京都大学学術情報リポジトリ
KURENAI 紅
Kyoto University Research Information Repository

京都大学
KYOTO UNIVERSITY

Title	DEVELOPMENTAL ANOMALY OF GLIAL CELLS IN VARIOUS PARTS OF THE BRAIN OF MALFORMED HUMAN FETUSES AND ABORTIVE FETUSES AND ITS POSSIBLE RELATIONSHIP WITH OCCURRENCE OF GLIOMAS
Author(s)	YAMAZOE, YOSHIRO
Citation	日本外科宝函 (1959), 28(4): 1237-1263
Issue Date	1959-05-01
URL	http://hdl.handle.net/2433/206848
Right	
Type	Departmental Bulletin Paper
Textversion	publisher

Kyoto University

DEVELOPMENTAL ANOMALY OF GLIAL CELLS IN VARIOUS PARTS OF THE BRAIN OF MALFORMED HUMAN FETUSES AND ABORTIVE FETUSES AND ITS POSSIBLE RELATIONSHIP WITH OCCURRENCE OF GLIOMAS

By

Yoshiro Yamazoe

From the 1st. Surgical Diviston, Kyoto University Medical School

(Director : Prof. Dr. Chisato Araki)

(Received for publication Mar. 20. 1959)

INTRODUCTION

Not a few papers are available which deal with the rough parallelism between the actual seats of predilection for occurrence of gliomas of the brain and the frequent sites of persisting and displaced immature glial cells in the brain of apparently normal man, including human fetus.

Brzustowicz and Kernohan[7] have recently studied systematically on the cell rests of the 4th ventricle and its surrounding structures, correlating the presence of these cell rests with the incidence of ependymomas, astrocytomas and subependymal plate gliomas in that same region. They pointed out that the nodulus of the posterior vermis is not only the most frequent site of gliomas but at the same time the most frequent site of mixed cell rests. Having performed a histological examinations on human fetal brains from third to tenth fetal month and studied in detail persistence and displacement of immature glial cells in various parts of the brain, Shimada[13] from our laboratory expressed the view that it would be more reasonable to assume that gliomas arise from normally persistent immature cells rather than from heterotopic or heterotaxic cells. On the other hand, several authors studied the histological characteristics of developmental anomalies in the fetal brains of mice and rats caused by applying exogenous harmful factors, in the early stage of gestation, which seemed to be effective for inducing malformation (Wilson[14], Kaven[5], Shirota, Yamazaki and Yamazoe) and tried to make some correlation between the preponderating localizations of the anomaly and those of the glioma formation. It may naturally be presumed that the human fetal brain with macroscopical malformation should have far more histologic anomalies than apparently normal brain does. Accordingly, developmental features of both nerve cells and glia cells in various parts of the brain of malformed fetuses and abortive fetuses were investigated in the present study, comparing the results with the findings obtained by Shimada, and it was studied whether they have any possible correlation with occurrence of gliomas or not.

MATERIALS AND METHODS OF THE STUDY

(A) Materials (Table I)

Table 1.

Case No.	Fetal month and sex	Gross appearance of body	Gross appearance of brain	Neck-heel length(cm)	Parieto-coccygeal length(cm)
No. 1	2M. uncertain	Bulging out on the head (Fig. 1)	Opened and turned out mesencephalic aqueduct (Fig. 9)	2.2	2.1
No. 2	4M. male	Microsomia, Twin	Hydrocephalus	10.2	6.5
No. 3	5M. female	No malformation, Natural abortive fetus	No abnormity	21.5	14.0
No. 4	6M. female	〃	〃	26.8	18.7
No. 5	6M. male	〃	〃	29.0	19.8
No. 6	8M. female	Defect of both arms, Syndactylism, Pronounced malformation of head and face	Pronounced hydrocephalus, Widened and opened telencephalic ventricle, Arhinencephalon. (Fig. 5)	24.9	18.5
No. 7	9M. male	Polydactylism, Cheilognathopalatoschisis, Microcephaly (Fig. 2)	Ill-developed distal half of pallium Hydrocephalus, Defect of septum of telencephalic ventricle, Arhinencephalon (Fig. 6)	33.0	24.5
No. 8	9M. female	Shortened four limbs and trunk (Fig. 3)	Hydrocephalus, Porencephalic cyst (Fig. 7)	18.7	22.3
No. 9	10M. female	Cheilognathopalatoschisis, Microphthalmus dextra, Very defective right auricula, Widely opened foramen interventriculare cordis (Fig. 4)	Under-developed callosal body, Very defective rhinencephalon, Hydrocephalus	47.5	31.0
No. 10	Full term male	Rachischiis, Under-developed skull	Hydrocephalus	49.0	33.2

(a) Fetuses of either artificial or natural abortion and normal parturition with gross malformation,

(b) Apparently normal fetuses of natural abortion.

(B) Methods

The following methods were mainly used for the staining :

1) Penfield's silver carbonate method, modification II,

2) Rydberg's silver diamino-carbonate method, and

3) Rydberg's combined gold-silver method.

To meet with these staining methods and for making serial sections, the

materials were embedded in carbowax and in gelatine, with which frozen sections were made. Rhombencephalon and midbrain were cut in sagittal plane and prosencephalon in frontal plane. For the contrast, histological specimens made by SHIMADA of 22 normal fetal brains from third to tenth fetal month and those of fetuses of 2 (Case No. 11) and 5 months (Case Nos. 12 and 13) by the author himself were available.

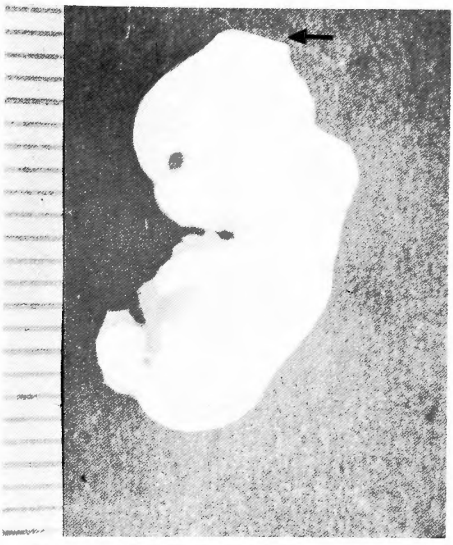


Fig. 1 Case No. 1. 2-month-old fetus. Note the crater-like bulging out on the head (indicated by arrow).

DEVELOPMENTAL ANOMALY OF CELLS OF GLIAL ORIGIN IN VARIOUS PARTS OF THE BRAIN

Classification of immature cells in the present examinations was based on the same standard as was adopted by SHIMADA and SHIROTA (Fig. 8).

Fig. 2

Fig. 3

Fig. 4

Fig. 2 Case No. 7. 9-month-old fetus. Microcephaly, cheiloschisis and polydactylism (6 fingers on the right and 6 toes on the left).

Fig. 3 Case No. 8. 9-month-old fetus. Four limbs are markedly shortened and the trunk also appears comparatiyvely short.

Fig. 4 Case No. 9. 10-month-old fetus. Cheiloschisis and microphthalmia on the right side.

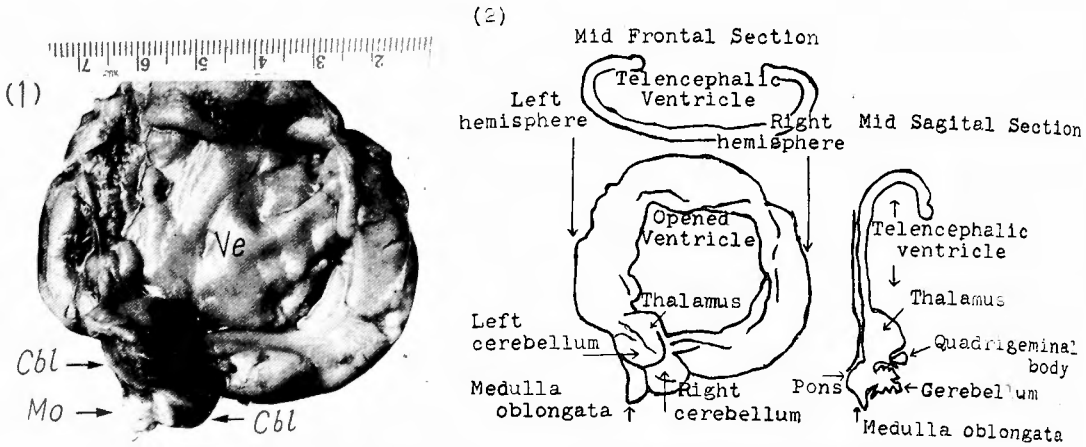


Fig. 5 (1) The brain in Case No. 6. (2) Schematic drawing of this brain.

The ventricular cavity of the telencephalon is deprived of its septum, which is widened and opened. Ve··· ventricle of the telencephalon, Cbl···cerebellum, and Mo···medulla oblongata.

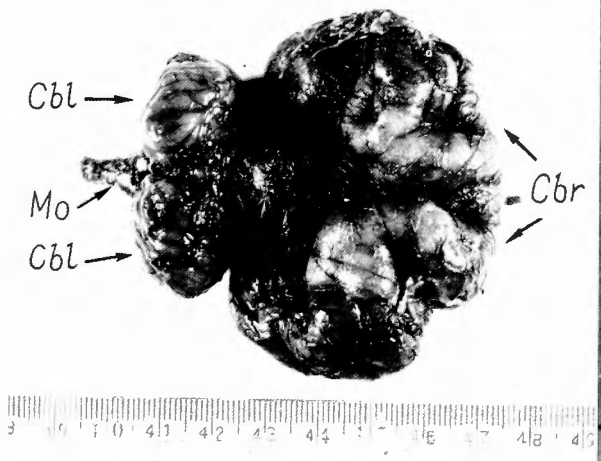


Fig. 6 The brain of Case No. 7.
The distal half of the convexity of the cerebrum on both sides is ill-developed.
Cbr ···cerebrum, Cbl ···cerebellum, and Mo ··· medulla oblongata.

