The Problem of Multicentric Gliomas*

ULRICH BATZDORF, M.D., AND NATHAN MALAMUD, M.D.

Laboratory of Neuropathology, Langley Porter Neuropsychiatric Institute, San Francisco, California

This paper is concerned with a consideration of multiple intracerebral gliomas. Multiple intracranial lesions of diverse other types, such as combinations of gliomas with meningiomas, with pituitary chromophobe adenomas, or with tumors of the acoustic nerve, have been reported and discussed more frequently in the literature. Moreover, multiple gliomas present special problems of theoretical and practical significance, which we believe justify the present communication.

The older literature recognized the rare occurrence of multiple gliomas. Numerous individual cases have been reported sporadically in the literature. Courville's report in particular focused attention on the problem of multiple primary brain tumors, and included a tabulation of all cases reported previously. Among these reports there were several of a sufficiently large series of cases to permit calculation of the incidence of multiple lesions among gliomas (see Table 1).

Following the monumental study by Bailey and Cushing, our knowledge of the mode of growth and spread of gliomas became more precise. Although relatively little information about the general behavior of growth of gliomas has been added in recent years, our present knowledge and techniques permit us to view more critically some of the previous reports of multiple gliomas. Thus it becomes apparent that some tumors were designated as multiple solely on the basis of macroscopic examination of the material, whereas microscopic study might have revealed a point of continuity. In other instances tumors were referred to as multiple, although it was not stated that continuity was ruled out by cutting multiple sections of intervening areas. In some cases apparently it was not realized that the masses of tumor communicated through an infiltrated fornix, massa intermedia, or corpus callosum. Some authors even included tumors of the corpus callosum that had extended into the frontal lobes among multiple tumors. In other instances seeding through cerebrospinal-fluid channels would appear to have been the more likely cause of multiplicity. It is obvious, therefore, that the greatest care must be used in evaluating the literature, and this more critical view is reflected in some of the recent case reports.

As yet there remains lack of general agreement as to which tumors are to be included among multiple gliomas. Taking cognizance of some of the points brought out by Russell and Rubinstein, the following classification is suggested:

Multiple Gliomas

a. Multiple tumors, which can be interpreted as a result of dissemination or growth by an established route:

(1) Spread via commissural or other pathways, such as the corpus callosum, fornix, internal capsule or massa intermedia.

(2) Spread via cerebrospinal-fluid channels, either through the subarachnoid spaces, or emanating from a point of breakthrough into the ventricular system.

(3) Local metastasis through satellite formation in the immediate vicinity of the main mass of tumor.

b. Multicentric tumors in the form of

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widely separated lesions in different lobes or different hemispheres, which do not find a ready explanation by one of the pathways mentioned previously. Among these one also might include tumors that are separated not only in location but, also, in time. Russell and Rubinstein and Werner have cited cases of this type, in which a second neoplasm at a different site appeared several years after removal of a glioma. The multicentric group of tumors is of particular interest because it raises important theoretical questions with regard to the origin and behavior of growth of gliomas in general, and also because it poses practical problems in diagnosis and treatment.

Incidence

The incidence of multiple and multicentric tumors reported in the literature varies widely. Table 1 refers to the most comprehensive studies in the literature. It should be pointed out that medulloblastomas and ganglioneuromas are not included in either the survey of the literature or in our own case material.

It can be seen that there is considerable variation in the reported incidence of these lesions. The majority of figures fall roughly into two groups: those in the range of 7–10 per cent, and those in the neighborhood of 1–2.5 per cent. Unfortunately, these statistics do not lend themselves to an accurate comparison, as no doubt different criteria were used by various authors for establishing multicentricity but were not defined clearly. It would appear that authors reporting a higher incidence were citing cases that others, including ourselves, would group among multiple rather than multicentric lesions. In our opinion, if a more careful search had been made to rule out any possible connection between the tumors, a much lower incidence might obtain.

Case Material

Analysis of all gliomas in the autopsy material, examined at the Neuropathology Laboratory of the Langley Porter Neuro-psychiatric Institute between the years 1944 and 1961, revealed the following incidence of solitary, multiple and multicentric gliomas (Table 2).

It can be seen that tumors that we designated as multicentric comprised 2.4 per cent of the total gliomas in our series. This figure is in close agreement with the incidence reported by Russell and Rubinstein and by Willis.

