Recent Results in Cancer Research

Gliomas

Current Concepts in Biology, Diagnosis and Therapy

Edited by
J. Hekmatpanah

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Symposium on "Cerebral Gliomas" held at the University of Chicago, May 18—19, 1974

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Recent Results in Cancer Research 51

Fortschritte der Krebsforschung
Progrès dans les recherches sur le cancer

Preface

When I was asked by the Cancer Teaching Committee of the University of Chicago to set up a Symposium on Brain Tumors, I welcomed the opportunity to do so. But I felt that "Brain Tumors" was far too broad a subject to cover in a day and a half meeting. Furthermore, during the past decade, there have been a great many papers and symposiums on technical advancements in the treatment of benign brain tumors. On the other hand, while gliomas make up somewhere around 50% of all brain tumors, there have certainly been far fewer communications about them. For this reason I thought that it would be highly valuable to invite some of the leading investigators to share with us their experience with gliomas. The hope was to learn the current concepts about these tumors biologically and therapeutically, specifically to find out what we are doing and where we are going in these respects. Naturally all aspects could not be covered. Nevertheless, it was a widely expressed opinion by the speakers that they too learned while they came to teach. It is therefore hoped that the publication of their works and ideas through this monograph will also be useful for the reader. Most of the manuscripts were handed in at the time of the Symposium, and a few were sent later. Except for minor editorial changes the words are entirely those of the speakers and authors.

Dr. WISSLER introduced those who helped to set up the Symposium. To them, and to the speakers, I too extend my gratitude. I would like to thank Dr. WISSLER himself for initiating the concept and helping to make this and other Cancer Teaching Symposiums possible. Finally, I wish to thank EMILY SCHMIDT for her many hours of help in typing, editing, and proofreading.

JAVAD HEKMATPANAH, M. D.

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Contents

Session III

Chairman: M. L. GRIEM
Co-Chairman: D. H. PEARSON

Opening of the Symposium

R. W. Wissler

This is the 6th biennial cancer teaching symposium that we have organized and held at the University of Chicago under the auspices of the Clinical Cancer Training Program which is supported by a grant from the National Cancer Institute. Four of these have been published previously as a part of this Springer-Verlag series, Recent Results in Cancer Research. This is the fifth one.

The main purpose of these teaching efforts has been to bring to our house staff, students and young faculty and to many guests from Chicago and more distant centers the most up-to-date information on various aspects of a significant subject in the field of clinical neoplasia. We have attempted to present a coordinated overview of that subject, something that it is difficult to do on most medical school campuses with the locally available faculty.

Now to achieve this goal of a modern, up-to-date overview of an important subject in human cancer and to make it worth publishing, one has to have several ingredients:

1. One needs to have adequate financial support, in this case provided by 5 T12 CA-08077.
2. The subject needs to be important and timely. To choose the subject for these teaching symposia, including this one, we have had the constant help of a very talented advisory committee for the Cancer Training Program. They have spent a lot of time and effort on these decisions. They include: GEORGE BLOCK, MELVIN GRIEM, ELWOOD JENSEN, WERNER KIRSTEN, JOHN MULLAN, CHARLES PLATZ, HENRY RAPPAPORT, JOHN ULTMANN and GEORGE WIED.
3. One must have a knowledgeable, hardworking program chairman who should be an outstanding teacher. In this case Professor Dr. JAVAD HEKMATPANAH has devoted an immense amount of time and effort in organizing an excellent program, with well selected topics, and most important of all, superior teachers.
4. The faculty for the teaching symposium is the fourth ingredient. There must be an outstanding faculty and a thoroughly competent and experienced summarizer or rapporteur who has great skill. Both the faculty and the person chosen to summarize the conference must be outstanding. You can judge how well we have done but I believe you will enjoy great teaching as you read this volume.
   There is a spin-off from this, of course, because the faculty at each previous symposium has consistently told us that they also have learned a great deal!
   We can only express our very great appreciation for the efforts of the faculty, the time devoted to this symposium and the manuscripts and we hope that these illustrious teachers also found their participation in this symposium rewarding.
5. The fifth necessary component of any good teaching symposium is that small group of more or less anonymous people who help behind the

scenes - in this case JULIE KANT is the key person who has in her highly intelligent, cheerful and energetic way worked with EMILY SCHMIDT and LAURA STEELE to make all the arrangements for the meeting. She has, in addition, helped in many ways to bring the manuscript to fruition.

