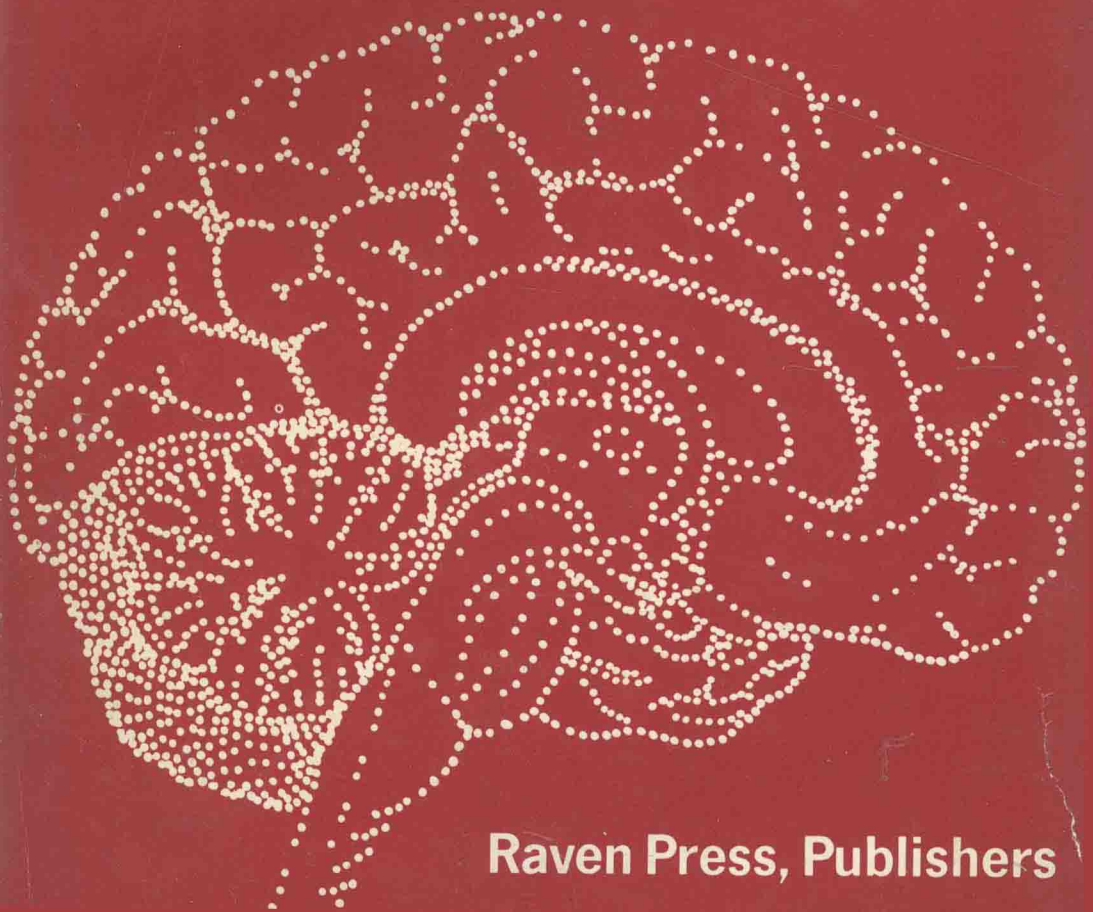
# Advances in Neurology

## Volume 15:

## Neoplasia in the Central Nervous System

Edited by

R. A. Thompson and J. R. Green



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# Advances in Neurology
# Volume 15

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# Neoplasia in the Central Nervous System

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# Preface

The clinical neurologist and the neurosurgeon are constantly confronted with the time-consuming dilemma of giving the best possible care to their patients and, simultaneously, the problem of maintaining their knowledge of the current state of their arts. The symposium on which this volume is based was designed to update the clinician's knowledge of recent developments and to delineate the future outlook concerning the problem of neoplasia in the central nervous system.

