A CYCLOPS AND A SYNOTUS

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INTRODUCTION

ONLY a small number of cases of cyclopia in human beings and mammals have been minutely examined. The number becomes still smaller if a more or less complete microscopic investigation of the central nervous system is stipulated. It is really only the cases of Davidson Black and Winkler and perhaps that of Naegli which answer this requirement. In contrast therewith there is an abundance of experimental studies in this field in urodela and other lower classes of animals.

For all that, unanimity does not by any means prevail here, although the views of Stockard and his followers—who held that the first determination of the eye lay unpaired in the median line—and those of Spemann—who pointed to a paired rudiment from the outset, which views were originally diametrically opposed—appear to have drawn somewhat nearer to each other in recent years.

Woerdeman, for instance, found that the paired rudiment of the eye shifts its position laterally downwards very early (when the folds of the medullary plate become visible) and he rightly says that this is not the same as Stockard's lateral growth of an unpaired eye rudiment. Yet, by saying this, he admits certain changes and growth conditions to which Fischel, for instance, did not do full justice. E. Manchot, on the other hand, who defends Stockard's views, admits that between the two regions of the eye rudiment there must be a tract of brain tissue (*lamina terminalis* and *regio chiasmatica*). She maintains that the *regio chiasmatica* belongs to the eye rudiment but admits that this does not imply that the last word about the determination itself has been said.

Petersen suggested three possibilities :—

- (1) in the material of the presumptive medullary plate there are two separate groups of cells for the left eye and right eye ;
- (2) the original unpaired rudiment divides into two ;
- (3) the original unpaired rudiment grows sideways.

Woerdeman modified the second possibility slightly ; the original unpaired rudiment divides into three parts, viz. two eyes and the *regio chiasmatica*.

Of these three possibilities, the experimental researches of Spemann, Woerdeman and others have shown with certainty that the third is precluded.

If our general survey of literature is correct, no choice can yet be made between the first and second possibilities. Experimental embryology, therefore, has not yet succeeded in furnishing certainty on the point whether in the case of cyclopia one should speak of a defect or of an inhibition (Hemmung). For if it assumed that the eye rudiment is originally unpaired, it follows that pure cyclopia is a consequence of an inhibitory action ; but if a paired 'Anlage' is assumed, one cannot avoid presuming that in the case of cyclopia a median sector has disappeared.

For that matter, put this way, the question has not been correctly formulated. It is inconceivable (at any rate if teratology is taken into account) that a defect should not at the same time have an inhibitory effect. That being so, the question becomes a different one and might be worded as follows : Are there any known cases of malformation in respect of which one can speak *solely* of inhibition ?

Our experience relates only to malformations of the nervous system and to the literature in this field. It shows that in the case of malformations of the central nervous system symptoms of inhibition frequently occur, but that there are no cases in which it has been conclusively proved that there are no defects. On the contrary, the general impression is that the same defects are nearly always found. However, *no* certainty in this sphere can be expected to be derived from teratology, which has to consider cases so much more complicated and composite than the physiology of development has to do.*

A teratologist cannot solve these problems. He is however in a position to describe his material as accurately as possible and to disclose valuable conditions and relationships in regard to certain functions of development.

Very special difficulties are encountered in examining cyclopia.

Much as is known about the formation of the eye out of the cerebral vesicle, little is known with certainty about the history of development of the telencephalon in the neighbourhood of lamina terminalis, infundibulum, and recessus opticus. Such knowledge is needed, however, to grasp the nature of the brains of cyclopes, and indeed to comprehend the formal genesis of cyclopia.

In this respect too, Woerdeman made an important research, whilst in regard to the end of the sulcus limitans at the neuroporus anterior there are numerous observations by neuroanatomists (Winkler, His, Kupfer, Bok).

In our opinion we are still far from having a clear insight into the history of development of these parts of the brain in higher classes of animals.

HUMAN CYCLOPS CASE

The first case of human cyclopia which is described here was discussed in 1909 by Prof. W. M. de Vries and by one of us (B.) at the Netherlands

* It is e.g. conceivable that changes in tissue which originally represent an inhibition may through secondary changes (resorption, fusions) present the appearance of a defect.

Physical and Medical Congress. Prof. de Vries stated at the time that in this case there was only one eye fissure which was bounded by four eyelids (this is still clearly visible in the photographs). The eye was perfectly simple. There was no trace of a nose. The philtrum was also lacking. In X-ray photographs and after preparation of the skeleton the following changes were found (fig. 1).

In the cranial bones there was a wedge-shaped defect situated medially, the acute angle of which passed through the sella turcica. That part of the os sphenoidale which usually lies between the two foramina optica was wanting. The foramen opticum was simple. Os ethmoidale, ossa nasalia, lacrymalia and a part of the os frontale were wanting. The remaining part of the os frontale was simple and small. The intermaxillary bone with the rudiment of the four incisors was absent. A medial part of the roof of the mouth cavity was absent from the inner surface of the skull, in consequence of which the vertical branches of the ossa palatina were very close to each

FIG. 1.—Skeleton of the cyclopic head.

other and the vomer was also wanting. The cavity of the nose and choanæ were entirely absent. X-ray films showed that on both sides of the lower jaw an incisor was wanting.

In regard to the condition of the perfectly simple eye Prof. de Vries stated at the time that it was not quite normal. Behind the eye there was a coloboma and a cyst. This cyst had a glia wall, an ependymal lining and was directly continuous with the optic nerve. Nervus opticus and cyst were enclosed by one connective-tissue sheath. This was therefore a cyst of the eyestalk. The cavity of the cyst was homologous with the cavity of the stalk of the primary eye vesicle. One of us (Bouman) then stated certain particulars regarding the general structure of the nervous system in this case.

EXAMINATION OF THE BRAIN

The following can be said of the examination of the brain.

