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Pathological Changes in the Central and Peripheral Nervous System of Young Long-term Diabetics

I. Diabetic Encephalopathy

By

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Summary. A study of the clinical observations and the neuropathological findings in the brain of 16 juvenile diabetics dying of diabetic angiopathy after many years of diabetes is presented. A characteristic histological pattern was observed in all the cases consisting of diffuse degenerative abnormalities of the brain tissue, often with severe pseudocalcinosis or with atrophy of the dentate nucleus, demyelinisation of the cranial nerves, fibrosis of the leptomeninges and angiopathy. The degenerative changes were so pronounced that a dual pathogenesis seems likely; viz. an ischemia caused by the angiopathy and a primary diabetic abnormality of the brain tissue. The clinical symptoms of cerebral disease varied from insignificant to pronounced. A correlation was found between the symptoms and the number of areas of softening in the brain. The histological pattern differs from that seen in other clinical conditions and justifies the term diabetic encephalopathy.

Résumé. Les auteurs rapportent les observations cliniques et les constatations neuropathologiques effectuées sur les cerveaux de 16 malades atteints de diabète juvénile, morts d'angiopathie diabétique après de nombreuses années de maladie. Un tableau histologique caractéristique fut observé dans tous les cas: anomalies dégénératives diffuses du tissu cérébral, souvent avec pseudocalcinose sévère ou avec atrophie du noyau dentelé, démyélinisation des nerfs craniens, fibrose des leptoméninges et angiopathie. Les altérations dégénératives étaient tellement prononcées par rapport à l'anomalie vasculaire, qu'il s'agit probablement d'une combinaison de causes: ischémie par angiopathie et anomalie diabétique primaire du métabolisme cérébral. Les symptômes cliniques de la maladie cérébrale variaient: ils étaient insignifiants dans certains cas, importants dans d'autres. Une corrélation a été trouvée entre les symptômes et le nombre de foyers de malacie présents dans le cerveau. Le tableau histologique diffère de celui observé dans d'autres états cliniques et justifie le terme d'encéphalopathie diabétique.

Zusammenfassung. Klinische Beobachtungen und neuropathologische Befunde im Gehirn von 16 juvenilen Diabetikern, die nach langer Diabetesdauer an ihrer Angiopathie gestorben sind, werden beschrieben. Ein charakteristisches histologisches Muster wurde in allen Fällen gefunden: diffuse Degenerationen der Gehirnsubstanz, oftmals mit „Pseudocalcinosis" oder Atrophie des Nucleus dentatus, Fibrosis der Leptomeningen und Angiopathie. Die degenerativen Veränderungen waren so ausgesprochen, daß eine komplexe Pathogenese angenommen werden muß: eine angiopathische Ischämie und eine primäre diabetische Abnormität des Stoffwechsels im Gehirn. Die klinischen Symptome waren in einigen der Fälle unbedeutend, in anderen sehr schwer. Eine Korrelation zwischen den klinischen Symptomen und der Anzahl der Malazien ließ sich aufzeigen. Das histologische Muster unterscheidet sich von dem Muster anderer klinischen Zustände und gestattet die Benennung „Diabetische Encephalopathie".

In the second half of the nineteenth century clinical and histological evidence of brain disease in diabetes mellitus was the subject of much discussion. One point of interest was whether cerebral changes were the cause or the effect of the disease (MARCHAL (DE CALVI), 1864, SEEGEN, 1893). Much of this literature is difficult to evaluate to-day.

DE JONG in 1950 published a case with severe clinical and histological central nervous system abnormalities and coined the term "diabetic encephalopathy". Apart from this paper very little has been published on the histology of the brain in diabetes during the last decades, and modern textbooks — with the exception of Henke-Lubarsch's (BODECHTEL and ERBSLÖH, 1958) — either ignore the brain or state that there are no cerebral abnormalities in diabetes mellitus (WARREN & LECOMPTE, 1952, JOSLIN, 1959, WILLIAMS, 1960).

BODECHTEL and ERBSLÖH (1958), discussing cerebral changes in diabetic coma, state that "a specific diabetic encephalopathy does not exist, not even a characteristic histological pattern." Under the heading of "Diabetic Vascular Disease and Softening of the Brain" they mention a special clinical type of juvenile diabetes with multiple cerebral insults, quoting DE JONG's patient (1950) and briefly summarizing some clinical and histological findings in three personally observed cases.

In the course of the last 10—20 years much knowledge has been accumulated on vascular disease in diabetes. It is known that vascular lesions of various organs occur in most patients after they have had diabetes for many years, and there are good reasons to assume that the vascular disease of diabetics is a specific diabetic abnormality (LUNDBAEK, 1953, 1954, 1957). However, no detailed neuropathological studies of the

brain in long-term diabetes seem to have been published.

In the following report, the clinical observations and the neuropathological findings in the brains of 16 cases of juvenile long-term diabetes will be presented.*

The results of studies of the spinal cord, the peripheral nerves, the muscles and of the end-plates of the neuromuscular junction will be published later.

