Medicine. — *Microscopic investigation of the brain in a case of craniosynostosis.* By CORNELIA DE LANGE. (Communicated by Prof. B. BROUWER.)

(Communicated at the meeting of April 26, 1941.)

This congenital anomaly was found in a man B who died in 1940, 68 years old of heartfailure. The post-mortem in the Pathological Institute of Prof. H. T. DEELMAN revealed a cicatrix myocardii, a thrombosis of the left coronar artery and partly of the right with sclerosis, pericarditis fibrinosa, kidneys with a large number of small cysts and multiple infarctus of the lungs.

Over a certain period of the patient's life there had been glycosuria, but during his last stay in hospital no sugar was found. At birth the anomaly of his skull was commented upon by the family doctor. The delivery was reported as difficult, but instrumental aid had not been necessary. The patient's only brother has a normal shape of head. B had a good intellect and passed through grammarschool in the ordinary way. He became a mason and married. His only child, a daughter, has a normal skull. B never suffered from headaches, fits of unconsciousness, attacks of sickness, diplopia or from a sense of oppression in the head. There never were any symptoms of acholuric icterus. In 1926 deafness of the left middle and internal ear was stated. Eighteen years before his death he suffered from a mild commotio cerebri, for which he was admitted to hospital. From February 12th 1940 till May 11th 1940 he stayed for heartdisease in the Wilhelmina-Gasthuis (Pavilion II) in Amsterdam. He was readmitted on June 6th 1940 and death occurred twelve days later.

I am indebted to the physicians in charge of the patient for the following status.

The patient's skull (Fig. 1 a 2) presents a high forehead and rises to an apex at the bregma. There is a pronounced asymmetry of the forehead, the left side rising higher than the right. Above the orbits a depression is felt, but the superciliary arches are prominent. The right orbit is larger than the left and of oval shape. There is no exophthalmus. On the right the temporal region of the skull protrudes. From the summit the posterior portion of the head slopes almost suddenly back to the pointed occiput. Over the head a ridge is felt in an antero-posterior direction.

Measurements of the skull.

length	20.2 cm
breadth	14.6 ,,
cephalic index	71.17 ,,

distantia subnaso-bregmatica	22.6	cm
distantia biparietalis	13.2	,,
distantia bifrontalis (just above the orbits)	11.2	,,
distance from the occiput to the anterior fontanelle	20.1	,,

From its appearance and these measurements a diagnosis has been made in the Clinic of: asymmetric, scaphocephalic skull.

Radiographic examination revealed a high pointed head with a straight forehead and a prolate occiput. The basis of the skull proves shortened and the orbital roofs are irregularly formed. The site of the anterior fontanelle is very thin and vascular. There are some so-called digital impressions, but they are not very pronounced. The processus clinoides are of different length. The sella turcica is shallow. The metopic suture (sutura coronaria) is not visible, nor is the sagittal one; only the lambdoid remains. On the antero-posterior radiogram the asymmetry is striking, the sphenoid bone showing on the right a steeper position than on the left and also the right orbit being larger than the left. On both sides the sphenoid reaches on its mesial side farther down than usual. The bones of the skull show a normal thickness.

Examination of the eyes. The left eyebrow drops a little. The ocular movements are intact. There is strabismus convergens, but the patient wears positive glasses. Visus L $^1/_3$. R $^1/_2$. Fields of vision grossly determined prove normal. Bilateral there is a slight paleness of the optic disks. Optokinetic nystagmus normal; normal rotatory nystagmus in extreme positions. Colourperception on the right eye better than on the left.

The patient's deafness has already been mentioned. The cranial nerves are normal; so are the motility and the sensibility all over the body, the reflexes and the co-ordination movements.

Hands and feet show no deformities.

The post-mortem did not reveal any *congenital* anomalies, save there being an incomplete fourth lobe of the right lung and a malformation of the arteriae communicantes cerebri.