6. Finally we must acknowledge the good audience of interested students, many of whom were already experts in the neurological sciences and some of whom came from great distances to attend.
We think that the people who really wanted to learn about gliomas were there and we hope that there will be an ever increasing circle of interested students who will profit from our efforts to produce both a learned and learning monograph on gliomas.

Introductory Remarks

J. F. Mullan

I would like to join with my colleagues in welcoming all of you here. As you can gather, one of the purposes of this meeting is to spare our students and residents from the labors of listening to the staff; they have listened to us for years. Consequently our participation is kept to a minimum, so I will try to make this a minimal introduction. As Dr. WISSLER mentioned, there are really two purposes in this type of meeting. One is the factual knowledge gained. Another is perhaps more important. It is that this meeting presents an opportunity for our younger people to meet the leaders in the field. All of us, as we have settled upon our careers, have been influenced somewhere or other along the line in that decision. It may have been that the intellectual content of our specialty drove us to it, but I think in many cases it has not been the intellectual content, but the contact with an individual or individuals who stimulated our interests and our enthusiasm for this particular line of work. That, I think, is probably the most important ingredient of today's meeting, because we have with us today, without any question, a top talent in this field.

For a long time the whole problem of brain tumors was in the hands of the surgeons, since GODLEE took the first tumor out in 1884, 90 years ago. Since then, neurosurgeons have been mainly responsible for tumors. They have been responsible for surgery, and they have been responsible to a large extent for pathology, particularly the founder of this department of neurosurgery, PERCIVAL BAILEY, who evolved the classic descriptive pathology of brain tumors. In contrast studies too, surgeons took a leading role in all these decades from DANDY'S introduction of air studies to the introduction of technetium scanning by PAUL HARPER, who is a general surgeon at this University. But just as it is not safe to leave wars to the generals, it was realized long ago, it is not quite safe to leave brain tumors to the surgeons. Some of the more astute pathologists many years ago recognized this deficiency, and we delight in welcoming Dr. ZIMMERMAN, who was responsible for really turning descriptive neuropathology of brain tumors into experimental neuropathology. That was a most significant development. We also welcome Dr. RUBINSTEIN, who now represents the second generation of neuropathologists dedicated to the study of brain tumors. There has been a long and close relationship between surgery and pathology. We have many individuals who did not quite know which discipline to pursue. Dr. FERNANDEZ-MORAN of this University, who unfortunately is not here today, was doing a neurosurgical residency in Stockholm when Dr. OLIVECRONA took him aside, saying "You've got to be either a basic scientist or neurosurgeon; what do you really want to do?". Dr. FERNANDEZ-MORAN chose basic studies, and he has been largely responsible for the introduction of the electron microscope and the development of its techniques into the study of neuropathology. He still feels himself something of a surgeon, and I think whichever way his career would

