CEREBRAL ASTROCYTOMAS AND THEIR DERIVATIVES

H. J. SCHERER, M.D.

(From the Department of Pathology, Bunge Institute, Antwerp, Belgium)

That the biological behavior of those tumors classified as cerebral astrocytomas—in opposition to the more perfectly studied cerebellar forms—is not at all clear, has been pointed out by Cushing (23, 24). Cairns (14) recently emphasized the considerable variations in rapidity of growth of these tumors, a phenomenon that is entirely unexplained. As the astrocytoma is considered by the majority of authors to be one of the most frequent brain tumors, the problem has a considerable practical importance.

A critical review of the recent literature reveals the existence of a large number of quite opposite opinions in respect to the clinical, biological, and pathological characteristics of the astrocytoma group:

(1) The relative frequency of astrocytomas among gliomas shows a surprising variation from one author to another. According to the statistics of Cushing, Bailey (4), and many others, astrocytomas are more frequent than glioblastomas, while Bergstrand (9, 10), Carmichael (15), Courville (20), Cox (22), Elsberg (26), Gagel (31), and Peers (45) have found many more glioblastomas than astrocytomas.

(2) While Bailey, Cushing, Penfield (28), McLean (40) and others consider very slow growth as one of the outstanding clinical characteristics of astrocytomas, Cox (22), Chiovenda (17), and Collins (18, for temporal lobe tumors) failed to find a much longer average duration than for glioblastomas. Cushing (23) and Alpers and Rowe (1) distinguish astrocytomas of rapid (cellular and piloid types) and of slow evolution.

(3) Cushing (24) and Bailey (4) as a result of their more recent studies consider the location essential for a clinical and a biological evaluation, regarding the cerebellar tumors as favorable and those in the cerebrum as less favorable; they do not attach special significance to the fibrillary or protoplasmic character. Their earlier classification (7), as fibrillary and protoplasmic astrocytomas, is still applied by others, who continue to disregard localization (Hortega, 35; Alpers and Rowe, 1; McLean, 40).
Some believe that cerebral astrocytomas always grow diffusely (Stroebe, 63; Waggoner and Löwenberg, 66), while others (Roussy and Oberling, 48; Eisenhardt, 25; Russell, Krayenbühl, and Cairns, 51; Courville, 20; Zülch, 67; Bailey and Ectors, 8) recognize both diffuse and circumscribed growths. No one, however, has attempted to separate the two groups or to determine their relative frequency. Recently Foerster and Gagel (30) went so far as to deny the existence of diffuse astrocytomas in the hemispheres!

Many authors limit the term astrocytoma to tumors with a very widely scattered cell distribution (Bailey and Cushing, 7); others include highly cellular tumors (Alpers and Rowe, 1) with abundant mitoses (Cushing, 23).

It is a general belief that astrocytomas show no necrosis, but a small group of observers (Waggoner and Löwenberg, 66; Alpers and Rowe, 1; Peers, 45) have included in their astrocytoma studies tumors with extensive necrotic areas.

The significance of the different histologic types of astrocytoma, as described by Roussy and Oberling (48), Penfield (46), Elvidge, Penfield and Cone (28), Alpers and Rowe (1), and others, is by no means established. Penfield's "piloid astrocytoma" is considered by some as identical with the fibrillary astrocytoma, while others (Bergstrand, 10; Cox, 22; Russell and Bland, 49) tend to identify it with the spongioblastoma polare. The differential characteristics between astrocytoma, astroblastoma and polar spongioblastoma are not clearly determined.

Among the most important questions under discussion are whether astrocytomas are able to dedifferentiate into glioblastomas, as is suggested by Bailey (4, 5) and denied by Cushing (24), and further, whether or not surgical treatment is able to determine such a malignant transformation (Tooth, 64; Globus, 32; Müller, 42; Scheinker, 53).

These examples are suggestive of the numerous problems requiring further study. The contradictions in the literature are due to the variety of methods used by different authors; there is, for instance, a sharp difference in opinion between those who have studied necropsy material exclusively (Carmichael, 15; Courville, 20; Cox, 21; Peers, 45; Waggoner and Löwenberg, 66) and those whose observations have been predominantly on biopsy material. Alpers and Rowe (1) based their conclusions on the cytological study of small sections of 128 cases, while Waggoner and Löwenberg (66) made a localization study of 12 necropsy cases, using Weigert-stained hemisphere sections without detailed histologic examination.

Our purpose is a better approach to the biological behavior of astrocytomas by a "complete" macroscopic and microscopic study of adequate cases, with equal emphasis on extension, limitation, modes and evolutionary stages of growth and structure (Scherer, 55, 56), cytologic variations, differences of cellularity, regressive changes, and localization in each case. The important problem of the transition from astrocytoma to glioblastoma will be especially dealt with. As we agree with the authors (Bailey, 4; Cushing, 24; Bucy and Gustafson, 13) who make a strict distinction between cerebellar and cerebral astrocytomas, and as the contradictory opinions in the literature concern especially the latter, this paper is limited to astrocytomas of the cerebral hemispheres.
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Material and Methods

The cases were chosen from a necropsy series of 125 gliomas which were completely studied by means of large celloidin sections. Blocks 15 mm. thick were cut, including the whole tumor from its frontal to its occipital end with the surrounding tissues. One thin but large block was sacrificed for frozen and paraffin sections. As each block was deeply cut from both sides, the method approximated an incomplete serial section study. A large number of apparently unchanged areas of the brain were also examined. Sections were stained by the Nissl, van Gieson and Achúcarro (celloidin sections) and by the Spielmeyer, Holzer, Cajal-Globus gold sublimate, Scharlach red and Bielschowsky (frozen sections) techics.

Celloidin sections were cut 20 μ thick to make possible a comparison of the cellularity of all cases. This was determined by counting the cells, with a magnification of 620, in a field corresponding to 0.1 sq. mm. In each instance at least ten different fields were counted and at least one field was photographed in order to allow objective control. The photographic method was also used in order to determine objectively variations in the proportion of different cell types encountered in these tumors.

Frequency of Cerebral Astrocytomas

Our series of 125 necropsied gliomas contained 94 tumors of the cerebral hemispheres; only 18 of these were astrocytomatous, and of this number only 5 were entirely "pure" astrocytomas. In 4 cases "complete" histologic examination revealed circumscribed areas of glioblastoma; in 4 others such large glioblastoma areas existed that the dual structure of the tumor had already been recognized macroscopically; 5 cases characterized by identical localization showed a more diffuse transition into glioblastoma. Between the two last groups, all grades of transition are seen. In 3 additional cases the primary astrocytic character was doubtful.

It must be emphasized that the designation "pure" astrocytoma does not imply that the glioma in question contains exclusively astrocytic elements: we have never seen such a "pure culture" tumor. The name indicates only the absence, in spite of complete examination, of areas which must be considered on the whole as formed by glioblastoma tissue; it does not exclude the presence of isolated cells of immature appearance or doubtful histogenesis, scattered throughout the tumor. Such cases are certainly identical with the cerebral astrocytomas of the literature.

As a detailed morphological description of all cases would be much too extensive, we have summarized our descriptions according to the four groups mentioned above, devoting the greater part of the text to an analysis of the general results obtained.

The Pure Astrocytomas

Case 214/34: Female, 36 years.
Duration of symptoms: 5½ years. Partial extirpation 2½ years before death.
Weight of brain after fixation: 1,590 gm.
Localization and extent of tumor: Diffuse bilateral lesion, predominantly left-sided,
involving left centrum ovale (especially parietal; occipital and frontal in less degree), left internal capsule, corpus callosum, large parts of right centrum ovale.

Cytology and fiber formation: Uniformly "pure" astrocytoma, rather polymorphous; partially "gemistocytic." Highly fibrillar parts in white matter, cortical parts afibrillar.

Average cellularity (0.1 mm.): About 70.

Mode of growth: Diffuse, without any limitation; predominantly in white matter. No intrameningeal growth.

Structure: Entirely amorphous, except local surface growth. No secondary structures. Preexistent structures: Nerve cells, myelin sheaths, nerve fibers preserved for long time; disappear without secondary structures.

Mesenchymal stroma: No vascular proliferation; moderate capillary vascularity.

Degenerative changes: Extensive microcystic degeneration. No necrosis. No large cysts. No calcification.

CASE 250/36: Male, 46 years. Fig. 9, A.

Duration of symptoms: About 4 years. Postoperative death.

Localization and extent of tumor: Diffuse infracallosal, unilateral, involving basal parts of the left occipital and temporal lobes, basal lateral parts of left basal ganglia and insula.

Cytology and fiber formation: Uniformly "pure" astrocytoma, only slightly fibrillary.

Average cellularity (0.1 mm.): 90-103.

Mode of growth: Diffuse infiltrative, predominantly in white matter. No intrameningeal growth.


Degenerative changes: Circumscribed microcystic degeneration. No necrosis. No large cysts. No calcification.

CASE 137/37: Female, 45 years. Figs. 3 and 6, A.

Duration of symptoms: About 9 months. Postoperative death.

Weight of brain after fixation: 1.510 gm.

Localization and extent of tumor: Entirely diffuse. macroscopically "invisible" process of the right hemisphere, involving especially the convexity from the frontal to the occipital lobe, right thalamus, striatum, internal capsule, corpus callosum, left striatum, pons.

Cytology and fiber formation: Uniformly "pure" astrocytoma, rather polymorphous. Partially fibrillar, partially afibrillar.

Average cellularity (0.1 mm.): 60-75.

Mode of growth: Primarily diffuse, infiltrating, without any predilection for gray or white matter. No intrameningeal growth.

Structure: Completely amorphous. No secondary structures. Preexistent structures: Nerve cells, myelin sheaths, nerve fibers preserved; disappear finally without secondary structures.

Mesenchymal stroma: No vascular proliferation, no increase of vascularity.

Degenerative changes: Beginning microcystic transformation in one place. No necrosis. No large cyst. No calcification.

CASE 251/37: Male. Figs. 6, D; 9, B.

Duration of symptoms: About 10 years. Partial extirpation 6 years before death.

Localization and extent of tumor: Diffuse infracallosal process of the left frontal and temporal lobes, left basal ganglia and commissura anterior, extending to the right side.

Cytology and fiber formation: Uniformly "pure" small-cell astrocytoma, slightly polymorphous. Only slightly fibrillar.

Average cellularity (0.1 mm.): Variable. In some parts 90-110; in others 140-155.

