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SCIENCE

Chronic Non-Psychiatric Hazards of Drugs of Abuse

A conference on Chronic Non-Psychiatric Hazards of Drugs of Abuse was held in San Francisco, 29–30 October 1969. The conference was cosponsored by the Center for Studies of Narcotic and Drug Abuse of the National Institute of Mental Health and by the recently formed Environmental Mutagen Society.

The conference focused on biological hazards of drugs of abuse and excluded their psychiatric and psychopharmacological effects. The major categories of hazards considered were toxicity, carcinogenicity, teratogenicity, and mutagenicity. The object was to review existing toxicological information on these drugs and to identify productive strategies for future research. A particular effort was made to interpret current data on biological hazards due to LSD.

Hazards posed by drugs of abuse were viewed against the perspective of therapeutic and prophylactic drugs, as well as from the wider perspective of environmental chemical pollutants. Drugs of abuse, however, present unusual toxicological problems. Their use, which has increased dramatically over the last decade, is generally restricted to young adults. Such drugs are self-administered in a variety of ways, including ingestion, injection, and inhalation; they are generally administered in unquantitated doses. They are often administered in highly impure or contaminated states in combination with a variety of other drugs and chemicals, and for prolonged periods of time. Finally, intercurrent infection and malnutrition are sometimes prevalent in user populations. In part, as a result of the restricted availability of these drugs, their chronic biological effects have been less well studied than other categories of drugs or environmental pollutants. The concept of matching benefits against hazards, generally considered appropriate in toxicological evaluation of therapeutic drugs, pesticides, or food additives, is complicated by other concerns implicit in the concept of "drug abuse."

Chemical structures of major categories of drugs of abuse were reviewed. The chemical crudity of most synthetic and semisynthetic formulations, and also the possibility of important biological activity of misidentified or unidentified chemical contaminants were emphasized. For example, the anesthetic Sernyl is commonly sold on the streets as synthetic marihuana. Background information on psychiatric, sociological, and pharmacological aspects of drug addiction and dependence were considered. Barbiturate dependence merited particular concern in view of the high mortality associated with abrupt withdrawal of this drug.

Biological interactions between different drugs of abuse and between them and other environmental pollutants were considered in relation to hepatic

microsomal enzyme function. For example, barbiturates are potent inducers of detoxifying microsomal enzymes; conversely, microsomal enzyme functions are inhibited by cannabinol constituents of marihuana and by 3,4-methylenedioxyamphetamine (structurally related to piperonyl butoxide, a pesticide synergist and potent microsomal enzyme inhibitor).

While population surveys are helpful in establishing shifts in usage patterns of various drugs of abuse, they are unlikely to be useful in monitoring or detecting chronic hazards. Epidemiological approaches were discussed both generally and in specific relation to mutagenic effects. Detecting such hazards typically requires very large population samples, which practical considerations limit. However, valuable epidemiologic data on drugs of abuse, as well as on a variety of other environmental influences, could well accrue from a uniform nationwide registration for congenital anomalies. For example, if LSD was a powerful teratogen, this might manifest by a significant clustering of birth defects in younger mothers in metropolitan districts. No such fluctuations have been observed. However, present systems of data collection are only marginally capable of detecting gross effects.

The scientific literature on carcinogenicity, teratogenicity, and mutagenicity of drugs of abuse is almost nonexistent, with the notable exception of that on cytogenetic effects of LSD. Carcinogenicity was discussed with particular reference to problems of biotransformation of precarcinogens and carcinogens, the need for enhancing the sensitivity of standard animal tests, and their high degree of human relevance. Feeding or other appropriate administration of high test doses to rodents, from early infancy onward, may help to reduce the insensitivity of current carcinogenicity tests which must use numbers of rodents incomparably smaller than the large human populations at presumptive risk. The recent Bionetics study on pesticides (sponsored by the National Cancer Institute) demonstrates that such techniques do not produce false positives. With regard to teratogenicity testing, while standard protocols are available, these could be made less empirical if modified in light of data on metabolic transformation and on the duration of sensitivity of any particular developing organ to any drug.

Infrahammalian models for [illegible] genicity testing—bacteria, *Neurospora*, *Drosophila*, and in vitro cytogenetics—were considered to yield useful information. Mammalian methods, however, provide information with a higher degree of presumptive human relevance. Such systems, which are both sensitive and practical, include in vivo cytogenetics, the host-mediated assay, in which bacteria or *Neurospora* are tested in a mammalian milieu, and the dominant lethal assay. A combination of mammalian and ancillary submammalian tests are likely to detect all chemicals producing point mutations or chromosome anomalies.

Early cytogenetic studies on LSD were reviewed and found difficult to interpret because of poor experimental design, inadequate controls, drug contaminants, and unresolved sampling problems. These studies reflect difficulties, sometimes inevitable, in the use of humans, notably the likelihood of previous or concurrent exposure to other drugs. It was considered that these problems would be avoided by well-planned serial in vivo animal studies. Recently, more adequate human studies have suggested that pure LSD administered under controlled conditions may not produce cytogenetic effects. Needless to say, such findings have no bearing on the psychiatric hazards of these drugs.

The confusion in regard to LSD underscores the critical need for programmatic development of information on genetic and other hazards of drugs of abuse, quite apart from other drugs and chemical pollutants, with currently available methods that are sensitive, relevant, and practical. Standard uniform reference samples of crude and synthetic drugs of abuse should be made more easily available to toxicologists. The possibility of integrating various methods—for example, the use of single animal groups for concurrent tests such as carcinogenicity tests, in vivo cytogenetics, the host-mediated assay, the dominant lethal assay, and psychopharmacological studies—should also be explored.

The proceedings of the conference will be published by the National Institute of Mental Health in monograph form.

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