency of the glia cells. Scholz makes no decision, whether the dystrophic process in the glia occurs primarily, or is perhaps dependent on a genotypic, endocrine lesion.

When there are changes in the lipoid metabolism, the conception of lesions on the side of 'building up' is much more difficult than on the side of the 'breakdown'; for the first there must be accepted a relatively slow rate; the last, once started, proceed relatively fast, and can be demonstrated therefore much more easily.

Bielschowsky and Henneberg[12] pay attention, as an index of the disturbed assimilation, to the conduct of the neuroglia in the territories apparently still intact. With Scholz they found in places remote from the areas large cells with many prolongations; they were swollen, indicating a special manner of reaction. They were peculiar in their staining with hæmatoxylin, fine granulated elements in their plasma being coloured dim-grey.

In the neighbourhood there are large round cell-forms as lipophages of glial origin, but without granules in their pale or diffusely grey-looking protoplasma. These are pictures more according to a retention of the elements necessary for the 'building up' and the continuation of the nerve-fibres.

Bielschowsky and Henneberg (who speak of a leukodystrophia) indicate especially the vessel changes in the territories of the brain as yet intact. The endothelium of the capillaries and the intima cells of the smaller vessels have everywhere accumulated a substance of thin granules stained by hæmatoxylin and Marchi, while no 'breakdown' cells of ordinary kind are present in the neighbourhood. These cells with thin granules are in normal tissue-cell connection and are also conspicuous by their increase in volume. The structure of the nucleus remains normal. This is the expression of an insufficiency of the total 'building-up' apparatus, of the vascular and the glial apparatus. There is not only a cessation of the transport, but also a suspension of the synthetic function of the vessel-wall cells and neuroglia, because the lipoid substances, necessary for the nutrition of the central parenchyma, are imported to the territory, where they are wanted, by vessel wall cells and neuroglia.

In the cases of Bielschowsky and Henneberg and the analogous cases of Scholz, the '*formal*' pathogenetic principle is due to a defective function of all elements active in the 'building-up' of the myelin fibres. Generally speaking, the disease is a disorder of the cerebral lipoid metabolism.

In favour of this conception the recent experiences in the domain of general lesions of lipoid metabolism can be utilized, especially the findings in the so-called Niemann-Pick type of splenohepatomegaly.

In this type an enormous lipoid accumulation is present not only in the reticulo-endothelial apparatus, but also in the specific parenchyma-cells of nearly all organs of the body. It is not so uncommon in this disease to see the typical clinical and anatomical findings of infantile amaurotic idiocy develop. A general lesion of the lipoid metabolism gives here central changes, analogous to those of a very well-known heredo-degeneration. Parenchyma-, glia-, and connective-tissue cells are not able to assimilate the lipoid material offered in excess.

The fundamental lesion in the familial diffuse sclerosis of the hemispheres is, according to Bielschowsky and Henneberg, in those tissue-components of the central organ which have to import the material for the 'building-up' of the nerve-fibres and to regulate the metabolism of the fibres.

The authors do not agree with Scholz's conception of a relatively defective vascularization of the white matter of the occipital lobes, resulting from the peripheral situation of these territories in the vessel system of the cerebral hemispheres.

The findings in the optic nerves and tracts where the alterations resemble those of the white matter of the hemispheres are not in agreement with this conception. They advocate the idea that the rude localization of the territories of the disease is genotypically fixed also.

Bodechtel and Guttmann[16] do not attach much importance to the views of Scholz and Bielschowsky. According to them, the prelipoids only characterize the stage of chemical change. They are stages which precede those of the neutral fats, which can be demonstrated later, but these pictures can neither be applied to the classification of the cases of diffuse sclerosis nor are they demonstrable for the etiological role of the glia—viz., the dysfunction of the 'building-up' and 'breakdown' tasks of the glia. We know too little about the chemistry of the formation of the lipoid bodies to be qualified to use the ideas obtained by the chemically crude staining-method as a basis of bold hypotheses concerning the physiology and pathology of the lipoids.

Besides a delimitation of the heredo-degenerative processes cannot be admitted, Schaffer's conceptions in this regard being, according to Spatz, inacceptable. Certain exogenous processes can give system-degenerations, e.g., spastic spinal paralysis and exogenous cerebellar atrophy.

Kaltenbach had already spoken of special products when myelin-sheaths are disintegrated, interfering with the changing into fat and also the transport, but, and in this regard he agrees with the authors just mentioned, a functional defect of the glia, while ordinary disintegrative products of the nerve-fibres have broken up, was supposed

more probable. He pointed to singular metachromatic 'breakdown' products, while he found that they were situated almost in the direction of the nerve-fibres of the white matter.

True lipoids (as in the product of secondary degeneration) recede into the background. Kaltenbach, too, had already pointed to these peculiarities of the lipoids, though he had not elaborated this question as the more recent authors did. His case, however, belonged to the adult group.

Ferraro admits not only the dysfunction of the glia, but he denies every faculty of change of the 'breakdown' cells against the products of the disintegration of the myelin. These cells are thought to represent a degenerative form of the glia, in which the prelipoid elements only passively penetrate.

Patrassi,[89] in my opinion, has given an acceptable conception of the glial function in diffuse sclerosis in connection with the findings in his case. Scavenger cells were found in the centre of the patches, the vessel-coats were exclusively filled up by granules, soluble in alcohol, and by lipoid-droplets intensely coloured by Sudan III. Products of partly similar, partly different content were visible at the edges of the patches and especially between the fibres which were beginning to be demyelinizated.

Besides these granules with special qualities, glaring red-coloured (*see above*), there were others of different form and size, resistant against alcohol and dim-yellow coloured by Sudan III. In the preparations coloured by the Vimtrup method these products were purely fuchsinophil. Either in their conduct in regard to colouring, or in their conformable morphology they can be looked upon as analogous with those granules (irregular and also fuchsinophil) in which the myelin-sheaths of the fibres are dissolved.

On that account Patrassi thinks he has a right in his case to admit that the gliogenous 'breakdown' cells are able to take up the pre-lipoid products of the disintegration of the myelin and elaborate these to their final state as neutral fat. The probable explanation of the facts points to the conception that the content of the lipophages is rather in connection with the primarily abnormal character of the myelin products of disintegration than with a defective elaboration of the material of the disintegration from the side of the glial 'breakdown' cells. This conception is in contrast with those of Scholz, Bielschowsky, and Henneberg. In a biological direction the conception of Patrassi is preferable to the other, which speaks of a changed function of the glia, and which cannot be demonstrated by facts.

Patrassi and I myself found, what after all was also observed by Scholz, Bielschowsky, and Henneberg, that at some distance from the

focus large cells were present, with abundant prolongations and a homogeneous and opaque protoplasm, especially in the neighbourhood of vessels. This pleads against a changed function of the glial tissue and is rather an affirmation of that which we expect from the glia in the central nervous system.

The question whether because of these findings we should speak of a definite state of irritation (Bodechtel and Guttmann) can be answered in the affirmative only when sufficient cases are observed in which it can be demonstrated. Bodechtel and Guttmann refer to the gliosis in the thalamus, but they themselves mention that in this regard difficulties arise (more or less differentiating with the Weigert-Pal stain gives differences in demyelinization). An estimation of the quantity of glial fibres in regions where normally much glial tissue is found, is not easy. They also point to the autonomous glia proliferation described by Gerstmann and Sträussler in encephalomyelitis. Here, too, it can be said that movement is a special function of the glia. It is already well known that the glia can replace the ordinary inflammatory cells in post-vaccinal and measles encephalitis, that it reacts in toxic and inflammatory processes by glia plaques (tetanus,[20] malaria). A proliferation of the glia in order to replace the lost tissue is certainly not present in all cases; beside that, there is room for an autonomous proliferation as was already described above.

Van Bogaert and Scholz[18] in a recent publication found very important points of contact with the familial processes, especially in the disintegration. They refer to the publication of van Bogaert and Bertrand. They found in their case the scavenger cells usually abundantly crowded with uncommonly rose-coloured masses, but not containing the light-red Scharlach lipoid. The glaring red lipoids are only in the scavenger cells which have already reached the vessel wall. Here also an insufficiency of the glia for the 'breakdown' of the degenerated material is supposed to be present. Not only a special species but all the cells of glial origin, according to van Bogaert and Scholz, in one function or in several functions are insufficient, especially, however, in the metabolic function. They find a great regularity with which these glial 'breakdown' anomalies occur in the familial diffuse sclerosis (also in the case of Ferraro). The findings of Bielschowsky and Henneberg in the endothelial cells of the capillaries (*see above*) stand alone; in their own case at least they were lacking. They plead for an anatomical separation of the group showing degeneration of nerve-fibres and abnormal comportment of the glia. There are also non-familial cases, very akin to the familial ones (Witte, Kaltenbach, Baroncini), but distinguished by their colour-properties; they have, however, not been sufficiently examined from the standpoint of heredity.