Mode of growth: Diffuse, infiltrating, in certain places respecting the cortex, in others not. No intrameningeal growth.

Structure: Completely amorphous. No secondary structures. Preexistent structures: Nerve cells, myelin sheaths, nerve fibers preserved. Mesenchymal stroma: No vascular proliferation; only slight increase of vascularity.

Degenerative changes: Very extensive microcystic degeneration. No large cysts. No necrosis. No calcification. Hyalin fatty degeneration of the walls of some large vessels.
CASE 89/38: Male, 48 years. Fig. 5.
Duration of symptoms: 6 months. Roentgen therapy. Death from perforated gastric ulcer.
Weight of brain after fixation: 1,655 gm.
Localization and extent of tumor: Unilateral, rather diffuse; right frontal lobe (especially F II and F III), anterior basal ganglia, insula.
Cytology and fiber formation: Typically "gemistocytic," highly fibrillary "pure" astrocytoma.
Average cellularity (0.1 mm.²): 40.
Mode of growth: Diffuse infiltrating, in white and gray matter. Slight intrameningeal growth.
Structure: Completely amorphous. No secondary structures.
Preexistent structures: Myelin sheaths and nerve fibers preserved for long time; ganglion cells disappear rather rapidly.
Mesenchymal stroma: No vascular proliferation. Moderate diffuse capillary increase.

Degenerative changes: Microcystic degeneration. No large cysts. No necrosis. Focal calcification of capillary walls. Diffuse fatty infiltration of tumor cells (x-ray therapy!)

The morphologic characteristics of the "pure" astrocytomas must be considered separately, since they form the indispensable criterion for the diagnosis of the "mixed" tumors as primarily astroclymatous.

(a) The macroscopic appearance of the astrocytomas is characteristic. The description here given encompasses also the cases of Group II, which macroscopically differed in no way from the "pure" forms.
Cerebral astrocytomas have never in our experience appeared as circumscribed "tumors." Neither their boundaries nor the color or structure of the tumor tissue make it possible to distinguish them clearly from the surrounding normal brain substance. As a general rule, the degree of recognizability as a tumor is proportionate to the extent of degenerative change which has taken place (Fig. 1); in the complete absence of degeneration the tumor may be
invisible. In that case, one sees only a diffuse increase in volume, perhaps accompanied by an edema-like yellowish discoloration of the involved regions, the general architecture of which is fairly well preserved. In the absence of any delimitation it is impossible to say where an astrocytoma ends and normal tissue begins (Fig. 2). A comparison of the gross photographs with stained sections taken at the same level demonstrates the errors inherent in macroscopic observation.

The cortex undergoes changes in color and size: the color is clearer than normal and frequently yellowish instead of gray; at the same time the cortex is enlarged and the normally sharp boundary line towards the white matter disappears. In spite of these modifications the cortical areas of a tumor remain recognizable as cortex for a long time.

In the white matter, the astrocytoma appears generally as a very large unlimited area of more transparent, slightly grayish, homogeneous, sometimes edematous aspect (Fig. 2), whose consistency, compared with the normal brain, may be diminished or increased. In most cases this aspect is modified, at least in certain parts of the tumor, by the appearance of numerous minute cysts (Fig. 1), which create a sponge-like aspect. Much rarer (only once in our material) is the appearance of a single large cyst (Fig. 2). Necrosis was never encountered. The generally accepted opinion that fibrillary astrocytomas are always hard, and the afibrillary (protoplasmic) soft, was not borne out by our study; 2 of our most fibrillary tumors (214, 34, 89/38) were quite soft. Another of our observations is that old astrocytomas are generally much more visible than “young” ones. The only one of our cases which was macroscopically invisible was the one with the shortest clinical duration (nine months).

We confirm fully the classical descriptions given in the last century by Virchow (65), Rindfleisch (47), Stroebe (63), and Borst (12), and repeated later by Carmichael (15), Nevin (43, 44), and others: cerebral astrocytomas do not appear as “tumors,” but as diffuse neoplastic glia proliferations. As Virchow pointed out in 1864–65, there is an enlargement of the involved parts without deep disturbance of their architecture, so that the whole picture resembles “hypertrophy” much more than a neoplasm. Like Waggoner and Löwenberg (66), we never have seen a circumscribed astrocytoma in the cerebral hemispheres. The general rule, of high practical importance, that glioma growth is in most instances much more extensive than can be deduced from the macroscopic aspects (Scherer, 58, 59), is true of astrocytomas with even more constancy than of any other glioma group.

The absence of a circumscribed “tumor” probably explains why the extensive brain swelling so characteristic even of small glioblastomas is entirely lacking in brains harboring astrocytomas. This may account for the fact that the latter rarely reach the high weights often observed in brains with glioblastomas, although astrocytomas are generally much larger lesions.

(b) Extension, Size, and Growth Form: Complete microscopic study confirms the macroscopic impression that cerebral astrocytomas always show a diffuse spread through large areas of the brain. At least two lobes are practically always invaded, or one lobe together with the basal ganglia; frequently an entire hemisphere is involved. Growth through the corpus callosum or
anterior commissure into the other hemisphere is not less frequent. The degree of extension for every case is included in the brief case summaries. Sometimes there is evidence of coexistent multicentric growth, but this is rather rare.

Even with the most careful microscopic study it is impossible to determine exactly where the neoplasm ends and entirely normal brain tissue begins. The difficulty is increased by the low degree of cellularity, the wide extension of the tumor, and the "amorphous" arrangement of its cells, which do not assume any architectural pattern.

The diffuse character of astrocytomatous tumors, together with some other particularities of their morphological behavior, gives an important lead as to the pathogenesis of these neoplasms. If they were the result of a secondary extension of a primarily small tumor (as assumed by Waggoner and Löwenberg), we should expect to find a progressive decrease of cellularity from the central parts towards the borders. Furthermore, astrocytomas with a long clinical evolution would in that case be of larger average size than those in which death has occurred early in their course, the latter being still rather circumscribed. Our observations show exactly the opposite behavior: never did we find systematized differences of cellularity making it possible to recognize the center of these diffuse neoplastic processes; nor was the clinical course by any means proportionate to the tumor's size; finally, an extremely diffuse spread may be observed in cases which for clinical and anatomical reasons must be considered as comparatively early lesions.

Sections from such a case are reproduced in Fig. 3. This patient died postoperatively after a clinical duration of only nine months. There was an increase in size of the whole right cerebral hemisphere, but no tumor was
visible except perhaps in the anterior central region, where the cortex seemed enlarged, slightly discolored, and not well delimited from the underlying white substance; some extremely small cysts were also present, just at the limit of visibility. The complete microscopic study revealed a diffuse astrocytomatosus growth, involving large parts of the convexity of the frontal, temporal (Fig. 3, A), parietal (B), and anterior occipital cortex, as well as the centrum ovale, where the tumor became fibrillary (C), the thalamus (B), and the tegmentum, with growth through the enlarged corpus callosum on the other side. The cellularity is quite low in all parts (D).

It is quite impossible to explain those cases by unicentric growth; we must admit a primarily diffuse neoplastic overgrowth of the neuroglia of large parts of the brain, comparable to the behavior of lymphosarcomatosis. As there is absolutely no sharp limit between these very diffuse cases and the "smaller" astrocytomas, we consider this diffuse type of growth as characteristic of all cerebral astrocytomas, the only exception being perhaps the rare purely "gemistocytic" cases. The only example of this type encountered in our material was macroscopically no better limited than the other cases; microscopically, however, it showed a rather round shape, although it was very large and infiltrating.

As to the other cases, it is still doubtful whether there is a possibility of grouping them among the entirely diffuse or the somewhat more tumor-like cases. The same is true for the tumors with predominantly cortical or white matter growth. Owing to their diffuse character, this predominance, when encountered, is never sufficiently pronounced to allow a clear grouping.

Invasion of the meninges has not been encountered in our pure astrocytomas, except in the "gemistocytic" case.

(c) Cytology and Fiber Formation: As indicated by their name, astrocytomas are formed by astrocytes, at least "predominantly" or, as Bailey (5) recently stated, by "more or less" characteristic astrocytes." The astrocytic character of a cell may be recognized by the morphology of its nucleus, which is larger and clearer than that of the oligodendrocyte; by impregnation of its cytoplasm, the shape of which is very characteristic; or by its ability to form glial fibers. In most modern accounts of the morphology of the isolated cell elements the writers seem to be satisfied with the simple impression that the element in question is predominant, but do not speak of exact methods of proving this predominance or determining its exact proportion. Some authors, however, have felt that here lies a real problem requiring careful research. Thus, Bergstrand (10) found a large number of nuclei suggesting oligodendrocytes, which did not stain positively with Hortega's method for astrocytes, but sometimes showed a specific oligodendroglia impregnation. For that reason he doubts whether the name astrocytoma is really justified. Cooper (19) came to similar conclusions for a considerable percentage of his cases. Singer and Seiler (61) went so far as to deny the existence of astrocytomas, considering the fiber network as a merely reactive stroma. Other authors have described diffusely growing astrocytomas under other names because they were surprised by the high percentage of elements which were unquestionably not astrocytic (Nevin, 43, 44, and many others).
FIG. 3. CASE 137/37: DIFFUSE ASTROCYTOMATOSIS OF LARGE PARTS OF FRONTAL AND TEMPORAL LOBES (A), THE CORPUS CALLOSUM, PARIETAL LOBE, CENTRUM OVALE AND THALAMUS (B)

Note the highly fibrillary character of the subcortical parts and corona radiata (c. r.), while the tumor in the cortex and the corpus callosum (c. c.) is a fibrillar (C); also the moderate cellularity and partial preservation of ganglion cells (D). A, B, D. Nissl stains. C. Holzer stain for glial fibers.

Our experience shows that cytologically there is great variation from one cerebral astrocytoma to another. Even in the most typical cases, a large number of astrocytoma cells, if considered as isolated elements, can hardly, if at all, be recognized as astrocytic, the nuclei often being hyperchromic or perhaps slightly polymorphous, even in "young," beginning cases. This is, of course, to be expected, as we are dealing with neoplastic and not with normal elements, but it makes it difficult to prove exactly that these tumors are really composed essentially, or sometimes merely "predominantly," of astrocytes. Specific stains do not always give clear results, at least on comparison with corresponding non-specific nuclear stains. Fig. 4 shows successive frozen sections, 20 μ thick, from a single case, stained with cresyl violet and impreg-
nated with gold sublimate for protoplasmic astrocytes (Globus-Cajal): A and B come from the same tumor area; C from an adjacent area of normal brain tissue, and the magnification is the same in each instance. One sees immediately that there is a considerable increase of astrocytic elements (which, as tumor cells, are of course less perfectly formed than the normal astrocytes) in the tumor; but comparison with the nuclear stain shows, on the other hand, that only a minority of the tumor elements (about 25 per cent) stain specifically, in spite of a particularly complete impregnation. In other cases, controlled in the same manner and in which the impregnation was certainly complete, we never obtained more than 30 per cent of cells with positive gold
sublimate impregnation. Bergstrand (10) obtained similar results working with the silver diamino-carbonate method.

