THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME XXXI JANUARY-FEBRUARY, 1955 NUMBER 1

THE NATURE OF GLIOMAS AS REVEALED BY ANIMAL EXPERIMENTATION *

H. M. ZIMMERMAN, M.D.

From the Laboratory Division, Montefiore Hospital, New York 67, N.Y.

Primary intracranial neoplasms in man comprise from 2 to 5 per cent of all tumors in the body. Of these neoplasms, somewhat less than half belong to the glioma group. The latter comprises at least seven universally recognized, distinctive types as well as a number of related subtypes. The major types are: astrocytoma, astroblastoma, ependymoma, glioblastoma multiforme, medulloblastoma, oligodendroglioma, and spongioblastoma polare. To the subtypes belong, among others, the ependymoblastomas, ganglioneuromas, and medullo-epitheliomas.

The problem of identification and classification of tumors of the glioma variety has not been simple, mainly for two reasons. One is that neurosurgical pathology is still in that early developmental stage which is preoccupied with descriptive morphology and with finding new tumor types to classify. Thus it is still considered somewhat of an achievement to have divided the astrocytoma into the piloid, fibrillary, and protoplasmic types, even though the histogenesis and biologic behavior of this tumor does not seem to warrant such subclassification. The other is that a vastly complicated terminology has developed which has greatly discouraged students in this field. The concept is also current that a battery of complicated and difficult staining techniques is essential for the identification of the various gliomas. The general pathologist has shunned the field of neurosurgical pathology because of his belief in the almost insurmountable complexity of the intracranial neoplasms.

* This investigation was supported by a research grant (C-1082) from the National Cancer Institute of the National Institutes of Health, Public Health Service. Published with the aid of a grant from the Sandy Schneider Memorial Fund.

Presented in the Symposium on Diseases of the Nervous System and of the Neuromuscular Apparatus at the Fifty-first Annual Meeting of the American Association of Pathologists and Bacteriologists, Philadelphia, April 9, 1954.

Received for publication, April 23, 1954.

Terminology of Gliomas

Gliomas have their origin from the cells of the glial stroma of the brain and spinal cord. These cells include the astrocytes, oligodendroglia, and ependymal cells. The fourth basic glial cellular component, the microglia, evidently does not participate in the production of neoplasms; at least there are no generally recognized tumors which can be traced to this cell type.

The morphologic variations in gliogenous neoplasms with the attendant complexity in their classification was brought into some order by Bailey and Cushing[1] in 1926. Their nomenclature of gliomas was based on the histogenesis of the nervous system. The classification they advocated has the advantage of long usage and wide acceptance. It has the added advantage of specific terminology for morphologically distinct entities and permits fairly accurate prognosis. It is their classification of the seven common types of glioma which was given at the outset of this presentation.

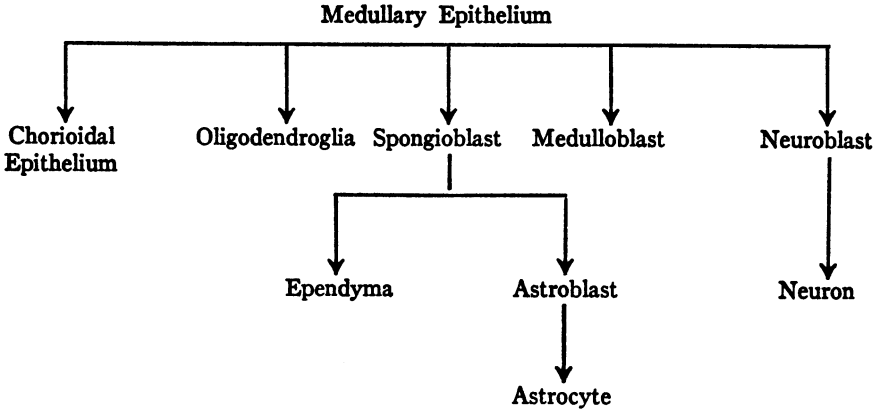
The obvious disadvantages of this classification are the rather large number of individual tumors included and the fact that certain gliomas are derivatives of more than one basic glial type; that is, certain gliomas are of "mixed" origin and defy classification. Efforts have been made from time to time to simplify the terminology, and recently by Kernohan, Mabon, Svien, and Adson.[2] These workers suggested a classification which is based on the idea that gliomas arise from the pre-existing adult astrocyte, oligodendrocyte, and ependymal cell. This concept provides three basic glial neoplasms: astrocytoma, oligodendroglioma, and ependymoma. Kernohan and his co-workers assumed that more malignant neoplasms develop from these basic types by a process of dedifferentiation. For example, in their classification the glioblastoma multiforme is merely an astrocytoma of grade III or IV as to degree of malignancy.

There are at least four important faults to be found with this approach. One is that in reality the classification is no simpler than the one adopted by Bailey and Cushing.[1] If four numerical designations for each of the three basic types of glioma are employed, as proposed by Kernohan and his associates,[2] to designate morphologically distinct tumors, there are still twelve gliogenous neoplasms to be diagnosed. Another objection is the one inherent in all classifications which resort to numerical grading of degrees of malignancy. It implies a prophetic capacity on the part of the pathologist which is often not fulfilled by the clinical outcome. Still another objection is the failure of the classification to provide for the medulloblastoma in a scheme of tumors originating from the three adult glial cell types. But perhaps the major

fault with the scheme is the assumption that each glioma takes origin from a single cell, such as an astrocyte, and that the developing tumor is merely the result of proliferative activity on the part of that glial element. Actually, as will be shown presently, many if not all gliomas contain mixtures of different proliferating gliocytes. Experience has further indicated that classification of any one tumor is valid only after extensive sampling, a fact which was stressed by Scherer[8] in 1940.

The Nature of Human Gliomas

It is generally accepted that the different glial cells of the mature nervous system, with the possible single exception of the microglia, are all derived from embryonal neurectoderm as shown in the schema.



Schema to show origin of adult cellular constituents of the brain from medullary epithelium.

This origin the glia share in common with the neurocytes. Further, the primitive neurectoderm or medullary epithelium differentiates by recognizable stages to the fully mature glia. These adult cells may give rise, under certain conditions, to glial neoplasms by dedifferentiation. Implicit in this concept are two conditions: (1) that the adult glial cells undergo malignant change and by proliferation give rise to the neoplasm; (2) that the proliferating cells proceed through stages of dedifferentiation ultimately to achieve degrees of uniformity which permit classification.

Almost every glioma contains, in addition to the distinctive cells from which its name is derived, variable numbers of other glial elements. Classification of a gliogenous neoplasm is thus based upon the identification of the most malignant cells present and/or the predominance of one kind of cell. Yet every neuropathologist frequently finds himself in a dilemma when he abides strictly by these criteria for classification. An example of this problem in tumor diagnosis is offered by

the following case of a white male, 53 years old, whose frontal lobe biopsy (Fig. 1) at an exploratory craniotomy revealed a cystic astrocytoma. Nothing in this neoplasm hinted of the course this patient was to follow, for within 1 year he returned for re-operation because of recurrence of the tumor. The second operation yielded an astrocytoma once again (Fig. 2). This time the tumor was no longer cystic and it was considerably more cellular, but the presence of calcium salt deposits was in keeping with a diagnosis of a benign astrocytoma. Yet within 7 months the patient was back in the hospital and after a stormy course of less than 4 months he succumbed. At necropsy a huge tumor was found replacing much of the right cerebral hemisphere, infiltrating the basal ganglions, and extending into the left hemisphere by way of the corpus callosum. Microscopic study of the neoplasm (Fig. 3) revealed large zones of necrosis with spongioblasts forming the typical pseudopalisades of a glioblastoma multiforme. There were thrombosed blood vessels and numerous multinucleated tumor giant cells. Parts of the very large neoplasm still consisted of astrocytoma.

A similar problem was presented by a white sales engineer, 31 years old, who had gradual loss of memory for about 1 year. Increasing somnolence brought him to the hospital where air studies disclosed a tumor in the region of the third ventricle. This was explored and a firm tumor mass was found within the cavity and extending into the adjacent structures. A biopsy specimen from the intraventricular portion (Fig. 4) consisted of a fibrillary astrocytoma. Experience with unusually large, hyperchromatic cells in an otherwise benign appearing astrocytoma counseled a cautious diagnosis, but re-examination of the tissue revealed only the benign astrocytic tumor. The patient failed to respond to the subtotal removal of the neoplasm and died in less than 1 week after craniotomy. The remainder of the tumor in the paraventricular region (Fig. 5) disclosed cellular pleomorphism, giant tumor cells, numerous mitotic figures, perivascular collars of lymphocytes, and necrotizing angiitis. All of these features are common to glioblastoma multiforme.

Neither of these patients received any therapy for their tumors except surgery. The next patient differed in this regard. He was a young man who had a tumor removed by Dr. Leo M. Davidoff in September, 1949. This proved to involve the brain stem, more especially the medulla oblongata, and some of it extended out of the medulla sufficiently to permit a biopsy (Fig. 6). The tumor was an ependymoma with typical cart-wheel perivascular rosettes. The patient made a surprisingly good recovery from his operation and radiation therapy, and was able to return to work for a period of about 2 years. He then

began to slip gradually and finally died in June, 1953. Remnants of the original tumor could still be made out at necropsy in and around the medulla, but much of the neoplasm was now composed of strikingly pleomorphic cells, giant tumor cells, and spongioblasts (Fig. 7). This tumor was no longer, if indeed it ever was, a "pure" or uniform ependymoma. It could best be classified as a malignant glioma if not a glioblastoma multiforme.