The insufficiency of the glia described by van Bogaert and Scholz was not found with the Sudan stain in our own non-familial cases; all scavenger cells in mutually corresponding manner were coloured light red, characteristic of lipoids. This was the case as much for the cells in the vessel wall as for those situated in the nervous parenchyma. Apparently the 'breakdown' products in our cases seemed to be immediately disintegrated in that lipoid form in which they are delivered up to the blood. The chemical 'breakdown' process thus seemed not to be delayed. The Scharlach staining method, however, gave results much resembling those of van Bogaert and Scholz.

Constitutional factors can be accepted without the possibility of demonstration. Besides the time-factor the glia-reaction will be dependent on the age (Bodechtel and Guttmann.)

VI. PATHOLOGICAL DIFFERENTIAL DIAGNOSIS

Disseminated Sclerosis.—It is very difficult to give the differential diagnosis from disseminated sclerosis. In the first place it is remarkable that typical patches of disseminated sclerosis can occur, as in our first case. Many authors have described transitional forms. Jakob already mentioned the close relationship between the two diseases. Before that Schilder and also Lewy had already discussed the question whether encephalitis periaxialis diffusa was perhaps an infantile form of disseminated sclerosis. The various criteria, indicated above by myself, have a relative value, because in many cases they are not valid. Kufs admits a difference in acuity and intensity of the same process, probably also a difference in changing sensibility, infectivity, and age. The criterion indicated by Benoit, the presence of Steiner's cells, is not yet valid, because the findings await confirmation by other investigators. There are gradual transitions from the slightest forms of disseminated sclerosis into the most severe forms of diffuse sclerosis.

Gozzano and Vizioli have paid attention to this point, and discuss the extent and distribution of the patches, the way in which the patches disperse (expansion or confluence of adjacent patches), behaviour of the axis-cylinders, relationship with vascular territories, participation of the cortex, and secondary degeneration of the spinal cord. Benoit may also be cited; he found typical patches of disseminated sclerosis in the spinal cord and also in the cortex. Schaltenbrand found them in both optic tracts; Gagel in the optic nerves and internal capsule. Bielschowsky and Maas, however, point to the difference in regard to localization and structure existing between numerous patches in the cortex in their case and the ordinary cortical

plaques in disseminated sclerosis. They mention the investigations of Spielmeyer,[110] who found in dementia paralytica a large distribution of patches in the cortex independent of the course of vessels and vascular factors and had compared these plaques with those in disseminated sclerosis. Bielschowsky and Maas, however, disapproved in their case the idea of dementia paralytica, because they found plaques from the spinal cord to the subcortical ganglia, at the subventricular edge of the deep white matter of the hemispheres, as well as demyelinization of the optic nerves. They grant that in their case incompleteness of the demyelinization in the sclerotic territory, and in regard to the 'breakdown' processes the principal rôle of the immobile cells of the neuroglia in the vascular connective tissue, do not correspond with the ordinary picture of Schilder's disease. The proliferative processes of the glia, if present, are bound to the production of fibre-forming astrocytes and plasmatic macroglia (not encephalitis, but a diffuse sclerosis in the strict sense).

The acuity of the process manifests itself in the histopathological picture by important demyelinization, and mobilization of Hortega and scavenger cells very closely connected with it. In acute cases the axis cylinders too can show an important diminution in number, so that in the final stage losses of substance with the stamp of local necrosis result, the out-growing 'mesenchymal' elements of the vascular connective tissue replacing them. The age of the patient, too, is of importance for the intensity and the course of the reactions in parenchyma and interstitial tissue.

In my *Case VI* and the still unpublished *Case VII*, differences in the anatomical picture also occur (the time of the process and the more distinct localization being very different).

In Wertham's Case I, with many areas in the spinal cord and in the cortex, these alterations were also compared with those in disseminated sclerosis and dementia paralytica. After having pointed out that the alterations in the cortex do not argue against diffuse sclerosis, Wertham discusses the question whether his case and that of Gans ought not to be considered as a special form. Bielschowsky and Maas also speak of a special form in their case, manifesting itself by close reaction of the macroglia, especially the fibre formation and the uncommon extensive dissemination of isolated patches. They think, however, that we have not reached the point of being able to indicate a relationship or separability of the various forms. In disseminated sclerosis, too, there are such scattered differences in regard to the pathological findings that it is not an absurdity to accept etiologically different factors.

Comparing our cases of diffuse sclerosis with a typical case of disseminated sclerosis, a complete demyelinization can be seen in the

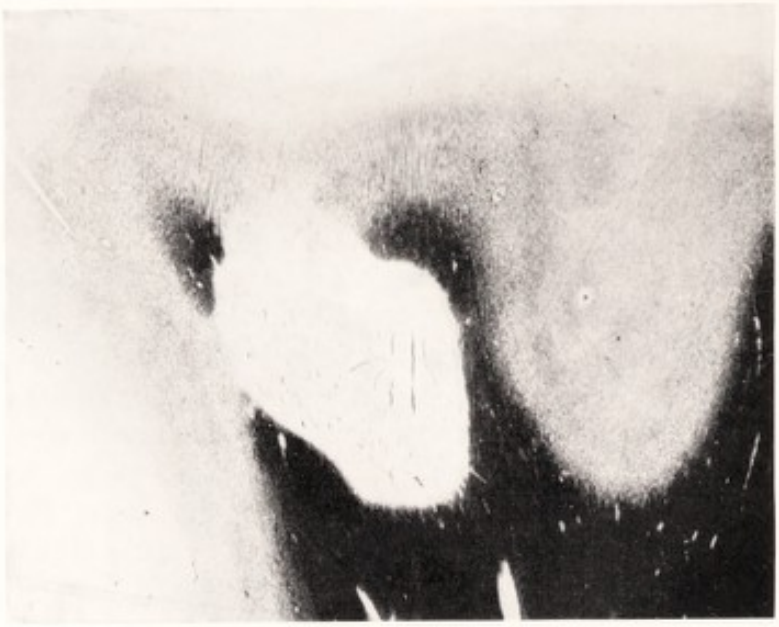


FIG. 66.—A cerebral patch of disseminated sclerosis. Survey photograph. (Weigert-Pal stain.) (× 4.)

FIG. 67.—In the cerebral patch of disseminated sclerosis all myelin-sheaths have disappeared. The lines in the photograph are blood-vessels. (Weigert-Pal stain.) (× 13.)

latter (*Figs.* 66, 67) in contra-distinction to the incomplete demyelinization in diffuse sclerosis (*see Figs.* 8, 29, 30). In the immediate surroundings of the patches in disseminated sclerosis (*Fig.* 68) the swellings of the myelin-sheaths are not so intense as in diffuse sclerosis (*see Figs.* 31–33).

A close relationship between diffuse and disseminated sclerosis can, however, not be denied, especially in regard to the cases published in the last few years. The etiology need not on that account be the same, though an exogenous factor may be considered for both diseases. That we have to do with an infectious agent may be considered as probable, but not as certain, because histopathology has not the last word in this question. At the same time we must reckon with the possibility of an endogenous factor, constitutional and hereditary. In diffuse as well as in disseminated sclerosis hereditary and familial cases have been described. In my *Case II* congenital anomalies in the cerebellum were present.

Fig. 68.—The varicose swellings of the myelin-sheaths at the periphery of the cerebral patch of disseminated sclerosis are less intense than in those found in diffuse sclerosis. (Weigert-Pal stain.) (× 650.)

The claimed difference in the perivascular distribution in disseminated sclerosis and the extent of the diffuse sclerosis, independent of vessel territories, has been discussed. Relations to the vessels have been mentioned in one of my cases, and in Kufs' case one of the small thalamic patches was dependent on a vein.

Siemerling and Creutzfeld have attached importance to the fact that the larger patches of diffuse sclerosis cannot be related to the area of one vessel as a distinction from disseminated sclerosis. They also point out that the patches of disease are not due to confluence of separate foci (their shape and their internal structure and the intact fibræ arcuatæ are against this hypothesis). The lateral extension of the central focus might be determined by secondary degeneration

of the adjacent parts of the white matter (but the inflammatory changes in these regions are against the view). Finally, there is the possibility that the extension of the noxious agent, which produces the changes in the glial tissue, might also determine the extension of the demyelinization, so that the disease progresses towards the convexity and is arrested only when it has reached the tectonic arcuate fibres, since these fibres are different in direction and structure and are supplied by the same blood-vessels as the cortex.

Siemerling and Creutzfeld also discuss whether the large patch takes its origin from the ventricle. Against this conception it could be argued that no ependymal proliferation was present, that no evidences of irritation on the part of the subependymal glia, where the focus touches the ependyma, were found. Besides, the patches in the neighbourhood of the ventricle showed the same alterations of fresh inflammation as other parts at the edge of the patch. When the noxa had primarily penetrated from the ventricle into the white matter of the hemispheres, subependymal cicatrices might rather have been expected.

It has been considered probable that a noxa has come into the central nervous system by way of the vessels (apparently only in the brain) which has given a patch-like non-purulent subacute inflammation of the white matter.

Against these conceptions may be remarked that apart from the fact that the spinal cord too has often shown changes, ependymal alterations are often found. Lauritzen and Lundholm say that the perivascular extension of the plaques in disseminated sclerosis is certainly not always present.