Neoplasia is no longer viewed as hopeless and incurable. Great advances have been made in basic oncology and the genetic, viral, and chemical etiologies of neoplasia, forming the basis for future developments in treatment. Advances are constantly being made in the radiographic diagnosis of neoplasia. Remarkable progress has been made in the areas of patient care and of the surgical attack on neoplasia. Finally, new developments in immunotherapy and chemotherapy offer promise for satisfactory treatment of metastatic and primary neoplasia.

With these thoughts in mind, the subjects were reviewed at the Second Annual Barrow Neurological Institute Symposium on January 23rd through 25th, 1975 at the Camelback Inn in Phoenix. This volume thus represents a comprehensive review of the subject for the clinician who has the ultimate responsibility to the patient.

*The Editors*

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# Contents


1 Current Concepts in Neuro-oncology
*L. J. Rubinstein*

27 Vasculature of Neural Neoplasms
*John D. Waggener and John L. Beggs*

51 Classification and Incidence of Neoplasms of the Central Nervous System
*John R. Green, John D. Waggener, and Barry A. Kriegsfeld*

57 Virus-Induced Experimental Brain Tumors and Putative Associations of Viruses with Human Brain Tumors: A Review
*Darell D. Bigner and Charles N. Pegram*

85 Chemical Induction of Brain Tumors
*James A. Swenberg*

101 Remote Effects of Neoplasm on the Central Nervous System: Encephalopathy
*William R. Shapiro*

119 Remote Effects of Focal Cancer on the Neuromuscular System
*W. King Engel and Valerie Askanas*

149 Differential Diagnosis of Neuropathy Associated with Cancer
*Peter James Dyck and Joseph M. Kiely*

163 Advances in Brain Scanning
*Robert E. O'Mara*

175 Brain Tumors Studied by Computerized Tomography
*Joseph P. Lin, Irvin I. Kricheff, Jose Laguna, and Thomas Naidich*

201 Role of Radiation Therapy in the Management of Neoplasms of the Central Nervous System
*Eric G. Mayer, Max L. M. Boone, and Silvio A. Aristizabal*

221 Recent Advances in Neurosurgical Techniques—Historical Considerations
*Robert G. Fisher*

235 Pre- and Postoperative Care of the Neurosurgical Patient
*Kemp Clark*

253 Anesthesia for Intracranial Surgery with Particular Reference to Surgery for Neoplasms
*Lisa Wilkinson*

261 Transsphenoidal Neurosurgery of Intracranial Neoplasm
*J. Hardy and J. L. Vezina*

275 A System of Operations for Skull Base Tumors
*William E. Hitselberger and William F. House*

281 Tumors of the Parasellar Region
*Leonard I. Malis*

301 The Biologic Basis of Malignant Brain Tumor Therapy
*W. M. Kirsch, J. J. Van Buskirk, D. W. Schulz, and K. Tabuchi*

315 Pharmacological Principles of Brain Tumor Chemotherapy
*Victor A. Levin*

327 Immunologic Depression in Cerebral Gliomas
*Harold F. Young, Romas Sakalas, and Alan M. Kaplan*

337 Immunotherapy of Gliomas: A Review
*Ayub K. Ommaya*

361 Chemotherapy of Brain Tumors
*Charles B. Wilson*

369 *Subject Index*

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# Current Concepts in Neuro-oncology