The 5 cases that we classified as multicentric will be analyzed below in order to point

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Incidence in Gliomas</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1896</td>
<td>Gowers</td>
<td>7 in 70</td>
<td>10.0</td>
</tr>
<tr>
<td>1912</td>
<td>Tooth</td>
<td>8 in 83</td>
<td>6.1</td>
</tr>
<tr>
<td>1956</td>
<td>Scherer</td>
<td>5 in 70</td>
<td>7.1</td>
</tr>
<tr>
<td>1956</td>
<td>Courville</td>
<td>21 in 239</td>
<td>8.8</td>
</tr>
<tr>
<td>1957</td>
<td>Flock</td>
<td>5 in 74</td>
<td>6.8</td>
</tr>
<tr>
<td>1948</td>
<td>Willis</td>
<td>2 in 84</td>
<td>2.4</td>
</tr>
<tr>
<td>1952</td>
<td>Manzini &amp; Serra</td>
<td>6 in 82</td>
<td>7.4</td>
</tr>
<tr>
<td>1955</td>
<td>Henschen</td>
<td>7 in 800</td>
<td>0.9</td>
</tr>
<tr>
<td>1959</td>
<td>Russell &amp; Rubinstein</td>
<td>4 in 173</td>
<td>2.3</td>
</tr>
</tbody>
</table>

* The figures reported by Tooth have been brought into agreement with other figures in this table by including only gliomas, and only those cases verified at autopsy.
† Courville’s series of 492 cases included 269 “gliomas,” from which pinealomas, gangliogliomas and medulloblastomas have been eliminated in order to bring the figures into agreement with the other figures in this table.

<table>
<thead>
<tr>
<th>Type of Glioma</th>
<th>No. of Cases</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary</td>
<td>151</td>
<td>72.2</td>
</tr>
<tr>
<td>Multiple</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Gross and/or microscopic continuity of lesions</td>
<td>25</td>
<td>12.0</td>
</tr>
<tr>
<td>2. Cerebrospinal-fluid spread</td>
<td>24</td>
<td>11.5</td>
</tr>
<tr>
<td>3. Local metastasis</td>
<td>4</td>
<td>1.9</td>
</tr>
<tr>
<td>Multicentric</td>
<td>5</td>
<td>2.4</td>
</tr>
<tr>
<td>Total</td>
<td>209</td>
<td>100</td>
</tr>
</tbody>
</table>
out their most significant clinical and pathologic features.

Case Reports

Case 1 (LPNI #5639).

Clinical History. J.W., a 44-year-old, white man, experienced his first symptoms approximately 2 1/2 years prior to death. These consisted of Jacksonian seizures that spread from the right hand to the arm and leg, followed by increasing listlessness, failing memory and blurred vision. Several months later, a right hemiparesis developed.

Neurologic examination at the time of hospitalization, 9 months following the onset of symptoms, revealed obliteration of the nasal margins of the optic disk, weakness of the upper and lower extremities on the right side associated with increased deep tendon reflexes and extensor plantar response, and impairment of the sense of position in the right leg. Arteriography and ventriculography were suggestive of a left-sided parasagittal space-occupying lesion. However, a biopsy from the left parietal lobe failed to reveal any tumor. Patient received roentgen-ray therapy postoperatively, followed by some improvement of his symptoms.

About 2 years after the onset of his right-sided signs, left-sided weakness and ataxia developed. Examination at this time disclosed a complete left hemiparesis, bilateral extensor plantar responses, and diminution of sensory perception on the left side of his body. The cerebrospinal fluid contained a total protein of 170 mg. per 100 c.cm. It was felt that a right cerebrovascular accident was responsible for the left-sided signs, in addition to the originally suspected left-sided tumor. He continued to deteriorate, became stuporous and died of bronchopneumonia.

Necropsy. The brain was enlarged diffusely and symmetrically, showing signs of increased intracranial pressure in the form of generalized convolutional flattening and bilateral uncal grooving.

Coronal sections revealed two masses of tumor, one in the left and the other in the right hemisphere (Fig. 1a, b). The left-sided lesion was located in the inferomesial part of the frontal lobe, extending from the frontal pole for a distance of 5 cm. to the rostral level of the striatum. The tumor measured approximately 2 X 3 cm. in its maximum diameters, and was quite discrete, firm, and homogeneously pinkish-gray except for scattered hemorrhagic foci. It bulged into the inferior sagittal fissure and rostrum of the corpus callosum without involving these structures, but causing displacement of the anterior horn of the left ventricle superiorly.