The final illustrative case is that of a white male, 30 years of age, who developed increasingly severe headaches for a full year preceding hospitalization and exploratory craniotomy. A large right frontoparietal tumor was found and excised. Microscopically, this tumor (Fig. 8) proved to be a cystic astrocytoma of strikingly uniform appearance. After operation, the patient never felt completely well, experiencing some mild headaches at first which gradually increased in severity. He stated that he felt his "skull just bouncing up and down." He developed photophobia and nausea. A course of x-irradiation totaling 6200 r. was given over the right hemisphere but without noticeable improvement. The patient's condition deteriorated and he died 4 years after operation. The tumor, which had recurred, was found to occupy much of the right cerebral hemisphere at post-mortem examination. Parts of it still presented the appearance of the cystic astrocytoma seen at biopsy; parts were composed of large protoplasmic astrocytes (Fig. 9) with coarse unipolar and multipolar processes; and parts had the wildly pleomorphic appearance of a glioblastoma multiforme (Fig. 10), with zones of necrosis and hemorrhage and a profusion of spongioblasts, astrocytes, and other glial cells.

To these examples of gliomas which are "mixed" tumors at the start and those which apparently become transformed from one type to another spontaneously, or following operative intervention or radiotherapy, may be added many more. Indeed, it is the exception rather than the rule to find gliomas which are composed of but a single cell type. Added examples can be given of oligodendrogliomas which are in part ependymomas, or astrocytomas, or even glioblastoma multiforme, and of polar spongioblastomas which are partially glioblastomas.

The Nature of Experimental Gliomas

At this point we may perhaps examine with profit the contributions which animal experimentation has made to an understanding of the complexities which surround the subject of human gliomas.

For nearly 15 years my associates and I have produced gliogenous neoplasms in several different inbred strains of mice by the expedient of implanting minute pellets of chemical carcinogens in different loca-

tions within the brains of these animals.[4-7] In this way it has been shown that many different adult and morphologically distinct glial cells begin to proliferate almost simultaneously under chemical stimulation to produce a neoplasm. This principle is illustrated in the photomicrograph (Fig. 11) of an incipient glioma which was produced by inserting a pellet of methylcholanthrene into the lateral ventricle of a mouse. The early lesion already shows some injury to, and perhaps also some proliferation of, the ependyma. But in addition there is a lively subependymal glial response in which a number of cells participate. More clearly perhaps can be seen the simultaneous proliferative activity of adjacent glial cells in another animal (Fig. 12). Here the yellow pigment of the carcinogen is found in several altered cells from which the glioma derives. Since the tumor springs into being, so to speak, from several progenitors, it is almost never a "pure" tumor, that is, composed of one cell type, but rather a mixture of several different cell types.

More than 12 years ago Dr. Arnold and I described a mouse which developed a "mixed" or multiple glioma (Fig. 13) in response to methylcholanthrene.[4] Part of the neoplasm was composed of spongioblasts forming pseudopalisades on the edges of necrotic foci as seen in glioblastoma multiforme and part was composed of an oligodendroglioma. More recently, Dr. Maier and I, recognizing that very few experimental gliomas were "pure" tumors and that most were constituted of several different cell types, that is, that they were "mixed," performed the following transplantation experiment.[8] Portions of a single primary brain tumor were implanted subcutaneously into a series of homologous animals. In this way it proved possible to establish sublines of two or more different "pure" tumors. From a single primary malignant glioma, one subline of a "pure" oligodendroglioma (Fig. 14) was obtained which has remained morphologically constant in over 100 serial transplants, and from the same primary tumor another subline of a "pure" ependymoma (Fig. 15) has been derived which has also remained constant throughout a similar number of transplants. This experimental evidence suggests that the glioma is multipotential, by which is meant that it has the ability to become one or another of the seven major types of this class of tumor. The preponderance of neoplastic cells of one type is the sole justification for the appellation chosen for any one tumor as a whole.

Certain experiments performed by my associate Alfred Cohn[9] have thrown some light on the reason for the preponderance of one cell type in a glioma which is "mixed" and therefore contains cells of quite other

types. Starting with a mouse glioma which had the appearance of an ependymoma (Fig. 16) in the original tumor and in a long series of subcutaneous transplants, he grew fragments of the rodent neoplasm in the allantoic membrane of the chick egg with rather startling results (Fig. 17). Each egg passage produced an amorphous mass of tumor cells whose identity even as gliocytes was questionable. When, however, these cells were transferred from the egg to the mouse, the characteristic morphology of an ependymoma was reconstituted. In as many as eight consecutive egg passages the tumor remained amorphous, only once more to become an ependymoma when transplanted subcutaneously to a mouse. These experiments emphasize the important influence which the environment of a tumor has on its microscopic structure. It is conceivable that environments or host factors exert important effects on the ultimate appearance which gliomas assume even in man. Heretofore, emphasis has been directed entirely to the tumor cell as the determining factor in tumor appearance.

Another factor which in large measure determines the appearance or type of an experimental glioma is the location in which the chemical carcinogen is placed within the brain. Dr. Maier and I[8] showed that when the chemical is within the ventricular system, an ependymoma or an ependymoblastoma resulted; in the subcortical white matter, a glioblastoma multiforme developed usually, and, far less frequently, an astrocytoma; in the occipital lobes, the usual tumor was an oligodendroglioma; in the corpus callosum, a spongioblastoma polare; in the cerebellum, the induced tumor was most often the medulloblastoma. This topographic distribution of the experimental gliomas corresponds closely to that of the similar tumors which occur spontaneously in man.

There are other factors which influence the microscopic appearance of gliogenous neoplasms. In experiments dealing with the effect of single doses of x-irradiation on the rate of growth and microscopic appearance of an ependymoma, my associates Netsky, Freid, and Corsentino[10] showed that microscopically detectible changes were obtained with doses as low as 400 r. Subcutaneous transplants of the tumor in control animals showed little or no necrosis and the tumor cells were arranged in the classical rosettes of an ependymoma (Fig. 18). Within 3 days after irradiation of the tumor with a single dose of 400 r. there was partial loss of rosette formation and a concomitant appearance of bizarre tumor cells (Fig. 19). The tumor so treated grew more rapidly than the controls.

With a dosage of 1200 r. to the subcutaneously transplanted ependymoma there was a definite diminution in tumor size at first, but then

its rate of growth exceeded that in the control animals. At 13 days after irradiation the neoplasm (Fig. 20) contained some cells which could be identified as ependymoma but, in addition, there were present many huge multinucleated tumor giant cells and a dense stroma of glial fibers.

The largest single dose employed was 5000 r. Within 4 days after treatment the tumor (Fig. 21) had lost the appearance of an ependymoma. Rosettes were absent and the individual cells were swollen and had pale nuclei. Small foci of necrosis appeared. By the 9th day following treatment the tumor was shrunken and barely palpable, and persisted thus until the 20th day. A photomicrograph (Fig. 22) of the tumor on the 14th day after treatment showed no cells which could be recognized as of ependymal origin. The viable cellular elements consisted of huge, bizarre, and often multinucleated structures. The tumor resumed growth by the 20th day and thereafter increased in size more rapidly than in the controls. Microscopically (Fig. 23), 20 days after the x-ray dosage of 5000 r. the neoplasm still had but scant resemblance to the original ependymoma, but some ependymal cells were in evidence. The tumor thereafter rapidly regained its normal appearance and by the 25th day it was indistinguishable from the control tumors.

These examples will suffice to illustrate the point that gliomas are not always what they seem. The environment in which they find themselves, their sites of origin, and such external influences as roentgen irradiation, all affect their appearance. Perhaps there are many more equally important and as yet undiscovered influences.

Summary and Conclusions

Animal experimentation with gliomas produced with chemical carcinogens has contributed to the clarification of a number of the problems which surround human neoplasms of this type. It has shown that under chemical stimulation many different adult and morphologically distinct glial cells begin to proliferate almost simultaneously to produce a glioma. The resulting tumor is therefore almost never a "pure" glioma composed of cells of one type, but rather a mixture of cells of several different types. In a true sense it is a multipotential neoplasm; i.e., it has the cellular composition and ability to become one or another of the seven major types of this class of tumor. Transplantation experiments have actually proved the validity of this concept, for by judicious selection of explants from a "mixed" glioma, multiple "pure" gliomas may be created by transplantation into homologous animal species. This experience justifies the view that all experimental gliomas are really variants of one tumor type, in the same sense that Hodgkin's

granuloma, lymphosarcoma, and reticulum cell sarcoma are variants of malignant lymphoma.

The principle of multipotentiality is equally applicable to the human gliomas. They, too, like the experimental tumors, are often composed of many different cell types. Some of them, like glioblastoma multiforme, also occasionally have a multicentric origin in different parts of the same or even in the opposite cerebral hemisphere. In these ways also the human gliomas are analogous to the malignant lymphomas. This raises an all-important question; namely, is there any justification for subclassifying the human gliomas?

There is a twofold answer to this question. Firstly, in the evolution of any given glioma a characteristic microscopic structure is usually attained which permits subclassification. The characteristic picture is provided by the predominating glial cell type, but may be influenced also by vascular proliferation, thrombosis, hemorrhage, and necrosis, and sometimes by the appearance of the most malignant of the glial cells participating in the neoplastic process. The second answer to the question, and the more important, is that clinical experience in many instances has shown the validity of prognosis based on the accepted schemes of classification.

What determines the sites of predilection of certain gliomas in the brain? A partial answer to this question is provided by animal experimentation as well as by study of human tumors. Repeated experiments have shown that ependymomas occur when carcinogenic agents are placed in contact with the ventricular wall; medulloblastomas originate almost exclusively in the cerebellum; oligodendrogliomas arise in the subcortical white matter of the cerebral hemispheres. The predominance and availability to malignant change of certain glial cells in different parts of the brain evidently determine the predilection of certain gliomas in different sites.

Animal experimentation has shown also that the environment or the host of a glioma is an important determinant of the type of tumor which develops. An example of this influence is the mouse ependymoma which grows as an undifferentiated malignant glioma in the chick embryo and reverts again to the ependymoma on transplantation to the mouse. And finally, animal experimentation with gliomas has shown that such external factors as x-irradiation may influence both rate of tumor growth and morphologic appearance.

