A NEW FAMILIAL, INFANTILE FORM OF DIFFUSE BRAIN-SCLEROSIS.

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IN a previous paper [12], three years ago, I described a case of a peculiar affection in the brain of a child. This case I regarded as an early stage of the disease named "diffuse sclerosis of the brain," and in consequence of the characteristic histological findings I called this preliminary stage "perivascular necrosis of the medullary substance."

In the case in question the patient was but 1 year old, and it struck me that few cases in earliest infancy were to be found in international literature. Soon afterwards, however, I had an opportunity of seeing such a patient demonstrated, and after the death of the patient I was permitted to perform an autopsy and make a microscopic examination of the central nervous system.

The chief peculiarity of this case was its familial occurrence, which, at any rate from a pathogenetic point of view, rendered it different from all other cases described as infantile diffuse sclerosis. Further examination now showed that besides this case four other similar cases had been observed at the Dronning Louise's Boernehospital (Queen Louise's Hospital for Sick Children) and in the private practice of Professor Bloch—viz., the sister of the above-mentioned patient, two members of another family, and an isolated case. Two of these five patients have been demonstrated by Professor Monrad in the Pediatric Society of Copenhagen. Specimens from one of them, moreover, were demonstrated by Dr. V. Poulsen in the Section for Morbid Anatomy of the Biological Society. The third case had been briefly mentioned in the Pediatric Society by Dr. Joergen Bech and Dr. Monrad, and the two last cases during a discussion in the Pediatric Society by Dr. Bloch.

A thorough comparative and detailed report of these cases does not, however, exist, and the present paper may therefore be of some interest.

In the following paper infantile sclerosis of the brain alone will be

discussed, as, according to my view, the disease in children is somewhat different from that in adults.

I have much pleasure in recording my indebtedness to Professor Bloch and Professor Monrad for kindly permitting me to publish these cases. I am also indebted to Dr. V. Poulsen, who meant to publish the clinical history of two of the cases, but kindly left them at my disposal. Furthermore, I wish to thank Dr. K. Malling, who had prepared specimens from one of the patients, but generously handed the case over to me; and Professor Friedenreich, who permitted me to work out one of the cases at the Psychiatrical Laboratory of the University (the main part of my investigation was carried out at the laboratory of the Children's Department of Rigshospitalet).

Case 1.—Kai Bn., son of a confidential clerk, born on November 25, 1912, died at thirteen months old. He was the second of a family of two; an elder sister suffered from the same disease, and is described below (Case 2). The father in his youth is said to have had hæmoptysis, the mother had always been healthy. Syphilis was denied. The patient was born normally at full time, the weight being at birth 3¾ kg. Up to the age of five months he developed fairly normally, was quick and gay, able to move his limbs freely. During the first four months he was suckled, but after that time was given milk-soup with bread and milk. When five months old he began to cry frequently and convulsively. At the same time fits of stiffness of all extremities appeared, with obstetrical posture of the hands and crossing of the legs. In the intervals between the attacks the patient was very weak and not able to sit up. The temperature was occasionally 38·2° C. in the afternoon, but generally normal. The stools were mostly normal, and, except during the first months, there was neither regurgitation nor vomiting.

On July 7, 1913, the patient was admitted to the Queen Louise's Hospital for Sick Children, where physical examination gave the following result: Weight, 7,050 grm.; length, 62½ cm.; circumference of the head, 43½ cm.; circumference of the chest, 42 cm.; greatest circumference of the abdomen, 37 cm.; fontanelle, 3 cm. by 3 cm., normal tension; teeth, 0; temperature, 37·3° C.; urine acid, turbid with urates, no pus nor albumen. The child was well nourished, sunburnt, normal appearance. Pupils large and active to light. No nystagmus. External examination of the eyes, ears and fauces showed no abnormalities; ophthalmoscopic examination showed greyish discs with veiled outlines (early optic atrophy). The patient followed things with his eyes. Slight universal micro-adenitis Stethoscopic examination and examination of the abdomen showed no abnormality. No signs of rickets. Intense sweating. Violent crying and gasping during the examination. Body and limbs stiffly extended, head turned backwards, back crooked, hands often clenched, sometimes in tetanic posture; lower extremities strongly extended and adducted, toes spread (figs. 1 and 2). The examination of reflexes was difficult,

but Babinski's sign was present. During the examination attacks of convulsion occurred, which made the lower extremities still more stiff, head and back were drawn more backwards, arms moved up and down in clonic spasms. The fits were accompanied by convulsive crying and gasping. The attacks appeared without any obvious cause.

The course of the illness during the six months' residence was as follows: The Wassermann test on July 13 was negative; v. Pirquet negative. Lumbar puncture on November 10 showed about 3 c.cm. slightly turbid fluid, containing

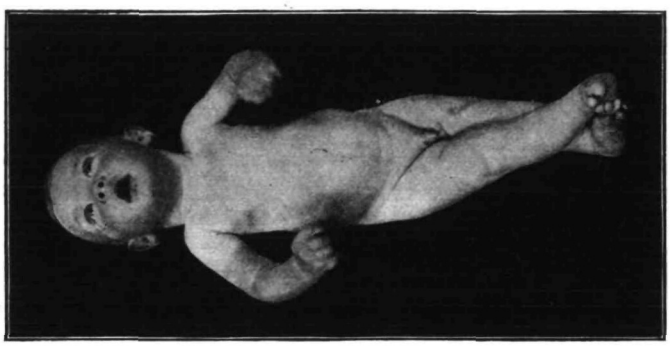

FIG. 1.—Case 1, Kai Bn.

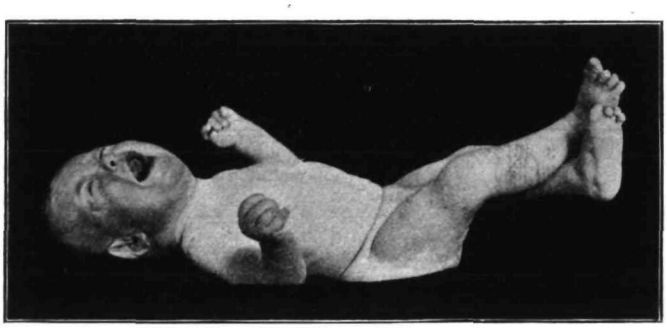

FIG. 2.—Case 1, Kai Bn.

a few endothelial cells but no other cells and no micro-organisms; there was no growth on agar, serum, bouillon, or ascites agar. The stools were nearly always normal even during the febrile periods. From July 23 to July 28 only were they found to contain some mucus, and on November 28 (during a period of fever) they were watery. There were, as a rule, one to three stools a day. Regurgitation occurred now and then, but no vomiting. The urine never contained sugar nor albumen, whereas on November 6 and the ensuing days

some pus was observed. When examined under the microscope (November 13) the urine was found to contain numerous leucocytes, a number of epithelial cells, and *Bacillu coli*, but no cylindrical cells or red blood corpuscles. The weight (on admission 7,050 grm.) increased during the first days some 100 grm., after which, during the following days, it dropped down to 6,300 grm. It then oscillated periodically between 6,200 and 6,800 grm., until it fell rather abruptly to 5,700 grm. The loss of weight, as a rule, appeared coincident with the febrile periods. The patient was fed at first on milk-soup and water (equal mixture), then pure milk-soup.

August 1: Patient sometimes dull, sometimes crying, falls into spasms at the faintest noise. Sleeps well at night; bathing appears to have a calming effect. He is able to follow movements with his eyes. No nystagmus. The stiffness of body and limbs unchanged.

August 25: Has gained in weight. Has been somewhat more quiet during the last days, but lies constantly in a spastic state; frequent exacerbations occur, in which his hands are clenched violently, arms moved to and fro, head drawn backward, and back crooked in arc de cercle, lower extremities extended, a slight indication of tetanic posture of the feet, no real nystagmus. The fits seem to cause pain, and are hardly followed by unconsciousness. In the upper extremities the reflexes are easily obtained, but ankle-jerks were not brisk. The knee-jerks were not obtained. Plantar reflexes normal.

December 1: Condition has grown worse, more difficulty in swallowing, and increased dulness.

December 29: Some cyanosis of the face since yesterday. No convulsions. Died at 12.30 p.m.

Dr. V. Poulsen, who saw the patient daily, characterized the case in the following way: An intense stiffness of all the extremities was observed during nearly all the time of residence in hospital. When examined, or when loud speaking took place in the room, he at once fell into tonic spasms. The dulness, however, did not appear until the last days, when he grew more debilitated, and the spasms were then excited only by stronger irritation. At the same time the eclamptic fits began, during which universal clonic and tonic convulsions appeared, combined with marked cyanosis.

It may be added that the elevations of temperature, before mentioned, were never followed by cough, dyspnœa, or other signs of pneumonia.

The clinical diagnosis was: sclerosis cerebri diffusa.

Post-mortem examination ten hours after death gave the following result: The body was that of a moderately nourished child; *rigor mortis* present. In both lungs extensive red, infiltrated, partly confluent portions of a typical pneumonic appearance. The mucous membrane of the bronchi hyperæmic. No signs of tuberculosis. Heart, stomach, intestines, liver, kidneys, spleen, pancreas, thyroid gland, and suprarenal bodies showed no abnormality. On opening the skull, theca and dura were found to be normal. From the subdural and subarachnoidal cavities a considerable amount of clear cerebrospinal fluid was evacuated. The brain occupied less room in the thecal cavity than is the

case with normal brains; its weight was 650 grm. Pia œdematous, not thickened nor of milky consistence. The ventricles of the brain were not distinctly dilated; no granulation of the ependyma. The consistence of the brain, cerebellum and spinal cord was found to be increased, so that the brain did not show any tendency to flow out after removal, as is generally the case with children's brains of that age, but kept its form, with medulla oblongata protruding into the air. The increase of consistence was most pronounced in the cerebellum and medulla. On the cut surface the cortex appeared to be soft without any abnormality, the medullary substance was harder and, especially in the most central parts, greyish-red, but whitish in the thin subcortical layers.

Blocks were immediately taken for microscopical examination, hardened in 96 per cent. alcohol, Müller's fluid, Weigert's stain for neuroglia, and 10 per cent. formaldehyde respectively. Some of the pieces hardened in formaldehyde were later on prepared in Flemming's fluid. The rest of the brain was kept in 4 per cent. formaldehyde and after some months large slices (transverse sections) were transferred into Weigert's brown chromic acid stain. The following methods of staining were carried out: Nissl's thionin staining, Weigert-Kulschitzsky-Wolters method, and Spielmeyer's method of staining for medullary sheaths, Marchi's staining, Bielschowsky's staining, staining of the fat with Sudan red, Alzheimer's method of staining for neuroglia with Mallory's hematoxylin, and Alzheimer's acid-fuchsin—vert-lumière staining. The last method especially gave fine glia pictures. As in my previous work on sclerosis of the brain, I have here embedded in paraffin at low temperatures.

Microscopic examination gave the following result:—

The hemispheres of the cerebrum.—The pictures of the medullary sheaths (stained by Weigert-Pal) show to the naked eye an enormous destruction, so that the white matter is found to be almost as pale as the cortex (fig. 3). Immediately under the cortex only a narrow streak (1 cm. to 2 cm. in width) of darker stained tissue is visible. Under the microscope, however, the destruction appears to be not quite total: a scanty number of medullated nerve-fibres are found crossing in all directions. The destruction of the medullary sheaths in the white matter is not quite evenly distributed, and a thin layer of much less destroyed tissue is found in the peripheral regions. In addition, the central part of the white matter contains small scattered islets of totally destroyed tissue, while the surrounding plexus is relatively less destroyed. On the whole, the destruction increases towards the centre. The areas around the smallest vessels are, as a rule, not specially affected by the destruction, while the bigger ones are surrounded by a thick border of totally destroyed sheaths. In the cortex, on the other hand, slight wasting only of the medullated fibres is traceable; both tangential

fibres and supra- and inter-radial fibres are present, although somewhat more scanty than usual.

In large sections (fig. 3) of the brain stained by the method of Kulschitzsky-Wolters and Pal the process was found to be uniform throughout the whole cerebrum, and no normal white matter was left except the thin subcortical layer, which was everywhere preserved. In Marchi specimens only a very small number of blackened granules are found in the white matter and in the cortical substance. In the big cells which surround the vessels and fill up the vessel sheaths only small collections of cells are occasionally observed, the granules of which are blackened with the osmic acid.

