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VOLUME FIVE

CLASSIFICATION AND BIOLOGY OF BRAIN TUMORS

CLASSIFICATION

Classification in its broadest sense is the division of individual things into groups or classes. Scientific classification additionally demands that the arrangement be systematic, that it be based on an important principle, that the classification be exhaustive, and that the categories be mutually exclusive. The most important feature of classification, however, is its clinical or theoretic usefulness.

Taxonomists may be classified as "lumpers" or "splitters." The "lumper" divides things into relatively large groups and accepts the fact that much variability will be encountered within these limits. The "splitter," at the extreme, regards every identifiable variant of living matter as a significant nameable natural unit.[248]

Early Schemes

Before the time of Virchow, pathologists and surgeons described brain tumors in great detail, according to external characteristics. Writing in 1839, Bressler was one of many authors who tried to create order with categories such as "induration of the brain," "blood tumors," and "bone tumors." He also recognized "brain cancers," of which he collected 45 cases, including three hypophyseal tumors.[26] In this same period, the epidermoid or "pearly" tumors were described, and gliomas were known as "medullary sarcoma" or "fungus medullare."

The present-day concept of classification of tumors was initiated by Virchow.[248] He recognized the supporting elements of the nervous system, labeled them neuroglia, and thus initiated the cytological approach to classification. Virchow created the term "glioma," and classified these tumors for the first time by the type of cell. Some descriptive terms from the older classifications were retained, such as soft, hard, telangiectatic, or hemorrhagic. He described ependymal tumors and eighth nerve neuromas, and offered an interpretation of dural neoplasms. He characterized gliomas as enormous tumors of firm, brain-like appearance, not clearly demarcated from the cerebrum, and resembling a hypertrophy of normal parts. Microscopically, the tumors were formed by glial cells, and on occasion contained fibers, clearly an account of astrocytic tumors.

He also described a hemorrhagic telangiectatic tumor that in places appeared well circumscribed and in others merged into surrounding tissues. Microscopically, it was hypercellular and contained some large cells. Fatty degeneration was prominent in the well-vascularized tumor. He thus gave one of the earliest descriptions of glioblastoma multiforme. Virchow distinguished between gliomas and sarcomas, although the latter group was established by predominantly gross criteria with little histological verification. His work was so well accepted that, for a time, only scattered attempts were made at further classification. More workers became interested in brain tumors and made rapid progress in histological techniques in the last half of the nineteenth century. Simon described the "spider-cell glioma," and Stroebe further contributed to the differentiation between sarcomas and gliomas begun by Virchow.[221,231]

New histological methods were devel-

oped in Spain by Ramon y Cajal and del Rio Hortega during the first quarter of the twentieth century. They used metallic impregnations on the cells of the brain, a work that had a strong influence on many surgeons and pathologists. Among these workers were Bailey and Cushing, who later concentrated on comparing types of tumor cells with cells in normal stages of development and extensively used these impregnation techniques.[13]

Tooth published a descriptive study of brain tumors collected at the National Hospital in London from 1902 to 1911.[241] This study comprised 500 cases, of which 258 were gliomas; for the first time, extensive neurosurgical material was studied histologically. In addition, he was one of the first to emphasize the correlation of morphological structure and clinical course. He discussed benign and malignant gliomas, and the presence of histologically different areas in the same glioma. He concluded that complete recovery from the diffuse form was "practically impossible."

In the meantime, Pick and Bielschowsky were classifying neuronal tumors according to the degree of maturation and resemblance to normal ganglion cells.[185] Ribbert studied gliomas and used the theory of Cohnheim pertaining to the development of tumors from embryonic rests.[191] Ribbert thought that morphological differences could be best explained by comparing the tumor cells with developmental stages of the glia. This concept was the foundation for many classifications used to the present time. It was influential in the systems proposed by Bailey and Cushing and by others who followed them. Ribbert contended that gliomas arose from cells *arrested* at different stages in their development. Although he did not use the newer metallic techniques, his work initiated a new phase of research on gliomas, placing emphasis on cytological studies.

Bailey and Cushing

The approach of Harvey Cushing to the study of tumors established a pattern of excellence. In his description of medulloblastoma, for example, Cushing thoroughly considered macroscopic appearance, point of origin, method of growth and spread, and life history, correlating these findings with the cellular architecture of the tumor.[12,48] In 1926 Bailey and Cushing proposed "A classification of the tumors of the glioma groups on a histogenetic basis with a correlated study of prognosis," from a study of more than 400 verified gliomas, including 167 necropsy specimens.[13] They used the metallic impregnation techniques of Cajal and Hortega as well as other staining methods. The histogenetic or cytogenetic concept of the types of glioma was based on the resemblance of tumor cells to embryonic cells in various stages of differentiation. In this regard, they differed from Cohnheim and Ribbert, who theorized that gliomas arose from "arrested" cells. Bailey and Cushing undoubtedly were influenced by this theory, but their writing makes it clear they were dealing with the resemblance of cells rather than with a theory of origin. They classified the tumors in terms of the morphological stages through which each cell was conceived to pass in embryogenesis. Twenty cell types were considered to arise from the medullary plate, from which they derived 14 tumors (Fig. 83–1). Bailey and Cushing were concerned about the awkward and probably unwarranted term neuroepithelioma, which might better have been called primitive spongioblastoma. They noted, perhaps as an afterthought, that the term "glioblast" could be used for bipolar and unipolar spongioblasts considered to be unipotential, that is, already determined as glial cells.

