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THE BEHAVIOUR OF GLIOMAS IN TISSUE CULTURE

I. ASTROCYTOMA-GLIOBLASTOMA GROUP

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The classification of brain tumours according to Bailey and Cushing [1] constituted the basis of the theoretical and practical questions of neuro-oncology for decades. The classification was based on analogy with the normal histogenetic succession in nervous tissue, which at the same time presumed the so-called unicentric theory of the rise of tumours, namely the rise of tumours from resting, usually ectopic cell groups at different stages of development [11, 12, 13].

As neurosurgery developed the inadequacy of classification became more and more prominent; even the authors called attention to some of these deficiencies. It is more urgent to define more closely the biological character of the tumours than to solve the histogenetic question, first of all in view of the operation and prognosis. At the same time our attention was more and more directed towards the theory, that the gliomata arise from intact, mature glia cells by the means of a stimulation unknown. This theory was supported among others by Zimmermann [34], Netsky et al. [26] by their experiments on animals.

This theory led to the simplification of the classification. In practice — taking into consideration the prognostic conclusions gained from the histological picture—in one respect they concentrated groups, on the other hand, they established different degrees of malignancy in certain groups. Thus Kernohan et al. [32] drew together the astrocytoma-astroblastoma-glioblastoma groups and established an astrocytoma category marked with four numbers. Ringertz [31] kept only three groups and retained the glioblastoma name; the so-called intermediate astrocytoma group represents the transition form. We also divided our material into three groups, first of all the above, taking into consideration the practical points of view: "astrocytoma", "astrocytoma of malignant tissue structure" and "glioblastoma multiforme".

Neither the conservative conception of Zülch [35] nor the innovations of Kernohan gave fully adequate classifications. Therefore it is necessary to seek for further data. To take a confirmatory stand or to seek for a new direction in this question is only possible after a more thorough investigation

and introduction of new technics. Thus the routine methods of histology must be complemented by other biological methods. To compare the histological picture and the biological behaviour of tumours, the tissue culture method seems to be above all the most appropriate.

Since the fundamental report of CANTI, BLAND and RUSSEL [4] on their investigation of gliomata in tissue culture, many other authors have dealt with the question. In tissue cultures, so far mostly cytological and cytopathological observations were made [2, 8, 17, 18, 19, 20, 24, 28, 29]. Likewise the effect of cytostatic compounds was studied with the same method [9, 13, 14, 21, 25]. Culture observations with the help of time-lapse films of the glial cell-types rendered it possible to observe differences in the movement phenomena. Studies on the pulsation of the glial elements, however, are conflicting. POMERAT [28] deems pulsation characteristic of the oligodendroglia cell; on the other hand, BERG [3] observed this phenomenon in the case of astrocytes as well.

In our first, present, communication we describe our observations in tissue culture on the behaviour of the histologically labelled astrocytoma, astrocytoma malignum and glioblastoma tumour groups. Within the possibilities of the method we endeavoured to determine the biological and cytological properties of the designated tumour groups and collate our observations with the histological diagnosis, to gain data concerning what might be expected of the tumours in vivo.

Material and method

The explants were of tumour material taken during operation under sterile conditions. During our investigations we made tissue cultures from 107 patients, 60 of them were supratentorial glioma species, belonging to the astrocytoma-glioblastoma group. 48 of the 60 specimens showed appreciable growth in tissue culture. From the 12 unsuccessful cases 7 failed in account of technical shortcomings, and only 3 astrocytoma and 2 glioblastoma cultures were unsuccessful. This shortcoming may have originated from the possibility that during the operation the selection of material was not always favourable and the piece of tumour removed for explantation may have been necrotic.

The above numerical data show, however, that the cultivation of astrocytoma-glioblastoma tissue from human tumour can be carried out with good results and the procedure mentioned below can be performed without particular difficulty.

In our present communication we only describe our observations of 21 explantations from the group of 48 successful cases. For uniformity of material and evaluation we do not deal at present with observations of tumour recurrence, further we exclude those materials still under culture and observation when we closed our present communication.

The histological diagnosis of the 21 examined tumours are as follows:

I. astrocytoma	4
II. astrocytoma malignum	4
III. glioblastoma	13

For comparison we made tissue cultures from human non-tumorous white matter of the brain. We got the material partially from the resected temporal lobe of epileptic cases, partially from the cerebellum when operating a ponto-cerebellar tumour. We made explantations from 5 patients and 4 gave satisfactory growth in tissue culture. One explantation of the cerebellum was unsuccessful.

After removing the tumour tissue we placed it in physiological saline solution and kept it in a $+4.0°C$ refrigerator till explantation. The explantations were carried out 12—48

hours after the operation. Even after 48 hours' storage there was no reduction in proliferative activity. In three cases we made an attempt to explant the material after 72, and 96 hours storage on ice but obtained no growth.

We made tube-, and Maximow cultures. The plasma clot consisted of cockerel plasma and 7-day chick embryo extract. The supernatant consisted of 50 per cent human serum, 45 per cent Tyrode solution and 5 per cent chick embryo extract. We changed the fluid phase weekly.

The cultures were studied as living and as stained preparations. We prepared the cultures taking in consideration the latent period of growth and treated them accordingly. The observations lasted for 36 days. After fixing the cultures in methylalcohol we stained them with May—Grünwald—Giemsa solution. We made a hundred cultures from one specimen.

To evaluate the cultures we observed the morphological character of the cells, the latent period of growth, the mitotic activity, further the intensity of clot liquefaction.