REFERENCES

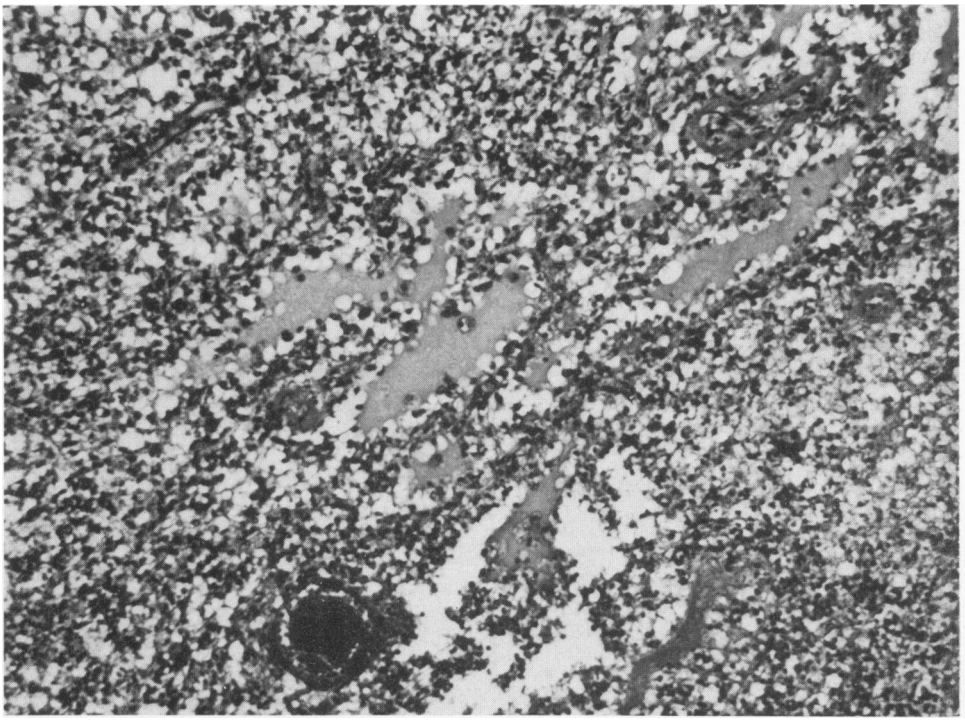
1. Bailey, P., and Cushing, H. A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis. J. B. Lippincott Co., Philadelphia, 1926, 175 pp.

2. Kernohan, J. W.; Mabon, R. F.; Svien, H. J., and Adson, A. W. A simplified classification of the gliomas. *Proc. Staff Meet., Mayo Clin.*, 1949, **24**, 71–75.
3. Scherer, H. J. The pathology of cerebral gliomas. *J. Neurol. & Psychiat.*, 1940, **3**, 147–177.
4. Zimmerman, H. M., and Arnold, H. Experimental brain tumors. I. Tumors produced with methylcholanthrene. *Cancer Research*, 1941, **1**, 919–938.
5. Zimmerman, H. M., and Arnold, H. Experimental brain tumors. II. Tumors produced with benzpyrene. *Am. J. Path.*, 1943, **19**, 939–955.
6. Arnold, H., and Zimmerman, H. M. Experimental brain tumors. III. Tumors produced with dibenzanthracene. *Cancer Research*, 1943, **3**, 682–685.
7. Zimmerman, H. M., and Arnold, H. Experimental brain tumors. IV. The incidence in different strains of mice. *Cancer Research*, 1944, **4**, 98–101.
8. Zimmerman, H. M., and Maier, N. Experimental brain tumors. *Proc. New York Path. Soc.*, 1948–49, pp. 40–42.
9. Cohn, A. Unpublished data.
10. Netsky, M. G.; Freid, J. R.; Corsentino, B., and Zimmerman, H. M. The effect of single doses of x-ray on an experimentally induced glioma. *J. Neuropath. & Exper. Neurol.*, 1952, **11**, 87–88.

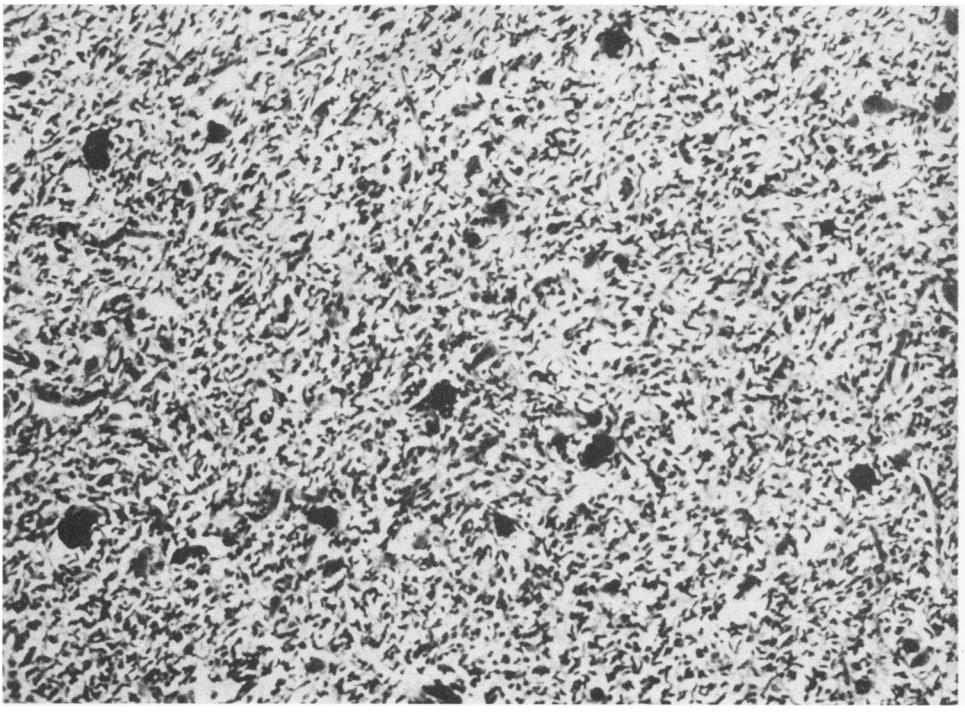
LEGENDS FOR FIGURES

FIG. 1. Cystic astrocytoma in biopsy material from frontal lobe at first operation upon a 53-year-old male. Hematoxylin and eosin stain. × 150.

FIG. 2. Astrocytoma with calcium salt deposits in biopsy material of frontal lobe tumor at second operation upon patient described under Figure 1. Hematoxylin and eosin stain. × 150.



1

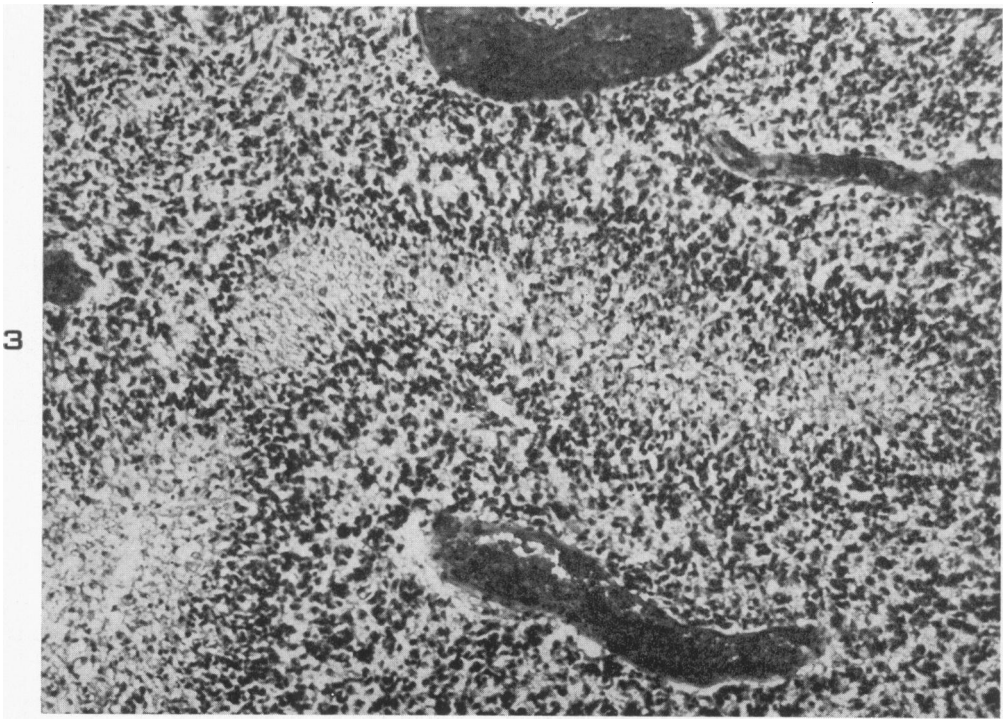


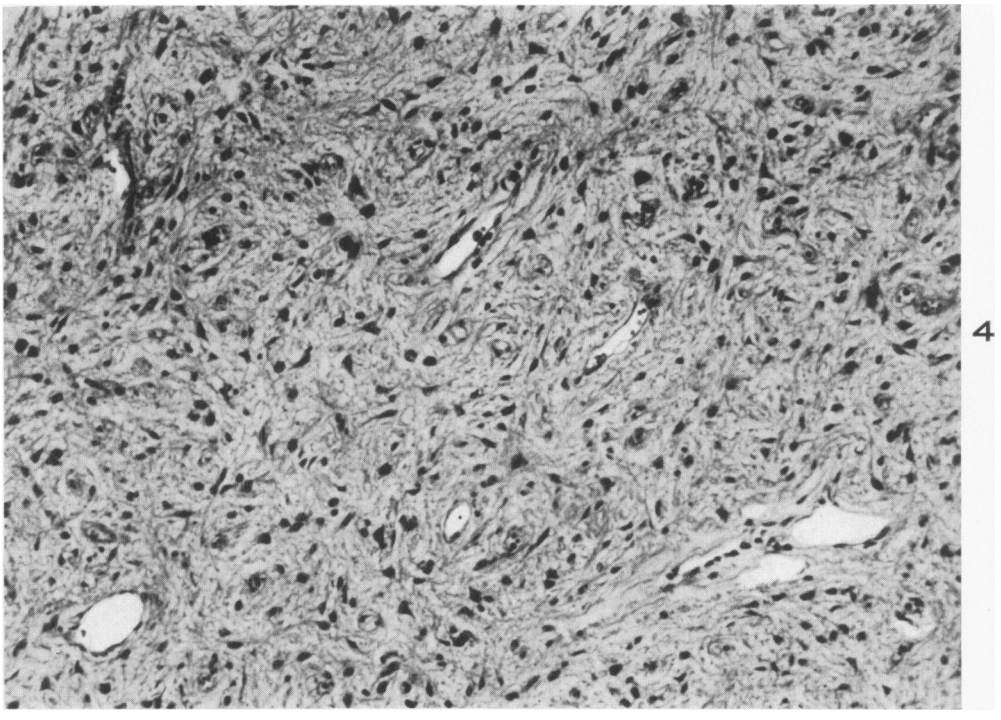
2

FIG. 3. Glioblastoma multiforme found at necropsy in much of right cerebral hemisphere of patient described under Figures 1 and 2. Pseudopalisading of spongioblasts around foci of necrosis may be noted. Hematoxylin and eosin stain. × 150.