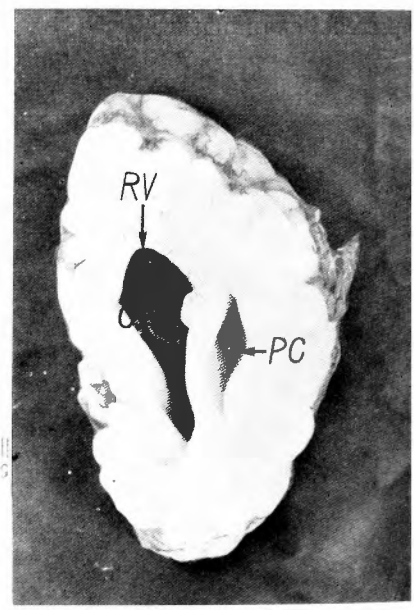


Fig. 7 Frontal section between the central third and the posterior third of the right cerebral hemisphere of case No. 8.
Note the porencephalic cyst (PC). O indicates the protrusion where the cyst is openend and communicated with the ventricle. RL···right lateral ventricle.

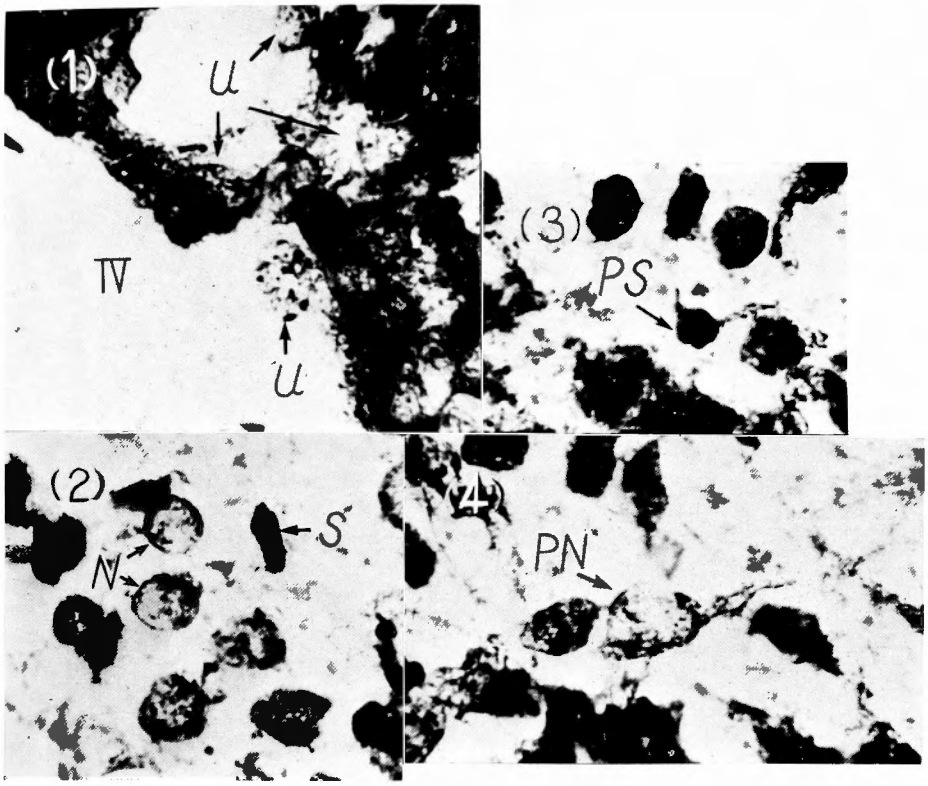


Fig. 8 Various types of immature cells found in the ventricular wall around the possterior medullary velum and its surrounding structures in Case No. 9. Penfield's stain Ⅱ ; × 900.

(1) Undifferentiated apolar cell(U)—Nuclear membrane appears somewhat indistinct. Nucleus stains in general light brownish with silver impregnation method. In a vesicular nucleus, 5 or 7 granules of inequal size are visible. IV···4th ventricle.

(2) Apolar neuroblast(N)—Nucleus is less argentophlic than that of an undifferentiated apolar cell. It has a relatively thick nuclear membrane and thin protoplasm. In a vesicular nucleus, from 3 to 5 granules of inequal size are visible.

Apolar spongioblast(S)—Nucleus is oval or roughly quadrilateral. It is somewhat smaller in size and more deeply stained than that of an apolar neuroblast.

(3) Polar Spongioblast (PS)

(4) Polar Neuroblast (PN)

(A) Rhombencephalon and Mesencephalon

1) Malformed 2-Month-Old Fetus (Opend and Turned Out Midbrain — Case No. 1, Fig. 1)

Apolar element appearing among the supportive (primitive) spongioblasts was generally less in number than that in normal fetus and the intramedullary cell layers were poorly developed (Figs. 9 and 10). The same tendency was observed in the cerebellum which was particularly ill-formed.

2) One of 4-Month-Old Twin Fetuses (Microsomia—Case No. 2)

In the nodulus, in the taenia rhombencephali, in the subpial structure of the pontine flexure (Fig. 11) and in the distal part of the inferior colliculus were found nests of apolar element. These cell nests differed not much from what SHIMADA

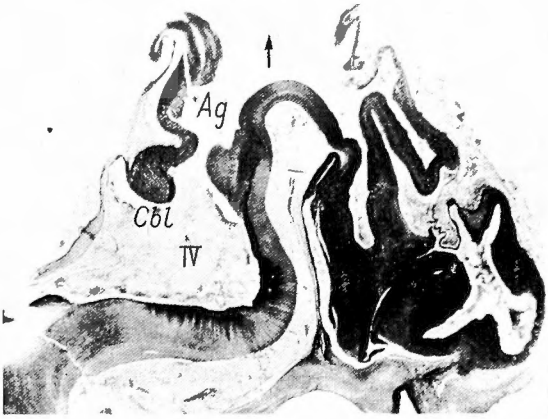


Fig. 9 Openend and turned out mesencephalic aqueduct at the level of superior colliculus (indicated by arrow). Cells in the subependymal zone of the floor of the 4th ventricle and in the medullary substance are decreased and the cerebellum is ill-developed. Aq···aqueductus mesencephali, IV···4th ventricle, and Cbl···cerebellum. Penfield's stain Ⅱ ; ×10.

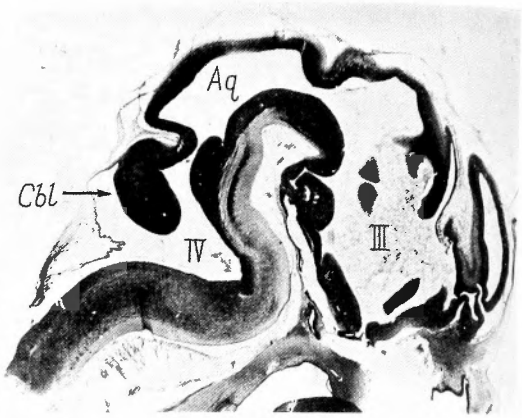


Fig. 10 Sagittal section of the brain of 2-month-old contrast fetus (Case No. Ⅱ). Ⅲ···3rd ventricle, Aq···aqueductus mesencephali, IV···4th ventricle, and Cbl···cerebellum. Penfiels's stain Ⅱ ; ×10.

pointed out in normal fetus and were, therefore, not to be considered as abnormal.

3) 5-Month-Old Fetus of Natural Abortion (No Gross Abnormality—Case No. 3)

4) Natural Abortive Fetus at the Begining of 6th Fetal Month (No Gross Abnormality—Case No. 4)

Immature cell nests, which very much resembled those in normal fetus, were observed in the taenia rhombencephali and the nodulus. Besides, funicular nests of apolar or polar spongioblasts along the blood vessels in the white matter antero-cranial to the fastigium, clusters in layer of apolar element persisting widely in the transitional zone between the inferior colliculus and anterior medullary velum, small cell conglomerates of apolar spongioblasts in the brachium conjunctivum, tubular or acinous structures made of aqueductal ependyma dipped in the base or roof of aqueduct, etc., were found, all of which were, however, not considered to be definitely abnormal.

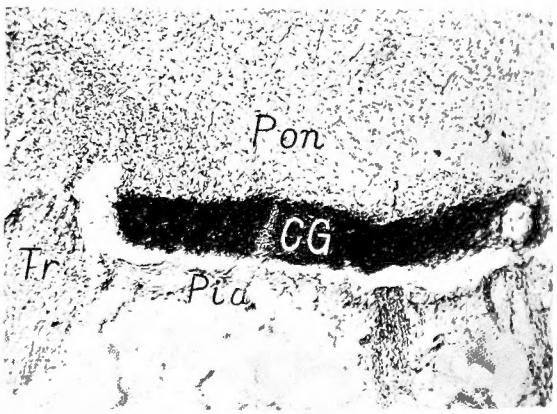


Fig. 11 Immature cell group (CG) in the subpial zone of the latero-ventral surface of the pons in Case No. 2. It is composed of argentophilic, slightly elongated and apolar elements. Tr···trigeminal nerve, Pia···pia mater, and Pon···pons. Penfeld's stain Ⅱ, ×50.

5) Natural Abortive Fetus at the End of 6th Fetal Month (No Gross Malformation—Case No. 5, Fig. 12)

Evidently more numerous immature cell clusters along the blood vessels were seen(Fig. 13) in various parts of the cerebellar medullary substance when compared

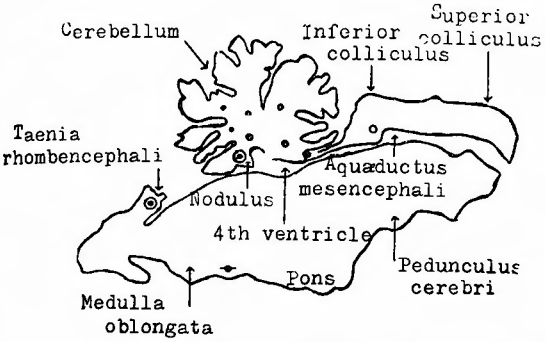


Fig. 12 Schematic drawing of the locations of immature cell clusters in rhombencephalon and mesencephalon of 6-month-old fetus of natural abortion (Case No. 5).
● Clusters of cells shown in the following figure.
) Tubular ependymal cell nest.
• Small cluster of polar element around the blood vessel.
⊙ Area of immature cell nest as will be seen in normal fetus.

