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Multidisciplinary Aspects of Brain Tumor Therapy

P. Paoletti, M.D. Walker, G. Butti & R. Knerich
Editors

MULTIDISCIPLINARY ASPECTS OF BRAIN TUMOR THERAPY

Proceedings of the International Symposium on Multidisciplinary Aspects of Brain Tumor Therapy held in Gardone Riviera (Brescia), Italy, June 8-10, 1979.

Sponsored by the Giovanni Lorenzini Foundation.

Editors:
P. Paoletti
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and
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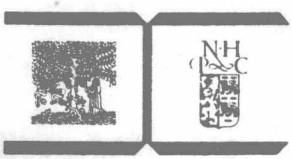

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PREFACE

This volume contains the proceedings of the International Symposium on Multidisciplinary Aspects of Brain Tumor Therapy held on June 8-10, 1979, at Gardone Riviera (Brescia), Italy.

The field of neurooncology is young and unique. The problems inherent in an understanding of the biologic entity with which we deal have inflamed the interest of many scientists well outside of the traditional neurologic fields. In the clinical setting, the multidisciplinary aspects of treatment are obvious as a team of neurosurgeons, neurologists, neurodiagnosticians, radiotherapists, and neuropathologists is required. However, the plurality of interest extends well beyond the clinical setting into the fields of molecular and cellular biology, pharmacology, immunology, biochemistry, and disease modeling. Only through the combined efforts of scientists in all these areas will the groundwork for significant improvement in the treatment of malignant glioma be prepared.

The intent of the meeting was to bring together basic and clinically oriented neuroscientists of many persuasions for the exchange of new and relevant ideas concerning the biology and treatment of brain tumor. The first portion was devoted to the induction and utilization of experimental brain tumor models as they might add to an understanding of this disease. This was followed by an examination of the biology and diagnosis of brain tumors from the morphologic, diagnostic, biochemical, immunologic, and kinetic point of view. A full session was devoted to the principles of therapy, including surgery, radiotherapy, chemotherapy, as well as combined modalities treatment. This was followed by a report of the principally controlled therapeutic studies being performed throughout the world.

The meeting was successful not only from the point of view of scientific material presented from the podium but also from the exchange of ideas during formal and informal discussion periods. Attendance at the meeting was truly representative of the extended neurooncologic field, and a large number of excellent free communications were delivered. The symposium achieved its goal of presenting new and relevant information and allowing scientists to meet with each other (often for the first time) in a most conducive setting.

The Editors would like to express their appreciation for the generous support and contributions of many individuals and organizations. In particular, we would like to recognize the Fondazione Giovanni Lorenzini and its staff for making the conference possible, as well as, Elsevier/North-Holland for its rapid publication of these proceedings.

M. D. Walker

P. Paoletti

June 11, 1979

CONTENTS

INVITED LECTURES

Multidisciplinary Aspects of Brain Tumor Therapy
P. Paoletti, M.D. Walker, G. Butti and R. Knerich, eds.

RESEARCH ON BRAIN TUMORS

Paul C. Bucy

To be sure the study of brain tumors has merits of its own from a purely scientific standpoint. However, no one would contend that research on brain tumors is other than an effort to improve the understanding of these tumors and of their treatment in the hopes that ultimately cure or cures will be developed.

Just one hundred years ago the intrepid Scot, Sir William Macewen of Glasgow, successfully removed the first brain tumor. Since then there have been striking improvements in the treatment of these tumors. Diagnostic means of demonstrating and localizing them have been improved dramatically. The means of surgical treatment have been enhanced in great measure. Many tumors formerly regarded as inoperable have steadily yielded to the surgeons' efforts. The mortality of operations for their removal has been materially reduced. The results in those patients which survive surgical removal have been improved. But most of the tumors which can now be recognized and satisfactorily treated have been those which arise outside of the nervous system and involve it by compression and impairment of its blood supply. Those tumors of the nervous tissues themselves, the gliomas, have for the most part eluded all of our therapeutic efforts. In short, in one hundred years we have accomplished little in their treatment. With the exception of the astrocytomas of the cerebellum and a very few isolated tumors limited to parts of the brain which can be sacrificed with relatively minor neurological damage, we have achieved no cures of gliomas of the brain. This is truly remarkable because these tumors are for the most part tumors restricted to part of the brain, tumors which do not metastasize as do malignant tumors which arise in other parts of the body. In short, these tumors are not malignant. They are regarded as such only because some of them grow relatively rapidly and practically all of them end in the death of the patient. It is obvious that we should be doing better and almost equally obvious that with renewed concentrated efforts properly directed, we can do better.