Pette[90] also remarks that the patches in disseminated sclerosis do not always correspond with the vessel distribution and he does not find a definite dependency. In the spinal cord, for example, the symmetrical seam-like patches in the region of the anterior fissure or in the marginal parts, and in the brain the patches along the ventricles, speak against the conception that all patches correspond with the territory of the blood-vessels.

Falkiewicz[37] also denies an exact topical relation between patch and vessels. The resemblance of the patches to true vessel patches is perfectly superficial and from the form of the patches we are not justified in arguing an origin by vessel processes.

In a recent publication Hallervorden and Spatz[56] speak of various patches in disseminated sclerosis: (1) Disseminated patches in the brain substance; (2) Patches at the internal surface; (3) Patches at the external surface.

1. The 'Blut-Gehirnschranke' ("gleichbedeutend mit dem Endothel der Capillaren des Gehirns") of the vessels of the brain is at an

arbitrary spot of a vessel broken up; the noxa then diffuses from this one spot more or less regularly into the brain substance.

2. The noxa comes from the ventricle, and the internal cerebrospinal fluid diffuses into the surroundings.

3. Here, too, the diffusion-hypothesis can be applied. Whether the noxa originates from the external cerebrospinal fluid or from a cortical or pial marginal vessel is open to discussion.

According to Hallervorden and Spatz, the same conception is valid for the extension of the patches in diffuse sclerosis. Here, too, is a diffusion of a substance noxious to the myelin. The difference between the patches in diffuse and disseminated sclerosis can be expressed as follows: In disseminated sclerosis the patches going out from the vessels predominate, the periventricular ones are regularly present, it is true, but more in the background. The reverse is found in diffuse sclerosis; here particularly large patches extending from the ventricles predominate, explainable by diffusion from the internal cerebrospinal fluid.

The authors accept the same explanation for the heredo-degenerative form of diffuse sclerosis, though they suppose that the product described above as noxious to the myelin is of an entirely different nature.

Sillevis Smitt and W. Smit[108] have described an hereditary form of disseminated sclerosis; so by the side of the exogenous (chronic and acute) disseminated sclerosis an endogenous heredo-degenerative form may be placed, perfectly corresponding with diffuse sclerosis, with the exogenous and the endogenous heredo-degenerative form.

Pierre Marie pointed to the significance of infectious diseases in disseminated sclerosis (Marburg pointed to measles, and he cited in his recent paper, "Allgemeine Pathologie der nichteitrigen Entzündungen des Zentralnervensystems,"[81] cases of Cramer and Schlesinger).

Walthard described a case of measles of four and a half week's duration where post mortem a process was found reminding him in a certain sense of diffuse sclerosis, and Greenfield speaks of spinal, cerebral, and pontocerebellar types of measles-encephalomyelitis with diffuse perivascular patches of demyelinization. It is well known that measles occasionally occurs as an etiological factor in diffuse sclerosis.

As to the axis-cylinders, it can only be said that no differences of general validity are present.

From all these data it is obvious that there is anatomically a very close relationship between diffuse and disseminated sclerosis. Trying to give differential diagnostic points between diffuse and disseminated sclerosis, we see that they appear to be not of decisive value, because they are found in either. The relationship must be very close.

Acute Disseminated Encephalomyelitis.—In this case the differential diagnosis is not difficult. Here is a rather acute disease, though

many patches may be present. Histopathologically there is a resemblance to the acute patches of disseminated sclerosis, distinguishable in that the cell-reactions are more numerous and the predilection for the white matter is less manifest. The perivascular infiltration-cuffs are thicker, consisting of lymphocytes and plasma cells. The microglia cells proliferate in great numbers, being for the greater part swollen into globule-like scavenger cells. At the periphery of the patches many hypertrophied macroglia cells are present. The patches are as a rule larger than in disseminated sclerosis and less sharply limited, and in this regard they resemble the patches in diffuse sclerosis.

Measles Encephalitis, and Post-vaccinal Encephalitis.—These conditions will probably never give rise to errors, because they show typical histopathological pictures with perivenous infiltrations in the white matter, and as a rule small demyelinated areas.

Demyelinization is also seen in *postvaricellar encephalitis*, and, as is cited above, in *dementia paralytica*.

'Neuromyélite Optique Aiguë' (with spinal symptoms associated with retrobulbar neuritis or papillitis).—This shows an extensive alteration of the white matter; myelin-sheaths and axis-cylinders are diseased and scavenger cells are found. A slight tendency to glia proliferation is present. The result is a true liquefaction of the white matter and formation of large holes. Necrotic patches are found in the optic nerve and sometimes in the subthalamic region and brain-stem. Compared with diffuse sclerosis, it is important to note that in 'neuromyélite optique' the spinal cord is much more altered; also that secondary degeneration is found. Though in this regard there is a difference from disseminated sclerosis, it corresponds much more with this disease. Sometimes also perivascular infiltrations of lymphocytes and even leucocytes are present. Some cases diagnosed 'neuromyélite optique' have proved to be instances of disseminated sclerosis.

Marinesco, Draganesco, Sager, and Grigoresco[83] found in their case of 'neuromyélite optique aiguë' a large patch in the white matter of the left hemisphere in addition to the alterations mentioned above. The U-fibres were not altered; at the periphery and at the centre of the patches the alterations resembled in many respects the diffuse sclerosis, there being in the centre a more intense destruction of the axis cylinders than at the periphery, but some were spared; the astrocytes were in a stage of regression and numerous alveoli were present. The authors speak of a transitional form between diffuse sclerosis and 'neuro-myélite optique'.

Beck points also to the relationship of the two diseases. In his case the lymphocytic infiltration was important and leucocytes also were present.

Guillain, Alajouanine, Bertrand, and Garcin described a form with only degenerative changes.

CHAPTER VI

SUMMARY

WHEN one compares the results obtained in my first publication with those given in this book, only a slight progress can be admitted. A disease varying much both in its clinical and its pathological features will necessarily give rise to many difficulties in establishing hard-and-fast rules for diagnosis.

Pathological Anatomy.—To begin with the anatomical alterations in diffuse sclerosis, the following can be said :—

The prominent pathological feature is the existence of large patches in the brain, principally in the white matter. The outstanding feature of those patches is the disappearance of most of the myelin-sheaths. This demyelinization extends throughout vast territories of the brain. As a rule one single big patch is distributed through both hemispheres, the two halves being connected by a demyelinated part of the corpus callosum. Often, however, distinct from this single patch (or separate from some large patches) some of a smaller size are found (mostly, however, rather important—for instance, of the size of a hazel nut). Sometimes a great number of small patches are present, many of which appear to become confluent. Those patches which possibly originated by confluence have a mulberry-like surface ; most patches, however, have a limitation by a fairly smooth surface, and this limitation is usually a sharp one.

The number of cases where the occipital region of the brain is more extensively affected than the frontal is rather great, giving the impression that the process has begun in the occipital area. There the patches usually come into contact with the ventricle over a greater surface. In not a few cases, however, an onset in the frontal part of the brain may be supposed. Sometimes a simultaneous and eccentric growth of both patches gives a confluence, for instance in the gyrus centralis.

A striking feature is that the patches often stop at a short distance (some millimetres) from the cerebral cortex. The borderline then extends over a large territory, parallel with the cortex ; a thin layer of white matter between the cortex and the patch is spared. In some places this apparently somewhat resistant layer (in which, of course, principally the U-fibres are found) is broken through and the patch impinges upon the cortex, which mostly at these places

becomes impaired in its whole thickness. In such a cortex again a sharp borderline between the diseased and the surrounding intact cortex can be observed. Not rarely a whole gyrus, or even a number of gyri lying next to each other, is included in the patch. In many cases many other parts of the brain have altered—for instance, the basal ganglia, and also the chiasma, optic nerve, claustrum, geniculate bodies, substantia nigra, nucleus amygdalæ, pons, medulla oblongata, cerebellum. Here, too, a great part of the grey matter remains free.

In most cases all these patches are clearly visible on the fresh section of the brain (though principally after fixation), but in some cases they only appear in specimens in which the myelin-sheaths have been stained for microscopical examination.

As said above, the most outstanding feature in these patches is an extensive demyelinization. Curiously, the remaining myelin-sheaths are of the thin type; all the thick ones have disappeared. Those still present show many varicose swellings. Especially large varicose swellings occur in those myelin-sheaths which are situated just outside the borderline of the patch.

In many cases the demyelinization is not equally intense in all parts of the same patch; areas with severe demyelinization alternate with others in which it is less advanced, and between these areas the borderlines are as a rule also sharp. Sometimes such areas with varying degrees of demyelinization are alternately arranged in a concentric manner, which can be compared with the annual rings of a tree or with the delineation of an agate. This has been the basis for the formation of a special type—the 'leuco-encéphalite concentrique subaiguë' of Baló.

Frequently, in other parts of the central nervous system, too, disseminated sclerotic patches are present; some small patches of demyelinization may occur in the brain-stem, the cerebellum, and also in the spinal cord. Secondary degeneration may be found, but not as a rule.