have gone would have been a gain to that area. This dilemma persists. I believe that Dr. BIGNER started off to be a neurosurgeon, but he too sidetracked somewhere along the way. And Dr. ARNOLD never really was sure which he was; he moved from surgery to pathology and back again. He was the individual who first observed the amytrophic lateral sclerosis in Guam because his vision encompassed more than the narrow range of technical neurosurgery. Currently he is back again into pathology, probing the uses of the scanning microscope. I think that during our training the designated direction of our career specialty should not outweigh all other considerations. I believe we should use all the neurosciences together to tackle any particular problem, whether it is a tumor, or multiple sclerosis, or a vascular problem. Whatever it is, we should not feel narrowly regimented by our training experience. I believe we surgeons are currently in danger of becoming less productive because we are too narrow. But for a long time neurosurgery was well represented, not only in pathology, but in other fields too. If PERCIVAL BAILEY was the surgeon's pathologist, I guess WILDER PENFIELD was the surgeon's physiologist. There were, however, several areas left unrepresented. We didn't have the surgeon's biochemist until WOLFF KIRSCH came along, and I believe now we can say we have one. We haven't had a clinical pharmacologist until CHARLIE WILSON and others of his generation came along. Just as we talk about the giants of 30 or 40 years ago, such men as BAILEY, DANDY, and PENFIELD, I believe 30 or 40 years from now we will recall today's guest faculty of biochemists, virologists, pathologists, radiologists, and clinical pharmacologists with corresponding indebtedness. As I see the future of neurosurgery, it doesn't consist of bigger and better surgery, it consists of more broadly trained neurosurgeons who are competent in the basic sciences, as competent in the basic sciences as they are in neurosurgery. Neurosurgery itself has probably come somewhere near the end of its technical evolution. An example of this: our chairman, Dr. HEKMATPANAH, finished his training in 1963, and as far as I know has not yet lost a patient in relation to the surgical treatment of brain tumor, either as a resident or subsequently. As far as surgical mortality goes, we have arrived; we cannot improve upon his record. Just as he is an example of a current product of a modern training program under JOSEPH EVANS, I think we would also like to welcome back the first neurosurgical graduate of the training program at the University of Chicago, Dr. PAUL BUCY -- Dr. PAUL BUCY of BAILEY, BUCY and BUCHANAN's textbook, of the Klüver and Bucy syndrome, BUCY the outstanding surgeon of the thirties, of the forties, of the fifties, of the sixties, and of the seventies, BUCY the founder of Surgical Neurology, the individual who has been mainly instrumental in getting the National spinal cord program on the way. Looking back, PAUL, we feel your spirit never really left us. I also welcome Dr. BRUCE HENDRICK of that exacting neurosurgical school of Toronto. I think that where clinical judgement and surgical skill reign supreme, the successors of MCKENZIE and BOTTERELL must always have a place upon the podium. Though the technical evolution of surgery is somewhere near the end, the role of neurosurgery is perhaps not yet defined, because, theoretically at least, if one can detect a tumor early enough, one can take it out entirely. Our problem has been getting at it early enough. And so we look forward to our colleagues from our sister Universities of this city, to Dr. PETER WEINBERG and Dr. HUCKMAN, to tell us where neuroradiology is going, because if we can get those tumors earlier, we can cure them; it depends upon how early. Dr. WEINBERG will discuss conventional methods while Dr. HUCKMAN will introduce us to computerized axial tomography. The rules of this meeting prevent us hearing from Dr. STEWARD, our Co-Chairman of the afternoon, who is working on the proton beam scanner; it's an interesting device. By focusing the Bragg peak on the receptor system rather than on the tumor itself, one can get an en-

hanced contrast with minimal radiation exposure. So one can at least theoretically envision at this moment getting a proton beam as simply and with as little radiation as one can get a routine x-ray of the chest now. If we can get a routine early radiological 3-dimensional view of the brain without invasive contrast, then surgery will have gained a new role in brain tumors. There are other areas that must be explored at the present time, and which have nearly reached the end of their potential, especially radiotherapy, so I look forward very much to hearing what Dr. SHELINE and Dr. CHANG have to say there. We have a conventional system of delivering radiotherapy five days a week. Maybe if we give a little radiotherapy every day for a year, it might be better. Maybe if we did this like LEKSELL, using stereotactic methods of focused beams, we would do better. Maybe, as Dr. GRIEM has suggested, we must simply change the cerebral metabolism. Maybe we should make more extensive use of the radio-protective drugs, the radio-enhancement drugs. This still is quite a wide field. We have not included in this program any major contribution on immunology, and the reason is, I think, this is not far enough along for proper evaluation. But as one aspect of neurosurgery has reached the limit, all these other aspects of investigation and treatment of brain tumors are on the rise. And certainly our position today will look as outdated 30 years from now as does the position of those who were working at the early, exclusively neurosurgical, phase. So I look forward with great enthusiasm to this symposium, and again would like to thank all the speakers who have come. I like to again remind the students and those early in their careers that you are here for these two days to hear the best that is going on in this area, from masters in their fields. And I think, for those of you who are undecided in your careers, it might be not so much in what these people say as in the satisfaction and enthusiasm in the investigative life, that you might find information and experience to your profit.

The Significance of Experimental Gliomas for Human Disease

H. M. ZIMMERMAN

EPIDEMIOLOGY OF HUMAN INTRACRANIAL NEOPLASMS

In 1962 KURLAND and his associates (1) compiled the available mortality data on cerebral neoplasms for the United States and Canada as derived from the International List of Diseases and Causes of Death (2). Their study revealed a remarkably even geographic distribution for all classes of intracranial tumors in the two countries. The mortality rates ranged from 3 to 5 per 100,000 population. If this mortality estimate was correct in 1962 and if it is still valid in 1974, one can expect between 6,300 and 10,500 deaths from intracranial neoplastic disease this year in this country based on a population of two hundred and ten million.