If, on the other hand, we take the morphology of the nuclei as an essential criterion, we obtain percentages of 40 to 80 per cent of astrocyte-like nuclei in astrocytomas, the remainder being oligodendroglia-like or definitely atypical. The latter are frequently called in the literature “spongioblastic,” although their histogenesis cannot be determined. Great variation of the nuclear be-
behavior was encountered in different astrocytomas of our material. In certain instances there was a predominance of large, clear nuclei, without polymorphism (Fig. 6, B and C); in others the nuclei were also very large, but often hyperchromic; in yet a third variety, the shape of the nuclei varied greatly (Fig. 6, A); finally there were cases where the majority of nuclei were surprisingly small and dark, giving a somewhat intermediary aspect between astrocytes and oligodendrocytes (Fig. 6, D). We have encountered the "polymorphonuclear" type in old as well as in young astrocytomas; our oldest case (ten years) showed the small cell type, while the large, clear, most astrocyte-like nuclei were found in some partially dedifferentiated cases of more rapid evolution (between one and two years). Whether these differences really correspond to different biological types should be systematically studied on a large material.

In respect to the cytoplasm in Nissl stains, the nuclei of most astrocytomas are "naked," except in the special gemistocytic type (Fig. 5); this absence of cytoplasmic coloration is especially striking when compared to the behavior of reactive glia proliferations, in which the Nissl stain always shows an increased staining of the cytoplasm. On impregnation with gold-sublimate (Fig. 4, B), the perinuclear cytoplasm generally appears rather increased, and the processes of the astrocytes less numerous and shorter than in normal or hyperplastic tissue (Fig. 4, C). In the gemistocytic (giant-cell) type, the picture is dominated by cells of the type of Nissl's "plump astrocytes," but with nuclei differing from those of benign reactive tissue, in that they show considerable polymorphism.

In our material, we encountered one pure astrocytoma in which these gemistocytic forms, with large cytoplasmic bodies and eccentric nuclei, dominated the picture. These tumors certainly form a special histologic type, as emphasized by Stroebe (63), Roussy and Oberling (48), Elvidge, Penfield and Cone (28), and others. We have found no proof for Bucy and Gustafson's (13) hypothesis that this is simply a degenerative form of astrocytoma. On the contrary, some features, such as an extreme tendency to form fibers (Fig. 5, B), a somewhat more "circumscribed" character than observed in other astrocytomas, and perhaps a shorter clinical evolution (six months, death from perforated gastric ulcer), gave a special aspect to this case. A complete histological study of further cases is desirable. The incomplete study of circumscribed tumor parts can lead to no definite conclusions, since the gemistocytic cell type was found by us in circumscribed areas in two other pure and in several dedifferentiated astrocytomas.

In regard to the fibrillary or afibrillary character of astrocytomas, we have never seen one which was entirely afibrillary; all stages of transition from slightly (frequent) to highly (infrequent) fibrillary cases, are observed, and one and the same lesion may be extremely fibrillar in one place and practically afibrillar elsewhere. The majority of our cases were only slightly fibrillar. The statement (Golgi, 1884) that "cortical" astrocytomas are generally protoplasmic, while astrocytomas of the white matter are more often fibrillar, is misleading, since there are no astrocytomas limited to the cortex alone; the invariably diffuse growth of these tumors does not respect the limits of white and gray matter. It is true that the cortical parts of astrocytomas are gener-
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**FIG. 6. CELL PICTURE (Nissl Stain) OF FOUR DIFFERENT CASES AT SAME MAGNIFICATION (× 620):**

* A. CASE 137/37.  
* B. CASE 6/36.  
* C. CASE 51/39.  
* D. CASE 251/37

Note the difference in nuclear shape, intensity of staining, and cellularity.

ally very poor in fibers, even though their white matter parts are highly fibrillary. In one highly fibrillary case, we even observed a striking increase of fibers (not of cells) around the vessels and in the subpial layer, such as is generally encountered in reactive glioses. This has a considerable theoretical importance, in so far as it shows that these neoplasms follow the same rule as reactive processes which, according to the “local factors” (Spielmeyer, 62), have a much greater tendency to produce fibers in the white than in the cortical gray matter, and especially around vessels and beneath the pia. This lends further support to the idea that astrocytomias grow by diffuse proliferation of preexistent elements and not by progressive infiltration. However, it explains
in no way all the differences observed in astrocytomas in respect to fiber formation.

One of the most fibrillary of our astrocytomas was the gemistocytic growth (Fig. 5). Two of the doubtful ("transitional") cases with gemistocytic areas, to be mentioned later, showed the same extreme fiber production, and in the same special form, characterized by the presence of a large number of proliferated fibrillary astrocytes, i.e. of elements in which the origin of star-like radiating glial fibers from the cell bodies is clearly recognizable. In these cases there is no possible doubt as to the fibers really arising from the tumor cells and not from the neoplastic stroma formed by included, preexistent, non-neoplastic, fibrillary astrocytes. This must be emphasized, since Singer and Seiler (61) denied the existence of astrocytomas, interpreting the dense fiber network in those tumors as an enormous stroma overgrowth comparable to what can be observed in scirrhus.

Much more frequent is the existence of a dense intertwining fiber network entirely independent of the nuclei scattered throughout it (Fig. 8, A), and comparable to glial scar tissue. We confirm fully the statement of Alpers and Rowe (1) that there is no strict relationship between the number of cells and the number of fibers in a given tumor; there may be very few cells surrounded by an enormous number of fibers. For this there is only one satisfactory explanation, namely that in such areas the tumor has become stationary. The existence of such "limits of growth" is well known in other tumors, as, for example, myomas of the uterus (see Ewing, 29). As we never have observed the picture in an entire astrocytoma, but only in certain regions, this behavior would not seem to have the same practical importance as a real arrest of growth affecting the whole tumor.

A final problem, and a complicated one, is presented by the so-called "piloid" astrocytoma (Penfield), characterized by the predominance of elongated cell forms, with the fibers following a definite parallel direction (Fig. 8, B) instead of forming a network (Fig. 8, A) as in other fibrillary astrocytomas. It is more than probable that the elongated form of the cells (or nuclei) is conditioned by this parallel arrangement of dense glial fibers, which include the nuclei. After a careful study of the literature and of our own material, we have the impression that the term "piloid astrocytoma" has been applied to wholly different lesions. Some of the tumors so called are doubtless those designated by certain authors as "spongioblastoma polare." With Bergstrand (10), Russell and Bland (49), and Cox (21, 22), we are convinced that these are, from a histogenetic point of view, fibrillary astrocytomas of "piloid" type, but strictly separated by their structural and growth characteristics from ordinary astrocytomas. As these tumors apparently do not occur in the cerebral hemispheres, they need not be discussed here. On the other hand, we have observed areas of "piloid" structure in oligodendrogliomas and forming circumscribed parts of diffuse cerebral astrocytomas of otherwise non-piloid structure. As this is not a cytological but a structural phenomenon, it will be discussed further under the heading of "Structure." Here we have only to emphasize the point that "fibrillary" and "piloid" astrocytomas are by no means synonymous.
FIG. 7. Normal Centrum Ovale (A), Typical Areas of an Ordinary Astrocytoma (B), and Dedifferentiated Area (C) of the Same Case (130/35), at Same Magnification as Fig. 6 (X 620)

The dedifferentiated parts are not more cellular, but their nuclei are much larger.
Some authors mention the difficulty of distinguishing neoplastic from reactive astrocytes. This difficulty is real for isolated cell elements, but does not exist for the process as a whole or, with a sufficient knowledge of general neuropathology, even for a given zone.

(d) **Cellularity**: The cellularity of a tumor is not only one of its most important morphologic characteristics, but pathologists frequently base upon it conclusions as to the biological behavior of a neoplasm. Under these conditions it seems surprising that so little attention has been given to this aspect of gliomas.
Before describing our results, we would emphasize one of the more technical aspects of our study; namely the observation that exact counting often gives results quite different from the impression obtained by the simple microscopic appearance of the tumor. The error is due to differences in the volume of the cells or nuclei. Macrocellular gliomas thus look much more cellular than microcellular ones, although the counting method reveals no difference (Fig. 7, B and C). This seems quite logical if one takes into account the fact that large cells in a given area leave much less intercellular space than small ones; thus the cellularity should be determined not by simple counting of cells in a given space, but as a function of the cell volume in respect to the space unit. Comparisons of different tumors by means of our simple method of counting have significance only for gliomas with cells or nuclei of approxi-
mately uniform size—i.e. for all cerebral astrocytomas, except the gemistocytic type. A comparison is possible, for instance, with microcellular glioblastomas, while the macrocellular and polymorphocellular type may show the same or only slightly increased cellularity as compared to many astrocytomas (see Figs. 7, B and C; Fig. 12, B and C).

In the centrum ovale of the normal brain (Fig. 7, A), we generally find 30 to 40 cells in a field of 0.1 sq. mm. In our less cellular astrocytomas the count reached 60–75 (Fig. 6, A); “average” astrocytomas (Fig. 7, B) generally showed about 80–100 cells in a like area, while for the most cellular case (Fig. 6, D), the number was about 160. It is thus seen that there are considerable differences of cellularity in astrocytomas, from one tumor to another, and in certain rare instances from one part to another of the same tumor. In most “pure” astrocytomas, however, the cellularity of different parts is surprisingly constant.

![Image](image_url)

**Fig. 10. Case 466/36: Typical Microcystic Degeneration; Cysts Entirely Empty. Nissl Stain**

Although no infallible rule can be deduced from our material, the following observations are suggestive. The least cellular of our cases had the shortest clinical evolution (with the exception of the gemistocytic astrocytoma, whose degree of cellularity was dependent upon the volume of its cell elements). The highest cellularity was encountered in the tumor having the longest clinical evolution. In the latter there were areas corresponding in cellularity (about 100) to the average, but in other parts the density of cells exceeded that found in any other astrocytoma, and this in spite of the absence of any but the slightest sign of cellular dedifferentiation.