The right-sided tumor was located behind the previous lesion superior to the right lateral ventricle and in adjacent basal ganglia. It extended for a distance of 5 cm. from the level of the head of the caudate nucleus to the level of the splenium of the corpus callosum. It measured approximately 3 X 3 cm. in its maximum diameters, was more homogeneous, less vascular and less discrete than the other tumor, and was surrounded by considerable edema. This tumor occupied the gray and white matter of the right cingulate gyrus, the dorsal parts of the caudate nucleus, thalamus, and internal capsule, and the entire body of the corpus callosum without appreciably invading the other hemisphere. Posteriorly, it extended from the thalamus into the right side of the brain stem as far down as the medulla.

Microscopic sections (Fig. 1c) showed both tumors to be similar in appearance, being composed of a compactly cellular and pleomorphic tissue. The cells varied from elongated to round forms possessing scant cytoplasm and hypochromatic nuclei to typical gemistocytic astrocytes. There were very numerous multinucleated giant

![Fig. 1. Case 1. (a) Two tumors, in inferomesial region of left frontal lobe and in superior periventricular region of right frontal lobe; (b) posterior extension of latter into right cingulate gyrus, basal ganglia and corpus callosum (note cyst in left hemisphere from old operative exploratory procedure).](image-url)
cells but relatively infrequent mitoses. Specific stains revealed sparse production of glial fibers by the neoplastic cells. Vascular proliferation and pseudopalisading necrosis were encountered but were not conspicuous. The histologic diagnosis was glioblastoma multiforme.

In the region of the uninvolved genu of the corpus callosum, rare tumor cells were seen either singly or in small nests, extending from one hemisphere to the other. The ependyma generally was intact except in the highly infiltrated inferior surface of the corpus callosum. The leptomeninges were invaded only in areas directly overlying tumor growing on the surface, as in the parasagittal region. The more extensive right-sided lesion failed to involve the opposite side except for very slight invasion through the corpus callosum and through the median raphe of the pons. There was thus no definite microscopic evidence of connection between the two tumors.

Case 2 (LPNI #5858).

Clinical History. E.L., a 58-year-old, white woman had her first symptoms 5 weeks prior to death. These began suddenly with nausea, dizziness, and left frontal headaches, followed rapidly by right hemiparesis involving both upper and lower extremities, expressive aphasia, perception of bad odors and alteration in taste. Following a brief period of improvement, her right hemiparesis increased and became associated with impairment of sensory perception on the right side and complaints of blurred vision.

Neurologic examination on admission to the hospital disclosed a right homonymous hemianopsia, a right central facial weakness, a right hemiparesis with increased deep tendon reflexes, and diminution of perception of light touch and pain, as well as astereognosis, on the right side. Electroencephalogram showed a left temporoparietal focus. Following left carotid arteriography, there remained some doubt as to whether the lesion was vascular or neoplastic in nature. A pneumoencephalogram then was performed, which showed a shift of the right anterior horn towards the right side. The cerebrospinal-fluid pressure was 540 mm of water, and the fluid contained 56 mg. of protein per 100 c.c.m. Following this procedure, the patient's symptoms became more marked; she lapsed into stupor and expired on the following day.

Necropsy. The brain was asymmetrical, showing enlargement and flattening of the left hemisphere. Signs of increased intracranial pressure were apparent in the form of uncal grooving and coning of the cerebellar tonsils, more marked on the left.
Coronal sections (Fig. 2a) disclosed two discrete masses of tumor, both situated in the left hemisphere. The larger was approximately $4 \times 3 \times 2.5$ cm. and was located within the paracentral and superior parietal lobules. In its rostral part this tumor was entirely subcortical, consisting of a large necrotic cavity, while posteriorly it was solid, homogeneously pinkish-gray, contained scattered hemorrhages, and infiltrated both the cortex and the white matter. It extended to the meningeal surface but did not come into direct contact with the ventricular system, merely compressing the left lateral ventricle.