It shows the typical structure of a cyclops' cerebrum. Medulla oblongata, pons Varolii and cerebellum are of normal structure.

When the cranium was being opened a bladder-like structure was seen to hide cerebrum and brainstem. On being incised, the ' bladder ' was found to communicate with the aqueduct of Sylvius, which opens crater-shaped into this cavity. When looking at this crater-shaped opening from above, one receives the impression that underneath it there are parts of the optic thalamus. An epiphysis and both habenulæ, which run frontal-wards, are visible. An apparently unpaired piece of brain tissue without furrows or convolution lies in front of this optic thalamus without any connection (figs. 2 and 3).

Seen from underneath, the infundibulum and an apparently unpaired optic nerve lie closely proximal to the pons.

The immediately adjacent broad piece of brain tissue seems to be fused here with the diencephalon. From underneath the distal parts of the telencephalon are seen to be paired and show a few furrows. The dorsal vascular membrane ' bladder ' arises

FIG. 2.—Cyclopic brain seen from above.

FIG. 3.—Cyclopic brain seen from below.

from epiphysis and habenulæ and disappears downwards between optic thalamus and prosencephalon.

The *microscopic examination* of this brain revealed the following (Schenk).

The *medulla oblongata* is seen in the sections to be well formed and larger than the normal control sections. The enlargement is almost entirely in the olives (fig. 4).

On measuring the surfaces the following figures were found :

						Normal.	Cyclops.
Olives	..	..	..	..	..	100	135
Tegmentum	..	..	..	..	..	100	106
Med. oblong. tot...	..	..	..	..	..	100	117

These figures have been reduced to 100 for normal. The place for fibres of the pyramidal tract has not been included.

Olives and inferior olivary bodies are well developed. Pyramidal tracts are entirely wanting. The lemnisci mediales exist, but are little developed. All other nuclei are normally represented together with their roots, primary and secondary fibres. The maturation of the medullary sheath appears to have advanced further than in

FIG. 4.—Drawing of a section through the medulla oblongata. The olivæ inferiores are seen here at the place where they are most enlarged.

normal preparations of a neonatus. When examining the nervous system further in a proximal direction, one meets with anatomical pictures which differ very little from those of a normal child. We shall hereinafter not discuss the points of resemblance with normal brains. Nervi abducentes, faciales and octavi, with their nuclei

FIG. 5.—Drawing of a section through the pons. On the left the nervi vestibularis and facialis are visible; on the right both parts of the nervus octavus.

and secondary fibre systems, are undamaged. The pontine nuclei, too, exist and are normal (fig. 5).

The cerebellum is fairly large. The lamina granularis externa is still entirely present. The maturation of the medullary sheath has advanced further than in normal preparations (the neocerebellar parts are also well myelinated). Deviations were found in the nucleus dentatus. Instead of one cell-band, numerous separate groups of cells are found side by side. Other windings are very small. This is therefore microgyria and fragmentation.

The nervus trigeminus with its spinal and mesencephalic tracts and nuclei is of a normal structure.

Just above the pons the mesencephalon assumes an unusual appearance. At the decussations of Meynert and Forel the infundibulum with both corpora mammillaria is visible ventrally in the section. The pedes pedunculorum are entirely devoid of fibres. They are crossed only by the roots of the nervus oculomotorius. As far as is ascertainable, the nuclei of this nerve are normal. The nervus trochlearis, too, has no deviations of importance.

In these sections the red nucleus becomes visible very soon after the disappearance of the pons. The dorsoventral size of the sections is large here. Ventrally, in the median line, there are numerous incoming fibres which cross and recross in an irregular manner. Dorsal to the nervus opticus lie the two corpora mammillaria and between them lies the infundibulum. Lateral to these there are only a few fibres and

FIG. 6.—Drawing of a section through the mesencephalon.

cells. The root fibres of the nervus oculomotorius intersect the red nucleus. Laterally and dorsally to this lie the two lemnisci, which lose fibres in a dorsal direction. The trochlearis roots cross dorsally to the aquæductus Sylvii.

The red nucleus reaches its greatest diameter in the next sections. The surface is considerably greater than in normal preparations (fig. 6).

The nervi optici do not form a distinct chiasma although a few fibres cross. On both sides these fibres are gathered into a fairly well-defined bundle. A part of them end in a nucleus, which also derives fibres from the lemnisci: ganglion geniculatum laterale. Laterally to the infundibulum lie two little bundles. One of them is fairly well medullated and the other slightly. The bundle which is deficient in myelin disappears proximally in the nuclei thalami and is possibly the mamillothalamic tract of Vicq d'Azyr. The other one soon curves lateroventrally and disappears in the mass of fibre which fills the ventral parts of the section.

In the next sections the radiatio optica can be followed further. After passing the ganglion geniculatum externum, in which a number of fibres terminate, other optic fibres radiate in the corpora quadrigemina which are formed in the dorsal parts of the mesencephalon. In this section the red nucleus loses, in a ventrolateral direction, fibres which disappear proximally in the nuclei thalami. The lemnisci also split up into fibres which run ventrally.

In the sections which succeed these, the red nucleus ends in a ventrolaterally directed radiation. The lemnisci, too, gradually merge. The radiatio optica also produces the lateral and ventral limits of the section. The fasciculus retroflexus of Meynert now occupies, as it were, the place of the red nucleus. Ventrally the first parts of the thalamus appear. In this section (fig. 7) it is probably the ventral nucleus

FIG. 7.—Drawing of a section through the proximal part of the mesencephalon. The nucleus ruber merges here in the thalamus.

which shows a broad radiation ventromedially. Recognition of the various nuclei thalami presents great difficulties, and for this reason a few names have, hereinafter, been applied with some degree of hesitation; the anatomical situation is aberrant; the capsula interna is wanting, and the corpus striatum likewise.