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Numerous hypotheses have been formulated in an attempt to unify within a common framework a number of divergent and even contradictory concepts about the basic mechanisms of cancer. Most of these unifying theories seek, either explicitly or implicitly, to apply to eukaryotic cells the orderly scheme of gene interactions originally postulated for the regulation of protein synthesis in bacteria (1), or more elaborate extensions of this scheme appropriate to higher cells (2). The concepts that the various hypotheses usually attempt to accommodate are: (a) the somatic mutation theory of cancer, including the experimental and statistical data which suggest that neoplastic transformation is the end result of multiple progressive stages due to the presumed accumulation of several mutations; (b) the role of virus-mediated carcinogenesis with the incorporation of new genetic information in the host cell; (c) the role played by immunological factors in the control of abnormal growth, especially the relationship that exists between disturbances of immunological mechanisms and tumor induction; and (d) the operation of epigenetic mechanisms in neoplastic development, particularly their relevance to certain forms of malignancy. Epigenetic mechanisms are those regulatory mechanisms that are not due to, or associated with, a permanent alteration in the genome, but which are brought into play during any of the stages at which the genetic information is expressed (gene expression). Since it is generally accepted that each cell in the organism possesses in its DNA all the genetic material that will code for the entire repertoire of differentiation, epigenetic mechanisms may be regarded, almost by definition, as being directly concerned with differentiation as an expression of the selective utilization of the encoded genetic information. In the following discussion, I briefly review a few observations on naturally occurring and experimentally induced nervous system tumors that have a bearing on these different concepts.

## SOMATIC MUTATION THEORY OF CANCER

The somatic mutation theory of cancer postulates that cancer is an irreversible cellular change that follows either a spontaneous or an induced mutation which permanently alters the stable, inheritable genome of the

somatic cell. This concept has long held a central place in cancer cell biology and, although it has recently been eclipsed by the viral oncogene theory, it nevertheless continues to receive support (3–5). One of its corollaries is that each cancerous growth originates from a single cell; in other words, cancer operates as a clone in the case of a spontaneous mutation or results from the summation of several (or many) clones in the case of induced mutations. Genetic cell marker studies (6–8) have provided evidence to support a clonal origin in some neoplasias (as in leiomyomas, chronic myelocytic leukemia, and Burkitt's lymphoma) but not in others (e.g., carcinoma of the colon, liver, or breast). The statistical incidence of spontaneous cellular mutation rates is not, on the other hand, incompatible with the somatic mutation theory. The spontaneous mutation rates for nondividing somatic cells have been estimated to approximate $10^{-6}$ to $10^{-7}$ per cell per locus per year (9,10), but it is generally agreed that a single mutation is unlikely to account for cancer initiation (11,12).

One of the models of carcinogenesis recently proposed presupposes that nonviral neoplastic transformation follows a double mutation involving a diploid pair of regulatory genes (13), that is, an event that might take place at the rate of $10^{-14}$ per year. Assuming a total cell population in each human organ of $10^{13}$ or less, this means that the mutational event(s) necessary for the initiation of malignancy might occur in every human organ once every 10 years at the most. If we take into account the approximate range of such an estimate as well as other factors such as the role of immunological mechanisms in the elimination of transformed cells, we may regard this figure as falling within the range of biological acceptability. A genetic mechanism of this kind is consistent with the experimental and epidemiological evidence that cancer incidence is related to the number of cells at risk (11), with the increased incidence of cancer with age (14), and with the additive mutagenic effects of radiation and chemical carcinogens. It is also compatible with the relatively high incidence of neoplasia in early life on the assumption that the postulated genes coding for neoplastic transformation would also be temporarily activated at some stage of embryogenesis or organogenesis (13).

There is strong evidence from epidemiological data that any mutational event responsible for naturally occurring cancer is a multistage process and that the clinical manifestations of cancer are dependent on the cumulative effects of a series of mutations (11,12). At least two stages, but usually more, are postulated. Also it would be reasonable to expect that the number of stages involved would be reduced in circumstances where an increased mutation rate is presumed to be determined by genetic factors, such as in inherited malignancies. This appears to be the case. The incidence of retinoblastoma suggests that the tumor is caused by only two mutational events, each occurring at a rate compatible with accepted values for mutation rates (10). In the dominantly inherited form, one mutation is inherited via the

germinal cells and the second occurs in somatic cells. In the nonhereditary form, both mutations occur in somatic cells. On the other hand, most common cancers have been estimated to result from a series of three to seven mutations ("multiple hits"), while for brain tumors values slightly above two have been suggested (12). To what extent the "two-hit" or the "multiple-hit" hypotheses in human cancer can be made to conform with the two phases of induction (15,16) demonstrated in experimental carcinogenesis (initiation and promotion) is unclear. Each of the two phases could itself result from one or more genetic mutations, or the second phase might involve another cellular mechanism (e.g., abnormal circuits of gene expression).