The operatively removed tumour tissue was prepared according to the classical neuropathological methods. The histological diagnosis was performed after thorough examinations of the whole removed tumour tissue, — from time to time employing different methods — independently from the culture results.

Results

Clinical data

Some clinical data of the patients whose tumours were employed for explantation are reviewed in Table I.

Table I

	Average period of history till admission	Localization	Operative findings	Operative mortality	Post-operative survival after 12 months
Astrocytoma 4 cases	27.5 months	frontal: 2. frontopar.: 2	circumscribed not bleeding, congested, yellowish-white	∅	4
Astrocytoma malignum 4 cases	7 months	frontal: 2 parietal: 2	the same	∅	4
Glioblastoma 13 cases	6.5 months	frontal: 1 parieto-occip.: 5 temporal: 7	infiltrative, bleeding, soft, suctionable greyish-red	3	5

It appears from Table I that the data of the astrocytoma and glioblastoma groups display marked differences, while the astrocytoma malignum group as well as the indicated data appear to occupy the intermediate position between the first mentioned two groups. There is a conspicuous difference in the anamnestic periods, as between the operative mortality and survival. The location of the tumour and its macroscopic appearance also parallel the

biological differences between the two tumour groups. The history of the astrocytomic patients was a characteristically slow progressive one and at the time of operation they were in relatively good general condition without signs of severe intracranial pressure. Simultaneously the glioblastomas nearly in every case displayed a fast progressive clinical pattern with severe symptoms.

Histology

a) *Astrocytoma*

The 4 gliomas in the most benign group were histologically characterized as follows: isomorph structure, consisting of astrocyte type cells. The nuclei

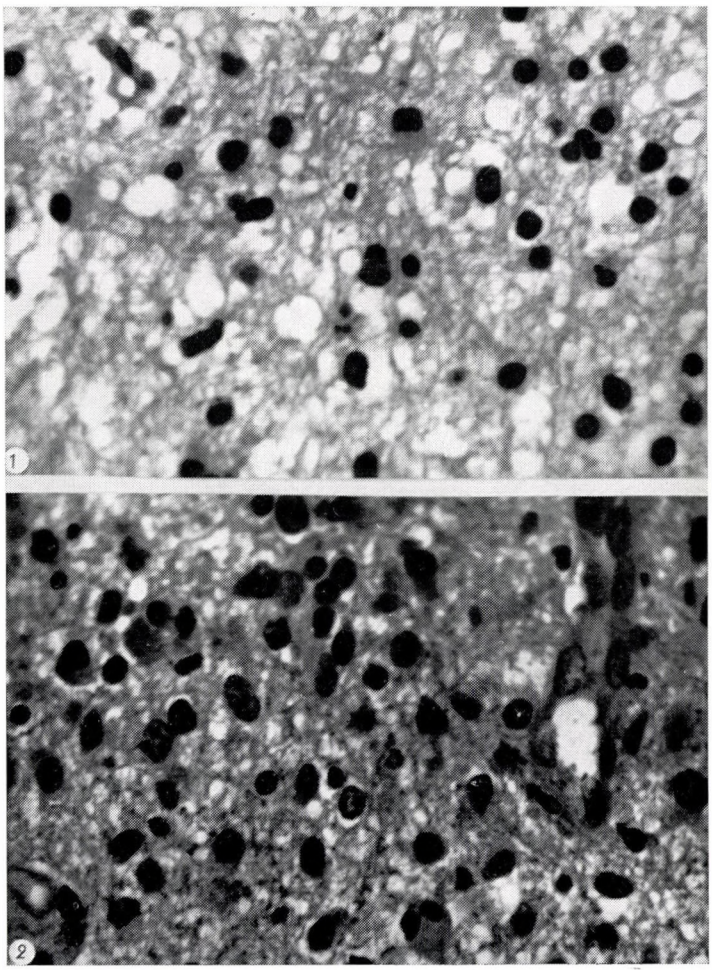

Fig. 1. Astrocytoma, section stained with haematoxylin-eosin
Fig. 2. Astrocytoma malignum, section stained with haematoxylin-eosin

are isochromatic, the basic structure loose and rich in fibres and generally poor vascularly (Fig. 1). In some cases here and there as a degenerative sign there is microcytic degeneration, generally with a moderate peripheral reaction.

b) *Astrocytoma malignum*

We ranged four other tumours in this group. The cells are in the majority of cases mature in type, rich in fibres, isochromatic astrocytes. In slight degree symptoms pointing to malignancy were also to be found in the former category but here they are greater and more explicit: density of cells is variable and amounts to four times of that of the normal. Large numbers of protoplasmic astrocyte types are to be found. The richness of vessels surpasses those of the former group and as a marked difference, proliferation of the capillary endothelium appears (Fig. 2).

c) *Glioblastoma*

From the 13 tumours proved to be glioblastoma 3 are mostly of fusiform cells, 2 are those of the round cell type, the rest according to the interpretation of ZÜLCH are of the multiform (gigantocellular) glioblastoma type. According to the classification of BUSCH–CRHISTENSEN the structure characterized as angionecrotic was observed in one of the tumours of the round cell group and in one of the multiform group.

The glioblastoma category is characterized by several signs pointing to malignancy and anaplasia, also an inclination for necrosis. Density of cells four-five times the normal and often extraordinarily varying from one visual field to the next. Within the wide scale of polymorphism mainly the anaplastic and polychromatic changes of the nucleus can be observed: giant cells with one or more nuclei, the nucleo-plasmic shifting markedly in favour of the nucleus, atypical mitoses (Fig. 3). Pathological changes of the vascular bed are also conspicuous, with extreme proliferation of the endothelium.