In the following section the corpus quadrigeminum anterius and the commissura posterior are visible. Laterally to the fasciculus of Meynert lie complexes of nuclei, which show some resemblance to the nuclei præbigeminales. There are, ventrally to them, a lateral nucleus which has derived fibres from the nucleus ruber, a nucleus ventralis and a nucleus reticularis, lying in the radiatio thalami. The latter forms a medial crossing.

In the next section the radiatio thalami turns towards the hemispheres which here lie ventrally to the thalamus. The thalamus has only a few fibres with myelin. It is

not certain whether there is a nucleus subthalamicus among these centres, which are but little distinguished; there is no trace of a corpus striatum.

FIG. 8.—Drawing of a section through the diencephalon after opening of the aquæductus Sylvii in the third ventricle. Ventrally telencephalon and diencephalon are fused.

FIG. 9.—Drawing of a section through the proximal parts of the nucleus anterior thalami in the diencephalon.

In the section which now follows there are a few fragments of the epiphysis. A number of cells are grouped round the fasciculus retroflexus, whilst a few fibres proceed dorsally towards the middle line (pes conarius).

In the next section (fig. 8) the aquæductus Sylvii opens up. There is on both sides a finely developed ganglion habenulæ with a nucleus lateralis and medialis. Not much change takes place in the mass of the thalamus. Ventrally, a broad irregular mass of fibres forms a connection with the hemispheres (radiatio thalami).

FIG. 10.—Diagram of ventricles in the cyclopien brain.

FIG. 11.—General aspect of mesencephalon, diencephalon, telencephalon and ventricles in the cyclopien brain.

In the next section the ganglion habenulæ has merged into the tænia thalami. The thalamus has diminished in size. In the sections which now follow, the size of the diencephalon rapidly diminishes. A broad bundle emerges from the tænia thalami, curves ventrally and disappears into the broad ventral mass of fibres. The nuclei thalami merge here into a single round nucleus (nucleus anterior) (fig. 9).

Telencephalon.—The telencephalon lies entirely ventrally to the diencephalon. Seen sidewise it is flat (dorsoventral dimension); seen from above it is round and shaped somewhat like a horseshoe in the occipitally situated part. The relationship between the ventricles has been made clearer in the diagrams (figs. 10 and 11). After changing into the third ventricle the ependyma of the aquæductus Sylvii covers the dorsal surface of the thalamus between habenulæ and tæniæ thalami as far as its front end. Then returning in a backward direction, the ependyma can be followed in a wide funnel lying between thalamus and forebrain. Finally, this canal ramifies in three directions in the brain itself. An ependymal fissure enters each of the two occipital lobes, whilst one branch enters the forebrain. The place where this division occurs might rightly be called the foramen of Monro. The third ventricle which dorsally forms a large 'bladder' (this has not been preserved in the sections, but is distinctly shown in the photographs of the undivided preparation) therefore narrows

FIG. 12.—Diagram of the division of the cortical areas. No I was cut occipitally and No. V frontally. The six-layer cortex is marked with hatching.

ventrally to a funnel, which in the case of a foramen Monroi divides into side ventricles. The cortex of the great brain is not built in the same way everywhere. In a few places there is a cortex consisting of six layers, such as one would expect to find in the neocortex of a newborn child (indicated in the diagram by hatching). Dorsally as well as ventrally the cortex is built differently in the median line. It is not difficult to distinguish in it a hippocampus, parts of a nucleus amygdalæ and olfactory cortex with verrucæ Arnoldi (left white in the diagram) (fig. 12).

In order to elucidate the complicated anatomical situation, we will describe a section near the foramen Monroi. The shape of the whole resembles somewhat that of an anchor, whilst the cavity of the ventricles looks much like an inverted V. The wall of the cerebral cavities has collapsed entirely. Basally, there is a strip of cortex with verrucæ Arnoldi; to the left and right it is continuous with the neocortex which occupies the lateral parts wholly. Not until it comes to the neighbourhood of the median line does this neocortex change dorsally into another type: the hippocampus formation. Without a distinct fornix a fusion takes place with the thalamus

here in the mediodorsal line. The fibres connecting cortex and thalamus run through this fusion. They form two groups : one group of fibres comes from the distally situated parts of the cortex and is connected with proximally situated parts of the thalamus. Another group springs from the more proximally situated parts of the cortex and goes at practically the same level in a left and a right bundle towards the thalamus. Both groups cross each other sagittally, so that the distal fibres end in the thalamus proximally to the other cortex fibres. There is also a crossing of fibres from the right and left hemispheres. This also applies to the corticothalamic fibres. These also cross in the median line.

In the spinal cord there are no great deviations except the absence of the pyramidal tracts. It gives the impression of being small.

SUMMARY

Recapitulation of the deviations in the central nervous system :—

A series of general disturbances in those parts of the brain which are not directly linked up with the eyes or olfactory brain : anomalies in the nucleus dentatus, changes in the relative size of olives, red nuclei and the other parts of the myelencephalon and mesencephalon. Absence of pyramidal tracts and corpus striatum.

A number of disturbances in the proximal parts of the nervous system :—

1. Absence of the chiasma opticum, but existence of a tractus opticus which on both sides goes to the homolateral ganglion geniculatum externum.
2. Absence of the hypophysis cerebri, pars posterior.
3. Absence of bulbus and tractus olfactorius.
4. Absence of fornix and corpus callosum.
5. The third ventricle has become a large ' bladder ' dorsally.
6. The foramen Monroi has been displaced ventrodistally and is under the thalamus.
7. The medioventral parts of the diencephalon (corpus mammillare, infundibulum and tractus opticus) have been displaced distally.
8. The lateral parts of the diencephalon have been displaced ventromedially (radiatio thalami) and a decussatio thalami has arisen.