The axis-cylinders in the patches are not intact. Many of them, especially the thick ones, have disappeared, others can only be stained with difficulty, the remaining ones (the number is distinctly greater than the number of the spared myelin-sheaths on the same spots) are provided with varicose swellings.

The glia tissue always shows strong progressive alterations with regard to the microglia cells, as well as to the macroglia cells. In some cases the macroglia reaction is predominant, in others the progressive alteration of microglia cells. The proliferated macroglia cells constitute many glial fibrils, but the glia felt-work proceeding from this reaction is as a rule apparently less dense than that seen

in disseminated sclerosis. Many macroglia cells show severe changes in the nucleus: excessive growth with lobulation, or, on the other hand, disintegration into a great number of small nuclear fragments, pyknotic or not, and often still partly connected.

The proliferated microglia cells soon become spherical (scavenger cells) and then they are laden with 'breakdown' products; their function is to take up the products formed by the demyelinization and to elaborate them. As a rule, they can be stained by all characteristic fat-staining methods.

In some cases, principally in the hereditary cases, it is stated that the 'breakdown' products are not so much disintegrated (prelipoid products) and do not give the characteristic fat reaction. In this case a deficiency of the 'breakdown' function of the glia cells has been accepted.

In nearly all cases the blood-vessels inside the patches are proliferated, and around each vessel the reticular connective tissue has grown out into a wide-meshed network, lying in the nervous parenchyma ('mesenchymal' reaction). Further, in the sheath of most medium-sized blood-vessels a well-marked infiltration with many lymphocytes, some plasma cells and rather numerous scavenger cells, fat granule cells, 'gemästete' glial cells (plump cells), polyblasts (now and then), macrophages, and 'mast' cells is found. The intensity of this infiltration varies considerably from case to case. Sometimes there is no infiltration whatever. A distinction has been made between infiltrative and degenerative forms (*see above*).

Pathophysiology.—Pathophysiology has not yet reached the stage whereat we can derive all clinical symptoms from the anatomical lesions. They are so extensive in many cases that an exact localization cannot be given. Interference with the projectional system of fibre tracts will be an important factor in the production of alterations in the reflexes, pyramidal signs, defects in the visual fields, and localized disorders of sensation or of motor power.

The alteration of the pyramidal tracts will give the disturbances of gait and later the contractures, of which the quadriplegia is so characteristic in children.

Convulsions, principally occurring in children, are sometimes connected with cortical alterations; in many cases, however, they are of subcortical character.

The psychical symptoms are analogous to what may be found in large tumours of the brain and are not at all specific. In the main, where the lesion has commenced in the frontal regions, the mental changes have been most and earliest marked.

Disturbances of vision and hearing can be explained by the bilateral extensive alterations of the white matter of the

occipital or the temporal lobes. Parietal involvement may result in unsteadiness.

The optic chiasma and the optic nerve may be affected separately. Implication of the intercortical commissural and associational fibres can give various speech disorders, and may also partly contribute to the mental changes. A comparison with the experimental decerebrate rigidity gives some interpretation of the many automatisms and reflexes which may be observed.

Pseudobulbar symptoms find their usual explanation in the breaking-up of the fibre tracts from the cortex to the bulbar centres.

In many cases a high pressure in the cerebrospinal fluid is present. Headache, vomiting, and slight papillœdema and occasional convulsions can be explained by the raised intracranial pressure.

To give a satisfactory explanation of the choreo-athetosis, tremor, biballism, and hemiballism is impossible, because analysis of such functional disorders already presents difficulties in less complicated affections (release phenomena ?).

Diagnosis.— In the introductory chapter the difficulties with regard to the diagnosis have been discussed and from our wider experience we must concede that in some degree these difficulties have not been solved. Meanwhile the publications concerning diffuse sclerosis (encephalitis periaxialis diffusa) have furnished an opportunity to take account of this diagnosis in those cases where an extensive brain process may be supposed. The practical value of the better knowledge of diffuse sclerosis lies in the eventual avoidance of superfluous brain operations.

Several other diseases of the brain have to be excluded before establishing the diagnosis of diffuse sclerosis.

The multiplicity of symptoms is a drawback, partly avoidable, however, by exact information about the onset and the course of the disease.

The number of heredo-degenerative cases is increasing ; a more exact history with regard to diseases in the family may be of importance for the diagnosis in the special case under examination. This is especially of value in children.

Diagnosis in Children.—In the main the diagnosis in children gives fewer difficulties than that of adolescents and adults. A child previously healthy and without tangible causal factors will begin to show disorders of gait, fits, and psychical symptoms in various order. In some cases cerebral blindness, occasionally combined with deafness, will bring the child to the eye or ear specialist. Very characteristic is the increase in the psychical or in the spastic symptoms after a variable period, and with regard to these, the extension of the

spasticity and crossing of the legs, with feet in crooked position, to spasticity of the arms. The disturbances of the intellect advance, combined with incontinence of urine.

There follow subcortical tonic attacks, disorders of speech of articulatory character; later on, mutism, disturbances of swallowing, and pseudobulbar symptoms. Myo-acoustic reflexes, Magnus de Kleijn reflexes, alternating hyper- and hypotonia, alternating posture of arms and legs, forced grasping and groping, sucking and snatching at objects, screaming and crying, jerking movements, opisthotonos, and athetoid, choreiform, or hemiballastic movements can be observed. Very exceptionally an increased pressure or changes in the cerebrospinal fluid are noted; as to the colloidal reactions, information is almost entirely lacking (in my sixth case positive). Elevation of temperature from different causes is observed, but, generally speaking, is not characteristic. Very typical is the final stage with the 'attitude of adoration' (Collier and Greenfield). After an increasing amentia the child dies as a rule through intercurrent illness.

Considering the possibility of diffuse sclerosis in children, it is necessary to pay more attention to cases with epilepsy, and mental debility ordinarily combined with encephalitis and with or without convulsions. Moreover, the cases considered as Little's disease and those of acquired blindness should make one bear in mind the possibility of diffuse sclerosis.

Diagnosis in Adolescents and Adults.—Cases in adolescents and adults give more difficulties in diagnosis. The disorders of vision as well as the psychical disorders attract attention, and the general practitioner seeks a consultation with the ophthalmologist or the psychiatrist. Photophobia, acute blindness, central scotoma for colours, and hemianopia are found. In addition, blurred papillæ or papillitis are present, and the diagnosis of retrobulbar neuritis, optic neuritis, or raised intracranial pressure is made when no other neurological symptoms can be observed.

In my opinion the appearance of psychical symptoms is of great importance in this initial stage, and especially the changes of character and conduct, combined with forgetfulness and dullness. In some cases a complete psychosis has been apparent from the very beginning.

The neurological examination reveals eventually a mono- or hemi-paresis, or other hemi-symptoms, sometimes disorders of gait. Later on the disorders of vision and also of the ocular muscles are present. The to-and-fro swinging movements of the eyeballs must especially be mentioned. Various psychical symptoms are observed, originating from various causes, also dependent upon the localization of the disease. Very suggestive of diffuse sclerosis is the development

of bilateral motor symptoms with spasticity—not so intense, however, as in children. In some cases of adolescents tonic convulsions combined with pain and screaming are observed.

I would draw especial attention to the symptoms of biballism manifesting themselves in larger swinging movements. Disorders of speech are to be observed in various forms; exceptionally bulbar or pseudobulbar symptoms are present. Now and then a syndrome recalling disseminated sclerosis is present, even with apparent remissions. Headache, vertigo, vomiting, with moderate choked disc, remind us of the symptoms of brain tumour; the principal symptoms mentioned above may lead in the right direction. Raised intracranial pressure, rise of temperature, and positive globulin reactions are occasionally found. For the differential diagnosis from brain tumour and disseminated sclerosis, *see* pp. 90, 95.

Prognosis.—The duration of the illness varies (*see* the table p. 150) between some days or months and ± 13 years; mostly between three months and a year. Remissions (temporary) are observed. The prognosis is otherwise fatal.

Is it possible to distinguish various clinical forms of diffuse sclerosis, or, more exactly, to postulate special forms more or less resembling diffuse sclerosis? In my opinion the attempts made in this direction are not demonstrative. Foix and Julien Marie expressly indicate that 'sclérose centrolobaire' and encephalitis periaxialis diffusa represent two stages of the same disease. In a later case they speak of a 'sclérose centro-lobaire subaiguë'.

As to conceding a special place to the leuco-encephalitis concentrica of Baló, for which Barré and van Bogaert[6] plead, so many cases of diffuse sclerosis correspond with the clinical picture described by them as rather typical for the concentric form of Baló, that we cannot accept their special type. It is possible, however, that some cases of the concentric form have been overlooked; in my *Case III* I found it only after minute examination.

There is every reason to accept a polysclerotic form, and many examples are present where symptoms are found in many ways resembling the symptoms of disseminated sclerosis. Close relationship with disseminated sclerosis must be admitted, not only because anatomically there are transitional forms and disseminated sclerotic patches in diffuse sclerosis, but also in regard to many clinical symptoms. For practical purposes they must be separated for the present, although so many facts speak for their relationship.