When we examine human and experimental tumors of the nervous system, we find much evidence to support the general concept that neoplasia is the result of a stepwise progression of events. For example, the frequent evolution of cerebral and pontine astrocytomas into glioblastoma (17,18); the rapid late phase of growth (characterized by increased cellularity and anaplasia) that may supervene on the relatively stationary clinical picture of a long-standing, focally irritative oligodendroglioma (18,19); the development of sarcomatous change in the hyperplastic vascular stroma of malignant gliomas (20–24), which may culminate in a terminal phase in which the sarcoma is preponderant; or the rarer, reverse kind of tumor induction in which the reactive glia surrounding an invasive meningioma or sarcoma may show morphological features suggestive of malignant transformation (22–24). An obvious demonstration of the multistage process in tumor induction is provided in the case of experimental neural tumors produced transplacentally following a single pulse of ethylnitrosourea (ENU): Tumors do not clinically develop in the offspring until some 150 to 400 days after their short-lived exposure to the carcinogen. A similar latency is, of course, well known in the case of radiation-induced tumors.

A well-recognized property of many human gliomas is that, in their growth and apparent spread, they often corroborate the view held by Willis (25) and many others that neoplastic transformation occurs concurrently or consecutively over a definite "field." In such a predisposed field, a neoplasm may either arise multicentrically or manifest itself as a very diffuse process. The multifocal nature of the malignant change operating within the field may be apparent only in the early stages of growth and often becomes masked in the later, more accelerated phase. This perhaps accounts for the wide differences in the incidence of multicentricity that have been reported in human gliomas. In our experience (18), multifocality can be demonstrated grossly in 4.5% and microscopically in 6% of gliomas of the astrocytic series, whereas widely separated multiple gliomas, that is, gliomas occupying either different lobes or different hemispheres, amount to 2.5%, a figure that closely agrees with that of other observers (26). It has been argued (27) that the field theory of Willis contradicts the somatic mutation theory be-

cause the probability of causal genetic changes occurring simultaneously in the cells comprising such large areas of tissue would be infinitesimal. However, such an assertion seems unjustified: in the case of chronic lymphatic leukemia, statistical evidence suggests that multicentricity should on theoretical grounds be expected to occur as the result of the selective proliferation of clones of preleukemic cells (9).

By analogy, it is reasonable to conceive that older individuals will carry proliferating clones which, from a histological point of view, may manifest themselves in the form of premalignant hyperplasia. There is in fact no fundamental contradiction between the somatic mutation theory and the field theory once it is accepted that secondary environmental conditions and agents may affect spontaneous mutation rates. The proliferation of multiple neoplastic clones as the result of additive environmental factors thus leads to confluent multicentric tumorigenesis as well as to distinct multiple neoplasms. This has of course long been known to occur in the case of tissues exposed to common carcinogenic influences. Multicentricity may therefore be an expected feature in many, although not in all, human malignancies. Diffuse malignant gliomas not infrequently disclose, on histological examination, fields that suggest a proliferation of separate clones of anaplastic cells, a picture that is intermediate between that of tumor multiplicity and the late phase of growth, in which invasion and destruction of preexisting tissues have obliterated the earlier stages of malignant transformation.