Tissue culture

a) *Non-tumorous glia.* The glial cells of the non-tumorous white matter show very slow growth in explantation. The latent period was 14—28 days. The outgrowing cells form a slack mesh-work (Fig. 16). As for their shape we can distinguish two types of cells: small cell bodies, with small nucleus and few short branching processes, which remind us of the oligodendro-gliacell; and the cell resembling the astrocyte type: larger cells with long, fine branching processes (Fig. 17). The nuclei in general are of the same size, orthochromatic, round or oval shaped. The proliferation of endothelium is not conspicuous. Round the explant there is a narrow zone of liquefaction. Mitosis occurs only sporadically. Granular plasmatic macrophages can be seen among

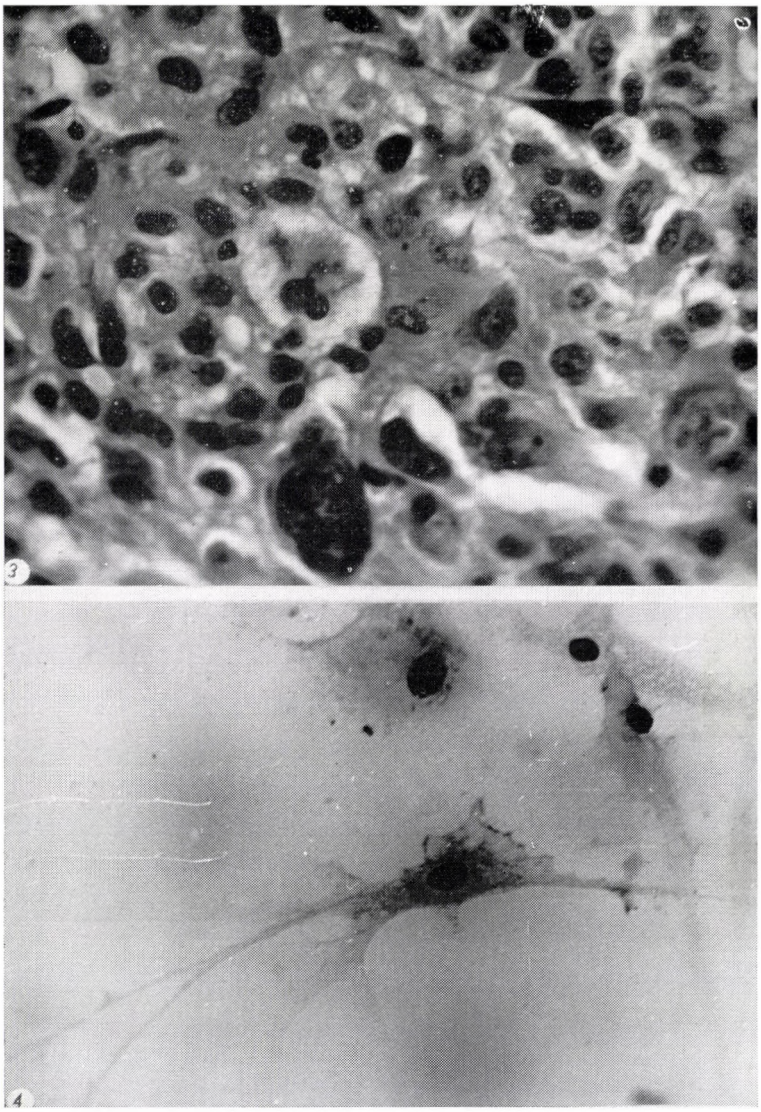

Fig. 3. Glioblastoma, section stained with haematoxylin-eosin
Fig. 4. Astrocytoma culture of 7 days, stained with MGG

the glia individuals, further there is a fibroblastic growth of the perivascular connective tissue.

b) *Astrocytoma.* The outgrowth zone is characteristically isomorphic. Multipolar and bipolar cells dominate the picture (Figs. 4, 5). These are mononucleated cells, the plasma processes are very long. There are a few cells with hardly stained nucleus, the border of plasma dissolves into the surroundings