FIG. 3.—Section from the occipital lobe of the brain of Case 1, Kai Bn. Staining of Weigert-Pal. The black line between the cortex and the medullary substance represents the only remains of the white substance, the lighter part inside this line is medullary substance, who is replaced by neuroglia and therefore uncoloured.

Bielschowsky specimens show an immense destruction of the axis cylinders corresponding with that of the medullary sheaths, so that only a small number are found to radiate widely, and even these are to some extent in granular decay. In the cortex, however, the nerve-cell processes seem to be quite as numerous as in a normal brain, although some of them are in granular decay and irregularly thickened, possibly due to *post-mortem* changes. Cajal's corpuscles cannot be observed.

The specimens stained for neuroglial changes clearly illustrate the positive corresponding with the negative findings of the medullary sheaths. In specimens stained with acid-fuchsin—vert-lumière (figs. 12 and 13, pp. 104, 105) a red substance is visible to the naked eye, corresponding with the white matter. When examined under the microscope this substance is found to consist of glia-fibres, the number and density of which are fairly uniform throughout the whole field of view. In a thin layer surrounding some of the largest vessels, the glia-fibres, however,

seem most closely packed together, taking here the same longitudinal direction as the vessels. Among the glia-fibres cells of very different shape and size are traceable. Some of them are small and mononuclear, containing but a very thin protoplasmic layer. In other cells the protoplasm is of almost gigantic dimensions, forming a roundish or irregular outline, sometimes homogeneous, sometimes slightly granular, with big vacuoles or recesses. Between these cells and the smaller ones transitional forms are found, mostly irregular or lobed in outline. The contents of chromatin of the nuclei varies greatly: the bigger the cell, the more scanty the chromatin. The nuclei generally contain one or two nucleoli, and as a rule are arranged excentrically. It is not, however, evident from these glia pictures whether or not the cells are sending out processes, while in specimens stained by Alzheimer-Mallory's method (fig. 16, p. 107) cell processes enclosing the glia-fibres are distinctly visible. On the other hand, the typical amœbic glia-cells are here extraordinarily few in number. The distribution of cells is fairly uniform throughout the glia substance; in the outer subcortical layer perhaps the number may be somewhat smaller than in the central regions round the vessels, where the bigger glia-cells are replaced by cells which fill up the adventitia sheaths of the blood-vessels (fig. 13). A great number of these cells have a large round protoplasm, similar to that of the bigger glia-cells; they are, however, more degenerated and contain pale homogeneous nuclei and nucleoli which have entered the protoplasm, and finally oblong cells which seem to fit into the shape of the vessel sheaths. Granules stained by osmic acid are, however, of very rare occurrence in these cells. On comparing these specimens with those stained with Sudan red only a very small number of them will be found to contain fatty granules. This is quite in keeping with the pictures of the medullary sheaths, where only very few bluish-black granules are found in the cells. It may be added that the vessel sheaths only contain these "empty fatty granule-cells" and "scavenger cells" (Alzheimer's Abräumzellen), and nowhere any sort of inflammatory cells —in fact, neither plasma-cells lymphocytes, nor polymorphonuclear leucocytes.

In the cortex the condition is quite different to that of the white matter. The outer glia is hardly thickened, and only occasionally in the cortex itself a single thread-forming glia-cell (*see* fig. 14, p. 105) may be observed. The vessel sheaths nowhere contain scavenger or other cells. The boundary between cortex and the white matter stands out rather distinctly in the glia pictures macroscopically. On microscopic examina-

tion, however, a transitional region is observed in which the number of glia-fibres and cells is seen to decrease towards the cortex. This region apparently corresponds with the thin layer of preserved medullary sheaths. In specimens stained by Nissl's method, protoplasmic glia is found corresponding with the white matter, and scavenger cells similar to those mentioned above. More distinctly than in the real glia pictures, these specimens present small, intensely stained corpuscles resembling the calcareous concretions of the meninges and pineal gland arranged round the blood-vessels. The nerve-cells of the cortex apparently show no abnormality; the condition of the Nissl granules cannot be made out definitely, as the *post-mortem* examination was not carried out till ten hours after death; at any rate, no important Nissl changes can be seen. The appearance of the nuclei is normal, there is no pycnoid change of the protoplasm, and no abnormal number of big cells. On the whole, no destruction of the nerve-cells can be seen.

In some places the pia appears to be somewhat thickened and rich in cells, but is nowhere infiltrated. The vessels of the cortex are normal, whereas those of the white matter at the first glance look pathologically changed. When examined more closely, the intima and media, however, appear to be normal, and the changed appearance of adventitia is due to the great number of scavenger cells.

The mid-brain shows on the whole the same changes. The destruction of the medullary sheaths, however, does not seem quite as extreme as that of the hemispheres, and apparently diminishes towards the pons. Marchi degeneration cannot be seen, and fatty granules are only rarely visible. The destruction of the axis-cylinders of the white matter seem to be parallel with that of the sheaths. The nerve-cells of the great ganglionic centres present a similar appearance to those of the cortex. In the nuclei of the cranial nerves the Nissl pictures show unchanged nerve-cells; distinct Nissl granules are seen, and there are no acute changes. A glial increase is seen in the mid-brain similar to that of the hemispheres, although somewhat less sharply limited, and similar glia-cells and scavenger cells are traceable. Furthermore, pathological changes are seen similar to those found in gliomata (*see* fig. 15, p. 106), gigantic cells with a large, irregularly outlined protoplasm and several nuclei placed peripherally or embedded in niches. In addition to these, a number of smaller cells with degenerated nuclei and thick protoplasmic processes are found. Among these cells a multitude of processes are seen crossing each other obliquely, or in some places showing a parallel course. Among these thicker fibres, ordinary thin glia-fibres

are noted, and finally in addition transitional stages. The giant-cells, which at the first glance had some resemblance to degenerated nerve-cells, are pathological forms of glia-cells if anything, as some of the processes are found to contain glia-fibres.

Cerebellum.—In specimens showing the medullary sheaths a still greater destruction is to be seen, which does not decrease in the most peripheral part of the white matter. In the grey matter also destructive processes are observed, proportionately less marked in the stratum granulosum. Marchi degeneration is nowhere traceable. The axis-cylinders are somewhat better preserved than the myelin sheaths. In the glia specimens the white matter is seen to be replaced by dense fibrillar glia, containing both big and small glia-cells. The increase of glia, however, is not only found in the white matter, but also in the granular layer, and even in the molecular layer, where some isolated glia-fibres passing radially are seen. The vessel sheaths contain scavenger cells, in some places filled with fatty granules. The stratum granulosum does not show anything particular in the Nissl specimens, whereas Purkinje's cells appear to be somewhat shrunk and seem to have somewhat defect processes.

Bulbus olfactorius was examined by Nissl's method only; no prominent changes of the cells nor infiltration of the vessel wall can be observed.

In the *tractus opticus* and *chiasma* an intense destruction of the medullary sheaths is seen, especially perivascular, around the vessels; rarely the denser bundles are preserved. Except in some places around the vessels the axis-cylinders have also been destroyed for the most part, corresponding with the regions where the medullary sheaths are totally destroyed. Corresponding with the destruction of the myelin sheaths, an immense number of glia-fibres and cells are seen, showing the same appearance as those of the hemispheres. In the adventitial sheaths of the vessels and round the vessels, scavenger cells and fatty granule-cells are of very rare occurrence.

The spinal cord and medulla oblongata.—Throughout all the sections of the spinal cord a diffuse destruction of the medullary sheaths is to be found in the white matter. It is most advanced in the pyramidal tracts, which at this period of life ought to be developed and least pronounced in the root entrance zones. In the grey matter no signs of destruction can be seen. The Marchi degeneration is just as scanty as was the case in the cerebrum. The destruction of the axis-cylinders seems less pronounced than that of the sheaths. In the pyramidal

tracts, however, very few axis-cylinders are present. The grey matter shows a fine figuration of axis-cylinders and of the intercellular fibrillæ. Corresponding with the destruction of the medullary sheaths a very conspicuous proliferation of the glia is observed. In the outer parts are seen strong radial projections, among which lie a scanty number of fibres, crossing into all directions. Among the glia-fibres cells are observed of very varying appearance, as was the case in the brain. The glia has no particular relation to the vessels. The adventitial sheaths are usually filled with big scavenger cells, which in specimens stained with Sudan red appear to contain no fatty granules at all.

In the grey matter no glia increase is found, and there is no abnormality in the tissue surrounding the central canal. Here, too, the nerve-cells appear to be preserved and the Nissl's figures and neurofibrillæ are clearly defined and normal.

Case 2.—Bodil Bn., daughter of a clerk, was born on February 21, 1911; died at the age of 1 year. The patient, the elder sister of the first patient, was born normally at full term. The weight at birth was 4 kg. It was noticed by the midwife that the child was unusually stiff, and immediately after birth rigidity of the nape of the neck was discovered. Up to the age of four months she was suckled; then she was given barley broth, milk, water-gruel, Nestlé's food, and unboiled milk. The patient, however, after weaning had fits of crying and frequent vomiting, which abated as soon as the patient was put upon buttermilk. She was often slightly febrile for a few days in succession. Development proceeded normally until the fourth month, after which she did not advance mentally and was hardly able to recognize her mother. The stiffness of the neck and legs continued, and the fits of crying were spasmodic, accompanied by severe congestion, but regular convulsions did not occur.

On November 7 she was admitted to the Dronning Louise's Boernehospital (Queen Louise's Hospital for Sick Children), and physical examination there showed: weight of body, 4,700 grm.; length of body, 64 cm.; circumference of head 40½ cm.; circumference of the chest, 39 cm.; greatest circumference of the abdomen, 31 cm. The expression was rather stupid and vague, the cry hoarse and convulsive. The pupils were active to light. The child was lying stiffly bent backwards, with marked opisthotonos and strong lordosis of the lumbar region. Universal rigidity of the muscles was most pronounced in the lower extremities, which were hyperextended and adducted. Hands and feet were in the tetanic posture. The appearance of skull and eyes normal. Ophthalmoscopic examination (September 9) showed the right disc white and atrophic, the left pale. Fauces normal; stethoscopic examination normal; abdomen somewhat contracted (figs. 4 and 5).

The patient seemed conscious and sensitive to pain. Examination ten days later showed almost continuous tonic rigidity of all muscle groups

combined with the tetanic posture. Now and then periods of violent spasm appeared, especially in the lower extremities and in the back and neck, so that "arc en cercle" appeared. Nystagmus was sometimes present. The pupils reacted rather slowly to light. She never smiled, never seemed to be conscious. The fontanelles were large and sunken. The plantar reflexes brisk, but of uncertain form. The patellar reflexes could not be obtained on account of the rigidity.

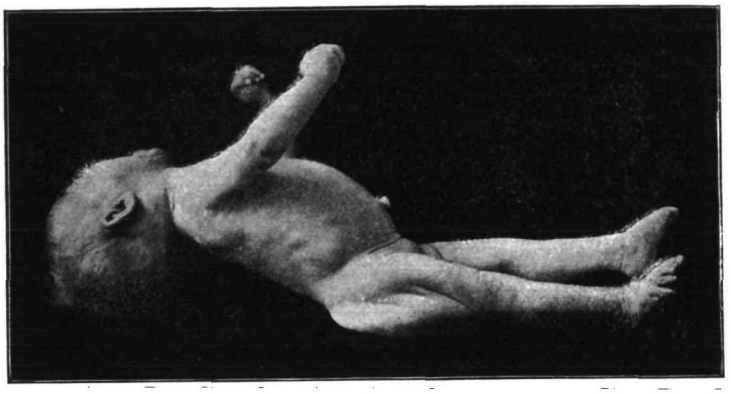

FIG. 4.—Case 2, Bodil Bn., aged 7 months.