The second tumor measured approximately...
3.5×3×2 cm., was solid throughout and was only slightly hemorrhagic. It occupied the left hippocampal formation throughout its extent, and ended posteriorly in the cortex forming the superior lip of the calcarine fissure. This tumor came into direct contact both with the meningeal surface and the ventricular wall. Hemorrhagic foci were scattered throughout the upper brain stem as a complication of uncal herniation.

Microscopically (Fig. 2b), both tumors were identical in appearance, being compactly cellular but not conspicuously pleomorphic. They contained slightly elongated to round cells with scant cytoplasm and vague processes, hyperchromatic nuclei with frequent mitotic figures, but rare multinucleated giant cells. There was no evidence of glial-fiber production by the tumor cells. The degree of vascular proliferation and endothelial hyperplasia was moderate in both tumors. Hemorrhage and necrosis were more apparent in the cystic lesion of the parietal lobe, where necrosis often assumed the characteristic pattern of pseudopalisading. The histologic diagnosis was glioblastoma multiforme.

The microscopic sections failed to disclose a direct connection between the two masses of tumor since there was no neoplastic infiltration of such intervening connecting structures as the corpus callosum and fornix. The leptomeninges were infiltrated only locally and although the ependymal lining of the temporal horn was disrupted by tumor cells, distant implants were not observed.

Case 3 (LPNI #7564).

Clinical History. A.S., a 56-year-old, white man, was in good health until 5 months prior to his death. He was known to be a chronic alcoholic. The first symptoms noted by his family were mental confusion, loss of memory, and hostile behavior. Patient then was committed to a state hospital with the diagnosis of chronic brain syndrome caused by alcoholism.

Examination on admission confirmed that the patient was confused and that his memory was impaired. His motor activity was decreased, and his pupils reacted sluggishly. Over a period of approximately 4 months he became increasingly unable to walk, tending to fall backwards, but no localizing neurologic signs or symptoms were noted. Towards the end he became comatose, at which time he exhibited bilateral extensor plantar responses, and died of bronchopneumonia.

Neuropsy. The brain was enlarged diffusely, particularly the left temporal lobe, where marked hippocampal herniation was present.

Coronal sections (Fig. 3a) revealed three separate, poorly circumscribed, highly vascular, hemorrhagic, and necrotic masses of tumor. The largest lesion occupied the left temporal lobe, extending along its dorsolateral surface from the pole to the posterior end of the lobe, surrounded by edema which resulted in partial occlusion of the temporal horn. A second tumor involved the genu and anterior part of the body of the corpus callosum whence it grew downwards into the septum pellucidum; it bulged into the anterior horns of both ventricles, more on the left side, resulting in shift of the ventricles to the right. A third apparently separate tumor was located near the second lesion within the right hemisphere, just dorsal to the putamen at the level of the anterior limb of the internal capsule, whence it extended ventrolaterally to involve the adjacent external capsule and insula. Multiple hemorrhages and infarcts were disseminated throughout the upper brain stem and left temporo-occipital regions as a result of hippocampal herniation.

Microscopically (Fig. 3b), all tumors were equally pleomorphic and vascular but showed some variability in structure. In some, elongated and round cells with hyperchromatic to vesicular nuclei with numerous mitoses and occasional giant cells predominated, while in others, astroblasts arranged in perivascular rosettes were present, and in still others, gemistocytic astrocytes with sparse glial fibers were most abundant. There were corresponding degrees of vascular hyper-
plasia, being most marked in the least differenti-
dated neoplastic tissue. Necrosis varied from dif-
fuse to pseudopalisading patterns. The diagnosis
was glioblastoma multiforme.

Although the tumor tended to invade the adja-
cent meninges and the ependyma of the lateral
ventricles, there was no evidence of widespread
dissemination nor were there signs of connection
by continuity to account for the multiple growths.

Case 4 (LPNI #7577).
Clinical History. A.S., a 62-year-old man, was
well until 2 years prior to death, when he was
stated to have had an operation for removal of an
intracranial blood clot, presumed to have been a
sequel to trauma. In the following year he began
to have seizures, and showed changes in personal-
ity with threatening behavior. He was committed
to a state hospital with the diagnosis of chronic
brain syndrome caused by trauma.