CALF SYNOTUS CASE

Prof. C. Winkler kindly enabled us to study a case belonging to his collection, and placed at our disposal a series of sections of the central nervous system and a few photographs of a misshapen calf.

The calf in question, when examined with the naked eye, showed a large number of severe malformations. The photograph (fig. 13) shows the front of the head with two ears, which are near each other in the median line. Nothing can be seen of eyes or of a nose. In the middle there is a hole, about which we possess no information.

It is possible to conclude from X-ray films that the occipital and parietal bones are well developed, that there are two large petrosal bones and that the facial skull has been reduced to a meagre residue which it is difficult to unravel.

In the photograph of the brain preparation (fig. 14), as removed from the skull, it is possible with the unaided eye to discern the following remarkable situation.

Whilst the medulla oblongata and the cerebellum are normal in appear-

FIG. 13.—Front aspect of the synotical calf.

ance, the proximal parts of the brain are completely abnormal in structure and outward appearance. When examined with the unaided eye, this part of the brain reminds one of the earliest stages of development of the nervous

FIG. 14.—Brain of the synotical calf.

system, when the thalamus is high up cranially and the telencephalon curves sharply ventrally. But here at this bend the comparison ends, as there is no trace of eye vesicles or windings in the ventrally curved proximal piece. This mass does, however, show a fairly sharp sagittal fissure.

In the prolongation of the metencephalon and mesencephalon lies a

membranous vesicle which, compared with the 'bladders' that are usually found in cyclopes, may be said to be very small. When this vesicle is opened, the crater-shaped opening of the third ventricle is visible (as will be seen later on). Many tela chorioidea are found here.

MICROSCOPIC EXAMINATION (SCHENK)

The preparations had been previously put into chromate and stained alternatively, according to the Weigert-Pal method, with hæmatoxylin and carmine.

The nuclear systems and fibre systems of the medulla oblongata, of pons and cerebellum only show a few deviations. Whilst the nuclear and fibre systems of the nervi XI, X, IX and VIII are strongly developed, the nervi XII, VII, VI and V are represented only by a few fibres and nuclei. However, none of these nerves has disappeared or been reduced beyond recognition. The cerebellum is also completely developed. The fibres are well medullated and the cortex is normally built. In the mesencephalon the posterior corpora quadrigemina are strongly developed. The place of the olivæ superiores is indicated on both sides by a dense network of fibres, but they are extremely deficient in cells.* The nuclei trapezoides mediales have large cells. The nuclei trapezoides laterales have disappeared entirely. In the corpus quadrigeminum posticum the brachium posticum, the connecting arm with the corpus geniculatum mediale and the cerebral cortex, contains very few fibres. The cells in the corpus quadrigeminum posterior are small and few in number. The corpora quadrigemina anteriora are fairly strongly developed. In them various layers are found, which decussate in the case of mammals, and many cells of normal size, with the exception of the large cells of stratum griseum intermedium, which are wanting.

When continuing the series in a proximal direction, fibres and cells of the nervus oculomotorius are found. They are weak, but distinctly developed. Medioventrally lies a large ganglion interpedunculare. The part with large cells of the nucleus ruber is large and well developed. In the mediodorsal parts of the corpora quadrigemina there are numerous transversely cut fibres which are gathered in a bundle. This bundle derives fibres from the layers of fibre of the corpora quadrigemina and increases more and more in size in a proximal direction.

In the sections which follow now, the structure of the corpora quadrigemina anteriora disappears. The dorsomedian bundle remains. Between the commissura posterior and aquæductus Sylvii one can see the distally situated parts of the sub-commissural ependymal organ, which is of large extent. Remains of eye muscle centres lie between the fasciculi longitudinales posteriores. It is possible to distinguish a lemniscus medialis and lateralis. The latter continues to lie laterally and it ends, in the sections which now come, in a centre, which is therefore in all probability the corpus geniculatum mediale. The first (lemniscus medialis) gradually begins to radiate in dorsolateral direction. Here is the beginning of the tract of Meynert with large ganglia interpeduncularia.

The changes which can be ascertained when proceeding further in a proximal direction are of two kinds. In the ventral parts of the mesencephalon an irregular connexion arises between the two halves which are prolonged on both sides laterally in tangential fibres. Not a single fibre of the nervus opticus can be traced. These

* This atrophy corresponds fully to the function of the nuclei olivares superiores and the nuclei trapezoides laterales connected therewith, as described by Winkler (Vol. II, p. 256).

ventral fibres form a decussation in the middle; bundles which have been cut transversely can also be found in it, but it is not possible to trace any resemblance here to the tuber cinereum which should gradually appear here. The other peculiarity of these sections is the formation of the corpora geniculata. It follows from the situation and supply of fibres that the ventrally situated centre must be the medial corpus geniculatum, and the dorsally situated centre the lateral corpus geniculatum.

The formation of the epiphysis is visible in the sections which follow. Fully distally, a small quantity of gland tissue is cut, in which it is soon possible to ascertain a lumen. This opening rapidly increases in size. The gland tissue continues to exist in the dorsal wall of the tube for a considerable distance. Fibres then become visible, ventrally at first and also dorsally further on, and the gland gradually disappears. When it has disappeared the space is lined with a palisade epithelium. Still further

FIG. 15.—Drawing of the diencephalon of the synotus. There is no gland tissue here in the wall of the pineal body.

proximally the fibres in the wall of this epiphyseal organ are continuous with pedes conarii which disappear entirely in the corpora geniculata lateralia, in the commissura posterior, and are probably also connected with the dorsomedial bundles from the corpora quadrigemina anteriora (as far as they have not already disappeared in the corpora geniculata lateralia) (fig. 15).