This is no minor problem. Approximately two out of every 100 persons will develop a brain tumor some time during their life time. In the United States that will be 4,400,000 cases of brain tumor. If we accept the life of the average person as 70 years (of course the average is much less) there will be

approximately 65,000 cases of brain tumor in that country each year. Throughout the world about 40% of all brain tumors are gliomas. Accordingly, in the United States there must be approximately 26,000 cases of glioma of the brain each year, and throughout the world approximately 472,700 cases each year. Conquest of this problem is a worthy goal.

This symposium is devoted largely to the consideration of treatment of these tumors once they have reached a size which gives rise to serious symptoms and threatens the patients lives. You have been concerned primarily with various chemotherapeutic measures. Past results have not been encouraging. To be sure there has been evidence that some chemotherapeutic drugs can ameliorate symptoms and that others can result in a decrease in the size of the tumors. But there have been few if any cures. Yet the feeble response to the use of these drugs is in itself evidence that they have some restraining effect. It is also evidence that we must continue in our efforts to increase their effectiveness and to find more effective drugs.

The same might be said of radiation therapy. There can be little doubt but that it too can decrease the symptoms resulting from a tumor and can decrease the size of some tumors. In other words, that to some degree it, too, is effective. But its beneficial effects are, for the most part, of short duration and it produces no cures. In this field, however, one is impressed and disturbed by the lack of any significant investigations to improve the results from radiation therapy. Such investigations have long been needed.

If improvement in treatment with chemotherapeutic agents and radiation therapy is achieved it seems unlikely at this time that it will be forthcoming in the near future. Our efforts at improving the results of treatment of brain tumors must not be tied exclusively to these two forms of therapy. It also appears unlikely that mere improvement in surgical techniques will, at the present time, result in curing these tumors. Something more and in many respects something far simpler is now needed. They must be recognized much earlier when they are considerably smaller.

As was noted earlier these tumors are limited as to the area of the brain involved and they do not metastasize. If they can be completely removed they can be cured. We are frustrated from accomplishing this because when the tumor is operated upon it is too large and has impaired the function of far too much of the brain.

Obviously these tumors do not begin as the large masses which are now encountered clinically and which are depicted in our neurological and neurosurgical textbooks. They begin with the neoplastic differentiation of a single

cell or a small group of cells. There is no evidence, except in very rare cases, that they develop in multiple centers of the brain. We know nothing about these tumors at this very early stage. In fact, we know little about them when they are considerably larger but still "asymptomatic". We do not know whether a tumor which is finally classified as a glioblastoma showed similar microscopic characteristics when it first began to develop. As a result we do not know how long the tumor had been present before it was recognized. The fact that a glioblastoma, once recognized, results in the death of the patient in approximately nine months to two years, does not by any means indicate that it had not been present, smoldering in its slow growth as a more benign neoplasm, for many years. We do not know the answers to these questions because we have not looked. How many asymptomatic gliomas of the brain have been reported in the literature? Very few. If we are to attack these tumors intelligently and successfully we must learn more about them.

It will not be sufficient to learn only when they start and what their microscopic appearance is at the outset. We must learn the etiological factors which produce these tumors. We must learn what are the effects, if any, of race, sex, occupation, geographical distribution, upon the initiation of these tumors. Here and there we see bits and pieces of evidence that these factors do play a role but details are still lacking.