The compilation of data of this kind is subject to innumerable inaccuracies, as pointed out by KURLAND and his associates. They noted, for example, that the rate for deaths due to brain tumors in Japan was very low, being about half that in Western countries, and they felt that at least in part this low rate could be attributed to diagnostic and reporting artifacts.

These investigators further reported the results of a 10 year survey among the population of Rochester, Minnesota. They found a prevalence ratio of intracranial neoplasms of 46 per 100,000 population and an incidence rate of about 19 per 100,000 per year. In this population, about 1 per cent of all deaths was due to primary intracranial tumors, which was about twice that reported in official mortality statistics.

Other studies have been carried out in the United States that disclose rates that vary from 3.0 - 8.4/100,000 of the population (3, 4, 5), and in other parts of the world the incidence also varies considerably (6, 7). Based upon confirmed tumor diagnosis at biopsy or autopsy, it has been estimated that primary intracranial neoplasms constitute 2-3 per cent of all neoplasms to which man is heir (8). There exist published accounts of the incidence of various expanding, space-occupying intracranial lesions, not all new-growths and not all primary neoplasms of the brain, that have been collected in different countries of the world. Some of these statistical reports have been presented in table form by this author (3), revealing wide discrepancies in the incidence of certain categories of tumors from country to country and even from series to series of cases collected by different authors in the same country.

Despite the reported variations in incidence of intracranial tumors in different series, all contributors agree that the gliomas rank first on a numerical basis. They constitute between 31 to 43 per cent of all

intracranial masses, including metastatic tumors and granulomas such as tuberculomas. Simply eliminating the latter two categories of expanding intracranial lesions from consideration has the effect of raising the glioma incidence to between 40 and 50 per cent. Thus it can be seen that for numerical considerations alone this class of brain tumors is the most important (9). But there are many additional factors, some subject to experimental probing, as will be discussed below, that make it so important.

Among the human gliomas, this author has found that the relatively malignant astrocytic tumor of the glioblastoma multiforme variety occupies first place numerically with an incidence of over 51 per cent (3). Next in frequency is the more slowly growing, hence more benign, astrocytoma (incidence of 24.5 per cent). The ependymoma is next with an incidence of slightly more than 6 per cent, followed by the oligodendroglioma (5.5 per cent). The polar spongioblastoma, confined essentially to the pons and brain stem and occasionally to the corpus callosum, was present in 3.4 per cent of the 1,633 glioma tumors of this series. Attention is drawn to the fact that 57 (3.4 per cent) of all the gliomas were mixed tumors; i.e., they contained more than one identifiable gliogenous component. Among these "mixed" gliomas were some that were composed of both ependymomatous and oligodendrogliomatous parts, and some that had additional astrocytomatous as well as sarcomatous portions.

THE EXPERIMENTALLY PRODUCED GLIOMAS

It is fortunate that the experimentally produced gliomas often resemble morphologically their human counterparts so closely as to be virtually indistinguishable from them. Thus the cerebral astrocytoma, produced in mice by intracerebral implantation of compact pellets of chemical carcinogens such as methylcholanthrene, dibenzanthracene or benzpyrene (10), is a microcystic tumor composed of stellate astrocytes (Fig. 1) very much as are the human astrocytomas. In general, the more slowly growing tumors of astrocytic origin are produced less frequently with the aromatic hydrocarbons than are the more malignant neoplasms.

By far the most frequent murine glioma produced experimentally is the glioblastoma multiforme (Types III and IV astrocytoma). It is this tumor, as already mentioned, that occupies first place among the human gliomas. Like the latter, the murine neoplasm is highly pleomorphic, with foci of necrosis and marginal spongioblasts usually arranged in palisades (Fig. 2). Multinucleated tumor giant cells are common. Vascular thromboses and hemorrhages are also frequent features of this neoplasm.