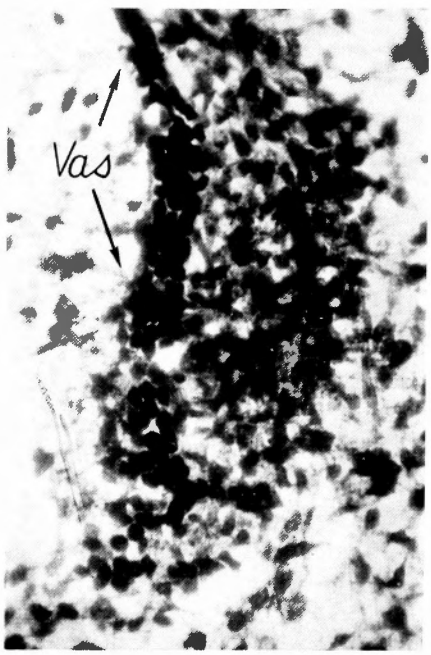


Fig. 13 Immature and markedly argentophilic cell nest in the perivascular zone of the medullary substance of the cerebellum in Case No. 5. Vas···blood vessel. Penfield's stain Ⅱ ; ×400.

with the foregoing 2 cases. The main constituting cells were probably apolar spongioblasts, which morphologically were quite identical with the cells of the external granular layer of this fetus. In the nuclei of the roof of the 4th ventricle were present globiform cell aggregates of nearly the same kind. In the cerebellar lingua were observed small fungiform excrescences of cells of the external granular layer. Rosette-like structures presumably of ependymal cell rests were seen in the caudal part of the inferior colliculus, and perivascular cell clusters of polar spongioblasts resembling "embryonic rod-cells" of RYDBERG on the ventral side of the olivary nucleus.

6) 8-Month-Old Malformed Fetus(Malformation of the Four Limbs and Brain —Case No. 6, Figs 5 and 14)

The malformation was so pronounced that the 4th ventricle was almost obliterated in its entirety, only excepting its posterior portion, and the aqueduct appeared as a residual blind duct running through the dorsal part of the mesencephalon. As abnormal immature cell conglomerates, heterotopic cell rests (Fig. 15) possessing a structure simulating that of cerebellar cortex on one side of the basilar part of the rhombencephalon and fungiform outgrowths of the external granular layer cells were uncovered. In the case here, marked proliferation of pial(?) tissue on the dorsal

part of the anterior medullary velum and on the ventral surface of the cerebral peduncles was additionally found (Fig. 16)

7) 9-Month-Old Malformed Fetus (Polydactylism, Microcephaly and Cheiloschisis—Case No. 7, Figs. 2, 6 and 17)

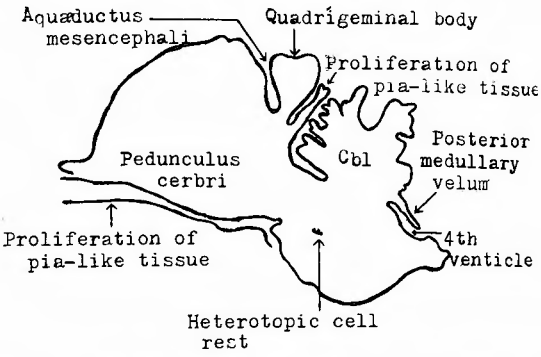


Fig. 14 Sagittal section of rhombencephalon and mesencephalon of Case No. 6. Cbl···cerebellum

Many small clusters presumably of apolar and polar spongioblasts, which encircled the blood vessels, were seen to invade into the dentate nucleus and the nuclei of the roof of the 4th ventricle (Figs. 18 and 19). In the central portion of the cerebellum, clusters of immature apolar or bipolar cells resembling the external granular layer cells were irregularly mixed together with the cells simulating the internal granular layer cells, forming altogether numerous nodules of large size (Fig. 20). Cell clusters of nearly the same nature were also found in the nodulus and lobulus.

On the latero-ventral surface of the pons was observed mushroom-like growth of pial(?) tissue (Fig. 21), rich in blood vessels, and in its vicinity proliferation in layers of small round cells (Figs. 21 and 22). And the cell layers adjoining to the

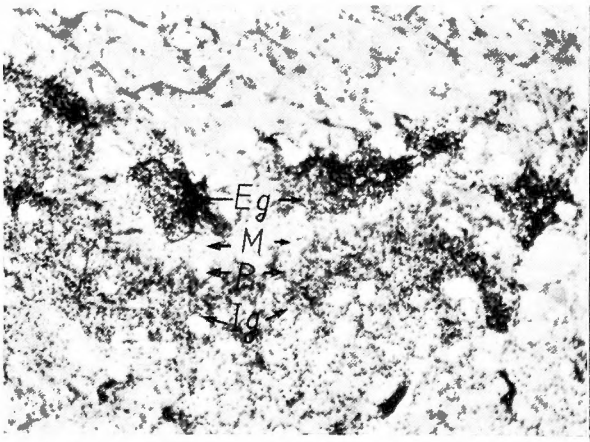


Fig. 15 Heterotopic cell rests in the ventro-lateral portion of the rhombencephalon of Case No. 6, which are quite analoguous with the structure of the cerebellar cortex. Eg ·The part resembling the structure of the external granular layer, M···that resembling the molecular layer, P···that resembling the layer of Purkinje' cells, and Ig···that resembling the internal granular layer Penfield's stain ‖ ; ×100.

Fig. 16 Pia-like tissue growths in septums around the anterior medullary velum of Case No. 6 indicated by arrow. Cc ·inferior colliculus, and Cbl··cerebellum. Penfield's stain ‖ ; ×50.

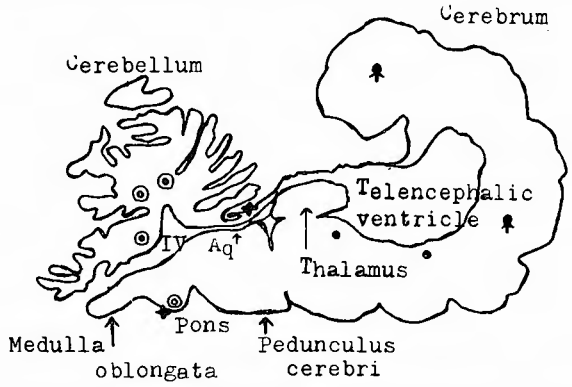


Fig. 17 Schema of localizations of abnormal cell groups in Case No. 7.

● Immature glial cell group.
• Cell group composed predominantly of astroblasts.
◉ Cell group principally of immature cells probably of glial nature.
◎ Cell group of small round cells ; whether they are glial in nature or not is not clear.
\+ Pia-like tissue proliferation.
IV···4th ventricle, and···aquaeductus mesencephali.

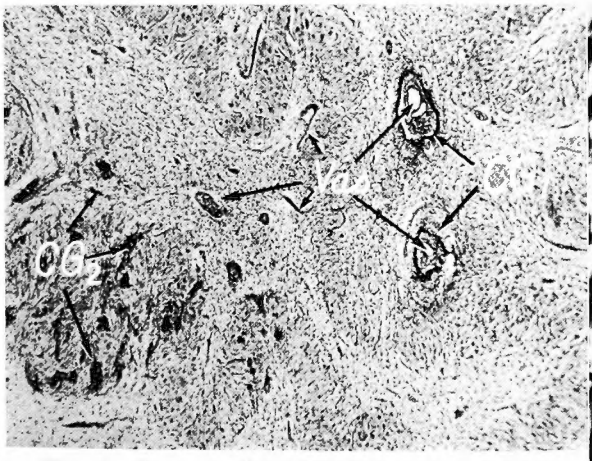


Fig. 18 Clusters of small size of markedly argentophilic immature cells inside the dentate nucleus in Case No. 7. CG_1···tubular clusters encircling the blood vessel of comparatively large calibre and its perivascular tissue, CG_2···funicular clusters along the small blood vessel, and Vas··· blood vessel. Penfield's stain ‖ ; ×50.

Fig. 19 Higher magnification of CG_1 in the preceeding figure. AE···Zone where argentophilic apolar elements cluster, PE···zone predominantly of polar eelments, PV···perivascular tissue, and Vas···blood vessel. Penfiele's stain ‖ ; ×400.

pia mater grew out on to the surface of the cranial nerve roots. Whether these small round cells are glial in nature or not was yet undetermined, but both the neuroblast-like cells with clear vesicular nuclei and the argentophilic spongioblastic cells with ellipsoid or pear-shaped nuclei certainly constituted a tissue architecture which seemed to be analoguous with that of the external granular layer of the cerebellum. On the dorsal surface of the quadrigeminal body was likewise found proliferation of pial (?) tissue connecting with the nervous tissue by pedicles (Fig. 23). Caudally in this pial (?) tissue, cells resembling those of the external granular layer were seen to proliferate near the anterior tip of the external granular layer.

8) 9-Month-Old Malformed Fetus (Shortened Four Limbs and Trunk—Case No. 8, Fig. 3)

Fig. 20 Large tubercular cell cluster(T) in the central portion of the cerebellum of Case No. 7. IV···roof of the 4th ventricle, and Vma···anterior medullary velum. Rydberg's combined gold-silver method ; ×10.

Diverticulum-like widening of the posterior part of the 4th ventricle towards the vermis posteriorly was seen. However, abnormal changes of glial cells were hardly

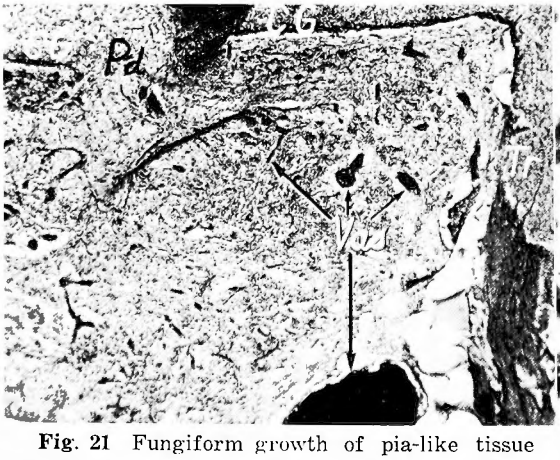


Fig. 21 Fungiform growth of pia-like tissue on the lateroventral surface of the pons of Case No. 7. Pd···pedicle of proliferated pial (?) tissue connecting with the parenchyma of the pons, CG ···immature cell clusters on the outer surface of the pons, Tr···trigeminal nerve, and Vas···blood vessel. Penfield's stain Ⅱ ; ×50.