In the absence of any data as to the etiology of the disease, and considering the possibility of a diverse etiology, it is too early to

make divisions by combining special groups of symptoms or reckoning with the duration of the disease. When we accept various causes for the same anatomical feature, it is possible to postulate a common basis, bound up with the constitution of the white matter itself, a congenital or acquired weakness of the myelin-sheaths (Patrassi). As in so many cases a co-operating of endogenous and exogenous factors must probably be admitted.

A special group is formed by the heredo-degenerative cases. Some authors bring the familial group into connection with the dysfunction of the glia. It is, however, not possible clinically to distinguish these cases from the so-called sporadic ones.

ADOLESCENTS AND ADULTS

Reporter	Sex	Age	Duration of Illness	Headache—Vertigo—Vomiting	Incontinence	Disturbances of Swallowing	Psychical Disorders	Screaming	Disorders of Vision—Blindness	Deafness	Optic Neuritis or Atrophy—Choked Disc	Oculomotor Paresis	Paresis of VIth Nerve	Nystagmus	Pupil Reaction (Sluggish, Absent)—Unequal Pupils	Aphasia—Mutism—Anarthria—Scanning speech—Dysarthria	Chorea—Athetosis—Hemiballism	Ataxia	Intention Tremor	Tremor	Spastic Paresis and Contractures in 1, 2, 3, or 4 extremities—Pes equinovarus	Epileptic or Spastic Attacks	Knee- and Achilles-jerks—Clonus	Babinski-reflex	Abdominal-reflex (diminished or absent)	Globulin Reaction in Liquor	Special Symptoms and Remarks
Jakob	M	30	1½ y.		+		+					+			U.	M.						+	+		A.		Hypertonia R.
Braun	F	39	4 m.*	H., Ve.	+		+		+					+							3		+			+	* Post-oper., hemianopia L., apraxia
Stauffenberg ..	F	21	8 m.	Vo.			+	+	B.		N.,+L	+	+	+						+		+	+	+	A.		Optic agnosia, cells increased, anaesthesia
Redlich	F	41	1 y.	H.			+		+*		N., Ch.		+									+					* Hemianopia, hemiparesis, anaesthesia L.
Klarfeld	F	23	1 y.	H., Vo.			+		+*							Ap.						+	Cl.,A.	+R.			* Hemianopia, hemiparesis R.
Kaltenbach ..	M	24	11 y.		+		+								U., Sl.	Sc.,				+			+				
Bouman I ..	F	32	6 m.	H., Ve., Vo.			+	+	+		N., Ch.										3	S. R.			D.	+	* Hemianopia, operation, high pressure
Bouman II ..	M	29	5 m.		+		+					+				M.		+			2, p.c.	+	+				Hyperesthesia, R. leg, elevation of temp., sub finem vitae
Bouman III ..	F	28	3 m.	Vo.	+	+	+				Ch. L., N. R.		+		U.		H.	+R.									High pressure, elevation of temp.
Bouman IV ..	M	21	4 m.	H.	+		+		B.		Ch., N.										2			+L.			Elevation of temp.
Rossolimo ..	M	16	1 y.				+					+	+	+	Sl.	D.					2		+				
Walter	M	40	3½ y.				+									Ap.					2		Cl.	+	A.		
Henneberg I ..	M	39	8-9 m.		+		+				N.	+	+	+				+					Cl.	+			
Henneberg II ..	F	43	7 m.			+	+			*		+	+	+	U.	D.					2		+	+L.			* Hearing diminished
Claude and Lhermitte	M	18	17 m.	Vo.																							

																						sia
Schröder	M	25	6 m.			+												1	E.			Cells increased
Rochon-Duvignaud	F	22	2½ m.	H.	+		B.	Ch., N.				A.								+		High pressure
Matzdorff	M	64	6 m.			+ +							D.					2				Pains, left leg
Guttmann	M	70	7 y.			+											+					
Schilder	F	37	9 m.	H.	+	+	+	Ch.										2				Post-oper., elevation of temp.
Kraus and Weil ..	M	34	13 y.				+		+	+		A.	Ap.		+	+		2				Hemi-anæsthesia
Barré, Morin, Draganesco, and Reys	F	17	3 y.	H., Vo., Ve.				Ch.	+				D.					2, R.	E.R.		+R.		
Ferraro I ..	F	26	6 y.		+	+		+	+			Sl.	Sc.			+				+			
Ferraro II ..	M	30	5 y.			+		+	+				Sc.							+			
Ferraro III ..	M	21	10 y.		+	+		A., R.	+				Sc.			+		2, R.		+	+		
Kogerer	F	23	2 y.	Vo.		+	+ B.	A.				A.						2					
Baló	M	23	3 m.*	H., Vo.	+			N.					Ap.					3		+		* Post-oper.	
Foix and Julien Marie	F	18	10 y.						+				D.					3		+	+		
Coenen and Mir ..	M	41	1½ m.	H.		+	+ B.	+ N.				U., Sl.						3			+R.		Elevation of temp., thorax, paræsthesia
Shelden et al. ..	F	27	1½ m.	H., Vo.	+		B.	N.								+		2				High pressure	
Austregesilo ..	F	18	2¾ y.	H.	+	+	+ B.	N.	+			Sl.	D., Sc.			+		2			+L.	A.L. D.R.	Remissions
d'Antona	M	34	5 m.			+	B.	A.								+		2	+	+			
M. Bielschowsky and O. Maas ..	M	36	13 y.			+		+					Ap.	A., R.				2, R.	E.				Hemianopia
Casper	M	34	½ m.	H., Ve., Vo.		+			+		+	Sl.	D.					2, R.			+	A.R.	Elevation of temp.
Gans	F	20	10 y.			+					+		Sc.			+		2			+		
Londen, v., and Frets	F	22	4½ m.	H., Vo.		+							D.					2, L.			+L.	A.L.	Post-oper., tongue-atrophy
Weimann	M	36	16 m.	H., Ve.		+	+					Sl.								+			Elevation of temp.
Kufs	M	63	8 y.			+					+							2, L.	E.			A.	Apoplectic attacks
Fr. Bielschowsky	M	53	3 y.										Ap.						E.L.				Elevation of temp.
Wertham I ..	F	45	8 y.		+	+						U., A.						4	E.	+			

ADOLESCENTS AND ADULTS—*continued.*

Reporter	Sex	Age	Duration of Illness	Headache—Vertigo—Vomiting	Incontinence	Disturbances of Swallowing	Psychical Disorders	Screaming	Disorders of Vision—Blindness	Deafness	Optic Neuritis or Atrophy—Choked Disc	Oculomotor Paresis	Paresis of VIth Nerve	Nystagmus	Pupil Reaction (Sluggish, Absent)—Unequal Pupils	Aphasia—Mutism—Anarthria—Scanning speech—Dysarthria	Chorea—Athetosis—Hemiballism	Ataxia	Intention Tremor	Tremor	Spastic Paresis and Contractures in 1, 2, 3, or 4 extremities—Pes equinovarus	Epileptic or Spastic Attacks	Knee- and Achilles-jerks—Clonus	Babinski-reflex	Abdominal-reflex (diminished or absent)	Globulin Reaction in Liquor	Special Symptoms and Remarks
Wertham II ..	M	18	11–12 y.	H.			+		+						A.				+	+R.		E.					
Stewart, Greenfield, and Blandy ..	F	43	9 d.	H., Vo.			+		B.		N.													+	A.		Hemianopia
Bodechtel and Guttmann ..	M	47	?				+									Ap.					4						
Benoit I	F	32	8 y.	Vo., H., Ve.			+				+				U., Sl.	Sc.											Remissions ?
Benoit II ..	F	26	10 m.	Vo.									+			Ap.					2, R.	S.		+R.	A.R.		Hemianopia R., cells increased, remissions, apoplexia
Benoit III ..	M	47	3¼ y.	H., Vo., Ve.			+					+		+	Sl.	D.				+L.					D.		Remissions, apoplexia
Russkich-Krylov	F	17	?				+																				
Gozzano-Vizioli ..	F	35	4 y.			+	+		B.		N., +					Sc.	Ch.	+		+			+	+	A.		Amyotrophy
Urechia-Mahalescu	F	33	3 y. *	Ve.			+					+			Sl., U.						2		+	+	A.	+	* Post-oper., cells increased
CHILDREN																											
Schilder	M	7	2 y.	H.	+		+		+		−	+			Sl.	Ap.			+		2, p.e.	+	Cl.	+	A.		
Schilder	F	14	4½ m.*	H., Vo.	+		+		+		Ch.		+	+		An., M.					1×			R+		+	* Post - operative. Wassermann +
Ceni	M	9	7 m.	H.	+				B.		+	+		+	A.	M., Sc.			+		2, p.e.		Cl.	+	D.		
Hermel	F	4	17 m.		+		+	+						+		M.					4		Cl.	+			
Krabbe	M	1	5 d.			+	+					+			Sl.							S.,E.		+			Alternately hyper-