On admission, the patient was described as
confused and aphasic. There was sustained ankle
clonus and there was impairment of perception of
depth pain on the right side. The deep tendon
reflexes were more active on the left side. Electro-
encephalogram showed a focus in the left parieto-
temporal area. Cerebrospinal fluid contained 137
mg. of protein per 100 c.c.m.

A craniotomy was undertaken, revealing tumor
in the left temporoparietal region. The patient
died in the immediate postoperative period.

Necropsy. The brain was enlarged diffusely,
showing bilateral flattening of gyri, and hippo-
campal and cerebellar pressure cones. Localized
operative trauma was observed at the base of the
left temporo-occipital region.

Coronal sections (Fig. 4a, b) revealed four
separate masses of tumor, two in the left and two
in the right hemisphere. The largest lesion was
located at the operative site in the left temporo-
occipital region. Part of it had been removed and
the remaining tumor occupied the roof of the
blood-containing surgical cavity, appearing as a
discrete grayish and moderately vascular tissue.
It obliterated the posterior horn and was sur-
rrounded by edema. A second similar, though
smaller, tumor occupied the posterior end of the
right cingulate gyrus just dorsal to the splenium
of the corpus callosum, at about the same level as
the previous lesion. Two additional, small tumors
were located respectively within the left thalamus
and the right parasagittal frontal region; they
were relatively avascular, especially the one in the
thalamus.

Microscopically, there were histologic differ-
ences between the various tumors (Fig. 4c, d).
The two vascular lesions contained a compactly
cellular and pleomorphic tissue, the cells varying
from bipolar spongioblasts around areas of necro-
sis, to astroblasts arranged in pseudorosette pat-
terns, to diffuse sheets of astrocytes with sparse
glial fibers. They contained scattered and proli-
fated blood vessels. On the other hand, the right

![Fig. 3b. Case 3. Microscopic structure of a pleo-
morphic glioma with prominent areas of necrosis with
pseudopalisading. Hematoxylin-van Gieson, X15.](image)

![Fig. 4a. Case 4. Two tumors, in base of left temporo-
occipital (operative site) and in right posterior cingulate
regions.](image)
frontal and especially the left thalamic lesions were quite avascular, microcystic and sparsely cellular, the neoplastic cells being predominantly fibrillar astrocytes that produced a network of glial fibers. The over-all diagnosis was considered to be astrocytoma, showing varying degrees of anaplasia.

Despite the occasional local infiltration of the leptomeninges, there was no evidence of connection between the several tumors.

Case 5 (LPNI #8708).
Clinical History. E.E., a 55-year-old, white man, was in good health until 3 months prior to death, when he began to feel unusually tired, became irritable, and pain developed in his neck, followed soon by episodes of nausea, vomiting, and severe frontal headaches. Patient was known to have been a heavy smoker, and had lost 44 lbs. in the previous 2 months.

Neurologic examination on admission showed him to be mentally confused. He had bilateral papilledema. His right arm was weak, and a right extensor plantar response was elicited. The cerebrospinal fluid contained 65 mg. of protein per 100 c.cm. Electroencephalogram revealed a right temporal focus. An arteriogram was inconclusive.

Fig. 4b. Case 4. Two tumors, in left thalamus (above) and in right parasagittal frontal region (below). Weil stain.

Fig. 4c. Case 4. Structure of anaplastic astrocytoma of left temporal region. Hematoxylin and eosin, X128.
while a ventriculogram was interpreted as consistent with multiple tumors in both hemispheres. The patient was believed to have multiple metastatic intracerebral lesions. A needle biopsy was attempted but showed no tumor.

The patient’s condition deteriorated following the operative procedure, and he died 3 days later.

Necropsy. The brain was symmetrical and showed signs of increased intracranial pressure with diffuse flattening of the gyri and bilateral uncal herniation.

Coronal sections revealed three separate tumors; the largest one (Fig. 5a) occupied the right lateral ventricle, extending from the level of the optic chiasm to the trigone. This tumor appeared to originate from the inferior surface of the corpus callosum and underlying fornix on the right side, to which it was firmly adherent. It filled the ventricle completely and compressed the thalamus. It was a grayish, vascular, partly necrotic lesion which measured approximately 3×2.5 cm. in its maximal diameters. The second tumor (Fig. 5b, c) was an ill-defined, small, grayish lesion approximately 1 cm. in diameter that occupied the suborbital white matter of the left frontal lobe. The third tumor (Fig. 5d, e) was the least distinct, appearing as a simple downward enlargement of the left side of the corpus callosum at the level of the anterior horn, into which it bulged.