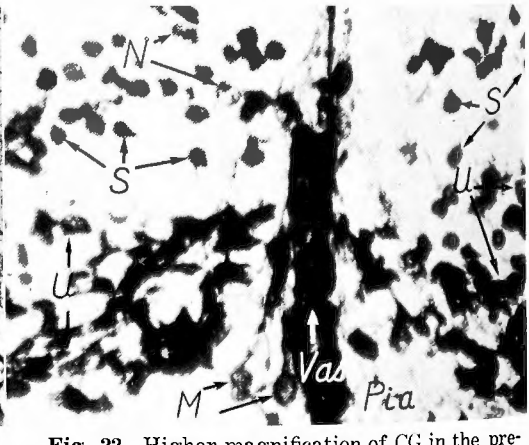


Fig. 22 Higher magnification of CG in the preceeding figure. N···apolar neuroblast, S···apolar or polar spongioblast, M ·cell of the leptomenix possessed of fibrillary processes, U···cell in the immediate subpial tissue : whether they are of glial nature or not is unknown, Vas···blood vessel, and Pia···pia mater. Penfield's stain Ⅱ ; ×400.

noticeable. In the nodular-velar region where SHIMADA found undifferentiaed apolar cells in 10-month-old normal fetus, nodular clusters of immature cells were seem persisting and there were present a few funicular clusters of predominatingly apolar spongioblasts in the roof

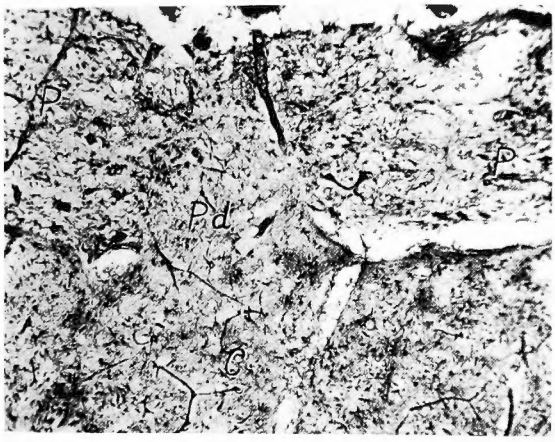


Fig. 23 Pial(?) tissue growth(P) on the upper surface of the quadrigeminal body. Pd···pedicle of pial (?) tissue connecting with the quadrigeminal body, and C···quadrigeminal body. Penfield's stain II ; ×100.

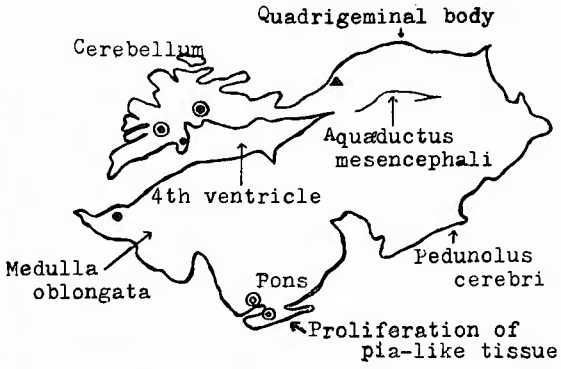


Fig. 24 Schema showing the locations of immature cell clusters in the rhombencephalon and mesencephalon of Case No. 9.

- ● Immature cell rests around the ventricular system.
- (•) Immature cell cluster, probably of glial nature.
- ◎ Cluster of immature cells ; whether they are glial or not is not known.
- ▲ Immature cell cluster, presumably of microglial nature.

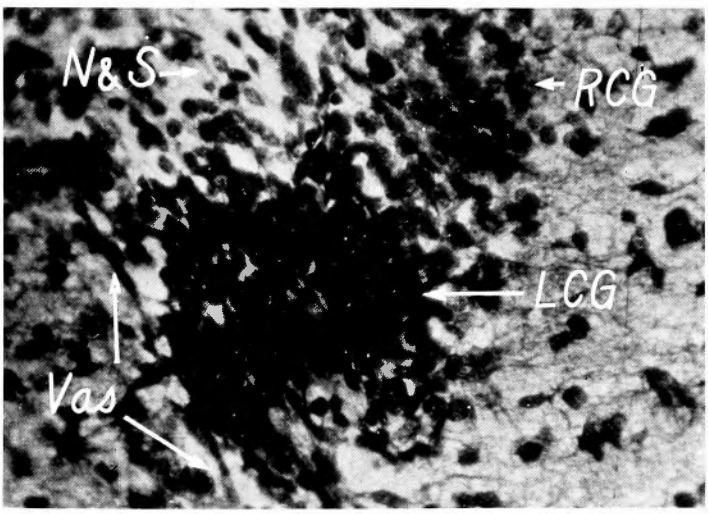


Fig. 25 Abnormal cell group in the central white matter of the cerebellum of Case No. 9. LCG···the site where markedly argentophilic, elongated or ellipsoid cells probably of immature glial nature aggregate, RCG···the part where less argentophilic small and round cells, resembling immature internal granular layer cells, cluster, S & N···apolar or polar spongioblasts and immature neuroblasts are scattered, and Vas···blood vessel. Ryberg's combined gold-silver method ; × 400.

of the 4th ventricle.

9) 10-Month-Old Malformed Fetus (Cheiloschisis—Case No. 9, Figs. 4 and 24)

Although gross malformation was not evidenced in any part caudal to the mesencephalon in this case, remarkable changes were present histologically. The same was true of Case No. 7 (with cheiloschisis—Figs. 17-22). Ellipsoid or elongated cells probably of glial nature aggregated around the blood vessels and invaded into the cerebellar nuclei. In the adjacent white matter, too, were frequently observed clusters of similar cells (Fig. 25). In the posterior vermis such cells together with small round cells resembling internal granular layer cells and with immature PURKINJE's cells grew to form nodes of larger size. Nearly the same tissue architecture as these nodes was seen in the pedunculus flocculi. The principal cells which formed the clusters, or nodes, as mentioned above were ellipsoid or elongated in shape which had a tendency to get in close contact with the blood vessels or the pia mater. It seems that those cells correspond with the elongated, darkly stained and medulloblast-

Fig. 26 Cluster in layers of small bacilliform of irregularly elongated argentophilic cell (CG) in the latero-caudal part of the inferior colliculus in Case No. 9. Pia···pia mater, and Co···inferior colliculus. Rydberg's silver diamino-carbonate method ; ×200.

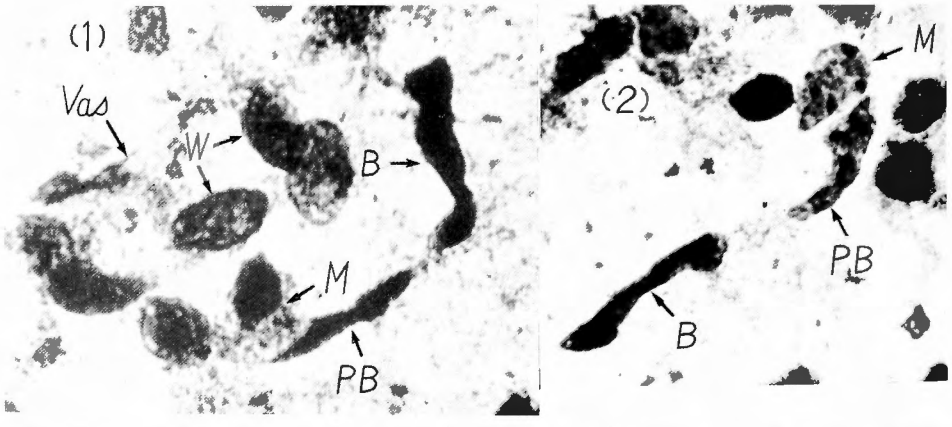


Fig. 27 Course of formation of the small bacilliform cells which constitute the cluster in layers shown in the foregoing figure. B···markedly argentophilic, small and bacilliform cells. PB···fore-stage cell of B, and M···mother cell of PB. Rydberg's silver diamino-carbonate method; ×1200.

(1) PB appears as a thick process, markedly argentophilic, of M, which is thought to be the cell emigrated from the wall of the blood vessel. Vas···blood vessel and W···cell of the wall of the blood vessel.

(2) A limiting membrane is visible between PB and M and they are considered as resultant cells from inequal cell division. M resembles the ellipsoid cell deprived of any processus and can be abundantly found in the neighboring pia mater.

like cells in the mixed cell rests in the white matter of fetal cerebellums which were noticed by BRZUSTOWICZ and KERNOHAN[2]. Such cells, on the other hand, resemble the apolar elements to be seen in the external granular layer and near the pia mater.

In the ventricular wall around the posterior medullary velum rest of undifferentiated apolar cells as pointed out by SHIMADA were seen and, in its surrounding parts, apolar neuroblasts and spongioblasts.

The ependymal layer of the floor of the 4th ventricle varied in its thickness in different parts of the rhombencephalic fossa, but abnormal proliferation was not evidenced. In the subependymal layer, however, clusters of apolar spongioblasts and neuroblasts persisted, especially in the posterior portion near the taenia rhombencephali.

In the subpial tissue of the latero-caudal portion of the inferior colliculus were observed clusters in layers of bacilliform or irregularly elongated small cells (Fig. 26). These cells seemed to be formed from uneven division of large ellipsoid cells emigrated from the wall of blood vessels in the pia mater on the dorsal surface of the quadrigeminal body (Fig. 27). The irregularly elongated cells were quite analogous with the pseudopodic form of cells which was pointed out by KERSHMAN[7] as the immature form of microglia in the human fetal brain. Besides, there were found microglias of early branched form of KERSHMAN surrounding these cells. However, there is no definite proof that these cells are in fact microglias.

On the basal surface of the pons laterally, fungiform growth of pia-like tissue as seen in Case No. 7 was observed. And in the subpial tissue clusters of apolar elements resembling those in Case No. 7 were found, although it remained unclear whether such elements are of glial nature or not.

10) Full Term Malformed Child (Rachischisis—Case No. 10)

The child died three days after the delivery of infection of the spinal canal and intracranial cavity by bacillus pyocyaneus, which invaded through the open slit of the rachischisis. There was seen on the wall of the 4th ventricle cell infiltration as the result of acute inflammation. Persistence of ependymal cells in the roof of the posterior aqueduct was the only congenital tissue anomaly found. Even in the nodulus, immature cell rests were entirely absent.

(B) Prosencephalon

1) 2-Month-Old Malformed Fetus (Case No. 1, Figs. 1 and 9)

Histologically, no abnormality was disclosed, probably owing to the fact that the developmental stage was too early, although the cerebral hemisphere appeared more irregular and rich in folds than in normal fetus, due presumably to dysrrhaphy of the mesencephalon.

2) One of the Twin Fetuses, 4-Month-Old (Case No. 2)

Along the blood vessels around the ganglionic ridge (Ganglienhügel) and just posterior to the rhinencephalon, clusters of apolar elements were uncovered. Such cell clusters may be visible also in normal fetal brain and, consequently, not considered to be abnormal.

