A FOURTH TYPE OF PHAKOMATOSIS

STURGE-WEBER SYNDROME[1)]

BY

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In 1917 one of us (V. D. H.) grouped two closely related diseases under the name of *phakomatosis,* because they frequently had a cutaneous naevus (Greek- φακός) as a common characteristic sign. In this name is implied a congenital or hereditary factor. These conditions are usually characterized by the presence of cutaneous naevi, malformations and/or true tumours. The first two conditions grouped under this name were tuberous sclerosis (sclérose tubereuse des circonvolutions cérebrales, BOURNEVILLE's disease) and neurofibromatosis multiplex (VON RECKLINGHAUSEN's disease) (10). These diseases have in common the presence of

1. Small skin blemishes, frequently spoken of as naevi, and similar abnormalities of the mucous membrane in any part of the body.
2. Localized tumourous malformations such as hamartomata, choristomata etc.
3. Blastomata which occasionally undergo malignant change.
4. True malignant tumours.
5. Other congenital abnormalities.

The more recently described entity, angiogliomatosis retinae et cerebelli (VON HIPPEL-LINDAU disease), was later included in this group of phakomatoses (11). In this condition vascular abnormalities of the retina and cerebellum, tumourous malformations, cysts and occasionally cutaneous naevi are found.

These three conditions show sufficient resemblance to be considered in one group and sufficient difference to remain nosological entities.

This paper reports a case of naevi venosi, congenital abnormalities of the eye with tumour formation and pathological changes in the brain with calcification. This combination has been termed by BERGSTRAND, OLIVECRONA and TÖNNIS in their recently published monograph on vascular tumours and malformations of the brain (2) as STURGE-WEBER syndrome. The anatomico-pathological study of this case led us to conclude that this syndrome should be included as a fourth type of phakomatosis.

In STURGE-WEBER's syndrome cutaneous telangiectases in the face and other parts of the body are associated with buphthalmos, abnormalities of the blood vessels of the choroidea, cerebral abnormalities manifesting themselves by imbecility, epilepsy and paralyses usually on the side contralateral to the facial naevus. The best known case is that of KALISCHER (15) who described the brain of an eighteen month old infant with left sided facial telangiectasis and epileptic manifestations on the opposite side of the body. The left cerebral hemisphere was smaller than the right and numerous fine coiled blood vessels were enmeshed in its pia mater. HEBOLD (9) was the first to show that as well as angio-

matosis, hypoplasia and microgyria, an extensive calcification might occur in the brain in this condition.

In 1922 WEBER (21) reported a case of a 22 year old woman with a left facial naevus, a left buphthalmos and a congenital right-sided hemiplegia. In roentgenograms of the skull he saw parallel dark streaks on the left side. The practical importance of this demonstration was so great that BERGSTRAND, OLIVECRONA and TÖNNIS have given WEBER equal distinction with STURGE who in 1879 first described the combination of unilateral congenital glaucoma, ipsilateral naevus flammeus and epileptic attacks localized to the side of the body contralateral to the naevus. WEBER interpreted the shadows as an angioma racemosum and this interpretation has been followed for many years by others. In 1934 KRABBE (16) showed however that these calcifications were not always in the walls of blood vessels but occurred in the cortex itself. He reported five cases of facial naevi associated with intracranial calcification, and gave the post-mortem findings in one instance. His paper gives a full bibliography of the reported cases of facial naevi associated with intracranial calcification. In 1935 MONIZ and LIMA (17) showed by arteriography in one case that the intracranial calcification associated with a facial naevus did not coincide with the shadows of the bloodvessels thus confirming the findings of KRABBE. BERGSTRAND came to a similar conclusion from the study of tissue removed from such cases at operation by OLIVECRONA. For a detailed study of this syndrome we refer to the paper of SCHIÖZ (18), in which a complete survey of the literature is given. Clinical observations have been also reported recently by APPELMANS (1), FURTADO (7), VAN BOGAERT (3), VERBEEK (20), VAN WESTRIENEN (22), a.o.

Finally we would call attention to the studies of YAKOVLEV and GUTHRIE (23) (1931). These investigators brought the cases of angiomatosis of the brain with naevi in the skin of the trigeminal area in one group with two other congenital neurocutaneous syndromes, RECKLINGHAUSEN's neuro-fibromatosis and BOURNEVILLE's tuberous sclerosis.

CASE REPORT.

CLINICAL HISTORY.

J. B., a girl born on April 26 1932, was admitted to the Ophthalmological clinic of the University at Leiden on April 17 1935.

Family History: Father, mother, and five brothers and sisters are living and well. Two cousins are imbeciles, one of which is also epileptic. There are several alcoholics in the family. A halfbrother of the mother of the child is a demented epileptic with a slight hemiparesis. Roentgenograms of his skull show a small shadow of calcification so that it is highly probably that he is afflicted by a forme fruste of the same disease as described in this paper. Hence in our case an heredity factor is present.

Birth and *Development:* The child was delivered at term with the help of forceps which is said to have injured the right upper eyelid. It was further noted at birth that the child was not normal because the greater part of the face was covered with a naevus. Her mental development was so retarted that even the mother regarded the child as backward. Convulsions occurred at the age of 5 weeks.

Subsequent History: The child was admitted to Saint Elisabeth's Hospital at Haarlem on February 24 1933 because of fever and vomiting for 1½ days. Examination revealed a heavy, fat child with a reddish blue face due to telangiectases which covered the face, excepting the left forehead and lower jaw, and extended over the occiput, neck, anterior thorax and vulva. There was a lesion probably congenital of the right upper eyelid, which was discharging pus. The heart and lungs were normal: the liver and spleen were not enlarged. There was no rickets. The reaction of VON PIRQUET was negative. The neck was not stiff. As the child continued to vomit lumbar puncture was done on March 2, 1933. The pressure was elevated, and the fluid, which contained 10 cells, was clear. The reactions of NONNE and PANDY were positive, and the sugar content was normal. Subsequent lumbar punctures gave similar results. The presumtive diagnosis was encephalitis (?).

The child was discharged from the clinic on April 22, 1933, to be followed in the Out Door Department. It was then evident that she was blind in the right eye, which was quite dark due to old blood in the chambers. The lesion of the right eyelid was thought to be coloboma, although birth trauma was considered and the changes of the right eye were associated with the naevi of the face as developmental defects (DR. C. WINKLER PRINS).

On March 13 1934 the child was admitted for the second time to the same hospital because of an abscess the size of a pigeon's egg in the occipital region. After incision and drainage the patient recovered in a short time. On this occasion it was noted that the child was bloated and pasty in appearance. The naevus vinosus of the face had become larger. The left eye was normal and the right blind. There was paresis of the left arm. The child was discharged on 3 April 1934.

One year later she was brought to the Ophthalmological Clinic of the University at Leiden. At that time the left eye, including the fundus, was normal. The right eye protruded and was turned upward by a hard tumour (angioma?). The cornea was opaque and was covered by the upper lid on which was a coloboma. The maxillary glands were swollen. A naevus flammeus covered the right half and most of the left side of the face (Fig. 1); the tongue and the palate were also involved in the process. The left arm was paretic and atrophic and some fingers of the left hand

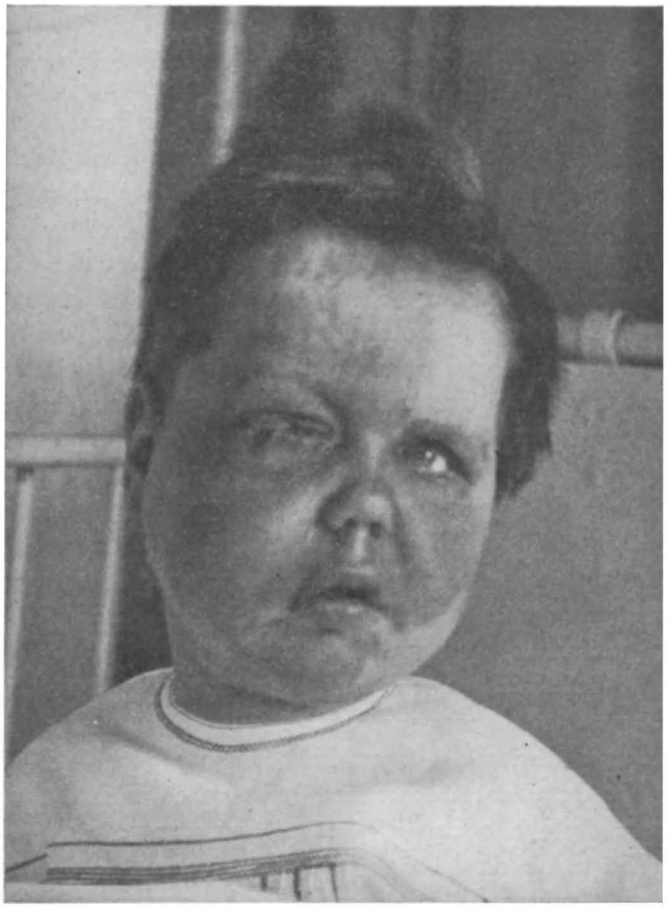


Fig. 1. Naevus of face, tumour in right orbit and coloboma of the right upper eyelid.

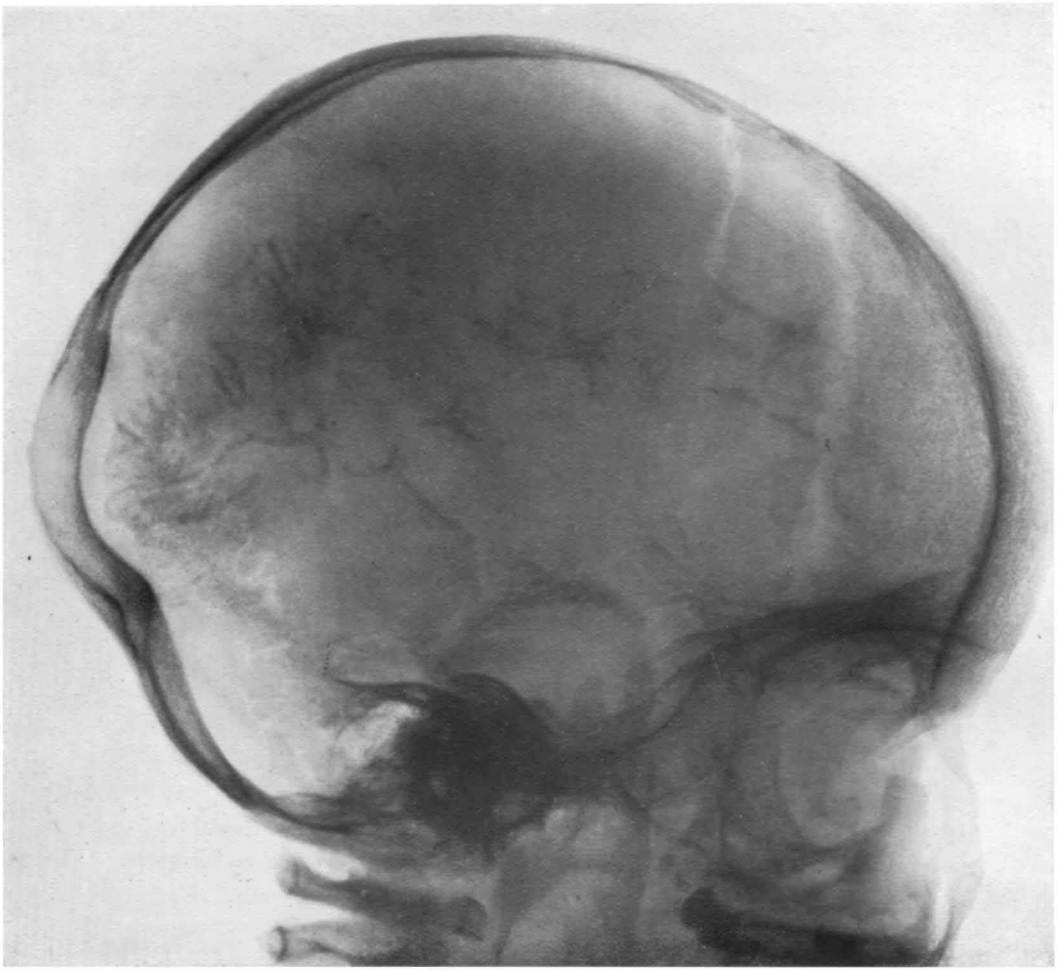


Fig. 2. In the roentgenogram of the skull are shadows caused by extensive calcification in the cortex of the right cerebral hemisphere.

were dislocated. The left knee jerk was more lively than the right. On the left a positive BABINSKI response was elicited, and on the right the STRÜMPELL reflex.

Roentgenological examination of the head revealed shadows which had the pattern of the gyri of the cerebral cortex (Fig. 2). They extended on the right side from the frontal to the occipital pole and were considered by the roentgenologist to be caused by a calcified angioma of the right cerebral hemisphere. The examination also demonstrated enlargement of the right orbit but no erosion of bone.

Operation was recommended and the bulbus with an intraocular tumour and an intraorbital tumour were removed on 26 April 1935. Diagnose of the tumour gliomaretinae, see p. 9. Postoperative radiation treatment was begun one week later.

Neurological examination by DR. G. W. KASTEIN on 8 May 1935. The left arm was adducted to the body in spasm, the elbow and wrist flexed. The fingers and thumb were all adducted and their tips brought together to a point. On the left the fingers and thumb were more resistant than on the right side. The left hand was bluer in colour than the right. There was clonus of the left foot and a positive BABINSKI response of the same. Mentality was impaired. It was concluded that there was a lesion of the right pyramidal tract in the forebrain and that the right frontal lobe was not normal on the ground of mental disturbance with a distinct grasp reflex of the left hand.