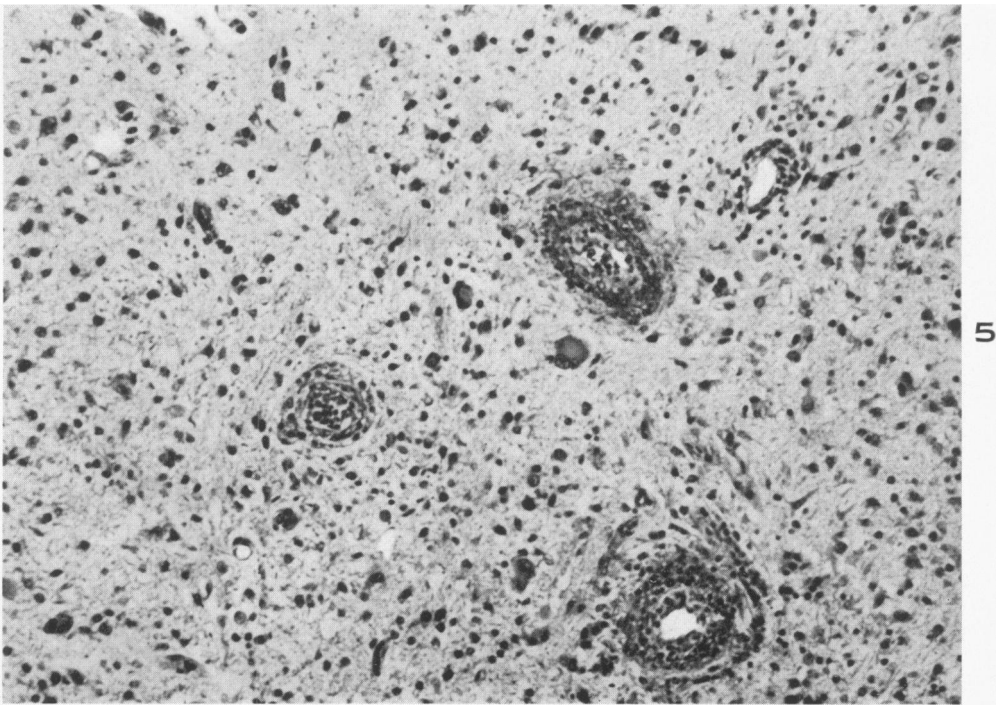
FIG. 4. Fibrillary astrocytoma in 3rd ventricle of a 31-year-old male. Hematoxylin and eosin stain. × 150.

FIG. 5. Necrotizing angiitis and multinucleated tumor giant cells in glioblastoma multiforme of paraventricular extension of the tumor in patient described under Figure 4. Hematoxylin and eosin stain. × 150.





4

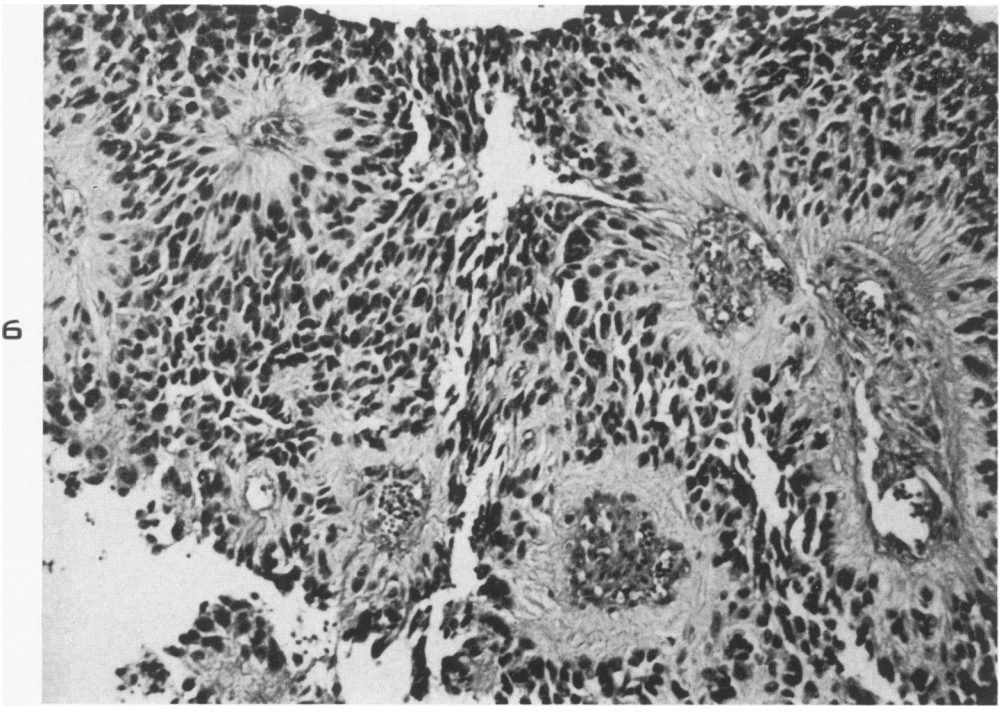


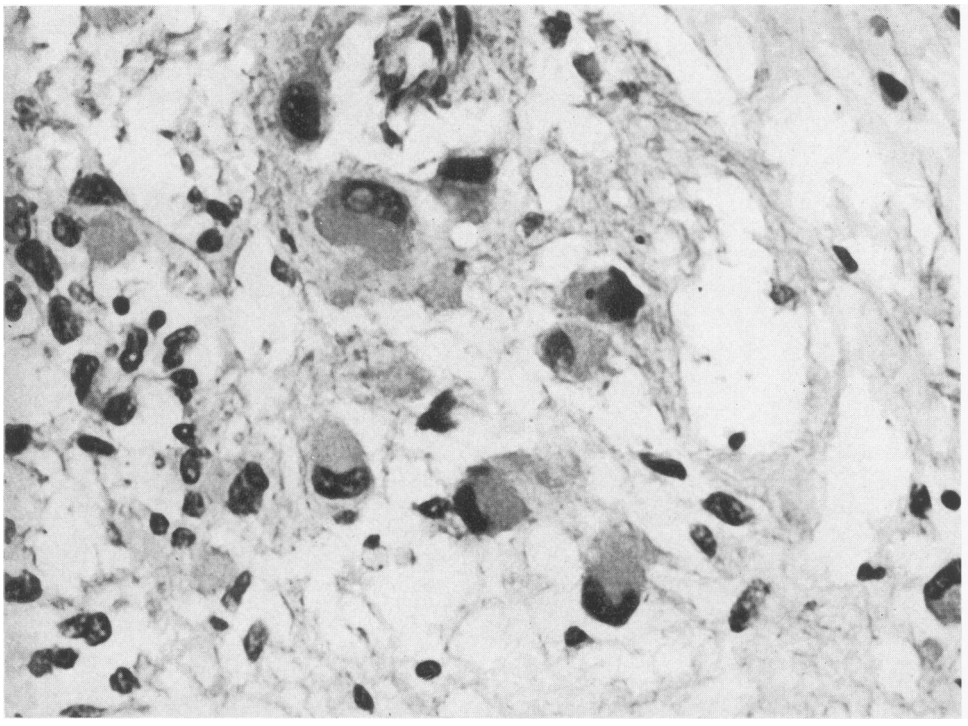
5

FIG. 6. Ependymoma in medulla oblongata of a young male. Of note are the typical rosettes. Hematoxylin and eosin stain. × 150.

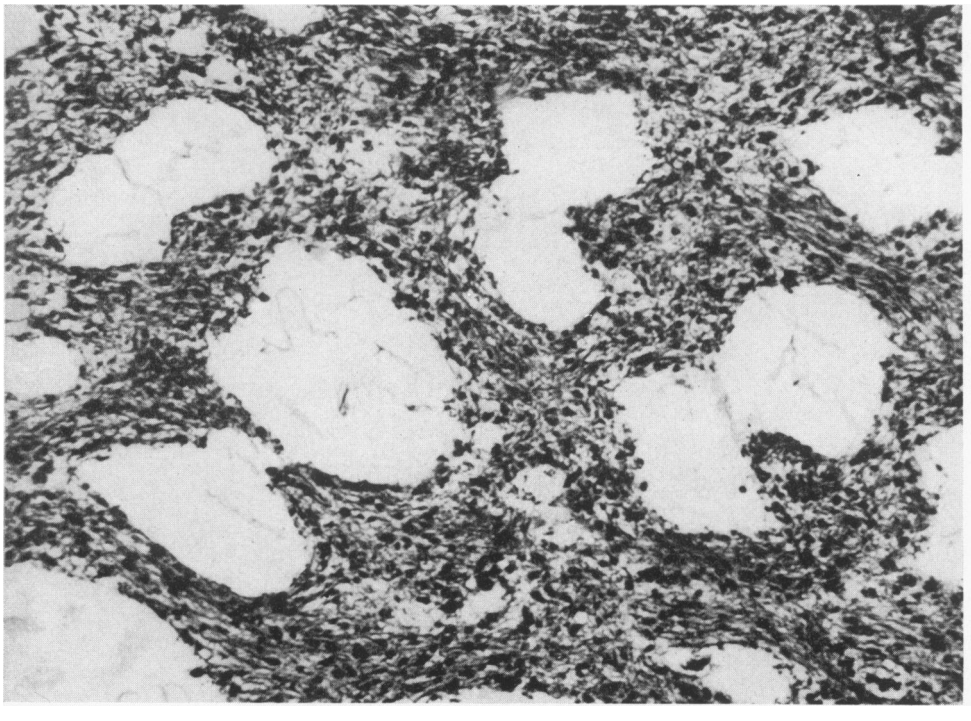
FIG. 7. Giant tumor cells and spongioblasts of the malignant glioma found at necropsy in patient described under Figure 6. Following operation and radiotherapy the patient made a good recovery for about 2 years. Hematoxylin and eosin stain. × 550.