3) 5-Month-Old Fetus of Natural Abortion (Case No. 3)

4) Natural Abortive Fetus at the Beginning of 6th Fetal Month (Case No. 4)

In both cases, funicular or islet-like clusters of apolar elements which seemed to be the extension of matrix cells either in the ganglionic ridge or temporal horn of the lateral ventricle were seen in large numbers in the medullary substance near the nucleus amygdalae (Fig. 28). On the ventral or lateral side of the caudate nucleus, small clusters of apolar spongioblasts in the main around the blood vessels were observed. Fungiform excrescences of the matrix protruding into the ventricular cavity as described by RYDBERG[12] or SHIMADA[13] were seen in Case No. 3 near the sulcus terminalis. All these findings were not to be regarded as abnormal, since they might be found in the normal fetal brain of the same fetal month.

5) Normal Abortive Fetus at the End of 6th Fetal Month (Case No. 5)

Clusters of apolar spongioblasts around the blood vessels, the condition termed as "perivascular cuff of apolar spongioblast" by ARAKI and SHIMADA, were obiously found on the latero-ventral side of the thalamus (Fig. 29). In this case,

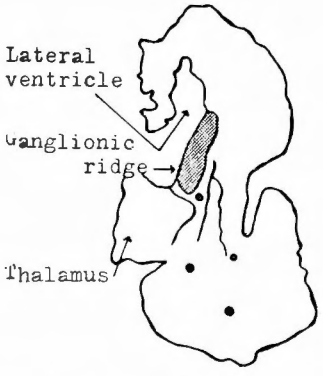


Fig. 28 Schema of immature cell rests around the ganglionic ridge and nucleus amygdalae in Case Nos. 3, 4 and 5. Frontal section of the cerebral hemisphere at the part a little bit anterior to the tip of the lower (temporal) horn of the lateral ventricle.

● Immature cell clusters composed predominantly of apolar spongioblasts.

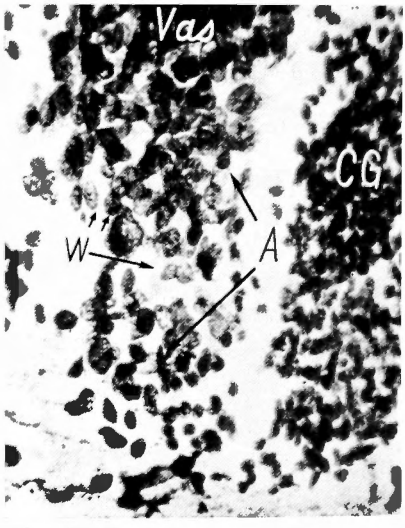


Fig. 29 Perivascular conglomerate of apolar spongioblasts (CG) on the ventro-lateral side of the thalamus in Case No. 5. Vas···blood vessel, W···cell of the vascular wall, and A···argentophilic cell of variable forms. Rydberg's combined gold-silver method ; ×40.

as in the foregiong two cases, changes to be considered as definitely abnormal were lacking.

6) 8-Month-Old Malformed Fetus (Case No. 6, Fig. 5)

The brain substance was very thin, its developmental interruption apparently intense, and normal structure of the cerebrum largely lost. In the cerebral cortex were observed funicular rests of neuroblasts and spongioblasts (Fig. 30) and in the medullary substance, perivascular aggregates predominnatly of immature glial cells were found. On the undersurface of the cerebrum, as on that of the midbrain, pial(?) tissue proliferated ; besides, it invaded in several parts the cerebral parenchyma (Fig.

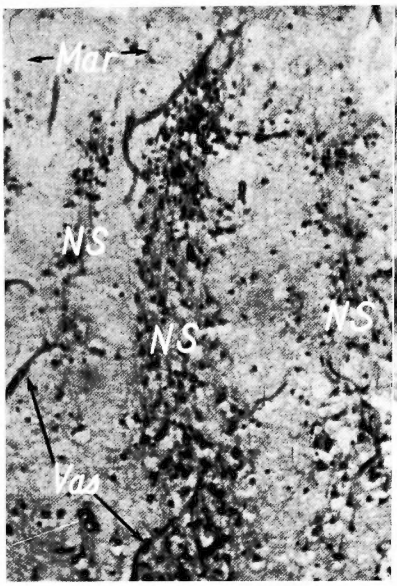


Fig. 30 Severe changes of developmental hindrance in the cerebral cortex of Case No. 6. NS···funicular areas where neuroblasts and spongioblasts persisted, Vas···blood vessel, and Mar···marginal zone of the cortex. Penfield's stain Ⅱ ; ×200.

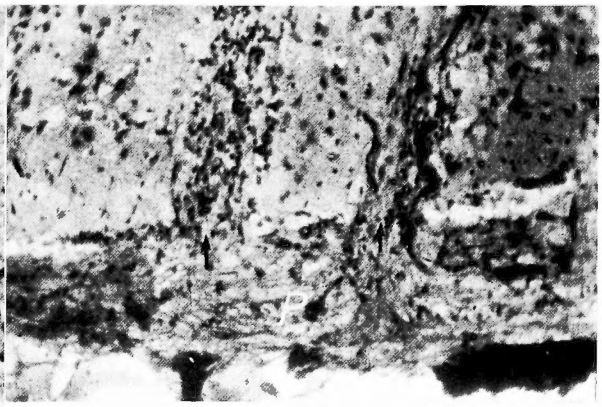


Fig. 31 On the undersurface of the cerebrum in Case No. 6 is seen pial (?) tissue growth(P) which penetrates in the cerebral parenchyme (indicated by arrow). Penfield's stain Ⅱ ; ×200

31).

7) 9-Month-Old Malformed Fetus (Case No. 7, Figs. 2, 6 and 17)

As the corpus callosum and the septum pellucidum were defective, the anterior half of the 3rd ventricle together with the lateral ventricle on both sides constituted a large cavity. In the posterior half of the 3rd ventricle, the ventral part of the massa intermedia became a small residual tube and the dorsal one a narrow residual slit (Fig. 17).

Immature cells of the subependymal layer (matrix) rather decreased in number, probably due to the malformation of the ventriclular system of such a high degree as just described above. Along the subependymal blood vessels in the lateroventral wall of the lateral ventricle were disclosed rests of immature cells composed predominantly of apolar spongioblasts. It was thought that these cells differed essentially not very much from the apolar elements to be found around the walls of the terminal vein and its branches in normal fetus.

In the medullary substance but just beneath the cortex of the parietal and frontal lobes, nodular conglomerates of polar elements around the vessels were seen (Figs. 32 and 33). In these conglomerates, polar spongioblasts and astroblasts predominated but neuroblasts were also seen in considerable number. These conglomerates were thought to be analogous with the subcortical nodular conglomerates in Case No. 9 which will be mentioned later. Inside and around the nodular clusters of neuroblasts, which seemed to be the malformed nuclei corresponding to

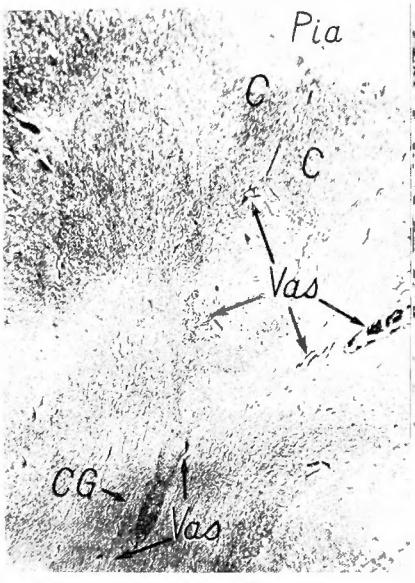
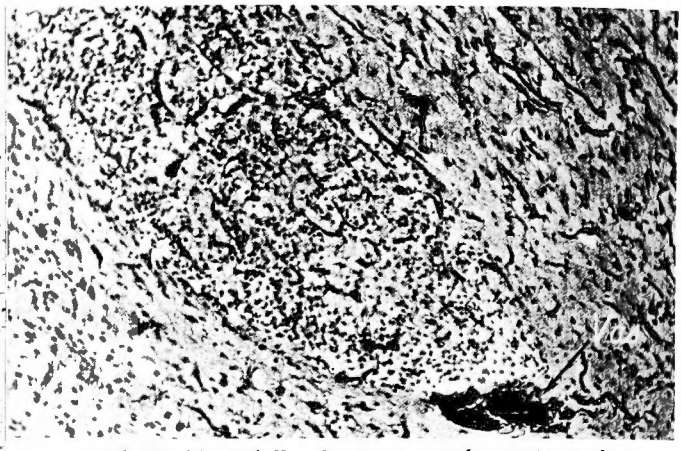


Fig. 32 Nodular cell conglomerate (CG) in the perivascular zone in the frontal medullary substance in Case No. 7. Pia···leptomeninx, C···cortex, and Vas···blood vessel. Penfield's stain Ⅱ; ×20.



Fgi. 33 Essentially the same conglomerate as shown in Fig. 32. The constituent cells are rather differentiated polar cells. Vas···blood vessel. Penfield's stain Ⅱ; × 200.

the corpus striatum and its surrounding structures, there were rather many small aggregates of apolar or polar spongioblasts of small size.

In the cortex near the defective posterior pole of the cerebrum, glial cells of small size were found to form small clusters in between the nerve cell layers (Fig. 34).

8) 9-Month-Old Malformed Fetus (Porencephalic Cyst—Case No. 8, Figs. 3 and 7)

In the medullary substance of the posterotemporal region of the right cerebral hemisphere was uncovered a porencephalic cyst which communicated with the right lateral ventricle through an irregular slit (Fig. 7). The wall of this cyst was macroscopically smooth-surfaced but microscopic examination revealed no particular lining with the tissue of the medullary substance exposed (Fig. 35). In this case, developmental anomaly of glial cells was not evidenced in any part of the brain by microscopy. In the frontal lobe, however, funicular clusters of immature cells, which seemed to be the extension of the matrix, were present, slightly more in number than they might be found in normal fetus. In the occipital lobe, tubular structures in the subependymal zone were comparatively abundant, which were recongnized by Rydberg and Shimada also in normal fetal brain.