By the 26 June 1935 the tumour had grown so rapidly that it had already extended outside the orbit. It had ulcerated and exuded a haemorrhagic fluid. The glands anterior to the right ear and the parotid were very much swollen. The tumour was attacked again but recurred very quickly so that on 13 September 1935 the lower part of the right orbit was destroyed as shown by Roentgen films. Ophthalmoscopic examination at this time revealed hyperaemia and beginning tortuosity of the blood vessels of the left fundus but no other retinal changes. The child's condition became worse and death occurred on 28 October 1935.

ANATOMICAL EXAMINATION.

The post mortem examination was made 14 hours after death by Professor DR. G. O. E. LIGNAC of the University at Leiden. His principal findings were as follows:

The body is extremely emaciated and the face deformed. The right eye is not present and in its place is a large hard tumour which protrudes 6 cm. beyond the ridge of the nose. It is 8.5 cm. in cross section. The nose is displaced to the left and the right maxilla downwards. The tumour is ulcerated and the eyelids are covered with brown crusts. There is also a swelling which extends from the right mastoid process, under the right ear (which is almost closed), to the middle of the right mandible. The

posterior part of the tumour is nodular, the anterior part fluctuant, and the skin over it is bluish purple. There is a loss of superficial epithelium over the fluctuant area. The left eye is turned to the inner side and the conjunctiva is oedematous. In the left orbit is a hard swelling and several other small ones are found under the left ear and mandible. There is a conglomeration of lymph glands on the right side of the neck and a firmly fixed swelling over the right parietal region of the skull which can be impressed.

The musculature is poorly developed, grey-brown in colour, and contains very little moisture. There are no malformations of the thoracic or abdominal viscera. The lungs are emphysematous and there is inflammation on the right side. The para-aortic lymph glands are grey-white and swollen. The abdomen is filled in great part by the liver which extends 2 cm. below the right costal margin. It is grey-yellow and on its surface are a number of sub-capsular foci some of which are purple and others grey-white and translucent. The liver weighs 600 grams. The kidneys are studded with superficial red star-like flecks. When sectioned the kidneys appear swollen and there is tumour tissue to be seen between the capsule and cortex. There are also tumours of the walls of the stomach and gall-bladder, the ovaries, and the pancreatic lymph glands. The bone marrow is red.

The skull is asymmetrical, the right side being flattened, and the cranial bones have grown together with the dura. In the right occipital and parieto-frontal regions there are many brittle purple-red masses fixed to the dura mater on its outer surface. The arachnoidea on the right side is purple, thick, and attached to the dura; on the left it is free. The right half of the brain is diffusely red over the convexity and there is subarachnoidal oedema. The veins entering the superior saggital sinus from the left side are filled with firm tumour masses. The superior saggital sinus contains tumour tissue and a thick mural thrombus. The reddish purple tumour masses within and above the left orbit are in connection with each other by way of the posterior openings of the orbit.

The right cerebral hemisphere is smaller than the left. The left cerebellar hemisphere is hard and atrophic and the convolutions are small and flat. The left posterior fossa is much smaller on the left than on the right; this runs parallel with the left cerebellar atrophy.

Microscopical examination reveals that the different tumour masses within the skull, liver, kidneys, ovaries, lymph glands, hypophysis, stomach, gall-bladder, bone marrow and veins have the same characteristics. The tumour is very sanguineous. It is composed of groups of erythrocytes arranged in trabeculae, now and then bordered by endothelial cells. Between these is a cellular picture composed of polymorphonuclear leucocytes, karyorrhectic nuclei and round or oval nuclei which are generally larger than or of the same size as the leucocytes. They have a diffuse distribution of chromatin which is granular and without clear

structure. A small zone of protoplasm is to be seen around only a few of the nuclei. The tumour nuclei lie directly against the endothelial wall. From the VAN GIESON sections it is clear that there is also a trabecular network of connective tissue containing blood vessels. In some places the tumour cells penetrate in groups into the connective tissue of the dura mater.

The liver is diffusely fatty. The tumour cells are as described above for those within the skull. There is a very fine karyorrhexis of the nuclei which vary considerably in size. They have scarcely any protoplasm surrounding them. Bridges of atrophic liver cells are to be seen between groups of free lying tumour cells. The latter are also to be found in the blood of the liver veins, and in the mucosa, submucosa, and muscularis of the gall-bladder.

The same type of tumour cell is found in the glandular tubes of the gastric mucosa and in the muscularis mucosae, also in the kidneys and ovaries. The bone marrow is replaced almost completely by blastoma tissue with typical karyorrhectic pictures. The anterior lobe of the hypophysis is likewise invaded. The para-aortic lymph glands are almost completely occupied by blastoma cells and only occasional groups of lymphocytes are still present. This is also true of the cervical, supraclavicular and pancreatic lymph glands. It is striking that the tumour cells have invaded the capsules of the kidneys, lymph glands and hypophysis in the same way as mentioned above regarding the dura mater.

DOPA preparations of the liver, kidneys and lymph glands did not demonstrate the pigment of a melanoma.

It was concluded that the tumour was a malignant blastoma of the right retina with metastases.

The central nervous system was by permission of Professor LIGNAC examined in the Neurological Laboratory of the University at Amsterdam.

Description of the tumour of the right eye: The bulbus oculi is filled with a mass of tumour which perforates the sclera over a great extent near the optic nerve. The latter is free as far as can be seen within the orbit although the whole papilla is occupied by tumour. Macroscopically and microscopically the tumour has the characteristics which ophthalmologists have associated with glioma retinae. The tumour cells stain best where they lie in thick walls around the blood vessels. At greater distances from these vessels they do not stain as deeply and here and there the tumour has become necrotic. There is nothing to be found of the retina or choroid. The corpus ciliare is very atrophic and has been pushed away from the sclera by the tumour. In the space for the corpus vitreum necrotic areas are found as well as necrotic tissue masses which are rests of the lens. Some of these masses are undergoing ossification. The tumour consists of immature cells which have not yet differentiated into glia or nerve cells. Architecturally they are sometimes arranged in rosettes. Although

this tumour is malignant it is in the final analysis composed of cells of the same origin as those found in the usually benign retinal growths associated with tuberous sclerosis. Since the cells of origin are undifferentiated retina cells, the tumour may be called a retinoblastoma and because the tumour consists of cells which differentiate later into glia and neuro-epithelial cells the glioneuroblasts it is best termed glioneuroblastoma malignum.

The eye is much enlarged, it is difficult to say whether this buphthalmos is only secondary to the growth of the tumour or that a primary buphthalmos was already present before the tumour enlarged the eye. It is highly probable that the buphthalmos is both primary and secondary.

The tumor has, as Fig. 3 and 3a show, perforated extensively the sclera. Within the tumour which is a glioma of very immature type we find calcification and ossification.

The chorioid as far as this tissue can be recognised, does not show the presence of vascular tumours.

DESCRIPTION OF THE BRAIN.

The right cerebral hemisphere is much smaller than the left and over it the pia arachnoidea is bluish grey coloured and thickened. (Fig. 4).

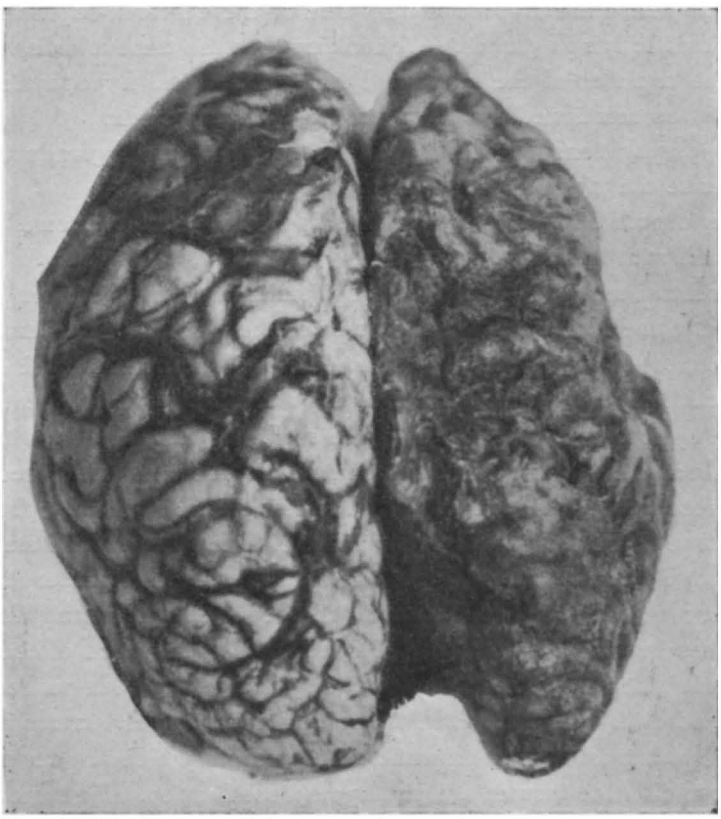


Fig. 4. Thickening and hypervascularity of the leptomeninges over the right cerebral hemisphere.

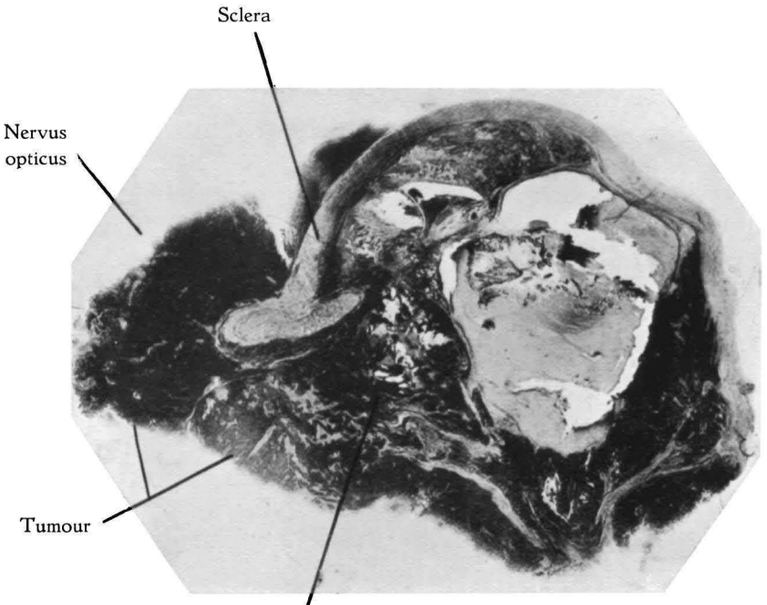


Fig. 3.

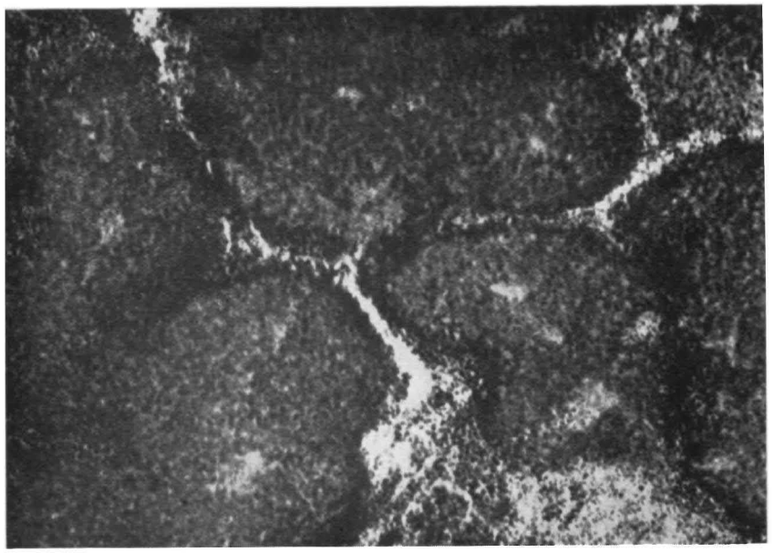


Fig. 3*a*. Glioma retinae.

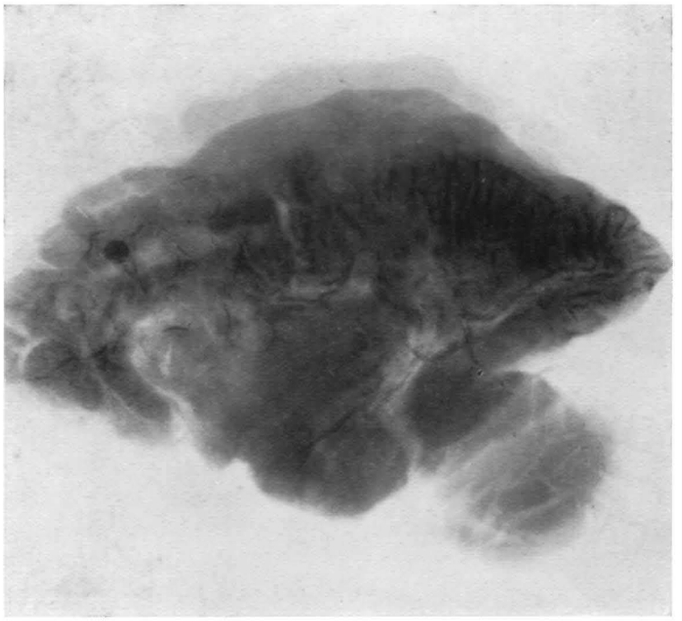


Fig. 5. Roentgenogram of the brain. Shadows showing extensive calcification through the whole right cerebral hemisphere.