At the autopsy the following measurements of the skull were taken: circumference 55 cm distantia bitemporalis 13.5, biparietalis 11.5, frontooccipitalis 20 cm. The soft parts were without peculiarities. The calvarium has a scaphoid shape, is asymmetric, the bones have their normal thickness. The interior fossae anteriores, mediae and posteriores are much deeper than usual, particularly the latter. Otherwise the base of the skull does not present any anomalies. The foramen magnum has been displaced to the left thereby enlarging the right medial and posterior fossa. This asymmetry holds also true for the brain itself as will be described later on. The dura mater, the bloodsinus and vessels are normal with the exception of there being a small aneurysma of the right arteria cerebri media. Weight of the brain 1500 grams. (Fig. 3 by courtesy of Prof. H. T. DEELMAN).

The pituitary body has its normal form and dimensions. The accessory sinus are well formed.

The brain, spinal cord, pituitary body and calvarium were presented by Prof. DEELMAN to the neurological laboratory of Prof. B. BROUWER.

Macroscopic description of the brain.

On the convexity there is a chronic leptomeningitis most pronounced on the mesial side of the frontal lobes. Some small aneurysmata are discovered. The total shape of the brain has altered (Fig. 4), it has a lengthened, scaphoid form (length 20 cm, breadth 14 cm). On its dorsal face the temporo-occipital region of the right hemisphere is larger than the left. On the ventral face on the contrary the left part proves larger than the right. This may be explained by a torsion of the brain which also shows on its base. It looks as if by a bend in the middle-line the pons Varoli has been displaced slightly to the left in a postero-anterior sense. The same holds true but in a minor degree for the tuber cinereum. The stalk of the pituitary body is directed to the right. The chiasma deviates somewhat to the left, but the brainparts anterior to it are again directed to the right. The right corpus mamillare is somewhat larger than the left. There is a minor dilatation of the infundibulum.

Left hemisphere. The sulcus Rolando runs its normal course and indents on the mesial wall. The sulcus praecentralis is not interrupted. The sulcus frontalis superior is distinct, so is the inferior; the sulci intraparietalis and temporalis medius can be traced. The pars triangularis is distinctly visible. The frontal pole shows a surplus of convolutions on its lateral and anterior part, but no real mikrogyria exists. The bulbus and tractus olfactorius are normal, the latter being imbedded in the gyrus rectus. In the middle of frontal pole on its basal side a pit of a certain depth is seen (length 4 cm, breadth 2½ cm).

Right hemisphere. Here the sulcus Rolando does not indent on the mesial wall. Over the base of the frontal lobe a slight polygyria is present, but there is no real microgyria. Here also a pit is seen on same spot as on the other side, but it is more shallow. The rest of the convolutions are normal, so are the bulbus and tractus olfactorius.

The brainstem and cerebellum are cut off through the pedes pedunculi; there is no widening of the Sylvian duct. The brain is cut in a fronto-vertical direction through the commissura anterior. There is doubtless a dilatation of the lateral ventricles, the right being larger than the left. The septum pellucidum proves a thin membrane, the corpus callosum is also meagre. The anterior part of the striate body looks normal. A second cut is made through the splenium; here also the ventricles show markedly dilated, the right more so than the left. The splenium is of a slight build.

The cerebellum does not present any anomalies, both parts are equal. On sagittal sectioning one sees a normal shaped dentate nucleus. The spinal cord also has a normal appearance.

Technique. Of the following convolutions parts are taken, imbedded in

celloidin, stained after NISSL and with hematoxylin-eosin: right frontal pole covered with pia, left frontal pole (basal part), "pit" in the left frontal lobe, gyrus frontalis primus near the middle-line, gyrus frontalis secundus and gyrus frontalis primus dorsally, all of them on the left side. Right and left gyrus centralis anterior (centre for the arm), left gyrus centralis posterior, lobus parietalis superior on the left side with pia, gyrus temporalis superior with and without pia, gyrus occipito-temporalis, gyrus occipitalis primus, upper and lower lip of the calcarine, all of them on the left.

Part of the chorioid plexus of the left lateral ventricle is treated in the same way.

From the cerebellum parts are taken of both hemispheres and of the vermis; from the spinal cord pieces of the cervical, the thoracal and sacro-lumbar region. Different parts of the cord, of the right cerebellar hemisphere and the nucleus dentatus are more-over treated after WEIGERT–PAL and VAN GIESON's methods.