9) 10-Month-Old Malformed Fetus (Cheilognathopalatoschisis—Case No. 9, Figs. 4 and 36)

Pronounced hydrocephalus with irregularly shaped gyri and shallowed sulci was remarkable. The callosal body was underdeveloped and in both hemispheres were

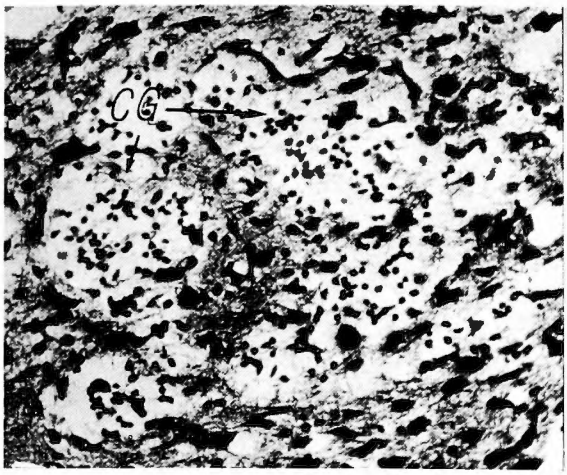


Fig. 34 Small intracortical clusters(CG) of small glial cells in the dorso-caudal portion of the right cerebral hemisphere in Case No. 7. Penfield's stain Ⅱ; ×400.

Fig. 35 The lateral wall of the porencephalic cyst in Case No. 8. Sf···the innermost medullary substance which underwent some regressive changes, Cy···cavity of the cyst, and Vas···blood vessel. Penfield's stain Ⅱ; × 50.

found considerable changes histologically.

Along the blood vessels entering presumably from the outer surface of the brain, nodular cell conglomerates were observed in the transitional zone between the cortex and the medullary substance (Fig. 37), most numerously in the upper lateral portion extending from the frontal to the occipital region. These conglomerates were composed of cells possessed of processes which were arranged in such a way that they encircled blood vessels and, consequently, were clearly identifiable from the surrounding structures. The main constituent cells were small glial cells or neuroblasts in the cortical conglomerates and astroblasts in the subcortical ones. They were intermingled with cells of other types in variable proportions.

In the subependymal layer of the lateral ventricle, small clusters of immature cells were frequently found to be present in close contact with the ventricular ependyma or along the blood vessels of the subependymal zone(Fig. 38 and 39). The principal cells which constituted the clusters were markedly argentophilic, round, ellipsoid or pear-shaped, and probably apolar or, occasionally, polar cells, which seem to belong to spongioblastic series. It was confirmed that the more nearly were situated the clusters to the ventricular cavity the more immature were the constituent cells and the opposite was likewise true. The great majority of the cells were spongioblastic but a few were neuroblastic in nature.

Outside the thalamus, proliferation of small round cells with a few processes

was seen in the nodular clusters of neuroblasts, which seemed to be the malformed nuclei (basalganglia) in this region (Fig. 40). Most of these cells were glial cells, small, round, argentophilic and possessed of two or three short processes, but some were immature neuroblasts.

10) Full Term Child (Rachischisis —Case No. 10)

The child was alive for three days after delivery. Pronounced hydrocephalus was present. Cell infiltration in the wall of the lateral ventricle and the basal surface of the cerebrum due to postnatal infection was observed. Congenital tissue anomaly was, however, nearly absent. Around the terminal vein and its branches and in the latero-ventral part of the caput nuclei caudati, where immature cell rests are liable to occur in normal fetus, clusters of somewhat immature cells principally of polar spongioblasts were seen to persist.

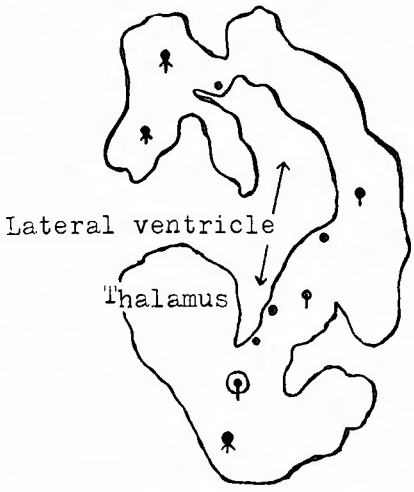


Fig. 36 Schema of locations of abnormal cell groups in the cerebral hemisphere of Case No. 9. Frontal section at the middle of the hemisphere.

● Cell group principally of apolar spongioblasts.

● Cell group principally of polar spongioblasts.

• Cell group principally of astroblasts.

Nodular cluster of small spongioblasts within the clustered neuroblasts.

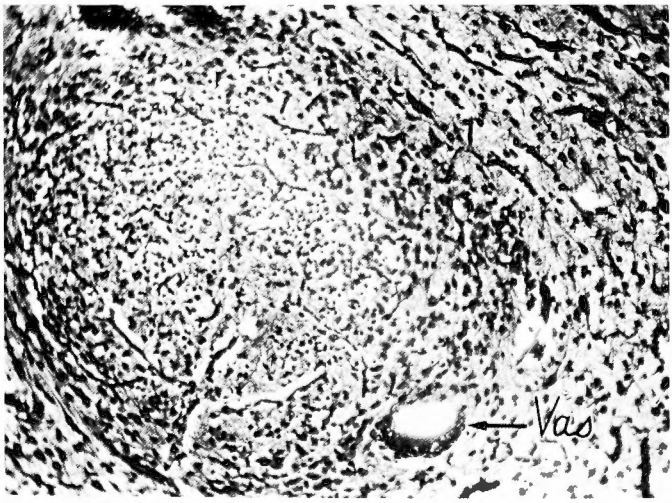


Fig. 37 Nodular subcortical cell conglomerate of the cerebrum in Case No. 9. The main constituent cells are astroblasts but neuroblasts and small glial cells are also intermingled in large numbers. Vas···blood vessel. Penfield's stain Ⅱ; ×200.

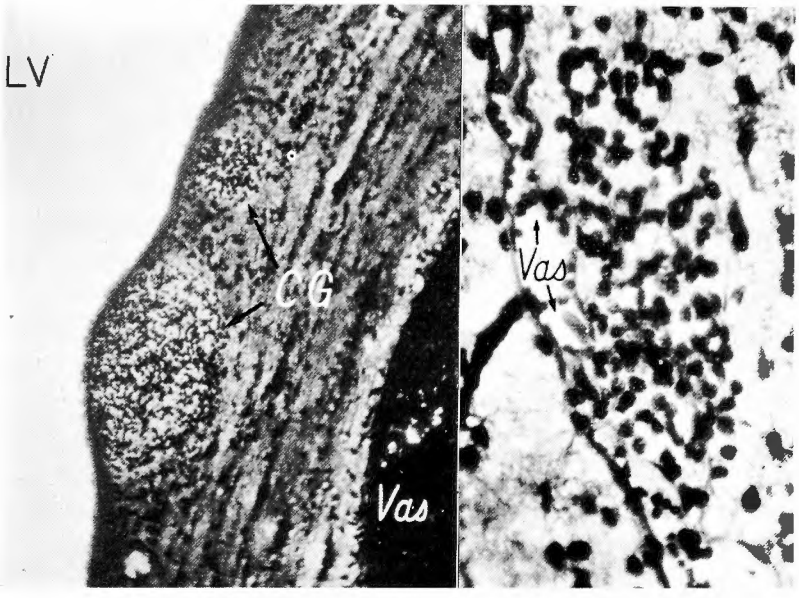


Fig 38 Fig 39

Fig. 38 Immature cell clusters(CG) are closely in contact with the ependyma of the lateral ventricle and around the sulcus terminalis in Case No. 9. Cells which seem apolar spongioblasts are seen to proliferate and persist. LV···lateral ventricle, and Vas··· blood vessel. Penfield's stain Ⅱ; ×100.

Fig. 39 Immature cell group in the subependymal perivascular zone of the wall of the lateral ventricle in Case No. 9. Not only apolar or polar spongioblasts but also apolar neuroblasts are visible in this cluster. Vas···blood vessel. Penfield's stain Ⅱ; ×400.

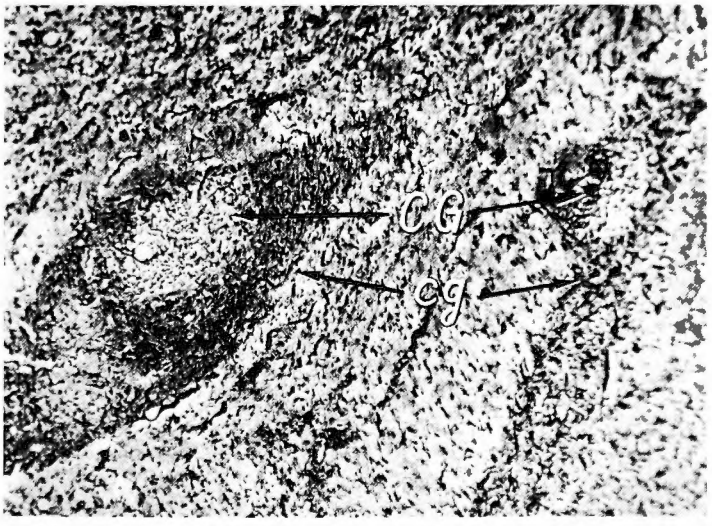


Fig. 40 Around the internal capsule of Case No. 9 is seen nodular cluster(cg) of neuroblasts, inside of which again is present cell group(CG) of small round cells. Penfield's stain Ⅱ; ×50.

COMMENT

The histological findings of grossly normal brains of the one of the twin fetuses (Case No. 2) whose body was obviously smaller than the other and those of the three fetuses (Case Nos. 3, 4 and 5) of natural abortion, either habitual after repeated artificial abortion or of unclear origion, were not much differing from those of normal fetuses. In the malformed fetuses with developmental anomalies in the bone system, i.e., with markedly shortened extremities and trunk (Case No. 8) or with underdeveloped skull and rachischisis (Case No. 10), the histological anomalies of the brain were not remarkable. In the malformed fetus at the beginning stage of gestation, in which the rostral part of mesencephalic aqueduct was opened and turned out dorsally (Case No. 1), apolar elements in the matrices of the rhombencephlon and mesencephalon decreased in number and in the case of pronounced malformation of the cerebrum (Case No. 6) changes seemed to have resulted from developmental hindrance of the brain. In either case, however, proliferative change in the brain tissue was absent. It is generally accepted that the fetus with cheiloschisis is apt to have arhinencephalon concomitantly. The two cases with cheiloschisis in the present series (Case Nos. 7 and 9) showed considerable malformation of the brain, accompanied with developmental disturbance of the rhinencephalon. As in such brains marked histological abnormalities, in the part caudal to the mesencephalon in particular, were observed, these will be commented in detail.