Is there anything else that can be done to improve the results of treatment of gliomas of the brain? Yes, there is. Forty years ago most of the patients with a brain tumor came to the surgeon dumb, deaf, blind, or even comatose. That situation has been improved, not because of improved surgical techniques, but because of improved education. Doctors in general now recognize the possibility that a patient has a brain tumor far earlier than he formerly did. This has been the result of the educational efforts of the neurosurgeon but he stopped too soon. He has let undergraduate medical education slip from his grasp. Medical students are once again becoming doctors without knowing what the earlier symptoms of a brain tumor are. Thirty and forty years ago the neurosurgeon spent much time teaching the general practitioners, the neurologists, the internists, and the general surgeons, those symptoms which should indicate that a brain tumor might be present. Such continuing education has become much less common. If brain tumors are to be recognized at the earliest possible moment the education of the medical student and of the medical profession in general must begin again.

Once the possibility that the patient has a brain tumor has been recognized it must be pursued until the existence of the tumor has been established or the possibility of its existence has been negated. Fortunately, we have available the diagnostic equipment to answer this question for the most part. In spite of the mistaken attitude of the Secretary of Health, Education and Welfare of the United States, we must utilize enhanced computerized tomography far more than it is now being done. Every patient who presents with symptoms slightly suggestive of the existence of a brain tumor should have an enhanced computerized tomogram. And if the results are negative, but his symptoms persist, it should be repeated a short time later.

Why do I address these words to you who are heavily involved in the investigation of chemotherapeutic agents? The reason is simple. You are among the few who recognize that we do not have to accept one hundred years of defeat and that there is hope if we try hard enough. The practicing neurological surgeons and therapeutic radiologists give every evidence of their willingness to continue to do what they have been taught and what they have always done and of their willingness to continue to accept the woefully inadequate results with cerebral gliomas which we have had over the years. The future depends upon those, like yourselves, who are not content with things as they are, who see a ray of hope that if we strive to learn more and to do better, success will ultimately reward our efforts.

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PATHOGENETIC FACTORS IN THE INDUCTION OF BRAIN TUMORS BY NITROSOUREAS

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INTRODUCTION

Experimental neurooncology demonstrates that a great variety of chemical carcinogens and oncogenic viruses may act as etiological agents of the tumors of the nervous system[1]. The incidence, type and localization of the tumors, however, are influenced by pathogentic factors. In the case of chemical induction of brain tumors the following modifying influences should be taken into consideration:

TABLE 1
PATHOGENETIC FACTORS IN THE DEVELOPMENT OF BRAIN TUMORS

Pathogenetic factors	Mechanism
organspecific susceptibility	different velocity of DNS repair[2]
age dependent susceptibility	different rate of cell division and metabolic activities[3]
species and strain dependent susceptibility	genetic differences
hormonal imbalances	unknown
circadian and seasonal rhythms	metabolic differences

One of the most important pathogenetic factors is the genetic one. None of the carcinogens displays its neurooncogenic effect in all species. Methylnitrosourea (MNU) induces brain tumors in rats[4, 5], rabbits[6, 7] and dogs[8], whereas Rhesus monkeys[9], swine and sheep[10] are not susceptible to MNU. Strain-dependent differences in the incidence of neurogenic tumors emerge in experiments on rats, exposed to ethylnitrosourea (ENU)[11, 12]. The different susceptibility of various inbred strains of rats is evident in experiments with MNU, too:

TABLE 2
INCIDENCE OF BRAIN AND PERIPHERAL NERVE TUMORS IN TWO DIFFERENT INBRED STRAINS OF RATS (AFTER MNU)

Strain	Total number of rats	With brain tumors		With nerve tumors	
Wistar	121	37	31 %	31	26 %
hooded rats	286	209	73 %	31	11 %

Reasons for the resistance of various species and inbred strains to tumor induction remain unknown. Since such knowledge could be the key to prevention and treatment we made efforts to find out how the genetic disposition influences the tumor development in the nervous system. The genetic codes direct all biological processes in the organism. They act through the metabolism. Thus it may be assumed that the species and strain dependent differences in the neurooncogenic action of a given carcinogen are the consequence of metabolic dissimilarities. This working hypothesis in mind, we tried to assess some aspects of the metabolism by bio- and histochemical studies of enzyme activities.

In investigating a large number of enzymes we found that a particular phosphatase shows significant differences in its activity in various species. The findings are reported and discussed in relation to their significance for the development of tumors of the nervous system.