In making clinical correlations, Bailey and Cushing first considered modifying factors, such as position of the tumor, effect of radiation, age of the patient, and results of the surgical procedure itself. They found that tumors with less differentiated cells, resembling those of earlier embryonic stages, grew more rapidly than tumors composed of more differentiated cells. The groups of tumors were arranged in series according to the average survival period; longevity was significantly related to greater degree of differentiation of the neoplastic cells. The authors found later that certain groups, such as the cerebellar astrocytomas, did not fit into this scheme, and more was to be written on this at a later time. They concluded that the diagnosis, localization, and surgical treatment of a brain tumor was important, but also essential "is a clear understanding of the life history of the lesion treated, for on this depends more

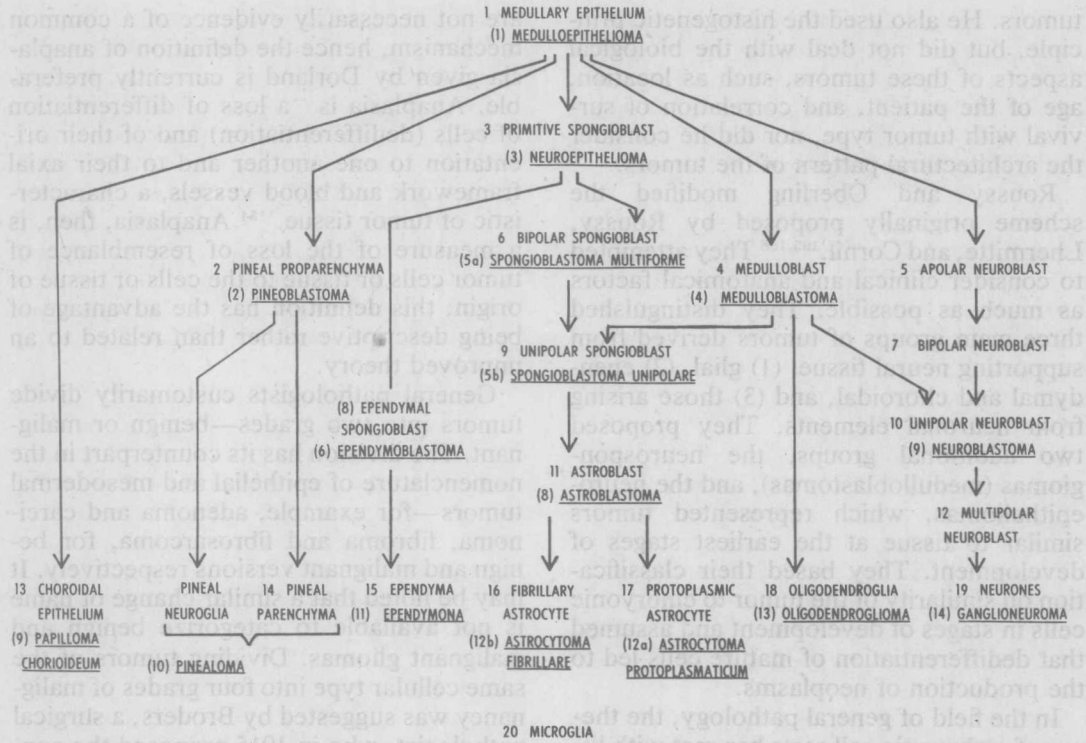

Figure 83–1 Diagram modified from Cushing and Bailey. Twenty types of cells identified in the development of the nervous system are numbered. The 14 types of glial tumors presumably derived from these cells are numbered in parentheses.

than anything else the nature of the procedure appropriate to the particular kind of tumor which happens to be disclosed.[13]

Although this classification was not universally accepted and lacked confirmation, particularly in the embryological scheme and the comparison with stages of histogenesis, it was a practical system bringing order to the existing confusion. Bailey and Cushing moreover created a classification of clinical value by correlating the types of tumor with survival times.

With increased use, Bailey decided to change the term "spongioblastoma multiforme" to "glioblastoma multiforme," reserving the term "spongioblastoma" for tumors related to the primitive spongioblast.[11] The term "glioblast" was used for the unipolar and bipolar spongioblast, and "glioblastoma" for the tumors in which they were found. He also proposed that the categories of medulloepithelioma, pineoblastoma, ependymoblastoma, and neuroblastoma be eliminated. Although originally Bailey and Cushing placed papillomas of the choroid plexus among the gliomas, Bailey did not include them because they "are not usually considered as gliomas."[11,13] Little doubt exists as to the origin of the epithelial cells of the choroid plexus from the same ependymal cells as the remainder of the glia, hence these papillomas are properly viewed as gliomas.

The revised system was presented by Bailey and Cushing in 1920.[14] The 10 categories (plus papilloma of the choroid plexus) then were as follows: (1) medulloblastoma, (2) glioblastoma multiforme, (3) spongioblastoma, (4) astroblastoma, (5) astrocytoma, (6) neuroepithelioma, (7) ependymoma, (8) pinealoma, (9) ganglioneuroma, (10) oligodendroglioma, and (11) papilloma choroideum.

Other Classifications and Grading

Hortega published a classification similar to that of Bailey and Cushing, but it lacked correlation with patient survival.[90] Hortega was far removed from his material, being in Spain while the surgeon from whom he received the specimens was in Paris. Hortega excelled in cytological observation of brain

tumors. He also used the histogenetic principle, but did not deal with the biological aspects of these tumors, such as location, age of the patient, and correlation of survival with tumor type, nor did he consider the architectural pattern of the tumors.

Roussy and Oberling modified the scheme originally proposed by Roussy, Lhermitte, and Cornil.[195,196] They attempted to consider clinical and anatomical factors as much as possible. They distinguished three main groups of tumors derived from supporting neural tissue: (1) glial, (2) ependymal and choroidal, and (3) those arising from neuronal elements. They proposed two additional groups, the neurospongiomas (medulloblastomas), and the neuroepitheliomas, which represented tumors similar to tissue at the earliest stages of development. They based their classification on similarity of the tumor to embryonic cells in stages of development and assumed that dedifferentiation of mature cells led to the production of neoplasms.

In the field of general pathology, the theory of embryonic cell rests has met with little enthusiasm in interpreting the pathogenesis of tumors, except for teratomas and congenital tumors. The idea that tumors develop from dedifferentiation of adult cells is more often accepted. Support for this theory was gained from the experimental induction of tumors in mature animals with carcinogens and radiation. That these adult cells stimulated by known or unknown agents to become neoplastic actually follow an embryological path is unproved, although it is often tacitly assumed.

