Progress in Experimental Tumor Research

Recent Advances in Brain Tumor Research

17

Volume Editor:
W. G. Bingham, jr., Columbus, Ohio
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Recent Advances in Brain Tumor Research

Guest Editor: W. GEORGE BINGHAM, jr., Columbus, Ohio

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Series Editor's Foreword

Inclusion of a Brain Tumor Symposium in this series continues our attempts to cover clinical approaches when they result in fundamentally new knowledge or methodology. This symposium, furthermore, is a near ideal mixture of clinical and experimental studies, which demonstrates widely the interdependence of these disciplines. It is hoped that this volume will be helpful to neurophysiologists, pathologists and surgeons alike, but that beyond this it will stimulate cancer researchers with more fundamental inclinations to address themselves to this difficult subject.

The Series Editor is grateful to Dr. W. GEORGE BINGHAM for having offered his symposium for publication in this series and expresses his appreciation to all authors for their cooperation.

F. HOMBURGER, M.D.
Series Editor
Bio-Research Institute, Inc.
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Guest Editor's Foreword

This volume consists of the proceedings of the Brain Tumor Symposium organized by the several divisions of the neurological sciences of The Ohio State University Medical School and School of Veterinary Medicine as part of the University Centennial Celebration program and held in Columbus in October 1970. The impetus for this particular topic was sparked by the development of a multidisciplinary research project on experimental brain tumors utilizing the intravenous nitrosourea rat tumor model originally developed by DRUCKREY.

The formation of a large and productive colony of tumor-bearing rats in the Department of Veterinary Pathology resulted from the considerable efforts of Dr. ADALBERT KOESTNER and Dr. JAMES SWENBERG in collaboration with Dr. WOLFGANG WECHSLER of the Max Planck Institute, Bonn, Germany. Exploitation of these tumors with tissue culture and biochemical, immunological and ultrastructural analysis by the several participants has been most fruitful and the early results produced a sense of urgency and need to communicate with fellow investigators in oncology on both basic and clinical levels.

Additional motivation to share our experiences and information evolved from the recent Brain Tumor Chemotherapy Program of the National Cancer Institute, of which the Division of Neurological Surgery is a member. Several authorities were invited to take part in the symposium and to a man they conveyed not only their willingness but a genuine eagerness to participate.

The first morning of the symposium was devoted to the several experimental models currently being utilized throughout the country. An introductory definition of the problem by LISS stressed the dynamism of glial biology and anticipated the results of tissue culture to be presented later. KOESTNER then discussed the program at The Ohio State Universi-

ty, the use of resorptive carcinogens in the production of experimental tumors and the types of tumors found in the rat following direct or transplacental administration of the nitrosourea compounds. This particular tumor model utilizing resorptive carcinogens has considerable clinical significance in that a single dose of nitrosourea in the pregnant rat will induce CNS tumors in the fetus. Such compounds are known to be quite ubiquitous in nature and are used in industry.

The technique of producing brain tumors by injecting highly purified preparations of Rous sarcoma virus into brain of hamsters and dogs was presented next by MAHALEY, BIGNER and VICK. The relationship of this rapidly produced tumor to human glioma is difficult to assess. Tumors resembling typical gliomas were produced only when the injected area involved the subependymal glial tissue of the lateral ventricle. When injected into the cerebellum or parietal lobe, sarcomas were produced – an infrequent tumor in human brain. It seems unlikely that this tumor possesses a blood supply or bears a relationship to the adjacent brain vasculature similar to that seen in autochthonous gliomas of man. Caution in ascribing etiologic significance to viral particles within tumore cells was voiced by YOHN. Evidence of viral genomic integration is more conclusive of viral oncogenesis than particles per se.

The use of tissue culture as a routine procedure in the diagnosis of human brain tumors was presented by LISS and by UNTERHARNSCHEIDT, who exhaustively reviewed the entire subject.

Energy metabolism of experimental brain tumors was then presented in 3 papers by LEHRER, KIRSCH and ALLEN. Structural alterations in tumor vessels and growth of tumors beyond the capacity of their blood supply were described as factors influencing the supply of oxidative enzymes, high energy phosphate compounds and overall energy metabolism of the proliferating tumor cells. Metabolic activities of tumor cells are extremely variable and substrate utilization extends to include fatty acids, proteins and other substances. Metabolic potential of actively growing tumor cells may be more a product of the microenvironment of the tumor and its anomalous blood supply than the result of inherent characteristics.

The second day of the symposium was devoted to completing the discussion of the biochemistry of brain tumors and to considering the clinical applications of these biological concepts to tumor therapy. Dr. WECHSLER discussed the advantages of the nitrosourea-induced tumors as a model for studying the biology, biochemistry and response to

chemotherapy of primary gliomas. Being purely autochthonous and developing along lines of glial evolution, these tumors should provide greater similarity to human gliomas compared to models requiring injection and surgical manipulation of animal brain and producing a reactive blood supply and inappropriate tumors.