This proves that differences of cellularity in cerebral astrocytomas do not necessarily correspond to differences in “malignancy”; they do indicate frequently the age of the tumor, in that “young” tumors show a low and “old”
ones a high cellularity, at least in certain areas (probably the oldest). Whether this is a general rule must be determined by systematic study of an appropriate material. A relatively high cellularity was encountered in our series in a few "young" astrocytomas with apparently rapid transition into glioblastoma.

(e) Structure: As pointed out in previous publications (Scherer, 55, 56) the structural behavior is an important morphologic feature of the gliomas. One of the most characteristic aspects of pure cerebral astrocytomas is their complete lack of any architectural pattern, in other words an entirely uniform distribution of their nuclei (amorphous structure); there are neither secondary nor proper structures (Scherer, 55, 56) at any stage. We have seen no exception to this rule as far as pure astrocytomas are concerned. Beginning lesions, as well as that of ten years' duration, showed the same amorphous structure in all their parts. Dedifferentiation, on the contrary, is in most cases accompanied by the appearance of various secondary (especially perineuronal, perivascular, and perifascicular) and sometimes also proper structures. The former, in locally dedifferentiated astrocytomas, may appear only in circumscribed areas, but are more often present in an extensive field, even in regions which show no dedifferentiation. In a few dedifferentiated cases, perineuronal structures appeared so regularly and were so widely spread that there was some doubt in regard to their merely secondary appearance after dedifferentiation; even in these cases, however, the peripheral zones showed an amorphous character. We have never seen secondary structures either in pure or in very old astrocytomas (over five years' clinical duration), but always in tumors containing glioblastoma areas and (or), on the whole, with a more rapid evolution than other astrocytomas. Thus, in our experience, secondary structures encountered in biopsy material indicate a rather poor prognosis, even when the cytological aspect is that of an astrocytoma.

The same seems true—as far as our material is concerned—for the polar fascicular proper structures which characterize the "piloid" type of astro-
cytoma tissue. This type we have seen in the cerebral hemispheres only in circumscribed nodules in otherwise amorphous, but partially dedifferentiated, astrocytomas. We never have seen an entire cerebral tumor showing this aspect, nor have we encountered these nodules in pure astrocytomas.

(f) Preexistent Tissues: The conservation over a long period of the preexistent nervous parenchyma surrounded by the astrocytoma tissue is one of the essential characteristics of the cerebral astrocytoma. This fact was known to Stroeb in 1895, Henneberg in 1897, and others, but has been forgotten by some modern writers, who have described such tumors as “gangliogliomas.” Recently Bucy and Gustafson (13) mentioned this preservation in a thalamic astrocytoma. Our material shows that the preservation of ganglion cells and, probably to a less degree, of nerve fibers and myelin sheaths is one of the most constant characteristics of cerebral astrocytomas (Fig. 9). It is quite difficult to say whether or not all the preexistent elements remain preserved, since the normal distance between nerve cells and fibers must of course be increased by the presence of the tumor elements between these parenchymatous structures, so that their more scattered appearance proves no real diminution. A slight loss of parenchyma is, however, very probable when all factors are taken in account. As observed in our ten-year case, the preservation may be very pronounced even after a long period of evolution (Fig. 9, B). The statement, sometimes encountered in the literature, that the preexistent structures are preserved at the edge but not in the center of the tumor is not consistent with our observations. We never have seen such a difference.

This behavior of astrocytomas, although characteristic, is by no means sufficiently specific to permit of itself a diagnosis. It is encountered, in a less marked degree, in many other gliomas (see Scherer, 59). It is, however, one of the distinctive differences between astrocytomas and the so-called polar spongioblastomas (a certain number of piloid astrocytomas), the latter showing a rapid destruction of the invaded nervous parenchyma.

(g) Vessels: While in Nissl pictures astrocytomas do not show more vessels than the normal brain tissue, silver impregnation reveals a moderate increase in capillaries. Their relative invisibility with nuclear stains is the expression of the total absence of cellular proliferation in these vessels, in striking contrast to many other gliomatous tumors. “Angioplastic” proliferations are never encountered in non-dedifferentiated astrocytomas (Scherer, 54).

Both the large vessels and capillaries may show degenerative lesions: the former, a curious hyalin thickening of the walls, which gives a pronounced Scharlach red reaction; the latter calcification. The first lesion is rare and was encountered by us in a single old pure astrocytoma, and then only in circumscribed areas. Capillary calcification is also rather infrequent; it is generally limited to certain areas, in which a large number of capillaries are calcified. We have not encountered in pure astrocytomas such pronounced calcification as is frequently seen in oligodendrogliaomas.

(h) Degenerative Lesions: Astrocytomas have a very characteristic behavior in respect to degeneration. As long as they remain “pure” they never show the smallest necrotic area. We have never seen hemorrhages in pure astrocytomas. On the other hand, a great majority show large areas of microcystic degeneration (Fig. 10), giving to the parts involved the aspect of an
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This lesion has been observed in very early stages of astrocytomatos tissue. In our experience—which in this respect confirms the descriptions of Stroebe (63), Henneberg (34), and others—it is this sponge-like microcystic transformation which, both macroscopically and microscopically, is the most characteristic degenerative lesion encountered in cerebral astrocytomas and not, as has been stated by some more recent

Fig. 12. Same Case as Shown in Fig. 11 (288/37): A. Glioma Nodule under Low Magnification. B. Astrocytoma Area. C. Glioblastoma Area. × 620

"emphysematous lung" (Tooth, 64). This lesion has been observed in very early stages of astrocytomatos tissue. In our experience—which in this respect confirms the descriptions of Stroebe (63), Henneberg (34), and others—it is this sponge-like microcystic transformation which, both macroscopically and microscopically, is the most characteristic degenerative lesion encountered in cerebral astrocytomas and not, as has been stated by some more recent
writers, the development of a single large cyst. This latter may be frequent in cerebellar astrocytomas, but in the cerebral growths it is rather the exception than the rule. We observed it in only one instance (Fig. 2).

The contents of both the small and the large cysts are macroscopically a clear, uncoloured or slightly yellowish fluid in contrast to the jelly-like, dark greenish or brown substance encountered in oligodendrogliaomas or the (rare) glioblastoma cysts. Microscopically, the cysts are characterized by the absence of any cellular or acellular content and lack of any wall formation. There is never a mesenchymal or a glio-fibrillar capsule: only round holes are seen in the tumor tissue, without any reaction. Thus this microcystic transformation has nothing to do with fatty degeneration and the "status spongiosus" which it provokes in certain degenerative processes; there are never granular compound bodies either in the cyst or in the surrounding tumor tissue, and the nerve cells and fibers in the immediate neighbourhood are generally preserved. We seem to be dealing with a sponge-like transformation due to a simple excess of tissue fluid. No other type of glioma ever shows this picture which, if present, is one of the essential characteristics of the astrocytoma.¹

Fatty infiltration of tumor cells was not observed in our series, except in the gemistocytic astrocytoma, which had been submitted to intensive x-ray therapy.

**Microscopically Dedifferentiated Astrocytomas**

**Case 130/35**: Female, 38 years. Figs. 7, B and C; 8, A.
Duration of symptoms: Several years. No operation.
Localization and extent of tumor: Diffuse growth in the right temporal and occipital lobes, insula, sublenticular region, deep parts of centrum ovale, thalamus, pallidum, pons, beginning in corpus callosum with spread in the other hemisphere.
Cytology and fiber formation: Typical, highly fibrillary astrocytoma with several very small circumscribed areas of dedifferentiation into "glioblastoma," in which glial fibers are absent.
Average cellularity (0.1 mm.²): 80–100 in both parts.
Mode of growth: Diffuse infiltrating and multicentric, in certain places respecting the cortex, in others not. No intrameningeal growth.
Structure: Completely amorphous. No secondary structures even in dedifferentiated areas.
Preexistent structures: Generally well preserved, but completely destroyed in the dedifferentiated areas.
Mesenchymal stroma: No vascular proliferation. Vascularity generally low, except that the dedifferentiated areas are rich in capillaries.
Degenerative changes: No cysts. Fatty degeneration and very small patches of necrosis in dedifferentiated parts only. No calcification.
**Case 348/35**: Female, 40 years. Fig. 1.
Duration of symptoms: 4½ years (epilepsy). No operation.
Weight of brain after fixation: 1,510 gm.
Localization and extent of tumor: Diffuse infracallosal unilateral growth, involving left frontal and temporal lobes, left basal ganglia and diencephalon (anterior parts), insula.
Cytology and fiber formation: Typical astrocytoma very poor in fibers. Definite transition to giant-cell glioblastoma multiforme in basal-posterior parts of tumor.
Average cellularity (0.1 mm.²): 70–102.

¹ In oligodendrogliaomas, a small-cystic degeneration of entirely different aspect occurs; here the cysts are filled with a homogeneous substance staining intensely with thionine, as well as with numerous mobile cell elements (oligodendrocytes in "mucoid" degeneration). Macroscopically the cysts never are as clearly visible as in astrocytomas.
Mode of growth: Diffuse infiltrating; gray and white matter equally involved. No intrameningeal growth.

Structure: Completely amorphous. No secondary structures, even in the dedifferentiated areas.

Preexistent structures: Generally well preserved, except in dedifferentiated parts.

Mesenchymal stroma: No vascular proliferation. Vascularity generally low, except in dedifferentiated areas.

Degenerative changes: Typical, very extensive microcystic degeneration. No large cysts. No necrosis. Fatty degeneration only in dedifferentiated parts. No calcification.

CASE 466/36: Male. 27 years. Figs. 2 and 10.

Duration of symptoms: Unknown. No operation.

Weight of brain after fixation: 1.550 gm.

Localization and extent of growth: Diffuse growth in the right parieto-occipital centrum ovale, involving internal capsule, upper parts of basal ganglia; through corpus callosum to left centrum ovale.

Cytology and fiber formation: Large parts typical astrocytoma with very little fiber formation. Deeper parts (capsula interna, basal ganglia, corona radiata) resembling glioblastoma.

Average cellularity (0.1 mm²): Astrocytoma 84–93. Dedifferentiated parts 130.

CASE 51/39: Male. 49 years. Figs. 4 and 6, C.