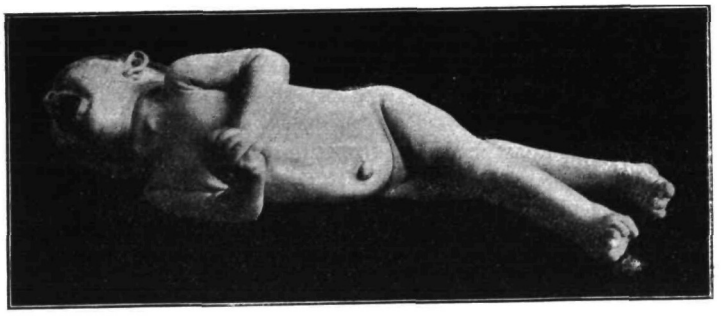

FIG. 5.—Case 2, Bodil Bn., aged 7 months.

Examination of the organs showed nothing abnormal. No rickets. Wassermann's test (October 19) negative; v. Pirquet (September 17 and October 10) negative.

As to the course of the illness, the following facts were stated: The temperature was normal at first; after a fortnight slight elevations (to 38° C.) were noted during the following week. Then again a week passed with normal temperature, succeeded by a febrile period.

Up to October 27 the temperature remained raised, but then became normal again after a week. Then it ran an irregular course ranging between normal

and 38° C.; for a few days a subnormal temperature was noted, then again a normal and slightly raised temperature alternately. For about a fortnight from December 21 the temperature remained normal or subnormal, and then after a short febrile period began to oscillate between 34° C. and 38·3° C.

The stools were normal throughout, except on one day. In the beginning there was frequent vomiting, which later occurred once or twice a day. In the last month vomiting did not occur at all. The urine contained traces of albumin and epithelial cells, urates, a number of cylinders, but no leucocytes. No growth occurred. On later examinations it did not contain albumin. The weight on admission was 4,700 grm., was steadily increased during the following months up to 5,600 grm., then decreased during the next month, until at last it fell rather abruptly to 4,800 grm.

The patient was given buttermilk for the first two days, and after this milk and barley water in equal parts seven times a day; this was increased to pure milk 150 grm. seven times a day.

Her progress was as follows :—

October 18: Patient drinks well; good stools; has gained in weight; condition all but unchanged, more or less spasmodic, sometimes interrupted by violent tonic spasms, which are nearly always accompanied by screaming. These attacks are evidently very painful, and are roused by the faintest influence from without, as, for instance, by sudden light or touch. More marked nystagmus than before. Corneal reflexes scarcely obtained, the pupils are but slightly active to light. Circumference of head, 42 cm.; circumference of chest, 39½ cm. The fontanelle: 3 cm. by 3½ cm., distended only during the attacks. Regurgitation and vomiting are frequently reported. Action of the heart regular.

October 28: Drinks poorly, condition much worse since the last note, scarcely any reaction to noise, attacks produced only when she is touched. Vomiting again of frequent occurrence.

January 13: Previous fits of crying all but ceased; very insignificant spasmodic stiffness. Plantar reflexes still rather brisk, most of the other reflexes abolished. Nystagmus rarely observed. During the last few days difficulty in swallowing has supervened.

February 6: Patient is lying unconscious, not able to swallow. Died at 8 a.m.

Post-mortem examination, nine hours after death (Dr. Oerum), gave the following results: Small scattered, apparently hypostatic, pneumonic patches, but no other special abnormality; no signs whatever of lues.

The most conspicuous pathological changes were found in the central nervous system, examined by Dr. Malling, who has given the following description: The brain and the spinal cord, in contradistinction to the soft, nearly confluent central nervous system generally found in children, is solid and hard and keeps its shape. There is no difference as to hardness between different regions; the sclerosis is diffuse and affects the cerebellum and the mid-brain. The gyri throughout the brain stand out distinctly and are

unusually small and slender. The nerves of the base, especially the optic nerves, are solid, hard, and thickened. The pia is somewhat thickened and indistinct. The cortex is of normal colour and depth, and immediately under it a streak of normal white medullary substance (2 mm. in width) is seen, but more centrally the white matter presents a peculiar greyish translucent colour, the knife passes easily through the cortex, whereas the rest of the substance of the brain is tough and hard to cut.

Sections were made from the frontal and occipital lobe, from the gyrus paracentralis, from the cerebellum, and from the dorsal, cervical and lumbar regions of the spinal cord, the optic and facial nerves. The following methods of staining were pursued: The ganglion cells were stained with thionin (method of Nissl), van Gieson, Weigert's staining for elastine and for neuroglia, Kultschitzsky-Wolters' staining for medullated nerves, Marchi staining and Bielschowsky's method of staining for neuro-fibrils, various methods of staining glia (Alzheimer), Levaditi's silver method of staining spirochætes.

Dr. Malling's description of the microscopical examination is as follows. To this, after having re-examined the specimens, I have added some supplementary notes in parentheses.

Cerebrum.—Pia appears to be somewhat thickened, especially above the motor region, but no great infiltration of cells is traceable. Most of the cells are fibroblasts and fatty granule-like cells. No plasma cells. (The thickening seems to be due essentially to œdema.) On examining under low magnifying powers specimens of the brain stained with thionin, the cortex is found to be, on the whole, fairly well preserved; it contains the usual layers of cells, but in the motor region the giant pyramidal cells are diminished. Just inside the cortex a light zone is seen, visible also to the naked eye, which contains a few cells only; more centrally, the whole white substance stains intensely, the colour increasing towards the centre. The most prominent feature of this zone is a multitude of blood-vessels, surrounded by large intensely stained cells, and it is clear that the main incidence of the process falls upon the vessels. Under high magnifying powers a chronic inflammation of the ganglion cells is seen, the nuclei are diffusely stained blue, the protoplasm is in granular destruction, otherwise the cortex appears to be quite normal. There is no noteworthy increase of the glia, nor any new formation of the vessels. No cells of infiltration. In the more highly stained zone, just internal to the cortex, no abnormality of the vessels can be seen; as a rule polynuclear glia-cells are visible. Still more centrally in the white matter a confusion of various cell forms appears. On examining a typical blood-vessel the lumen is not particularly diminished, and is as a rule empty; then comes the endothelial

layer with nearly normal cells and without any special proliferation; then, in most cases, a more or less light zone. But as soon as we reach the adventitia and perivascular region an enormous proliferation of large epithelial cells is observed, felted together and more or less angular, in contradistinction to the round cells of the tissue. These cells often contain a number of nuclei, peripherally arranged and always degenerated. The protoplasm is stained diffusely, and, in some of the cells, large dark clumps, like degenerated nuclei, are found. The said cells are placed in one or several layers round the vessel. The tissue contains similar cells, the dimensions of which are often gigantic, but they seem here more prone to vacuolar degeneration; sometimes they contain several small, sometimes one big vacuole, and thus perhaps are transitional stages to the real fatty granule (basket?) cells. The latter are found in great numbers in the tissue or in some of the vessel sheaths, as may be seen from the Marchi specimens (black-stained lipoid grains). The large cells mentioned above do not contain lipoids. In addition to these cell forms, a number of small dark nuclei with a scanty and somewhat tattered protoplasm are noticed in the glia-cells. Some of the vessels are apparently normal. The above changes are also present in the frontal, occipital and paracentral gyri.

In specimens stained for medullated nerves, scanty remnants only of the sheaths are traceable. The tangential and supra-radial fibres appear to have been completely destroyed, possibly owing to a too strong differentiation, and in the central part of the white matter there are practically no fibres; whereas, corresponding to the above "light zone," immediately under the cortex some fibres are seen, although they are considerably degenerated.

So much for the frontal and paracentral gyri. In the occipital gyri more fibres are found, and the zone of Baillarger is extraordinarily well preserved. As a sort of compensation for this almost complete destruction of nervous substance in the white matter, specimens stained for neuroglia by Weigert's method show an enormous proliferation of the glia to a degree that cannot be equalled in any other affection of the brain. The number of glia-nuclei is rather small in proportion to the glia-fibres. The fibres are, as a rule, thin and slender. In contradistinction to this enormous subcortical gliosis no increase worth mentioning is found in the cortex or marginal glia.

Similar changes are observed in the cerebellum. In the central part of the white matter the cells and changes are exactly the same as in the cerebrum; they decrease towards the granule layer, which is less

compact than usual and swarms with a number of cells, evidently glia-cells. The cells of Purkinje are somewhat degenerated and the medullary sheaths are totally destroyed, but for some few traces in the granule layer. Small bundles of medullary sheaths are also found to be intact in the white matter. In specimens stained by Bielschowsky's method, it is seen that the axis-cylinders are also destroyed. In the cerebellum also the degenerated nerve tissue has been replaced by glia, which stretches into the granule layer and runs as fairly parallel fibres right through the molecular layer to the surface (Bergmann's fibres).

The optic nerve and, to some extent, the facial nerve show more or less complete destruction, the former being transformed into glia tissue.

The cervical spinal cord, when examined in thionin specimens, appears to be somewhat effaced, so that the line of demarcation between the grey and the white matter is not easy to make out. In the grey matter large portions, especially the anterior horn-cells, are destroyed. This, however, is in our opinion somewhat doubtful, as the large motor cells of the anterior horn are also extraordinarily well preserved. All through the grey and white matter a conspicuous new formation of blood-vessels is observed, and cells similar to those of the brain, with vacuolation and a multitude of glia-cells, are present. In specimens stained for medullated nerves the whole transverse section of the spinal cord appears to be greatly degenerated, although not quite uniformly; the grey commissure, the spinal cerebellar tracts and the root-zones are the best-preserved portions, the anterior and Burdach's columns are moderately degenerated, and Goll's columns and the pyramidal tracts are completely destroyed. The fibres of the grey matter are much degenerated. In glia specimens the enormous marginal gliosis sending out thick glial septa into the substance is the most dominant feature; for the rest, the glia tissue is strongly increased throughout the transverse section.

Changes similar to these are found in the dorsal and lumbar cord. In the dorsal region the degeneration of the medullary sheaths is found somewhat more centrally in the posterior column, whereas in the latter place moderately preserved spinal cerebellar columns are not observed. In the cervical and less distinctly in the lumbar cord, in front of the central canal, a rather deep lateral fissure and several smaller fissures are noted.

Weigert's elastic tissue stain does not show any pathological changes in cerebrum, cerebellum, or in spinal cord.

Levaditi's silver method for staining spirochætes gave a negative result.

On the whole, stained specimens from this patient present much the same pictures as those of Case 1, the essential difference being, in my opinion, that the scavenger cells of the vessel sheaths in Case 2 are found to contain far more fatty substances than those of the previous case. It may be remarked that no inflammatory processes were found in these specimens, any more than in those from Case 1.

Case 3.—Agnes A. B., daughter of a bricklayer, born October 10, 1904, died in the Dronning Louise's Boernehospital (Queen Louise's Children's Hospital) at the age of nine months.

The patient was the eldest child; her younger sister is described as Case 4. She had a convergent squint from birth. She was brought up on the breast and thrived well, except for the stools, which were green; this caused the mother to apply to the polyclinic of the hospital. The meals were regulated, bismuth was given, but the stools remained unchanged. At the age of five months attacks of diarrhœa occurred, and a week later stiffness of the body with opisthotonos and violent screaming. Patient took fluid food poorly, vomiting being rather frequent.

On April 5, 1905, she was admitted to the hospital and physical examination showed: weight, 4,358 grm.; temperature, 37·5° C. She was a slender, well-nourished child. Stethoscopic examination normal; ears and fauces normal; a small umbilical hernia was noted; the fontanelle was not distended, but if anything somewhat sunken. Strabismus convergens present. No facialis or Trousseau's symptoms. During examination there were frequent attacks of total stiffness of the body and extremities, followed by opisthotonos; the arms were flexed at the elbow-joint, fists clenched with the thumb partly within, partly outside the other fingers. The lower extremities were extended and the feet in plantar flexion. Nystagmus of both eyes; patient yawned often and violently, smacking her lips now and then; colour did not change. The stools at first were thin, greenish, acid, aromatic-smelling, then mucous with an alkaline reaction. When examined under the microscope they were found to contain only mucus and a few decaying cells (epithelial and pus). The stools remained thin and mucous; on repeated examination (February 15) a few fatty acid crystals and mucus with a few cells were noted. During the whole residence in the hospital the stools remained mucous and thin in spite of change of diet. Vomiting was of almost daily occurrence and regurgitation very frequent.