The Patients

Clinical observations of the patients included in this series are shown in the Table.

Ten of the 16 patients were men. The average age of onset of diabetes was 7 years; 14 of the cases having been diagnosed before puberty. The average duration of diabetes was 24 years (range 16—34 years). With this duration of diabetes at that age, about 85 per cent of an unselected diabetic population can be expected to show one or several signs of diabetic angiopathy (LUNDBÆK, 1953).

The cases selected for this study were young patients with severe and widespread vascular disease. All of them had *retinopathy*. The retinal lesion was severe in 14 of the patients and 9 of them were blind or nearly blind. Clinical signs of *nephropathy* were present in 11 and heart disease in 10. *Hypertension* was present in 10 cases at the time of death, but in most of them it had only been severe for a few months.

14 of the patients showed signs or symptoms of *nervous disease*. Areflexia (often with reduced vibratory sensibility) was present in all of them and 8 had mental disturbances. In 4 of the patients there were more pronounced signs of a central nervous system abnormality. A short summary of these four cases will be presented here.

Patient no. 1 began to have attacks of vertigo and paresthesias in the left hand 6 years before death. During the last two years of his life, there were numerous episodes of unconciousness with right or left hemiparesis lasting from a few hours to a few days. Between attacks neurological examination showed various abnormalities, e.g. difference in deep-tendon reflexes of the arms with dyspraxia and dysdiadochokinesis.

Patient no. 2 had neurological and cerebral symptoms for the last seven years of his life. He had severe attacks of dizziness with and without loss of conciousness of one to two hours' duration and one attack of hemiparesis with hemianopsia. His speech became increasingly slurred and his intellectual capacity deteriorated. During the last part of his life he was demented and showed rightsided spastic hemiparesis with involvement of cranial nerves VII, VIII, IX and XII.

Patient no. 3 had paresthesia and lancinating pains of the arms and legs, orthostatic hypotension and a single transient attack of mild left-sided hemiparesis. In the final stage of his life he was demented and slightly paranoid with anosognostic euphoria.

Patient no. 4 showed increasing intellectual impairment during the last 4 years of his life. He had muscular wasting of the legs and a Charcot type gait.

The *main cause of death* was renal insufficiency in 10 cases, coronary disease in 4, cerebral hemorrhage in 1 and pulmonary embolism in 1. However, in most of the patients a number of concurring causes of death were present.

Pathological Report

Autopsy of the Brains

The brains were fixed in four per-cent neutral formalin. 8 brains had slightly, 2 moderately and 6 heavily thickened leptomeninges. 5 showed a normal optic chiasm, 8 mild and 3 severe atrophy of the chiasm. The cortex revealed no atrophy in 5 brains, slight in 6, moderate in 2 and severe in 3. The circle of Willis was normal in 8 cases, showed slight alterations in 6 cases and in 2 severe degenerative changes. Only 5 brains revealed macroscopical softening. One brain showed a large hemorrhage of the brain stem (case no. 9).

Parts of the circle of Willis with ramifications, the chiasm, the cortex of the brain, the corpus striatum and the thalamus on both sides and parts of the brain stem with cranial nerves and the cerebellum were removed for histological examination. In 4 patients both Gasserian ganglions were also removed. All regions of the brain were thus represented.

In addition to the stains routinely used in the study of the central nervous system — hematoxylin-eosin, van Giesen, gallocyanin-chromalum (Einarson), toluidine blue and Mahon — the following special techniques were employed: staining for lipids (scarlet-red) and elastic tissue, a modified McManus, a modified Ziehl-Nielsen, axis-cylinder staining (Davenport), and Hale's technique for demonstration of acid mucopolysaccharides as modified by Rinehart and Abul-Haj.

Histological Examination of the Brains

Diffuse Changes. The *leptomeninges* are thickened and fibrosed with proliferation of the superficial cells and are infiltrated by numerous macrophages with PAS-positive material and lipid droplets in their cytoplasm and by lymphocytes.

The *chiasm* shows loss and degeneration of both the myelin sheaths and the axis cylinders of varying degrees. The astrocytes are proliferating and contain break-down products. Some of the chiasms are almost completely destroyed and transformed into a cicatrix of glial and connective tissue (Fig. 1).

In the *cortex* cerebri there are subpial gliosis and corpora amylacea. The ganglion cells show diffuse and focal loss. Many of the remaining ganglion cells reveal chronic degenerative changes with PAS-positive, acid-fast and Scarlet-red-positive granules in their cytoplasm. (Fig. 2). These granules are stained by gallocyanin-chromalum (Einarson), as well as with Hale's

* A preliminary report of three of these cases has been published earlier (RESKE-NIELSEN and LUNDBÆK, 1963).

