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microsomal enzyme function. For example, barbiturates are potent inductors of detoxifying microsomal enzymes; conversely, microsomal enzyme functions are inhibited by cannabinoids 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 bio-transformation 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 Bioletics 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.

Inframammalian models for mutagenicity 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 psycho-pharmacological 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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