FIG. 8. Cystic astrocytoma found at exploratory craniotomy in a 30-year-old male. Hematoxylin and eosin stain. × 150.





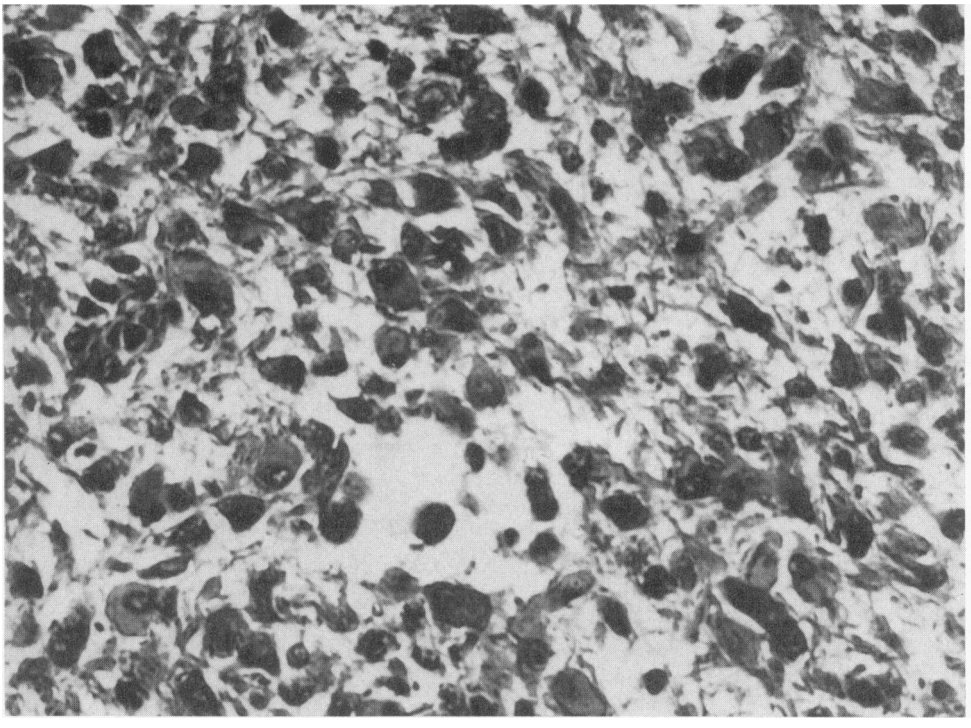
7



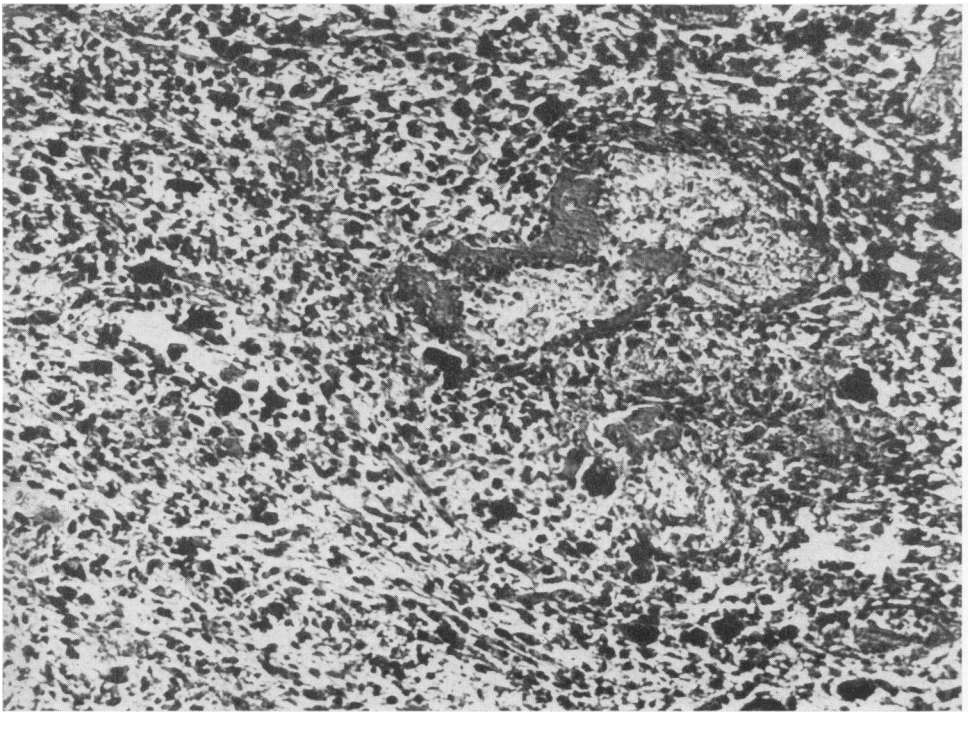
8

FIG. 9. Protoplasmic astrocytes in parts of tumor found 4 years later in right cerebral hemisphere of patient described under Figure 8. Hematoxylin and eosin stain. × 550.

FIG. 10. Pleomorphic appearance of glioblastoma multiforme in parts of same tumor shown in Figure 9. Hematoxylin and eosin stain. × 150.



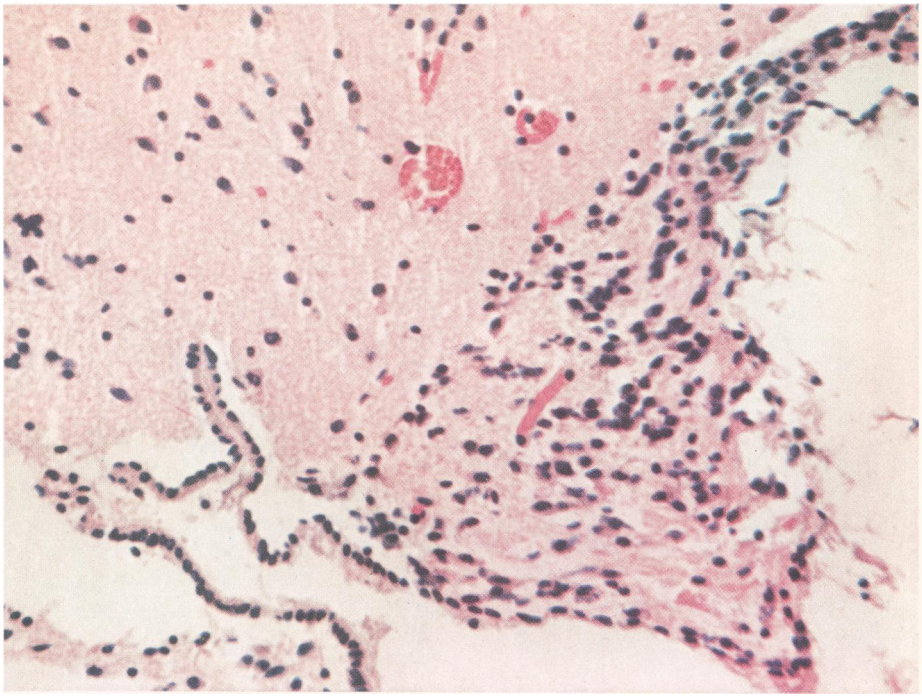
9



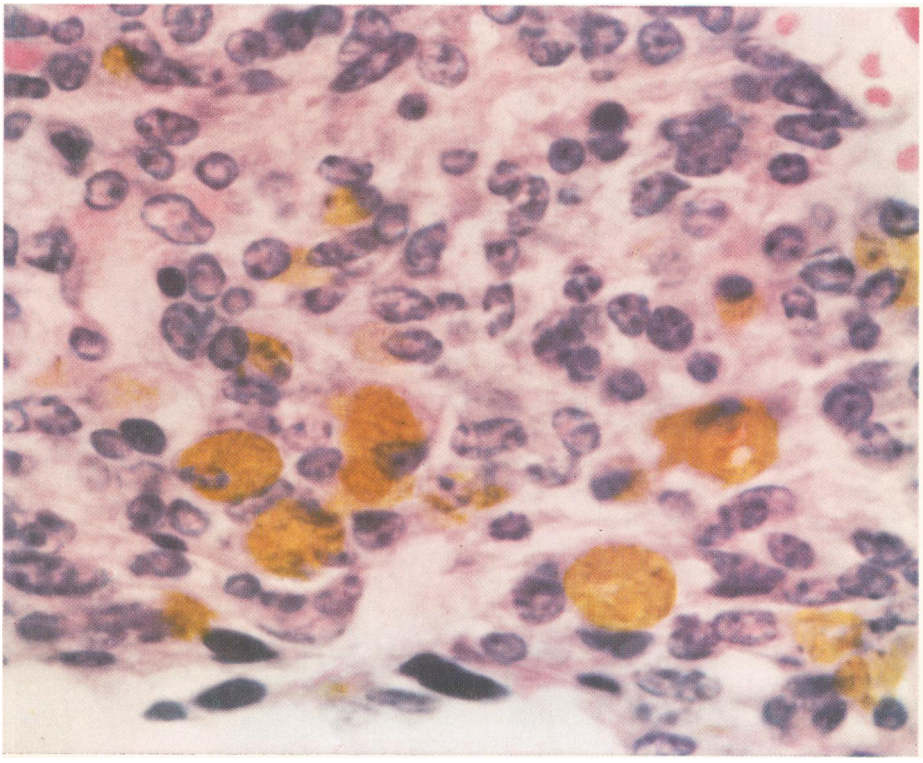
10

FIG. 11. Incipient glioma arising from ependyma and subependymal glia at site of methylcholanthrene implant. Hematoxylin and eosin stain. × 250.