Table 1. *Clinical and neuropathological findings*

Retinopathy: + diabetic retinopathy, ++ proliferative retinopathy, +++ severe proliferative retinopathy or enucleated eyes. — Nephropathy: (+) slight *proteinuria*, possibly with slight elevation of serum creatinine, + moderate decrease of kidney function, ++ clinical uremia. — Heart disease: + symptoms and/or signs of heart disease. — Arterial hypertension: (+) diastolic pressure 100—110, + diastolic pressure ≧ 110. — Hypoglycemic episodes: (+) seldom, + often, ++ numerous

No.	Initials	Sex	Age	Diabetes Age Onset	Duration of Diabetes	Retinopathy	Visual acuity	Heart Disease	Nephropathy	Uremia	Arterial Hypertension	Hypoglycemic Episodes	Neurological	Angiopathy	Areas of Softening	Diffuse Degeneration of the Brain	Pseudocalcinosis	Atrophy of Nucleus dentatus Cerebelli	Degeneration of Ganglion Gasseri	Fibrosis of Leptomeninges	Atrophy of optic Chiasm	Neuropathy of cranial Nerves
1	KG	M	32	4	28	+++	blind	+	++	+	+	(+)	Severe neuro-encephalopathic syndrome with multiple cerebral episodes	+++	+++	+	++			+++	+++	+
2	BGN	M	40	4	36	++	0.67—0.50	+	++	+	+	+	Severe neuro-encephalopathic syndrome with multiple cerebral episodes and dementia	+++	++	+	++	++		++	+	+
3	KLJ	M	38	14	24	+++	blind	+	++	+	+	(+)	Severe neuro-encephalopathic syndrome with dementia	+	++	+	+	+		+++	+++	+
4	PFN	M	27	3	24	+++	blind	+	++	+	+	(+)	Neuro-encephalopathic syndrome with mental impairment	+	++	+	+++			+	++	+
5	BGH	M	28	8	20	+++	blind	+	++	+	+	++	Areflexia. Some mental impairment	+	++	+	+++	++		+++	+++	+++
6	KGL*	M	29	6	23	++	0.05—0	+**	(+)	+	+****	(+)	Areflexia. Paresthesia	(+)	++	+	+	++		++	+++	++
7	BEH	F	39	18	21	+	0.05—0.1	+	++	+	+	+	Areflexia	+	++	+	+	++	+	++	+++	+
8	HN	M	28	8	20	++	reduced on one side	+	++	+	+	+	Areflexia. "Slow witted"	+	+	+	+	+		+++	+	++
9	HRJ	F	34	3	31	++	0.67—0.5	+	(+)	+	(+)	++	Areflexia. "Nervous breakdowns"***	++	+	+	+	+		+++	+	+
10	ESO*	M	21	3	18	++	0.67—0.33	+	+	+	+	(+)	Areflexia	(+)	+	+	+	++		+	+	+++
11	EIS	M	30	13	17	+++	blind	+	++	+	+	(+)	Areflexia. Agitated depression	+	+	+	+	++	++	++	++	+++
12	MMJ*	F	31	6	25	+++	blind	+	+	+	+	(+)	Areflexia	+	+	+	+++		++	+	+++	+++
13	JBC	F	32	2	30	+++	blind	+**	(+)	+	+	++	Areflexia	+	+	+	+++			+	+++	+++
14	EP*	F	43	9	34	++	0.67—<0.1	+**	+	+	(+)	++	Symptoms of severe peripheral neuropathy	+++	+	+	++			+	++	+
15	KMJ	F	25	5	20	+	reduced	+	++	+	+	+	No symptoms or signs	(+)	+	+	+	+	+	+	+	+++
16	FKH	M	24	8	16	++	reduced on one side	+	++	+	+	(+)	No symptoms or signs	(+)	+	+	+++			++	++	+++
Average			31	7	24																	

* hypophysectomized. ** died of coronary thrombosis, no symptoms or signs before. *** died of acute brain stem hemorrhage. **** only last 2 weeks of life.

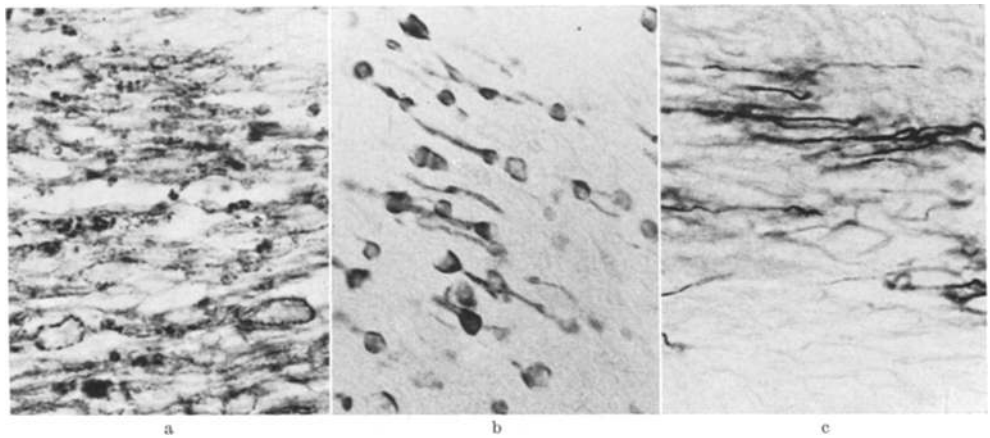

Fig. 1. Optic chiasm. a: Severe degeneration of the myelin sheaths, (Mahon, high magnification). b: Almost completely destroyed chiasm with remains of myelin sheaths, (Mahon, high magnification), c: and axis cylinders, (Davenport, high magnification)