Anaplasia (dedifferentiation) may be defined as "reversion of form of a cell or cells toward the embryonal."[22] This definition rests on the assumption of similarity between embryogenesis and carcinogenesis, and that the latter reverses the path of the former. Ewing thought that carcinogenesis is not a type of embryogenesis.[62] More recent evidence indicates that some tumors of the digestive tract have antigens in common with the fetal organ in which the tumor arises (carcinoembryonic antigens, or CEA).[72] These fetal antigens are not present in the adult organ unless the neoplasm occurs. Carcinoembryonic antigens were described in gliomas, but confirmation has been lacking.[242] Mahaley was unable to detect specific glioma antigens or specific antiglioma antibodies.[139] Common antigens are not necessarily evidence of a common mechanism, hence the definition of anaplasia given by Dorland is currently preferable. Anaplasia is "a loss of differentiation of cells (dedifferentiation) and of their orientation to one another and to their axial framework and blood vessels, a characteristic of tumor tissue."[54] Anaplasia, then, is a measure of the loss of resemblance of tumor cells or tissue to the cells or tissue of origin; this definition has the advantage of being descriptive rather than related to an unproved theory.

General pathologists customarily divide tumors into two grades—benign or malignant. The division has its counterpart in the nomenclature of epithelial and mesodermal tumors—for example, adenoma and carcinoma, fibroma and fibrosarcoma, for benign and malignant versions respectively. It may be noted that a similar change of name is not available to categorize benign and malignant gliomas. Dividing tumors of the same cellular type into four grades of malignancy was suggested by Broders, a surgical pathologist, who in 1915 proposed the concept and then published a report in 1920.[28] The classification arose from histological examination of many epitheliomas in which he found similarities. The tumors were divided into four groups of different degrees of cellular anaplasia, on the theory that tumors were derived by dedifferentiation of mature cells. Broders stated that if about three fourths of the tumor were differentiated and one fourth dedifferentiated, it was graded I, and so on. Later, he changed this system by placing emphasis on the percentage rather than the proportion of anaplastic cells.[29] Grade I tumors thus contained cells in which differentiation ranged from almost 100 per cent to 75 per cent, but in grade IV tumors, differentiated cells constituted from 0 to 25 per cent of the total.

Kernohan and associates introduced a system of grading gliomas based on Broders' ideas, and correlated the findings with prognosis.[104,105] These authors proposed a scheme with four grades of malignancy, and applied these grades to astrocytomas, ependymomas, oligodendrogliomas, and "neuroastrocytomas." Medulloblastoma was considered a type in itself and was not graded. The most exact description was given for the four grades of astrocytoma. The authors proposed eliminating the

terms "glioblastoma multiforme," "astroblastoma," and "polar spongioblastoma" because they were variants of astrocytoma. Their classification was based on the idea that "gliomas arise from pre-existing adult cells still capable of proliferation by a process of dedifferentiation or anaplasia." They found a direct relation between the degree of anaplasia and the postoperative survival period. Supporting their theory, they noted the occasional change in histological appearance from that of well-differentiated astrocytoma to glioblastoma, as shown by specimens obtained at succeeding operations on the same patient. Shein has shown experimentally that a single cell of astrocytoma can become a glioblastoma multiforme.[215] Kernohan and co-workers failed to note that oligodendrogliomas and ependymomas, when recurrent, may also finally appear as glioblastomas.[105]

Ringertz developed a similar system at the same time, but used three grades.[193] In 1950, he applied this classification to astrocytomas, ependymomas, and oligodendrogliomas. Ringertz compared the histopathological appearance and postoperative prognosis of the different types of gliomas. He stated that these gliomas could dedifferentiate into a common type of anaplastic glioma, and preferred the term "glioblastoma" for these anaplastic tumors without "recognizable special character." Ringertz probably is correct in his belief that, in adults, gliomas of many initial cell types may ultimately become glioblastomas. Medulloblastoma, as in Kernohan's classification, was not graded. Ringertz also showed that some astrocytomas of the cerebral hemispheres had the same histological appearance and prognosis as the cerebellar astrocytomas of childhood and adolescence.

Many objections have been raised to grading, none of them overwhelming in nature. The use of four grades is arbitrary: it cannot be applied to medulloblastoma; oligodendrogliomas do not differ so greatly as to require four grades; the varieties of astrocytoma could readily be divided into 10 or more grades by an enthusiastic "splitter." Nevertheless, any other subdivision may be equally arbitrary. A more important objection to grading is raised when, as in cerebral ependymoma, the histological findings are not correlated with prognosis.[118] The invasiveness of the tumor, a biological rather than a histological characteristic, is more important in determining the outcome. Furthermore, grade IV ependymomas are seldom encountered, and probably would be called glioblastomas by most nongrading neuropathologists.

The importance of considering factors other than histological has been re-emphasized by Zuelch.[283] He proposed five grades of malignancy based not only on the histological type but on overall behavior. Grade 0 thus would consist of completely resectable tumors, and grade IV of tumors associated with survival of a year or less.

The original system of two grades, benign or malignant, thus can be expanded into three (Ringertz), four (Kernohan et al.), or five (Zuelch). Each further split of the unknown adds additional complexity and calls for prophetic qualities of successively greater nature. Simplicity suggests that "benign versus malignant" is the easiest distinction to make, and that further subdivision could be made most usefully by dichotomy (more benign, less benign, and the like) if the pathologist thinks it necessary to satisfy his psychological needs or those of the surgeon.

Any ordering of tumors by degree of differentiation usually will have some statistical justification; usually, a patient with a better differentiated tumor will live longer than a patient with a poorly differentiated neoplasm. The individual patient, however, has the capability of transgressing the statistical conclusion; the wise clinician keeps in mind both the individual and the statistics.

If these classifications are considered apart from their theoretic base, we find that similar tumors may be given dissimilar names. If the various names indeed describe the same entity, it matters little whether a tumor is called glioblastoma multiforme or astrocytoma grade III or IV. When a spongioblastoma of the cerebellum, is called astrocytoma of the cerebellum, only the name has been changed. From the point of view of the patient or the practical neurosurgeon, the outcome is the same.