The abnormal cell clusters in the cerebellum (Figs. 18, 19, 20 and 25) may be considered to be analogous with the heterotopic cortical tissue of PFLEGER[9] located in between the nucleus dentatus and the cortex of the cerebellum or with the heterotopic or heterotaxic mixed cell rests of BRZUSTOWICZ and KERNOHAN[7] composed of neurons, astrocytes, oligodendrocytes, granule cells, deeply stained elongated cells resembling medulloblasts and blood vessels in varying proportions. The superior portion of the nodular clusters in the cerebellar white matter in case No. 7, showed the structure resembling the external and the internal granular layer with the molecular layer-like tissue between them. This structure was quite simulating that of the cerebellar cortex (Fig. 20). In the central parts, on the other hand, tendency to form the molecular layer-like tissue was not evident, but there were irregularly admixed cells of the external and internal granular layers with little tendency to make up organization. The cell clusters in other portions in this case as well as those in Case No. 9 were also mixed cell rests of this latter type.

In such clusters the cells considered to be quite immature were considerably argentophilic and ellipsoid or elongated in shape (Fig. 41). These cells seemed to be identical with the ellipsoid and elongated immature cells found in the external granular layer adjacent to the pia mater (Fig. 42). Furthermore, immature cells probably of the external granular layer were at times identified inside the cerebellar nuclei and the surrounding structures of the deeper parts and along the blood vessels in Case No. 5 of the present series as well as in the 8-month-old normal fetus of SHIMADA (Fig. 13).

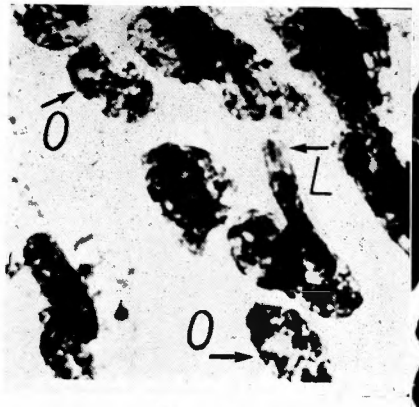
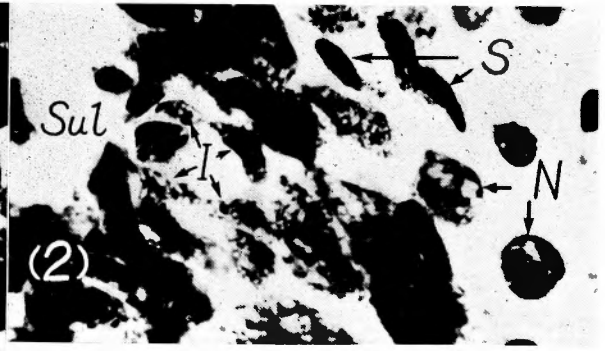


Fig. 41



↑ Fig. 42 (2)

← Fig. 42 (1)

Fig. 41 Immature cells constituting abnormal cell cluster in the cerebellum of Case No. 7. Note the ellipsoid cell (O) and the elongated cell (L), both of which have scanty cytoplasm, indistinct nuclear membrane and rather many argentophilic intranuclear granules of variable sizes. Penfield's stain Ⅱ ; ×900.

Fig. 42 Immature cells in the external granular layer of the cerebellum in Case No. 9. Penfield's stain Ⅱ ; ×900.

(1) Cerebellar gyrus

(O) Most immature ellipsoid cell probably of neuroblastic nature, resembling O in Fig. 41.

(L) Most immature elongated cell probably of spongioblastic nature, resembling L in Fig. 41.

(ON) Ellipsoid cell containing 5 – 6 argentophilic intranuclear granules and appearing more light, which is now obviously of neuroblastic nature. Pia···leptomeninx.

(2) Cerebellar sulcus

(N) Immature cell of neuroblastic series which seems to become internal granular layer cell.

(S) Immature cell of spongioblastic series.

(I) Irregularly shaped immature cell undergoing cell division, which has scanty cytoplasm, indistinct nuclear membrane and comparatively many intranuclear granules, argentophilic and of different sizes. Whether it is of spongioblastic or of neuroblastic nature is yet unknown. Sul···cerebellar sulcus.

The cells of the external granular layer have hitherto been believed to be analogous with the medulloblasts and, accordingly, the essential features of the cells have been studied with undivied attention[6),11)].

RAAF and KERNOHAN[11)] stated that the germinal bud at the posterior tip of the posterior medullary velum, from which the external granular layer is derived, disappeared within one month after birth, and in the child at this period abnormal collections of cells might be found in the posterior medullary velum.

Another remarkable change in the rhombencephalon was proliferation of pia-like tissue on the latero-ventral surface of the pons. It was interesting to note that the clusters of cells, whether glial or not was not yet clear, to be found immediately under the pial membrane in this region (Figs. 22 and 43) also resembled very much the cells of the external granular layer.

Fig. 43

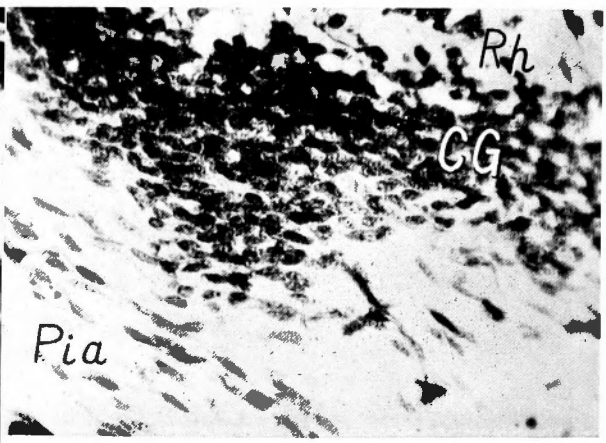


Fig. 44

Fig. 43 Immature cells in the abnormal cell layer of the latero-ventral surface of the pons in Case No. 7.

(O) The ellipsoid cell, resembling O in Fig. 41. Note similar features to U in Fig. 8.

(L) The elongated cell, resembling L in Fig. 41. Pia…pia mater. Penfield's stain Ⅱ ; ×900.

Fig. 44 Immature cell nest (GG) on the ventral surface of the rhombencephalon in the 3-month-old normal fetus of SHIMADA. The more superficial cells in this nest, the more similar to pial cells. Pia…embryonic pial tissue, and RH…rhombencephalon. Rydberg's silver carbonate method ; ×200.

In the two fetuses (Case No. 1 and its contrast, Case No. 11) 2 months of age, when formation of pial membrane is still indistinct, layers of immature cells in the immediate subpial tissue were absent. These layers were, however, present in the 4-month-old fetus Case (No. 2) and in the 3-month-old normal fetus of SHIMADA on the cerebellar surface as well as on the latero-ventral surface of the pons (Figs. 11 and 44).

In the normal fetuses of more than 4 months in SHIMADA's series and the

contrasts of 5 months (Case Nos. 12 and 13) in the present series, such cell layers in the cerebellum persisted as external granular layers while those of the pons were no longer recognized. However, it is conjectured that such cell layers of the pons may be responsible for the changes(Fig. 21) seen in Case Nos. 7 and 9 if they undergo developmental disturbance leading to malformation.

The presence of outgrowths of pia-like tissue in the transitional zone between the quadrigeminal body and the cerebellum, directly continuing to the anterior tip of the external granular layer, and the tendency of neuroblastic cells with clear vesicular nuclei and of argentophilic ellipsoid or fusiform cells to proliferate and emigrate from the immediately subpial layer of the latero-ventral surface of the pons into the inside of it(Figs. 22 and 43), obviously indicate that the cells proliferated in the subpial tissue of the pons characteristically resemble those of the external granular layer.

Furthermore, it seems probable that the changes both in the cerebellum and the pons are essentially alike, since abnormal cell clusters found in the white matter of the cerebellum in Cases Nos. 7 and 9 were very much resembling the cells of the external granular layer. However, such cells can not always be considered as abnormal by themselves, for they may be found also in the normal fetuses of the same period. Among such cells are contained spongioblastic and neuroblastic cells and often others which are hardly classified in either of the two ; just as SCHAPER's indifferent cells and medulloblasts of BAILEY and CUSHING. According to BAILEY and CUSHING[1], the typical cells of medulloblastoma contain round or slightly oval nuclei with abundant chromatin ; their cytoplasm is scanty, and either surrounds the nucleus in a ring, or streams away from one pole in an indefinite tail. The cells of the external granular layer are, as shown in the cases of the present series too, resembling the constituent cells of medulloblastoma[6),11)]. In the present experiment, however, pseudo-adenomatous structures or pseudorosette formations were entirely absent, which are readily to be found in medulloblastomas. The locations of the embryonal tissue malformations and the seats of predilection for occurrence of medulloblastoma were not always coincident. Medulloblastomas occur most frequently in nodulus while the changes in the cerebellum of Cases Nos. 7 and 9 were found extensively in the central portions of the cerebellum, including the dentate and other nuclei. But, the causal relations can not be neglected between such changes and medulloblastomas, as the changes extended also to the nodulus. It has already been mentioned that the cells in the latero-caudal surface of the pons resembled medulloblasts, although it is not known that medulloblastomas ever occur in such a region. The cells of the clusters in the subpial layer, accompanied by pia-like tissue proliferation, are presumed to be related to the cells of meningoblastoma (OBERLING), which originates from the leptomeninges although structurally analogous to medulloblastoma. OBERLING and HARVEY and BURR maintain that meningoblasts forming the leptomeninges are emigrating cells from the ganglionic crest.

The pial cells growing out of the immature cell layers in the immediate subpial zone of the undersurface of the rhombencephalon in SHIMADA's 3-month-old normal

fetus (Fig. 44) and the pial(?) tissue proliferation on the dorsal surface of the quadrigeminal body and ventral surface of the pons, connecting with the neural substance, in the malformed fetuses in this series (Figs. 16, 21 and 23) show that proliferation of meningoblasts in localized clusters may not infrequently occur both in normal and malformed fetal brains.

In this connection, it should be noted that the clusters in layers of the irregularly shaped bacilliform cells found near the surface of the caudal part of the quadrigeminal body in Case No. 9 may likewise be considered as pial in nature. The location of such cell clusters seems to correspond with the tip of the rhombic furrow which KERSHMAN[7] pointed out as the seat of nests of the amoebic form of microglia in 8-week-old fetus. The cells in such clusters are not unlike microglias, although there is no definite proof that they represent undoubtedly the earlier stage of microglias.