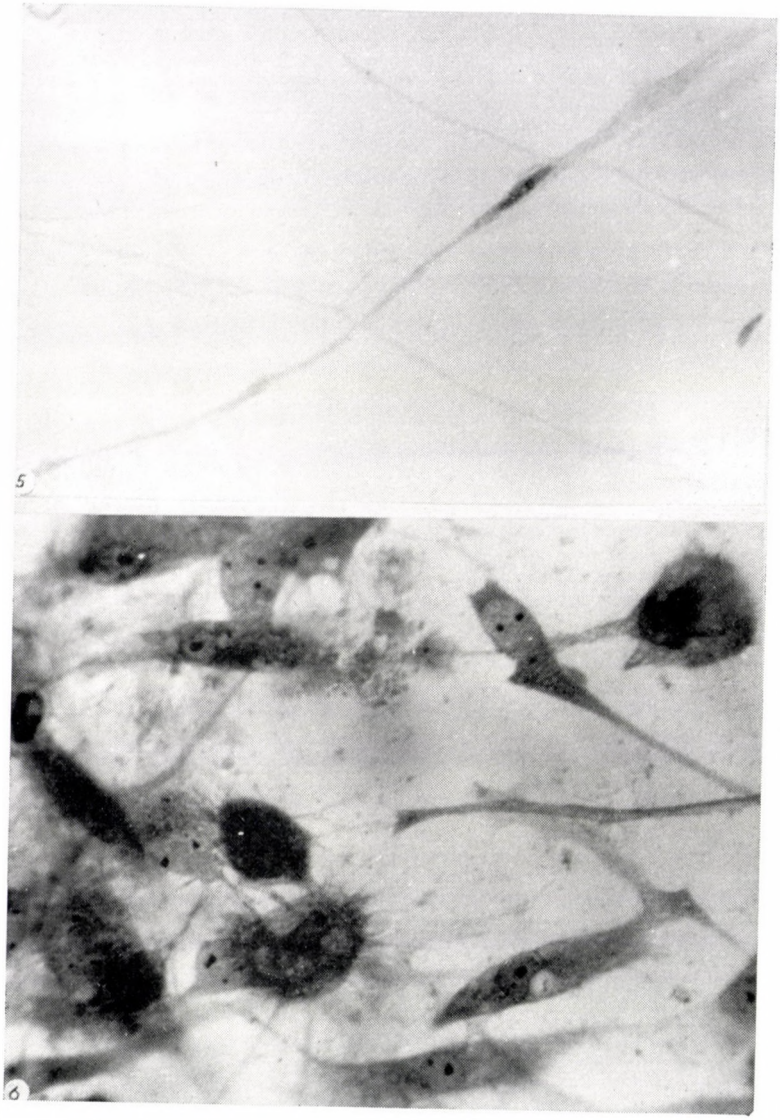

Fig. 5. Astrocytoma culture of 17 days, stained with MGG
Fig. 6. Astrocytoma culture of 30 days, stained with MGG

(Fig. 6). The capillary endothelial proliferation becomes marked in the older cultures (Fig. 7). Under such circumstances there is a very rich capillary network in the loose structure of the explant. The glial elements can be well observed at the beginning of growth, but their growth activity decreases and thus the endothelial proliferation overgrows and frequently covers them. The explant is surrounded with a narrow liquefaction zone. The glial elements

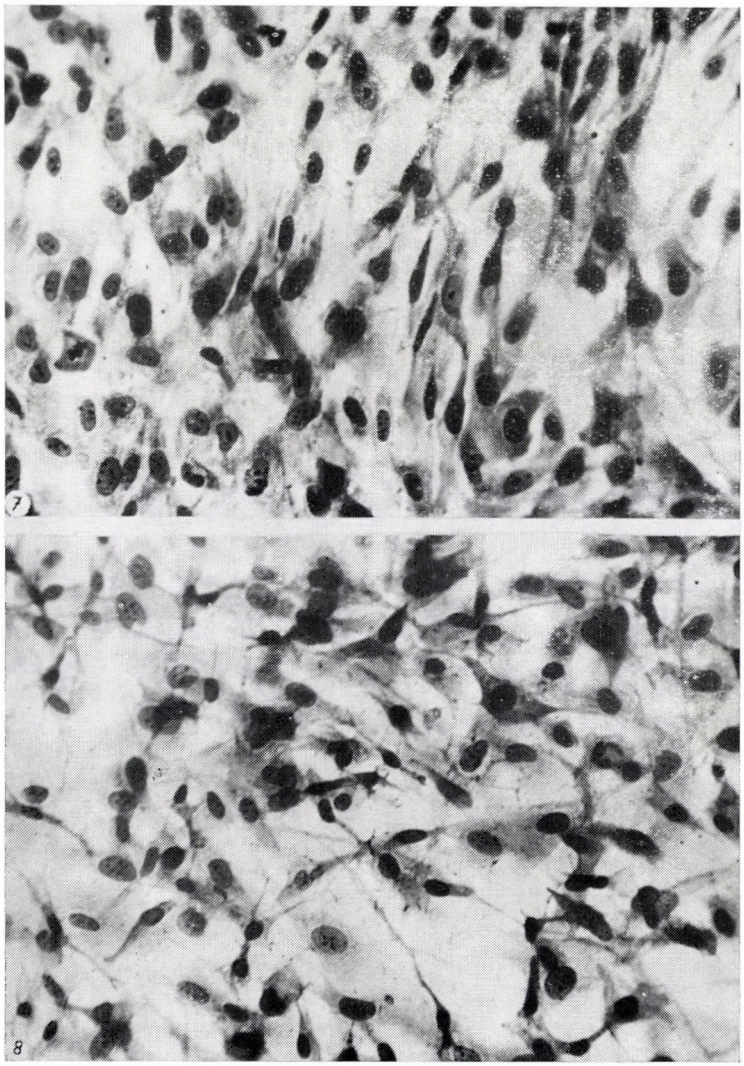

Fig. 7. Astrocytoma culture of 30 days, stained with MGG
Fig. 8. Astrocytoma malignum culture of 10 days, stained with MGG

in the growth zone show a small degree of mitotic activity, no atypical cellular division can be observed. There is only a slight difference between the morphological character of the normal, non-tumorous glial elements and the astrocytoma cells in tissue cultures. The intensity of the outgrowth of the normal glia, however, is much less, which is manifested in the long latent period. The normal, human glia cells begin to migrate only after the second week, while from the astrocytoma a more intensive cell proliferation is observable.