In the ventral parts of these sections there is no trace of incoming fibres and no trace of a mammillary body. Perhaps one of the little bundles which has been cut transversely is a very atrophic mammillothalamic tract.

In the next section (fig. 16) aquæductus Sylvii and the cavity of the epiphyseal organ meet and form the third ventricle. The pedes conarii are continuous with the corpora geniculata. The fasciculi retroflexi approach the floor of the third ventricle. Here the lemnisci already merge partly in the beginning of the thalamus. Ventrally a connection has arisen between the telencephalon and the diencephalon. The fornix lies on both sides ventrally against the diencephalon.

In the next section the fasciculus retroflexus merges in the ganglion habenulæ.

The third ventricle does not increase in size. The corpora geniculata become smaller and increasingly poor in fibres. At the side of a radiatio thalami a nucleus anterior can be discerned. The fornix presses up to the radiatio thalami.

In the next section both ganglia habenularum can be seen to be well developed. Here the tænia thalami which arises from this centre already radiates partly into the nucleus anterior. The ventral parts of the section continue to be indistinct; the end of the fornix fibres cannot be determined. It is uncertain whether there are any nuclei here.

In the next section the size of the nervous system diminishes. Here the whole of the ganglia habenularum is continuous with the tænia, while the latter loses many

FIG. 16.—Drawing of a section through diencephalon after the opening of the aquæductus Sylvii in the third ventricle. Ventrally telencephalon and diencephalon are fused.

fibres in the nucleus anterior. In the dorsal roof of the third ventricle the plexus chorioideus is inserted here; the ventricle continues to be small and is continuous sideways with a sort of side ventricle which is situated entirely lateroventrally. The foramen Monroi (?) therefore lies laterally to the thalamus here.

In the succeeding sections the nervous system ends quickly. In fig. 17 six sections through the telencephalon have been drawn. There is no trace of a ventricle. In the first section only the dorsal part is lined with ependyma, which is found to be the floor of a paired (?) ependymal 'bladder.' In the next sections, which are situated more proximally, this 'bladder' divides into two and a part of the lateral surface of the telencephalon is also covered with ependyma. When, proximally, the telencephalon again ceases to be connected with the thalamus, we find an unpaired ependymal 'bladder.' We receive the impression that in a few places a slip or funnel of the

ependyma penetrates into the telencephalon and cannot be followed any further in a vascular mass. It would have to be followed in distal sections medially to the fornices. It is not possible to decide whether the ependymal lining of the brain is primary or secondary : the so-called side ventricle might possibly have been fused subsequently with the brain in the former case ; in the latter case no ependymal funnel would penetrate the brain, and that part of the brain which is lined with ependyma would correspond to the cornu ammonis formation which is turned towards the ventricle. The solution of this problem presents great difficulties but is of extreme importance to the solution of the question how this nervous system is built. Unfortunately no good starting-point in the shape of ganglion cells can be found ; they are built irregularly. Nor are there any remnants of ependyma in the central mass. and if there had been any they would have been displaced by a vascular mass. The

FIG. 17.—Six drawings of sections through the telencephalon of the synotus.

whole surface of the telencephalon is covered with a thin tangential layer of fibres. Dorsally this is continuous with the fornix. There are few or no fibres in the centre. At those places where the ependyma covers the surface, we may therefore think of the possibility of an alveus formation. In that case the tangential fibrous coat would have to correspond to the white matter, and this would force us to suppose that the brain vesicles were turned completely inside out—the white matter outside and the surface of the cortex inside. It is difficult to defend this supposition.

We should advance a step if in the ventrally situated parts there were parts of cortex with a distinct structure. To a certain extent this is the case. At a few places, immediately beneath the tangential layer of fibres, there is indeed a layer of cells which shows some resemblance to a second cortical layer. Underneath this lies a layer of ganglion cells which is broad and deficient in cells and corresponds to the lamina ganglionaris. This induces us to assume that the exterior layers of this brain are indeed the outer ones ; that there must be a collapsed ventricular cavity in the centre and that in this cortex the tangential fibres have continued to be the principal centri-

petal and centrifugal way of impulses, whilst the way along the central marrow has not developed at all (fig. 18).*

FIG. 18.—The proportions of thalamus, telencephalon and ventricular system in a synotus; No. 1 has been cut distally, No. 8 proximally.

The foregoing has not solved all the difficulties, because the situation here is very complex and can in point of fact only be understood in connexion with other cases of cyclopia.

SUMMARY

Recapitulation of the deviations in the case of synotia in a calf :—

In addition to the profound changes of the facial bones, where the eyes were entirely absent and the nose and mouth cavities formed a single opening, the following abnormalities were found in the central nervous system :—

1. Absence of the large ascending and descending tracts running through pons, medulla and spinal cord (pyramidal tract, lemniscus).
2. Absence of nervus, chiasma and tractus opticus.
3. Absence of nervus, tractus olfactorius and all primary and secondary olfactory fibres.
4. Absence of the greater part of optic thalamus, corpus striatum, of corpus mammillare and hypothalamus.
5. Radical defects of the remaining parts of the telencephalon which, as in the previous case, have been displaced ventrally and reduced to a very simple form.
6. Formation of an epiphyseal organ with fibres derived, inter alia, from the corpora quadrigemina anteriora and geniculata lateralia.

DISCUSSION

When these two cases are compared with the cases described in the literature, a few points of similarity will be observed, besides many differences.

* This agrees with Davidson Black's findings in his case of cyclopia. In it, too, the tangential layer of fibres *alone* had developed.

Before proceeding to make comparisons we are justified in inquiring whether we have the right to bring together certain malformations of the proximal basal plate of the central nervous system.

Do the cyclocephali (Geoffroy St. Hilaire) and the synoti belong together and do certain forms of anencephaly also belong to this group?