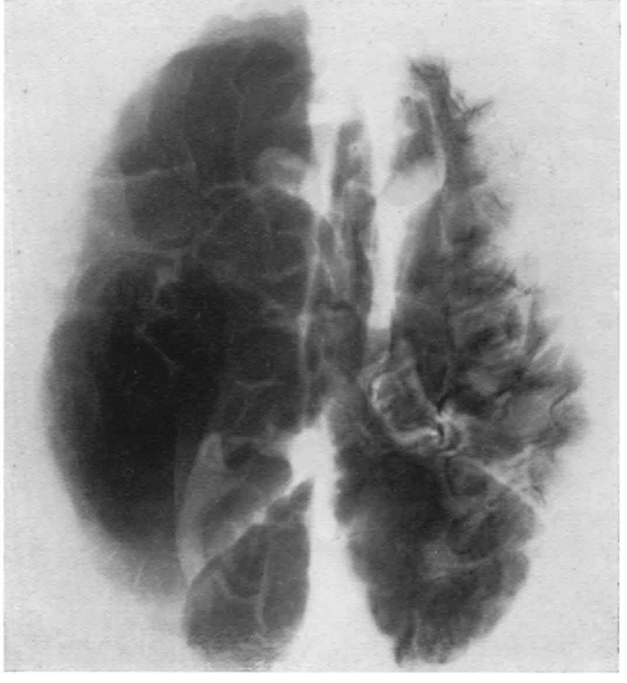


Fig. 6. Roentgenogram of the brain. Shadows showing extensive calcification through the whole right cerebral hemisphere.

This alteration of the leptomeninges is more pronounced over the convexity than at the base of the brain where the gyrus hippocampus and the adjacent parts of the cortex are better preserved. Roentgenograms of the brain show an extensive calcification through the whole right cerebral hemisphere and give the impression that this process is localized in the cortex itself because the shadows have an outline similar to that of the gyri of the cerebral cortex (Fig. 5 and 6). No calcification is seen in the Roentgen films of the left cerebral hemisphere, brainstem or cerebellum. Fig. 7 shows the atrophy of the right cerebral and crossed cerebellar hemisphere.

Several sections of the cerebral cortex with pia attached are cut out

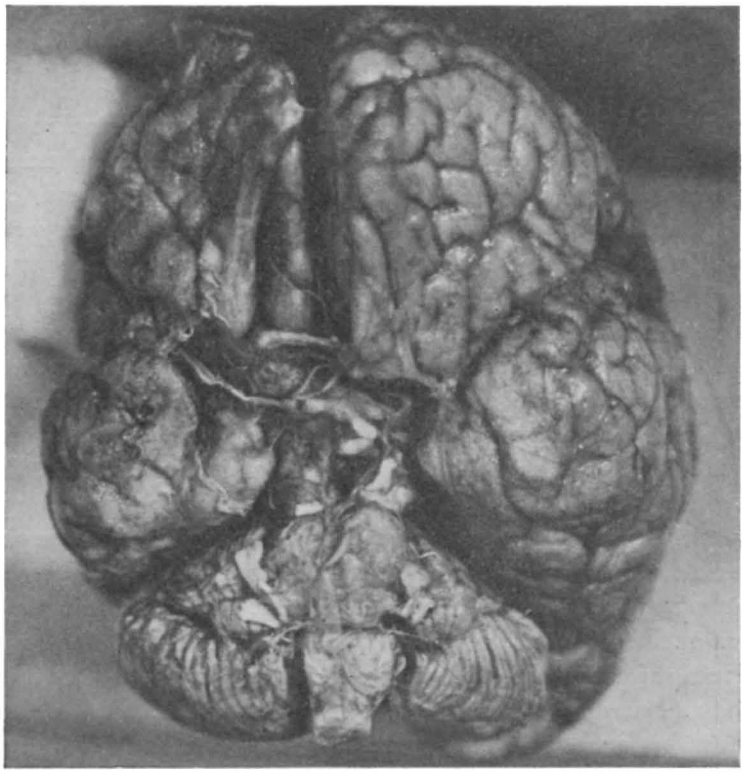


Fig. 7. Atrophy of the right cerebral and crossed cerebellar hemisphere.

for NISSL, KOSSA, BIELSCHOWSKY and haematoxylin-eosin staining. The pia arachnoidea is then removed very carefully. On the right side it is attached by many fine fibres to the cerebral cortex. The grey and blue colour of the surface of the brain is then definitely known to have been caused by the thick pia for the bare cerebral surface is completely white. There are many small blood vessels in the pia arachnoidea of the right side and even the left side is vascularized to a greater degree than normal.

All the sulci and gyri of the cerebral hemisphere can be recognized.

The gyri are all too small but there is no true polygyria. The right uncus and hippocampus are strikingly good. The right operculum is open, thus the right insula lies partially exposed. The right sulcus rectus is very deep. There are no alterations of the sulci or gyri of the left hemisphere. Small pieces are removed from corresponding parts of both hemispheres for finer histopathological examination with the special staining methods mentioned above.

A frontal section is made just before the optic chiasm. There is slight hydrocephalus ex vacuo on the right and the deep central white matter is very much reduced on this side. The second section, made behind the thalamus, reveals these same conditions. The corpus callosum is unusually thin.

Serial sections 35 micra in thickness are made through the whole cerebrum and stained with the WEIGERT-PAL and VAN GIESON methods. Every fifth section is mounted excepting through the frontal and occipital poles where every tenth section is preserved. The most striking points regarding the cerebrum are the extreme shrinking of the whole right hemisphere with extensive degeneration and calcification of the cortex and central white matter with the exception of the gyri adjacent to the sulcus rectus, of the cornu Ammonis, the gyrus hippocampus, the substantia perforata anterior, the gyrus fusiformis and parts of the gyrus cinguli and of the temporal lobe. There is no calcification in the thalamus or the corpus striatum.

Following the serial sections from an oral to a caudal direction we find that the hypoplasia is very pronounced in the right frontal lobe. Even the first sections show calcification of the cortex which extends into the central white matter. Only the medio-ventral gyri have escaped. On the right side this part alone has not lost its myelin completely although the myelinization is not as good as on the left side (Fig. 8). The number of blood vessels is enormously increased in the remains of the pia arachnoidea attached to the right cortex. The anterior horn of the ventricle is first seen on the left but the right appears soon after. At this level the myelinization of the right side has improved although the centrum semiovale is still greatly reduced in comparison with the left. Much calcification is to be found in it. No alterations are seen in the left hemisphere in the WEIGERT-PAL and VAN GIESON sections.

When the oral pole of the nucleus caudatus appears in the series it is clear that it is better developed on the left than on the right but further study shows that this is due only to the angle at which the sections are cut. No calcification is found in it throughout the whole series. The same is true for the putamen and the globus pallidus. The centrum semiovale is very poorly developed. The nervus olfactorius lies in its sulcus rectus on each side and is quite normal. It is striking to see that the gyri adjacent to the sulcus rectus are free of calcification.

When the corpus callosum appears it is exceptionally thin and poorly myelinated although no circumscribed secondary degeneration is seen.

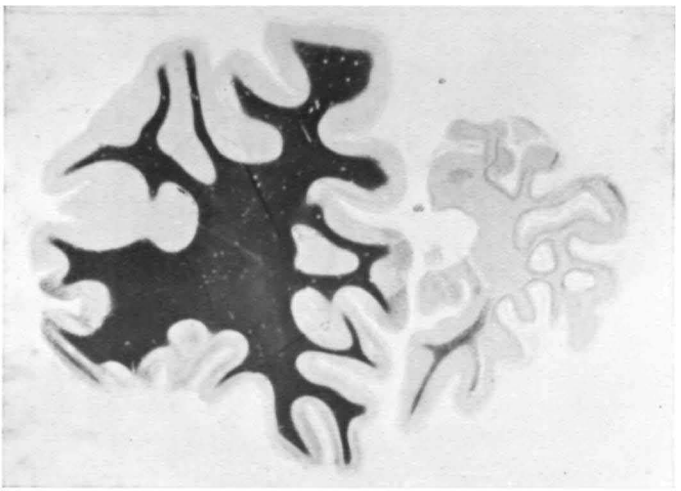


Fig. 8. Hypoplasia of the right frontal lobe with degeneration. (WEIGERT-PAL stain).

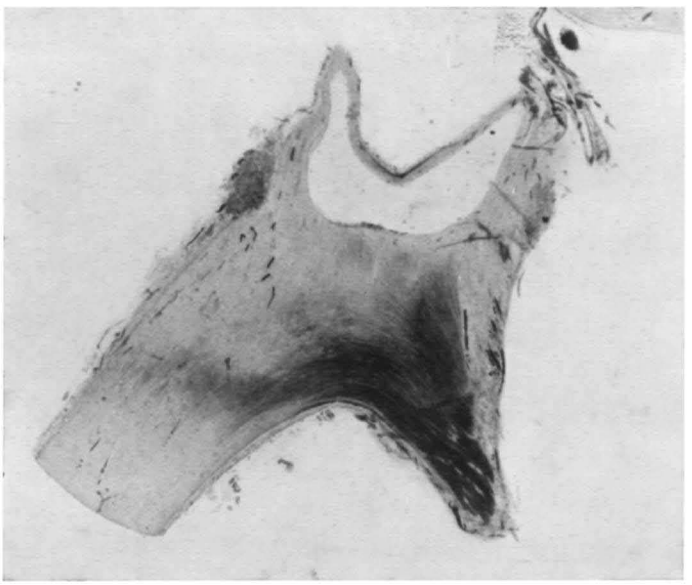


Fig. 9. Chiasma. Degeneration of the right optic nerve. (WEIGERT-PAL stain).

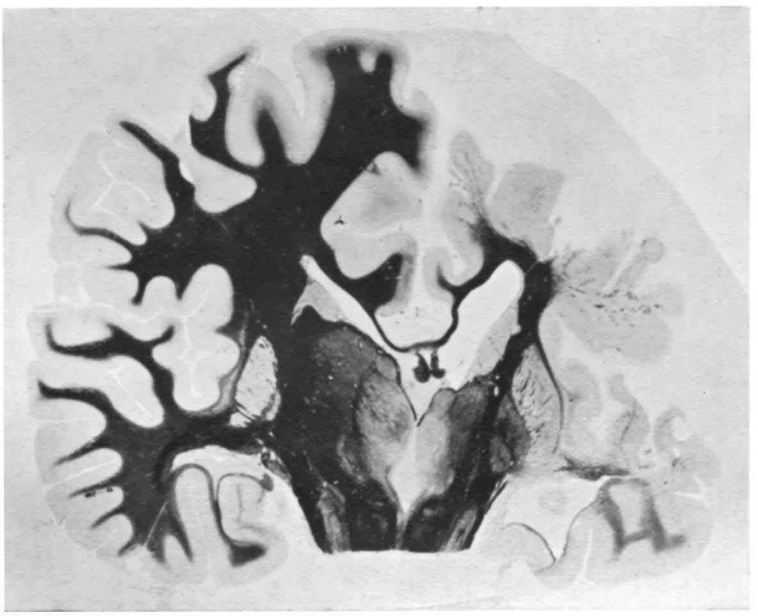


Fig. 10. Hypoplasia of the right neopallium with degeneration. Retrograde degeneration of the right optic thalamus. (WEIGERT-PAL stain).

The septum pellucidum is in a much better state. The internal capsule is very poor in fibres as is the centrum semiovale. The latter is full of calcified granules. The gyrus cinguli is smaller on the right than on the left but it is much better myelinated than the rest of the neopallium of the hypoplastic side.

On following the optic pathways from the optic nerves to the lateral geniculate bodies we see that there are no myelinated fibres in the right optic nerve while the left optic nerve is completely myelinated. This alteration must be the result of destruction of the optic papilla by the tumour and the subsequent extirpation of the right eye. It has to be regarded as secondary degeneration and progresses into the central and dorsal parts of the chiasm (Fig. 9). The site of this degeneration changes according to the different levels. In the oral half it is found over the whole dorsum of the chiasm as well as in the centre just to the left of the midline. In the caudal half the dorso-lateral part is affected on the right and the ventromedial part on the left. In the degenerated areas the VAN GIESON stain shows that the glia is increased. The degeneration of the right optic tract is more severe than that of the left and is especially localized in the centre and over the dorso-medial border. The left optic tract on the other hand has a very small area of degeneration on its medio-ventral surface. It is of significance to note that there is no increase of blood vessels in the pia arachnoidea around the optic nerves and chiasm. There is strikingly good myelinization of the uncus of the temporal lobe where no calcification is to be seen. The gyrus cinguli looks quite good. There is much calcification in the centrum semiovale and the cortex but there is none in the substantia perforata anterior, the hypothalamus or the claustrum. Slight hydrocephalus is found on the right side. There are also changes in the cytoarchitecture of the right cerebral cortex but these changes can be seen better in the NISSL sections and will be described later from the study of these.

At the level of the anterior commissure the following points are to be noted. The commissure is present on both sides and is well stained. The corpus callosum remains very thin although there are myelinated fibres in it. The internal capsule is very poorly developed on the right. The right lateral ventricle is wider than the left and the third ventricle is somewhat dilated. The centrum semiovale is reduced to a small area in which some myelinated fibres are present especially in the medial part. Laterally the staining is poorer and there is considerable calcification. On the left the globus pallidus is well developed while on the right only the first part of it is seen. The right nucleus caudatus and putamen are normal. The capsula extrema and claustrum are present but they are thin on the right side. There is no clear difference between the corpus striatum or the fornix on either side. They are both well developed. The cells of the nucleus caudatus and putamen are well stained in the VAN GIESON preparations as are the cells on both sides of the third ventricle. The most oral part

of the gyrus temporalis superior is very pale and contains much calcium as does the insula and all the gyri of the neopallium at this level except the gyrus cinguli. The substantia perforata anterior is normal on both sides.