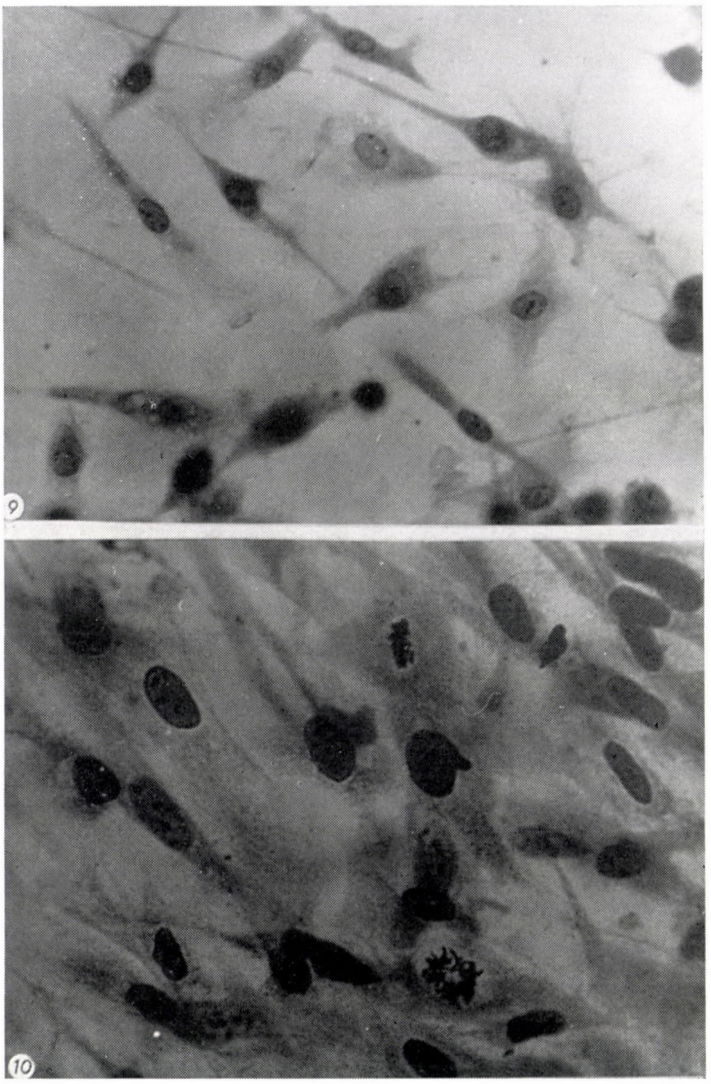

Fig. 9. Astrocytoma malignum culture of 10 days, stained with MGG
Fig. 10. Astrocytoma malignum culture of 10 days, stained with MGG

c) *Astrocytoma malignum.* The tumour begins to grow 5—14 days after the explantation. The nuclei are isomorphic, while the morphology of the cytoplasm is very variable (Figs. 8, 9). The cells are richer in plasma, bear many processes, with borders blurred (Fig. 10). Besides these large cells with several processes there are many fusiform and round cell bodies observable as well. The large plasmatic cell with two nuclei is frequent. The nuclei are round, oval shaped. Hyper- and hypochromatic nuclei can be observed alike. During

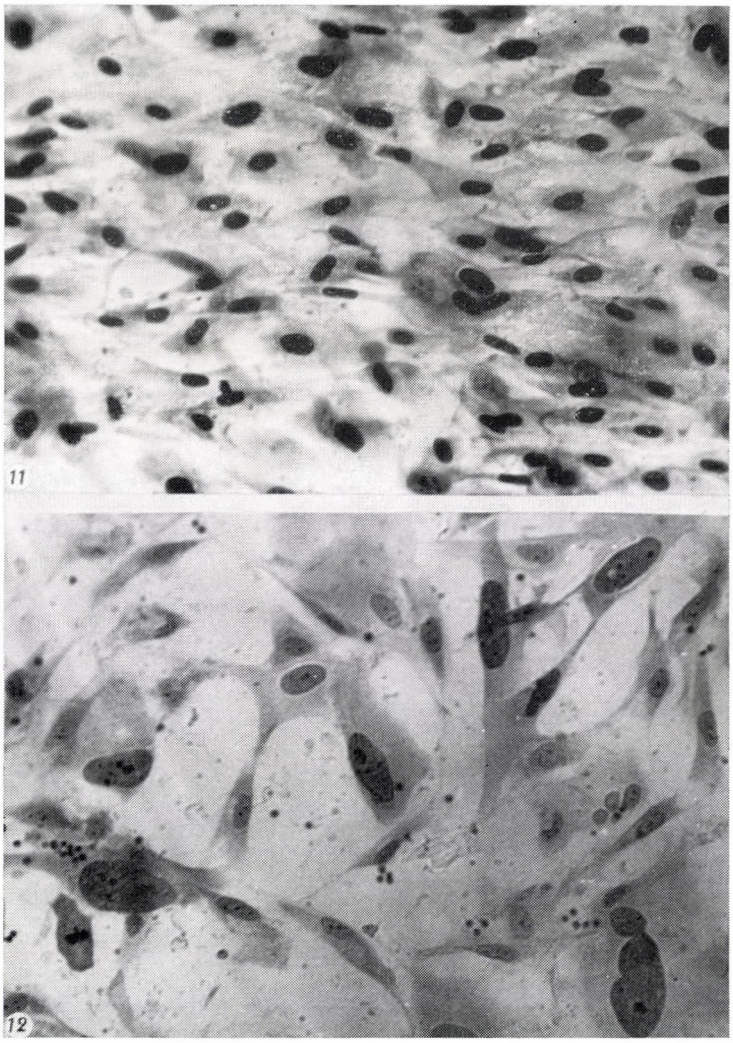

Fig. 11. Astrocytoma malignum culture of 32 days, stained with MGG
Fig. 12. Glioblastoma culture of 13 days stained with MGG

cultivation the glial elements are predominant for a long time. The capillary endothelium, as well as the perivascular connective tissue show more intensive growth only in older tissue cultures (Fig. 11). A large liquefaction area is observable round the explant already at the beginning of the explantation. Besides the normal mitoses a few atypical divisions can also be seen.