Duration of symptoms: 14 months (jacksonian epilepsy). Death 13 days after operation.

Weight of brain after fixation: 1,620 gm.

Localization and extent of tumor: Diffuse unilateral right parietal process, centered on the right motor cortex, involving also the neighbouring parts of F I and F II, of the insula and the lateral half of centrum ovale. Relatively small lesion.

Cytology and fiber formation: Large parts typical astrocytoma, in some places gemistocytic; moderately fibrillar in the white matter. Circumscribed glioblastoma nodule and diffuse transition to glioblastoma multiforme.

Average cellularity: 80 (astrocytoma) to 130 (glioblastoma).

Mode of growth: Diffuse infiltrating, involving gray and white matter. Pronounced intrameningeal growth.

Structure: Astrocytoma amorphous. In dedifferentiated parts pronounced perineuronal, perivascular, superficial secondary structures.

Preexistent structures: Nerve cells and fibers, myelin sheaths preserved a long time.

Mesenchymal stroma: No vascular proliferation. Moderate diffuse capillary vascularity.

Degenerative changes: No cysts. No necrosis. No fatty degeneration. No calcification.

Four of our tumors had the typical macroscopic aspect of astrocytomas and on microscopic study, also, proved to be typical astrocytomas, except for certain areas, circumscribed in 3 cases and more extensive in one. These cases were typical in every respect: diffuse growth without the formation of any real "tumor," total absence of any limitation, large size, typical astrocytoma cytology with a cellularity under 100 in 0.1 sq. mm., an entirely amorphous structure, preservation of preexistent nervous elements, absence of angioplastic
proliferations and of necrosis and hemorrhage, and the presence (in 2 cases) of typical microcystic degeneration or, in one instance, a very large cyst (Fig. 2). Complete microscopic study, however, revealed in 2 cases (one highly fibrillar) the presence of quite circumscribed areas of definite glioblastomatous nature, characterized by highly polymorphous nuclei with giant cell formation, increase of vascularity, a more rapid destruction of myelin sheaths and ganglion cells, fatty degeneration and, in one instance, the appearance of minute necrotic areas. An apparently pronounced increase of cellularity in these parts, simulated by the considerable increase of nuclear dimensions (Fig. 7, C) proved to be non-existent after counting. No modification of the structural behavior was observed in these 2 cases.

The third case (466/36) showed a somewhat more extensive dedifferentiation accompanied by a striking change of structural behavior. This very large tumor of the parietal and occipital parts of the centrum ovale showed in about nine-tenths of its area the typical astrocytoma morphology, with extensive microcystic degeneration in the posterior part and a very large cyst in its upper lateral anterior part. No boundaries were visible and, as in all astrocytomas, microscopic study revealed a much greater extension than the macroscopic aspect had led us to assume (Fig. 2). The deeper parts, situated in the corona radiata, corpus callosum, caudate nucleus, upper parts of the internal capsule and putamen, were distinguished from the remainder of the lesion by a definite increase in cellularity, pronounced cellular and nuclear polymorphism of typical glioblastoma aspect, the appearance of beautiful perineuronal, perivascular, and intrafascicular secondary structures, and one very small patch of necrosis surrounded by typical angioplastic proliferations. These dedifferentiated parts showed no circumscribed character, but a slow progressive transition into the "pure" astrocytoma.

In the last of the 4 cases (51/39) showing microscopic dedifferentiation the macroscopic aspect and diffuse growth were entirely typical for astrocytoma, and large areas were not less typical microscopically (Fig. 4) in respect to cytology, cellularity, amorphous structure, preservation of preexisting tissue, vascularization, and absence of necrosis. The sole differences were a more intensive coloration of the cytoplasm of the tumor cells by Nissl stains than is usually observed in astrocytomas and the specially large character of the nuclei (Fig. 6, C). Here the dedifferentiation took two different forms: there was one strictly circumscribed round glioblastoma nodule 1 mm. in diameter and, in addition, a quite diffuse dedifferentiation in considerable parts of the tumor. The cellularity in these dedifferentiated areas was not very high, but the cells were much larger and very polymorphous, monstrous nuclei were frequent, and there was an enormous development of pronounced perineuronal, perivascular, and surface growth. Perineuronal structures were also formed by elements of undoubted astrocytic character. This is never observed, however, as a precocious phenomenon, the growth zone having always an amorphous structure. There was extensive intrameningeal growth.

These 4 cases offer striking proof that absolutely typical fibrillary and afibrillary cerebral astrocytomas may show undoubted areas of glioblastoma, either in circumscribed or more extensive areas, and this in spite of an entirely
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Astrocytomatous macroscopic aspect. In other words, only "complete" microscopic examination of such lesions offers an opportunity of finding the dedifferentiated areas. The primary astrocytic character of these tumors cannot be denied. The glioblastoma areas are quite circumscribed. They have all the characteristics of recent proliferations. They cannot, therefore, be considered as the primary or main tumor with a secondary astrocytoma, which in that event would be as much as one hundred times as large as the glioblastoma. Furthermore, the morphologic characteristics of these tumors, taken as a whole, are absolutely typical, as described for the pure astrocytomas. Especially in the last case all grades of transition from pure astrocytoma elements into dedifferentiated cells are clearly to be observed. Finally, the very long clinical evolution observed in some of these cases excludes glioblastoma. Three patients have not been operated upon, and the fourth only so shortly before death that the dedifferentiation certainly existed before the operation. In respect to the structural behavior, the cases demonstrate the following points: Dedifferentiation may be (466/36, 51/39) but is not necessarily (130/35, 348/35) accompanied by a change in the structural behavior, the amorphous structure being replaced by extensive secondary structures either in the dedifferentiated parts (466/36) or also in parts of still astrocytomatous cytology (51/39). The cases of the following group confirm the fact that these are general rules.

MACROSCOPICALLY VISIBLE COMBINATION OF ASTROCYTOMA AND GLIOBLASTOMA

CASE 1360/32: Male, 29 years.
Duration of symptoms: 3½ years (epilepsy). No operation.
Weight of brain: 1.380 gm. before fixation.
Localization and extent of tumor: Diffuse unilateral infracallosal growth in the right temporal and occipital lobes, deep parts of centrum ovale, striopallidum. Astrocytoma-like aspect, certain points more glioblastoma-like.
Cytology and fiber formation: In parts moderately fibrillary astrocytoma. In certain parts "gemistocytic" astrocytoma. Others parts polymorphous glioblastoma.
Average cellularity: Undetermined because of thickness of sections (more than 20 μ). Mode of growth: Diffuse infiltrating; cortex in certain places preserved, in others infiltrated. Intrameningeal growth.
Structure: Completely amorphous, even in dedifferentiated parts.
Preexistent structures: Nerve cells and fibers, and myelin sheaths relatively well preserved, even in dedifferentiated parts.
Mesenchymal stroma: No angioplastic proliferations. Moderate diffuse capillary vascularity.
Degenerative changes: Extensive microcystic degeneration with formation of two larger cysts. Small necrotic areas in glioblastoma parts. Extensive calcification of capillaries.
CASE 299/35: Female, 51 years. Fig. 13.
Duration of symptoms: About 5 years. Sudden aggravation and rapid course beginning 5 months before death. No operation.
Weight of brain after fixation: 1.580 gm.
Localization and extent of tumor: Diffuse, predominantly right-sided, infiltrating the under-median three-fourths of the right frontal lobe, growing through the corpus callosum into left frontal and parietal lobes, filling the right lateral ventricle up to its occipital end. Tumor patch in right Ammon's horn. Orbital parts of astrocytoma-like aspect; upper half glioblastoma-like aspect. No sharp limits between two parts.
Cytology and fiber formation: Orbital parts typical fibrillary astrocytoma, with pro-
gressive transition into glioblastoma multiforme towards the upper posterior parts. The glioblastoma constitutes about three-quarters of the whole tumor, especially the intraventricular parts.

Average cellularity (0.1 mm.²): Astrocytoma 72–80. Glioblastoma 152–175.
Mode of growth: Diffuse infiltrating, in gray and white matter. Curious intraventricular growth with infiltration of the immediately subependymal tissue. Intrameningeal growth.
Structure: Astrocytoma completely amorphous. Glioblastoma predominantly amorphous, with various primary structures in places. No secondary structures.
Preexistent structures: Nerve cells and fibers, myelin sheaths rather well preserved in astrocytoma areas. Rapid destruction in the dedifferentiated areas.
Mesenchymal stroma: In astrocytoma parts no vascular proliferations; moderate vascularity. In glioblastoma parts typical angioplastic proliferations in a few places; high vascularity.
Degenerative changes: Microcystic degeneration in some places. No large cysts and no necrosis (in spite of the enormous size of glioblastoma areas). No calcification. Some fresh hemorrhages in the glioblastoma part.

CASE 27/37: Male. Fig. 14.
Duration of symptoms: Not exactly determined, but unquestionably for long period. Operation a few days before death.
Localization and extent of tumor: Diffuse unilateral, infracallosal process in the left centrum ovale, especially in the parieto-temporal parts, advancing into the basal-frontal and occipital parts; insular cortex, claustrum, and internal capsule invaded; striatum and thalamus spared. Astrocytoma aspect, with some large, clear-cut, circumscribed nodules of glioblastoma-like appearance.
Cytology and fiber formation: The largest parts are a typical, partially afibrillary astrocytoma. One circumscribed nodule shows a typical "piloid" structure. Other large nodules are typical glioblastoma multiforme. Certain other parts show diffuse transition into glioblastoma or astroblastoma.

Average cellularity (0.1 mm.²): Astrocytoma 82–91–102. Glioblastoma 127–170.
Mode of growth: Diffuse infiltrating in numerous places, ceasing at the gray matter; increase of cellularity at this edge. The different atypical areas have a nodular form with clear-cut edges. Intrameningeal growth.
Structure: Generally amorphous. In some places perifascicular and in the cortical parts beautiful perineuronal, perivascular and surface secondary structures. Primary fascicular structure in the "piloid" nodule.
Preexistent structures: Nerve cells, fibers and myelin sheaths preserved for a long time. Mesenchymal stroma: No angioplastic proliferation. Generally low capillary vascularity, except that the glioblastoma nodules are rich in capillaries.
Degenerative changes: No cystic degeneration. One rather large area of necrosis in one of the glioblastoma nodules. No hemorrhage. No calcification.

