The Kentucky Conference on Brain Tumor Chemotherapy

Edgar A. Bering, Jr., M.D.,* Charles B. Wilson, M.D.,† and Horace A. Norrell, Jr., M.D.‡

The Kentucky Conference on Brain Chemotherapy was held in Lexington, Kentucky, on December 3, 1965, sponsored by the American Cancer Society, Kentucky Division, and cosponsored by the National Institute of Neurological Diseases and Blindness. The organizational efforts were shared by Dr. Edgar A. Bering, Jr., Dr. Charles Wilson, and Dr. Horace Norrell. Colonel Charles E. Tucker, Executive Vice-President of the American Cancer Society, Kentucky Division, provided invaluable guidance and support, which are gratefully acknowledged.

This paper represents a summary of the conclusions reached at the meeting. Because of limitations of space much detail has been omitted, but the bibliographic references lead one to the detailed material (see Table 1 at the end of this report).1–20 The paper, of course, reflects the ideas of the many participants. Several topics were considered and these will be presented under the following headings:

1. Evaluation of the effectiveness of chemotherapy on patients.
2. Modes and techniques for administering chemotherapeutic agents.
3. Evaluation of results achieved by various techniques of administration.
4. Chemotherapeutic agents, their actions and problems of selection.
5. Experimental approaches to chemotherapy.

Evaluation of the Effectiveness of Chemotherapy in Patients

The subject of brain tumor chemotherapy was introduced and reviewed by Dr. Lyle French. He noted the enormous difficulties in evaluating therapy of intracranial lesions because of the physician's inability to judge events taking place within the tumor itself. For example, was improvement in the patient due to a decrease in the size of the tumor or to a decrease in the related cerebral edema? No matter what techniques are used to study patients, unless the changes in the tumor mass itself can be delineated, the effectiveness of any given agent cannot be determined.

This point was elaborated upon by Dr. Zubrod of the National Cancer Institute. He described experiences with chemotherapy in extracranial tumors, pointing out that the only solid tumor against which chemotherapeutic treatment has been highly successful is the choriocarcinoma, a tumor whose activity can be followed by means of chorionic gonadotrophin excreted in the urine. There is a great need for other biochemical means of following the growth of tumors within the brain. It was suggested that a hepatic catalyst which is depressed in the presence of some tumors should be evaluated in patients with brain tumors.

Many techniques for following the course of brain tumors were discussed. These included echoencephalography, measurement of intracranial pressure, radioisotope scanning and isotope uptake, angiographic demonstrations of changes in tumor size, electroencephalography, cytologic examination for tumors cells in spinal fluid, myelography, and biochemical studies of cerebrospinal fluid. No single method permits adequate assessment of the effects of therapy upon a brain tumor, however. In the last analysis the best tool we have is the judicious opinion of a good clinician interpreting the clinical course, physical examination, and the several diagnostic procedures mentioned above.

Finally, if one considers the survival data on malignant gliomas, the results have been surprisingly uniform all over the world. Given a reasonably large group of patients,
it is likely that any significant change in survival rates due to chemotherapy would have been detected fairly early in the course of a study.

Techniques of Administering Chemotherapeutic Agents

Topical Drug Application. Dr. Bertram Selverstone gave the rationale for introducing an agent into a tumor cyst or creating an artificial cyst in a tumor bed for the purpose of instilling a chemotherapeutic agent. The agent initially tested was 8-azaguanine. The objective of topical application is a high local concentration of a cytotoxic agent which, as it leaves the site of tumor, will spread so thinly in the rest of the body that metabolism will occur sufficiently rapidly to avoid the problem of general toxicity. The agent selected (8-azaguanine) is rapidly destroyed by the enzyme 8-azaguanine deaminase (guanase), which is present in normal tissues. This action is a simple deaminization which renders azaguanine entirely harmless. Because glioblastomas contain only negligible amounts of this enzyme, 8-azaguanine warrants further study.

Intrathecal Drug Administration. Dr. Edgar Bering discussed the three principal techniques for introducing drugs into the cerebrospinal fluid, namely, single repeated injections, a constant drip infusion, or perfusion of the ventricular system. Each of these methods has been used in other conditions, and all are being brought to bear on the problem of brain tumor chemotherapy.

The interesting problem here is not the technique but the rationale for the use of intrathecal therapy. The intrathecal mode of administration has been suggested because it is assumed that brain tumors as well as brain tissue are subject to the blood-brain barrier phenomenon, so that drugs do not easily enter the tumor where they are to be effective. Drugs administered directly into the cerebrospinal fluid enter the tumor in much higher concentrations than can be achieved by the vascular route. The blood-brain barrier retains such drugs, allowing them to escape slowly from the tumor at rates which are less than the general elimination of the drug from the body, thereby avoiding many toxic problems. On the basis of this hypothesis and the assumptions that drugs enter the tumor from the cerebrospinal fluid by simple diffusion and that the lethal tissue concentration of a drug is known, optimal perfusion concentrations and times can then be calculated.

The question arises, however, as to whether there is a blood-brain barrier in tumors. In the final analysis, from what is known about various drugs entering the brain, every drug being used in the treatment of brain tumors will have to be tested separately for entry into tumors of different types.

Most of the relevant studies on the movement of substances into brain tumors are based on brain scanning and isotope uptake by tumors. It has been shown that a degree of lipid solubility aids the entry of drugs into the tumor, although certain nonlipid soluble drugs seem to enter experimental ependymomas easier than they enter normal brain. Important observations have been made on tagged albumin extracted from the extracellular space of frozen tumor cells. Albumin within tumor cells can occasionally be identified in this fashion. Radioactive albumin is not strongly attracted to the ependymal cells either in tissue culture studies or in vivo.

The great variability of the microscopic structure of tumors is significant. One can anticipate considerable leakage of any drug in areas of necrosis, whereas in other areas where the tumor is very solid, as around capillaries, the chemical agent should enter quite slowly from the blood stream. In tumors which border on cerebrospinal fluid spaces, intrathecal administration should be extremely valuable and probably more effective than intravascular administration. One example is meningeal leukemia, where the cells are confined to the cerebrospinal fluid pathways.

Intravascular Drug Administration. There are two general techniques of intravascular therapy: 1) regional perfusion of the area, where the total circulation is isolated and perfused with blood containing high concentrations of the drug; and 2) intravenous or intra-arterial therapy. Regional perfusion of the brain has been accomplished but has not produced any startling results because of the extreme difficulty in completely isolating any segment of the cerebral circulation. As