At the level of the corpora mamillaria no difference is to be seen between these two bodies on the right or left side. The fornices are equally well stained in the WEIGERT-PAL sections. The corpus callosum remains very thin and this condition persists throughout the whole series, hence it will not be referred to again in the description. The corpus striatum is as described above. The internal capsule has more fibres than in the previous sections and those present are well stained so that a circumscribed secondary degeneration is not seen although the whole is much smaller than the left. The centrum semiovale is reduced to a small group of fibres. The gyrus cinguli is myelinated but it remains paler than the left. The sulcus calloso-marginalis and the other sulci of the neopallium are recognizable but the gyri are very small. The fossa Sylvii is surrounded by cortical layers which stain very poorly in the WEIGERT-PAL preparations and show severe lesions with much calcification in the VAN GIESON sections. Calcification is absent only from the gyrus cinguli. The capsula externa contains myelinated fibres but remains smaller on the right. The right claustrum is also smaller and the capsula extrema is considerably paler on the left.

When both peduncles appear the right being encountered more caudally than the left — the latter is normal, but the right is reduced to a small number of fibres. The zona incerta is normal on both sides. Ammon's horn appears somewhat later on the right than on the left and contains no calcification. There is no calcification in the archipallium or paleopallium but only in the neopallium. It has finally appeared in the gyrus cinguli.

In the regio subthalamica the columnae fornicis descendens are still present. The bundle of VICQ D'AZYR is not to be seen at this level, but the radiation H_2 of FOREL is as on the left. There is a beginning of the anterior nucleus of the thalamus but the number of fibres in it is small and on the whole it is very much reduced. Comparable levels of the nucleus anterior of the thalamus of both sides show that the usually larger cells are fewer and smaller on the right. There is also an increase of glia in the same area on the right side. The nucleus amygdalae is free of calcification as well as the medial part of the third temporal gyrus. However there is calcification in the cortex of the insula and also in a part of the gyrus cinguli.

At the level where on the right side the bundle of VICQ D'AZYR is in connection with the anterior nucleus it divides the thalamus in the usual way into medial and lateral parts. The nucleus lateralis thalami has lost many of its cells and those found in it, mostly in the lateral parts, are reduced in size (Fig. 10). Both the nucleus medialis and nucleus anterior

are small and pale and only a few cells are to be found. There is an increase of glia in these degenerated nuclei of the thalamus. The relations of the centrum semiovale and cortex have not changed since the previous description. It is clear that the cornu Ammonis, the gyrus hippocampus and the gyrus fusiformis show no cellular changes. The gyri of the temporal lobe can be recognized but the myelinization is poor and there is much calcification in the deeper layers. The right nucleus ruber is always somewhat smaller than the left. It contains many myelinated fibres on the right but the cells are smaller and fewer than on the left. The dorsal cap of fibres of the nucleus ruber is smaller on the right than on the left. No difference can be seen between the cells of the two sides of the substantia nigra but there are fewer finer fibres on the right. The right pes pedunculi is but a small band of fibres in which no circumscribed secondary degeneration of tracts can be seen. The cells of the corpus subthalamicum are not degenerated on the right and this nucleus is well myelinated and of the same size as the left.

When the lateral geniculate body appears on the left the thalamic nuclei are well developed but the globus pallidus has disappeared. At this level the conditions in the cortex of the right side have not changed much. There is a great reduction of all the gyri of the neopallium although this is less marked in the gyrus cinguli. The various cell layers have changed and there is calcification in the whole cortex of the neopallium excepting the gyrus cinguli and part of the adjacent gyrus centralis posterior. The calcification is also present in the centrum semiovale which is much reduced in size and has a limited number of myelinated fibres. The same is true of the cortex of the insula and of the temporal lobe. Calcium crystals are also found in the deeper layers of the temporal lobe, but the gyrus hippocampus, gyrus fusiformis and part of the gyrus temporalis inferior are free. This is also true of Ammon's horn. There are no cellular changes in the fascia dentata. The inferior horn of the right lateral ventricle is enlarged. The tuberculum anterius is always smaller than on the left but is now better myelinated than in former sections. All the nuclei of the thalamus are much reduced in cells and fibres. The internal capsule is small but no secondary degeneration is seen.

At the level of the beginning of the aquaeductus Sylvii the nucleus medialis of the right side is much smaller and has fewer medullated fibres in it than the left. The cells have for the greatest part disappeared and have been replaced by glia. The same also applies to the lateral and ventral nuclei. The posterior commissure is present and the aquaeduct is not enlarged. The general form of the left external geniculate body has not changed although some myelinated fibres have disappeared.

There are slight changes in the cell layers in some of which the cells are smaller than in others. The VAN GIESON sections do not permit going into further analysis. It is however certain that in this left external geniculate body no retrograde degeneration is found as will be described

later for the right external geniculate body when it appears in the sections. The conditions in the cortex and centrum semi-ovale have not changed since the last description. Calcification is found here in the gyrus cinguli although very little. The cells of the cornu Ammonis, of the gyrus fusiformis, and of part of the gyrus temporalis inferior remain normal. The centrum semiovale is much reduced and the fibres present come mostly from the gyrus cinguli. The other convolutions are very pale and full of calcium deposits.

In the subsequent sections the calcification in the gyrus cinguli increases greatly. In the right external geniculate body cells are preserved only in the ventral layer while the rest are replaced by glia. Many medullated fibres are absent from this nucleus. The ganglion habenulae is the only nucleus of the thalamus in this region which is normal. All others have lost the greatest part of their cells. In the WEIGERT-PAL sections the ventral nucleus of the pathological side is stained darker than that of the left side. This is due to a closer arrangement of the fibres of the medial lemniscus terminating in this nucleus from which the cells have disappeared. The normal architecture of the right external geniculate body is lost. Many myelinated fibres have disappeared from this ganglion so it is paler than normal in the WEIGERT-PAL sections. The pulvinar is also degenerated (Fig. 11). The midbrain is properly formed and the anterior colliculus is well myelinated. There are calcium deposits in all the gyri excepting the gyrus hippocampus and cornu Ammonis. The cells in the latter are well developed but the myelinization of the same is not as good as on the other side because of the loss of association and projection fibres.

Immediately behind the splenium corporis callosi there are calcium salt crystals in all the gyri with the exception of Ammon's horn. The gyrus cinguli is only slightly affected. The deeper layers of the parietal and temporal lobes are very small and the myelinated fibres are much reduced. The optic radiation is already to be seen on the right and is smaller than on the left. There is no systematic degeneration in it, but there are various unmyelinated spots which are caused by the same pathological process as in the deeper layers of the parietal and temporal lobes.

In the occipital lobe the centrum semiovale remains very much reduced. (Fig. 12). There is calcification everywhere excepting in the oral part of the striate area. The right fasciculus longitudinalis inferior is less deeply stained than the left but is not degenerated. Small unmyelinated interruptions are seen as have also been found in the deep layers of the occipital lobe. The tapetum is smaller and is less intensively stained than on the left side. The right ventricle is enlarged. The myelinization of the deeper layers of the lobus parietalis superior and of the area striata is better than of the other parts.

Within the right lateral ventricle a mass is found which is first seen at the level of the parietal lobe and ends at the beginning of the striate

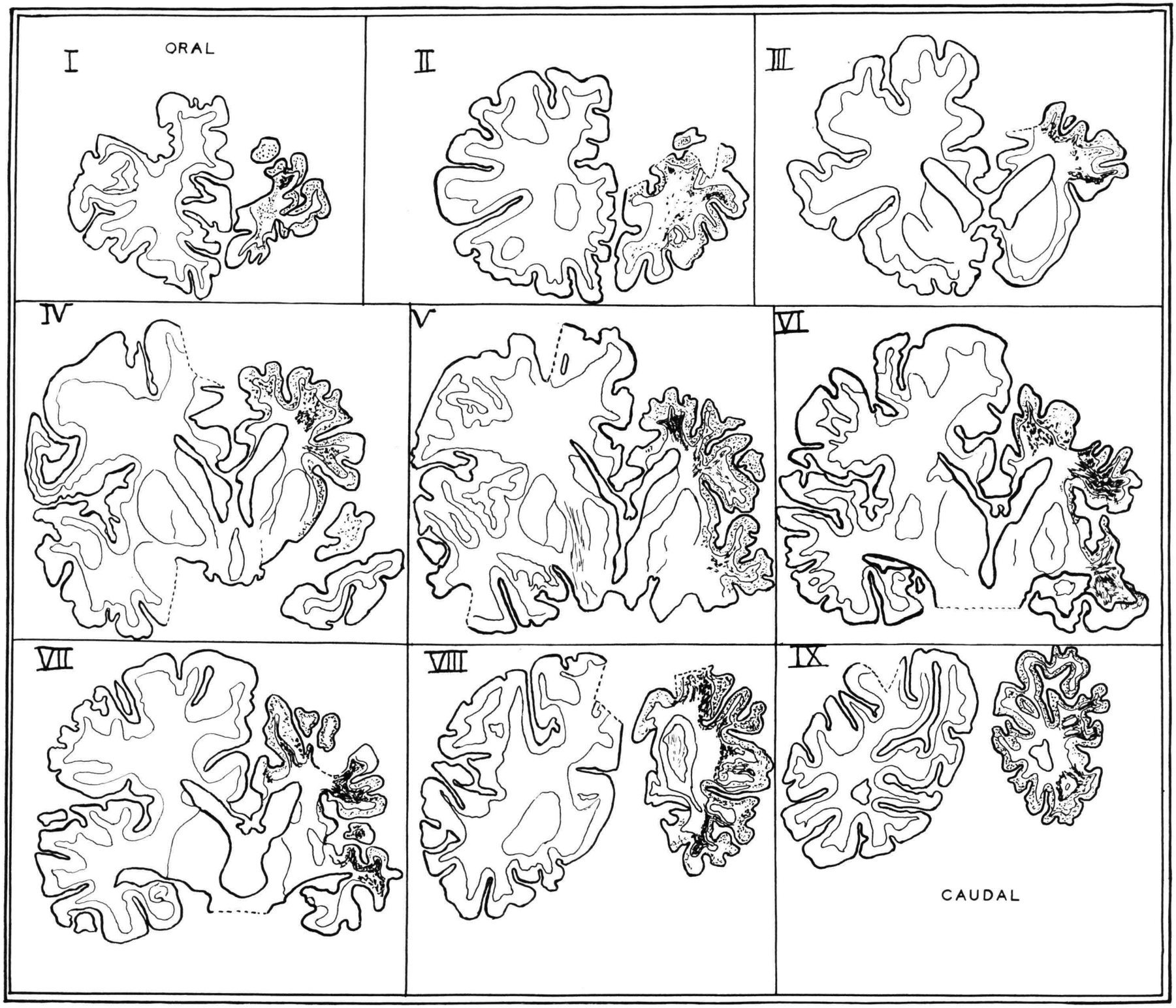


Fig. 13. Distribution of the calcification in the hypoplastic right cerebral hemisphere.

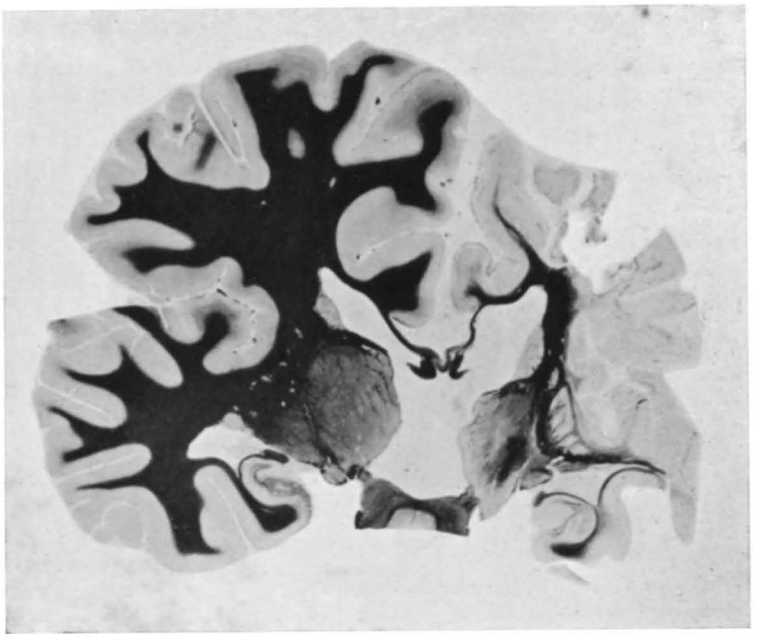


Fig. 11. Hypoplasia of the right neopallium with degeneration. Retrograde degeneration of the right pulvinar. (Weigert-Pal stain).