d) *Glioblastoma.* Growth begins within 2—6 days. The polymorphism of the cells is very conspicuous. Not only the cytoplasm shows large variations but the nuclei also show large differences in shape (Figs. 12, 13). A great number

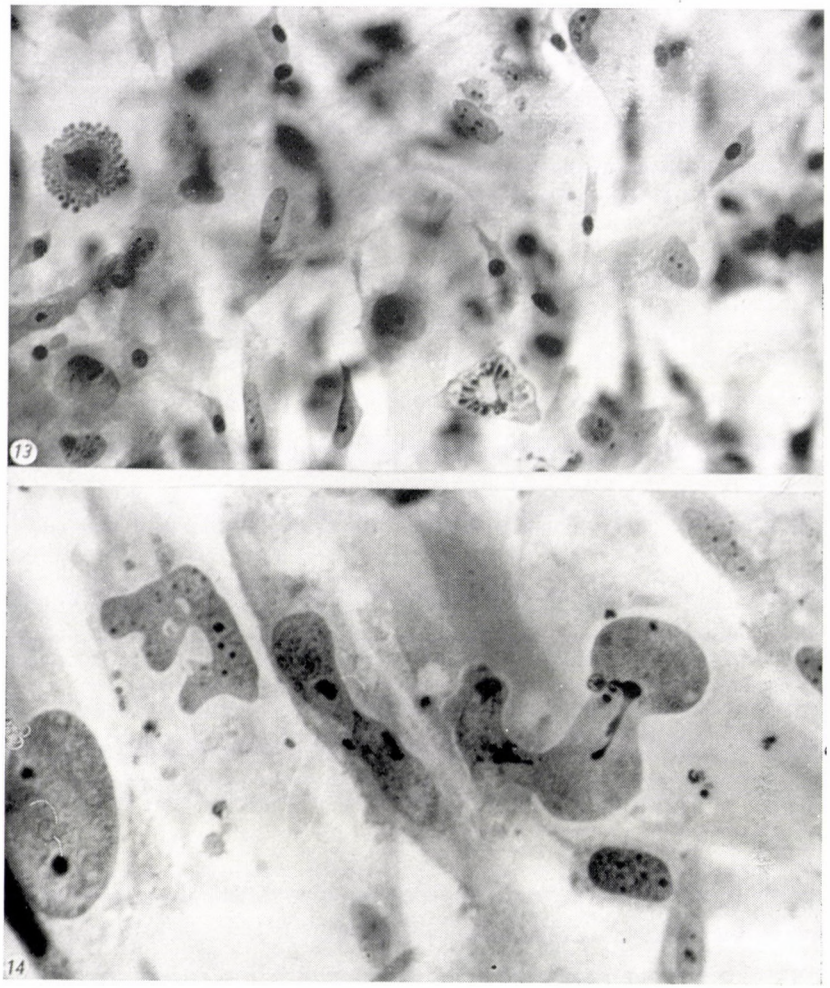

Fig. 13. Glioblastoma culture of 6 days stained with MGG
Fig. 14. Glioblastoma culture of 13 days stained with MGG

of cells with several nuclei giving the impression of a giant cell also appeared. The nuclei are crescent, oval, round or lobulated with distributions of chromatin material varying from fine dust to rough clumps. Structureless dark-stained nuclei can also be observed. The liquefaction zone is very marked and very conspicuous shortly after explantation. Among the mitotic cells there are many atypical cell-divisions (Fig. 14). The old cultures maintain their polymorphism on a large scale (Fig. 15).

Within the glioblastoma group the histologically separated fusiform, small, round, further multiform cell types can be distinguished also in the

