Brain Injury Research: Emphasis on the Gray

In a recent clinical study, the survival rate of experimentally treated patients with severe head injuries was nearly double that of conventionally treated victims. While the drug treatment used in the study is not considered suitable for widespread use in that application, the search for a safer chemical cousin eventually may lead to the successful treatment of brain injury — the leading cause of accidental death in the United States. The first leg of that search, along with the details of the clinical experiment, are reported by chemist Edward J. Cragoe Jr., neurosurgeon Robert S. Bourke and their colleagues in the May JOURNAL OF MEDICINAL CHEMISTRY. Cragoe told SCIENCE NEWS: "I've been in this business for more than 35 years, and I've never seen anything as exciting as this."

Accidental head injury causes edema, or swelling due to an increase in tissue-water content, of the brain, explains Cragoe of Merck Sharp & Dohme Research Laboratories in West Point, Penn. Effective therapeutic agents do not yet exist for this life-threatening situation, he says, because the molecular mechanism of the cerebral insult is not fully understood.

Past attempts to understand the chemistry behind brain edema have focused on the white matter — the axon (nerve pathway)-containing substance that constitutes about one-half of the brain volume — because this portion was presumed to be the site of clinically relevant cerebral swelling. However, recent studies by various groups including Bourke and colleagues of Albany Medical College of Union University in New York suggest that swelling of gray matter — the cerebral substance that contains the cellular bodies, or central parts, of neurons — also may be clinically important. Specifically, injury of the brain has been shown to cause swelling that is predominately limited to a single cell type, the astrocyte, in gray matter. Therefore, Bourke, Cragoe and associates decided to base their search for effective therapeutic agents for brain injury on what happens at the chemical level to gray matter astrocytes.

The research team noted that astrocyte swelling begins when chloride ions (Cl^-) move into the cells. Then, "Sodium follows chloride, and as soon as you have sodium chloride — which is salt — in there, water comes in to dilute it," Cragoe explains. The team also remembered from previous experience that some of the chemicals in a general chemical class called (aryloxy)-alkanoic acids block the transport of chloride ions across cellular membranes (the first step in astrocytic swelling).

In the search for an effective treatment, this class of compounds seemed a logical beginning. One of the members of the class is Edecrin, a compound now on the market as a powerful diuretic — an agent that increases the secretion of urine. After some preliminary studies of this diuretic, Bourke decided to test its ability to treat severely brain-injured patients in a controlled clinical experiment. Specific criteria for inclusion — patients who were between the ages of 15 and 50 years and were unresponsive to verbal commands, for example — limited the number in the study to 18 out of a possible 615 head-injured patients hospitalized at the Albany Medical Center Hospital for 4 or more days between July 1976 and January 1980. Eight of those included in the study were "control" patients who received "vigorous standard care"; the remaining 10 received intravenously administered doses of Edecrin along with the standard treatment. Based on the Glasgow Coma Score — an internationally accepted measure of neurological status following brain injury — a 50 percent survival rate was expected among the controls.

The results of the study were reported as follows: "The survival rate in the treated group was 90 percent as compared to 50 percent in the controls. Moreover, half of the controls that survived remained in a persistent vegetative state, whereas none of the treated survivors was so afflicted."

Despite these dramatic results, Cragoe and colleagues strongly recommend against the general use of Edecrin or other powerful diuretics to treat seriously head-injured patients. Their study was "limited in scope," they explain, and rapid loss of renal fluid "could seriously jeopardize neurological recovery in a patient with an insulted brain."

However, the clinical results do suggest that Cragoe and colleagues may be on the right track with their ongoing search for agents for the treatment of brain injury: the researchers are looking for compounds that block chloride transport but that lack diuretic activity. Test tube and animal studies of (aryloxy)alkanoic acids other than Edecrin already have turned up some potential candidates, the team reports.

—L. Garmon

Tempering humid tropic development

During the next 20 years, about 90 percent of the world's population increase, 1.5 billion people, will occur in countries that contain moist tropical forests. These people are going to turn to sparsely populated, underexploited lands like the Amazon jungle to meet their needs for food, fiber, fuel and forage. Already large tropical areas have suffered environmental damage because of poor logging and agricultural techniques (SN: 10/4/80, p. 218). How to provide for the short-term needs of growing populations without closing off opportunities for research and long-term environmental protection is the focus of a report from the National Research Council's Committee on Selected Biological Problems in the Humid Tropics.

The report, "Ecological Aspects of Development in the Humid Tropics," suggests that development of these areas is inevitable. It acknowledges that "current humid tropic development projects are buying time to permit the achievement of long-term, environmentally balanced strategies and new technologies." The report notes that too often projects have concentrated on roads, infrastructure and marketing systems while ignoring technology or assuming that temperate-zone technology was appropriate. As a result, many projects failed economically and ecologically.

Committee chairman Jay M. Savage said last week at a briefing organized by the study's sponsors, the U.S. Agency for International Development and the National Park Service, "In most portions of the world, these areas have resisted human migration because they're so difficult to manage." One reason is the heavy rainfall (between 5 and 35 feet per year). In addition, the forests have "a tremendous species diversity, and they appear to undergo extensive, rapid environmental degradation after they are modified," said Savage. The environmental constraints are "unique, stringent and seldom taken into account in the attempt to develop these areas," he said.

For example, Committee member Pedro A. Sanchez of North Carolina State University said fertile soils are not uncommon in tropical areas. With fertilizers, some areas can be cultivated continuously to produce three crops a year, he said. Research shows that manual slash-and-burn land clearing is superior to mechanized methods because the ash is a valuable fertilizer and less topsoil compaction and loss occurs. Techniques such as growing a mixture of crops and introducing new tropical plants for cultivation can also increase the productivity of the land.

The committee also looked closely at the sustained use of forested lands for timber and other products because tropical forests had adapted to high levels of rainfall and sunlight. "The most logical utilization of these forested areas is to use them in a natural way," Savage said.

—I. Peterson