Loss of sodium-potassium ATPase activity in areas of necrosis of experimentally induced tumors was demonstrated by HESS. She proposed that peritumoral edema may be due to breakdown of Na + K ATPase activity and a failure to control extra- and intracellular concentrations of sodium and potassium.

Recent work on the blood-brain barrier was summarized and investigations into the effect of neoplasia on the barrier systems was brought up to date by SHUTTLEWORTH. The problem remains a highly complex and poorly understood one, despite a vast amount of investigational effort. Conceptually, a gradient of barrier activity may exist, beginning at the periphery where early invasion has caused little alteration in brain vasculature and autoregulation and barrier activity are preserved. Further into the depths of the tumor, structural alteration of brain vessels has occurred with impaired barrier activity, and large molecular compounds such as radioactive proteins are capable of entering in quantities sufficient to be detected clinically. The problem has great relevance to the field of chemotherapy. Conceivably, these agents enter the tumor in areas where cells are already dying and are thus wasted. In areas of active growth, however, the barrier activity is sufficiently preserved to prevent their ingress in lethal concentrations. It is in this concept that the blood-brain barrier becomes applicable and the need for lipid-soluble chemotherapeutic agents becomes apparent.

Hydrolytic enzyme activity was the subject of three papers by ALLEN, BINGHAM and SWENBERG. Malignant gliomas have remarkably high levels of β-glucuronidase activity. Neither the role of this enzyme in gliomas nor the substrate upon which it acts is known. Acid *p*-nitrophenylphosphatase activity was also very high in several human glioblastomas as well as in the nitrosourea-induced rat gliomas.

Histochemically, β-glucuronidase and acid phosphatase were in greatest concentration in deep, compact cellular areas in which lysosomes were also abundant. Enzyme activity and lysosomes were less apparent about the tumor margin. Cell cycle studies of tumors produced by the resorptive carcinogens have not been completed and it is uncertain which phase predominates in these more deeply situated cell popu-

lations. Enzyme activity, however, appears to be associated with early cellular degeneration.

Clinical oncology was introduced by YASHON, who described a rapid technique for identifying brain tumors at the time of surgery. This was followed by a discussion of cell cycle studies of human malignant gliomas by WILSON in which double labeling techniques were employed. By staging the administration of chemotherapeutic drugs, interruption of the malignant cell cycle might be achieved. The use of combination therapy may overcome the problems of toxicity, which has been a limiting factor to date. RALL expanded the philosophy of recently established chemotherapeutic programs under the auspices of the National Cancer Institute.

Recent emphasis on the role of the neurosurgeon in the treatment of brain tumors was underscored by HUNT and SAYERS. Far from being supplanted by the inroads of chemotherapy, the neurosurgeon may find his skills in greater demand not only to establish positive histological diagnosis but also to attempt as complete removal of tumor as feasible without encroaching on functioning neural elements. Reduction of the cell population acts as a stimulus to cell division, according to the Gompertzian curve of tumor growth. By combining this with chemotherapy a greater proportion of cells will enter the same phase of the cell cycle and larger populations will become vulnerable to combined therapy. It should also be noted that surgery has the additional effect of disturbing the blood-brain barrier at the periphery of the tumor, which may aid in penetration of chemotherapeutic agents in the area of active tumor invasion. The continued participation of the radiotherapist in treating brain tumor was emphasized by BATLEY. Good results have been obtained in cases of medulloblastoma in children.

Panel discussions were held at the end of each daily session, allowing an opportunity for the participants to probe in greater depth one another's opinions as well as to respond to questions from the registrants. ALLEN summarized concisely the results of 2 full days of discussion and ended the symposium on a high note, emphasizing those avenues of investigation opened up by current research which appear likely to lead to positive results and definitive answers. One could hardly fail to be infected by the invigorating feeling of optimism and imminent successful penetration into a problem too long covered by a cold shroud of pessimism and despair.

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Classification of Brain Tumors and Experimental Models

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Contents

I. Introduction

'What's in a name . . .' [Shakespeare]
'By their fruits you will know them.' [Matthew 7: 16]

Classification of the central nervous system tumors is a topic which lends itself either to a listing of headings of 30-sec duration, or to a week-long symposium at which various ideas are presented, the points argued and nothing positive achieved. It is a pleasant task in which the speaker has a chance to show his erudition, especially if one decides on a so-called 'historical approach' in which he will begin with something non controversial, such as a photograph of Harvey Cushing, followed by a scheme of the origin of cells forming the cerebral tumors. Yet this venerable and not controversial approach was eliminated, since my task is to present a 'classification' rather than to discuss various types of tumor 'classifications'.