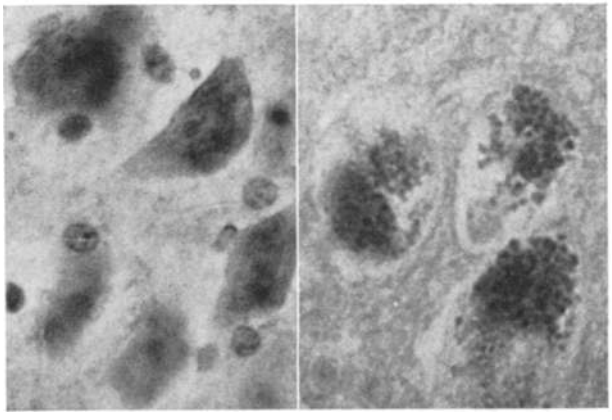

Fig. 2. Ganglion cells. a: Lipid breakdown products in the cytoplasm, (Scarlet red, high magnification). b: PAS-positive granules in the cytoplasm, (PAS-staining, high magnification)

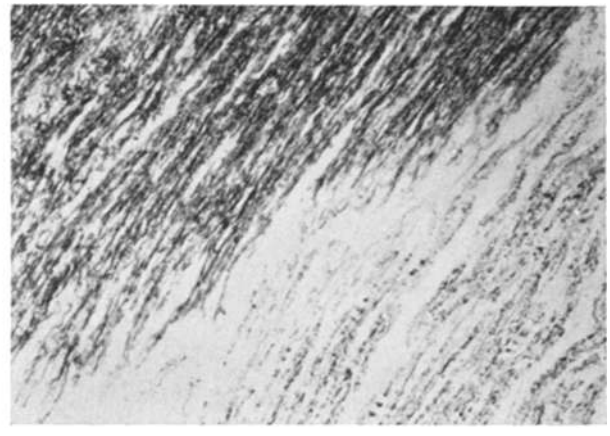

Fig. 3. A trigeminal nerve. The myelin sheaths of only the central glial part are degenerated and the peripheral part almost totally demyelinated, (Mahon, high magnification)

technique for demonstration of acid mucopolysaccharides as modified by Rinehart and Abul-Haj. They are self-fluorescent. The same break-down products are seen free in the tissue, in the glial cells and along the vessels. The nuclei are eccentrically placed, swollen and partly faded. Some of the cells are shrunken and surrounded by satellites.

The *white matter* is swollen showing status spongiosus, especially around the vessels. The myelin sheaths are unequally calibrated and sometimes broken up inflakes. The axis cylinders are thinned, thickened or corkscrew-like. Interspaced between the myelin sheaths, astrocytes with PAS-positive material are observed. Along the vessels, occasional oligodendroglia cells show proliferation.

The *ventricular walls* show subependymal gliosis and small, naked glial nodes. The ependymal cells contain lipid droplets and PAS-positive granules in their cytoplasm.

In the *basal ganglia*, *brain stem* and *cerebellum* the same diffuse changes are to be found.

The *cranial nerves* are normal in two of the patients. In the others, the peripheral part of the nerves, that part containing Schwann's cells, shows severe or total demyelinisation. The axis cylinders here are preserved, although sometimes degenerated. However in the central glial part, that part where oligodendroglia cells have replaced Schwann's cells, only swelling and unequal calibration of the myelin sheaths is seen. The axis cylinders here are only slightly degenerated (Fig. 3, 4).

The *ganglion Gasseri* shows loss of ganglion cells, which are replaced by Nageotte's nodes. Many of the remaining cells are degenerated with displaced, blurred nuclei and coarse vacuolization of their cytoplasm. In spite of the relatively slight changes in the ganglia, there is considerable, sometimes almost total, demyelinisation of both the centrally and peripherally direct-

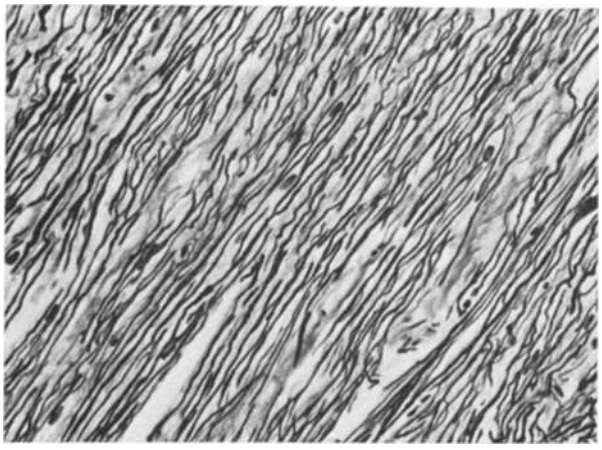

Fig. 4. A trigeminal nerve, (the same part as fig. 3) in axis cylinder-staining. The axis cylinders are only slightly degenerated, both in the glial and peripheral part, (Davenport, high magnification)