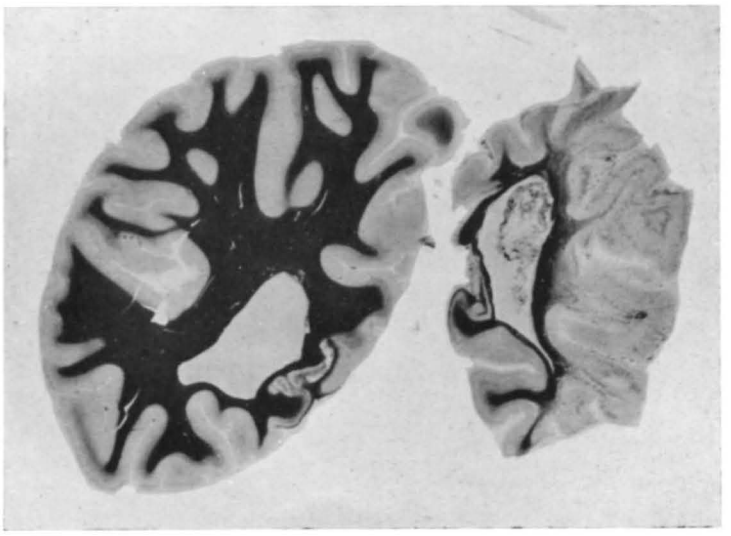


Fig. 12. Parieto-occipital Lobe. Fibrotic angiomatous growth associated with the choroid plexus of the right lateral ventricle. (Weigert-Pal stain).

area. It is pear shaped, 7 × 14 × 15 mm. in size and is attached to the choroid plexus at its inferior pole. It is composed of a central body of loose connective tissue with a cluster of small arteries and veins at its superior and inferior poles. Fewer vessels are found on its lateral borders or in the centre. The whole is irregularly and incompletely enclosed in a dense connective tissue capsule. The choroid plexus does not enter into the formation of the tumour itself nor is there any disordered increase of the endothelium. The vessels are full of blood but there are no hemorrhages. There is no calcification in this mass.

The severity of the pathological process increases in the direction of the occipital pole. The myelinization is very poor and there is calcification of the whole deep layer of the cuneus and the lateral occipital gyri. The area striata is gradually invaded so that in the region of the occipital pole the whole cortex is full of calcium deposits. The tapetum is smaller and paler than on the left and the same is true for the fasciculus longitudinalis inferior. The ventricle remains enlarged.

Fig. 13 gives a drawing of the distribution of the calcification in the various levels of the neopallium.

MICROSCOPICAL EXAMINATION OF THE CORTEX CEREBRI.

Gyrus frontalis superior: In the NISSL sections the right side is much more altered than the left, but the latter is not normal. In the sections of the left side from which the pia arachnoidea has not been removed there is a considerable increase in the number of veins and arteries in the leptomeninges. The pia is thickened but not as much as will be mentioned later in the description of the right side. The cytoarchitecture is normal and the cells themselves do not show any changes. There is no evidence of activation of the glia. In some parts of this gyrus there is a diffuse increase in the number of blood vessels the walls of which are a little thicker thans normal and are collapsed in folds. In the deeper layers of the central white matter some of the sections contain a collection of capillaries which give the impression of an angioma.

In the sections from the right gyrus frontalis superior there are two different states found. In the first there are areas where there is much calcification with angiomatosis. Here the cytoarchitecture is destroyed and the various layers can not be properly recognized. (Fig. 14). Compared with the left side there are many more cells which lie closer together, but these are mostly glia cells of the different types and nerve cells are difficult to find at all. Those present have suffered changes in structure. In the other area there is no angiomatosis and scarcely any calcification. The cytoarchitecture is in much better state although not completely normal. There is an increase of glia but not to the extent found in the first mentioned part. Nerve cells with well preserved structure can be readily seen.

From the NISSL as well as from the haematoxylin-eosin and KOSSA stained sections the distribution of the calcium material is clearly seen. (Fig. 15). There is none in the outer two layers but calcification is met in the third layer. The heaviest deposits are in the fourth, fifth and sixth layers and in the central white matter. In the NISSL sections the calcium salt crystals are seen in profusion (Fig. 16) and it is very clear that they bear no relation to the blood vessels. They lie diffusely in the tissues between the cells. No calcified material has been seen in the nerve cells themselves.

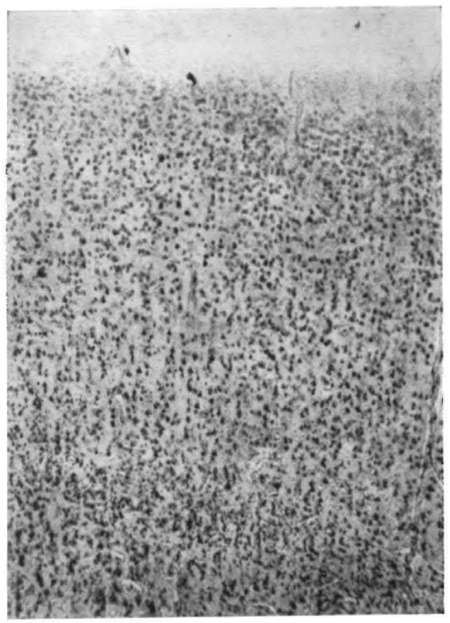
Gyrus frontalis medialis: BIELSCHOWSKY stained sections of the right side show that there are still many well formed nerve cells present.

Gyrus centralis anterior: NISSL sections of the right side reveal the disappearance of the normal architecture. The cells are mixed through each other in no orderly manner. Most of these are of the various types of glia but both normal and degenerated nerve cells of pyramidal form can be seen. However no BETZ cells are found. There is a border of fibrillary glia which lies on the surface of the lamina zonalis and forms a kind of thin capsule for the gyrus. Because of the very great number of glia in this gyrus one might speak of it as a sclerosis of this area.

Gyrus centralis posterior: NISSL sections show no changes at all on the left side but the right is severely damaged. Many calcium salt crystals are seen which extend more peripherally than in the frontal gyri. The lamina granularis externa is now involved and some deposits are seen even in the lamina zonalis. The heaviest calcification has occurred in the third layer but no part of the cortex has been spared. Again the cytoarchitecture has been wiped out. Most of the cells present are glia so we may again refer to the condition as sclerosis of the cortex. As in the gyrus centralis anterior there is here a layer of fibrillary glia covering the first layer. It is important to note that although the calcification is very extensive here as well as in the gyrus praecentralis there is no increase of blood vessels in the cortex or central white matter.

Gyrus temporalis superior: In the NISSL sections the left side is normal. On the right side the cells lie closer together and seem to be more numerous than on the left. Most of these cells are glia. Nerve cells are present but many show signs of degeneration. There is much calcification which is found mostly in the second, third and fourth layers and in the central white matter. There is no increase of the number of blood vessels nor perivascular infiltration. The lamina zonalis is covered with a fibrillary layer which is thicker than on the left side.

Gyrus temporalis inferior: There is nothing abnormal to be seen in the NISSL sections of the left side. The right side consists of two different areas. In one of these there are the same extensive changes described for the gyrus centralis posterior: disturbance of architecture, increase in the number of glia, degeneration of nerve cells, and deposits of calcium salts in all layers. In the other area there are only a few spots of calci-



Left side (normal).

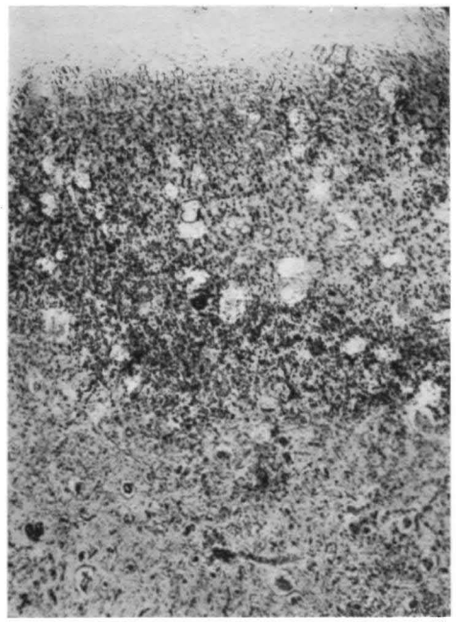
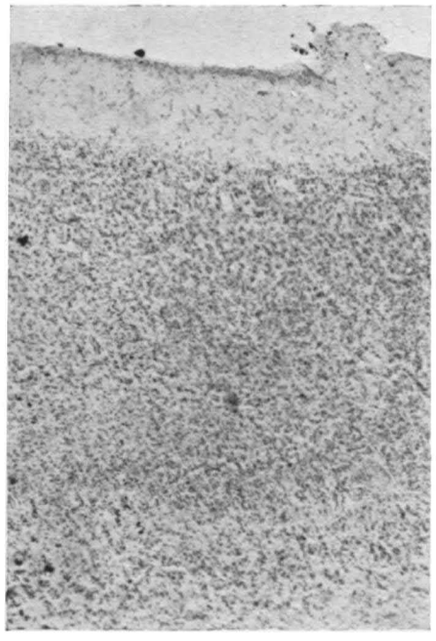


Fig. 14. Gyrus Frontalis superior. (Nissl stain).

Right side. Degeneration of nerve cells and gliosis.



Left side (normal).

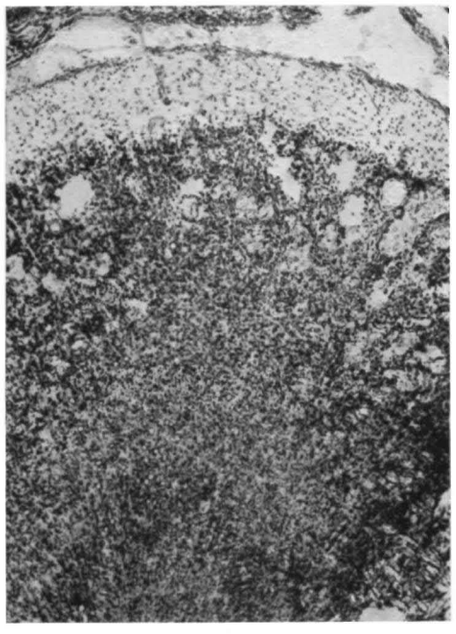


Fig. 18. Area striata. (Nissl stain).

Right side. Degeneration of nerve cells and gliosis.

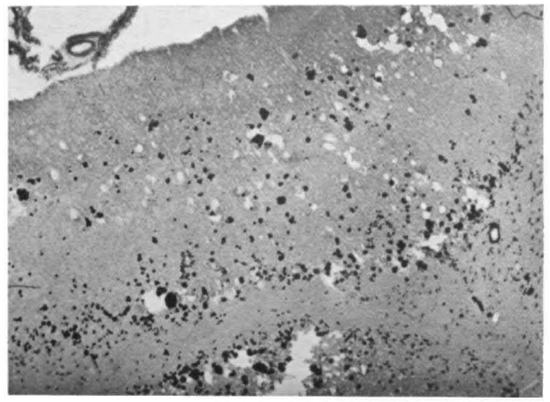


Fig. 15. Deposits of calcium in the cortex cerebri. (Kossa stain).

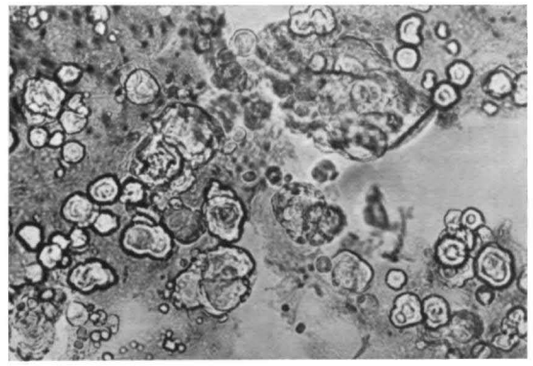


Fig. 16. Calcium salt crystals in the cortex cerebri. (Nissl stain).

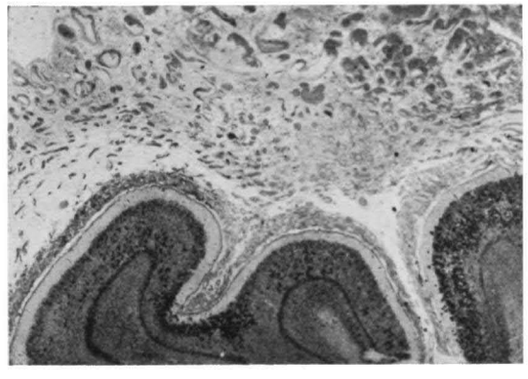


Fig. 17. Angiomatosis of the pia-arachnoid over the right cerebral hemisphere. Calcification limited to the cortex. (Nissl stain).

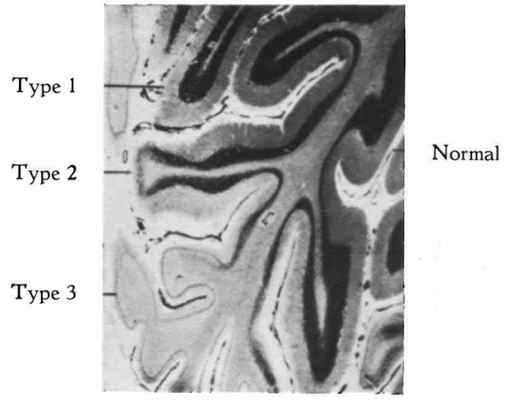


Fig. 20. Left cerebellar hemisphere to demonstrate three degrees of degeneration. (Van Gieson stain).

fication to be seen, the cytoarchitecture is not disturbed, there is no increase in the number of glia, and many nerve cells are normal. There is no sign of angiomatosis in either the NISSL or haematoxylin-eosin sections. There is no perivascular infiltration. No tumour cells have been seen in any of the sections of the cortex so no further mention will be made of this point. From a study of this gyrus it is obvious that the intensity of the calcification runs parallel with the destruction of nerve parenchyma and is not linked with the angiomatosis.

Gyrus hippocampus: In the NISSL and haematoxylin-eosin sections both the right and the left sides are normal.

Fissura parieto-occipitalis: The NISSL and haematoxylin-eosin sections show very pronounced calcification in all layers of the adjacent gyri including the lamina zonalis. There is extensive angiomatosis of the blood vessels of the pia arachnoidea, but the walls of the vessels appear normal and there is no calcification the pia arachnoidea (Fig. 17). The veins are particularly enlarged and filled with blood. There is no angiomatosis of the cortex. The changes in the nerve parenchyma are the same as described for the right gyrus centralis posterior.