After all these parts have been removed, the left hemisphere is put into MÜLLER's solution, imbedded in celloidin and cut in serial sections of 35 μ. 1 : 5, stained 1 : 10 after WEIGERT–PAL and VAN GIESON's methods. The right hemisphere is imbedded in celloidin for staining after NISSL and with hematoxylin-eosin in the same way as stated above but the sections measuring 25 μ.

The brainstem is treated in the same way as the left hemisphere, so are the optic nerves.

The following special techniques have been employed: BIELSCHOWSKY's method for left lobus parietalis superior, the "pit" in the left frontal lobe, right neocerebellum, left gyrus centralis posterior (centre for the leg), left gyrus occipitalis primus, left gyrus temporalis primus, cervical, thoracal and sacro-lumbar cord. HOLZER's method for gyrus praecentralis, frontalis superior and temporalis superior, all of them on the left side, vermis, right cerebellar hemisphere, cervical, thoracal and sacro-lumbar cord. Staining after PENFIELD for left gyrus centralis anterior (centre for the arm) left gyrus temporalis primus, right cerebellar hemisphere and cervical, thoracal and sacro-lumbar cord.

Microscopic investigation.

In the spinal cord no anomalies were present with the exception that in the thoracal part the lumen of the central canal was very narrow and in some of the sections of the cervical part the same was seen. In a more cranial cervical region the canal proved slightly dilated. In the cerebellum nothing abnormal could be found and the same may be said of the brainstem. The study of the small parts removed for different techniques and of the large sections of the hemispheres did not reveal any peculiarities. All was within range of the slight individual variations, which one encounters in studying the brains of various individuals.

Stress may be laid upon the fact that the regio hypothalamica proved

quite normal. The same was the case with the pituitary body, which was examined in sagittal sections stained with hematoxylineosin.

In the striate bodies no anomalies could be detected, dorsally some conglomerations of glial cells could be found. The thalami optici presented their normal aspect; in the corpora mamillaria the pars magno- and the pars parvicellularis showed distinctly. The "pits" in the frontal poles were examined with great care, but they did not reveal any structural anomalies. Histological differences between the right and the left hemisphere could not be detected. In the sections stained after WEIGERT–PAL the semi-oval centre shows some pale spots, but microscopic examination does not reveal a degeneration of the myelin-sheaths. The HOLZER technique made apparent a slight degree of bordergliosis in some of the cerebral convolutions. The plexus chorioides of the lateral ventricles was seen to contain corpora arenacea with concentric layers, also structureless conglomerations of chalk. One sees also a calcification and a hyalinisation of the walls of the bloodvessels. The epiphysis contains sandy deposits, which facts are in accordance with the patient's age.

Taken all in all one may say, that the ample histological investigation of the brain which has been performed in this case, has shown not only a complete absence of congenital deformities, but also an admirable accommodation of the brain during its growth and development to unfavorable circumstances, id est to the hindrance of its expansion, provided by an abnormal skull with synostosis. We must come back to this point in discussing the possibility of surgical intervention in cases of congenital craniostenosis.

What name must be applied to the deformity of the skull in our case? It cannot be oxycephaly or scaphocephaly for "in true oxycephaly where the skull bones meet, they fuse" (GREIG [1])), the skull is sutureless. After IDA MANN [2]) oxycephaly is a primary synostosis of the transverse sutures (lambdoid, metopic and basal) and scaphocephaly is the primary fusion of the sagittal suture. Moreover both are a symmetrical deformity. In the patient B the shape of the head showed asymmetry. In oxycephaly the accessory sinus are flattened and shallow; in B they were normal and moreover the lateral ventricles were dilated. Plagiocephaly is caused by local synostosis of different sutures. False oxycephaly is an example of localised premature synostosis occasionnally congenital. True oxycephaly and scaphocephaly are congenital and may be hereditary. False oxycephaly is a fortuitous production and is never hereditary (GREIG). So it may be the wisest course to adopt in our case the term of congenital craniostosis.