Microscopic sections (Fig. 5e) of the right intraventricular tumor showed predominantly slender bipolar cells with elongated hyperchromatic nuclei, amongst which were occasional mitoses and multinucleated giant cells. There was moderate vascular hyperplasia accompanied by focal hemorrhage and necrosis. The tumor in the white matter of the left frontal lobe (Fig. 5f) was less vascular but, though pleomorphic, contained many gemistocytic astrocytes. The lesion of the corpus callosum was quite avascular yet pleomorphic, being composed of cells varying from spindle-shaped spongioblasts to fibrillary astrocytes, the latter producing abundant glial fibers. In addition, there was extensive seeding of spongioblasts throughout the leptomeninges and the ventricles, especially in the 4th ventricle. Because of the pleomorphic nature of the several tumors, the diagnosis was considered to be glioblastoma multiforme.

Despite the seeding through the cerebrospinal-fluid channels and occasional isolated tumor cells scattered through the uninvolved parts of the corpus callosum, no definite connection could be established between the several primary tumors.
Discussion

The principal clinical and pathologic features of our 5 cases are summarized in Table 3. It is apparent that multicentric tumors present problems in accurate diagnosis, both clinically and radiologically. While the diagnostic difficulties are not entirely peculiar to multicentric tumors, they may be summarized as follows:

1. Absence of localizing signs referable to either one or both of the neoplasms.

2. Confusion of localizing signs referable to one of the tumors by signs caused by the second lesion.

3. Difficulties in interpretation of radiologic studies when tumors are located in opposite hemispheres, because of the balancing of opposing pressures from the two lesions.

It should be pointed out, however, that
recognition of the possibility of multiple or multicentric tumors could lead to a more precise diagnosis.

Therapeutically, these tumors also pose a problem, since removal of or interference with one lesion, which may be the only suspected one, permits rapid and frequently fatal shifts in intracranial-pressure dynamics. In 3 of our 5 cases death followed ventriculography or pneumoencephalography. Thus we agree with the other authors (Courville, etc.) that the survival period in such cases is apt to be short, being 5 months or less in 3 of our 5 cases.

TABLE 3
Clinicopathologic data on multicentric gliomas

<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical Diagnosis</th>
<th>Radiologic Evidence of Multiplicity</th>
<th>Operation</th>
<th>Duration (mos.)</th>
<th>Site of Tumors</th>
<th>Histologic Type of Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1. Left parietal lobe tumor 2. Right cerebrovascular accident</td>
<td>Yes</td>
<td>Ventriculography and craniotomy</td>
<td>30</td>
<td>1. Left inferomesial frontal region 2. Right cingulate, callosal, basal-ganglia and brain-stem regions</td>
<td>Glioblastoma multiforme</td>
</tr>
<tr>
<td>2</td>
<td>Left parietotemporal tumor</td>
<td>No</td>
<td>Pneumoencephalography, followed by death</td>
<td>1.25</td>
<td>1. Left paracentral and superior parietal lobules 2. Left hippocampus</td>
<td>Glioblastoma multiforme</td>
</tr>
<tr>
<td>3</td>
<td>Chronic brain syndrome caused by alcoholism</td>
<td>No</td>
<td>None</td>
<td>5</td>
<td>1. Left superior temporal region 2. Genu of corpus callosum 3. Right dorsal putamen-insular region</td>
<td>Glioblastoma multiforme</td>
</tr>
<tr>
<td>4</td>
<td>Chronic brain syndrome caused by trauma</td>
<td>No</td>
<td>Craniotomy, followed by death</td>
<td>24</td>
<td>1. Left inferior temporo-occipital region 2. Left thalamus 3. Right frontal parasagittal region 4. Right posterior cingulate region</td>
<td>Anaplastic astrocytoma</td>
</tr>
<tr>
<td>5</td>
<td>Multiple metastatic tumors</td>
<td>Yes</td>
<td>Ventriculography and needle biopsy, followed by death</td>
<td>3</td>
<td>1. Right lateral ventricular region 2. Left orbital region 3. Left side of body of corpus callosum</td>
<td>Glioblastoma multiforme</td>
</tr>
</tbody>
</table>
Problem of Multicentric Gliomas

Fig. 5f. Case 5. Structure of frontal tumor, composed chiefly of astrocytes accompanied by vascular proliferation. Hematoxylin and eosin, X128.

