Meetings

Drugs and Poisons in Mental Retardation

Drugs and poisons as etiological agents in mental retardation was the subject of a meeting of an interdisciplinary group of scientists, ranging from molecular biologists to behavioral psychologists, held in Palo Alto, California (26 February to 1 March 1967).

Edgar A. Bering, Jr. (NINDB), reviewed the objectives of this meeting; it was the second in a series of seven research conferences on the various etiological aspects of mental retardation, initially suggested in 1962 by the President's Panel on Mental Retardation. Its purpose was to provide an opportunity for an exchange of information by scientists with different backgrounds and points of view. It was hoped that in this way a conceptual framework would be established within which studies designed to advance our knowledge of the role of drugs and poisons in mental retardation might be pursued. Bering pointed out how this conference demonstrates the importance of basic research in the context of an important social problem. The ultimate goal of this meeting, as stated by Kretchmer (Stanford University School of Medicine) was to devise means of effective prevention. He outlined the following principal themes of the conference: (i) Parameters of the developing nervous system; (ii) epidemiological approaches; and (iii) specific neurotoxic agents as model systems.

Sidman (Harvard Medical School) outlined the behavior of cells in the developing brain, the target organ of noxious agents. This outline was presented as a framework for discussion of disease mechanisms which may alter such parameters as cell proliferation, migration, synapse formation, and neuronal processes leading to the finer organization of the central nervous system. As an example of the various stages of development of an organ system, Coulombré (NINDB) presented the results of an experimental analysis of the sequential steps in the development of the vertebrate eye and described the types of eye defects that result from interference with this sequence. He thus called attention to the critical importance of the time during organogenesis at which exposure to potentially harmful exogenous agents occurs.

Cohen (State University of New York at Buffalo, Medical School) demonstrated the usefulness of tissue culture techniques for analysis of chromosomal aberrations. Such techniques are used in the qualitative and quantitative evaluation of the effects of exogenous agents on both in vivo and in vitro systems. Gross congenital malformations, including malformations of the central nervous system as produced in animal experiments by a variety of drugs, were reviewed by Warkany (University of Cincinnati College of Medicine). He also reported on isolated observations of brain malformation in children, which was attributable to the taking of drugs by the mothers.

Chemical parameters of the developing nervous system were considered by Burton (Washington University School of Medicine). Changes in the chemical composition occurred in the brain of a newborn rat as the rat developed. With special emphasis on the gangliosides, Burton described the increasing biosynthesis of glycolipids which takes place during the immediate postnatal period. Sokoloff (National Institute of Mental Health) stressed the vulnerability of the immature brain to a deficiency of thyroxine, which can result in cretinism, thus pointing out the dependence of protein synthesis on the thyroid in the developing brain. The biosynthetic processes involved in the formation of myelin were reviewed by McKhann (Stanford University School of Medicine); he also reviewed the vulnerability of this system.

The functional parameters of the developing nervous system were described by Woodbury (University of Utah College of Medicine). The maturation of excitatory and inhibitory systems in the brain can be affected by the use of such drugs as strychnine, picrotoxin, and diphenylhydantoin. Drugs can also affect active transport of anions and cations during the development of the central nervous system, the blood-brain barrier, and extracellular space. Ellingson (University of Nebraska College of Medicine) presented data on the electrophysiological development of the human brain as judged by electroencephalography and the study of evoked responses. Maturational changes in the EEG patterns of infants were outlined by Parmelee (University of California School of Medicine, Los Angeles) with reference to techniques for judging delays in rates of maturation in infants with neurological disorders.

Epidemiological approaches to the study of correlations between the incidence of mental retardation and exposure to drugs or poisons were explored in depth. Drage (NINDB) gave a report on the Collaborative Perinatal Research Project of the NINDB. Mellin (College of Physicians and Surgeons, Columbia University), using the Fetal Life Study of Columbia University as a model, alluded to the difficulties of accurate data collection and suggested automation of clinical experience through the use of computers. Such automation would alleviate the problems of communication that stand in the way of the establishment of reliable baseline data from which to proceed to further retrospective and prospective studies. During discussion of these papers, Yeurshalmy (University of California, Berkeley) called attention to the difficulty with which specific drugs can be incriminated in serious adverse effects on the nervous system and other body systems.

The lack of follow-up information concerning cases of poisoning was emphasized by Done (University of Utah) in a paper on the short and long-term effects of acute poisoning. The difficulty of assessing the role of drugs and poisons in mental retardation is compounded by the fact that neurological damage may result not only from primary effects but also from secondary effects due to involvement of other body systems. He pointed out that although salicylates have long been known as the most frequent cause of accidental poisoning in children under 5 years of age, no long-term follow-

up studies on such cases of poisoning have been performed. Among other common poisons of significance at all age levels, Done cited carbon monoxide, barbiturates, tranquilizers and sedatives, glutethimide, and psychedelic substances. Thus, in addition to accidental poisonings, we must consider suicidal and environmental poisonings as well as the growing problem of intentional abuse of drugs and solvents.