Heubner	M	4½	1 y.	Vo.	+	+	+				N., A.					An.			+	+	4, p.e.		+		A.		
Siemerling and Creutzfeldt ..	M	7	2 m.			+	+									°					4, p.e.	+	Cl.	+	D.		* Monosyllabic
Schröder I ..	M	9	9 m.			+					+ [left]		+ [right]			D., M.	Ch.	+			4		+	+		+	* * Cells increased
Schröder II ..	M	11	1½ y.		+		+														3						
Neubürger ..	M	12	A few days		+										U., A.							E.		+			
Neubürger ..	F	4½	1½ y.					+	+		+				Sl.			+		+	4		Cl.	+			
Collier and Greenfield ..	M	7	9 m.			+	+	+	B.	+					Sl.	D., M.					2	E.	+	+			
Collier and Greenfield ..	F	5	15 m.		+	+	+	+	B.							M.		+			4			+			Opisthotonos
Scholz	M	8½	3 y.				+	+	+		A.	+	R		U.	D., M.					2	S.					Salivation
Scholz	M	7½	1½ y.		+	+	+	+	+	+						M.					2	E.					
Brock, Carroll, and Stevenson ..	M	9	16 m.			+	+	+	+	+		+		+		Ap.	Ch.	+	+		4, p.e.	S.		+	D.		Opisthotonos Elevation of temp.
Foix and Julien Marie	F	4½	10 y.		+		+		B.												4, p.e.	E.	+	+			
Stewart, Greenfield, and Blandy ..	F.	3	3½ m.	Vo.			+	+							U.					+	2	E.		+	A.	+	Cells increased
Stewart, Greenfield, and Blandy ..	M	8	1½ y.		+	+	+		B.	+	A.			+	A.									+			Hemiplegia L. Elevation of temp.
Schaltenbrand ..	F	14	3 m.	H., Vo.	+	+		+	+	B	Ch.		+	+	Sl., U.	Ap.	A.				4		Cl., L.	+			Elevation of temp. Pains, fossa iliaca dextra
Flatau	M	14	11 m.	Vo.	+		+	+	B.	+	A.				U., A.						2	+	+		D.		
Symonds	M	6	5 m.		+		+														2			+	A.		Sighing, elevation of temp.
Globus and Strauss	M	3½		Vo.				+			Ch.	+				M.					4	+					
Globus and Strauss	M	1	8 m.					+	B.		A.										4		+				
Globus and Strauss	F	9 m.	16 d.																		4						
Globus and Strauss	F	6½ m.	4 d.	Vo.																	4		−				
Gasul	M	8	3 m.	Vo.		+										Ap., M.					4		Cl.				
Bodechtel and Guttmann ..	M	8	4 m.			+	+					+			A.		Ch., H.				3	+		+		+	Opisthotonos

CHILDREN—*continued.*

Reporter	Sex	Age	Duration of Illness	Headache—Vertigo—Vomiting	Incontinence	Disturbances of Swallowing	Psychical Disorders	Screaming	Disorders of Vision—Blindness	Deafness	Optic Neuritis or Atrophy—Choked Disc	Oculomotor Paresis	Paresis of VIth Nerve	Nystagmus	Pupil Reaction (Sluggish, Absent)—Unequal Pupils	Aphasia—Mutism—Anarthria—Scanning speech—Dysarthria	Chorea—Athetosis—Hemiballism	Ataxia	Intention Tremor	Tremor	Spastic Paresis and Contractures in 1, 2, 3, or 4 extremities—Pes equinovarus	Epileptic or Spastic Attacks	Knee- and Achilles-jerks—Clonus	Babinski-reflex	Abdominal-reflex (diminished or absent)	Globulin Reaction in Liquor	Specia Symptoms and Remarks
Patrassi	M	10	10 m.	H., Ve.	+			+			A.,Ch.				Sl.						3			+			High-pressure liquor, elevation of temp.
Krabbe	M	5 m.	8 m.					+			A.											S.		+			Opisthotonos, remission
Krabbe	F	4 m.	5 m.	Vo.		+	+	+			A., R.																Opisthotonos, elevation of temp.
Gagel	M	9	15 m.			+	+	+			A.	+				D., M.	A.			+	4, p.e.			+	A.		Measles
Bielschowsky and Henneberg I ..	M	8	11 m.		+			+	B.	+	A.	+			A.	M.					2			+R.			
Bielschowsky and Henneberg II ..	M	10	2½ y				+	+		+	A.					Ap.	A. [arms]				2	E.	−L.	+	D.		
Shelden	M	7	6 m.	H., Vo.			+		B.	+		+			Sl.	M.							+R.		A.	+	
Ford and Bumstead	M	14	6 w.	H., Vo.		+	+	+			Ch.	+		+		D.					3		+	+			Chicken-pox
Ford and Bumstead	M	2	1 y.*				+					+	+			D.					4			+			* Post-oper., cells increased
v. Bogaert and Scholz I. ..	F	2⅝	3 y.			+										D.					4	+	Cl.				
v. Bogaert and Scholz II ..	F	2½			+	+															4	E.		+			Myo-acoustic reflexes
Leenhardt.. ..	F	7	3 y.				+				A.										3	E.					
Bouman V ..	M	3½	1½ y.				+	+								D., M.	H., A.	+		+		+		+			High-pressure, opisthotonos
Bouman VI ..	F	10	2 y.			+	+	+							Sl.	D.					3	+		+		+	Opisthotonos, colloid react. +
Macnamara	M	3																									

Kuts	M	1	4 y.				+										A.			2	+					Elevation of temp.
Bodechtel and Guttmann II ..	M	13					+													4	E.					
Bodechtel and Guttmann III ..		5	16 y.			+	+									M.			+	4, p.e.	E.		+R.			Measles
Bodechtel and Guttmann IV ..	M	6					+														E.					
Davison and Schick	F	13½	1½ y.	H.			+	+			A.				Sl.	D.	A.			3, p.e.	+	Cl. L.	+L.			
Lauritzen and Lundholm ..	M	6½					+	+		+					U.,Sl.	D.	A.			2	E.		+		+	Influenza, cells increased
Bullard-Southard	M	6					+	+			A.															Measles, trauma

BIBLIOGRAPHY

[1] Anton, G., and Wohlwill, F., "Multiple nichteitrige Enzephalomyelitis und multiple Sklerose", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1912, xii, 31.

[2] d'Antona, "La encephalitis periaxialis diffusa di Schilder", *Riv. di Patol. Nerv. e Ment.*, 1927, xxxii, 461.

[3] Austregesilo, Galloti, and Borges, "Leucoencéphalopathie diffuse", *Rev. neurol.*, 1930, i, 1.

[4] Baló, J., "Encephalitis periaxialis concentrica", *Arch. of Neurol. and Psychiat.*, 1928, xix, 242.

[5] Barré, Morin, Draganesco, and Reys, "Encéphalite périaxiale diffuse (type Schilder)", *Rev. neurol.*, 1926, ii, 541.

[6] Barré, J. A., and Bogaert, L. v., "Contribution à la Dissociation anatomique et clinique des Leuco-encéphalites subaiguës. La Type concentrique de Baló", *Ibid.*, 1933, i, 547.

[7] Benders, A. M., "Das Wesen der anormalen Anlage bei den endogenen organischen Nervenkrankheiten", *Psychiat. en neurol. bladen*, 1916, xx, 337.

[8] Beneke, "Ein Fall hochgradigster und ausgedehnter diffuser Sklerose des Zentralnervensystems", *Arch. f. Kinderheilk.*, 1908, xlvii, 420.

[9] Benoit, "Zur Frage der diffusen Sklerose", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1932, cxl, 517.

[10] Bielschowsky, F., "Die Bedeutung des Infektes für die diffuse Sklerose", *Jour. f. Psychol. u. Neurol.*, 1927, xxxiii, 12.

[11] Bielschowsky, M., and Gallus, "Ueber tuberöse Sklerose", *Ibid.*, 1913, xx, Erg. H. i, 1.

[12] Bielschowsky, M., and Henneberg, R., "Ueber familiäre diffuse Sklerose (Leukodystrophia cerebri progressiva hereditaria)", *Ibid.*, 1928, xxxvi, 131.

[13] Bielschowsky, M., and Maas, O., "Ueber diffuse und multiple Sklerose", *Ibid.*, 1932, xliv, 138.

[14] Bodechtel, G., "Zur Frage der Pelizaeus-Merzbacherschen Krankheit", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1929, cxxi, 487.

[15] Bodechtel, G., and Guttmann, E., "Diffuse Encephaiitis mit sklerosierender Entzündung des Hemisphärenmarkes", *Ibid.*, 1931, cxxxiii, 601.

[16] Bodechtel, G., and Guttmann, E., "Zur Pathologie und Klinik diffuser Markerkrankungen", *Ibid.*, 1932, cxxxviii, 544.

[17] Bogaert, L. v., "Erreur de Diagnostic: Neuromyélite optique aiguë, premier Stade d'une Sclérose en Plaques typique", *Jour. de Neurol. et de Psychiat.*, 1932, xxxii, 234.