The weight on admission, 4,350 grm., in the following fortnight was increased to 4,600 grm., after which it dropped down to 3,400 grm. During the last time again it rose to 3,900 grm. Lumbar puncture gave a negative result. The urine passed was scanty on April 9, 10, 11, but later became abundant, and on April 9 was slightly turbid, contained a slight amount

of albumen and no sugar. On ensuing examinations albumen was sometimes found, sometimes not. The fontanelle remained retracted during the whole stay in hospital. The patient was given the breast once or twice a day, and besides that barley water without admixture at first, then with milk, later on buttermilk soup, children's food, Liebig's soup. Her progress was as follows:—

April 10: Stiffness not diminished; this morning transitory clonic spasms of the lower extremities. More willing to take her food, has sometimes taken fluids well. Somewhat more lively. In the left half of the mouth a considerable reddening of the mucous membrane is found, and on the left side of the palate in the sulcus alveolo-lingualis yellowish mucous projects, which can be removed without difficulty.

April 16: During the last twenty-four hours some convulsive attacks. The patient is rather cold.

April 17: Drinks well. No convulsions, no stiffness of arms and legs. The nape of the neck is now and then drawn backwards, but the spinal column is not stiff. The mucous membrane of mouth and throat clean, red, moist; the palate wound is healing up.

April 19: Again frequent crying. Spastic rigidity of body and extremities. The patient looks very pale. The mucous membrane of the mouth dry, red; here and there ulcerated. Skin elastic.

April 23: Spastic stiffness, slight convulsive spasms of the lower extremities. Condition on the whole unchanged.

April 25: Œdema of hands, feet and thighs.

April 29: Yesterday afternoon one attack of clonic convulsions in the arms and tonic stiffness of legs and spinal column. The nape of the neck bent backwards. Consciousness preserved, no crying, sweating, or congestion during the fits. Occasional nystagmus has been noted. The lower extremities stiffly extended, nearly hyper-extended in the knee-joints. Arms stiffly flexed. Spine not rigid. Œdema of the back of the hand. In the lower extremities scarcely any œdema.

May 7: Dozing; cries only when touched. The lower extremities stiffly extended. In the bath this morning opisthotonos was noted for a moment. No clonic convulsions or laryngeal spasms. Hands cold, otherwise warm. Abdomen somewhat extended in the epigastrium, else otherwise soft; no visible peristalsis, the stomach cannot be marked out.

May 13: Permanent rigidity of legs and spinal column. Heart sounds faint and low.

May 23: Is lying quietly, only wails when touched; is still able to take the bottle; keeps fairly warm. Abdomen intensely sunken. Opisthotonos in the bath, not otherwise. The lower extremities stiffly extended. Some squinting. Scanty secretion from conjunctivæ. Dorsal kyphosis and lumbar lordosis more pronounced than before. In heart and lungs no abnormality. Perpetual yawning.

May 27: Extreme emaciation. Lower extremities constantly stiffly

extended, arms stiffly flexed, nape of the neck bent backwards. Abdomen flattened in the lower part. Epigastrium sunken. On examination the lungs are normal. Heart sounds strong and normal. No hæmorrhages anywhere. No conjunctivitis.

June 6: Œdema of both hands.

June 7: No thrush during the last days. Slight œdema of the upper part of the foot and of thighs. Lower extremities stiffly extended at the hip- and knee-joint. The legs are kept parallel, tightly pressed against one another, and cannot be abducted nor bent passively. Sometimes they are crossed at the ankles. The ankle-joints are slightly plantar-flexed, and the toes, especially the big toe, strongly flexed. The arms are kept at a distance from the body, slightly bent in the elbow, pronated, with the hands dorsally flexed and the fingers tightly clenched into the fist. The thumb is placed at the side of the other fingers. The rigidity of the arm muscles, however, is not so completely wooden as that of the legs. The degree of flexion varies. The spinal column has throughout been intensely arched: a dorsal kyphosis with a corresponding lumbar lordosis. The nape of the neck is stiff and the head is bent backwards, sometimes slightly, sometimes more considerably. The fontanelle is somewhat retracted. Now and then convergent strabismus is present. Some nystagmus. The pupils are equal, of moderate size and active. Perpetual intense yawning, which causes a subluxation of the jaw-joint. No clonic convulsions, no laryngeal spasms. No affection of the face. Abdomen formerly contracted, now rather tympanitic and distended. Taches cérébrales only just traceable. In spite of the evident emaciation she had gained 500 grm. in weight during the last ten days. Pulse not palpable. Heart sounds scarcely audible. Suggillations in the abdominal wall. Ophthalmoscopic examination normal. Left pupil bigger than right.

June 8: Difficulty in swallowing. Discharge of urine ceased. Rigidity as before, spasms did not occur. Died quietly at 8.30 a.m.

Post-mortem examination six hours after death gave the following results:—

An abundance of clear serous fluid was found in the subcutaneous tissue and in all serous cavities. The posterior parts of both lungs, especially the upper lobes, were infiltrated and collapsed. The bronchial and mesenteric glands not swollen. The mucous membrane of the digestive tube seemed normal; no hæmorrhages or swelling of Peyer's patches or of the follicles, which were not even visible. Œsophagus coated with a thick layer of thrush. No thrush in stomach or mouth. Heart, liver, spleen and kidneys were small and normal. The epiphyseal lines of the ribs normal. Spinal cord normal to the naked eye.

The pia and arachnoid were œdematous, but no distinct exudate was found. The gyri were very little flattened. Both lateral ventricles were greatly dilated and separated from the surface by a thin layer of brain tissue only (about 3 cm. to 4 cm.). The cerebellum was small, and in consistence cartilaginous. The rest of the brain, was, if anything, soft.[1] On the cut surface the glia

[1] Regarding this point some divergence of opinion appears. The account of the autopsy was written to the dictation of the then (now deceased) chief physician, Dr. Wichmann,

tissue of the latent lobes seemed to be increased (the brain was sent to the Anatomical-Pathological Institute of the University of Copenhagen).

Case 4.—Gudrun Marie A. B., daughter of a bricklayer, born 1905, died February, 1907.

According to information from Dr. Kiær, in Hammel, the child, when visiting Hammel, was suffering from constipation. She is *the younger sister of the above patient*, was never admitted to the hospital, but treated at home by Dr. Bloch, who has given the following information :—

The disease was similar to that of her elder sister. The child was normal during the first months of her life, but then began to suffer from stiffness of the extremities and tonic cramps. Ophthalmoscopic examination was not undertaken. Frequent periods of elevated temperature occurred, during which the cramps grew stronger and the patient more debilitated. No stethoscopic changes nor intestinal symptoms were discovered during these periods of elevated temperature; on the other hand, vomitings were of frequent occurrence throughout the disease. She lived somewhat longer than the other patients and was 1½ years old when she died.

The parents taking an interest in knowing whether or not the child had suffered from the same affection as her elder sister, Dr. Bloch was permitted to perform the autopsy at the home; the result was as follows :—

Brain (figs. 6 to 7) and spinal cord remarkably hard, almost cartilaginous, but did not present any abnormal configuration. The brain was placed in formaldehyde. When examined now (seven years later) the brain showed the following appearance to the naked eye : it was normal in shape and showed no macroscopic defects. It deserves to be mentioned that the shape had been so perfectly preserved that the organ had not flowed out by its own weight, as is usually the case with children's brains, but had remained remarkably hard, even before fixation. On the photograph (figs. 6 to 7) it is seen that the medulla oblongata straddles in the air, an unusual condition for a child's brain. On palpation the consistence of the cortex is found to be normal, whilst the white matter is extraordinarily hard—much harder than usual in a brain hardened in formaldehyde. This hardness is uniform throughout the organ. On the cut surface the cortex appears to be of normal colour and thickness, and is distinctly marked off towards the white matter, which is apparently somewhat diminished and of a reddish, somewhat marbled, grey colour. Immediately under the cortex lies a thin layer of substance which is still white.

whilst the then assistant physician, Dr. Bloch, also took part in the autopsy. He informs me that, according to his view, the rest of the brain was also extremely hard, though not quite as hard as the cerebellum. There is, on the whole, some reason to suppose that the process was not quite so far developed in this case as in the four other cases, as evidenced by the following circumstances : (1) the normal ophthalmoscopic appearances ; (2) the severe gastro-enteritis, which in all likelihood caused the death at an earlier point of time than in the other cases.

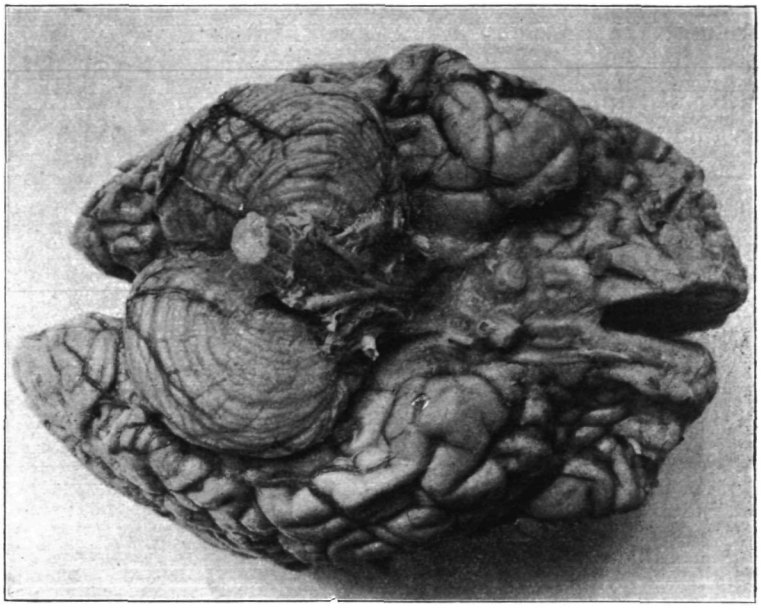

FIG. 6.—The brain of Case 4, Gudrun A. B.

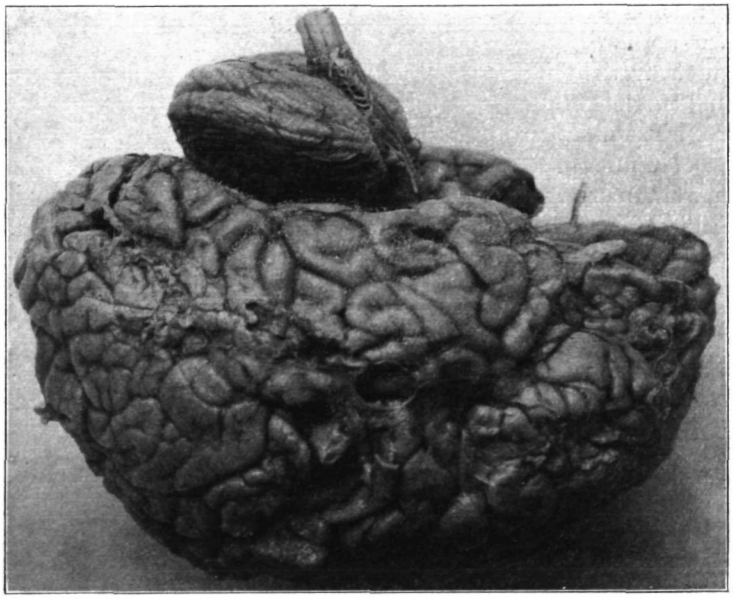

FIG. 7.—The brain of Case 4, Gudrun A, B.

Pieces of the brain were prepared: smaller sections for transference into chrom-acid acetic-acid mixture for the purpose of acid-fuchsin—vert-lumière staining, and larger slices, which were treated with Weigert's brown chrom-stain, and stained according to the methods of Kulschitzsky-Wolters and of Pal. When examined under the microscope these specimens, representing all regions of the brain, were found to contain changes (figs. 8 to 10). The white matter of the cerebrum, excepting a thin subcortical layer, was almost completely destroyed. The nerve-tracts in the pons were fairly preserved. Corresponding with the destruction of the medullary sheaths, an enormous increase of glia-tissue with large protoplasmic glia cells and infiltration of the vessel sheaths with scavenger cells was seen. As in Case 2, these cells for the most part were filled with fatty granules.