W. M. de Vries discussed in 1912 the grouping of these monstrosities. In agreement with Kundrat he calls the mildest deviations in this group *cebocephali*: in these cases the eyes are separated although the two orbits are close together, and the nose is still present rudimentarily. In the case of *ethmocephali* the separated eyes also lie near each other, but the rudimentary nose has taken the shape of a proboscis. In the case of *cyclopes* proper, both eyes are found to be more or less fused in a single orbit, and in addition various deviations of nose, mouth, ears, etc., occur.

G. St. Hilaire mentions cases in which in addition to deviations of the eye there is only a proboscis where the nose should be (rhinocephalus); cases in which the nose is only atrophic (cyclocephalus); cases where in addition to a proboscis an atrophy of the mouth can be found (stomocephalus).

Still more pronounced deviations link up in a natural manner with the foregoing. Where eye, nose and mouth cavity are united, the ears approach nearer to each other; the defect in the median line is more extensive, the eye disappears, the ears approach nearer to each other, the nose disappears.

We therefore see a series ranging by gradual transitions from slight cebocephaly to the extremely marked anomalies of the synotus. Moreover, experimental embryology justifies the assembling of these monstrosities which are apparently so heterogeneous, because—apart from other deviations which are found in each of these monsters—there is in all, in common, a defect (possibly an inhibitory process) in the front wall of the neural plate in its earliest periods of development.

Former investigations rightly paid great attention to the slight cases, because these are so near the normal type. However, the severe cases also throw a clear light on these monstrosities and their formal genesis, because in them the disease has persisted radically. An example of this is given in each of the cases described.

They are therefore forms of monstrosities in which through some cause or other those parts of the embryo which lie in the median line basally to the neuroporus anterior are injured and remain retarded in development. In both cases extensive defects have been found, relating to the skin, organs of sense, bony cranium and brain.

A few points require further discussion: (1) The anatomy of the roof of the third ventricle and the place of the foramen Monroi and the telencephalon; (2) the epiphyseal organ in the case of synotia; (3) the relative size of nucleus ruber and olives in the case of cyclopia.

Winkler drew attention to the dorsal 'bladder' which is said to be found on the plate of the third ventricle in all cyclopes. In substantiation

of this view he cites researches by Davidson Black and refers to his own experiences of cyclopes and to a number of cases mentioned in the literature. He considers that the 'bladder' is responsible for this and other malformations and imagines that the primary hydrosy of the third ventricle (he left undiscussed the question how it arose) bursts ventromedially and destroys those parts of the embryo which are situated medioventrally to the neuroporus anterior. The fusion of eyes and forebrain is therefore alleged to take place secondarily and not primarily. It is in this manner that Winkler thinks it possible to avoid assuming a primary cause of inhibition of development.

The difficulty and danger of all teratological researches is the fact that one has to deal with scars and remnants of diseases and disturbances in the development of the embryo, which arose and terminated months previously in very young tissue, the regenerative power of which is completely, or at any rate largely, unknown to us. Consequently, the way is opened for numerous suppositions which cannot be proved.

Winkler's theory has not escaped entirely from these risks. He had however an apparently solid basis in the frequency of the hydrops ventriculi, which is also present in our cyclopes. It was therefore justifiable to recognize in this 'bladder' an important factor in the pathogenesis of these monstrosities. As opposed to the somewhat vague and unsubstantiated suppositions of Stockard's school, which still clung to a mysterious primary inhibition of growth, this view, which indicated a well-defined defect, was no doubt attractive.

However, the study of our second case, synotia, presents unforeseen difficulties. In order to obtain a general view of these data, it is necessary, however, to recapitulate what we found in the telencephalon.

If we wish to form a clear idea of the structure of the telencephalon in these two cases, we should recall to mind that the great brain also arises from a plate. The infundibular region therefore corresponds to the floor plate; the plexus chorioideus which is attached to the fimbria fornicis corresponds to the roof plate; whilst the brain cortex itself corresponds to wing and floor plate. (It is noteworthy that in the case of acrania, described by one of us, these original conditions were demonstrated in a foetus of five months.)

In the accompanying diagram (fig. 19) the original situation is shown (A) and it is indicated what situation arises in a frontal section if the plate closes up and forms a tube (B). In both cases of cyclopia the walls of the tube collapsed in the end (C). In the case in which the brain cortex has developed more strongly, both side ventricles arise. In the case of synotia, the brain cortex continues to be very meagre. In the frontal section (fig. 20) the defect situated ventrally in the median line has still to be discussed. In both cases olfactory cortex is found medioventrally in the parts of the great brain. This is clear particularly in the first case. We are obliged to assume that we are dealing here with derivatives of parts of the cortex which are situated

medially in the front brain wall. As a matter of fact, the rhinencephalon is found in the diagrams of His proximoventrally to the pallium and proximodorsally to the primary eyestalks. There is however a defect in the median line. Here is wanting the *margo reuniens* (His) and what it changes into. Furthermore, the rhinencephalon has not developed, although there are pieces of cortex which have retained the structure (fig. 21).

In continuation of the foregoing, it is necessary, in the second place, to form an idea of the situation of the telencephalon in respect of the thalamus. This can best be done in sagittal sections.

Fig. 22 is a schematic drawing of such sections of our cases and of a few

FIG. 19.—Diagram of tube-forming in telencephalon.

FIG. 20.—Diagram of frontal sections through four cyclopic brains.