Pathologically, the tumors in the 5 cases could be classified as glioblastoma multiforme or in 1 instance as anaplastic astrocytoma. This is in agreement with the experience of other authors (Russell and Rubinstein, etc.). Within these histologic classifications, the tumors do not reveal any characteristic features, which would distinguish them from similar gliomas not exhibiting multicentric behavior of growth. The histology of the separate lesions in any one case usually is similar, with variations no greater than those observed commonly in different regions of a solitary tumor.

On occasion oligodendrogliomas and ependymomas have been reported to exhibit multicentric behavior. Reports of multicentric ependymomas must be viewed critically, in light of the known tendency of these tumors to seed within the cerebrospinal-fluid channels. While we feel that the tumors described here satisfy the criteria for multicentric lesions set forth initially, we, nevertheless, think it is desirable to point out that even some of these cases display features that may, at some future time, lead to their designation as multiple rather than multicentric tumors. In Case 1, scattered tumor cells in the corpus callosum may have served as a link between the lesions in the two hemispheres. Our observations, however, lead us to believe that, in general, extension of gliomas takes place massively and over a broad area, rather than through tenuous bridges of neoplastic cells. The latter process, mentioned by Taylor and by Zülch, raises the interesting problem of why tumor cells may grow singly or in clumps in one area, while they blossom into a massive growth at a more distant site. Perhaps some substrates within the central nervous system are more suitable to growth of tumor than others.

Local infiltration of the leptomeninges and ependy whole adjacent to the glioma was not a rare observation in our cases. It is quite possible that cells may enter the cerebrospinal-
fluid channels through this route, and that superficially placed distant foci may result from their implantation in a suitable substrate. Case 4 contained several such superficial areas of tumor. One can also question whether such foci originate from tumor cells that become lodged in the potential Virchow-Robin spaces or whether they reach distant points by other means. However, the relatively great rarity of multicentric lesions as compared to the frequent observation of local leptomeningeal infiltration over gliomas, must be taken into consideration, and would tend to speak against an explanation on these grounds.

The pathogenesis of multicentric tumors has remained unknown in our present state of knowledge. Various hypotheses of the mode of growth in gliomas, in general, have been advanced, which might offer an explanation for multicentricity.

Based on the Cohnheim theory of embryonal rests, Ostertag was of the opinion that gliomas grow from primitive cells that were displaced during development of the central nervous system. Such cells have a blastomatous potential, which finds its expression in later life. If displaced multipotential cells are assumed to be present simultaneously, they may develop into “coordinated blastomas” at various points throughout the central nervous system, thus accounting for multicentricity. This dysontogenetic concept fails, however, to account for the long delay between development of the brain and clinical manifestations of the tumor, which may not take place until 40 or 50 years later. Other objections, in particular the scant direct evidence for the presence of such multipotential cells, have been raised against this theory.

Willis suggested that multicentric lesions could result from a twofold process, the first stage being one of neoplastic transformation, which makes a wide field, perhaps even the entire brain, more susceptible to neoplastic growth. The second stage, which may overlap the first, can be considered as a process of progressive neoplastic proliferation, which then might occur simultaneously at several sites. The stimuli for these processes conceivably might be of a wide variety, including biochemical, hormonal, or even mechanical.

Zülch stated, with reference to multicentric lesions, that “the possibility of metastases along some pathway as yet unknown to us,” such as via the subarachnoid cerebrospinal fluid, has to be considered.

Our knowledge of the mechanisms of origin, growth and extension of tumors within the central nervous system is still too limited to permit us to arrive at a solution to these hypothetical considerations. However, the establishment of more precise criteria for multicentricity and multiplicity of gliomas may at least help us to focus more sharply on this most interesting aspect of tumor growth.

**Summary**

1. A survey was made of the incidence of “multicentric gliomas” based on reports from the literature.
2. Out of a total of 209 gliomas in authors’ own autopsy material, 5 instances of multicentric gliomas were found and their clinicopathologic features were analyzed.
3. The theoretical basis for multicentric growth is discussed.

**References**