Area striata: This is the most severely affected part of the whole cortex. Calcification is found in all the layers and in the central white matter. The architecture is wiped out and it is very difficult to find normal nerve cells in the sclerotic calcarine area. There is an increase in the number of the blood vessels of the pia but not of those of the cortex itself (Fig. 18).

CEREBELLUM AND BRAINSTEM.

The left cerebellar hemisphere is about one fourth smaller than the right hemisphere. The gross specimen gives the impression of a pure left neocerebellar atrophy because the vermis, the right and left flocculus, and the right hemisphere are normal. The arteriae vertebrales form a normal basilar artery. After removal of these blood vessels it is clear that the right pyramidal tract is too small and the colour is grey; the right half of the pons is also distinctly smaller than the left.

The various lobuli and sublobuli of the left cerebellar hemisphere can be recognized very well and it seems that the hemisphere has been reduced in size in its totality. The tonsil also takes part in the atrophy. There is no gross evidence of inflammatory disease of the cerebellum or brain stem. Small sections are removed from the atrophied and normal parts of the cerebellar cortex and are stained by the methods of NISSL and BIELSCHOWSKY and with haematoxylin-eosin. Serial sections are made of the caudal part of the oblongata and stained according to NISSL and SPIELMEYER, and furthermore, serial sections of the other parts of the brainstem and cerebellum are made and stained with the WEIGERT-PAL and VAN GIESON techniques.

Fig. 19. *Cerebellar cortex.* The severe cellular degeneration is indicated by black, the moderate cellular degeneration by vertical lines and the slight changes by stippling. The normal parts are white.

The damage to the left hemisphere is not of the same degree or distribution throughout, the more superficiallly lying lobules being affected to a greater degree than the more central regions. It is also striking that in the longitudinal plane the severity of the pathological process becomes progressively greater in the caudal direction. The vermis and left flocculus, where they have suffered at all, have likewise been damaged in the more caudal part. The distribution of the different degrees of degeneration in the VAN GIESON sections is presented in the drawings according to the following plan: three degrees have been registered-slight (type 1), moderate (type 2), and severe (type 3) — and have been represented by the stippled, lined, and black areas respectively (Fig. 19).

The right cerebellar hemisphere is quite normal save for a small area in the dorsal half of the hemisphere, 50 mm from the surface, and 3 to 4 mm in diameter, extending for 8 mm in the oral caudal direction. This part of the cerebellar cortex is remarkable because of some calcification in the same region where there is loss of PURKINJE cells and atrophy of the granular and molecular layers. It is very striking to note that, in sharp contrast to the conditions in the right cerebral hemisphere, no further calcification is found either in the cerebellum or in the brainstem.

From examination with higher power magnification it is certain that the atrophy of the left hemisphere is not limited to any particular element of its formation, but is the result of involvement of all components. The lobules are individually much thinner than normal and appear shrunken. The most severely affected parts (type 3), involving the greater part of the hemisphere, show a marked reduction in the size of the molecular layer, and complete loss of PURKINJE cells. The granular layer is not recognizable as such and appears as a pencil stripe just within and parallel to the surface of the lobule, having lost its characteristic undulations. It is replaced by a pseudo granular layer composed of glia cells (Fig. 21). The staining of the WEIGERT-PAL sections is too pale in the neocerebellum and there is undoubtedly degeneration of fibres; still these changes are not as severe as might be expected from the study of the cellular changes. It should be noted that in the BIELSCHOWSKY sections the tangential fibres of the zona molecularis are absent, and this layer is only one half the width of the normal.

In places where the damage is not as extensive (type 2), the architecture of the zona granularis is better, but it is difficult to find a proper layer of PURKINJE cells anywhere. In the parts of the cerebellum showing the least pathological alterations (type 1), these are limited to degenerative changes in the layer of PURKINJE cells. There is an increase of glia in the pathological sections of the three types; this increase also extends into the deeper myelin substance of the lobuli.

Consideration of the other parts of the cerebellum makes it clear that the central white matter of the atrophic side is greatly reduced. In the WEIGERT-PAL preparations the myelin substance of the affected side is

paler in the hemisphere than normal. The left flocculus and paraflocculus are darkly stained. The left nucleus dentatus is smaller than, and does not stain as well as the right. This is evident in the WEIGERT-PAL and in the VAN GIESON series. Its general architecture is also changed, for the right nucleus dentatus has more folds, and its molecular bands are 25 percent wider, so that the impression is given that on the unaffected side the nucleus is about twice as large as on the atrophic side. In the WEIGERT-PAL sections there is obvious loss of fleece of the left nucleus dentatus; the fibres of the hilus are not affected in the more cranial sections, but there is some loss of hilus fibres in the more caudal regions.

The pathological changes in the left nucleus dentatus are neither equal nor general, although no part of this nucleus had escaped. The cells are smaller and lie closer together than on the normal side. The atrophy progresses in severity in a caudal direction, and, while the more cranial are only moderately affected, the intermediate sections show that most of the dorsal half of the nucleus is involved. The ventral part becomes severely affected only in the most caudal sections. This is presented schematically in the drawings which demonstrate two degrees of atrophy. (Fig. 22). There is also an increase of glia and the ground substance is very pale on the left.

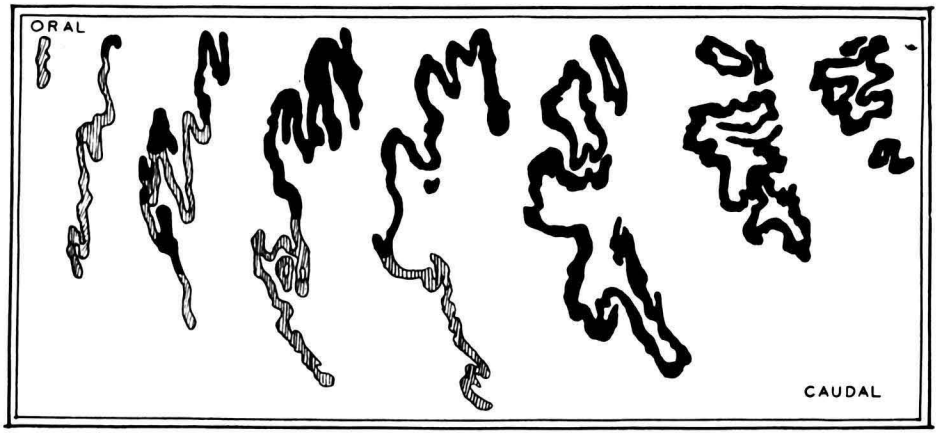


Fig. 22. *Dentate nucleus.* The severe cellular atrophy is indicated by black, the moderate changes by vertical lines.

The left nucleus emboliformis is very slightly affected in the middle part of its oral-caudal extent. No changes are to be noted in the nucleus globosus or fastigius on either side, or in the nucleus dentatus or emboliformis on the right.

No signs of infection, hemorrhage or tumour are found on microscopical examination. It should also be stressed that there is no evidence of malformation or of arrest of development (no heterotopia, no heterotaxia, nor lamina granularis superficialis).

Medulla Oblongata: There is a noticeable difference in size between

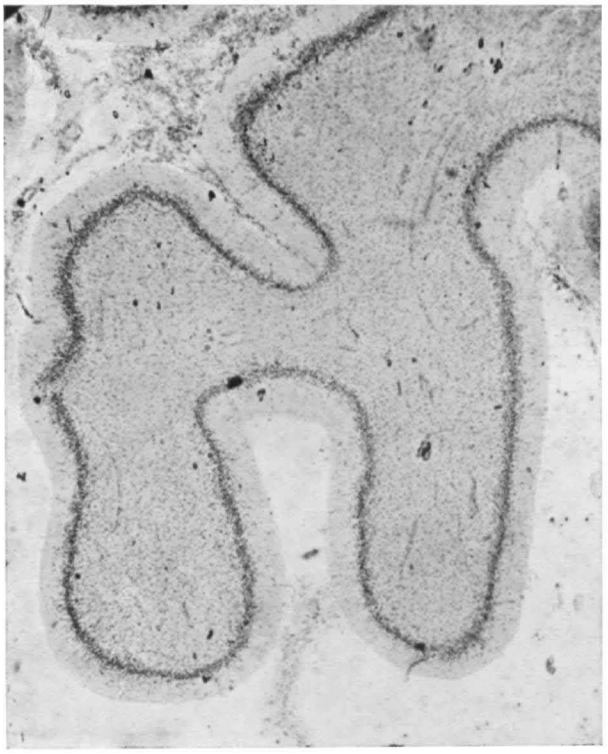


Fig. 21. Severe degeneration of the cortex of the left cerebellar hemisphere (NISSL stain).

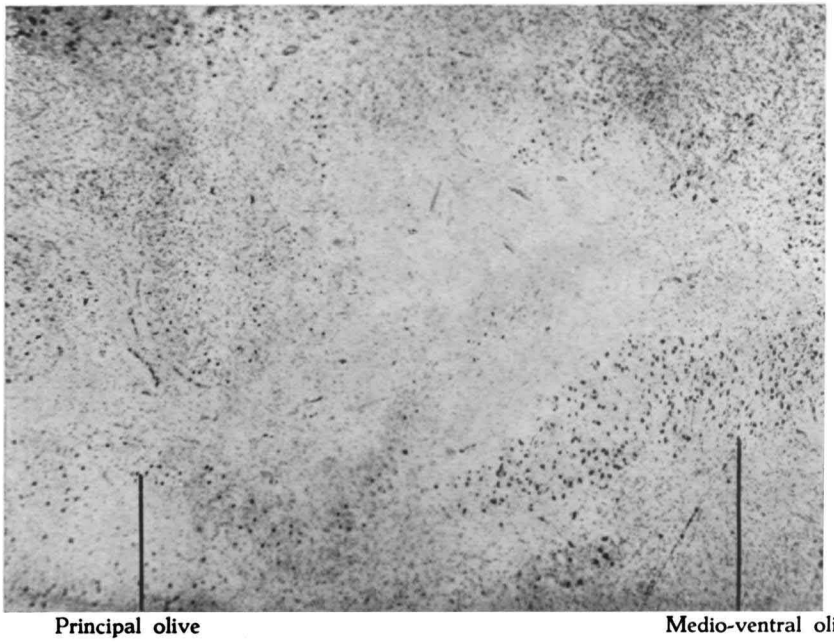


Fig. 23. Degenerated cells in the principal olive and normal cells of the medio-ventral olive on the right side (NISSL stain).

the two sides, due mainly to the atrophy of the right pyramidal tract, which is less than half as large as the left, and to the fact that the right inferior olive is smaller than the left. Closer microscopical study reveals marked loss of fibres of the right pyramid and an increase of glia in the same. The left corpus restiforme is smaller than the right although there is no isolated degeneration of fibre tracts.

Analysis of the olivary system shows that the right inferior (principal) olive is practically nowhere normal while the parolivary groups of the same side are almost entirely unchanged, the dorsal accessory olive being nowhere affected, and the medioventral olive having very slight involvement of the cells in its middle portion. On the left there is no alteration from the normal. The right inferior (principal) olive shows varying degrees of degeneration. The most severe affection has occurred at its caudal tip where the cells either have been completely lost or have been very severely damaged (Fig. 23). Progressing orally it is to be noted that in the mid portion of its longitudinal extent the dorsal half of the olive is more severely damaged than the ventral. Still farther frontally the changes are less pronounced as may be seen in the schematic drawings (Fig. 24). In these, three types of changes have again been recorded: type 1 in which the cells are smaller than and have not stained as well as the normal, type 2 in which, over and above the changes of type 1, there has been some disappearance of cells, and type 3 in which all cells have been lost. These are represented respectively by the stippled, lined, and black areas. It is not clear that there is an increase of glia on the right side. From the WEIGERT-PAL sections it is obvious that the right olive is smaller than the left and that the hilus fibres are fewer on the right. It has not been possible to examine the relations of the fibrae olivo-cerebellares carefully because at the levels concerned the sections have been stained chiefly according to NISSL. In the SPIELMEYER preparations no clear diminution of the size of the right olivo-cerebellar tract could be seen.

The other nuclei of the medulla oblongata are unaffected. In this connection special mention should be made of the nucleus gracilis, nucleus cuneatus, nucleus von Monakow (nucleus cuneatus externus), and also of the nucleus reticularis lateralis. However, the nucleus arcuatus, which must be regarded as the most caudal part of the pontine nuclei, is moderately degenerated on the right side.

The nuclear components of the VIII nerve, including the nuclei of DEITERS and BECHTEREW, are not affected. In the WEIGERT-PAL sections the left IAK (MEYNERT) does not stain as well as the right, but no degeneration can be traced in it to the cerebellar nuclei.