FIG. 12. Incipient glial proliferation involving many different cell types simultaneously. Pigment of methylcholanthrene may be noted in several adjacent and altered gliocytes. Hematoxylin and eosin stain. × 750.

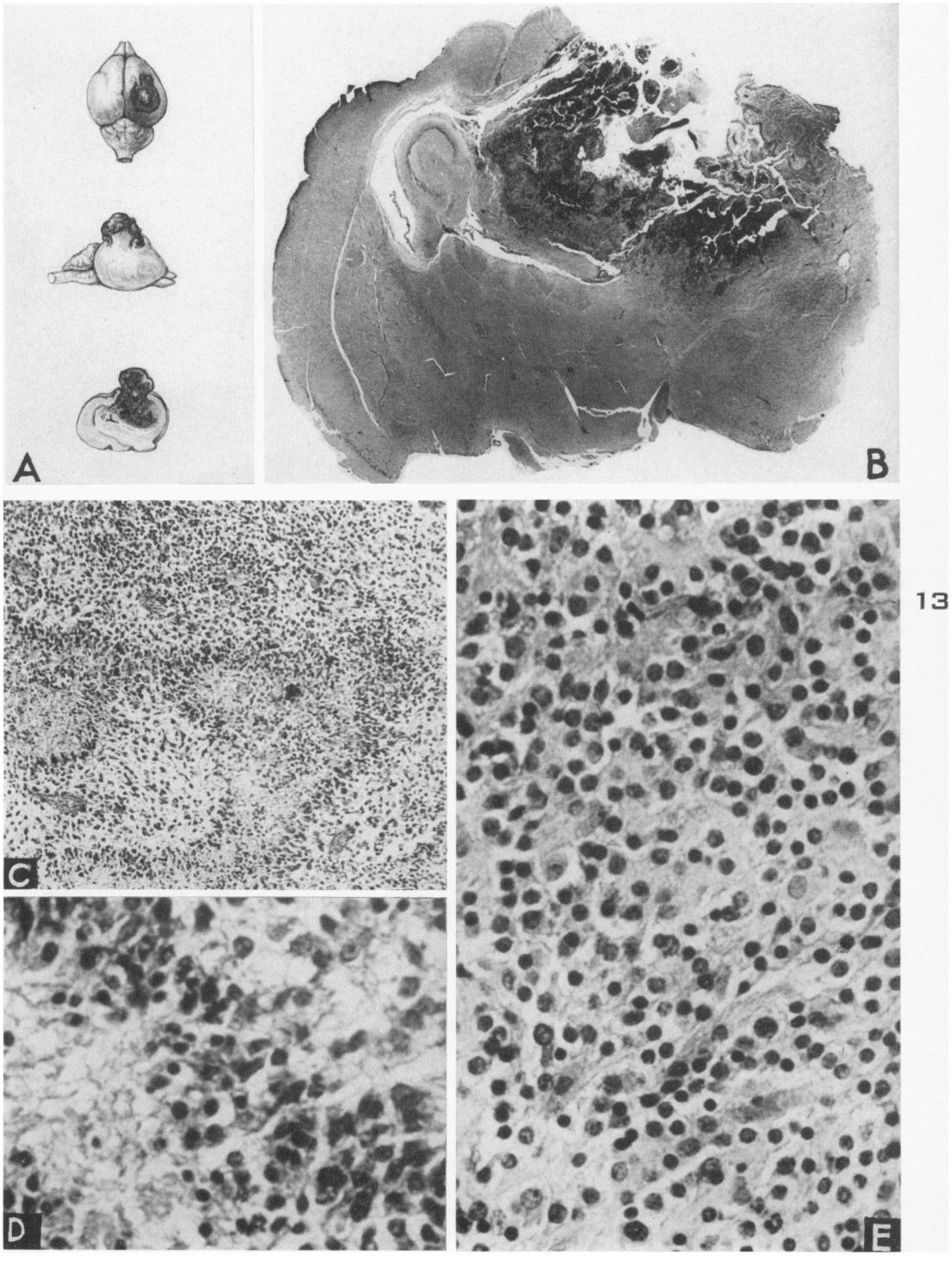


11



12

FIG. 13. Multiple or "mixed" glioma in mouse brain at site of chemical carcinogen. A. Drawing of tumor in right cerebral hemisphere. B. Destruction of basal ganglions by tumor. Hematoxylin and eosin stain. × 5. C. Spongioblasts forming a pseudopalisade as frequently seen in glioblastoma multiforme. Hematoxylin and eosin stain. × 100. D. Spongioblasts under higher magnification. Hematoxylin and eosin stain. × 400. E. Oligodendroglioma as part of the main tumor. Hematoxylin and eosin stain. × 400. Reproduced with permission from Cancer Research, 1941, 1, 919–938, Figure 7.

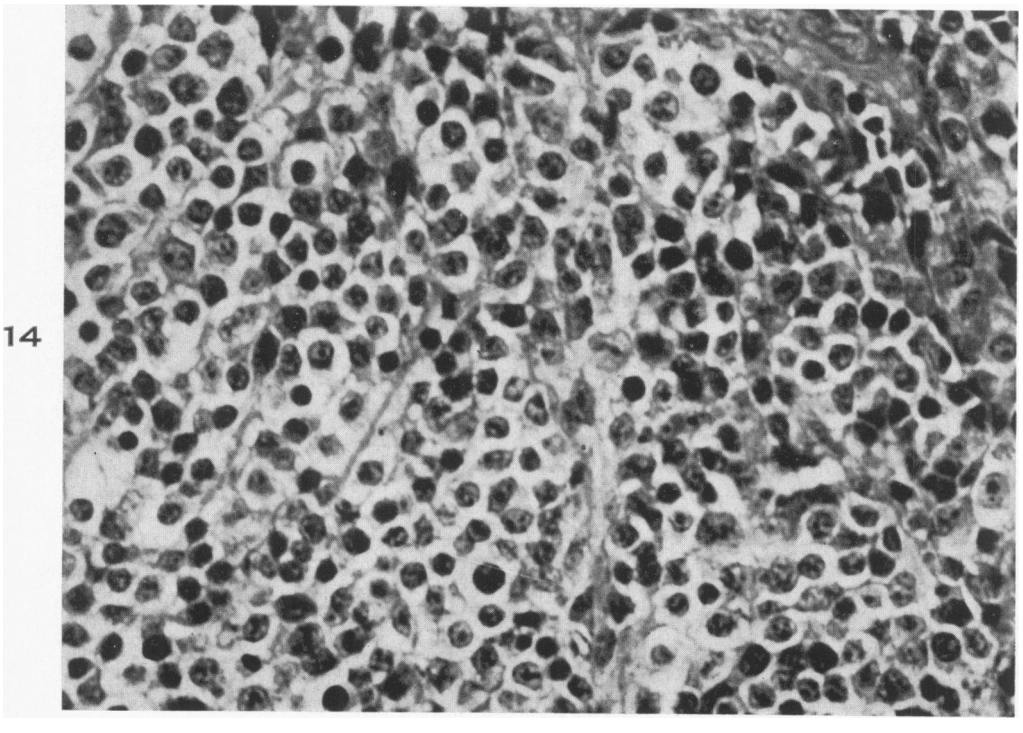


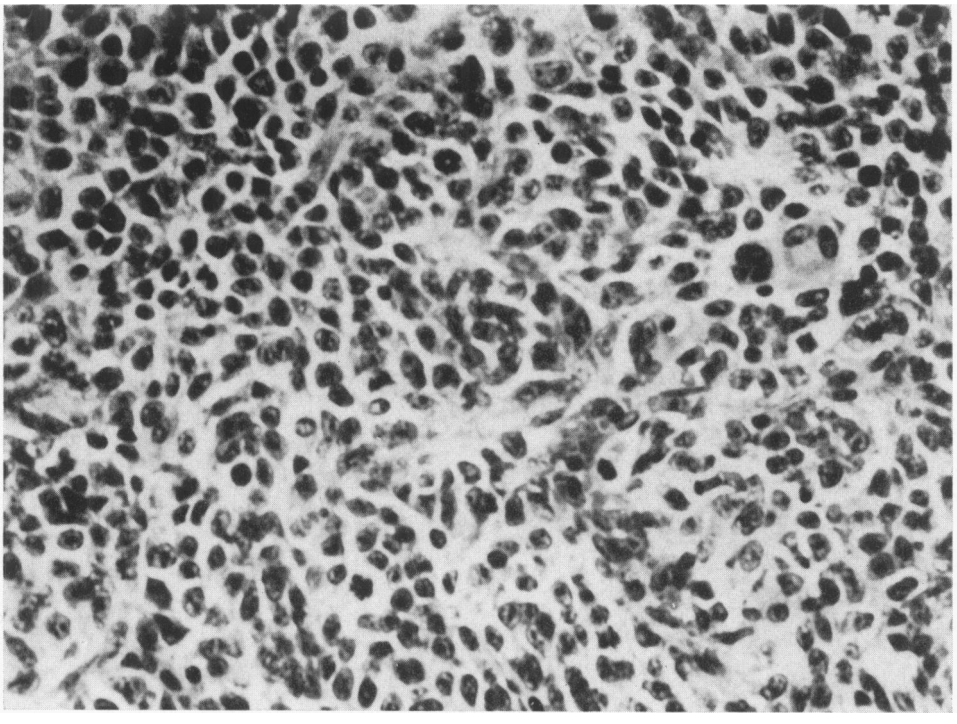
13

FIG. 14. "Pure" subline of oligodendroglioma established by subcutaneous transplantation of a portion of a primary malignant glioma in a mouse. Hematoxylin and eosin stain. × 550.