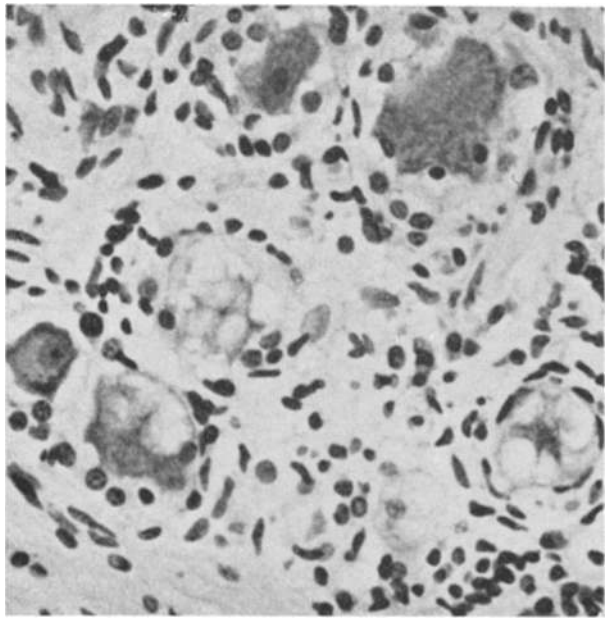

Fig. 5. The ganglion Gasseri with shrunken and coarsly vacuolized ganglion cells, (Gallocyanin-chromalum (Einarson), high magnification)

ed branches of the originally bipolar ganglion cells. The axis cylinders show only slight loss and degeneration. The motor root is normal in some cases; in others, it is demyelinated (Fig. 5).

Vascular Changes. The *large* and the *medium-sized arteries* of the leptomeninges and the brain reveal small nodular intimal thickenings consisting of a fine meshwork of elastic tissue and fibroblasts, in which there are cholesterol crystals and phagocytes with fat droplets and a few PAS-positive granules located in the cytoplasm. In a few of the vessels the phagocytes have penetrated through the lamina elastica interna into the musculature, which is destroyed. The lamina elastica interna is often degenerated at the nodular thickenings, while reduplication of it is seen in other places. Calcification between the elastic membrane and tunica media extending into the musculature is occasionally found. In one case an organized, recanalized thrombus was seen. Several *small arteries* and *arterioles* show accumulations of large, refractile, fat-laden phagocytes or a rim of lipid products beneath the endothelium or between the intima and the lamina elastica interna. In places the walls are completely transformed into lipid products. In some vessels the fibrils of the walls are thickened and show increased PAS-positivity. Along the ventricle walls arterioles show hyalinosis. PAS-reaction is negative or very slight here. In three of the cases the small arteries and arterioles show enormously thickened, homogenous walls with heavily PAS-positive substances. The lumina are irregularly narrowed or occluded. In a few of the brains the *capillaries* reveal diffuse or focal thickenings of the basement membrane (Fig. 6, 7).

Diffusely stained lipid or fat-laden phagocytes can be seen in the lumina of both large and small arteries. Around the vessels a variable number of lymphocytes and phagocytes with lipid droplets, bi-refringent lipids and PAS-positive material in their cytoplasm are seen.

The perivascular connective tissue of the arteries and veins, especially those adjacent to the ventricular walls is increased. It is very loose or made up of closely aggregated fibrils in which phagocytes and a few lymphocytes are embedded. The connective tissue is confluent with the adventitia of the vessels and the surrounding brain tissue in which a

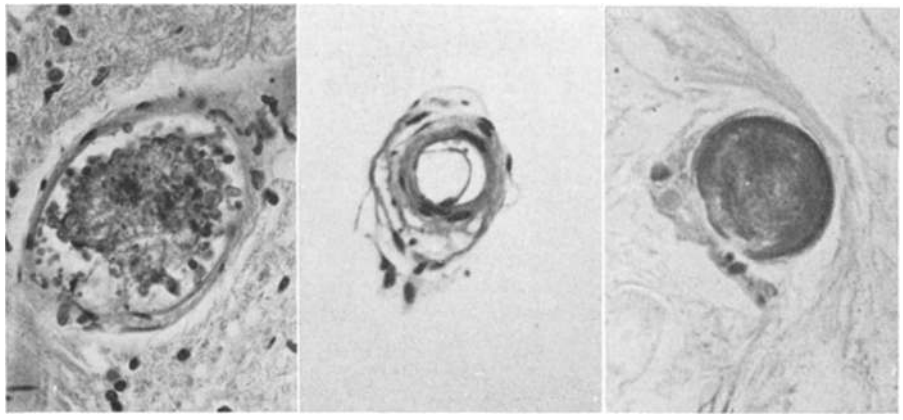

Fig. 6. Angiopathy of cerebral vessels. a: A small artery with fat-laden, PAS-positive phagocytes beneath the intima. The phagocytes are calcified. The lumen is narrowed and excentrically placed, (Haematoxylin-eosin, high magnification). b: A small artery with a rim of lipid products beneath the endothelium, (Haematoxylin-eosin, high magnification). c: An arteriole with enormously thickened, homogeneous, heavily PAS-positive wall. The lumen is nearly occluded, (PAS-staining, high magnification)

festoon-like border is visible. The astrocytes extend processes into the connective tissue.