CASE 288/37: Male. 46 years. Figs. 11 and 12.
Duration of symptoms: 3 years. No operation.
Weight of brain after fixation: 1,600 gm.
Localization and extent of tumor: Diffuse unilateral, infracallosal process filling the whole right temporal lobe, the adjacent parts of the occipital white matter, and the deep centrum ovale, insular cortex, and lateral posterior parts of basal ganglia. Generally astrocytoma-like aspect with one large circumscribed glioblastoma-like nodule.
Cytology and fiber formation: Large parts typical astrocytoma, very poor in fibers; in certain places gemistocytic astrocytoma. Progressive diffuse transition of large parts into glioblastoma-like tissue; one circumscribed nodule of typical glioblastoma multiforme present.

Average cellularity (0.1 mm.²): Astrocytoma 84–108. Glioblastoma (magnonuclear) 132.
Mode of growth: Diffuse infiltrating; cortex and white matter equally invaded. Slight intrameningeal growth.
Structure: Completely amorphous, even in dedifferentiated parts.
FIG. 13. CASE 299/35. DIFFUSE TRANSITION OF ASTROCYTOMA (A) INTO GLIOBLASTOMA (G1)

The upper photograph shows the macroscopic aspect; the lower shows the same section stained with Nissl stain.

Preexistent structures: Nerve cells, fibers and myelin sheaths rather well preserved; disappear without any secondary structure.
Mesenchymal stroma: No angioplastic proliferations, but high capillary vascularity increased in the glioblastoma nodule.
Degenerative changes: Very extensive microcystic degeneration, with some larger cysts. No necrosis, hemorrhage, or fatty degeneration. Extensive calcification of capillaries.

A considerable percentage of our cases showed macroscopically a distinctly dualistic structure. While large parts of these tumors had the morphology of astrocytoma and the tumor as a whole showed the typical diffuse, unlimited type of growth and enormous size, other parts presented a quite different aspect: they were soft, reddish, sometimes hemorrhagic, of more granular aspect. These differences were more striking when the dedifferentiated areas were strictly limited, circumscribed nodules, with clear-cut boundaries, as observed.
A. Horizontal section through hemisphere, showing extension of the tumor through the whole centrum ovale and internal capsule (i.c.), thalamus (th.) and putamen (p) being free; circumscribed glioblastoma nodule in the lateral posterior parts. B. Boundaries of the astrocytoma (a) and glioblastoma (gl.) areas with perinecrotic "pseudorosettes" (below). C. Gold sublimate impregnation of atypical cell elements. D. Typical nodule of "piloid" astrocytoma. A. Nissl stain. B. Van Gieson stain. C. Globus-Cajal gold sublimate. D. Holzer stain.

in three instances (Figs. 11 and 14). They may, however, be clearly visible even with more diffuse dedifferentiation (Fig. 13). Circumscribed and diffuse dedifferentiation may occur in one and the same case. The brief summaries give the details of these cases. Not only the cytology of the purely "astrocytomatosus" parts (Fig. 12, B), but the whole morphologic picture, as empha-
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FIG. 15. CASE 33/38: SPECIAL TYPE OF DEDIFFERENTIATED BILATERAL ASTROCYTOMA WITH ENORMOUS THICKENING OF CORPUS CALLOSUM AND INVOLVEMENT OF BOTH PARIETAL (LEFT) AND FRONTAL (RIGHT) LOBES

More circumscribed tumor in lower part of photograph, with cystic degeneration. Extensive calcification.

ized in the previous sections, and the long period of evolution (usually several years) allow no doubt as to these tumors being true astrocytomas. Nor can the glioblastomatous character of the dedifferentiated parts be contested (Fig. 12, C). The cytology, cellularity, abundant mitoses, and frequently the structural behavior and angioplastic vessel proliferations, make it impossible to distinguish these areas, if examined alone, from pure glioblastomas, except for one very important point: the absence, or presence in only very circumscribed areas, of necrosis. This must be emphasized, since most "pure" glioblastomas, at the moment of death, contain much more necrotic than living tissue and frequently show precociously small necrotic areas, even in quite young parts of the zone of growth. Typical microcystic degeneration in a glioblastoma, on the other hand, is always an important indication that it is dedifferentiated from an astrocytoma. We have never encountered it in glioblastomas without other definite signs of a primary astrocytoma.

Frequently also areas of somewhat intermediate structure between typical astrocytoma and typical glioblastoma are observed. These are characterized by considerable cellularity and atypical cell forms, a great number of which still stain with gold sublimate (Fig. 14, C).

In all other points, these cases confirm the conclusions drawn at the end of the previous section, especially as concerns the structural behavior. Two of these cases showed circumscribed nodules of absolutely typical "piloid astrocytoma" (Fig. 14, D), which must be considered according to our nomenclature (Scherer, 56) as fascicular proper structures. Intrameningeal growth, almost always absent in our pure astrocytomas, was found in most of the dedifferentiated cases. Confirmation is again obtained that the more or less fibrillary character of the astrocytoma has nothing to do with the presence or
absence of dedifferentiation. Finally, it must be emphasized that in this group, as in the second group, operation was performed in only one case, and then only a few days before death, so that the time factor excludes any relationship between surgical intervention and the development of dedifferentiation.

It must be remembered that the occurrence of glioblastoma nodules in astrocytomas was well known as early as at the end of last century (Stroebe, 1895; Henneberg, 1897).

**Diffuse Transition of Bilateral Corpus Callosum Astrocytomas into Glioblastomas: A Special Tumor Group**

CASE 260/33: Details of age, course, and weight of brain unavailable.

Localization and extent of tumor: Diffuse bilateral process, especially in the parietal and adjacent frontal parts of both centra ovalia. Enormous thickening of corpus callosum. Participation of the upper parts of both basal ganglia. Multiple cortical growth zones at the convexity. Partially astrocytoma-like, partially glioblastoma-like aspect.

Cytology and fiber formation: Certain parts show the typical aspect of highly fibrillary astrocytoma. Larger parts of the tumor are doubtless glioblastoma, partially "isomorphic," partially polymorphous.

Average cellularity (0.1 mm.³): Astrocytoma 66-83. Glioblastoma 125-147.

Mode of growth: Entirely diffuse infiltrating; white and gray matter equally involved. Extensive intrameningeal growth.


Preexistent structures: Nerve cells and fibers and myelin sheaths relatively preserved in the astrocytoma parts, but rapidly destroyed with development of secondary structures in the dedifferentiated parts.

Mesenchymal stroma: No angioplastic proliferations. In the astrocytoma parts moderate, in the dedifferentiated parts high capillary vascularity.

Degenerative changes: Only circumscribed microcystic degeneration. No large cysts. No necrosis. No fatty degeneration.

CASE 121/34: Male, 35 years.

Duration of symptoms: 4 months. Postoperative death.

Localization and extent of tumor: Diffuse bilateral process involving both frontal lobes and the anterior part of parietal lobes; enormous thickening of anterior half of corpus callosum. Large parts astrocytoma; others glioblastoma-like; no sharp limits between.

Cytology and fiber formation: Large parts typical highly fibrillary astrocytoma. Circumscribed "piloid" nodules. Parts of gemistocytic astrocytoma. Large parts glioblastoma multiforme.

Average cellularity (0.1 mm.³): 74-116.


Structure: Completely amorphous, even in the dedifferentiated parts. Circumscribed parts with primary fascicular structures (piloid astrocytoma).

Preexistent structures: Nerve cells, nerve fibers, myelin sheaths, preserved for a long time; disappear without secondary structures.

Mesenchymal stroma: In astrocytoma parts no vascular proliferation; moderate vascularity. In glioblastoma parts pronounced typical angioplastic proliferations.

Degenerative changes: Microcystic degeneration in some circumscribed spots. No large cysts. No necrosis. No hemorrhage. No calcification. Hyalin-fatty degeneration of some large vessels.

CASE 6/36: Female, 60 years. Fig. 6, B.

Duration of symptoms: ½ years. No operation.

Localization and extent of tumor: Diffuse bilateral, predominantly left process, especially in the upper frontal and parietal parts of centra ovalia; pronounced thickening of the anterior
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half of corpus callosum; involvement of the upper parts of both basal ganglia and internal capsule, left thalamus to the midbrain.

Cytology and fiber formation: Large parts, especially cortical and subcortical parts of frontal and parietal lobes and thalamus, typical astrocytoma. Corpus callosum, supracallosal convolutions, deep parts of centra ovalia, diffuse transition to glioblastoma. Multiple small nodules of glioblastoma multiforme.

Average cellularity (0.1 mm²): Astrocytoma 66–109. Glioblastoma (magnonuclear) 116–142.

Mode of growth: Absolutely diffuse, infiltrating white and gray matter without any limitation. Intrameningeal growth in numerous places.

Structure: Large cortical and white matter parts amorphous. Others show pronounced perineuronal, perivascular and intrafascicular secondary structures. Symplastic proper structures in dedifferentiated areas.

Preexistent structures: Nerve cells and myelin sheaths well preserved in the astrocytoma parts; progressive destruction in the dedifferentiated areas.

Mesenchymal stroma: No angioplastic proliferation; moderate capillary vascularity increased in dedifferentiated parts. Mesenchymal capsule around central necrosis.

Degenerative changes: No cystic degeneration. Extensive central necrosis in the anterior part of left corona radiata and upper parts of left basal ganglia. No calcification. No fatty degeneration.

Case 33/38: Male, 51 years. Fig. 15.

Duration of symptoms: About 2 years.

Weight of brain after fixation: 1,550 gm.

Localization and extent of tumor: Diffuse bilateral process especially in the parietal and adjacent frontal parts of both centra ovalia and enormous thickening of the corpus callosum. Participation of the upper parts of both basal ganglia and thalamus; independent cortical patches. Large asymmetrical, more circumscribed supracallosal tumor at the left frontoparietal convexity. Anterior parts astrocytoma-like, posterior more like glioblastoma.

Cytology and fiber formation: Large parts resembling an extremely cellular, only slightly fibrillary, sometimes gemistocytic astrocytoma. Diffuse transition into more and more atypical cell elements with ultimate formation of very large areas of spongioblastoma and typical glioblastoma multiforme. Enormous cellular polymorphism in different parts.

Average cellularity (0.1 mm²): Astrocytoma 83–110. Corpus callosum 128. Circumscribed tumor 135–276.

Mode of growth: Diffuse infiltrating, sometimes using the preexistent fasciculation for progression. White and gray matter equally involved. Extensive intrameningeal growth.