I look at this task somewhat as a keynote speaker before his party adopts a platform. Out of all the possibilities open at such a moment I should not be restrictive but all-inclusive, since the guidelines which I intend to present should be realistic, practical, scientifically correct and elastic enough to accommodate everybody, within reason. The classification of brain tumors, in contrast to other topics to be presented today, does not represent a new frontier, but a task which has been little modified since the first succesful attempts, and which subsequently has been augmented and modernized to accommodate mainly new ideas and, infrequently, new findings. The subsequent presentations of this symposium, on the contrary, deal with the frontiers in research on brain tumors and it is conceivable that the findings about to be presented may contribute to further modification of our way of thinking. Almost every self-respecting neuropathologist, and I mean present company included, has through the years contributed something to either understanding, classification or clouding of the issue of brain tumor classification.

II. Classification of Intracranial Tumors

In order to set the stage for a consideration of various approaches and philosophies applied to the classification of intracranial tumors, and before we address ourselves to the question: 'Classification, how?', let us first consider the prolem of motivation in various approaches to classification; in other words, 'Classification, why?'. The approaches do vary to a considerable degree. On one side of the spectrum there is the consideration for the clinical manifestations, and the key words of the classification are of secondary importance as long as the implications of the biological behavior are clearly understood. For this approach we may as well dispense with names and substitute numerals, letters or any other agreed-upon set of symbols.

A. Taxonomical Approach

This taxonomical approach found its expression in grading the types of tumors as a group, in which the group designated as grade I represents the slowly growing, demarcated, easily excisable tumor, where the successful completion of surgical removal is equivalent to permanent cure. In this category belong, obviously, such tumors as meningiomas,

acoustic tumors and benign papillomas of the choroid plexus. At the other end of the line we place tumors such as glioblastoma multiforme, which grow rapidly, infiltrate the brain tissue, defy any attempt toward successful treatment, and result in the early demise of the patient. Between these two extremes any number of steps can be inserted to accommodate neoplasms according to the degree of success of finite or palliative treatment.

B. Morphological Approach

On the other hand, there is a morphologically puristic approach where the cellular components are analyzed, recognized and categorized with a blatant disregard for any clinical consideration. The earliest tumor classifications have already recognized that the aggressiveness of the neoplasm is of equal importance as is the identification of a cell type responsible for its formation. Yet many important discrepancies are created if the histological criteria of the cellularity, pleomorphism, number of mitoses and bizarre cell forms are used with disregard for the nature of the tissue. For example, glioblastoma and monstrocellular sarcoma, although histologically equally awesome, give the patient different prognoses, reflected in the period of survival.

III. Histological Criteria vs. Nature of Tissue

From the time of the earliest therapeutic approaches of surgical removal and decompression, through the advances and refinements of surgical and radiation therapy, to the promising era of chemo- and immunotherapy, the question of nomenclature and classification has been in the forefront of the problem, always of importance, never completely answered, and never yielding completely to any rigid mold.

Let us look at the cells comprising the intracranial contents and consider all the neoplasms which arise in this location. In establishing criteria by which to recognize these neoplasms and their cellular components, one cannot avoid correlating their morphological characteristics with those of the normal cellular elements which we consider to be their origin. By using this approach, which appears to be the most logical one, we preclude our complete understanding of the cellular components of the nervous system throughout their normal development and their adaptation, alterations and modifications. I submit to you that this is a fal-

lacy. Anyone who cares to look into the problems connected with the nomenclature is immediately swamped by the plethora of names and synonyms, the overlapping and confusing application of terms.

A. Reactive Cells

The task of the diagnostician is also considerably complicated by the well known, if little publicized, fact that cells appearing in the central nervous system, i.e., astrocytes, sometimes have an insufficient number of characteristics which could be applied to answer the basic question of neoplastic vs. non-neoplastic nature of such cells. Reactive astrocytes, especially those surrounding metastatic neoplasms, demonstrate a sufficient degree of pleomorphism, binucleated cells and mitotic divisions to indicate the possibility of neoplastic growth, especially if contrasted with some of the well differentiated, slowly growing astrocytomas. Such problems are minimal if sufficient material is available for examination, but an inconclusive or erroneous answer might result from even a generous biopsy.

To determine the correlation between tumor type and cell type let us concentrate upon something obviously clear and simple, as, for instance, the glial cells; the astrocytes, the oligodendrocytes and the ependyma. Here we should feel confident when we attempt to correlate the morphology of the neoplasm with that of elements found in a mature or maturing nervous system. While this holds true for the great majority of instances, there are cases which persistently defy our attempts to catalogue and regiment them. Fortunately, the majority of neoplasms are obliging to the morphologist by containing only one cell type. In any situation where more than one cell type is present, immediate confusion and panic in the literature results in an abandoning of the sane haven of sound classification. This is caused by our inability to define morphologically a neoplastic cell and, subsequently, it is impossible to answer the questions: 'Who in the crowd is the culprit, who is an innocent bystander and who attempts to react to the pathological process?'.

B. Germinal Origin and Prognosis

For the purpose of setting the stage for the following papers we are going to move from the theoretical considerations and research ap-