[18] Bogaert, L. v., and Scholz, W., "Klinischer, genealogischer und pathologisch-anatomischer Beitrag zur Kenntnis der familiären diffusen Sklerose", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1932, cxli, 510.

[19] Bostroem, A., "Ueber die Pelizaeus-Merzbacher'sche Krankheit", *Deut. Zeits f. Nervenheilk.*, 1927, c, 63.

[20] Bouman, L., "Hirnveränderungen bei Tetanus", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1920, lviii, 301.

[21] Bouman, L., "Encephalitis periaxialis diffusa", *Brain*, 1924, xlvii, 453.

[22] Bouman, L., "Diffuse sclerose bij kinderen", *Nederl. Tijds. v. Geneesk.*, 1933, lxxvii, 491.

[23] Braun, E., "Ueber einen Fall von diffuser Encephalo-Myelitis", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1923, lxxx, 310.

[24] Brock, Carroll, and Stevenson, "Encephalitis periaxialis diffusa of Schilder", *Arch. of Neur. and Psychiat.*, 1926, xv, 297.

[25] Bullard, W. N., "Diffuse cortical Sclerosis of the Brain in Children", *Jour. Nerv. and Ment. Dis.*, 1890, xv, 699.
[26] Bullard and Southard, "Diffuse Gliosis of the Central White Matter", *Ibid.*, 1906, xxxiii, 188.
[27] Casper, "Zur Pathologie der diffusen Sklerose", *Frankf. Zeits. f. Pathol.*, 1932, xliii, 69.
[28] Cassirer, R., and Lewy, F. H., "Die Formen der Glioblastose und ihre Stellung zur diffusen Hirnsklerose", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1923, lxxxi, 290.
[29] Ceni, "Ueber einen interessanten Fall gliomatöser Infiltration bei der Grosshirnhemisphären", *Arch. f. Psychiat.*, 1899, xxxi, 809.
[30] Claude, H., and Lhermitte, J., "Leucoencéphalite subaiguë à Foyers successifs", *L'Encéphale*, 1920, xv, 89.
[31] Coenen, L., and Mir, L., "Encéphalite périaxiale diffuse. Maladie de Schilder-Foix", *Ibid.*, 1931, xxvi, 357.
[32] Collier and Greenfield, "The Encephalitis Periaxialis of Schilder", *Brain*, 1924, xlvii, 489.
[33] Cramer, A., "Beginnende multiple Sklerose und acute Myelitis", *Arch. f. Psychiat.*, 1888, xix, 667.
[34] Curtius, F., "Familiäre diffuse Sklerose und familiäre spastische Spinalparalyse in einer Sippe", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1930, cxxvi, 209.
[35] Davison and Schick, "Encephalopathia Periaxialis Diffusa", *Arch. of Neurol. and Psychiat.*, 1931, xxv, 1063.
[36] Erler, "Ueber diffuse Sklerose des Gehirns", Inaug.-Diss., Tübingen, 1881.
[37] Falkiewicz, "Zur Frage der multiplen Sklerose", *Arbeiten a. d. Neurol. Institut in Wien*, 1926, xxviii, 172.
[38] Ferraro, A., "Familiar Form of Encephalitis Periaxialis Diffusa", *Jour. Nerv. and Ment. Dis.*, 1927, lxvi, 329.
[39] Flatau, "Encephalopathia scleroticans progressiva", *L'Encéphale*, 1925, xx, 475.
[40] Foix, Ch., and Marie, J., "La Sclérose cérébrale centro-lobaire", *Ibid.*, 1927, xxii, 81.
[41] Ford and Bumstead, "Encephalitis Periaxialis Diffusa of Schilder", *Bull. Johns Hopkins Hosp.*, 1929, xliv, 443.
[42] Frankl-Hochwart, L. von, "Zur Kenntnis der Pseudo-sklerose", *Arbeiten a. d. Neurol. Institut in Wien*, 1903, x, 1.
[43] Friedmann, R., and Scheinker, J., "Ueber eine familiäre Heredo-Degeneration vom Typus der Pelizaeus-Merzbacherschen Krankheit", *Deut. Zeits. f. Nervenheilk.*, 1932, cxxvii, 62.
[44] Gagel, "Zur Frage der diffusen Hirnsklerose", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1927, cix, 418.
[45] Gans, "Diffuse sclerose", *Nederl. Tijds. v. Geneesk.*, 1923, lxvii, 1043.
[46] Gasul, "Schilder's Disease", *Amer. Jour. Dis. Child.*, 1930, xxxix, 595.
[47] Gerstmann and Sträussler, "Zum Problemgebiet der Encephalomyelitis und der multiplen Sklerose", *Arch. f. Psychiat.*, 1931, xciii, 182.
[48] Globus, J. H., "Ein Beitrag zur Histopathologie der amaurotischen Idiotie", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1923, lxxxv, 424.
[49] Globus and Strauss, "Progressive Degenerative Subcortical Encephalopathy", *Arch. of Neurol. and Psychiat.*, 1928, xx, 1190.
[50] Gozzano, M., and Vizioli, F., "La Encefalopatia periassiale diffusa di Schilder ed i suvi Rapporti con la Sclerosi a Placche", *Riv. di Neurol.*, 1932, v, 3.
[51] Guillain, "Rapport sur la Sclérose en Plaques", *Rev. Neurol.* 1924, xxxi, 648.
[52] Guttmann, E., "Zur Kasuistik der 'sklerosierenden Encephalitis'", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1925, xciv, 62.
[53] Guttmann, E., "Die diffuse Sklerose", *Zentralb. f. d. g. Neurol. u. Psychiat.*, 1925, xli, 1.
[54] Haberfeld and Spieler, "Zur diffusen Hirn-Rückenmarkssklerose im Kindesalter", *Deut. Zeits. f. Nervenheilk.*, 1910, xl, 436.

[55] HALLERVORDEN, J., "Eigenartige und nicht rubrizierbare Prozesse", *Bumke's Handbuch der Geisteskrankheiten*, 1930, xi, 305.

[56] HALLERVORDEN, J., and SPATZ, H., "Ueber die konzentrische Sklerose und die physikalisch-chemischen Faktoren bei der Ausbreitung von Entmarkungsprozessen", *Arch. f. Psychiat.*, 1933, xcviii, 641.

[57] HENNEBERG, "Ueber disseminierte Enzephalitis", *Neurol. Centralb.*, 1916, xxxv, 652, 984.

[58] HERMEL, "Ueber einen Fall von Encephalo-myelomalacia chronica diffusa bei einem vierjährigen Kinde", *Deut. Zeits. f. Nervenheilk.*, 1921, lxviii–lxix, 338.

[59] HEUBNER, "Ueber diffuse Hirnsklerose", *Charité-Ann.*, 1897, xxii, 298.

[60] HOEVE, J. v. D. "Augengeschwülste bei der tuberösen Hirnsklerose (Bourneville) und verwandten Krankheiten", *Arch. f. Ophthalmol.*, 1923, cxi.

[61] HORSLEY, V., *On the Topographical Relations of the Cranium and Surface of the Cerebrum*, 1892. Dublin.

[62] IBRAHIM, *Handbuch Pfaundler und Schlossmann*, 4th ed., iv, 295, 348.

[63] JAKOB, A., "Zur Pathologie der diffusen infiltrativen Encephalomyelitis in ihren Beziehungen zur diffusen und multiplen Sklerose", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1915, xxvii, 290.

[64] KALTENBACH, H., "Ueber einen eigenartigen Markprozess mit metachromatischen Abbauprodukten bei einem paralyse-ähnlichen Krankheitsbild", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1922, lxxv, 138.

[65] KELP, *Arch. f. klin. Med.*, 1872, x, 224.

[66] KLARFELD, B., "Einige allgemeine Betrachtungen zur Histopathologie des Zentralnervensystems", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1922, lxxvii, 80.

[67] KLARFELD, B., "Zur Frage der subakut verlaufenden diffusen Erkrankungen des Hemisphärenmarkes", *Allg. Zeits. f. Psychiat.*, 1923, lxxix, 294.

[68] KOGERER, H., "Beitrag zur Kenntniss der Encephalitis periaxialis diffusa", *Jahrb. f. Psychiat. u. Neurol.*, 1927, xlv, 109.

[69] KRABBE, "Beitrag zur Kenntnis der Frühstadien der diffusen Hirnsklerose", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1913, xx, 108.

[70] KRABBE, "A New Familial Infantile Form of Diffuse Brain-sclerosis", *Brain*, 1916, xxxix, 74.

[71] KRAEPELIN, E., "Tuberöse Sklerose", *Klin. Psychiatrie*, 9th ed., 1927, ii, 242.

[72] KRAUS, W. M., and WEIL, A., "Encéphalite périaxiale diffuse (Type Schilder)", *L'Encéphale*, 1928, xxiii, 775.

[73] KRAUS, W. M., and WEIL, A., "An Unusual and Protracted Case of Schilder's Disease", *Jour. Nerv. and Ment. Dis.*, 1925, lxii, 620.