Structure: Large parts entirely amorphous. Others (corpus callosum, corona radiata) dominated by pronounced intra- and perifascicular growth. Perineuronal, perivascular secondary structures only in some rare places. In some places primary fascicular structures.

Preexistent structures: Nerve cells, fibers and myelin sheaths preserved for a long time. Disappear generally later without formation of secondary structures.

Mesenchymal stroma: High diffuse capillary vascularization. In certain places rather extensive angioplastic proliferations.

Degenerative changes: Extremely extensive microcystic degeneration with formation of some large cysts. Only very rare and small necrotic patches in glioblastoma parts of corpus callosum. No hemorrhages. Enormous extensive capillary calcification. Some larger vessels with hyalin swelling of walls.

Case 240/38: Male, 26 years.

Duration of symptoms: About 4 years (epilepsy). Rapid aggravation 3 months before death. No operation.

Weight of brain after fixation: 1,630 gm.

Localization and extent of tumor: Diffuse bilateral, rather symmetrical orbital, frontal, parietal process and enormous thickening of corpus callosum with involvement of both basal ganglia and internal capsules and left thalamus. Large but well defined asymmetrical glioblastoma in the supracallosal parts of left frontal and parietal lobes.

Cytology and fiber formation: Parts situated in the left parietal lobe, dorsal and medial to the circumscribed tumor are a typical fibrillary astrocytoma. The circumscribed tumor
is a highly polymorphous glioblastoma. The remaining parts are a more transitional form of "isomorphous" glioblastoma.

Average cellularity: Astrocytoma 89-94. Glioblastoma (magnonuclear) 112-118.

Mode of growth: Absolutely diffuse; infiltrating without any limitation. Extensive intrameningeal growth.


Preexistent structures: Nerve cells, fibers and myelin sheaths well preserved in the astrocytoma, moderately preserved in the diffuse "transitional" gliomatosis, entirely destroyed in the circumscribed glioblastoma.

Mesenchymal stroma: Typical pronounced angioplastic proliferations in the circumscribed glioblastoma. Remainder without angioplastic formations, rather poor in capillaries.

Degenerative changes: No cystic degeneration. Extensive central necrosis in the "glioblastoma." No necrosis, no hemorrhage in the other parts. Very slight calcification of some capillaries.

Our material included 5 cases characterized by similar localization and mode of extension, with a comparatively diffuse transition into glioblastoma, the primarily astrocytomatos character of the tumor being still clearly recognizable. These we separate from the foregoing group, not so much because of the more diffuse type of degeneration—encountered to a certain extent in other cases—as because of the general behavior of the lesions, which unites them in a single family.

These general characteristics are as follows. A quite diffuse growth is observed in both centra ovalia, especially in the parietal and frontal parts, the center apparently being in the anterior two-thirds of the corpus callosum, with great thickening evident in coronal sections (Fig. 15). The superior third (sometimes more) of both basal ganglia, with the internal capsules, shows a slight but definite infiltration, and the thalamus on one side is always invaded. The cortex of the parietal and frontal convexity, as well as the parasagittal cortex, shows diffuse zones of tumor growth with more or less extension; these cortical zones are not always in local relation with the growth in the centrum ovale and give the impression of a rather multicentric process. While all these parts have a quite diffuse and in general a macroscopically astrocytoma-like aspect, one may find a more tumor-like formation asymmetrically located in the upper half of one hemisphere, either frontal or parietal; macroscopically this "tumor" may have the appearance of astrocytoma or glioblastoma. Microscopically, the first finding in the enormous neoplastic process is the absence of necrosis or its presence in one-tenth or less of the living tumor tissue; microcystic degeneration and calcification may be present, but are more frequently lacking. The cytological aspects show an enormous variability. There are always typical astrocytoma and typical glioblastoma areas, the transition being more often diffuse, considerable areas of the tumor showing a somewhat intermediate aspect. The structure is amorphous in certain parts. In others, large cortical zones show a pronounced precocious and elective perineuronal, perivascular and surface growth, formed either by astrocytes or by dedifferentiated elements, while the dedifferentiated areas may develop various "proper" structures (fascicular and symplastic types). The clinical course is generally several years without operation.
The morphologic and biological characteristics of this group will be described in a later paper. It is mentioned here because it also represents a transition of astrocytoma into glioblastoma. The entirely diffuse character and enormous size of the lesions, the absence or comparatively small extent of necrosis, the prolonged clinical course—none of which characteristics is encountered in glioblastomas— together with the cytological aspect and low cellularity of large areas, exclude other interpretations, such as primarily combined astrocytoma and glioblastoma. This becomes especially evident when these growths are compared with the rather rare tumors which probably represent such a primary combination (Scherer, 57). Such cases are typical of glioblastomas in their evolution of some months duration, and in their macroscopic appearances, being rather well defined, although sometimes large, with extensive necrosis and hemorrhages. Microscopic study, however, shows small zones of typical astrocytoma tissue apart from the typical glioblastoma structure which forms the greater part of the tumors.

Doubtful Cerebral AstrocytomAs

Our material includes 3 cases whose morphological characters have much in common both with astrocytomas and glioblastomas. These are large tumors involving one frontal lobe and adjacent parts of the basal ganglia, macroscopically of rather astrocytoma-like aspect, but somewhat more circumscribed than our other astrocytomas, with extensive microcystic degeneration, and containing only small areas of necrosis. The greatest part of the tumor shows a clear glioblastoma cytology, with high cellularity, and in one case very pronounced angioplastic proliferations were observed. Fairly large areas, however, are representative of a typical gemistocytic astrocytoma with enormous fiber production. Tumor cells of variable but often piriform shape, having a pronounced affinity for gold sublimate, were observed. In one of these cases the nerve cells were well preserved; in the others they showed rapid destruction; myelin sheaths disappear rapidly in all cases.

The possibility cannot be excluded that these lesions are primary gemistocytic astrocytomAs in which differentiation has reached such an extent that only small parts still show the primary structure. It is impossible, however, to prove this interpretation and to exclude a primary less differentiated character of these growths. They correspond probably to "transitional gliomas" (Globus, 32; Levin, 39), "astroglioblastomas" (Kino, 36) and many "astroblastomas" (especially Hortega, 35; Carmichael, 15; Morelli, 41) of the literature. With Bergstrand (10), we have the definite impression that most of the so-called astroblastomas are closely related to the gemistocytic astrocytomAs. Our material did not contain a single tumor which showed in all its parts astroblastoma structures such as are described by Bailey and Bucy (6). The existence of pure astroblastomas has still to be proved by "complete" study of appropriate cases, just as the exact position of "transitional" gliomas needs further study. Our material shows that those doubtful cases are certainly much rarer than dedifferentiated astrocytomAs whose origin from pure astrocytomAs is clearly recognizable.
Localization Types

The diffuseness of astrocytomas makes it impossible in certain instances to speak of localization. However, certain localizations repeated with impressive constancy in our material and in the reported cases make it possible to isolate the following groups:

(1) Infraclosal anterior astrocytomas (Fig. 1), involving the inferior part of one frontal, the anterior part of one temporal lobe, and the inferior, lateral and anterior parts of the basal ganglia and insula or central lobe. These may extend further into the diencephalon, or by way of the anterior commissure into the opposite hemisphere.

(2) Infraclosal posterior astrocytomas (Fig. 11), involving the inferior anterior parts of one occipital lobe, one whole temporal lobe, the posterior inferior parts of the basal ganglia and insula, and sometimes the thalamus and the opposite side.

(3) Supraclosal, unilateral or predominantly unilateral growths (Fig. 2), infiltrating the convexity of the parietal and adjacent regions of the frontal, occipital and insula cortex, the entire centrum ovale, and upper parts of the basal ganglia with the capsula interna. The thalamus and midbrain may be infiltrated and, by way of the corpus callosum, the corona radiata of the opposite side is more or less involved.

(4) Callosal growths with bilateral predominantly supraclosal involvement of both centra ovalia, especially their parietal and frontal parts, and infiltration of the upper parts of both basal ganglia and internal capsules, the thalamus and insula being also sometimes involved (Fig. 15).

Types 1, 2 and 3, so far as has been observed, differ in no other particular than localization. Group 4, however, seems to be a special natural sub-group, with special morphological and biological properties as outlined above. For that reason, it will be described in a later paper in more detail.

General Discussion

In this paper we have tried to isolate a natural group of tumors characterized not by a single arbitrarily chosen aspect of their morphology (such as cell form or localization), but by the morphological picture as a whole, the same weight being given to each property. This general principle is the basis of all the descriptive natural sciences. In glioma pathology, however, it has found less and less application among modern research workers, though it was fairly well respected by workers at the end of the last century. For the astrocytoma group, this explains partially the disappointing confusion of the modern literature, as pointed out in the introduction. Many of the observations resulting from the present study had already been made at the end of the last century (Virchow, 65; Rindfleisch, 47; Stroebe, 63; Henneberg, 34, and others), but were apparently forgotten. The only shortcoming of these older studies is that they generally deal with only a few cases, with the result that generalization was difficult.

Our systematic study, being the first effort made to analyze cerebral astrocytomas in this way, leaves a large number of questions requiring further
study. However, it allows the following statements to be made and thereby gives an answer to certain much discussed points indicated in the introduction:

Pure cerebral astrocytomas, at the time of death, are certainly of rare occurrence. We encountered only 5 instances among 125 gliomas, 94 of which were located in the cerebral hemispheres. Thirteen other cases were found in which astrocytoma predominated, containing small (4 cases) or large areas of true glioblastoma tissue. Even when these combined cases are included, astrocytomas of the cerebral hemispheres remain much rarer in our material than glioblastomas.

For reasons enumerated above, these cases of combined astrocytoma and glioblastoma should be regarded as primary astrocytomas with subsequent dedifferentiation into glioblastoma. Until now, the existence of such a process was largely a question of opinion (see Cushing, 1937), being accepted by some and denied by others. Writers who accepted the possibility of transformation of astrocytoma into glioblastoma either gave no proofs for this opinion (Bailey, 4, 5) or based it on the discovery of glioblastoma tissue at necropsy or at subsequent operation in cases where an earlier operation showed astrocytoma-like structures (Tooth, 64; Globus, 32; Müller, 42; Scheinker, 53; Elsberg, Davidoff and Brewer, 27). This alone, however, is no proof, since the examination of small biopsy fragments cannot exclude a primary coexistence of both tissues in the same tumor, a possibility which must always be taken into account because of the great frequency of such tumor mixtures (Scherer, 57). Furthermore, no precise indications are given as to the frequency of such dedifferentiation in cerebral astrocytomas. Courville (20) alone makes the important general statement that in the majority of astrocytomas found at necropsy evidence of malignant change is observed.