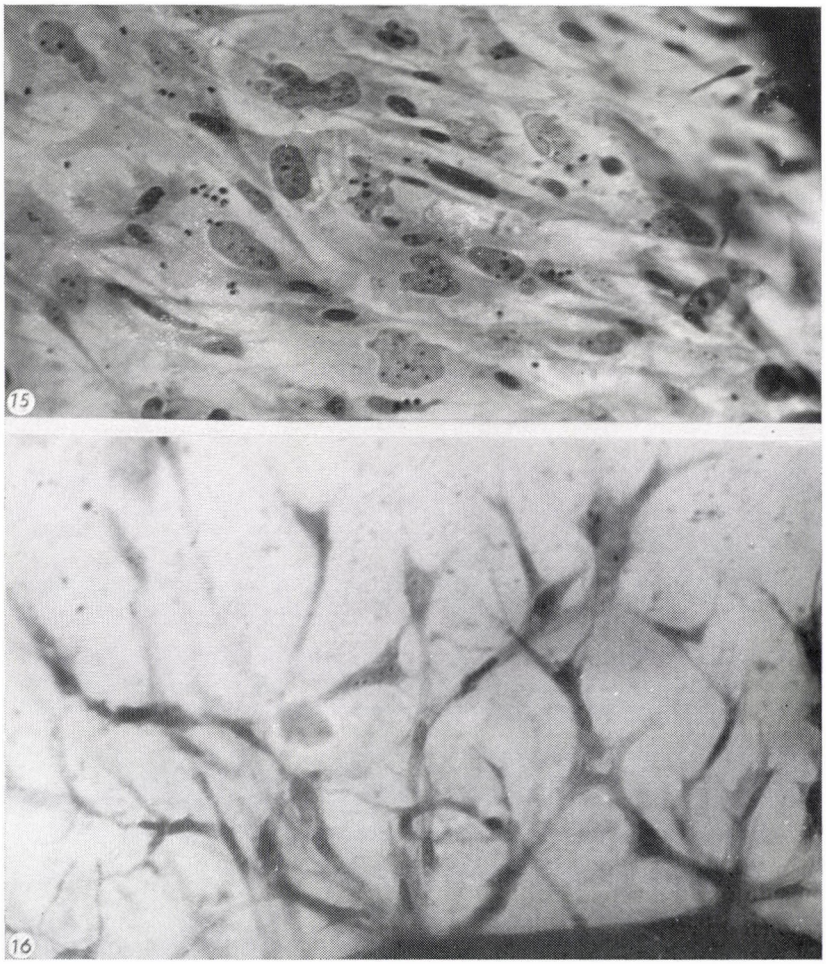

Fig. 15. Glioblastoma culture of 32 days stained with MGG
Fig. 16. A 13 days' culture of the white matter of a normal human brain stained with MGG

culture, but the cell types of the tissue cultures do not closely parallel the histological classifications. Thus the histologically proved fusiform cell type of glioblastomas show similar cell morphology in the culture. Among those glioblastomas, however, which showed the small round cell type or multiform characters histologically, several offered a preponderance of fusiform cells in the tissue cultures. The multiform type in the cultures corresponded mostly with the histological picture; some showed rather dominant small round cell proliferation. The tumours belonging to the little, round cell group histologically, however, showed always a growth of fusiform cells.

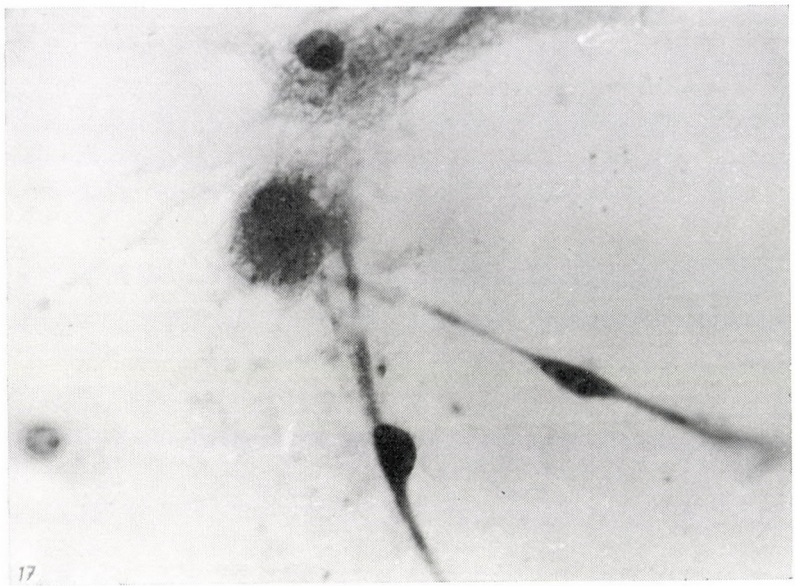

Fig. 17. A 13 days' culture of the white matter of a normal human brain

Discussion

In our experiments we used human brain and human tumours of the glioma type to study the tissue cultures. We know those glial cell types from the literature that appear in the cultures of the animal or human brain [3, 23, 27, 30, 33, 5, 15, 16, 28, 29]. We deemed it necessary to examine the non-tumorous human glial cells, partly in order to compare them with the described cell types in the former communications, partly also for the evaluation of our own tumour cultures. Several authors have pointed out that different methods and media used for cultures influence the results.

Naturally the question of cell dedifferentiation also emerges. The deficiency of the tissue cultures is in general that we do not examine the tissue in the organism. Thus the examination takes place without the mutual humoral and neural effects. That observation that the histotypical growth of the organisms promotes dedifferentiation of the cells in the tissue cultures probably concerns our experimental material as well. According to KUHLENBECK [22] in the glia cultures the dedifferentiated cells are of neoplasmatic character, namely the normal biological space becomes restricted and perhaps the neoplastic growth bears the same reason. Thus some authors presume that there is a comparison between the growth of tumours and normal tissue in vitro. In our glioma cultures of long duration we did not find the cell picture to be homogeneous. Some groups preserved their growth and morphological characters, whereas progressive differentiation should lead to cell homogeneity. As is

well known from the studies of KERSTING [18, 19] meningioma tissue dissociated by trypsin displays in vitro reorganization of the concentrical formations characteristic of the tumour. After trypsin treatment, tumours of animal origin show the characteristic reorganization of the original tissue. We believe therefore that the basic biological changes which represent the deviation of cells towards the tumorous character are operative also under tissue culture conditions.

We observed the cell shapes in the tissue culture of the white matter of five human brains. The fibroblasts arising from the perivascular connective tissue are well discernible in stained preparations and are fusiform, oval nucleated cells and when spread may assume a histiocyte shape. There are many mitotic cells and in the cultures after two weeks vacuoles appear as a sign of degeneration. We deem these cells similar to the former ones with granular cytoplasm to be macrophages, which partly take origin from microglia elements and partly connective tissue. We could not separate these from one another. We ranged the glia cells in four type groups according to their shape. Oligodendroglia type: bulky cells with short processes. Bipolar type: elongated cells with pointed ends, with extended oval nuclei. Multipolar type: large-bodied cells, with bulky processes and large nucleoli; and cells with several nuclei. Astrocyte type: large-bodied, rich in cytoplasm; fine cells with many branching processes.

