



Drugs of Abuse:
Their Genetic and
Other Chronic
Nonpsychiatric Hazards

edited by Samuel S. Epstein

associate editors:
Joshua Lederberg, Marvin S. Legator,
Eleanor E. Carroll, and Jack D. Blaine

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This book was designed by
The MIT Press Design Department.
It was set in Monotype Univers,
printed on Finch Textbook Offset
by Halliday Lithograph Corp.,
and bound
by The Colonial Press Inc.
in the United States of America.

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ISBN 0 262 05009 9 (hardcover)

Library of Congress catalog card number: 78-148969

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Based on a symposium
cosponsored by the Center for
Studies of Narcotic
and Drug Abuse, NIMH, and by
the Environmental Mutagen Society
San Francisco, October 29 and 30, 1969

edited by
Samuel S. Epstein
with associate editors
Joshua Lederberg
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Dedicated by Samuel S. Epstein
to his wife Elizabeth

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Foreword

There have now been two conferences held under the aegis of the National Institute of Mental Health principally concerned with the nonpsychiatric hazards of drugs of abuse. The first, held in the fall of 1967, at a time of considerable public alarm over possible genetic implications of LSD use, did much to place the problem in perspective and to encourage additional research. The second conference, two years later, has, we hope, contributed further awareness of what is still needed to assess adequately the possible mutagenic, teratogenic, and carcinogenic aspects of drugs of abuse. Drug abuse remains a refractory problem to which there are few simple solutions. Assessment of the physical and mental health implications of drug abuse, particularly from the standpoint of chronic use, is not easy. It is the task of the National Institute of Mental Health to develop the research support strategies to deal flexibly with the many facets of drug abuse. Publication of this volume is part of the long-term effort to foster a greater awareness of the present state of our scientific knowledge and to further the research effort upon which enlightened public policy must inevitably rest.

Bertram S. Brown, M.D.

Director

National Institute of Mental Health

The use of an ever widening range of drugs for nonmedical purposes has engendered some of the most contentious and perplexing controversies of our social policy. The possible biological hazards of such drugs as LSD, which presently derive from conjecture as much as from controlled experiments, have attracted interest disproportionate to more plausible concerns on direct and residual psychotropic effects. Nevertheless, both an understanding of these side effects and an assessment of their potential hazards are important for the design of reasonable policies.

Available information on potential biological hazards due to drugs of abuse is extremely limited. However, a confusing variety of experimental data has been reported for the biological effects of LSD. These in turn have stimulated a variety of research projects submitted for funding to the National Institute of Mental Health (NIMH). Some of these projects were inadequate in concept or design; others still left unanswerable questions on the significance of their possible findings; yet others were potentially duplicative. Nevertheless, the growing dimensions of drug abuse necessitate urgent development of reliable data on adverse biological effects, particularly the chronic hazards of mutation, cancer, and teratology, as well as on psychotropic effects.

At the suggestion of the National Advisory Mental Health Council, the NIMH in association with the Environmental Mutagen Society sponsored a conference in October 1969 whose aims were to evaluate existing information on potential chronic biological hazards of drugs of abuse, and to outline the most effective methodologies for developing necessary information on the subject [Epstein and Lederberg 1970]. It was hoped that the findings of the conference would assure that the limited resources of the NIMH could be most productively deployed. However, the findings of the conference rest on the scientific reputation of its members, and

they should not be taken as an NIMH policy statement.

The conclusions of the conference are not easy to summarize, and they may well be judged unsatisfactory by defenders of categorical positions. This is partly a reflection of some limitations in the methodology available until recently for answering questions on chronic hazards to man. Promising new approaches based on well-established theoretical and empirical principles, particularly in mutagenicity testing, have recently emerged. Such approaches have not as yet been properly exploited in the study of drugs of abuse, let alone in the more general study of environmental chemical pollutants [Epstein and Lederberg 1970].

Even in an idealized laboratory setting, there are still many complicating problems in dealing with drugs of abuse, as compared with therapeutic or prophylactic drugs, apart from the wider perspective of environmental chemical pollutants. Psychotropic agents often exhibit different effects in different species, which may reflect differences in metabolism, although plausibly attributed to differences at higher levels of neural organization. The use of drugs of abuse, which has increased dramatically over the last decade, is generally restricted to young adults. The street drugs are rarely pure or uncontaminated, and even if they were, with the possible exception of cannabis, very few drugs claim the undivided attention of their users; the drug habitué is likely to practice ultimate polypharmacy and to be relatively unaware of what and how much he has actually taken by diverse routes, including ingestion, inhalation, and injection. The habitué may well be relatively idiosyncratic in other life styles as well, and he may experience bouts of intercurrent infection and malnutrition that may have their own chronic effects on health, besides specifically interacting with the drugs. Drugs of abuse

thus present quite unusual toxicological problems.

A most pressing question for which the conference found no satisfactory solution, was how to establish *quantitative* standards for the putative human cost of a given exposure to a chemical inducing adverse effects such as mutagenicity in an experimental animal. What level of mutagenicity would have to be imputed to LSD or to other more acceptable drugs, or to synthetic chemicals such as food additives, to be relevant to social controls? The well-authenticated chromosome-breaking activity of a cyclamate metabolite, cyclohexylamine, prompted no early administrative action, owing partly to present lack of consensual standards; this fact is all the more surprising in view of the questionable utility of cyclamate for the population at large. It may be argued, however, that our existing methods are unlikely to detect and prove mutagenic effects in man unless they exceed a 10 percent increase in the spontaneous mutation rate. This is an effect that would be comparable to a doubling of the background level of natural radiation. *Any* mutagenic effect that is demonstrable with present *in vivo* methods in mammals should thus be ample cause for concern.