W. : Winkler's cyclops.
D.B. : Davidson Black's case.

cases known to us from the literature. These drawings show that in our first case the telencephalon had been displaced ventrally and slightly distally to the thalamus. The connexion between the third ventricle and the side ventricles when these are formed after the division of the foramina Monroi consists of a tube which runs in a distal direction under the thalamus (the thalami optici are closely fused in the median line) and connects the third ventricle (inclusive of the dorsal 'bladder') with the collapsed cavities in the telencephalon. Foramen Monroi is the name which we gave to the place where this tube divides into two. The back wall of the tube corresponds to the infundibular region, the front wall to lamina terminalis and roof of the front part of the diencephalon. The structure and relative size of the ventricular system of the synotus show a resemblance here to the foregoing in many respects, but they also show certain peculiarities. In the first place

the roof of the third ventricle is distended either a little or not at all. In the second place the entrance to the ventricular system of the telencephalon has collapsed entirely. In the third place, the connecting tube between the ventricles of the telencephalon and the third ventricle has collapsed for a certain distance in the median line and has remained open laterally only, so that there are apparently two side ventricles with a foramen Monroi here too. (A closer examination shows that this division into two only appears to exist.) For the rest, the same ventrodiscal displacement of the telencephalon in respect of the thalamus is found here. How did this situation arise?

Winkler assumed that through some cause or other a hydropsy of the third ventricle had arisen with a distension of the roof, with secondary breach and destruction of parts of the brain. He held this to be responsible for the

FIG. 21.—Diagram of the enlargement of the older parts of the cortex (dotted).

FIG. 22.—Sagittal diagrams of different cyclopes. A. The case of cyclopia described by Winkler. B. By Davidson Black. C. The cyclops. D. The synotus.

overturning of that part of the occiput in which the fissura calcarina is situated dorsally and not medially. The difficulty is, that in the case of synotia there is a 'bladder,' but that it is far from certain whether it should be considered to belong to the third ventricle. Furthermore, this hypothesis obliges us to make a series of suppositions which are rather uncertain (the fissure in the ventral parts, the regular defects which in many instances are found in the case of severe mechanical injury, the question why the hydropsy in this early stage has such serious consequences).

In order to acquire a good insight into the matter it is necessary to examine more closely the structure of the cortex of the brain of cyclopes. Winkler and Davidson Black drew a wedge on the surfaces which are seen basally, by which they effected an imaginary removal of a medioventral part of the olfactory convolutions. The remaining part showed much resemblance to the brains of their cases. This argument applies most forcibly to the

olfactory bulbs themselves, which are absent in every case of arhinencephaly. For the other parts of the brain, however, the situation is not so plain. In our second case little could be said with certainty about the matter, although there seemed to be a great similarity to the first case. It was possible to examine with considerable accuracy the remnants of the brain cortex of the human cyclops. In the drawings and diagrams given here, the structure of the cortex is indicated. These investigations showed (1) that the brains of cyclopes are not built unpaired, but consist definitely of two symmetrical halves (confirmation of older investigations); (2) that the olfactory cortex, notwithstanding the disappearance of the olfactory bulb, still occupies a fairly large surface of the medially situated parts of the brain (fig. 21).

We therefore find that important parts are wanting, but we also find

FIG. 23.—Diagram of origin of cyclopic brain. I. Normal young embryonal brain. II. Normal adult brain. III, IV. Cyclopic brains.

that the telencephalon forms, in its shape and cytoarchitectonic structure, a primitive organ which has remained at a lower stage.

Both defect and inhibition can be clearly shown. How must we co-ordinate all these apparently disconnected data? They consist of (1) defects of the medioventral parts of the diencephalon; (2) membranous degeneration of certain medioventral defective parts and of the border planes between thalamus and telencephalon; (3) ventrodistal situation of the telencephalon in respect of the thalamus opticus; (4) inhibition of development as well as defect in the cortex of the telencephalon.

One of the possibilities which we wish to deal with, and in respect of which conjectures are utilized as little as possible as aids, is the following.

The situation of the telencephalon in respect of diencephalon and mesencephalon in both cases which have been examined here, recalls to mind the models of young embryonal brains known from the literature (figs. 23

and 14). If one supposes that the parts which lie distally to the foramen Monroi continue to grow fairly normally and that the parts lying proximally are either inhibited so severely as to enable one to speak of a defect (infundibulum region) or less severely (such as the cortex), it follows that the forebrain vesicle, which has continued partly membranous, remains lying half-way under parts which are growing normally. Infundibulum remnants and opticus remnants fix this vesicle to the base of the brain, which is also severely inhibited and defective. The result is that the thalamus in growing overlaps it and pierces itself, as it were, in a forward direction. Davidson Black's case can also be explained in this way without great difficulty. Winkler's case shows very little ventral displacement; it was, however, a much less severe case than ours. Indeed, it is striking that according as ophthalmic and facial deviations increase in severity, the displacements increase. We imagine that in a case such as that described by Winkler the connexion between diencephalon and telencephalon was only slightly injured (he also found a corpus striatum, which we did not find in any of our cases); there was no membranous degeneration of the margo thalamicus of His. Probably, therefore, there was here a less extensive change in the shape of the base of the skull and less membranous degeneration in the forebrain vesicle. The reason why the ventricle roof has become so large is a further question. In Davidson Black's case it is found that the aquæductus Sylvii has closed up. It is necessary also to postulate the influence of the pathogenic agent upon the material closing the tube. One should think of compensatory ependymal increases, to which von Monakow often drew attention, and finally of the possibility of a vacuum which has arisen.

In our opinion a teratologist cannot say much more about these matters. He cannot solve the question: defect or inhibition. He raises again and again the question as to the anatomical conditions in the front wall of the neural plate, but finds no solution for it in these pathological products and he is likewise unable on the ground of these few data to pronounce an opinion on the point whether such connexion applies generally. It is likely that diverse kinds will be met with among cyclopes as well as among anencephalics.