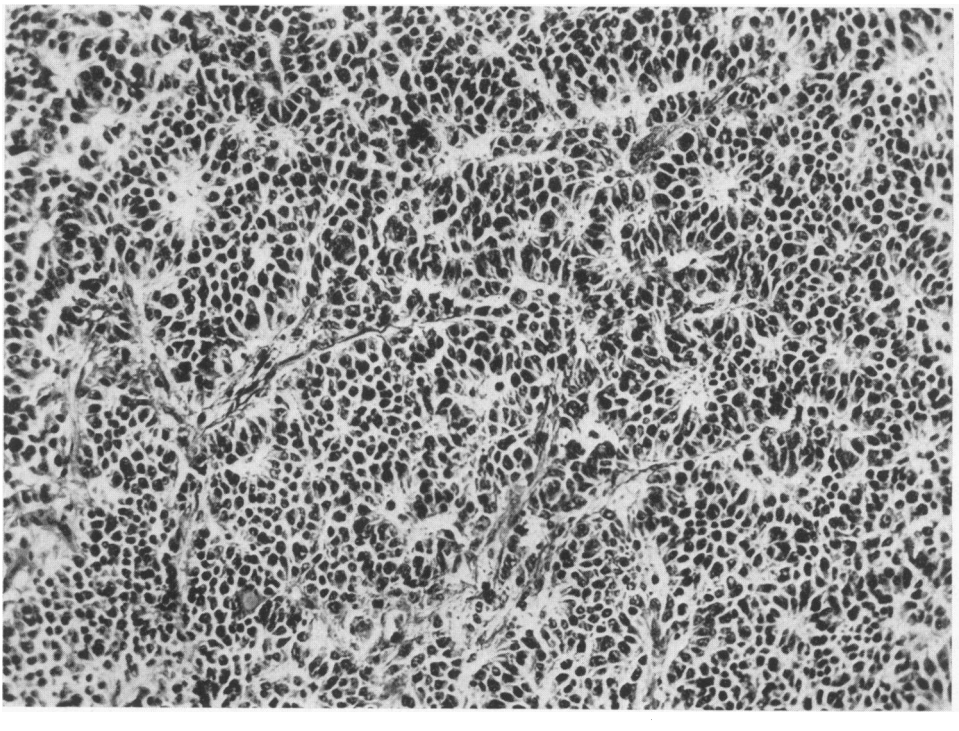
FIG. 15. Ependymoma established as a "pure" subline from same primary "mixed" tumor described under Figure 14. Hematoxylin and eosin stain. × 550.

FIG. 16. Appearance of ependymoma produced in mouse brain with methylcholanthrene. Hematoxylin and eosin stain. × 185.





15

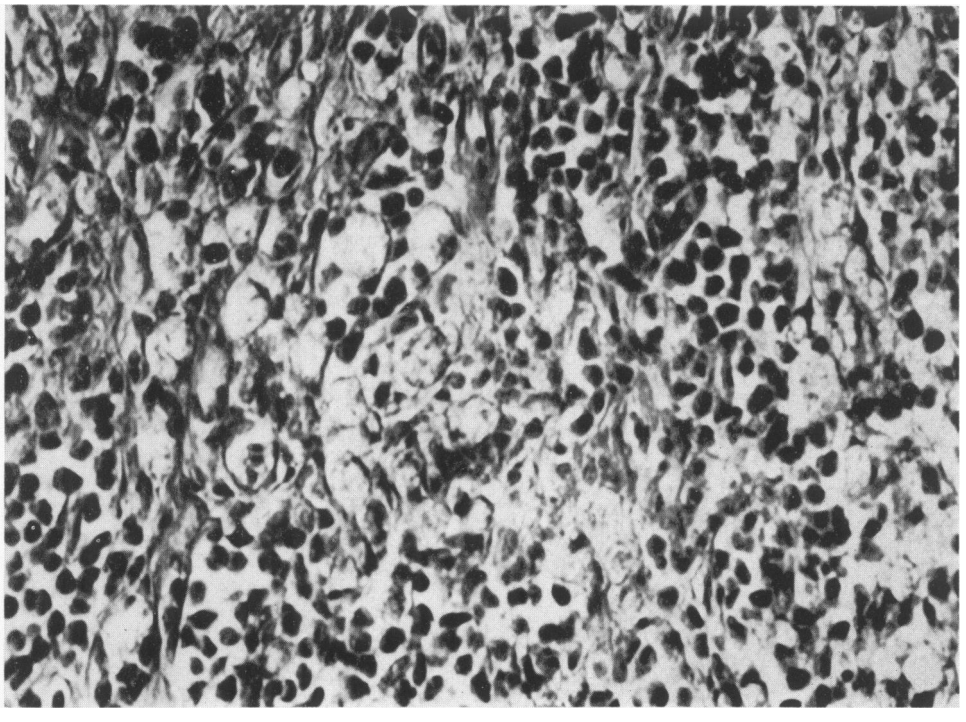


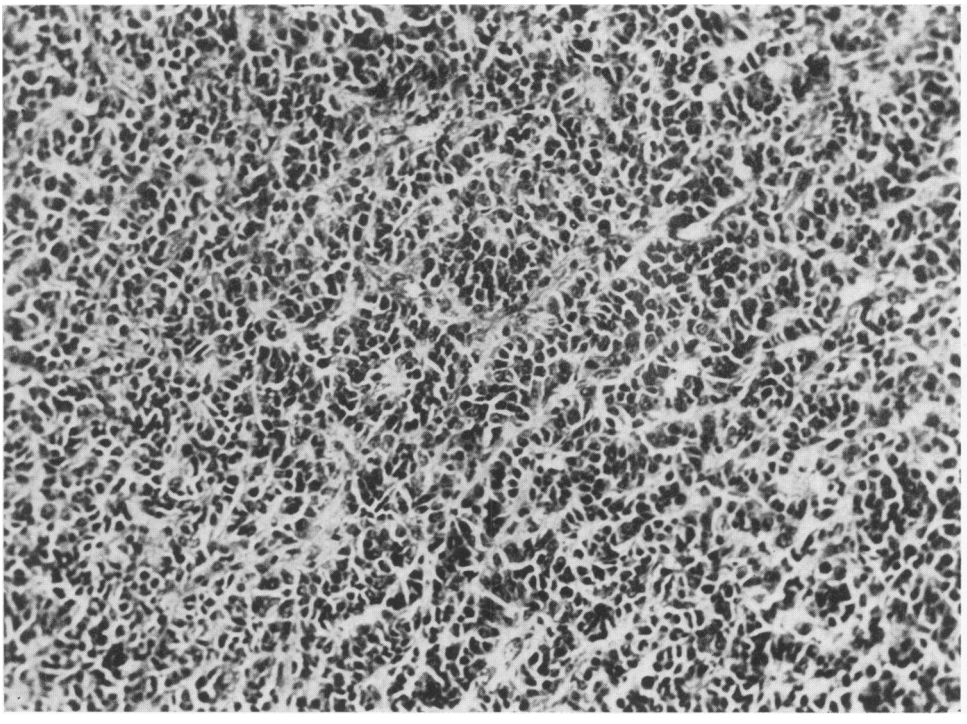
16

FIG. 17. Appearance of glial tumor cells, originally a typical ependymoma in a mouse, growing in the allantois of the chick. Hematoxylin and eosin stain. × 550.

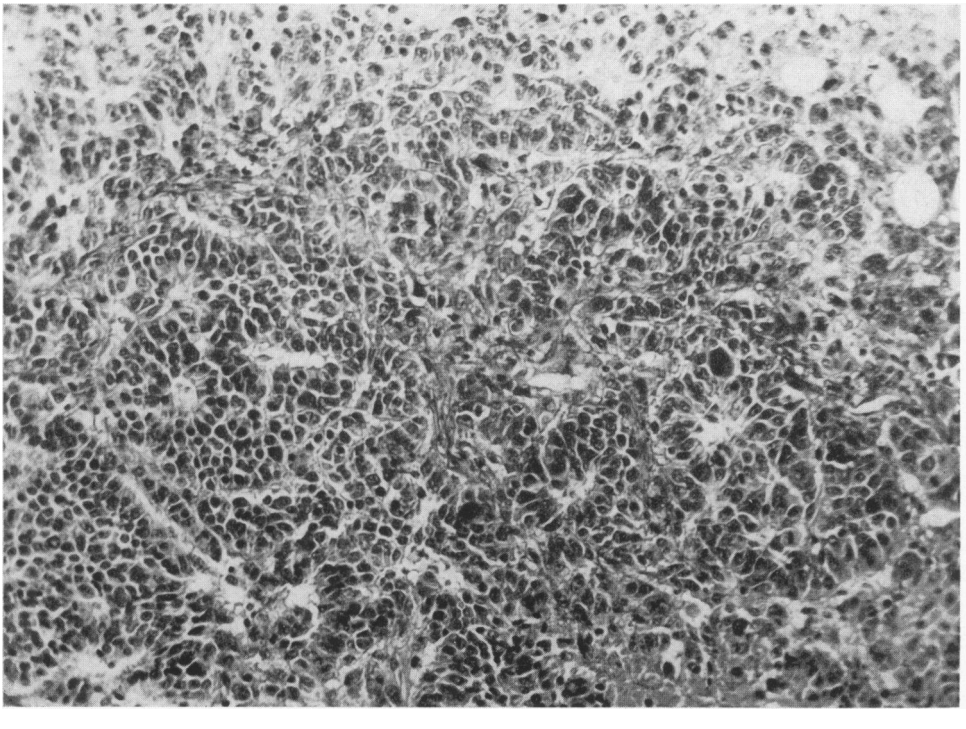
FIG. 18. Appearance of original ependymoma grown subcutaneously in the mouse. Control animal. Hematoxylin and eosin stain. × 185.