The insensitivity of mammalian systems for prediction of chronic toxicity in man, especially carcinogenicity, teratogenicity, and mutagenicity, is now well recognized. Such insensitivity is a function of the restricted numbers of animals tested, commonly under 50 per dose of compound, in contrast with the millions of humans at presumptive risk. Let us assume that a new compound, such as a food additive or pesticide, produces cancer, birth defects, or hereditary genetic effects at the alarming rate of 1 per 10,000 humans; let us assume further that the sensitivity of man and the test animal is of a similar order. Then test groups of 10,000

animals would be required to demonstrate a single adverse effect; for statistical significance, groups of approximately 30,000 animals would thus be required. Of course, in any particular instance, man may be more or less sensitive than the test animal to the toxic effects of the compound in question. Thus, testing at the low levels of presumptive human exposure would preclude the possibility of detecting any but the grossest possible adverse effect.

For these reasons, it is routine practice to test up to maximally tolerated doses, in an effort to reduce the gross insensitivity of animal systems. Such overloading is the only practical method for detecting carcinogenic, teratogenic, and mutagenic effects, especially those due to agents with relatively low biological potency. In testing for carcinogenicity, commencing exposure of animals during early infancy is also helpful in enhancing sensitivity. Calculation of human risk by extrapolation from animal assays, with or without overload, is necessarily complex. In the absence of very specific information that overload induces abnormal metabolic pathways—due to saturation of enzyme receptor sites or to abnormal feedback—data based on overload responses are clearly legitimate and should be used for regulatory purposes and for the quantitative prediction of human risk. There are other cogent reasons, including problems of interaction and synergism, for the view that there is no acceptable method for predicting safe levels of carcinogens, teratogens, or mutagens, based on arbitrary fractions of no-effect doses in animal tests, with their built-in insensitivity as a function of small sample size [Epstein 1970]. Indeed, such considerations form the basis of the Delaney amendment, with reference to establishment of zero tolerances for food additives found to be carcinogenic by feeding at any level; this concept could well be

extended to both teratogens and mutagens.

The conference emphasized that the restriction of the discussion to the evaluation of drugs of abuse alone, without consideration of other chemical pollutants of the environment such as pesticides and food additives, is an artificial restriction. Factual data on drugs of abuse are grossly inadequate; there is, furthermore, no rationale to single these drugs out as worse potential hazards than many environmental pollutants and common therapeutic or prophylactic drugs, such as tranquilizers, whose *abuse* is less widely recognized and labeled as such. The same methodology would apply to the evaluation of environmental pollutants, which would be somewhat less complicated by the secondary factors associated with drugs like LSD.

The conference's deliberations emphasized the need for more systematic and programmatic evaluation than is currently required of potential chronic hazards of drugs and other environmental pollutants, including food additives, pesticides, and fuel additives [Epstein 1970]. The conference discussed a wide range of specific toxicological procedures that are currently available, some of which could well bear improvement. The importance of the effect of a drug on *metabolism* was underscored; this effect can provoke suspicions about unusual kinds of hazard, and it is necessary for correlating human with animal responses, especially if results in different animal species prove discordant. Individual differences within human populations, be they of genetic or environmental origin, must be expected; drugs will interact with one another in the process of metabolism, and therefore also in side effects; the fetus cannot be expected to show the same metabolic patterns as the adult; infection and malnutrition may also complicate individual responses.

The impact of a chemically induced cancer falls so heavily on the afflicted patient that the cost of environmental cancer is likely to be perceived in very personal terms. The costs of mutations are mortgages against the future. The responsible citizen, when he functions in his social role, should give the same weight of passionate concern for his helpless posterity that he gives to his own health in one of the soundest, if not always best honored, of human motives, self-preservation.

J. Lederberg
S. S. Epstein

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I. General Considerations

1 Chemistry and Sources

A. T. Shulgin

The purpose of this chapter is to assemble in a single convenient location the chemical and botanical definitions of those materials which may contribute to the drug abuse problem.

Many questions that concern these materials are now being answered, both socially as well as pharmacologically, but to a large measure these are questions that should have been asked years ago, before specific problems arose. A much larger number of questions can be anticipated now concerning drug problems of the future, and current research plans should be molded to provide needed answers as soon as possible. The instruments and skills required are available (see Sections II and III), and the only requirements that must be met are that the questions be honestly asked, and the subsequent research be supported without prejudice. It is hoped that this chapter will provide a compendium of factual information that might provide a reference foundation for future research.

1. Atlas of Drugs

Many of the drugs grouped under the general headings actually constitute mixtures of many different chemicals. The possibility always exists that some component other than the generally accepted "active principle" of a drug mixture may contribute to its hazard potential or to its undesirable side effects. For this reason, each drug presentation is expanded upon from the viewpoints both of congeneric contaminants and of synthetic by-products.

Those materials that are substantially of synthetic origin may generally be expected to be relatively pure. The contaminants that may be present will reflect the synthetic routes that have been employed. This debris, although both chemically and forensically meaningful, is rarely related pharmacologically to the synthetic end product. An exception to this must be made in those instances, such as the manufacture of LSD, where the end drug