Present Views of Classification

A compromise has been offered by the Unio Internationalis Contra Cancrum.[84] Multiple names for a particular tumor are

given in this system, and most of the common brain tumors are included. The classification has imperfections, such as the mixing of categories of cells (e.g., nerve cells, glia) with organs (e.g., nose, eye), but it is an attempt to obtain agreement on names used throughout the world, a desirable but difficult goal.

The presentation given in this text is a synthesis of various views, and is an attempt to simplify ("lump") a subject often made complex by "splitters." Astroblastoma is classified as either an ependymoma or a form of astrocytoma; careful examination will almost always disclose multiple processes on cells arranged in cartwheel fashion, and the need to imagine a relation to an embryonic cell is eliminated. Spongioblastoma polare is an astrocytoma in which the multiple processes are compressed as the cells grow in the tight spaces of the optic nerve or brain stem. This newer concept is in accord with the clinical fact that the duration of illness usually is long; a poorly differentiated cell, the "spongioblast," should not be associated with prolonged survival. Pinealoma is considered as a teratoma in accord with the findings of Russell; a teratoma is composed of two or more types of tissue foreign to the part in which they arise.[199] This view explains the instances in which "pinealoma" occurs although tumor is not seen in the presumed tissue of origin. The need to invoke aberrant pineal tissue is also obviated. Neoplasms arising from the stroma of the pineal body are tumors of glial cells, and are properly called astrocytoma, ependymoma, and so on. The possibility of a tumor of pineal tissue as such is not eliminated, but it is extremely small.

The modification of the original Bailey-Cushing scheme as shown in Table 83–1 is a reasonable one. The first three diagnoses may also contain the phrase "well differentiated" or "poorly differentiated" to serve as an additional guide to prognosis. The suffix "-blast" is generally avoided to prevent confusion with embryological forms. The degree of differentiation can be seen microscopically, but the analogy with embryological forms is a supposition.

Readers desiring an even simpler approach may be attracted to the suggestion that the first three diagnoses may be lumped into a single group. This concept does not violate clinical or anatomical facts. The life span of patients with these gliomas is generally measured in years, rather than months as with medulloblastoma or glioblastoma. Oligodendroglial cells are often present in ependymoma;[103] astrocytes are almost always found in oligodendrogliomas;[194] and ependymal cells in some places may not be distinguished from astrocytes except by processes radiating around blood vessels. Transitional cells abound in normal tissue;[189] it is often difficult to distinguish an astrocyte from an oligodendrocyte in either normal or neoplastic tissue. Radioautographic data and other findings indicate these cells may be interchangeable, and that different appearances are dependent on altered functional states.[114]

Any attempt to simplify complex matters must be counterbalanced by awareness of the complications. Therefore, "mixed" and "unclassified" have deliberately been added to Table 83–1. Mixed gliomas in the brain are of four varieties: mixtures of well-differentiated glial cells, of well- and poorly differentiated glial cells, of glial cells and neurons, and of glial and mesenchymal

TABLE 83–1 COMPARISON OF MODIFIED CUSHING-BAILEY CLASSIFICATION AND GRADING OF KERNOHAN ET AL.

MODIFIED BAILEY-CUSHING	KERNOHAN ET AL.
Astrocytoma	Astrocytoma, grades I and II
Oligodendroglioma	Oligodendroglioma, grades I to IV
Ependymoma	Ependymoma
Medulloblastoma	Medulloblastoma
Glioblastoma multiforme	Astrocytoma, grades III and IV
Pinealoma (teratoma)	Pinealoma
Ganglioneuroma (ganglioglioma)	Neuroastrocytoma, grade I
Neuroblastoma (sympathicoblastoma)	Neuroastrocytoma, grades II to IV
Papilloma of choroid plexus	
Mixed	
Unclassified	

cells. Further, mature oligodendrocytes, astrocytes, and ependymal cells mingle in many gliomas, a finding not related to anaplasia of the cells. In these cases, pathologists usually name the tumor for the predominant type of cell; hence clinicians are often unaware of the mixture. In a tumor containing both differentiated and anaplastic cells, neuropathologists conventionally name the tumor for the most histologically malignant feature, not by the largest number of cells identified. This usage gives the neurosurgeon the best approximation of the prognosis. If 98 per cent of a tumor is composed of mature astrocytes, but anaplastic cells and foci of necrosis are present, the appropriate diagnosis is glioblastoma multiforme. Glial cells and neurons may be mixed in a tumor in combinations ranging from a predominance of neurons ("ganglioneuroma"), an approximately equal mixture ("ganglioglioma"), to largely glial, so that the diagnosis of astrocytoma alone might be offered.

Combined gliomas and sarcomas have been reported increasingly in recent years. Rubinstein offered two possibilities to explain this mixture: either the invasive sarcoma produced a malignant change in the adjacent neuroglia or a sarcomatous change arose in the vascular proliferation of the glioblastoma.[198] More explicitly, experimental evidence from use of chemical carcinogens and viruses suggests that a single agent is capable of transforming cells of both glial and mesenchymal origin into neoplasms. The need to invoke the concept of *one* cell reacting to the presence of another stems largely from the commonly accepted but unproved assumption that all tumors arise from the neoplastic transformation of a single cell.