In the patient B clinical symptoms of a raised brainpressure were almost

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[1]) DAVID M. GREIG. Edinburgh med. Journal. N.S. Vol. XXXIII, p. 189, 280, 357 (1926).

[2]) IDA MANN. Transactions of the Ophth. Soc. of the United Kingdom. Vol. LV (1935).

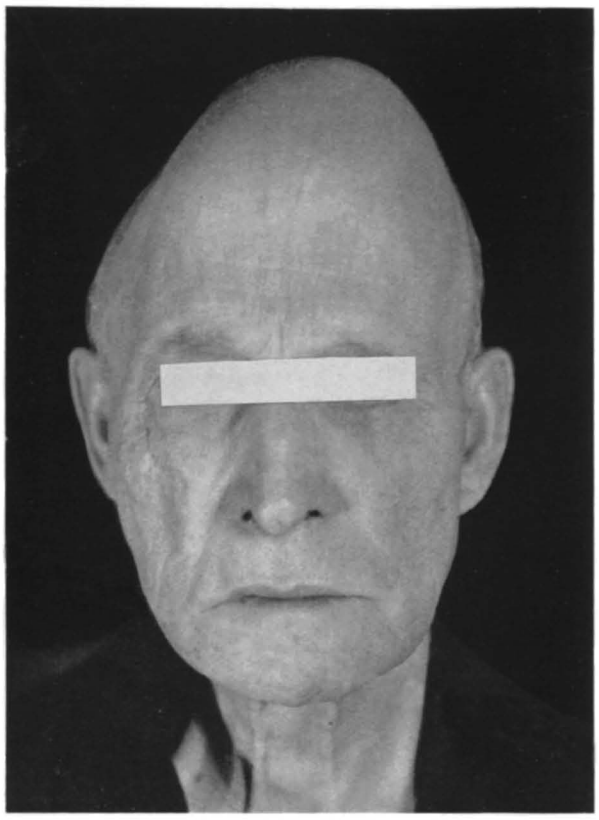

Fig. 1.
Photo by courtesy of the internal Clinic.

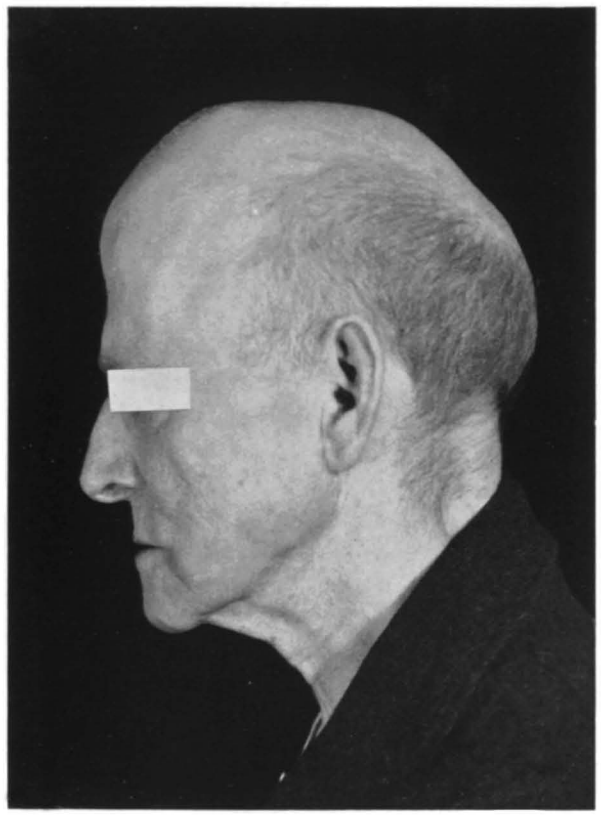

Fig. 2.
Photo by courtesy of the internal Clinic.

Fig. 3.
Photo by courtesy of Prof. H. T. DEELMAN.