Case 5.—Frederik Ernst Ed., son of a baker, born October 12, 1905, died at the age of 11½ months.

Family history: Parents healthy, patient second of a family of two. The elder was healthy (according to later information subsequent children were also healthy). The patient was fed on nothing but the breast until admission to the hospital. During the first three to four months he was fairly well and thrived well. Then for some time he began to suffer from constipation; a fissure of the anus necessitated division of the sphincter. After this his condition improved and stools occurred spontaneously. Shortly afterwards, however, attacks of screaming and tetanic rigidity of the upper and lower extremities appeared. Now and then there was transitory elevation of temperature. Patient looked dull, and there was a peculiar smacking and masticating motion of the mouth, and moving of the tongue forwards and backwards. Examination of the chest and urine showed nothing abnormal. At the age of 6 months a kyphosis appeared in the dorsal region. The patient grew somewhat more quiet, but was admitted to Dronning Louise's Hospital (Queen Louise's Hospital for Sick Children) on May 23, 1906.

Physical examination then showed: Weight in full, 5,050 grm.; circumference of head, 43 cm.; circumference of chest, 38½ cm.; temperature, 37·5° C.; pulse 140. Urine contained much urates, but no albumen nor sugar. State of nutrition rather good; no signs of rickets. Skin greyish and cool; fontanelle normal; no gaping sutures. Ears and fauces normal; stethoscopic examination normal; glands in the neck only just of the size of a pea. Abdomen normal; liver and spleen not palpable. Pupils equal, active to light; no strabismus, sometimes pronounced nystagmus. No difficulty in swallowing. The nape of the neck was drawn backwards. Kyphosis of the spinal column in the dorsal region. Hands firmly clenched and only extended with difficulty. Arms reflexly bent at the elbow and resist extension. The legs are kept adducted at the hip-joint, stiffly extended at the knees, the right leg hyperextended at the knee and not flexible, whereas the left leg yields to flexion, though after great

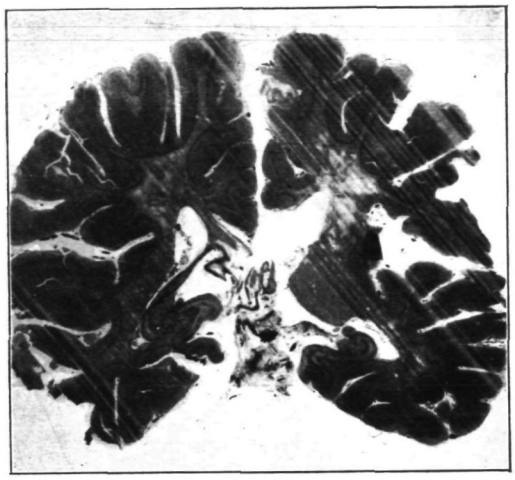

Fig. 8.

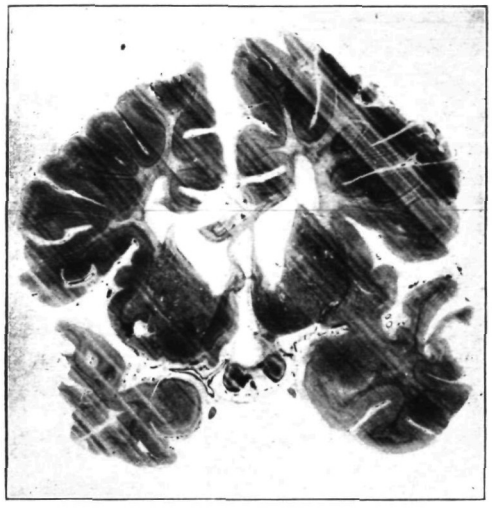

Fig. 9.

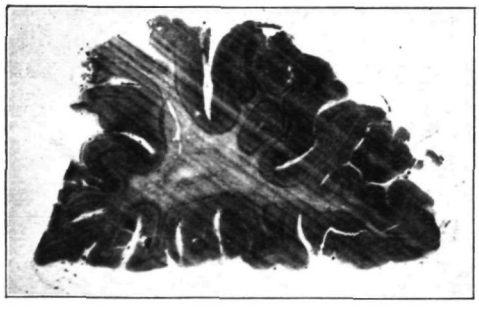

Fig. 10.

FIGS. 8 to 10.—Sections from the brain of Case 4, Gudrun A. B. Staining of Weigert-Kulschitzky-Wolters. For explanation of the figures see fig. 3, p. 79.

resistance. The feet are slightly in the equinus posture; they are not cold or œdematous. Patellar reflexes not obtained, no clonus of the foot. Periodic attacks of strong tonic rigidity, followed by screaming. Lumbar puncture on June 30; no fluid obtained.

The course of the illness during the six months' stay at the hospital was as follows:—

Temperature being at first normal, rose after a few days.

The stools at first were rather thin and gritty; later on they became normal, and remained so (July 3, 17 and 18 excepted). On September 17 the child began to get thinner. Vomiting occurred frequently once or twice daily; sometimes, however, the food was simply returned. The weight at first was increased from 5,050 grm. to 5,200 grm., then it fell rather evenly to 4,300 grm., and during the following months kept oscillating between 4,450 grm. and 4,300 grm. Finally it dropped to 4,000 grm. The urine was never found to contain albumen or sugar. In the beginning the patient was fed on milk and milk-pottage; later, on infants' food and barley water.

The following notes as to further course of the disease were taken from the ward journal:—

May 28: Condition not improved. Lies dozing most of the day; the spastic stiffness does not even cease during the sleep.

June 17: Ophthalmoscopic examination (Dr. V. Hertz) shows small equal pupils, active to light. As a rule, spasms of the downward movements. Under homatropine the discs were found to be bluish (probably physiological). The nasal edges were blurred, the veins strongly congested.

July 10: Mostly dozing, only cries when touched; no convulsions; nystagmus; no appetite; losing considerably in weight; no change of posture. Spastic hyperextended lower extremities, the head drawn backwards, and the back bent in the dorsal region; the hands clenched. Pupils equal; active to light.

July 25: Not able to swallow; nearly always dozing; purulent catarrh; lips dry.

August 31: Ophthalmoscopic examination: Pupils as before small, equal, active to light. Discs pale, especially in the left eye, veins prominent, nasal half more normal than before.

September 5: Nystagmus less pronounced than before. The spastic hyperextension of the lower extremities is unchanged. Upper limbs flexed at the elbows, hands clenched, stiffness of the neck, and curving of columna in the dorsal region. Fontanelle not distended, sutures firm. Circumference of the head, 43 cm.; circumference of chest, 37 cm.

September 28: Died at 11.30 p.m.

Autopsy fifteen hours after death showed abundance of serous fluid in the subdural cavity. Dura in some places adherent to pia; scattered smaller hæmorrhages. Pia not clear, somewhat œdematous. The lateral ventricles normal. The brain apparently rather diminished in size, but of normal shape. Consistence hard, almost cartilaginous. The cerebellum was in the same

condition. On the cut surface the glia tissue appeared to be increased. No further abnormality to naked-eye examination.

The posterior and basal portions of both lungs showed early infiltration. The mucous membrane of colon was swollen; the follicles stood out distinctly. Ductus Botalli closed.

Among the five cases described above, two (Cases 1 and 2) resembled one another so closely, both from the clinical and pathological aspect, that they obviously belonged to the same group. Case 4 must also be added to this group from the anatomo-pathological aspect, and, according to the rather imperfect description, from a clinical point of view as well. In Case 5, no microscopical examination was carried out, but the clinical picture, the naked-eye appearances and the consistence of the brain, entitle us to refer this case, too, to the same group.

With regard to Case 3 it may be maintained that—(1) the clinical picture bears a close resemblance to that found in the other cases (stiffness, spasms, &c.); and (2) it revealed the same macroscopical changes as those mentioned above, at any rate as far as the cerebellum was concerned. In considering the fact that in this case the rigidity remained unchanged till death, and that a severe dyspepsia was present, the most natural conclusion will be to rank this case along with the four others; this patient seems to have suffered from the same disease as the others, but owing to the gastro-intestinal complications died in an earlier stage, before the brain was fully sclerosed.

Summary of the Clinical Findings of the Cases.

The clinical picture of the above cases is very characteristic, but I should not dare to use it as the only point of support for diagnosis.

The first peculiarity about these cases—the family occurrence—will be discussed later on.

A characteristic feature of all the five cases is their acute onset at the age of 4 to 6 months in children who up to then had always been quite healthy. Only in one case (Case 2) was the child said to have been extraordinarily stiff all the time; it is, however, questionable how much stress may be laid upon this statement of the parents. As prodromal symptoms of the disease, causeless fits of crying and screaming were noted. Among the typical symptoms is the universal rigidity of the musculature of the body and the limbs, most pronounced in the lower extremities. A further stage of this rigidity is shown by the universal tonic spasms, which appear to be evoked by such stimuli as noise, light, or touching.

During the attacks the patients generally show the following posture: the head bent backwards, the back curved in opisthotonos; in Case 3, however, only the lumbar region was in lordosis, strong kyphosis being present in the dorsal region. The upper extremities are flexed at the elbow-joint, the hands in some cases clenched, in other cases placed in the obstetrical posture. The lower extremities are extended at the hip-, knee-, and ankle-joints, often adduced until they cross. As far as the cranial muscles are concerned, the spastic attacks were less pronounced. In two cases strabismus convergens was observed from birth and throughout the course of the illness; it did not, however, seem to increase during the attacks. In Case 5, on the other hand, no squinting was noted. In all cases nystagmus occurred, especially during the fits, and did not decrease till towards the end of the illness.

More difficult to settle is the question whether or not the muscles of the face were influenced by the spasms, as during the fits the patients cried and screamed violently. To the observer this conveyed the impression that the cries were a real reaction to the pain caused by the fits. The frequent occurrence of yawning in Case 3 may possibly be regarded as a spastic phenomenon of similar origin. The difficulty in swallowing occurring towards the end is rather a paralytic than a spastic phenomenon.

In addition to these attacks of tonic spasms, which seemed to be a higher stage of the permanent rigidity, regular eclamptic attacks, accompanied by strong clonic convulsions, were noted in several cases, although not very frequently. True paretic symptoms did not manifest themselves till towards the end of the disease, when the spastic condition gradually passed into a relaxed paralytic state. In Case 3, however, the rigidity remained till death.

It was impossible to make any observations on the sensory side. In Cases 2 and 3 there was at first reaction to pain, and in all cases reaction to all such pains as accompanied the convulsions. The presence of ataxia could not be determined, as the movements were at first so intensely spastic and then paretic that the patients were able to catch things (except in Case 1).

With regard to the sense organs, hearing seems to have been unaffected at first, as the patients were very sensitive to sound. In Case 2 this reaction was lost at the end. Sight, so far as Case 1 is concerned, was present for a few months, the patient being able to follow things with her eyes. The ophthalmoscopic results were, as a rule, characteristic; in three cases (1, 2, and 5) optic nerve atrophy

was observed, in Case 5 neuritis. In Case 4 no ophthalmoscopic examination was performed, and in Case 3 it gave a normal result. This, as already mentioned, may be due to the fact that the patient died before the affection had reached the same advanced stage as in the other four cases. The optic atrophy, therefore, seems to us to be a characteristic symptom, at any rate in the latest stages of the disease, and probably a sign of great diagnostic significance. The pupils in all cases were active to light, even in the latest stages (?). In Case 2 only was the reaction sluggish, and later on almost extinguished. The tendon reflexes of the upper extremities only are mentioned in Case 1 and described as brisk, whereas in none of the cases could the patellar reflexes be evoked, probably on account of the rigidity. As to the plantar reflexes, nothing can be judged from the notes at hand.

Restlessness and screaming were the chief symptoms in the beginning, succeeded by dulness. The mental faculties did not develop after the disease had begun. As a last sign pointing to the conditions of the central nervous system, the fontanelle presented a characteristic want of distension, and it was generally distinctly sunken.