A number of panelists talked about the role of oxygen poisoning and of cerebral anoxia and asphyxia. Sokoloff (NIMH) postulated a possible correlation between rate of cerebral blood flow and sensitivity to anoxia. He noted that in the middle of the first decade of life the brain may account for as much as 50 percent of the total basal oxygen consumption of the body. Lowden (Hospital for Sick Children, Toronto) reported the experimental finding that asphyxia in cats produced a fall in the sialic acid content of cerebral gangliosides; he related the observation that the concentration of this acid in the gangliosides of patients dying from cyanosis was also sharply reduced. Behrman (University of Oregon Medical School) discussed basic concepts of placental transport as they relate to the administering of a particular drug to pregnant women, and the pathophysiology of the development of fetal anoxia. Rubinstein (Stanford University School of Medicine) essayed an analysis of the pathogenesis and mechanism of neonatal anoxia, drawing attention to the age-dependent differences in histologic responses to anoxia of the human brain.

In an examination of model systems of chemically induced mental retardation, the role of vitamin D was discussed by Wiltse (University of California School of Medicine, Los Angeles). Lowe (University of Florida, College of Medicine), who is chairman of the Committee on Nutrition of the American Academy of Pediatrics, reviewed this Committee's investigations into the vitamin D problem. The Committee found that the daily requirement of this vitamin can be fully met by a ration of 400 units per day. Lowe touched upon the complex problems inherent in any attempt by government agencies, such as the Food and Drug Administration, to impose limits on the permissible use of food additives or drugs without arousing unwarranted public apprehension about the dangers involved.

Other model systems of brain dam-

age caused by exogenous agents were the heavy metals, notably lead, mercury, and thallium. Harrison (Baltimore City Hospital) appraised the problem of lead poisoning and its possible mechanisms; he described measures being taken in Baltimore and other cities to control this environmental problem. He stressed that lead poisoning is most commonly seen in children from slum areas, who have easy access to lead contained in paint on walls and other surfaces. As many as 5 percent of children from such slum areas were found to have significant blood levels of lead. Harrison raised the question of possible chronic brain damage from continuous, low-level exposure to lead, thus resulting in subclinical blood lead levels. Preventive steps must include changes in the physical environment; cases of frank poisoning can be effectively treated with chelating agents. Kurland (Mayo Clinic) described an example of industrial water pollution which led to an outbreak of a disease resembling cerebral palsy among children in Minamata, Japan. The disease was caused by organic mercury compounds that were discharged into the bay as waste from a vinyl chloride-producing plant. The compound was subsequently ingested with the water by fish fed to the victims. (Brief mention was also made of thallotoxicosis.)

Comments by Eeckels (University of Lovanium, Republic of Congo) illuminated the perspective from which mental retardation is viewed in some of the underdeveloped countries. In such countries the phenomenon is commonly due to states of deficiency rather than to intake of exogenous agents. Mentally retarded children do not pose a serious problem simply because the environment is too harsh to allow them to live very long.

A highlight of the conference was an address by James L. Goddard (commissioner of the Food and Drug Administration). He canvassed the broad responsibilities of his agency in the realm of consumer protection, reviewed experience to date in the fields of drug, food additive, and pesticide regulation, and sketched future plans and projects.

In remarks concluding the conference, Goldstein (Stanford University School of Medicine) reformulated the major problems raised; cited the difficulty of screening drugs with potential neurotoxicity in animals; and underscored the need for vastly intensified

efforts aimed at full clarification and prevention of cases of brain damage due to exogenous chemical agents. Protection of the public is the primary goal.

In their final recommendations the participants made the following points:

1) There is a strong need for continued and greatly expanded basic research relating to the developing nervous system.

2) Another paramount need is for the development of more effective monitoring systems for the collection and dissemination of data on drugs and toxic agents. The group welcomed the initiative of the FDA in embarking on a comprehensive review of drug efficacy, which should be immensely helpful in facilitating the evaluation of drug effects.

3) Long-term, follow-up studies should be undertaken of patients known to have been intoxicated, and surveillance of intoxicated patients should be maintained so that possible latent effects leading to manifestations of brain damage may be detected.

4) Massive efforts should be instituted to gather data to determine whether a relationship exists between the incidence of damage to the central nervous system and changes in environment and continued exposure to drugs and other agents. There was strong emphasis on the need for planning and study to devise appropriate, effective, methodological approaches in order to attain these objectives.

The meeting was held under the sponsorship of the National Institute of Neurological Diseases and Blindness. Detailed proceedings of the conference will be published by the Institute.

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Forthcoming Events

April

20–22. **Biological Energy Conversion,** conf., NASA Ames Research Center, Moffett Field, Calif. (Letters and Science Extension, Univ. of California, 2223 Fulton St., Berkeley)

20–22. **Ohio Acad. of Science,** 76th annual mtg., Dayton, Ohio. (J. H. Melvin, Executive Officer, The Academy, 505 King Ave., Columbus, Ohio 43221)

21–24. American **Oil Chemists'** Soc.,