On the other hand, the existence of extremely diffuse forms of glioma, such as gliomatosis cerebri (18), in which the neoplastic change involves the neuroglia about equally throughout widespread areas that include not only the cerebrum but also occasionally the cerebellum, the brainstem, and even the spinal cord, argues against a concept of tumor formation based on the premise of a sequence of somatic mutations affecting a restricted number of cells. Other observations on nervous system tumors are also difficult to reconcile with the somatic mutation theory. First, the existence of mixed cell populations suggests in some cases an interdependency in neoplasia that must operate through mechanisms that are unlikely to be random. In practice, three forms of central nervous system tumors with mixed cell populations are found. In the first group, only the glial elements are involved, as in mixed astrocytomas and oligodendrogliomas. The different cell types are either closely intermixed or form distinct contiguous zones. Mixed gliomas are indeed common, and probably more than half of those that are conveniently labeled oligodendroglioma are in fact composed of mixed cell elements. Second, it is well recognized that most, if not all, tumors made up of ganglion cells actually are composite growths in which neurons and glia participate in the neoplastic process (gangliogliomas). An important distinction between the two cell elements lies in their malignant potential; in the exceptional instances where an anaplastic change

occurs in a ganglioglioma, it is found to be solely confined to the glial elements (28,29). In the case of these two broad groups of mixed neuroepithelial neoplasm, the argument might be advanced that they resulted from the proliferation of a reserve population of undifferentiated cells that exhibited divergent differentiation. However, the hypothesis of a multipotential reserve cell population in adult tissues has never convincingly been established except in those tissues and organs that are actively involved in regular tissue renewal and therefore are normally endowed with a proliferating stem cell population. There is little evidence that such reserve cell populations are present in the adult human brain, although embryonal tumors of the central nervous system, which display a capacity for divergent differentiation, may perhaps permit such an inference in the case of the infantile or juvenile brain (30). Recent experiments on regeneration in amphibia and insects also have challenged the concept of a reserve population of undifferentiated cells by showing that regenerating cells are not derived from such hypothetical cells but from highly differentiated elements that will first undergo dedifferentiation (27). In any event, the presence of a reserve cell population would not account for the entirely separate directions of differentiation that characterize the third category of brain tumor with mixed cell population, namely, the mixed or combined gliomas and sarcomas. In this type of tumor, the application of reliable neurohistological stains has permitted its composite histogenesis to be demonstrated so much more convincingly in the central nervous system than elsewhere in the body, that the possibility of neoplastic induction by one type of tissue on another is most apparent, an interpretation that is at variance with the spontaneous somatic mutation theory.

Mixed cell populations, however, may also result from divergent differentiation within the same tumor, as characteristically demonstrated in embryonal neoplasms. In the nervous system, such tumors are represented by the medulloepithelioma, which may exhibit ganglionic, astrocytic, oligodendroglial, and ependymal differentiation (30), or by the peripheral neuroblastoma, which may differentiate partly into ganglioneuroma and partly into pheochromocytoma (18). As will be discussed below, this phenomenon tends to imply that adaptive nongenetic mechanisms must also be operative in the development of these neoplasms.

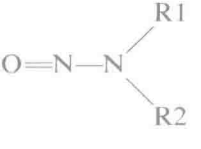
Genetic cell marker methods such as have been used for leiomyomas, chronic myelocytic leukemia, and Burkitt's lymphoma have not thus far been applied to tumors of the glioma group. However, these techniques strongly suggest that the multiple neurofibromas of von Recklinghausen's disease must each have a multiple cell origin, the minimal starting number of neoplastic cells in a given neurofibroma estimated to be no less than 150 (31). Here then we have a convincing instance of a neurogenic tumor in which either the initial oncogenic event must simultaneously have involved a large number of cells or, alternatively, a neoplastic change in a

single cell must subsequently have induced transformation in its neighbors. Admittedly, such a finding is expected in neurofibromatosis because here we have a condition for which there is strong evidence, on hereditary grounds and on the basis of tumor multiplicity, that neoplastic transformation is genetically determined rather than an expression of random somatic mutations. Indeed, mutation rates are known to be greatly affected by intrinsic genetic factors. The evidence of a multiple cell origin in hereditary peripheral neurofibromas and the statistical analysis of retinoblastoma, to which reference was made above, therefore support the hypothesis that mutator genes could be operative in those well-defined familial conditions of the nervous system (von Recklinghausen's neurofibromatosis, tuberose sclerosis, and Lindau's disease) in which a hereditary predisposition to neural and other tumors has been clearly established.