As in the ventricular walls, the ependymal cells of the *plexus choreoideus* contain lipid droplets and PAS-positive granules. The vessels show the same changes as mentioned above. Beneath the ependymal layer we find crescent-shaped, PAS-positive and lipid-positive structures, which are sometimes calcified (Fig. 8).

Ten of the brains show areas of softening of variable age. They are made up of microglial cells with PAS-positive and lipid positive granules in their cytoplasm, fine proliferating vessels, streaks of connective tissue and may show secondary calcifications. At the margins of the softened areas astrocytosis is found (Fig. 9, 10).

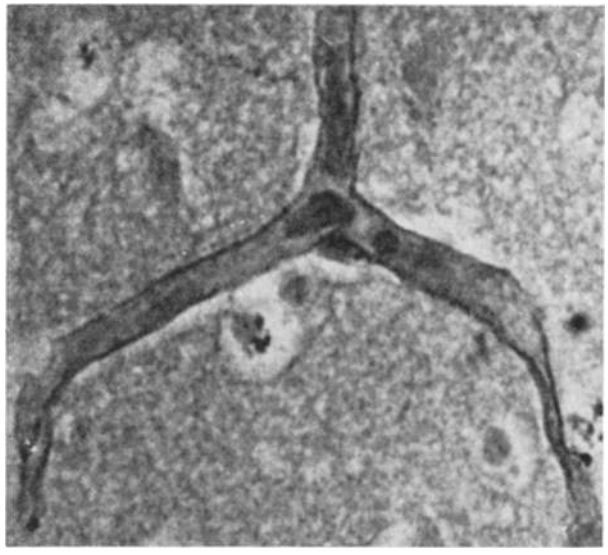

Fig. 7. A capillary with focal thickenings of the basement membrane, (PAS-staining, high magnification)

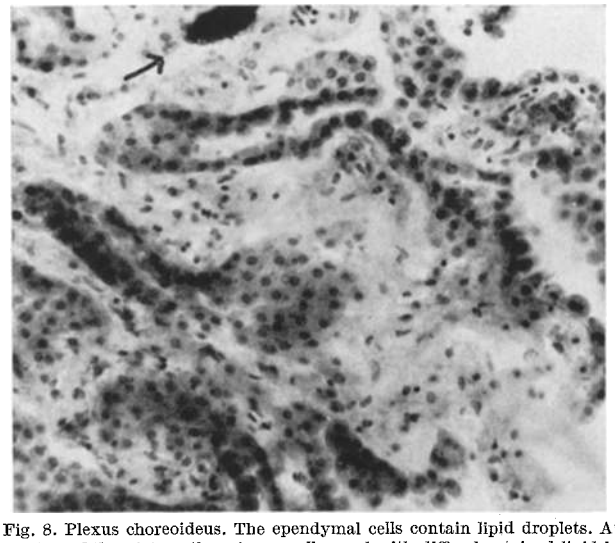

Fig. 8. Plexus choreoideus. The ependymal cells contain lipid droplets. At the top of the picture there is a small vessel with diffusely stained lipid in the lumen, (arrow) (Scarlet red, high magnification)

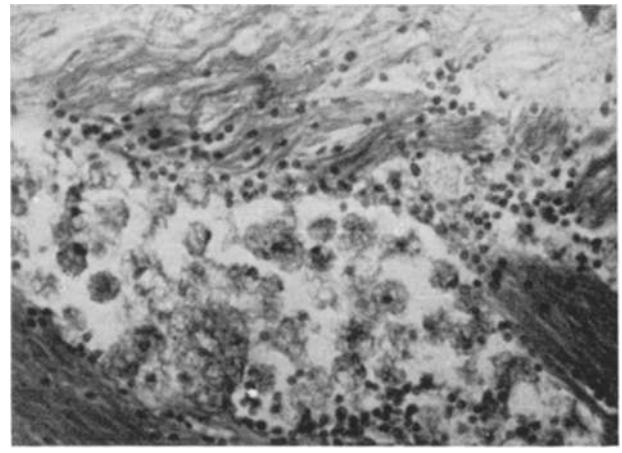

Fig. 9. Area of softening in the pons with fat-laden and PAS-positive microglial cells, (Mahon, high magnification)