[74] KUFS, H., "Ein bemerkenswerter Uebergangsfall von diffuser zu multipler Hirnsklerose", *Arch. f. Psychiat.*, 1931, xciii, 564.

[75] LAURITZEN and LUNDHOLM, "Schilder's Disease", *Arch. of Neurol. and Psychiat.*, 1931, xxv, 1233.

[76] LEENHARDT and CHAPTAL, "Triplégie spastique . . . Encéphalite périaxiale diffuse", *Gaz. méd. de France*, 1929, iii, 195.

[77] LONDEN, D. M. v., and FRETS, G. P., "Encephalitis periaxialis diffusa Schilder", *Psychiat. en neurol. bladen*, 1926, xxx, 235.

[78] LÜTHY, F., "Ueber einige anatomisch bemerkenswerte Fälle von multipler Sklerose, mit besondere Berücksichtigung der Grosshirnrinde und des Kleinhirns", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1930, cxxx, 219.

[79] MACNAMARA, "Encephalitis Periaxialis Diffusa of Schilder", *Proc. Roy. Soc. Med.*, 1928, xxii, 174.

[80] MARBURG, O., "Multiple Sklerose", Lewandowsky, *Handbuch der Neurologie*, 1911, ii, 911.

[81] MARBURG, O., "Allgemeine Pathologie der nichteitrigen Entzündungen des Zentralnervensystems", *Arbeiten a. d. Neurol. Institut in Wien*, 1932, xxxiv, 1.

[82] Marie and Foix, "Sclérose intracérébrale centrolobaire et symétrique", *Rev. neurol.*, 1914, xxvii, 1.
[83] Marinesco, Draganesco, Sager, and Grigoresco, "Sur une Forme particulière anatomo-clinique d'Ophthalmo-neuromyélite", *Ibid.*, 1930, ii, 193.
[84] Matzdorff, P., "Beiträge zur Frage der diffusen Glioblastose und der diffusen Sklerose des Zentralnervensystems", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1924, xci, 489.
[85] Neubürger, K., "Histologisches zur Frage der diffusen Hirnsklerose", *Ibid.*, 1921, lxxiii, 336.
[86] Neubürger, K., "Ueber die sogennante diffuse Gliaverfettung im Grosshirnmark bei Kindern", *Ibid.*, 1925, xcvii, 598.
[87] Ombredane, A., *Les Troubles mentaux de la Sclérose en Plaques*, 1929. Paris.
[88] Ostertag, B., "Entwicklungsstörungen des Gehirns und zur Histologie und Pathogenese, besonders der degenerativen Markerkrankung bei amaurotische Idiotie", *Arch. f. Psychiat.*, 1925, lxxv, 355.
[89] Patrassi, "Diffuse Gehirnentmarkungen und sogenannte Encephalitis periaxialis diffusa (Schilder)", *Virchow's Arch.*, 1931, cclxxxi, 98.
[90] Pette, H., "Ueber die Pathogenese der multiplen Sklerose", *Deut. Zeits. f. Nervenheilk.*, 1928, cv, 76.
[91] Redlich, E., "Demonstration eines Hirntumors mit regressiven Erscheinungen", *Wien. klin. Woch.*, 1913, xxvi, 82.
[92] Rochon-Duvignaud, Jumentié, and Vialeix, "Cécité à Marche rapide avec Stase papillaire modérée, . . . " *Rev. neurol.*, 1923, ii, 73.
[93] Rossolimo, G., "Zur Frage über die multiple Sklerose und Gliose", *Deut. Zeits. f. Nervenheilk.*, 1897, xi, 88.
[94] Russkich, V., and Krylov, E., "Encephalitis periaxialis diffusa (Schilder)", Ref. *Zentralb. f. d. g. Neurol. u. Psychiat.*, 1931, lix, 792.
[95] Sachs, E., *The Diagnosis and Treatment of Brain Tumors*, 1931. St. Louis.
[96] Schaltenbrand, G., "Encephalitis Periaxialis Diffusa (Schilder)", *Arch. of Neurol. and Psychiat.*, 1927, xviii, 944.
[97] Schaltenbrand, G., "Enthirnungsstarre zugleich ein Beitrag zur Theorie der proprioceptiven Lage- und Bewegungsreaktionen", *Deut. Zeits. f. Nervenheilk.*, 1927, c, 165.
[98] Schilder, P., "Zur Kenntnis der sogenannten diffusen Sklerose", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1912, x, 1.
[99] Schilder, P., "Zur Frage der Encephalitis periaxialis diffusa (sogennante diffuse Sklerose)", *Ibid.*, 1913, xv, 359.
[100] Schilder, P., "Die Encephalitis periaxialis diffusa", *Arch. f. Psychiat.*, 1924, lxxi, 327.
[101] Schmaus, "Zur Kenntnis der diffusen Hirnsklerose", *Virchow's Arch.*, 1888, cxiv, 1521.
[102] Scholz, "Klinische, pathologisch-anatomische und erbbiologische Untersuchungen bei familiärer diffuser Hirnsklerose im Kindesalter", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1925, xcix, 651.
[103] Schröder, *Neurol. Centralb.*, 1912, xxxi, 1048; 1914, xxxiii, 986.
[104] Schröder, P., "Encephalitis und Myelitis. Zur Histologie der kleinzelligen Infiltration im Nervensystem", *Monats. f. Psychiat. u. Neurol.*, 1918, xliii, 146.
[105] Schwartz, Ph., "Erkrankungen des Zentralnervensystems nach traumatischen Geburtsschädigung", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1924, xc, 263.
[106] Shelden, Doyle, and Kernohan, "Encephalitis Periaxialis Diffusa", *Arch. of Neurol. and Psychiat.*, 1929, xxi, 1270.
[107] Siemerling and Creutzfeldt, "Bronzekrankheit und sklerosierende Encephalomyelitis", *Arch. f. Psychiat.*, 1923, lxviii, 217.
[108] Sillevis Smitt, W. G., and Smit, W., "Ueber eine familiäre, der multiplen Sklerose ähnliche Erkrankung", *Nervenarzt*, 1933, vi, 173.
[109] Spatz, H., "Enzephalitis", *Bumke's Handbuch der Geisteskrankheiten*, 1930, xi, 157.

[110] SPIELMEYER, W., "Ueber einige anatomische Aehnlichkeiten zwischen progressiver Paralyse und multipler Sklerose", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1910, i, 660.
[111] SPIELMEYER, W., *Histopathologie des Nervensystems*, 1922. Berlin.
[112] STAUFFENBERG, v., "Ein Fall von Encephalitis periaxialis diffusa (Schilder)", *Zeits. f. d. g. Neurol. u. Psychiat.*, 1918, xxxix, 56.
[113] STEINER, G., "Diffuse Sklerose", *Bumke's Handbuch der Geisteskrankheiten*, 1930, xi, 305.
[114] STEWART, T. GRAINGER, GREENFIELD, and BLANDY, "Encephalitis Periaxialis Diffusa", *Brain*, 1927, l, 1.
[115] STEWART, J. PURVES, *The Diagnosis of Nervous Diseases*, 1920, 5th ed. London.
[116] STEWART, J. PURVES, *Intracranial Tumours and some Errors in their Diagnosis*, 1927. London.
[117] STRÜMPELL, "Ueber diffuse Hirnsklerose", *Arch. f. Psychiat.*, 1879, ix, 268.
[118] SYMONDS, "A Case of Schilder's Encephalitis with a Family History of the Disease", *Brain*, 1927, l, 256.
[119] SYMONDS, "A Contribution to the Clinical Study of Schilder's Encephalitis", *Ibid.*, 1928, li, 24.
[120] TENDELOO, N. PH., *Allgemeine Pathologie*, 1919. Berlin.
[121] URECHIA, MIHALESCU, and ELEKES, "L'Encéphalite périaxiale diffuse Type Schilder", *L'Encéphale*, 1924, xix, 617.
[122] VRIES, E. DE, "Cerebrale kinderverlamming". *Bouman-Brouwer Leerboek der Zenuwziekten Spec. Leer A.*, 1924, 449.
[123] WALTER, F. K., "Zur Symptomatologie und Anatomie der 'diffusen Hirnsklerose'", *Monats. f. Psychiat. u. Neurol.*, 1918, xliv, 87.
[124] WALTHARD, K., "Spätstadium einer Enzephalitis nach Masern", *Zeits. f. d. g. Neur. u. Psychiat.*, 1930, cxxiv, 176.
[125] WEIMANN, W., "Zur Kenntnis der sogenannten 'diffusen Hirnsklerose'", *Ibid.*, 1926, civ, 411.
[126] WEISS, "Ueber diffuse Sklerose des Hirns und Rückenmarks", *Arbeiten a. d. Neurol. Institut in Wien*, 1900, vii, 245.
[127] WERTHAM, F., "Small Foci of Demyelinization in the Cortex and Spinal Cord in Diffuse Sclerosis", *Arch. of Neurol. and Psychiat.*, 1932, xxvii, 1380.

3845.34 PRINTED IN GREAT BRITAIN BY JOHN WRIGHT AND SONS LTD., BRISTOL