Pons Varoli and Tegmentum: In the WEIGERT-PAL and VAN GIESON sections it is to be noted that the right side of the pons is smaller than the left. This is particularly marked in the oral half. The difference in size gradually changes so that in the most caudal sections there is no

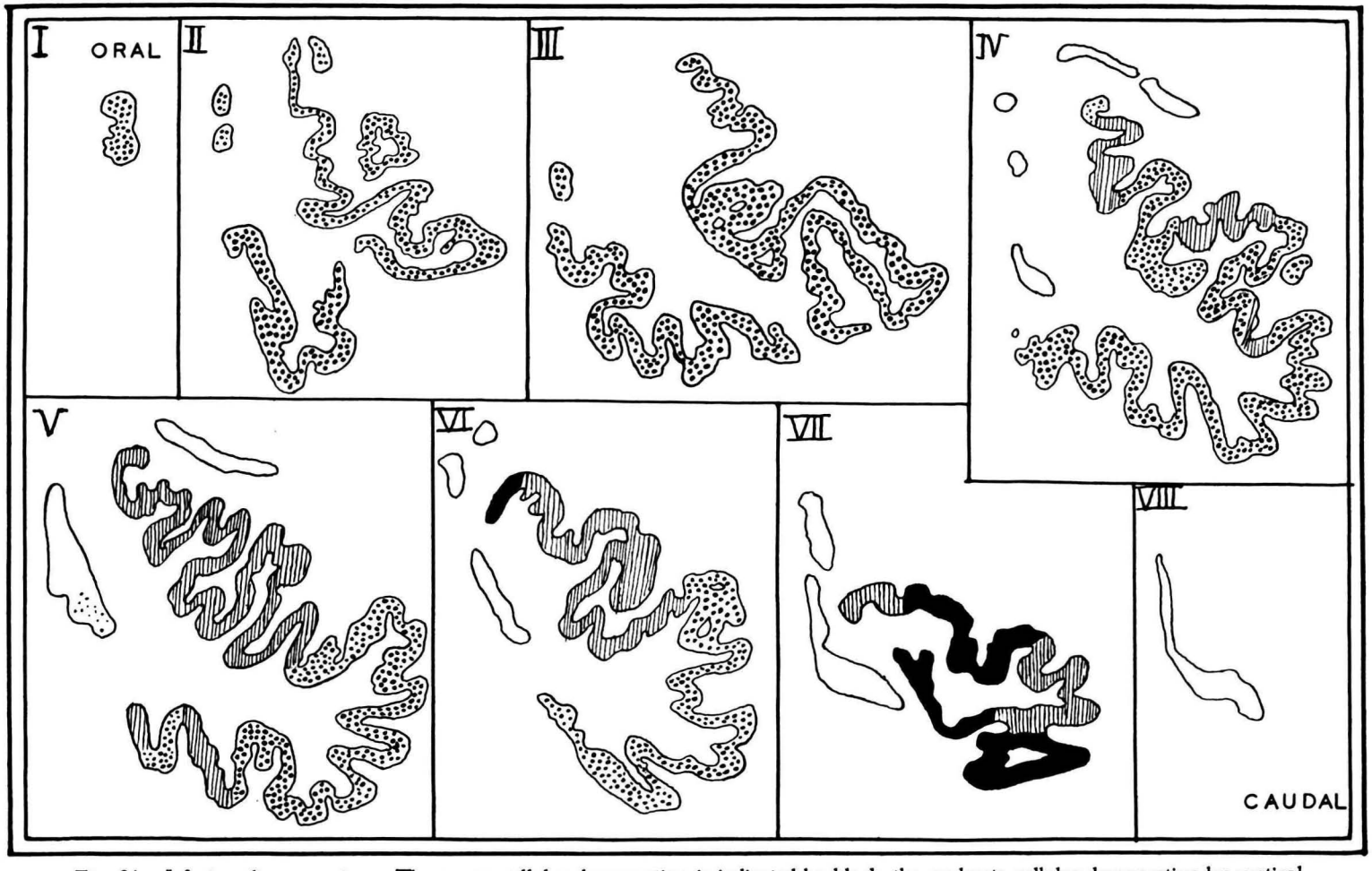


Fig. 24. *Inferior olivary system.* The severe cellular degeneration is indicated by black, the moderate cellular degeneration by vertical lines and the slight changes by stippling. The normal parts are white.

measureable variation between the two sides. The right half is smaller because of decrease in the size of the pons nuclei and loss of fibre tracts coming from the cerebrum.

From the VAN GIESON sections it is evident that on the right the nuclei of the pons are damaged practically everywhere. In a few of the oral sections some of the cells of the nucleus lateralis and nucleus dorso-lateralis (terminology of MASUDA), although not normal, are not as severely damaged as the others. The cells of the nucleus dorsalis, nucleus ventralis, nucleus paramedialis and of the intra- and peripeduncular nuclei are all smaller and do not stain as well as those of the corresponding nuclei on the left. The nucleus medialis raphe is strikingly divided in the midline into a good left half and a pathological right half (Fig. 25). There is an increase of glia on the right. The nuclei of the left side are normal.

The WEIGERT-PAL series shows that on the whole the right side does not stain as well as the left. More detailed study demonstrates that on the left side the temporo-pontine and fronto-pontine tracts are paler than the pyramidal tract, the first more so than the second. The left pyramidal tract is normal. On the right there is even more severe damage to the temporo-pontine and fronto-pontine tracts. The temporo-pontine tract is so badly affected that it is almost completely degenerated in its caudal part. The right fasciculus pyramidalis is reduced in size and does not stain as well as the left, but many fibres are still preserved. The transverse fibres, especially of the stratum profundum pontis, of the right side are fewer in the frontal region, but more caudally they are as numerous as on the left.

The brachium conjunctivum and brachium pontis show no changes on either side, and the commissure of WERNEKINK is normal. The lemniscus medialis and lateralis of both sides are likewise unaffected. No changes can be found in the nucleus reticularis tegmenti or in the trigeminal system. The aqueduct of Sylvius, as well as the fourth ventricle, is open, but not dilated. Nowhere is there any sign to substantiate a diagnosis of encephalitis. There is no evidence of tumour, hemorrhage or infectious disease throughout the whole brain stem, and, other than the degeneration changes, no pathological findings are seen.

DISCUSSION.

In the brain there are four chief types of changes:

A. Angiomatosis of the pia, arachnoidea and the cerebral cortex, much more pronounced in the right than in the left hemisphere. There are no separated tumours arising from the blood-vessels in the sense of CUSHING and BAILEY (6), but there is a diffuse increase of the blood-vessels especially of the veins.

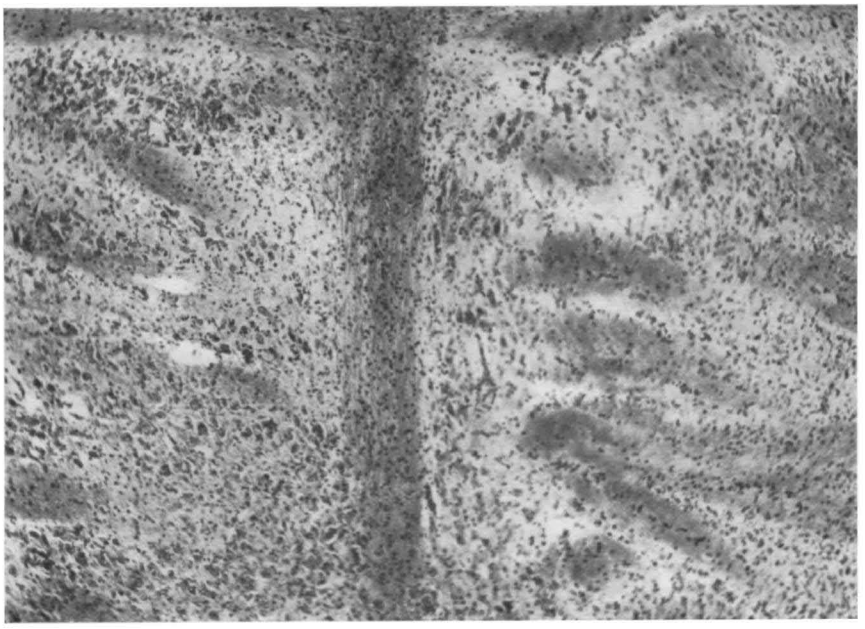
B. Hypoplasia of the right cerebral hemisphere with degeneration and calcification of the neopallium.

C. Secondary changes in the subcortical structures consequent upon the degenerations of the right neopallium.

D. Degenerative changes in the left cerebellar hemisphere and its associated bulbar systems, the inferior olive and the pontine nuclei of the opposite side.

The cerebral angiomatosis is a manifestation of the same vascular malformations as seen in other organs of the body in phakomatoses. These abnormalities are most pronounced in the arachnoid over the convexity of the right cerebral hemisphere but are also present in the cortex and the subcortical white matter. In the cerebrum the severity of the vascular abnormality shows no relationship to the degree of calcification or degeneration which run parallel. Another manifestation of the angiomatosis is the fibrotic angiomatous growth associated with the choroid plexus of the right lateral ventricle.

The angiomatosis must be considered as based upon a congenital abnormality in development. There are no other evidences of arrest of cerebral development in *early* foetal life. It must be assumed that the normal development of the right cerebral hemisphere was interrupted shortly before or immediately after birth. The configuration of the cortex is normal but the gyri of the neopallium are too small. The diminution of the nervous tissue of the right cerebral hemisphere is too great to be accounted for by the destructive process in the cerebral cortex alone. There must be an additional hypoplastic factor. Superimposed upon the hypoplasia of the cerebral cortex is a degenerative process with calcification, which we consider a parenchymatous degeneration because there is no histological evidence of an inflammatory process in the cerebrum. The deposition of calcium must be considered as secondary to the degenerative changes in the cerebrum, and is not at all specific. SPIELMEYER (19) among others has pointed out that in diseases of the brain in which degenerative changes or gliosis occur, calcium may be laid down from the tissue fluids themselves. In such areas which are functioning



Left side. Right side.

Fig. 25. Degenerated cells of the right pontine nuclei compared with those of the normal left side (VAN GIESON stain).

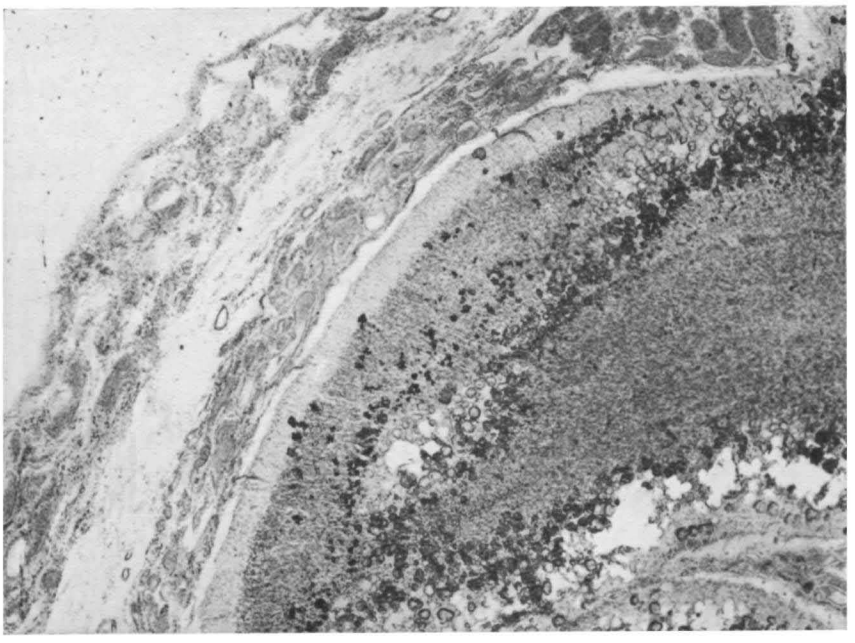


Fig. 26. Calcification in the cortex cerebri and in the central white matter. Angiomatosis in the pia-arachnoidea (NISSL stain).

poorly the tissue fluid have little carbonic acid because the metabolism is reduced to a minimum. The decreased content of carbonic acid which normally acts to keep calcium salts in solution in the tissue fluids, allows a deposition of calcium in such areas. This is probably the explanation of the calcification in our case. Calcification may be present in the blood vessel walls in these cases. BERGSTRAND (2) found that the calcification in the tissue in his material of STURGE-WEBER syndrome was due to calcification in the walls of the capillaries and precapillaries. BERGSTRAND considered as an example of STURGE-WEBER syndrome the case reported by GEYELIN and PENFIELD (8) in 1929. This was one of a family of epileptics, all of whom showed intracranial calcification roentgenologically. In this case an operative specimen showed endarteritis calcificans of the smaller blood vessels with deposits of calcium in the tissue about the vessels. Since these interesting cases of GEYELIN and PENFIELD did not have a cutaneous naevus or other congenital abnormality, they cannot be considered as the STURGE-WEBER syndrome. Their cases belong in our opinion to an independent disease. In the present case there was no calcification of the capillaries and precapillaries. In places calcification was present near the vessels, in other places isolated spots were found in the tissue. Hence, as BERGSTRAND has previously pointed out, the pathological substratum of the STURGE-WEBER syndrome although in general similar is not identical in every case. Very extensive intracerebral calcification usually occurs as the result of encephalic changes taking place in foetal life or shortly after birth. But such changes do not always occur, therefore we believe that there is some endogenous metabolic factor also involved. This calcification is seen in other organs of the body in phakomatoses. It is of great importance as originally shown by KRABBE (16) that the calcification is not in the pia mater but in the cortex itself. In his case the deposition of lime salts was mainly localized to the second and third layers of the cerebral cortex. In these layers the nervous tissue was severely destroyed and replaced by fibrillary neuroglia. KRABBE considered that the syndrome was but a part of a generalized disturbance in development of the organism such as for example occurs in tuberous sclerosis. The salient points of his case were angioma of the face, slight angiomatous modification of pia mater, aplasia of the occipital lobe of the brain with sclerosis and calcification of the aplastic part. He considered that the malformations originated in foetal life.

From the anatomico-pathological description of our case it is clear that in many respects it resembled KRABBE's. The hypoplasia and degeneration with calcification in our case however was both more extensive and intensive than in his. The deposition of calcium was not limited to the second and third layers of the cortex, but in several places the heaviest accumulations were in the deeper layers and in the central white matter. (Fig. 26). Furthermore almost the entire right neopallium showed severe degenerative changes. The calcification was not in the pia but in the

cortex itself. We share the opinion of KRABBE that congenital factors play a large role in this syndrome.