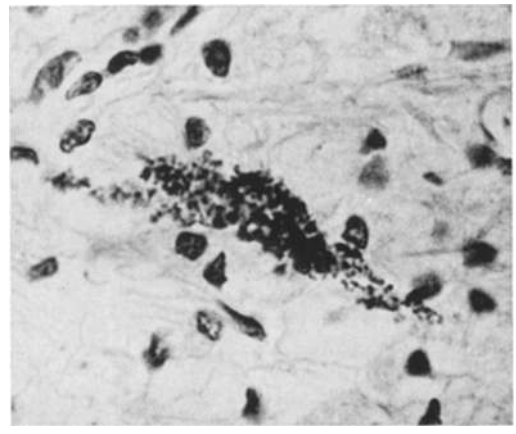

Fig. 10. A calcified ganglion cell in the periphery of an area of softening, (Haematoxylin-eosin, high magnification)

Areas of softening are numerous in only two of these brains. They are localized in the cortex as well as in the white matter, the basal ganglia and the brain stem. In six cases we find a single area of softening in the hemisphere and/or one or more in the brain stem. A large hemorrhage of the brain stem is seen in one case (case no. 9).

Other findings. Eight of the 16 brains show severe *primary symmetrical pseudocalcinosis.* In six of the brains this abnormality is seen both in the globus pallidus and in the dentate nucleus of the cerebellum, while in two other brains it involves only the globus pallidus (Fig. 11, 12).

In these areas the walls of the large and the small arteries as well as the veins and the capillaries are more or less encrusted with pseudocalcium deposits, which are placed in one or more of the following layers: the intima, the tunica media, the adventitia or the perivascular tissue. Sometimes there are conglomerates of this substance free in the parenchyma.

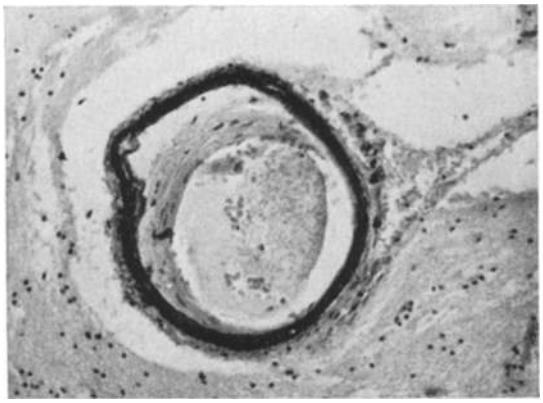

Fig. 11. A medium-sized artery from the globus pallidus with thickened intima and calcified lamina elastica interna and tunica media, (Haematoxylin-eosin, low magnification)

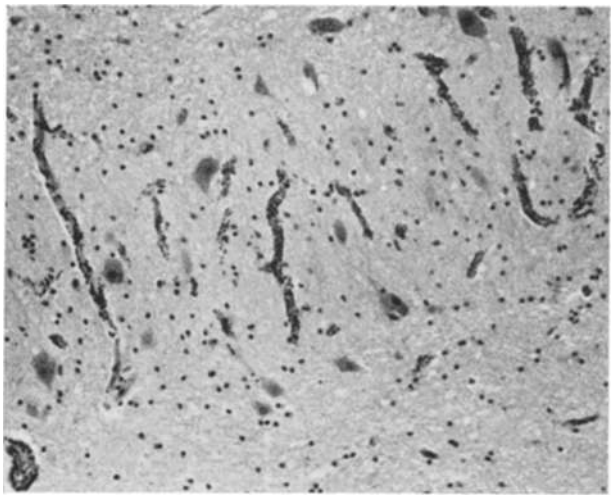

Fig. 12. Calcified capillaries of the dentate nucleus of cerebellum ("pseudocalcinosis"). The ganglion cells are well preserved. (Haematoxylin-eosin, low magnification)

The lumina of the vessels are often extremely narrowed as a result of the homogeneous thickening of the intima. However, the ganglion cells of these regions are not calcified and remarkably little damaged and no areas of softening are seen.

In six of the brains the dentate nucleus of the cerebellum shows considerable diffuse atrophy compared with the remaining parts of the brain. In two of the brains these alterations are combined with symmetrical pseudocalcinosis of the globus pallidus.

Correlations

Table 1 shows correlations between clinical and pathological findings. The patients have been listed according to the number of localized areas of softening.

Abnormalities of the small blood vessels of the cerebrum, similar to those observed in other organs in long-term diabetes, were present in all the brains. They were severe in four cases. There was no clear-cut correlation between the degree of small vessel change and the clinical picture. It appears, however, that except for patients no. 6 and 7, a reasonable correlation obtains between the number of softened areas found and the symptoms and signs observed during life.

Diffuse degeneration of the brain was present in all cases. It varied somewhat from case to case and from one area of the brain to another, but we found it impracticable to give a quantitative estimate of this abnormality.

Severe pseudocalcinosis was found in eight of the patients, atrophy of the dentate nucleus in six. These changes were present in patients both with and without symptoms of cerebral disease. The same applies not only to fibrosis of the leptomeninges, which was seen in all the cases and which was severe in seven, but also to neuropathy of the cranial nerves (14 cases). Severe atrophy of the optic chiasm was present in all the patients who were blind or nearly blind.

The diffuse damage of the brain tissue was more severe than would be expected from the angiopathy.