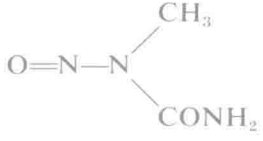
## RADIATION AND CHEMICAL CARCINOGENESIS

Like tumors elsewhere in the body, nervous system neoplasms provide instances that demonstrate the effects of agents such as ionizing radiation and chemical carcinogens that will greatly increase somatic mutation rates. The carcinogenic action of radiation is generally accepted to be due to this additive mutagenic effect and thus to provide indirect but convincing supporting evidence for the somatic mutation theory of cancer (32). This view has, however, recently been challenged on the basis of shielding experiments in radiation-induced murine leukemia, which suggest that the carcinogenic effect of radiation could also be mediated by indirect induction mechanisms, such as activation of a leukemogenic virus (33). Radiation-induced brain tumors in man thus far have been documented in the greatest detail as regards the occurrence of meningeal sarcomas, a development that has been recorded in a few instances following therapeutic radiation to the brain for the treatment of glioma or, more often, pituitary adenoma (18,24,34,35). The average time interval between initial radiation and the clinical appearance of the presumedly induced tumor is 5 to 10 years, but shows a range of 2 to 20 years. There are also a few tantalizing reports (36–38) suggesting that intracranial meningiomas may on occasion follow superficial radiation treatment to the scalp. On the other hand, the occurrence of gliomas in man following radiation for therapeutic purposes is very poorly documented. The possibility should not, however, be entirely discounted since glioblastomas have been shown to develop in monkeys 3 to 5 years after an exposure to 600 to 800 rads of 50-MEV protons (39).

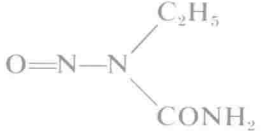
The resorptive N-nitroso compounds, which have the general formula



are now widely used for the experimental production of tumors of the central and peripheral nervous system. Like other alkylating agents (40), these carcinogens are known to be also mutagenic (41). Furthermore, they share with other carcinogens and mutagens the property of being powerfully teratogenic, especially when used in high concentration in early fetal life (42). One of their characteristic features is organ specificity, an attribute thought to be due primarily to the action of their guiding (R2) radical [although other factors such as the type of carcinogen, the dose concentration, the mode of application, and the strain and species of animals used play a part also (42)]. In the case of the most commonly employed of these alkylating agents, namely methylnitrosourea (MNU)



and ethylnitrosourea (ENU)



urea is the guiding radical and is believed to facilitate the diffusibility of the compounds into the nervous system, thus compensating for their marked instability as carcinogenic agents. The relatively simple molecule rapidly gains access to the nervous system tissues either after transplacental injection in the pregnant mother or following intramuscular, intravenous, subcutaneous, or intracerebral injection, as well as after gastric absorption.

The carcinogenic and mutagenic effects of the N-nitroso compounds are generally thought to be due to the action of their effector (R1) radical, which results in a permanent alteration in the DNA molecule of the target cell. This alteration is widely believed to be an alkylation of guanine, chiefly at the N7 position, although alkylation of guanine at the O6 position and of adenine at the N3 position are also known to occur (43,44). Possible consequences of alkylation include either anomalous base-pairing of the molecule at its guanine base (40,45) or splitting of the alkylated base from the DNA chain with subsequent deletion (40). However, the molecular basis for the induction of neoplastic transformation by these compounds is still very poorly understood. For example, MNU has been shown to alkylate mitochondrial DNA preferentially over nuclear DNA (46). Alkylation by ENU is also known to involve the DNA in the liver to an extent similar to that of the brain (45), yet hepatic tumors are not induced with this compound. Furthermore, in fractionated rat brain nuclei, MNU seems to alkylate neuronal nuclei in preference to glial nuclei (43), yet its carcino-