THE PINEAL BODY

The epiphysis of the synotus requires special discussion. The peculiarities which one finds in this case suggested to Prof. Winkler the need that it should be more closely examined. In doing so he pointed to the analogy with the epiphyseal organ of reptiles. The diencephalon is distinguished from the other parts of the brain by the lobes which it forms and by which the brain is in communication in various ways with the outside world: the eyes, infundibulum, paraphysis, glandula pinealis and parapineal organ. Occipitally the roof plate forms two little organs which are mostly distinguished. The hind lobe is the analogue of the epiphysis (glandula pinealis):

in the case of *petromyzon* and *anura* a kind of eye has been formed out of the top of the vesicle and lies immediately under the skin, which has become transparent. This little organ is connected by a *nervus pinealis* with *commissura posterior* and *right ganglion habenulæ*. In higher classes of animals the lobe is less elongated, the walls collapse and the gland tissue of the *glandula pinealis* develops. *Pedes conarii* are the analogues of *nervi pineales*. Immediately in front of the epiphysis there is found in *petromyzon* and *lacertilia* a second lobe which conducts itself correspondingly, with formation of a 'bladder' and a nerve which brings about a connexion with the other *ganglion habenulæ*. This eye was probably of great significance in extinct reptiles. After all, it is not precluded that both organs are of equal significance and form a pair of dorsally directed eyes, one of which does not develop any further.

In our case little of the gland tissue of the *glandula pinealis* is found. In its stead the hind part of the third ventricle is covered here with a palisade epithelium, underneath which fibres having myelin taper off on all sides. These form *pedes conarii* which turn ventrolaterally towards the place where the *corpus quadrigeminum anterior* should lie. Which organ is this? The supposition that it is the *glandula parapinealis* (i.e. the parietal eye) seems at first sight to be far-fetched: where then has the *glandula pinealis* itself remained, one might ask. Is it a much altered epiphysis? This too, cannot be said with certainty. Certain comparative anatomists do not, for that matter, see in *petromyzon* any sharp contrast between pineal and parapineal organ; both are closely adjacent lobes of the third ventricle roof, both send fibres to the *ganglia habenulæ*, both penetrate frontalwards as far as the skin. If this standpoint is adopted, no useful purpose would be served by inquiring which of the two pineal eyes has made its appearance here, because both have the same significance. At any rate we find here a form which never occurs either in young or in fullgrown mammals. It is in point of fact a form which is seen like this only in lower animals such as reptiles and *petromyzon*. In the second place it is a remarkable fact that the fibres of this organ not only go to the *ganglion habenulæ*, but also disappear in the *corpus quadrigeminum*. If we recall to mind the anatomy of the diencephalon in its entirety, we see here the absence of everything that relates to the eye, a renewed appearance of an eye-like organ which sends fibres to the *ganglia* of the optic system. This is indeed a remarkable change, a striking instance of the effect of syneidesis in the formative instinct (von Monakow). In this attempt at restoration older forms therefore make their appearance phylogenetically, and the restoration takes place at a lower level.

SIZE AND SITUATION OF THE NUCLEUS RUBER

We examined more carefully the size of the nucleus ruber in the case of cyclopia and compared it with a normal red nucleus of a new-born child. On

cursorily looking at the series, we received the impression that this nucleus was unusually large (like the oliva inferior). Measurements of the surface, as exact as was possible, confirmed this impression; in some places the nucleus is larger than the normal is anywhere. However, if account is taken of the axial extension, this enlargement proves to be merely local. In the diagram (fig. 24) the surfaces at various levels can be compared with each other. Thus we find that in the cyclops the red nucleus extends to a shorter distance from the mesencephalon (absolutely as well as relatively, compared with a normal nucleus ruber). We find that the nucleus ruber in its entirety is smaller than normal; this is due to the short distance to which it extends notwithstanding its relatively great thickness. The displacement in the direction of the cerebellum points to the possibility that the nucleus, which receives no impulses from the frontal parts of the brain and from the brainstem, has been displaced towards the normal cerebellum. It is also possible that in the

FIG. 24.—Diagram of surfaces of a normal nucleus ruber (neonatus) and the cyclopic nucleus ruber.

cyclops the mesencephalon has remained too small in its entirety. The displacement of the red nucleus is, indeed, a consequence of the axial shortening of the mesencephalon. We are inclined to accept the latter explanation because it accounts sufficiently for the deviations which have been found and because the importance of neurobiotaxis to teratology has up to the present been found to be very doubtful. (See Winkler's criticism in his *Handbook*, Vol. III, p. 9, and Schenk, *Z. Neur.* 146.) It is extremely difficult to form an idea of the displacement of a nuclear 'Anlage' before there can have been any question of stimulating influences of centres: these have not yet developed in the 'Anlage.' However, we more frequently find compensation symptoms than adaptation symptoms and it is accordingly conceivable that, in the absence of all higher centres, parts of the nucleus ruber, which here is one of the most proximally situated reflex centres, have developed strongly in contrast with its environment, which already shows signs of injury. This applies still more to the oliva inferior.

In the medulla oblongata of normal size, enlarged olivæ inferiores have

developed (fig. 25). The cerebellum, too, seemed much enlarged. With the aid of calculations of the surface it was possible to estimate the nucleus ruber as well as the oliva inferior in their entirety. The calculated contents of the oliva inferior was found to be fully 157 c.mm. in the normal neonatus, and fully 383 c.mm. in the cyclops (i.e. a proportion of 10 to 24.4).

FIG. 25.—Diagram of the axial distension of oliva inferior, pons and nucleus ruber in human cyclopia and a normal neonatus.

The contents of the region of the nucleus ruber amounted in the normal neonatus to slightly less than 42 c.mm., in the cyclops to 9 c.mm. (i.e. a proportion of 10 to 2.14).

Owing to the inaccuracies which result from this method of calculating, these figures are not reliable in every respect. However, the comparison of these values, which have all been obtained in the same manner, is of great importance and reveals gross deviations.