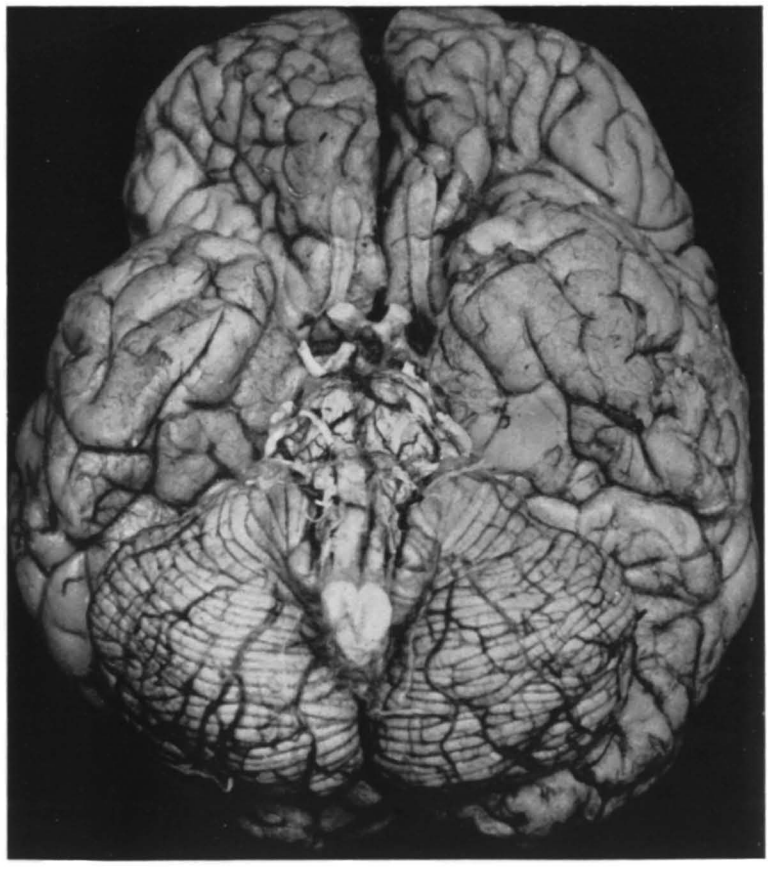

Fig. 4.
Photo Neurological Laboratory.

lacking; there was only a slight paleness of the optic disks, that need not be caused by it. The radiogram showed a somewhat shallow sella turcica and some minor digital impressions. The accessory sinus were not flattened or shallow, the bones of the skull had their normal thickness, only the site of the anterior fontanelle had thinned. The post mortem has corroborated these facts. The "Anlage" of the brain was quite normal; there was no vitium primae formationis. Nor were there histological alterations due to a raised brainpressure. The cerebrum had accommodated itself to its narrow surroundings.

In most cases of craniosynostosis however the misproportion between the narrow skull and the in youth rapidly expanding brain, gives rise to clinical symptoms, of which the menace of blindness lies in the centre.

A surgical treatment of craniostenosis has repeatedly been performed, as Professor B. BROUWER [1]) has recently exposed in a clinical lecture. It need not be said that operative aid can only have a palliative effect, if not only the skull, but also the brain itself is misshapen or if the raised pressure has caused irreparable alterations of the tissues. I was unable to discover in literature a histiological report of the brain in a case of craniosynostosis. Macroscopic details are also extremely scarce; only WHEATON [2]) mentions that in two cases the occipital parts of the brain were markedly underdeveloped.

In my opinion the value of the investigation of the brain in the patient B lies in the fact that craniostenosis may occur in cases, where the "Anlage" of the brain is quite normal and that the cerebrum may accommodate itself in a high measure to its narrow surroundings without the tissues undergoing irreparable damage. In general the clinical symptoms of raised brainpressure are already present in the early years and in those cases operation should not be postponed, but performed before the child has reached the age of four years.

So the congenital craniostenosis comes within the range of interest of the whole medical profession; it has ceased to be a mere curiosity.

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[1]) B. BROUWER. Over Oxycephalie. Nederl. Tijdschrift v. Geneeskunde, **84**, 501 (1940).

[2]) S. W. WHEATON. Transactions of the Pathol. Society of London, **45**, 238 (1894).