The etiology of the degeneration is not clear. Knowing that toxic factors may produce such changes we have considered the possible influence of toxic products originating from the orbital tumour. The unilaterality of the process and the fact that similar changes are observed in phakomatoses without tumour argue against this as an etiological factor. It must be remembered however, that hypoplastic tissue is more susceptible to noxious influences than normal tissue. It is interesting to note that the normally developed palaeo- and archipallium showed none of the degenerative changes or calcifications which were present in the hypoplastic neopallium (see Fig. 13). The limitation of the changes to the neopallium may be understood if we accept that the younger parts of the central nervous system are more vulnerable than the older ones and have their own pathoclisis (O. VOGT). In any case the degenerative changes are not confined to the area supplied by any specific group of blood vessels.

In the deeper subcortical structures such as the corpus striatum, thalamus and regio subthalamica of the right cerebral hemisphere there is no calcification. In striking contrast to the other structures the corpus striatum is not shrunken and must be regarded as normal. The right thalamus is markedly diminished in size but is not the site of a primary lesion. The loss of cells and fibers in most but not all of the thalamic nuclei (anterior, medial, ventral and lateral) is the result of retrograde and secondary degenerative changes respectively, due to interruption of thalamo-cortical and cortico-thalamic fiber systems by the degenerative process in the neopallium. Similarly the capsula interna, corpus callosum and cerebropontine tracts are shrunken by loss of fibers. The right optic nerve is devoid of myelinated fibers partly due to the damage by the tumour and partly to the result of the surgical removal of the eye. This secondary degeneration may be followed in the chiasma and the optic tracts on both sides to the lateral geniculate body. On the right side this ganglion is markedly shrunken from the loss of cells as a result of retrograde degeneration due to the degenerative processes in the striate cortex. Similarly the medial geniculate body is affected by the changes in the temporal lobe.

The changes in the cerebellar hemisphere are also secondary to the degenerative process in the cerebral cortex of the opposite side. Such crossed cerebellar atrophies probably have their genesis from specific areas of the forebrain, the exact location of which is not definitely known. They are usually the result of damage to such areas in early life. These changes may be merely a shrinkage of the cerebellar elements, but frequently they reach an intensity such as in the present case. It is important for an understanding of cerebral anatomy that the degenerations are limited to the neocerebellum while the paleocerebellum remains prac-

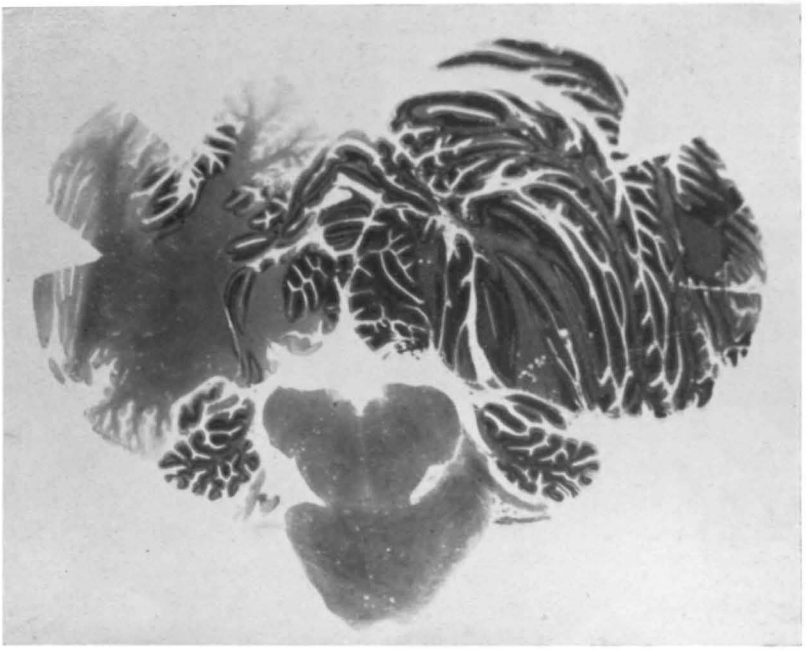


Fig. 27. Hemiatrophia neocerebellaris (VAN GIESON stain).

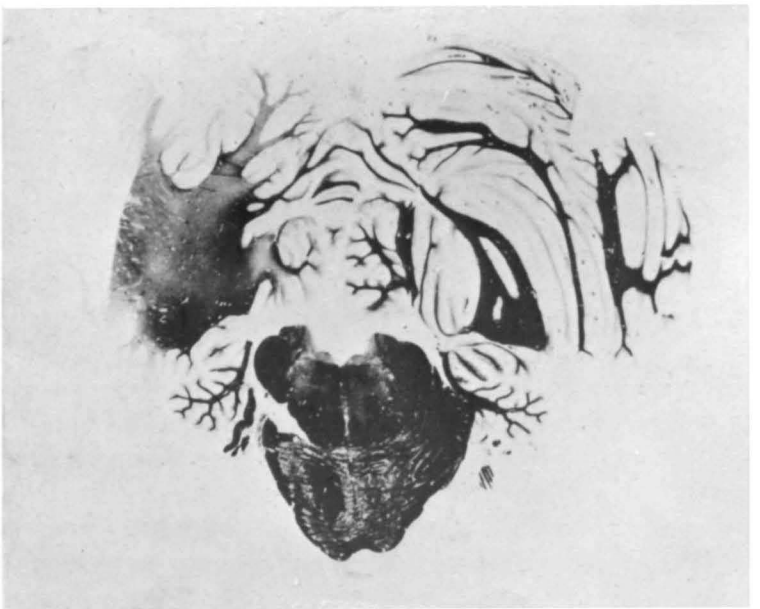


Fig. 28. Neocerebellar degeneration on the left side (WEIGERT-PAL stain).

tically unchanged. This crossed cerebellar degeneration from cerebral lesions confined to the neocerebellum is not uncommonly seen; recently JUBA (14) described three such examples. In the cell preparations of our case not the entire neocerebellar cortex is completely degenerated (Fig. 27), but in WEIGERT-PAL stained sections it is evident that the cerebellar hemisphere is too pale and diminished in myelinated fibers. The boundary between neocerebellum and the older parts, is thus made prominent (Fig. 28).

The alterations of the dendate nucleus are the result of the absence of fibers from the PURKINJE cells which normally terminate about its elements. The changes consist of a diminution in size but not of a secondary degeneration. The fact that these alterations are of different intensity in various parts of the dentate nucleus is a manifestation of topical cerebellar localization within the dendate nucleus. The most severely changed parts of the dendate nucleus are related to the areas of the cerebellar cortex showing the greatest degeneration (see Fig. 19 and Fig. 22).

The changes in the right inferior olives are the expression of retrograde degeneration as the result of the process in the cerebellar hemisphere. Likewise, the alterations are not of equal intensity throughout the olivary system (Fig. 24). The sparing of the parolives is the usual finding in neocerebellar atrophy because these are projected upon the palaeocerebellum. That the main olivary nucleus is not uniformily degenerated is the expression of the topical projection of this nucleus upon the cerebelllum. Examination of Fig. 19 and Fig. 24 leads to the conclusion that the oral parts of the main olivary nucleus are related to the oral and the caudal to the caudal parts of the opposite cerebellar hemisphere respectively. Thus there is not only a localization in medial-lateral and ventral-dorsal but also in the oral-caudal plane.

An outstanding feature of our case is the state of the crossed pontine nuclei. While degeneration of the opposite pontine nuclei is a characteristic of cerebellar lesions, the changes in our case are so intensive and the midline boundary so sharp that an additional factor must be considered. This is probably some retardation in development. Further confirmation of this is suggested by the locus of the most severe changes in the pontine nuclei— the caudal portion — which is known to develop latest.

Study of the rhombencephalon seems to indicate that the degenerative changes of the cerebellum had not reached their maximum at the time of the patient's death, but were still progressing. The crossed atrophy of the cerebellum, being a non-specific reaction to injury to the forebrain, gives us no clue to the pathogenesis of this disease. Some authors believe that there is a connection between the distribution of the naevus in the trigeminal area and the extension of the changes in the brain. They speak of encephalo-trigeminal cutaneous syndroms. This, however, does not

appeal to us because the naevus in our case was present on both sides of the face, while the primary changes in the brain were only found on the right side. Furthermore the naevus extended also in the cervical areas on the right side.

Until now we have considered as phakomatoses the diseases of BOURNEVILLE, RECKLINGHAUSEN and VON HIPPEL-LINDAU, all of which are of a congenital hereditary character and may show:

1. Phakoi, which are spots in the skin and different organs as for example the heterotopical spots in the brain.
2. Phakomata which are tumefactions in different parts of the body as the adenoma-sebaceum in the disease of BOURNEVILLE, the neurofibromata and ganglioneuromata in the disease of RECKLINGHAUSEN or the vascular tumours in the disease of VON HIPPEL-LINDAU.
3. Real blastomata, which may be benign or malignant.

In all three diseases we often find congenital aberrations and very frequently mental disturbances such as backwardness, imbecility, idiocy, epilepsy etc.

It is not necessary that all the symptoms or signs which are mentioned in the table on the opposite page be present in every case. Only a few of the symptoms may be found. Thus VAN DER HOEVE has reported a case in a girl of 20 with no other symptom than one small tumour in the retina. She was one of a family described by BOUWDIJK BASTIAANSE, the mother of which had 13 pregnancies four of which ended in abortions. Of the nine living children five had typical BOURNEVILLE's disease. The presence of a small tumour in the retina of one of the other four was sufficient evidence to enable VAN DER HOEVE to make the diagnosis of BOURNEVILLE's disease. When seen six years later, during which time she had married, the tumour of the eye had enlarged and a few others had appeared but there were still no other signs of the disease, and yet of her six children three showed tumefactions in the retina, and one had epileptic fits.

In a man diagnosis of RECKLINGHAUSEN's disease was made on the presence of a small tumour in the retina only. Later it was shown that he had a big ganglioneuroma in the chest and he died of a hypernephroma. It is not necessary that all the possible symptoms of those diseases be present in every case, but on the other hand every naevus does not belong to phakomatosis. Syringomyelia may be a sign of VON HIPPEL-LINDAU's disease as PUTSCHAR pointed out, but of course not every case of syringomyelia belongs to a phakomatosis.

If we compare the signs (table page) found in the syndrome of STURGE-WEBER with those of the three other phakomatoses then it is evident that the syndrome of STURGE-WEBER belongs to the same group. We find:

phakoi e.g. the naevus vinosus faciei;

phakomata, the vascular tumours in chorioid and in the brain;

phakoblastomata, the glioma retinae.

PHAKOMATOSES

	I BOURNEVILLE	II RECKLINGHAUSEN	III VON HIPPEL—LINDAU	IV STURGE—WEBER
Nervous-system	Cerebrum: tumefactions in the cortex; tumours in the ventricle; ependym; heterotopical spots in the white substance; cysts	Cerebrum: astrocytoma Cranial nerves / peripheral nerves / sympathetic nerves: tumours: ganglioneuromata; neurofibromata	Cerebrum / Cerebellum / medulla / spinal cord: angioma; angioplastic tumours; cysts; proliferation of the glia; glioma Syringomyelia	Meningi: naevi vasculosae Cerebrum: Atrophy; calcifications; heterotopical spots Cerebellum atrophy
Eyes	Choked disc Optic disc and retina: cysts and tumours: neurofibrillomata; neurocytomata	Optic disc: Choked disc; degeneration and glious proliferation Retina: Cysts; tumours with angiomatous parts; degeneration Tumours of the optic nerve Buphthalmos Exophthalmos pulsans	Optic disc: choked disc; angiomata Retina: angiomata; gliosis; cysts; degeneration	Chorioidea: proliferation of bloodvessels; angioma Retina: glioma Buphthalmos Glaucoma
Other Organs	Heart rhabdomyomata Kidneys: cysts; tumours: hypernephromata; leiomyomata; angiomata; fibromata; lipomata Uterus: fibromata; leiomyomata Intestinae — lipomata Thyroid / mammae: gland — adenomata Skin: naevi and other stains; tumours: adenomata; fibromata; angiomata; lipomata	Intrathoracic tumours Intra-abdominal tumours Bones: Defects in the skull; affections and deviations of the spinal column; cysts; tumours Endocrine glands: various affections Skin: Naevi etc.; tumours	Kidneys: cysts; hypernephromata Pancreas: cysts; cystadenomata Ovarium — cystadenomata Suprarenal glands / Epidymis: tumours Skin: naevi; angiomata	Skin — naevus flammeus
Congenital anomalies	Spina bifida Ectopia testis One kidney	Spina bifida Syndactyly One kidney	Anastomosis arterio-venosum	
Particular symptoms	Epilepsy Idiocy Imbecillitas	Epilepsy Backwardness		Epilepsy Idiocy Imbecillitas Paralysis

The disease is of a congenital, hereditary character and often mental abnormalities as backwardness, idiocy, epilepsy are found. Sufficient evidence to allow us to classify this syndrome among the phakomatoses as a fourth phakomatosis.

SUMMARY.

In this paper the results of the clinico-pathological examination is given of the combination of naevi vinosi, congenital abnormalities of the right eye associated with tumourformation, with angiomatosis and congenital and degenerative changes in the right half of the telencephalon. This observation is classified among the group of cases called the STURGE-WEBER syndrome. Among other things it is differentiated from observations found in literature by the presence of a retinoblastoma and by the wide — but systematical — distribution of the alterations in the brain. Here the chief lesions are angiomatosis of the pia-arachnoidea and of the cortex, hypoplasia with parenchymatous degeneration and calcification of almost the whole of the right half of the neopallium. A secondary atrophy of the crossed neocerebellum is present without calcification or angiomatosis. This combination of pathological changes has to be regarded as a fourth type of phakomatosis.

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