Table 83–1 also indicates that some brain tumors should be labeled "unclassified." Each specific diagnosis is based on certain rules set by the pathologist, but criteria as well as interpretations differ. One problem is that few authors state specific criteria in writing, and diagnosis too often is an arbitrary process. For example, should the diagnosis of glioblastoma multiforme be made on cellular characteristics alone? Is the presence of necrosis necessary for this diagnosis? Should ependymoma be diagnosed when a few perivascular radiations of glial processes are seen, and if not, how many are needed? Another problem is that criteria may need changing with new experience or added information, but old concepts tend to linger. The finding of blepharoplasts as a confirmation of the diagnosis of ependymoma, still cited in recent textbooks, offers an example. A small dark body near the surface often is found in tumor cells and may be a clump of chromatin or a precipitate of other protein as well as the blepharoplast (basal body) of a cilium. Electron microscopy has revealed that all cells in the nervous system are ciliated in embryonic life and that even adult neurons and glia may contain cilia.[53] Centrioles and cilia occur in meningiomas.[36] Indeed, rudimentary cilia have been found in smooth muscle cells and fibroblasts.[227]

Unclassified tumors occur more frequently if the cells are poorly differentiated. The diagnosis of tumors composed of small, round, and dark cells is influenced by the clinical data as well as by the microscopic appearance. Highly anaplastic tumors at times cannot be distinguished as to origin in glial, epithelial, or connective tissue.

Finally, the problem of classification should be approached clinically as well as by histological means. Pathologists classify tumors by a judgment as to the cells and tissues from which the neoplasm originated. Malignancy in the cranium, however, is not solely a function of cells of origin. For this reason, caution should be used in applying the terms "benign" and "malignant" to a histological classification of gliomas. The terms "well-differentiated" and "poorly differentiated" are preferable to "benign" and "malignant." Decisions about prognosis, repeated surgical procedures, radiotherapy, and the like must take into account factors other than the histological diagnosis: the state of intracranial pressure, position and size of the tumor, age and general condition of the patient. The concept of "total malignancy" suggested by Zuelch, including not only the histological dedifferentiation but also the effect of location as in the case of a well-differentiated tumor in a critical position, is of importance in the clinical use of any classification.[284]

Ability to predict the biological activity of a tumor is limited at the present time. Tumors of the same cellular type and even in the same position may behave differently in different patients.[164] For example, one medulloblastoma responds promptly to ra-

diation, but another in the same location does not. The fate of a patient with a cerebral ependymoma is more dependent on its invasiveness than on its histological appearance. A histologically indistinguishable astrocytoma may be harbored for 20 years in one case, but in another, dedifferentiates to glioblastoma and the patient rapidly dies. The variable behavior of gliomas is not unique, however, and similar examples can be cited for systemic neoplasms.

BIOLOGY

Etiological Agents

Genetic Factors

Genetic predisposition is infrequent in tumors of the central nervous system, but unfortunately this information often is not obtained in sufficient detail. Some tumors have a hereditary component, exemplified by three developmental disorders of the group called phakomatoses: von Recklinghausen's neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau disease. The evidence of hereditary influence is less striking in Sturge-Weber disease.

Multiple neurofibromatosis of von Recklinghausen is the major example of a tumor of the central nervous system with genetic influence. The frequency ranges from 1:2000 to 1:3000 in the general population. Inheritance is through an autosomal dominant or irregularly dominant gene. Sexual incidence is about equal, although Zuelch speaks of a female preponderance.[283] Neurofibromas of the spinal nerve roots and peripheral nerves are frequent, and the incidence of spinal ependymomas is increased. The most common associated intracranial tumors in this disease are schwannomas, gliomas, and meningiomas. The cutaneous and neural changes often occur in adolescence and adulthood, and a multiplicity of lesions is the common finding.

Tuberous sclerosis is less common than neurofibromatosis. The frequency is estimated between 1:30,000 to 1:150,000 in the general population. The sexual incidence is about equal. Transmission is as an autosomal dominant or irregularly dominant trait. The patients are usually children or adolescents. The cerebral lesions are firm hyperplastic nodules consisting of malformed and often extremely large glial cells. Most of the neoplasms are giant-cell astrocytomas of a benign nature. The estimated incidence of malignant changes is 1 to 3 per cent.

Von Hippel-Lindau disease has a dominant or irregularly dominant mode of inheritance. The disease most commonly includes hemangioblastoma of the cerebellum, and less frequently, of the brain stem and spinal cord. Another feature is angioma of the retina. The disorder usually becomes evident in adults.

Sturge-Weber disease is a combination of angioma of the brain and meninges, associated with an angioma on the same side of the face. Hereditary influence is less than in the other phakomatoses. Most instances are sporadic. The mode of transmission in the hereditary cases is occasionally dominant or irregularly dominant, and recessive inheritance has been reported. Chromosomal abnormalities have been found in some studies, a 22-trisomy in one case and a chromosomal translocation to a group D chromosome in another.[85,180] The fact that most patients have normal chromosomes suggests that these findings may be chance associations.

The phakomatoses thus are developmental defects in the mesoectoderm, and heredity often is important. The end-result is a group of disorders with considerable variation in penetrance of genetic factors and also in the clinical expression. Cases have been reported in which more than one of these diseases have occurred in the same individual or family.

The retina is embryologically related to the primary neural vesicle. Retinoblastoma, although not a primary intracranial tumor, may invade the cranial cavity. These tumors are of interest genetically. The incidence is estimated at from 1:20,000 to 1:34,000 live births. Most cases are detected before the age of 3 years. Sexual incidence is equal. Sporadic cases constitute about three quarters of the total. When the tumors are bilateral, other members of the family are likely to be affected. The hereditary cases have autosomal dominant transmission. Some authors have described an abnormal chromosome in group D.

These central nervous system tumors with a reasonably well-defined hereditary background are rare. Genetic relations in the remaining large group are still in ques-

tion. Hague and Harvald selected 535 probands with glioblastoma, astrocytoma, medulloblastoma, and meningioma.[83] The study included the relatives of probands and a small number of controls and their relatives. The authors found that the number of deaths from intracranial tumor among the relatives of the probands did not significantly exceed those found in the controls.