In the periodic elevations of temperature (fig. 11) we find a symptom, the significance of which is not easy to interpret. In Case 3 the permanently elevated temperature probably must be ascribed to the dyspepsia, but in all the other cases no affection was found of the digestive tract, of the lungs, or of the urinary system, to which the short febrile periods might have been referred. In fact, they may be due to some occult infection or intoxication, and thus be regarded as a merely accidental complication. But, on the other hand, they may represent a characteristic feature of the disease, and thus be due either to an influence acting upon the temperature-regulating system or to the fact that the destruction of nervous substance, being the fundamental process of the disease, takes place at intervals, and causes elevation of temperature due to products of its destruction. It is, however, a matter of difficulty to judge from the ward journals as to the cerebral symptoms during febrile periods. According to the statement of Dr. Bloch, these periods were followed by aggravated cerebral symptoms; in Case 4 the convulsions and the screaming were far more pronounced during the duration of the elevated temperature, and in Cases 1, 2, and 3 this also seems to appear from the notes.

Great lowering of temperature was succeeded by coldness, debility, even by collapse and sometimes by eclamptic fits (Case 1). In Case 3, however, eclampsia also occurred outside the periods of subnormal

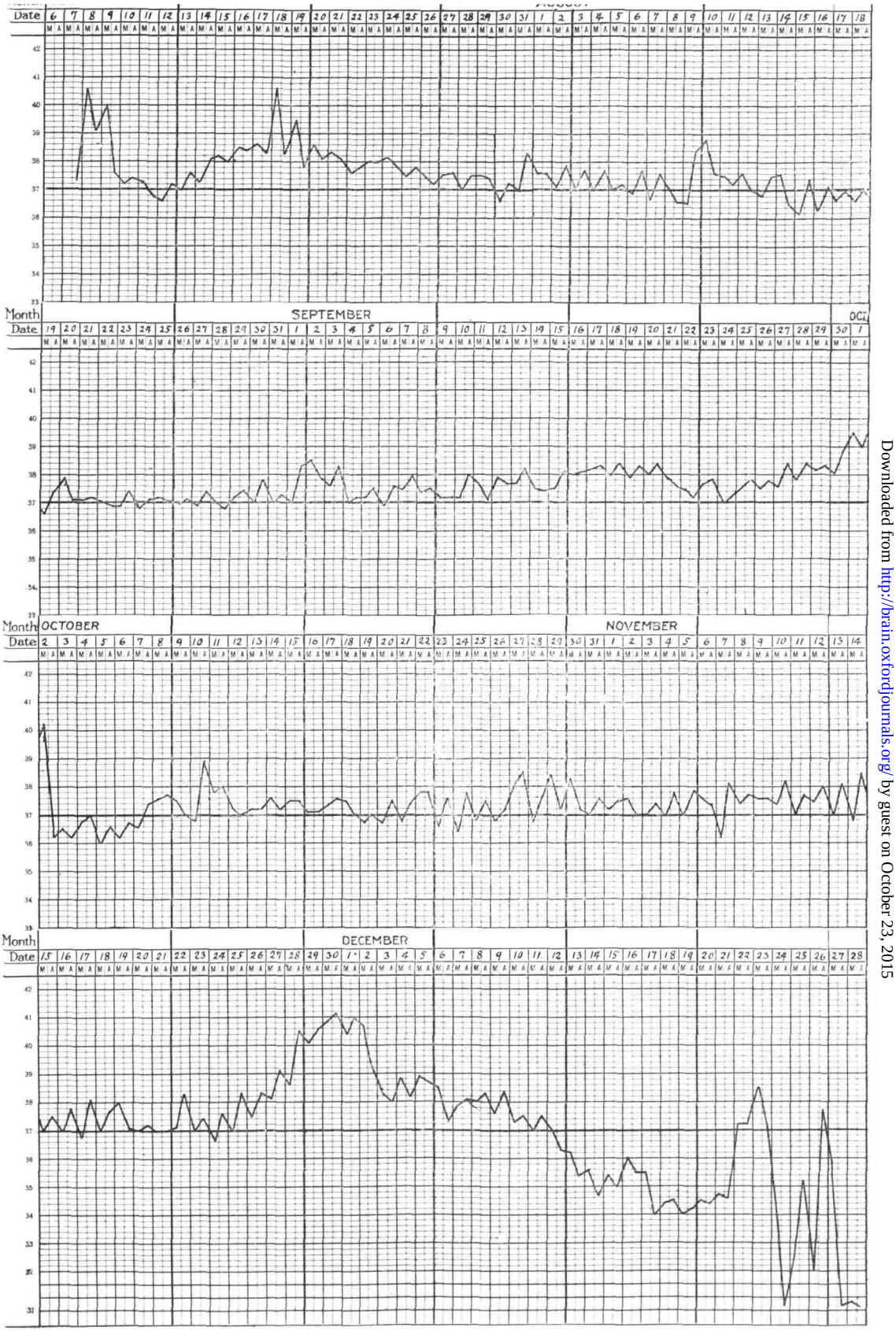

FIG. 11.—Temperature of Case 1 (Kai Bn.).

temperature. All the cerebral symptoms, the vomiting excepted, can be regarded as more or less casual complications. The vomiting was of rather frequent occurrence in the four last patients, but did not appear in Case 1, in which only slight regurgitation was noted. Diarrhœa occurred in Cases 1 and 5 a few times, in Case 2 not at all, but in Case 3 was almost permanently present, the stools being of a thin and mucous consistence. Here the dyspepsia probably had given rise to the albuminuria (the œdema), the stomatitis, the pharyngitis, the catarrh, the eczema and the conjunctivitis; some transitory catarrh and conjunctivitis in Case 5 and some pyuria in Case 1 excepted, no such severe complications were found in the other cases.

No affection of the heart nor the lungs occurred except the terminal pneumonia. The weight as a rule oscillated, decreasing during the latter period. The terminal increase of weight in Case 3 was due most probably to retention of urine.

It may be added that lumbar puncture and Wassermann's reaction, performed in two cases, gave negative results.

Anatomo-pathological Considerations of the Cases.

The most characteristic feature of the above cases, as far as their pathological anatomy is concerned, is the complete destruction of the axis-cylinders and medullary sheaths, the replacement of the destroyed tissue by neuroglia and the relative intactness of the nerve-cells. The destruction shows a peculiar distribution, as may be seen from the description of Cases 1, 2 and 4; the processes of all the nerve-cells of cortex cerebri and cerebelli are most affected; destruction of the processes from the basal ganglia represents the next stage and of those from the spinal centres the last stage of the disease.

This affection probably proceeds evenly, as, had it been of sudden occurrence, cysts and irregularity of the glia proliferation would have been present. The regular distribution of glia tissue without any deformation of the brain is most naturally explained by the steady substitution of glia in places where the nervous tissue was destroyed.

Furthermore the process must be looked upon as being no longer progressive in Case 1, and as nearly ended in Cases 2 and 4, on account of the extraordinarily scanty Marchi degeneration in the first case, and from the small number of fatty and of albuminous granules in the scavenger cells. To reconstruct the onset of the process from the existing pathological changes is, however, rather difficult, although it may be possible to draw some conclusions as to certain facts. The question is,

whether the affection is to be regarded as—(1) a variety of tumour-growth, (2) a repaired inflammatory process, or as (3) a simple degeneration of the nerve-cell processes.

The first explanation, that it is a kind of gliomatous formation, is entirely untenable. It is quite impossible that a tumour could occupy nearly all the white matter of the central nervous system, and abruptly terminate where it approached the grey matter, causing no deformation of the brain.

The explanation that it is due to an inflammatory process appears to be more probable, provided that we allow that when the presumed inflammation has passed away no infiltration with plasma cells, lymphocytes, or polynuclear leucocytes is traceable anywhere. In my opinion, the strict limitation of the lesions to the white matter seems to speak against an inflammation. Another objection to the theory of an inflammation in these cases is the peculiar distribution of the changes within the white matter. There is no distinctly marked focus, but a selective destruction which predominantly affects the processes of the cortical pyramidal cells, leaving the adjacent regions of the white matter, as, for instance, the tracts of pons, undamaged.

A third point of significance seems to me to be a comparison of the above cases with the one previously described by me under the name of "perivascular necrosis of the medullary substance." As was already emphasized in the previous paper, the changes—(1) were only found in the medullary substance, and not in the grey matter; and (2) consisted of a slight diffuse destruction of the medullary sheaths throughout the white matter and of a complete disintegration of the vessel sheaths. Corresponding with this was found—(3) a protoplasmic and partly fibrillary glia and great quantities of fatty granule-cells round the vessels, carrying away the decayed myelin sheaths.

This picture, in fact, corresponds exactly with the initial stage of the above cases of diffuse sclerosis. The age of the child being nearly the same, and other points of resemblance being present in the clinical history, I feel myself entitled to consider this case as an initial stage of those described in this paper, but a stage which was interrupted by death owing to gastro-enteritis.

If I am right in maintaining this assertion, it must also be supposed that the disease is not of inflammatory origin, as in the said case neither leucocytes nor lymphocytes nor plasma cells were found anywhere.

I am compelled, therefore, to refer the disease to a mere degenera-

tive process. I feel, however, inclined to alter my conception regarding the case previously reported. The fact that the destruction of the medullary sheaths was predominantly round the blood-vessels, and of a more scanty occurrence towards the periphery, was indicative of a perivascular origin of the process, and the slighter disintegration in the outer regions I referred to a secondary degeneration of such medullary sheaths as pass near the vessels.

This, however, might also be explained in the following way: the degeneration of the medullary sheaths sets in diffusely, and the more intense destruction round the vessels is due to the fact that the glia-cells, receptors of the products of destruction from the degenerated sheaths throughout the white matter, wander into the vessels and push aside the surrounding sheaths.

Which of these explanations may be acknowledged as the right one is difficult to decide. In the case here described the density of the fibrillar glia was more pronounced round the vessels than at some distance from them. But this dense glia only appears as a comparatively thin and sharply limited tube round some of the blood-vessels. The explanation might therefore just as well be based upon the supposition that the glia becomes particularly dense in places where the protoplasmic glia-cell wanders, carrying with it the products of destruction.

We are thus, on the whole, more inclined to believe that the perivascular destruction of the medullary sheaths and heaping up of glia-cells is not the primary but the secondary factor and the natural consequence of the diffuse destruction of the medullary sheaths and axis-cylinders. No final decision can be reached until a case has been examined which is more advanced than my first case.

In this place I might mention a case to which my attention was not drawn till after the completion of my first paper; this case was reported by Lewandowsky and Stadelmann, and a *post-mortem* examination showed a recent affection of the brain. The most characteristic feature was a heaping-up of glia-cells distributed in spots, but with no inflammatory symptoms, and the axis-cylinder processes were not preserved in places where the medullary sheaths were destroyed, as is the case in disseminated sclerosis. The patient in this case being an adult, I must, however, in spite of the parallel, look upon it as different from my own.

I have now come to the third possibility, which to my view is the most probable, namely, that the affection is a merely degenerative process, analogous to such degenerations as are frequently found in certain hereditary or familial nervous affections, as, for instance,

Friedreich's disease. This interpretation is not only based upon the advanced destruction of the medullary sheaths and of the axis-cylinders traceable without any signs of inflammation, but it chiefly rests upon the characteristic distribution of the degenerative processes. These, to a certain extent, are just as selective as the degenerations in the hereditary nervous diseases; the tracts destroyed consist of all the axis-cylinders of the pyramidal cells of the cortex cerebri and the cells of the cortex cerebelli, together with their medullary sheaths. Corresponding with this, the degenerations met with in the central part of the brain and in the spinal cord mostly affect the pyramidal and cerebellar tracts, whereas the spinal nerve tracts are relatively intact, and the nerve processes from the centres of the spinal cord are all but undamaged.

I therefore believe that the degeneration of this enormous amount of nerve tissue is the primary factor of the disease, whereas the glia proliferation and the infiltration of the medullary sheaths with the gliogenous fatty granule-cells and other scavenger cells represents a secondary process.

EXPLANATION OF FIGURES.

Figs. 12 to 16 are stained with Alzheimer's acid-fuchsin.

Fig. 16 with Alzheimer's staining with Mallory's hæmatoxylin. The background fibres are neuroglial fibres. All the sections are from Case 1, Kai Bn. The figures are drawn by the author with a Zeiss's microscope, ocular ii, objective immersion $\frac{1}{12}$.