A modification of the murine glioblastoma multiforme exists in which the neoplasm, in addition to disclosing all the cytologic details just enumerated, is also characterized by numerous huge multinucleated neoplastic cells (Fig. 3). This is the tumor which in man is sometimes called "gigantocellular" or "monstrocellular" glioblastoma multiforme. The suggestion that the human tumor may be of mesodermal, hence sarcomatous, origin is not valid for this tumour in the mouse, which is unequivocally a glioma as shown by special staining methods.

Still another variation of the malignant form of glioma of the astrocytic variety seen in the corpus callosum, pons or brain stem of the

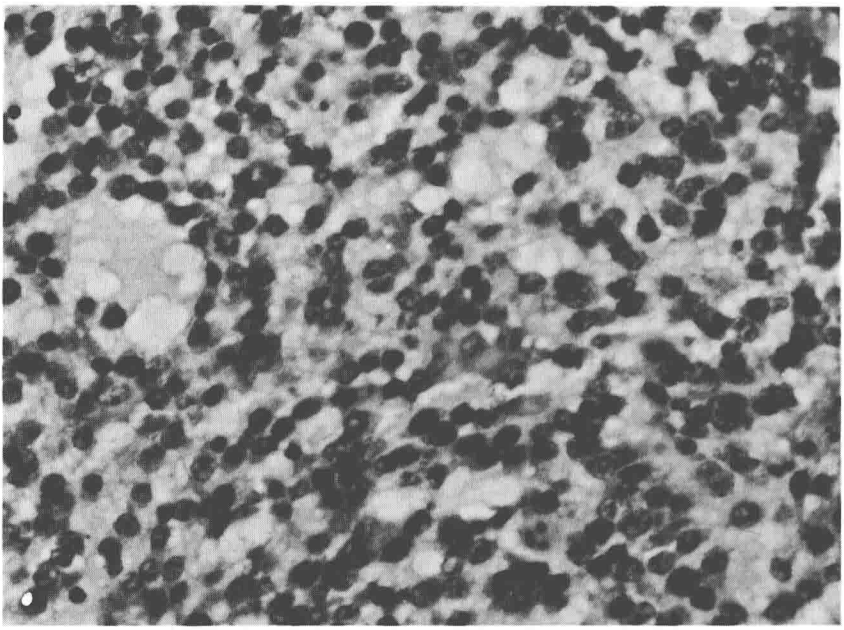

Fig. 1. Microcystic cerebral astrocytoma. x 425*

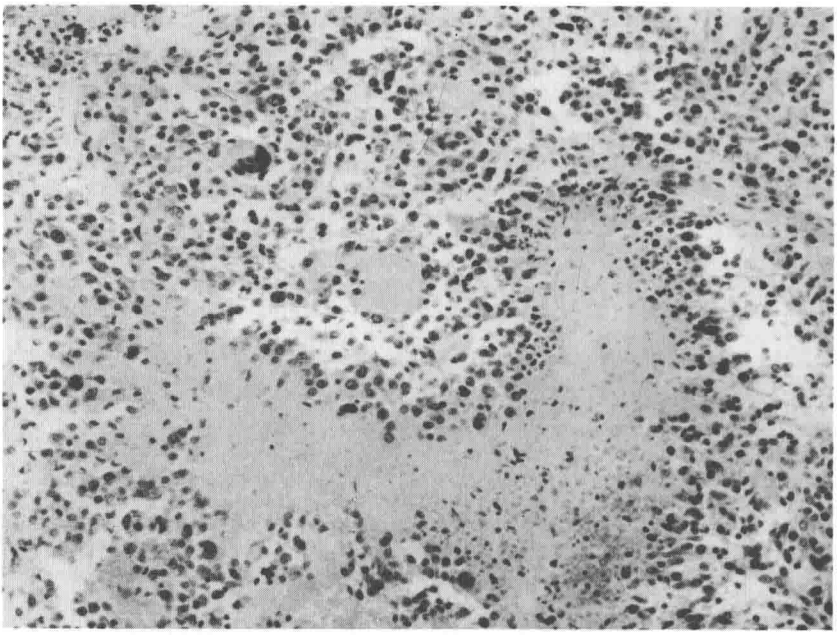

Fig. 2. Glioblastoma multiforme. The acellular area consists of necrotic tissue. The tumor cells are pleomorphic and a multinucleated tumor giant cell is present. x 180

* The first eleven figures are of tumors embedded in paraffin and stained with hematoxylin-eosin.