Van der Wiel studied brain tumors occurring in the relatives of 100 probands from the Utrecht Neurological Clinic in whom the diagnosis of glioma had been established by biopsy or necropsy.[246] One hundred controls were randomly selected. In the relatives of the proband group, 14 cases of cerebral tumor were found in 12 families. The diagnosis was confirmed by histological examination in eight cases: six gliomas, one medulloblastoma, and one meningioma. None of the relatives of the control group died with intracranial tumors. The death rate from gliomas in the relatives of the proband group was four times as great as expected in the population of the Netherlands. Additionally, the control group had a 7.8 per cent incidence of dysrhaphic phenomena, but the incidence in the close relatives of the glioma probands was 20.8 per cent. Van der Wiel, therefore, suggested a hereditary factor in the genesis of gliomas.[246]

The contradictory results in these two studies may be related to the hospitals from which probands were collected. Koch contended that glioblastomas were encountered less frequently in neurosurgical clinics than in institutes of pathology and in neurological clinics.[113] He thought that gliomas, particularly, occur in families, and that the predilection depended on a factor associated with defective embryological development rather than specific inheritance. The familial incidence of gliomas was noted by van der Wiel in 31 cases from the medical literature. In this group, 23 cases involved parent-child or sibling relationships, and the other 8 were in more distant relatives. From 1950 to 1965, 41 families were reported in which isolated brain tumors were found in two or more members.[2]

Of interest also are reports of brain tumors in twins. The best known case was one reported by Leavitt in which identical twins developed medulloblastomas.[127] Three more cases of this tumor in twins were added later by others. Koch found reports of 12 pairs of twins affected with brain tumors.[112] Five were concordant for brain tumor, but were not identical. He added 20 pairs of twins discordant for brain tumor, including 3 identical, 7 fraternal, and 10 of uncertain nature. Hague and Harvald noted that eight probands were twins, all discordant for intracranial tumor. Only two of the eight pairs were monozygotic. Twin studies have not been informative with respect to zygosity, and descriptions of family history are sparse. It seems likely that further studies of twins and the careful analysis of families with multiple intracranial tumors will contribute additional information on genetic mechanisms. At present, the genetic factor revealed by studies of families is weak but cannot be entirely ignored.

Cytogenetic Studies

Study of chromosomes in intracranial tumors is another method of investigating genetic mechanisms. Solid tumors and the leukemias have been analyzed extensively in the past, but recently attention has been directed to the central nervous system. These data have not been reviewed before, and hence are presented in detail.

Chromosomes may be studied only during cell division. A low mitotic index, that is, few cells in mitosis, is common in benign and even many malignant tumors of the central nervous system, decreasing the number of cells available for study. Culture methods therefore were developed largely to furnish more cells in mitosis. These methods of study have certain limitations. Analysis of chromosomes has improved since it was first introduced, but many artifacts still occur. Handling, diagnostic or therapeutic radiation, and cytotoxic drugs may alter cells, and spontaneous fragmentation also has been reported. In tumors of the central nervous system, as in other areas of the body, chromosomal analysis is performed either directly on tumor cells or after short- or long-term culture. Some described changes are related to these differences in preparation. When cells in culture are examined, the question arises whether in vitro findings can be translated to in vivo processes. The dividing cell cannot always be identified in cultured material, so that a diploid mode might represent an analysis of cells of nonneoplastic stroma, or blood ves-

sels or leptomeninges in the case of a tumor of the central nervous system. In some cultures, especially long-term ones, stromal cells overgrow the tumor. The environment in tissue culture may in some way alter the tumor cell.

Some methods of culture selectively favor the growth of diploid cells. Although the presence of diploid karyotypes in cultured cells might then be normal, studies of other tumors in which most chromosome numbers were not diploid are against this idea.

In considering the differences between culture and direct examination of tumor cells, Conen and colleagues found predominance of aneuploidy on direct examination of chromosomes, but few aneuploid cells in cultures from the same malignant effusions of pleura and peritoneum.[42] Their comparison of cultured and noncultured central nervous system tumors, although not from the same patients, indicated that the methods of study affected the results. It was suggested that short-term cultures are more valid than long-term cultures with regard to consistency of chromosomal number in comparison with fresh material.

Sampling error, as in other statistical evaluations of biological data, is of importance. A small number of tumors may be insufficient to draw significant conclusions from, even though a large number of cells is examined. Sampling of a few cells within a tumor also may not allow adequate evaluation, as for example, when a bimodal population of cells is encountered but only one of the cellular components is represented.

The chromosomal pattern of three intracranial gliomas was directly analyzed by Lubs and Salmon.[132] A glioblastoma contained chromosomes with a bimodal (diploid and tetraploid) distribution. Acrocentric marker chromosomes were identical in both cell lines. Chromosome fragments were also observed, as well as variations in the number of chromosomes in cells of both lines. A 4500 R dose of radiation given before removal of the glioblastoma may have created the described alteration of chromosomal pattern. An oligodendroglioma contained several cells in which the chromosomes were tetraploid and of normal shape. The authors suggested that the findings indicated a tumor with a simple tetraploid mode. A medulloblastoma, reported in greater detail at a later date, was obtained at craniotomy from an 8-year-old girl, and chromosomal analysis was done on the biopsy specimen.[133] Double minute chromosomes, probably chromosome fragments, were found in all mitoses, as were also an abnormal metacentric form and extra chromosomes in groups D and E. Cells in the bone marrow also contained the double minute fragments, abnormal metacentric forms, and extra chromosomes in groups D and E.

Cox and co-workers examined the chromosomes prepared directly from six neoplasms, five in children (medulloblastoma, rhabdomyosarcoma, and three neuroblastomas) and one carcinoma of the lung in an adult.[46] All cases had a similar feature: multiple small fragments in a structurally intact set of chromosomes. Each tumor had a different abnormal karyotype, but cells in the same tumor also varied. Nevertheless, these patients had not been previously treated, and the findings are similar to the case of medulloblastoma described by Lubs and Salmon.