We found in our tissue cultures belonging to the glioma group all the cell types which we observed in our non-tumorous white matter explantations. Nevertheless the latent period of the glioma tissue in comparison to the normal glia, became markedly short, the activity of proliferation markedly increased and the richer growth zone far richer.

There is only a little difference between the shape of cells in the normal glia cultures and of the cells of an astrocytomic tumour. Proliferation is remarkable and the increase of cell population is conspicuous in the astrocytoma cultures, also the shortening of the latent period of growth. At the same time the nucleus of the cell and the shape of the cytoplasm are essentially similar to the normal glia cells; the cell picture is isomorphic.

The cell picture of the astrocytoma malignum group shows a marked polymorphism. The cells do not display the bi- or multipolar arrangement, but show varied shapes. The nuclei are isomorphic, but already atypical scatterings of chromatin can be observed. Proliferation is increased in comparison to the former group and the liquefaction zone is more marked.

The glioblastoma cultures not only show a marked increase of proliferation activity, richness of cells and the shortening of the latent period of growth, but the polymorphism is characteristic of the cytoplasm and especially of the nucleus. The increased number of atypical mitoses and the intense liquefaction can be considered likewise as a sign of increased malignancy.

The difference is greater between cultures of the malignant astrocytoma and the glioblastoma than between the normal mature astrocytoma and malignant astrocytoma cultures. While a gradual progression can be followed in the cell picture of the astrocyte (astrocytoma) and astrocytoma malignum cultures — a qualitative change of character becomes apparent based on the properties of the nucleus in the glioblastoma.

HOGUE [15] found primitive "glioblasts" only in very young human embryo cultures, which displayed a similarity to fibroblasts, but were smaller; extended and granular, they have no long, thin processes. In our cultures we did not find a form corresponding with the embryonic glia cells, not even in our glioblastoma cultures. The glioblastoma cells display such a great difference from the glia cells in any stage of development — even from the neoplastic cells, with which we were acquainted in the astrocytoma — astrocytoma malignum grade that it seems reasonable to presume that there is an independent category within the glioma group. The described graduations within the astrocytoma group on the other hand seem to confirm the theory that the tumorous transformation is set off by an unknown stimulant in the intact mature glial individuals [26, 34].

The biological features of the tumor cells are dominant in the tissue cultures as they cannot be in classical neuropathology methods. In the classification debate of modern neuropathology the tissue culture method no doubt offers help, however, without being suitable alone to settle the dispute. From our observations up to now we deem KERNOHAN's grading system only justified in the astrocytoma – astrocytoma malignum group; it does not seem proper to classify the glioblastoma simply as a more malignant grade of tumour. It appears reasonable to separate the glioblastoma form in the future as an independent group since probably qualitatively different factors play a role in their genesis, while in the astrocytoma—astrocytoma malignum grades there is presumably a rather linear quantitative relationship in biological characters and genetic factors.

Summary

The authors during their examinations so far have made tissue cultures from 107 assorted human brain tumours. The present communication renders account of the tissue culture results from 21 tumour specimens belonging histologically to the astrocytoma—glioblastoma group. Observations of the biological and cytological phenomena in the tissue cultures are used in an attempt to provide data for the neuropathological classification. Results agree with KERNOHAN's classification in the astrocytoma—astrocytoma malignum group, but do not support the idea that glioblastoma multiforme represents simply a further degree of malignancy. The observations offer grounds for segregating this latter tumour in an independent group.

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DAS VERHALTEN DER GLIOME IN GEWEBEKULTUREN I. GRUPPE ASTROCYTOM-GLIOBLASTOM

I. PÁLYI, D. ÁFRA und E. CSANDA

Es wurden 107 Gewebekulturen aus humanen Hirngeschwülsten verschiedener histologischer Struktur untersucht. In der vorliegenden Mitteilung wird über die Ergebnisse der Gewebezüchtung aus 21 — histologisch in die Astrocytom-Glioblastom-Gruppe gehörenden— Geschwülsten berichtet, mit besonderer Hinsicht auf die Fragen der neuropathologischen Klassifikation. Anhand der bisherigen Ergebnisse scheint die Kernohansche Klassifikation in erster Linie für die Astrocytom-Glioblastom-Gruppe zweckdienlich zu sein.

Die Annahme, daß das Glioblastom uns einen weiteren Malignitätsgrad darstellt, wird durch die bisherigen Kulturversuche nicht unterstützt, vielmehr scheint die Absonderung des Glioblastome multiforme als selbständige Tumorgruppe auch weiterhin zweckmäßig zu sein.

ПОВЕДЕНИЕ ГЛИОМ В ТКАНЕВЫХ КУЛЬТУРАХ I. ГРУППА АСТРОЦИТОМЫ-ГЛИОБЛАСТОМЫ

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В ходе своих исследований авторы изготовили тканевые культуры из 107 человеческих опухолей головного мозга различной гистологической структуры. В настоящей статье они сообщают о результатах тканевых культур 21 опухоли, цитологически причисляемых в группу астроцитом-глиобластом.

Исследованием биологических и цитологических явлений, наблюдаемых в тканевых культурах, авторы хотели предоставить данные для выяснения вопросов невропатологической классификации. На основании полученных результатов, распределение по ступеням, предложенное Керноханом, кажется применяемым прежде всего для группы злокачественных астроцитом-глиобластом.

Выделение опухолей с диагнозом глиобластома, в качестве новой ступени злокачественности, не подкрепляется результатами экспериментов по тканевой культуры, но обособление **glioblastoma multiforme** как самостоятельная группа опухолей кажется более обоснованным.

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