FIG. 19. Ependymoma on third day after x-irradiation with single dose of 400 r., showing partial loss of rosette formation and appearance of bizarre cells. Hematoxylin and eosin stain. × 185.





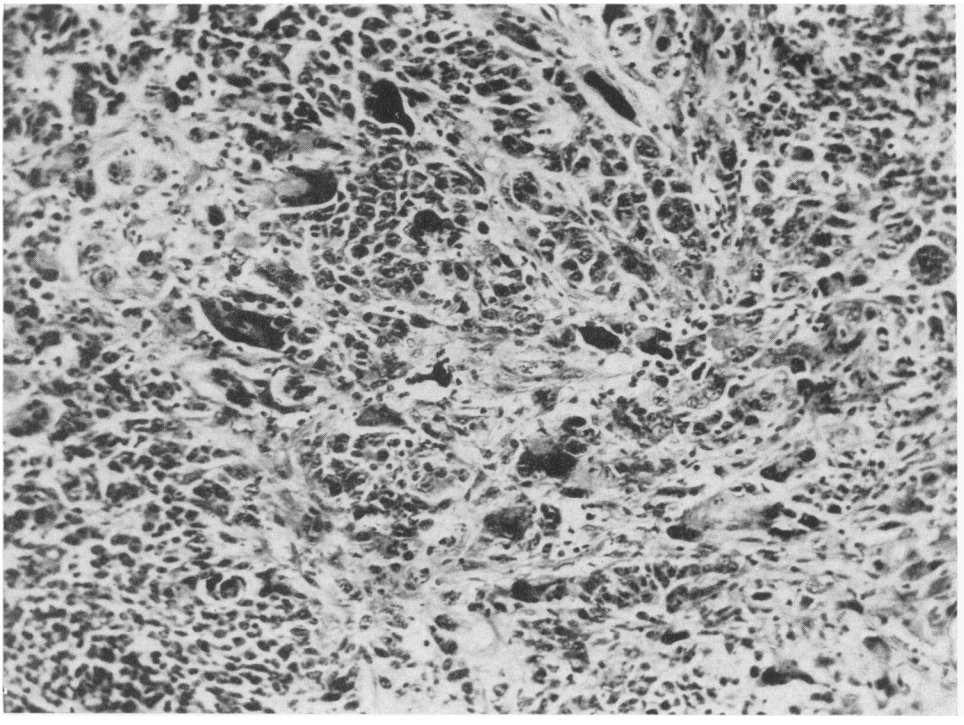
18



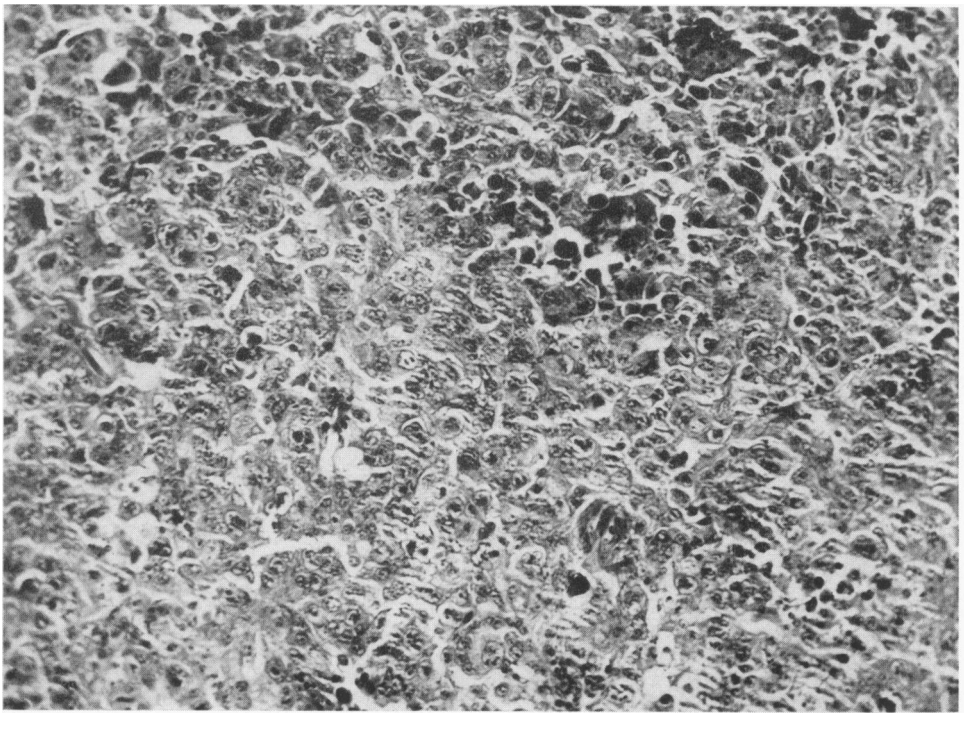
19

FIG. 20. Ependymoma seen on 13th day after irradiation with single dose of 1200 r. Mixture of bizarre giant tumor cells and ependymal glia. Hematoxylin and eosin stain. × 185.

FIG. 21. Appearance of ependymoma on fourth day after radiotherapy of 5000 r. Rosettes are absent; individual cells are pale and swollen. Hematoxylin and eosin stain. × 185.



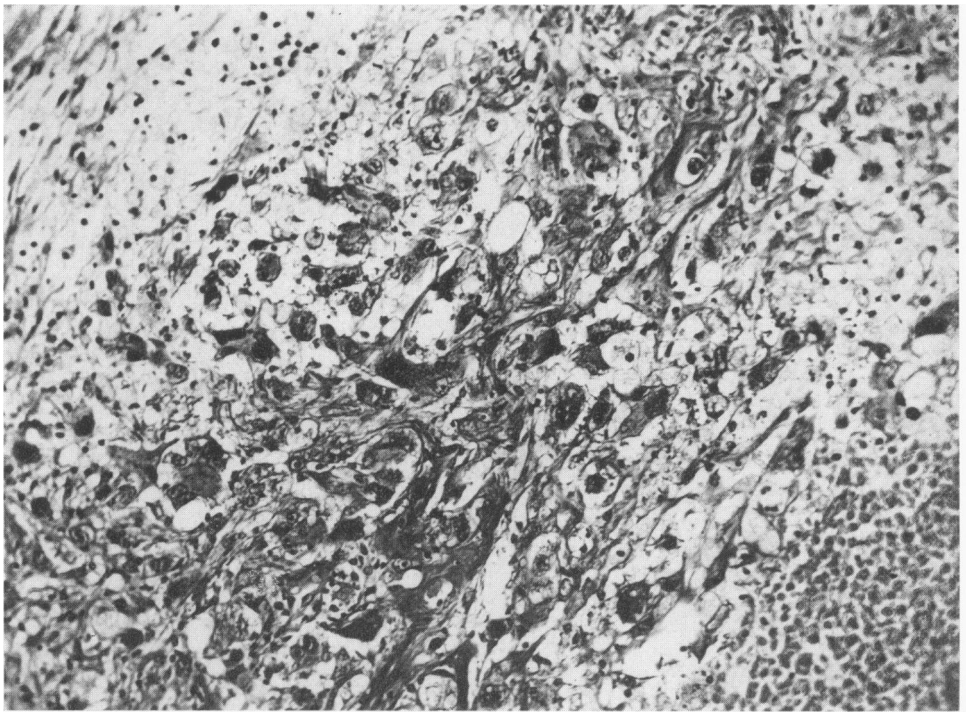
20



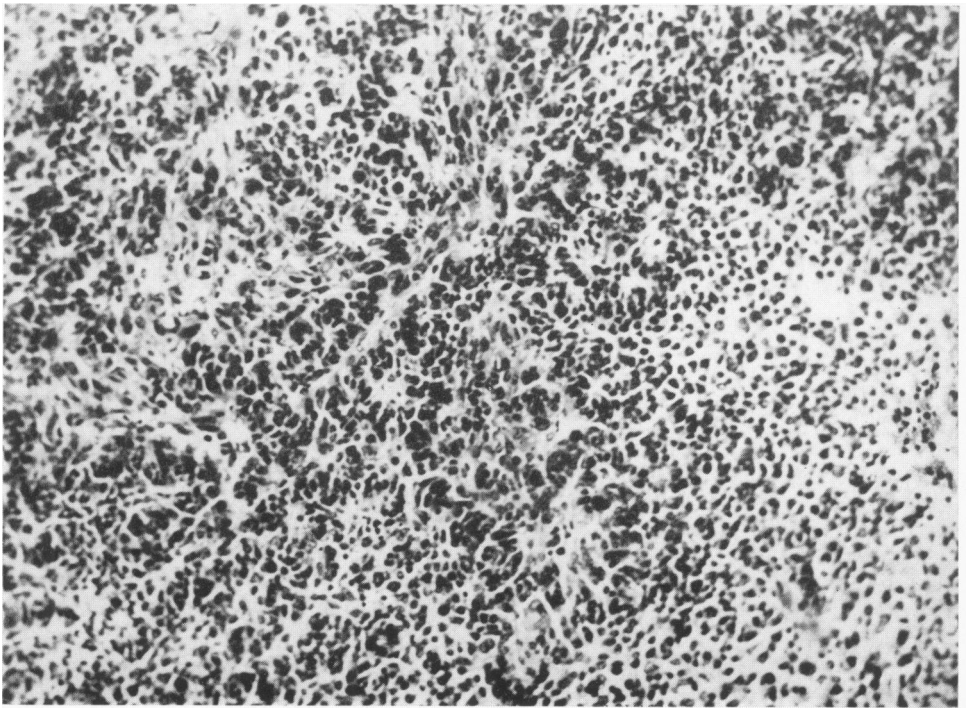
21

FIG. 22. Ependymoma on 14th day after x-irradiation with 5000 r. There is absence of cells resembling ependyma and in their place are huge tumor gliacytes. Hematoxylin and eosin stain. × 185.

FIG. 23. Twenty days after the x-ray dosage of 5000 r. the ependymoma once again has some identifiable ependymal cells. Hematoxylin and eosin stain. × 185.



22



23