Thirty-one fresh brain tumors were examined by Bicknell.[18] Cells satisfactory for analysis were obtained in only three: recurrent ependymoma, glioblastoma multiforme, and astrocytoma grade III (nomenclature of the author). The patient with ependymoma had been irradiated before chromosome study and had aneuploidy with extra chromosomes in group C and less frequently in groups D to G. Occasionally the chromosomes were abnormal and fragmented. Most chromosomal numbers were in the tetraploid range, but those in the glioblastoma were in the diploid range. Eleven of the cells in the grade III astrocytoma were tetraploid, six were hypertetraploid, and three were triploid. The greatest number of extra chromosomes was in group C, as in the recurrent ependymoma. It should be noted that group C of the karyotype has the largest number of chromosomal pairs, and the frequency of extra chromosomes in this group may be explained in this manner.

The chromosomal pattern was analyzed in 12 intracranial tumors in the fresh state, 8 of which had aneuploid or pseudodiploid patterns.[61] The chromosomes in five cases ranged closely around the diploid number (meningeal sarcoma with a pseudodiploid number, ependymoma, two grade IV astrocytomas, and a cerebellar sarcoma). Com-

bined normal and abnormal cell lines were found in a grade III and a grade IV astrocytoma. Completely abnormal patterns were found in a grade IV astrocytoma (hypertetraploid) and a grade IV astrocytoma (triploid). A medulloblastoma had a normal pattern.

Conen and Falk later studied chromosomes after tissue culture on 12 tumors of the central nervous system from children aged one week to 13 years.[41] The patients had not received radiotherapy or chemotherapy before chromosomal studies. Tissue culture was used to provide an increased number of dividing cells because mitoses were infrequent in many of the tumors. The chromosomal analyses were normal in most cases, in contrast to those made in their earlier work in which abnormalities predominated, suggesting to these authors that stromal cells outgrew cultured tumor.

A study of 11 glioblastomas was made by Wilson and co-workers.[270] Cells satisfactory for direct study were obtained from three tumors, and the others were studied in cultures ranging from 5 to 236 days. Chromosome preparations were obtained at five different ages in one glioblastoma in an established cell line, the oldest more than five years. The most frequent karyotype was near-diploid; deviations occurred most often in group C. Two of the original tumors contained tetraploid cells (92 chromosomes), but the chromosomal number of the cultured cells was always 52 or less. The karyotype was hypotriploid in the established cell line of glioblastoma.

In general, benign tumors are difficult to study because the number of mitoses may be insufficient for analysis. Meningiomas are among the few benign tumors in the body to show aneuploidy. Porter and associates, for example, found a group G chromosome missing in each of three cases.[186]

The variation in chromosomal number in group C may represent a common denominator. It was found by Lubs and Salmon in a medulloblastoma and glioblastoma, and in an irradiated recurrent ependymoma and a grade III astrocytoma.[132] Wilson also identified variations in group C in glioblastomas.[270] The liability of group C to changes, however, may be only a reflection of a greater number of chromosomes. The work cited has, in addition, confirmed the finding of aneuploidy and polyploidy in many tumors of the central nervous system, as found in systemic neoplasms.

Firm conclusions cannot be drawn from our present knowledge of the cytogenics of central nervous system tumors. Specific numbers or patterns of chromosomes are inconstant, as are excesses or deficiencies. Some similarities in number and karyotype exist, but consistent correlation cannot yet be made with the various types of intracranial tumors. Although these data relate to the extremely important process of formation of DNA and genetically coded information, they are largely descriptive. At this time, they offer little of clinical significance; they may become more valuable in the future.

Blood Groups

The ABO blood groups are genetically controlled and readily studied. The demonstration of associations between a blood group and a disease is a means of investigating genetic factors. Since about 1955, the relation between the blood groups and an increasing number of diseases has been reported. A study of 637 brain tumors revealed that the distribution of the ABO blood groups in the sample did not deviate significantly from that found in controls of a hospitalized population in Boston.[151] An excess of type O then was found in association with chromophobe adenomas in the Boston hospitals as well as in two hospitals in New York. This statistically significant finding was considered tentative because of the small size of the tumor group. Buckwalter and associates collected 565 brain tumors in patients of known blood type.[33] Voluntary donors were used as controls; the question may be raised whether these persons are a truly random population. Men with type A blood had an increased number of brain tumors, but not in any single diagnostic category.

A greater number of cases with type A also were found in a small series of 72 gliomas in children.[230] Considering that some of the previous reports might not have included a sufficient number of young persons, Yates and Pearce investigated 473 astrocytomas.[275] This tumor was used because it occurred in statistically useful numbers at all ages studied. The blood groups in patients less than 20 years of age were grossly disproportionate in cases diag-

nosed after 1945. This pattern was different from that noted in cases occurring before 1945. One possible explanation for this phenomenon is that patients with juvenile astrocytoma may have a weak A antigen not adequately detected by the grouping techniques used before 1945.

Selverstone and Cooper studied 139 consecutive patients with verified astrocytomas in which they found a significantly decreased prevalence of blood groups O and B in patients with this tumor.[213] A series of 630 consecutive patients undergoing craniotomy, including 132 cases of astrocytoma, was described by Garcia and coworkers.[69] They noted no statistical abnormality of blood group distribution in these cases of astrocytoma, compared with the distribution of blood types in patients with other cerebral tumors (279 cases), in patients undergoing operations for cranial trauma (124 cases), and in patients with nonneoplastic neurosurgical lesions (95 cases).

A still larger group of 3115 primary central nervous system tumors was analyzed by Pearce and Yates.[181] The only abnormal pattern was with astrocytoma, the proportion of type O cases being reduced. This finding, as reported by Yates and Pearce in 1960, was again particularly true in astrocytomas occurring in young people since 1945.

Many questions arise from these studies. The known rarity of type B in the populations of Europe and North America may complicate interpretation, as may the difference in frequency of blood groups in various races. Garcia's group found type B more common and type A less common in the American Negro than in the American Caucasian.[69] The frequency of type B in the region of Kings County Hospital Center in New York, where Negroes constitute 50 per cent of the inpatient population, was about twice as great as in the control group used by Yates and Pearce in England. Manuila noted that ABO frequencies differed greatly among the cities of Great Britain and often between districts of the same city.[143] This finding was confirmed by Wiener, who demonstrated considerable variation in the percentages of primary blood groups in geographic areas or ethnic groups.[264,265] These findings are of importance in evaluating the usual control groups. Technical errors are also a problem. Manuila stated that errors in grouping could be as high as 8.8 per cent. The histopathological criteria also must be considered in interpreting studies of tumors in relation to blood groups. Review of these data suggests that little has been accomplished with regard to establishing consistent statistical relation between the ABO blood groups and cerebral tumors.