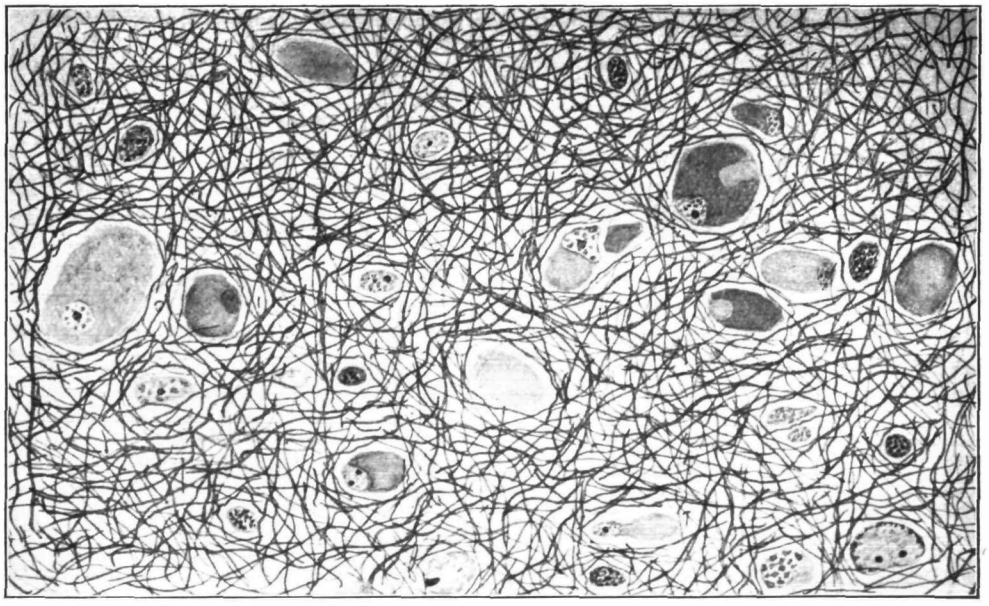

FIG. 12.—White substance of the hemispheres. The whole white substance is replaced by neuroglia in which may be seen many different types of neuroglial cells, small and large.

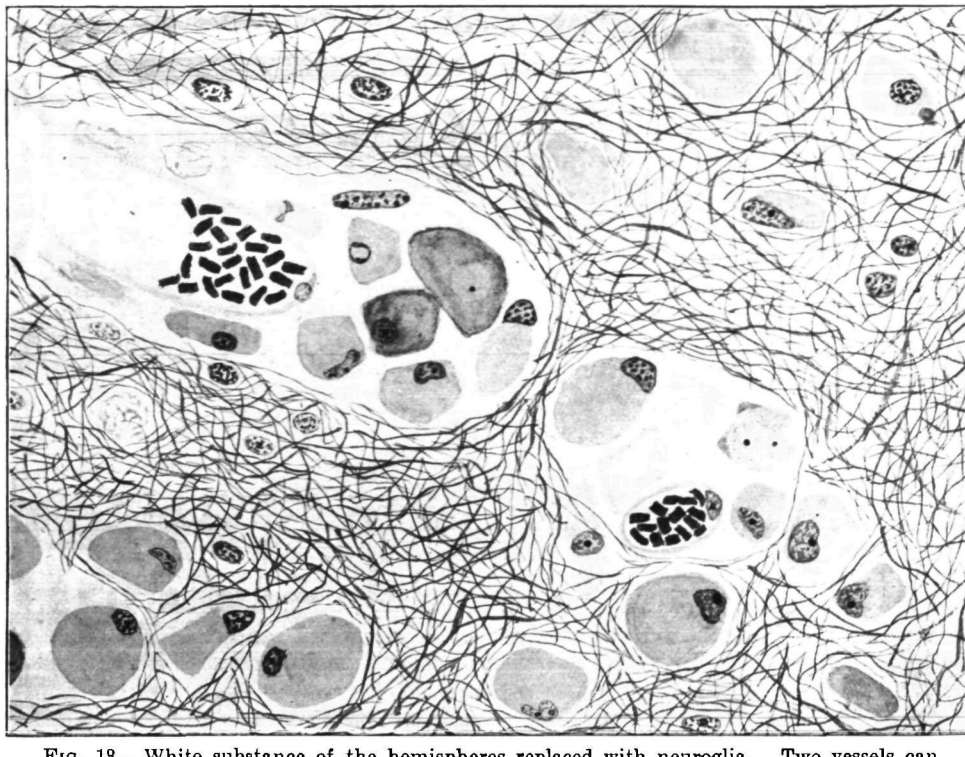

FIG. 13.—White substance of the hemispheres replaced with neuroglia. Two vessels can be seen (the erythrocytes are stained red) surrounded with gliogenous "scavenger" cells.

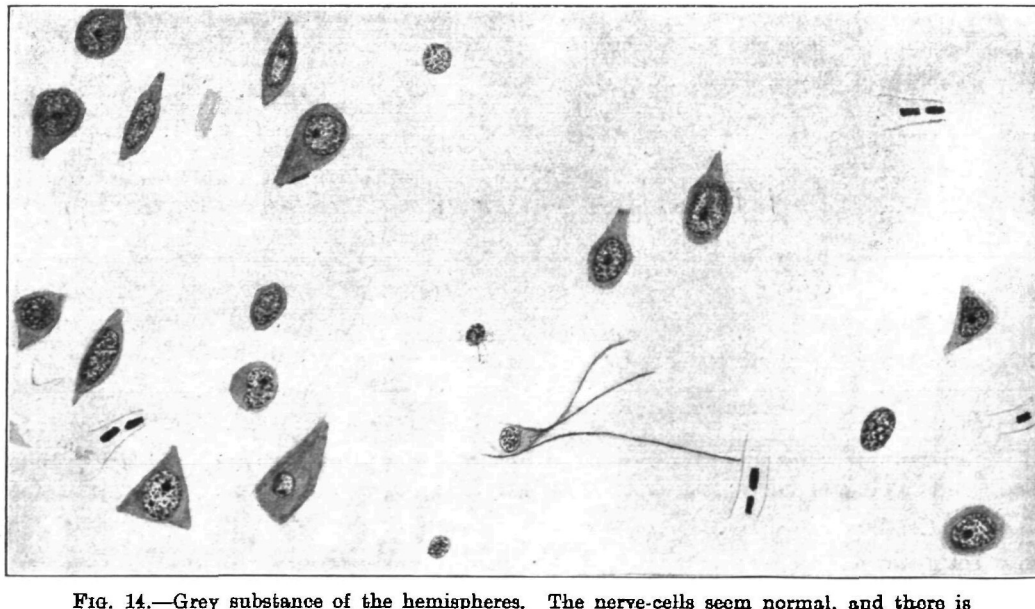

FIG. 14.—Grey substance of the hemispheres. The nerve-cells seem normal, and there is no augmentation of the neuroglia; only one neuroglia cell with fibres is seen.

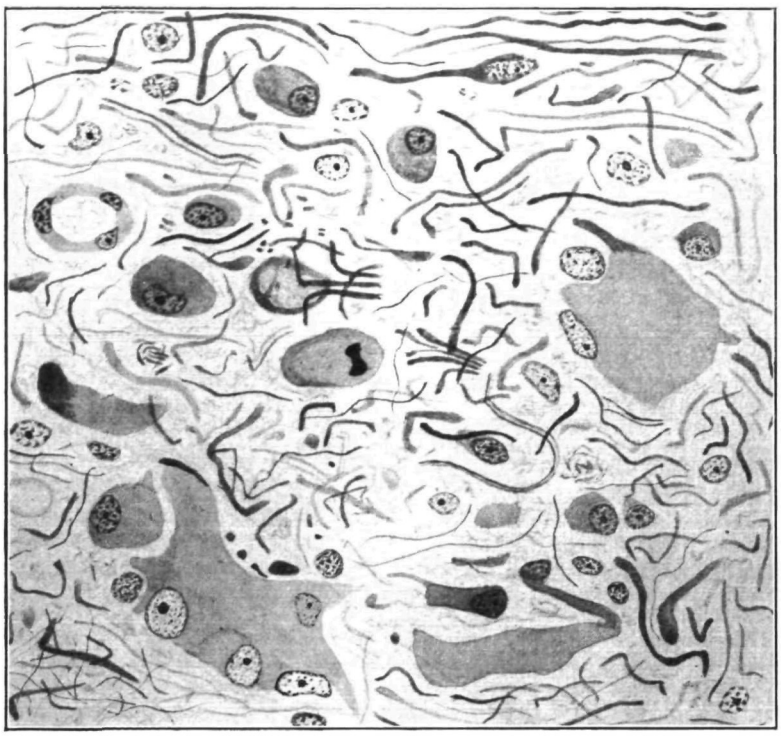

FIG. 15.—Partly from the internal capsule; the white substance is replaced by abnormal neuroglia, gigantic polynuclear glia-cells with big fibres and degenerated nuclei.

THE NOSOLOGICAL PLACE OF THE DISEASE.

The above five patients, and probably the one previously described by me, present so many points of resemblance from a clinical and especially from an anatomo-pathological point of view, that it can scarcely be doubted they belong together. The most conspicuous feature, as far as their pathological anatomy is concerned, is the extraordinary hardness of the white matter of the brain and the spinal cord.

Several cases have been reported in the literature under the name of diffuse sclerosis of the brain, in which the main characteristic has been just such hardness of the brain. In fact, no other cerebral affection presents a similar hardness, and I thus feel entitled to classify my cases temporarily in one disease-group.

On the other hand, it may be considered beyond doubt that such sclerosis of the brain in most cases represents the final stage of various processes which are pathogenetically different, and previous authors

have tried to discriminate special forms within the category of diffuse sclerosis of the brain. One of the most prominent papers on this subject is written by Schilder. He not only gave a detailed report of the clinical and pathological findings of his own case, but also instituted a re-examination of the literature, and called attention to the cases

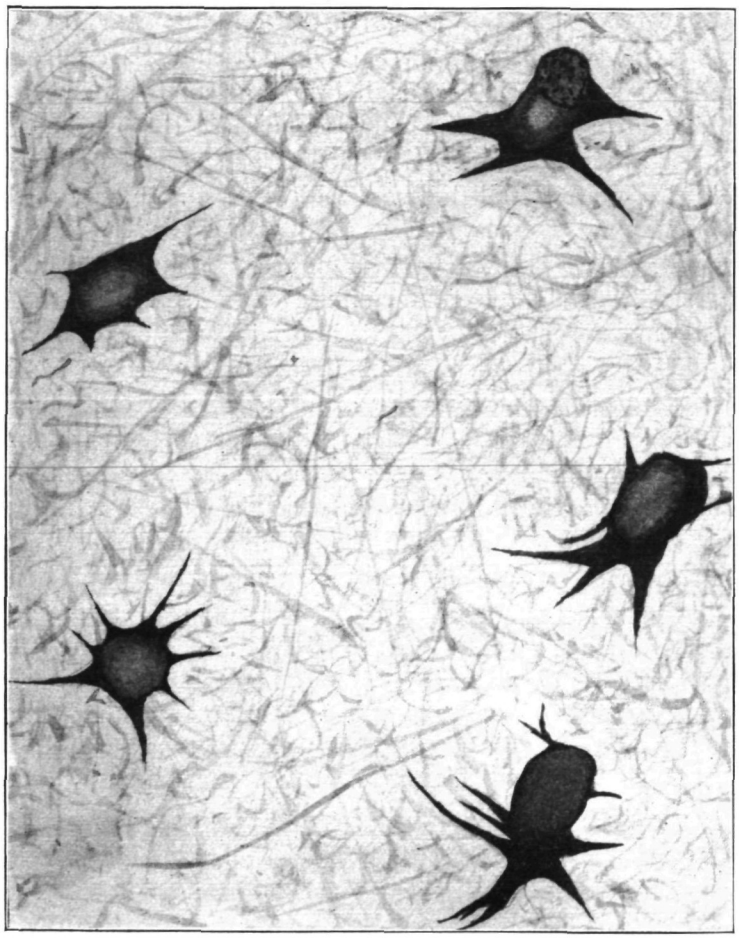

FIG. 16.—White substance of the hemispheres replaced with neuroglia. Shows the spider-cell forms.

already described as diffuse sclerosis of the brain; he gathered together such cases as have been published under other names, but which should be referred to this group. He thus separates four cases as a special group under the name of encephalitis periaxialis diffusa, considering them to be related to the disseminated sclerosis.