The changes in the medulla oblongata were slight and this part of the brain seems to be well resistant against agents leading to malformation. In only one case, Case No. 9, persistence in thin layer of immature matrix cells was observed which scattered in the subependymal zone of the floor of the 4th ventricle, though not to be regarded as definitely abnormal.

The principal changes in the cerebral hemispheres were those seen in Cases Nos. 7 and 9. Insufficient formation of the cortex and abnormal conglomeration of various cells along the blood vessels coming from the external surface were the most usual findings (Figs. 32, 33 and 37). The tendency that the cells are apt to proliferate and persist around the blood vessels was also noted in Casse No. 6 in which the malformation was actually very pronounced and the parenchyma of the cerebrum was almost deteriorated.

GLOBUS and KULENBECK[3] stated that tuberous sclerosis, which is the localized proliferation of glia cells in the cortex, has been found frequently associated with the spongioneuroblastic variety of tumors. The constituent cells of the nodular conglomerates in the present series were of the same variety as what will be found in the fetus of the same age, although it was remarkable that their processes were arranged in various irregular directions. GLOBUS and KULENBECK further described that numerous ependymal granulations were not infrequently found in spongioneuroblastoma and tuberous sclerosis as well. These ependymal granulations bear noticeable resemblance to the excrescences of the matrix cells protruding into the ventricular cavity, as reported by RYDBERG[12] and SHIMADA[13]. The subependymal immature cell rests (Fig. 38) in the Case No. 9 may also be considered as one of the similar changes.

The cell groups around the capsula interna in Cases Nos. 7 and 9 (Fig. 40) are presumably abnormal proliferation of immature small glial cells inside and around the nodular clusters, resulting from disturbed cell arrangement, of neuroblastic cells which ordinarily are designated to form thalamic or basal nuclei.

Similar small glial cells were observed to form small clusters in between the nerve cell layers of the cortex near the defective posterior pole of the cerebrum of Case No. 7(Fig. 34). GLOBUS and KULENBECK[3] were of the opinion that tumors of

the spongioneuroblastic variety might have close relation with the embryonal residues in the striato-thalamic junction, including the sulcus terminalis, and in other areas, i. e. the zone of coalescence of the anterior horns of the lateral ventricles and the subependymal cell plate about the nucleus caudatus and the septum pellucidum, as they frequently found those tumors in the same areas and in multiple form. In the malformed brain of Case No. 9 (ill-developed callosal body and residual rhinencephalon), irregularly aggregated immature cell rests were observed in the areas mentioned above. Since malformed brains have a tendency for the cells to form clusters in the very malformed region, no particular significance may be attached to the fact that immature cell clusters should be uncovered around the sulcus terminalis in the present case which had abnormality in the callosal body and its vicinity.

As the number of the cases in the present series were too small and the kinds of malformations and fetal ages in months were not uniform, it was not possible to ponit out definite and particular changes in glial cells of the brain. However, immature cell clusters of glial nature were in fact somewhat larger in number than in the case of normal fetus and, furthermore, they tended to appear in the places somewhat differing from those where normally they do. Although Ito[9] states that the patients who harbor a glioma tend to have some malformation in other parts of the body, it seems improbable that congenital abnormality of glias alone does give rise to glioma formation. Abnormal cell clusters seen in the present study may represent merely that the general development of the brain has been disturbed. Should another factor be added to such tissue malformations, it can be supposed that a tumor may more readily be formed than in the normal brain tissue.

SUMMARY

In seven fetuses with macroscopical malformation and three of natural abortion, the developmental anomalies were examined by staining the glial cells in various parts of the brain with silver impregnation.

In the two brains with pronounced malformation, changes of developmental hindrance were predominating. On the other hand, the brains of the two fetuses with malformation in the bone system revealed little changes. In the brains of the other two malformed fetuses with cheiloschisis, clusters of cells mostly of glial nature were frequently found in the parts somewhat different from those where they normally are present.

Cerebellum : The principal constituent cells of the abnormal clusters were ellipsoid and elongated cells resembling those in the external granular layer and round cells resembling those in the internal granular layer, all of which were found along blood vessels preponderatingly in the central white matter,

Pons : On the latero-ventral surface where cranial nerves originate, proliferation of pial(?) tissue was observed. In its immediate, subpial zone were present clusters in layers of apolar elements of presumably glial and neuroblastic nature.

Quadrigeminal Body : On the dorso-caudal surface were seen pial cell growths.

Cerebrum : Nodular cell clusters composed of spongioblastic, astroblastic and

neuroblastic elements were found, which encircled the blood vessels.

In one case of pronounced malformation as stated before, pial(?) tissue proliferation was noted, on the dorsal surface of the anterior medullary velum and on the entire undersurface of extending from the rhombencephalon to the prosencephalon. In the latter the proliferated tissue reached deep in the neural tissue.

Although it has been conceived that the seats of predilection for occurrence of immature glial cell clusters correspond with those of glioma formation, the change observed in the present study may merely be one of the representations that the development of the brain has been generally disturbed. And such changes alone may not give rise to glioma formation. It is, however, understandable that when some other additional factors are associated with, a glioma may more readily develop than it does in a normal brain.

The brains of the three fetuses of natural abortion revealed the changes within normal limits.

The present work was supported by a grant in aid of the Funds for Scientific Research from the Ministry of Education.

REFERENCES

1) Bailey, P. & Cushing, H. : A Classification of Tumors of the Glioma Group etc. Philadelphia, Lippincott, 1926.
2) Brzustowicz, R. J. & Kernohan, J. W. : Cell Rests in the Region of the Fouth Ventricle,
a) Their Site and Incidence according to Age and Sex. A. M. A. Arch. Neurol. and Psychiat., **67**, 535-591, 1952.
b) Histologic and Embryologic Consideration. Ibid, **67**, 592-601, 1952.
c) Their Relationship to the Development of Gliomas. Ibid, **67**, 602-611, 1952.
3) Globus, J. H., and Kuhlenbeck, H. : Tumors of the Striatothalamic and Related Regions. Their Probable Source of Origin and More Common Forms. Arch. Path., **34**, 674-734 (Oct.), 1942.
4) Ito, T. : Pathology of Brain Tumors. Proc. Jap. Path. Soc., **47**, 285, 1958.
5) Kaven, A. : Auftreten von Gehirnmissbildungen nach Röntgenbestrahlung von Mäuseembryonen. Z. menschl. Vererbs-u. Konstit. lehre, **22**, 247, 1938, cited from O. Ostertag : Die Einzelformen der Verbildungen in Lubarsch et al. ; Handbuch der speziellen pathologischen Anatomie und Histologie, **13**, **4**, 363-601, 1956.
6) Kershman, J. : The Medulloblast and the Medulloblastoma, a Study of Human Embryos. Arch. Neurol. & Psychiat, **40**, 935-967 (Nov), 1938.
7) Kershman, J. . Genesis of Microglia in Human Brain. Arch. Neurol. & Psychiat., **41**, 24-50, 1939.
8) Penfield, W. : Neuroglia, Normal and Pathological, in Penfield, W. . Cytology and Cellular Pathology of the Nervous System. Newyork, Paul B. Hoeber, Inc., 2, 422-479, 1932.
9) Pfleger, L. : Beobachtungen über Heterotopie grauer Substanz im Mark des Kleinhirns. Zentralbl.f.med. Wissensch., **18**, 468-470, 1880.
10) Podmaniczky, T. : Über kongenitale Neuroglioma. Ztschr. f. Path., **V**, 255-262, 1910.
11) Raaf, J., and Kernohan, J. W. : Relation of Abnormal Collections of Cells in Posterior Medullary Velum of Cerebellum to Origin of Medulloblastoma. Arch. Neurol. & Psychiat., **52**, 163-169 (Sept.), 1944.
12) Rydberg, E. : Cerebral Injury in Newborn Children consequent on Birth Trauma. Acta Path. et Microbiol. Scan., Supplementum X, 1932.
13) Shimada, M. : Persistence and Misplacement of Immature Glial Cells in Various Parts of the Human Fetal Brain and their Possible Relation to the Development of Gliomas. Folia Psychiatrica et Neurologica Japonica, **8**, 3, 237-267, 1954.

14) Wilson, J. G., Brent, R. L. and Jordan, H. C.: Neoplasia Induced in Rat Embryos by Roentgen Irradiation. Cancer Research, **12**, 222-235 (Nov.), 1952.

和文抄録

奇形胎児及び自然流産児の脳各部位に於けるグリア系細胞の発育異常並びに，そのグリオームの発生との関係

京都大学医学部外科学教室第1講座（指導：荒木千里 教授）
山　添　善　朗

脳グリアの胎生期発育異常とグリオームとの関係を伺う目的から，肉眼的奇形7例，及び自然流産児3例の脳各部位について，鍍銀染色を行い，グリア系細胞の組織学的異常を検索した．

奇形高度な2例の脳には主として発育阻止的な変化があつたが，骨系統の奇形児2例の脳には変化が殆どなかつた．兎唇を有する2例の奇形児の脳には正常と多少異つた部位に主としてグリア系と思われる細胞集団を認めた．

小脳．異常細胞集団の主な構成細胞は，外顆粒層の細胞に類似した楕円形乃至伸長形の細胞及び内顆粒層の細胞に類似した円形細胞で，血管に沿つて，主として髄質主幹部に見られた．

橋脳．側下面の脳神経の出る部位に近く軟膜様組織の増殖を認め，その附近の軟脳膜直下にグリア系及びneuroblast系と思われる，apolar elementの層状の集団があつた．

四丘体．尾側部背面に軟膜性細胞の増殖があつた．

大脳．血管に沿つて，spongioblast系及びneuroblast系の要素からなる結節状の細胞集団がみられた．

尚，先に述べた奇形高度な1例に，前髄帆部上面，又菱脳より前脳の下面全般に亘つて軟膜様組織の増殖があり，これが脳実質内にも侵入していた．

グリア系の幼若細胞集団の好発部位が，グリオームの好発部位に，ある程度一致している様に考えられたが，併し，本実験にみられた変化は，脳の発育が全般的に障害されていることの一つの表現に過ぎない様に思われ，これだけでグリオームの発生を来すことはないと思われる．併し他の補助因子が加われば正常脳よりもグリオームを発生し易いということは考え得る．

3例の自然流産児の脳は，大体正常範囲内の変化を示した．