Glossary of Terms in Genetics

Acrocentric—a chromosome with one long arm, the other small or imperceptible

Aneuploid—the condition when the number of chromosomes is not an exact multiple of the haploid number; if n designates the haploid number, the chromosomes may be represented by $2n + 1$, or $2n - 2$, or other combinations

Autosome—the somatic cell, not a germ cell; when referring to chromosomes, means all except the sex chromosomes, x and y

Centromere—the primary constriction of a chromosome and the point where the spindle fiber attaches; the position of the centromere determines whether a chromosome is acrocentric, metacentric, or submetacentric

Chromosome—a dark-staining body appearing in the nucleus at the time of cellular division; contains the genes and is composed of DNA

Chromosomal number—the total number of chromosomes in a cell, or, the arbitrary number assigned to identify each pair of chromosomes (see karyotype)

Concordant—twins sharing the same attribute

Deletion—the process whereby a fragment of a chromosome breaks off and is lost

Diploid—the full number of chromosomes in a somatic cell; the number in man is 46, also designated as $2n$, because it is twice the haploid number

Discordant—twins not sharing the same attribute, as when one twin has a brain tumor and the other does not

Euploid—a set of chromosomes in any balanced number, that is, an exact multiple of the haploid number; euploidy may thus be designated by n (haploid or monoploid, 23 chromosomes, the normal number in a human germ cell), $2n$ (diploid, 46 chromosomes, the normal number in a human somatic cell), $3n$ (triploid, 69 chromosomes) or $4n$ (tetraploid, 92 chromosomes)

Fragment—a small portion of a chromosome; often two homologous parts break off, as in double minute bodies described in the text

Haploid—only one set of chromosomes is present, as in germ cells; the number in normal human germ cells is 23, comprising 22 autosomal and 1 sex chromosome

Hypotetraploid—the number of chromosomes is less than $4n$

Hypertetraploid—the number of chromosomes is more than 4*n*

Karyotype—the chromosomes arranged by size and shape. Seven groups are labeled A to G, according to a convention agreed upon by geneticists. Each group contains two to seven homologous chromosomal pairs, one paternal and one maternal in origin:

Group	*Chromosomes*
A	1, 2, 3 (metacentric)
B	4, 5 (submetacentric)
C	6, 7, 8, 9, 10, 11, 12, and X (submetacentric)
D	13, 14, 15 (acrocentric)
E	16, 17, 18 (submetacentric)
F	19, 20 (metacentric)
G	21, 22, and Y (acrocentric)

Marker chromosome—a chromosome of distinctive configuration allowing it to be identified by inspection; it is unpaired and can be transmitted from one cell generation to another

Metaphase—a stage in the mitotic process of cell division when the chromosomes are concentrated in a mid-position and are splitting into two chromatids

Monozygotic—developed from a single fertilized egg, or zygote, as in identical twins

Metacentric—the two arms of the chromosome are almost equal; hence the chromosome is X-shaped at metaphase

Proband—the starting point of a family pedigree

Pseudodiploid—having the full number of chromosomes (2*n* or 46), but the grouping is abnormal; for example, group A contains two instead of three chromosomal pairs, but group B has three instead of two

Sex chromosomes—the X and Y chromosomes; the X chromosome is large and metacentric; the Y chromosome is small and acrocentric; two X chromosomes are present in women, one X and one Y in men

Submetacentric—a chromosome with unequal arms, one long and the other short

Tetraploid—having four haploid or two diploid sets of chromosomes; four times the normal number

Translocation—a segment of a chromosome changes position, either to a different chromosome, or another part of the same chromosome

Triploid—three times the normal haploid number

Trisomy—an abnormality in which three chromosomes of a given kind are present rather than two. The total number may then be 47, or, another chromosome may be lost and the total remains at 46 (pseudodiploid)

Zygote—the result of the union of two germ cells, the ovum and sperm; nonidentical twins develop from two zygotes

Physical Factors

Trauma

Trauma has long been considered a possible cause of meningeal or glial tumors. Two world wars and an increase in the destructive capability of the automobile have created a massive number of cerebral injuries, but an excess incidence of brain tumors has not been noted in this group. Head injuries were considered by Cushing and Eisenhardt to be of importance in the origin of some meningiomas; a history of head injury was obtained in 33 per cent of 313 cases.[49] They also noted depressed fracture in 24 instances of scar at the site of the tumor. Zuelch extensively reviewed cases causing physicians to consider trauma as an initiating factor.[283] He noted the work of Marburg and Helfand, who thought that trauma was significant in the genesis of intracranial tumors.[144] Zuelch suggested the following criteria for consideration of trauma as a causative factor:

1. The patient should have been healthy before the accident.
2. The trauma must have been adequate, that is, sufficient to injure a part of the brain or the meninges.
3. The site of tumor should correspond to that receiving the trauma.
4. The time between trauma and development of the tumor should be adequate.
5. The tumor should be proved histologically by biopsy or necropsy.

Little is known of the time necessary for development of intracranial neoplasms in man. Zuelch states that a tumor occurring a "few weeks" after an accident is unlikely to have been caused by the trauma. The statement seems reasonable, but data are unfortunately lacking on the time required for a cerebral neoplasm to appear after trauma.

Parker and Kernohan critically evaluated a series of brain tumors and found 4.8 per cent in which a connection between neoplasm and trauma to the head could be proposed.[179] They compared this group with two others. The first was a group of 431 patients with other diseases and of equivalent age, of whom 10.4 per cent had a history of head injury. The second was a series of healthy individuals of the same age, of whom 35.5 per cent had a history of trauma to the head. It was suggested that these