My cases, however, present certain peculiarities in which they differ considerably from the cases described by Schilder; thus they began in babyhood, they tended to occur in families, and they showed a complete absence of any signs of primary or secondary inflammatory processes. In the literature I have found one case—viz., Beneke's—which may be classified with the cases reported in the present paper.

Finally, there are certain cases reported in literature of syphilitic origin; but no syphilitic origin existed in Schilder's case or in my cases, and these syphilitic cases fall into a group by themselves.

In the following pages I shall discuss these three groups, giving, however, but a brief summary of the first and second group, whereas of the third a more detailed report will be given. I only refer to the disease in children.

Group I: the syphilitic.—It is no easy task to draw the line between syphilitic and the non-syphilitic cases. Some of the cases of the next group are probably syphilitic in origin, such cases, for instance, as are antecedent to the Wassermann reaction and where syphilis was present without being noted in the history. On the other hand, cases in which Wassermann's test proved positive, or cases in which syphilis was discovered in the history, might be ascribed to casual complications. Considering the varying forms under which syphilis generally appears in the central nervous system, I should, however, think it the most natural solution to explain these cases as syphilitic.

The first group, then, comprises the following cases:—

Buss: Hereditary syphilis in a child aged 2 years 6 months. Strümpell's case, in which the father suffered from typical tabes dorsalis. Haberfeld and Spieler's second case, in which the mother was syphilitic; and finally the case, reported and illustrated by Zappert, in the chapter on the central nervous system in the "Text-book of Pfaundler and Schlossmann," and a case observed by Pfaundler, in which syphilis was present, consanguinity of the parents, and paralysis of the father. Although the evidence of syphilis in these cases is not always to be relied upon, the disease must still be referred to a syphilitic affection, and the more so as *post-mortem* examination in several cases showed no particular limitation to the white matter, but an extension to the grey matter, combined with grave changes in the ganglion system, or with chronic meningitis. The case described by Bullard may also be placed among the syphilitic affections, which, although no history of syphilis was present, microscopically resembled general paralysis.

Group II: encephalitis periaxialis diffusa.—The second group comprises cases for which Schilder has proposed the name of encephalitis periaxialis diffusa, and which are in his opinion related to disseminated sclerosis. As to the relationship I shall not express myself any further, Schilder having thoroughly discussed the reasons for and against. On the whole, we may agree with the conception that some cases of diffuse sclerosis of the brain are especially extensive disseminated sclerosis. Schilder himself places in this group, in addition to his own case, the cases reported by Rossolimo, Ceri, Haberfeld-Spieler and Beneke. For reasons which will be discussed later on, I should, however, feel inclined to refer the last case to the next group. There are, moreover, a number of cases which may well belong to this group, in spite of the pathological-anatomical description not being always detailed enough to permit any sure definition of the disease. This, for instance, applies to the cases reported by Schüle, Longkamp (first case) and Meine. A copious description of the chief characteristics of these cases having been already given by Schilder, I shall only here refer to his paper.

Group III: the familial early infantile form of diffuse brain sclerosis.—Regarding the pathogenesis of our cases and their place within the nosology, it may at first be noticed that they are absolutely different from the syphilitic group; there was no clinical evidence of congenital syphilis, and the pathological-anatomical findings differed from those found in syphilitic lesions. My cases differed, moreover, fundamentally from Schilder's encephalitis periaxialis diffusa. This affection, as a rule, seems to be indicative of a reparative inflammation, and the process does not affect the whole central nervous system; but as far as the cerebrum is concerned it appears to be confined to certain regions. The disease sets in during later infancy, and is of no familial occurrence. Against the latter assertion, however, Halberfeld and Spieler's case may be quoted, in which a relative of the patient was said to have been subject to the same disease. Let it be remembered, though, that this statement was due to the parents and not to the physician, for which reason the family occurrence may be regarded as somewhat doubtful. The process in my cases has been degenerative and not inflammatory, and affected the whole cerebrum and cerebellum; it always began during the first six months of life, and in four out of five cases presented a familial occurrence.

All these conditions point away from encephalitis periaxialis diffusa, and are totally unlike any form of disseminated sclerosis. Furthermore,

disseminated sclerosis is very rarely of familial occurrence; in fact, authors such as Müller will not acknowledge cases of familial appearance as disseminated sclerosis. Finally this disease is very seldom found in children; among fourteen cases reported by F. Wolf (1912), only one (the author's own case) could be traced back to the first year of life, and this, too, must be considered very doubtful. At any rate, the diagnosis was not verified by autopsy.

The pathological-anatomical findings, however, and the familial occurrence point to another group of diseases—namely, the hereditary familial nervous affections. The isolated occurrence in Case 5 is of but small importance, firstly because all familial diseases may appear sporadically, and secondly because the case, on the whole, is in perfect keeping with the other cases as far as the clinical and pathological findings are concerned.

It is equally evident that there is just as deep a separation between my cases and Schilder's encephalitis periaxialis diffusa as between Friedreich's disease and disseminated sclerosis.

In attempting to place my cases of hereditary familial nervous affection, the point is, to which of these groups are they most intimately related? The two groups of disease to which my cases may belong are, on the one hand, Pelizaeus-Merzbacher's disease, aplasia axialis extracorticalis congenita, and on the other, Tay-Sachs' type of familial amaurotic idiocy.

My cases resemble aplasia axialis extracorticalis congenita in that they set in during the first years of life, and show pronounced destruction of the white matter of the brain. But there is a considerable difference in the clinical picture and in the course of disease. Aplasia develops to a certain point and then remains stationary. In my cases the pathological process, on the contrary, advances inflexibly and relatively quickly until a fairly complete destruction of the white matter of the cerebrum is produced. In this respect my case presents a kind of the relationship to familial amaurotic idiocy. This, on the other hand, forms a supplemental contrast to my cases, the most characteristic feature being the degeneration of nerve-cells, whereas it is the destruction of the axis-cylinders and myelin gains which characterize my cases.

It is universally recognized that there has been a somewhat exaggerated tendency to divide the familial nervous and muscle diseases into a countless number of types representing only transitional forms. It seems to me, however, that my cases show pictures so typical and distinct from all other cases, even from Pelizaeus-Merzbacher's disease,

that I am entitled to regard them as a special group within the familial nervous diseases, and, in fact, a group to which the name of *familial early infantile brain sclerosis* may rightly be given.

The next question of interest is, which of the cases previously described in the literature ought to be referred to this group? The most minutely reported case is that of Beneke, but unfortunately it contains no clinical history, only a pathological-anatomical description.

Beneke's case was a boy aged 1 year 9 months, 51 cm. in length. *Post-mortem* examination showed a double-sided pneumonia, ecchymoses on the abdomen, and contraction of the elbow-joints, but otherwise no abnormality, except in the central nervous system. The pia was hyperæmic and œdematous. The shape of the brain did not show much change other than a great increase of consistence. This increase was also found in the basal ganglia, in the bulbus olfactorii and in the optic nerves. In the cerebrum itself there was no sclerosis of the cortex, but only of the white matter and, to a certain extent, of the basal ganglia and the central nuclei, such as the nucleus caudatus, claustrum, &c. In the cerebellum an extensive sclerosis was noted coincident with a soft focus in the cortex. There was no encephalomalacia. The spinal cord was also intensely sclerosed. The sclerosis did not seem to be total as in my cases—it consisted of large confluent foci intermingled with traces of white matter. As in my cases, a narrow streak of white substance, fairly undamaged, was found immediately under the cortex. The occipital lobes and the frontal lobes presented the softest consistence. When examined under the microscope the tissue was found to show a copious increase of glia corresponding to the grey foci. The cell types showed all transitional stages from glia cells without a protoplasm to large polymorphonuclear homogeneous cells with a peripheral arrangement of the nuclei. The latter forms were generally found in dense layers round the larger or smaller blood-vessels, or formed isolated punctiform groups in the middle of the glia tissue. The substance between the cells was hard, fine and densely fibrillated. Within the dense sclerotic regions, medullated nerve-fibres were found which had escaped destruction, mostly arranged peripherally. Everywhere fatty granule-cells were noted, but not in very great quantities. In contradistinction to this, the sclerosis of the spinal cord chiefly consisted of dense masses of glia-fibres without any special increase of the glia-cells. The fatty granule-cells were quite wanting here and some of the ganglion-cells were degenerated. The process seemed to be progressive in the brain, and finished in the spinal cord.

The author calls attention to the difficulty of proving whether the process might be an inflammation, a congenital anomaly of growth, or a kind of tumour formation; the analogous large cells can be found in many gliomata, and also in regenerative processes.

Beneke's report seems to correspond with my cases in all essentials, the only difference being that the process was not so advanced here as in my cases. The child is presumed to have died during the development of the affection.

Among other reported cases from early infancy two only can be referred to this group—namely, the cases reported by Schmaus and by Heubner. In both cases, however, the patients were somewhat older children (Heubner's, aged 5; Schmaus's, aged 3). The pathological-anatomical findings do not permit me to classify them with certainty. It may be added that in none of these three cases were other members of the family affected.

As will be evident from this review of the literature, not many cases are recorded in early infancy, and it therefore appears remarkable that Zappert, in "Pfaundler Schlossmann's Text-book," states that the disease is of frequent occurrence in small children. ("Vorwiegend werden von der diffusen Sklerose Kinder in den ersten Lebensjahren selten grössers Kinder, oder Erwachsene betroffen.")

Nearly all his references to literature apply to adults or to older children.

Summary and Conclusions.

(1) The so-called diffuse sclerosis of the brain in children may be divided into at least three quite distinct types: (i) A syphilitic form; (ii) Schilder's encephalitis periaxialis diffusa; (iii) a familial infantile form, of which five cases are discussed in the present paper; the literature probably contains one other case.

(2) This form shows the following characteristics: it is usually a familial disease; it sets in somewhat acutely in about the fifth month in a child who up to then has been quite healthy; it progresses on a chronic course, ending with death, five to six months after the onset; universal rigidity of the musculature, violent tonic spasms, probably causing pain, and brought on by touching or noise form characteristic symptoms. As a rule, nystagmus is present, and in the latter stages atrophy of the optic nerve. Periodic elevations of temperature occur without perceptible cause, outside the central nervous system. Finally, extensive paresis and pronounced debility close the scene.

(3) The pathological-anatomical findings are: a marked hardness of the white substance of the brain without alteration of its shape. Microscopical examination of three cases showed relative intactness of cortex and the basal ganglia, the nervous centres of the brain and of the spinal cord; destruction of the medullary sheaths and axis cylinders throughout the white substance of the cerebrum (a 2-mm. layer, however, is preserved immediately under the cortex). Complete destruction of the white matter of the cerebellum and degeneration of the spinal nerve tracts are present. The destroyed tissue is replaced by dense fibrillar glia, in which are seen a considerable number of variously shaped glia-cells, mostly protoplasmic; the vessel sheaths are infiltrated with fatty granule-cells and other apparently gliogenous scavenger cells. There is a total want of new formation of vessels or infiltration of the vessel sheaths with plasma-cells, lymphocytes, or leucocytes.

(4) The affection must be regarded as a purely degenerative and not as an inflammatory process. The disease presents a certain relationship to Pelizaeus-Merzbacher's disease, aplasia axialis extracorticalis congenita, on one side, and to Tay-Sachs' form of familial amaurotic idiocy on the other side. In other respects, however, it differs conspicuously from both these groups.

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The Editor calls attention to the following additional papers bearing on this subject:—

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[36] CARGILL and MOTT. "Seven Cases of Tay-Sachs Disease," *Proc. Roy. Soc. Med.* (Path. Sect.), 1911, vol. iv, p. 147.

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[38] FOWLER and DICKSON. "Tuberose Sclerosis," *Quart. Journ. of Med.*, 1910-11, vol. iv, p. 43.

[39] TREDGOLD. *Arch. of Neurol.*, 1908, vol. ii, p. 403.

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