Our systematic examinations prove (1) that such a dedifferentiation really exists; (2) that it is extremely frequent, since 13 of our 18 cerebral astrocytomas were partially dedifferentiated at the moment of death; (3) that this dedifferentiation is independent of operation. This last point is especially important, inasmuch as some authors (Tooth, 64; Müller, 42, and others) have incriminated surgical intervention as the cause of the dedifferentiation. Of the 13 dedifferentiated tumors in our material, only 3 had been operated upon, and that immediately before death, so that any influence of surgery is excluded by the time factor. On the contrary, in 2 of the 5 pure cases operation had been done many years before death without the slightest subsequent dedifferentiation although there was ample time for it to take place. Thus, the frequent occurrence of dedifferentiation in astrocytomas is not in itself an argument against operation.

Why certain cerebral astrocytomas undergo dedifferentiation while others do not remains entirely obscure. The differences in the cellular aspect described in this paper give no clear indication; the oldest pure case showed a predominance of rather small, dark nuclei, while the largest, clearest nuclei, most closely resembling the astrocyte, were predominant in some, but not in other dedifferentiated cases. This question needs further study. The fibrillary or protoplasmic character certainly has no influence in this respect. The structural behavior indicates that pure astrocytomas remain amorphous and
free from secondary structures even after a course of ten years; on the other hand, beautiful secondary structures are encountered in most—but not in all—dedifferentiated cases, formed by dedifferentiated or, rarely, by typical astrocytic elements. Whether this means that such secondary structures appear only after or with dedifferentiation in astrocytomas of primarily amorphous architecture, or that astrocytomas with a primary tendency to secondary structures are predestined to dedifferentiation, is not yet known. Most indications are actually in favour of the first interpretation. In any case, secondary structures in astrocytomas, if encountered in biopsy material, indicate a rather poor prognosis. Their absence allows no conclusion.

From a biological and clinical point of view, the secondary glioblastomas developing in astrocytomas must be distinguished from "primary" glioblastomas. They are probably responsible for most of the "glioblastomas of long clinical duration" mentioned in the literature, and thus for the relatively high average life span attributed to glioblastomas in general by Bailey (twelve months) and others. If we exclude the glioblastomas obviously arising from astrocytomas and 3 other cases in which the primary astrocytic character remains doubtful, we do not have in our material any primary glioblastoma the duration of which reached one year; in the enormous majority of cases symptoms were present for less than six months. The absence of extensive necrosis and peritumoral brain swelling in secondary and their almost constant presence in primary glioblastomas may play a certain rôle in the different clinical behavior of the two types, the course in the first instance being conditioned by the slow growth and feeble destructive properties of the astrocytoma as long as it remained pure. The existence of dedifferentiated astrocytomas probably explains why certain authors found no striking differences of duration between their astrocytomas and their glioblastomas: incomplete examination of those cases may give at one time the impression of an astrocytoma of relatively rapid evolution (the glioblastoma parts not being examined) and on another occasion that of a glioblastoma with a long evolution (the astrocytoma areas not being recognized). Our complete examination thus shows a definite clinical difference, where incomplete studies of small fragments had caused some confusion. If we exclude the few cases in which death occurred postoperatively and the one gemistocytic case, in which death was due to a perforated gastric ulcer, every astrocytoma, whether pure or dedifferentiated, had a duration of over one year without operation, most of them two to six years. Two dedifferentiated cases showed a sudden aggravation and more rapid course several months before death, which may possibly correspond to the onset of dedifferentiation.

Most of the other contradictions encountered in the literature are also due to the incomplete examination of partially dedifferentiated cases. Complete study shows that there are no pure astrocytomas with necrosis, no pure astrocytomas rich in mitoses (Cushing, 23), none that are highly cellular (Alpers and Rowe, 1), and very probably none that are circumscribed, in the cerebral hemispheres. In a series of 125 gliomas we have not seen a single circumscribed cerebral astrocytoma, nor have we found any case described with sufficient detail in the literature. Thus the frequent statement that such cases exist has still to be proved by a completely studied example.
This last point needs special emphasis. As pointed out above (see pages 166 and 171) all cerebral astrocytomas should be considered as primary diffuse neoplastic proliferations of the neuroglia of considerable areas of the brain, not as primarily circumscribed nodules with subsequent diffuse spread. They are in this respect comparable to lymphosarcomatosis. Thus their very nature makes complete extirpation impossible, even in early stages, especially as their boundaries—and often the entire process—are practically invisible (Scherer, 59). All stages of transition are encountered, from astrocytomas infiltrating only parts of one hemisphere to those involving an entire hemisphere, or both hemispheres with basal ganglia and midbrain. It is obvious that the morphological, biological, and clinical characteristics, taken as a whole, unite these neoplasms in one large natural group, notwithstanding the fact that the percentage of unquestionable astrocytic elements may be in one instance about 80 per cent and in another only about 40 per cent. The excessive emphasis laid on cytological studies alone, with neglect of the other characteristics of gliomas, has caused the acceptance of artificial divisions by both pathologist and clinician. There is no reason for separating these identical processes on the sole ground of slight cytological variations; there is no reason for uniting under one and the same name entirely different processes, such as primarily diffuse growths and circumscribed tumors (as cerebellar astrocytomas) solely on ground of an apparently identical "histogenesis," in spite of absolutely opposite clinical, anatomical, and biological behavior. Most cases of diffuse "gliomatosis" of the brain, published under quite different names (Landau, 38; Angyán, 2; Bielschowsky, 11; Cassirer and Lewy, 16; Schwartz and Klauer, 60; von Sántha, 52'; Nevin, 43, 44, and others) have all the characteristics of dedifferentiated cerebral astrocytomas and have therefore to be included in this group.

Regarding the different histologic types of astrocytoma described in the literature (Elvidge, Penfield and Cone, 28), we have not encountered piloid astrocytomas as independent tumors in the cerebral hemispheres, but only circumscribed nodules of piloid astrocytoma in otherwise diffuse and invariably dedifferentiated astrocytomas. The existence of pure piloid astrocytomas of the cerebral hemispheres has still to be established by a completely studied case. We must, however, confirm the rare occurrence of pure "gemistocytic" astrocytomas. We have the impression that this group stands out not only because of the different cell type, but probably also by virtue of its morphological and growth characters. This important question also needs a more complete study, incomplete examination being useless and confusing because of the existence of circumscribed "gemistocytic" areas in otherwise typical diffuse astrocytomas.

Regarding the predominantly fibrillary or protoplasmic character of cerebral astrocytomas, there is not the slightest evidence that this is associated with any difference in the biological behavior.

The number of completely studied astrocytomas is still insufficient for solving the question whether there are several subgroups whose isolation would be justified on morphological grounds. Taking into account localization alone, there are certainly at least four fairly defined groups: anterior infracallosal, posterior infracallosal, supracallosal (predominantly) unilateral, callosal with
involvement of the anterior two thirds of both centra ovalia. Owing to the essentially diffuse growth character of these neoplasms, these localizations are only approximate. The last mentioned type alone seems to be sufficiently characteristic in its whole aspect to form a well defined group.

**Summary and Conclusions**

(1) The numerous problems presented by cerebral astrocytomas have been considered in the light of a complete pathological study of 125 gliomas. Only 5 pure cerebral astrocytomas were encountered in this material; in 13 cases microscopically (4 cases) or macroscopically visible areas of glioblastoma were present, but these cases must be considered as astrocytoma derivatives; their morphological and biological characteristics separate them from primary glioblastomas.

(2) Cerebral astrocytomas and their derivatives form a natural group of neoplasms with characteristic morphological and biological properties taken as a whole. They are diffuse neoplastic proliferations without visible boundaries. They do not present the macroscopic appearance of a well defined tumor. The existence of well circumscribed astrocytomas, such as are encountered in the cerebellum, has still to be proved for the cerebral hemispheres.

(3) The diffuse character of cerebral astrocytomas is not the result of a secondary extension of a primarily circumscribed tumor; astrocytomas, like lymphosarcomas, are primarily diffuse neoplastic processes involving parts of one hemisphere, an entire hemisphere, or both hemispheres.

(4) The outstanding characteristics of the astrocytoma group are: diffuse character of growth; generally enormous size; moderate and uniform cellularity (except for very old cases which may be very cellular); a uniformly amorphous structure (in all pure cases); astrocytic character of a high but variable percentage of their cell elements, the histogenesis of a considerable percentage of which is doubtful; production of glial fibers in small or extensive areas; preservation of preexistent nervous parenchyma (nerve cells and fibers) in the tumor; a tendency to microcystic degeneration of a type specific for astrocytomas; absence of necrosis; low vascularity without endothelial or adventitial proliferation; a slow clinical course.

(5) There are cerebral astrocytomas which show no dedifferentiation at necropsy even after a duration of ten years, in spite of operation performed long years before death.

(6) The majority of astrocytomas show, at the moment of death, a transformation into glioblastoma. This transformation may occur in a very small, macroscopically invisible area, as a larger, macroscopically recognizable nodule, or over very large areas without sharp limits. This “malignant degeneration” of astrocytomas occurs spontaneously, without a preceding operation, mostly after an otherwise typical clinical course of several years, but sometimes after a duration of one to two years. In two cases a rather sudden aggravation of the clinical picture occurred several months before death.

(7) In the partially dedifferentiated astrocytomas, there frequently appear extensive secondary structures, and sometimes circumscribed proper structures, none of which is encountered in pure astrocytomas. Necrosis may occur,
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but is frequently absent and always relatively inconsiderable in comparison to the enormous necroses encountered in "primary" glioblastomas at the time of death.

(8) Why certain astrocytomas become transformed into glioblastomas, while others remain pure, is still obscure. No morphological signs explaining or announcing this tendency could be found. Operation as a cause of this transformation is certainly excluded.

(9) Complete study of a large material is required to determine whether the natural group of cerebral astrocytomas and their derivatives, as defined in this paper, includes several natural subgroups. Cytological differences alone are certainly insufficient to justify the isolation of such subgroups; for the gemistocytic astrocytoma, further study has still to prove that its characteristics taken as a whole separate it from the other cerebral astrocytomas. One natural subgroup, briefly mentioned in this paper, will be discussed in a later communication.

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