Most of the patients were uremic at the time of death, but the six non-uremic patients also showed diffuse degeneration; one of them had areas of softening, and three had pseudocalcinosis.

There was no apparent correlation between the cerebral abnormalities and the blood pressure or the tendency to hypoglycemic episodes during life.

Discussion

Vascular abnormalities, sometimes localized areas of softening, and degeneration of the brain were found in these 16 young juvenile diabetic patients who had died of one or another manifestation of their diabetic angiopathy after 17 to 36 years of diabetes. Fibrosis of the meninges was present in all the cases, and the rare symmetrical abnormality known as "pseudocalcinosis" was found in 8. Abnormalities of the cranial nerves were present in 14 of the patients.

Histological changes in the brains of long-term juvenile diabetics not dying in diabetic coma have been mentioned by a few authors. DEJONG (1950) described the findings in a 28 years-old patient who had had very poorly controlled diabetes mellitus for 9 years and terminally developed severe signs and symptoms of cerebral disease. The histological examination of the brain disclosed changes apparently rather similar to those observed in our cases.

Severe symmetrical pseudocalcinosis, as observed in several of our cases, is a rare condition found particularly in some kinds of oligophrenia. A remarkably high and unexplained incidence in myxedema and hypoparathyroidism has often been discussed (ERBSLÖH and BOCHNIK, 1958).

Clinical signs of cranial nerve involvement has often been observed in patients with long-term diabetes

(Weinstein and Dolger, 1948), but we have found no pathological studies in the literature. In the present series there were several cases of demyelinisation and degeneration of the axis cylinders of the cranial nerves. Hemorrhages of the nuclei were not observed.

It is obvious that the various sequelae of diabetes, e.g. multiple hypoglycemic attacks, hypertension and uremia, may have some significance for the pathological changes observed in the brain. However, the correlation between brain pathology and hypertension, uremia and the occurrence of hypoglycemic episodes was poor in our series, and the pathological changes do not look like those of non-diabetic patients with these conditions.

In patients dying of *hypoglycemia*, severe changes of the central nervous system are found: focal or laminar necrosis of one or several layers of the cerebral cortex, Ammon's horn and the striatum. The globus pallidus is intact. The ganglion cells either show acute swelling and chromatolysis or have disappeared altogether (Greenfield, 1960).

This histological picture differs from the one observed in our cases where necrosis was absent and the ganglion cell abnormalities were usually of the chronic type characterized by PAS-positive and lipid cytoplasmic granules.

Arterial hypertension is accompanied by the well-known hypertensive angiopathy in the brain as well as in other organs. In their milder form these changes are not always distinguisable from those seen in long-term diabetics, with or without hypertension. However, muscular hypertrophy and typical reduplication of the internal elastic lamina of the arterioles was not observed in our cases, and mild hypertensive angiopathy of the brain does not give rise to severe degeneration of the brain.

There are few abnormalities of the brain in *uncomplicated uremia* in young patients; Steen Olsen (1961) observed slight nerve cell degeneration. This degeneration was seen particularly in the reticular formation and the sensory nerve nuclei. In those of his cases where uremia was combined with hypertension, focal necrosis of the pons was also often observed. Both of those histological pictures are different from the pattern found in our cases.

Severe symmetrical pseudocalcinosis does not seem to have been described in cases of hypoglycemia, arterial hypertension or uremia.

It is not clear whether or not the degenerative brain lesions are caused by cerebral vessel angiopathy. All the patients had some degree of vascular abnormality, but the correlation between the vascular and the neuropathological changes was not striking. The overall impression of diffuse damage to the brain tissue suggests an abnormality too severe to have been caused by the ischemia of the angiopathy *alone*.

It is possible that the lesions observed are caused by a combination of ischemia and a primary diabetic abnormality in the metabolism of the central nervous system. The same hypothesis has been advanced to explain several other neurological findings in diabetic patients. e.g. the paradoxical preservation of vibratory sensibility during ischemia (Steiness, 1959, 1961), the early changes in motor-nerve conduction velocity (Gregersen, 1964), and the occurence of cytoid bodies in the nerve fibre layer of the retina giving rise to the soft exudates seen at ophthalmoscopy (Esmann, et al., 1963).

The nature of the primary diabetic abnormality of central (and peripheral) nervous tissue metabolism is unknown, but insulin has been shown to influence the carbohydrate metabolism of the brain *in vitro* (Rafaelsen, 1961).

It seems reasonable to assume that the rather uniform pathological picture observed in these 16 brains from long-term juvenile diabetics — diffuse degenerative abnormalities, often with severe "pseudocalcinosis" or atrophy of the dentate nucleus of cerebellum, demyelinization of the cranial nerves, fibrosis of the leptomeninges and angiopathy — is the result of diabetes mellitus. It varies only in degree from patient to patient and seems to justify the term "diabetic encephalopathy". The individual changes observed are not specific, but they form a characteristic pattern not known in other conditions. The term diabetic encephalopathy is therefore to be understood in the same sense as the term diabetic retinopathy and diabetic nephropathy.

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