The New England Journal of Medicine

Founded in 1812 as the NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY and continued in 1828 as Vol. 1 of the BOSTON MEDICAL AND SURGICAL JOURNAL

PUBLISHED WEEKLY BY THE COMMITTEE ON PUBLICATIONS OF THE MASSACHUSETTS MEDICAL SOCIETY

MANUSCRIPTS, including references, must be typewritten double spaced and submitted in the original *with a duplicate copy including tables and figures.* References should conform to the usual style of the *Journal* (listing name and initials of author, title of article, journal, volume number, first and last pages and year), and should be cited numerically in the order in which they appear in the text; the number should be limited to the absolute minimum. Acceptable case reports will usually be published in the "Medical Intelligence" section of the *Journal.* Such reports should include only the pertinent details of each case and reference to articles reporting closely related cases. A complete review of the literature is rarely desirable. A preliminary report, a very short case report or a description of a technic submitted for publication as a "Brief Recording" should be limited to 1½ double-spaced typewritten pages.

PHOTOGRAPHS must be distinct and drawings done in black ink on white paper and each properly labeled.

MATERIAL printed in the *New England Journal of Medicine* is covered by copyright. Articles are accepted for consideration with the understanding that they are contributed for publication solely in this journal. The *Journal* does not hold itself responsible for statements made by any contributor.

NOTICES should be received not later than noon on Thursday, three weeks before date of publication.

REPRINTS: The *Journal* does not stock reprints of the articles published. Requests should be sent to the author.

ALTHOUGH all advertising material accepted is expected to conform to ethical medical standards, acceptance does not imply endorsement by the *Journal.*

SUBSCRIPTION PRICES (U.S. Funds): Domestic $8.00 per year (students, interns, residents $5.00 per year); Canada $9.00 per year; other foreign $10.50 per year.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine,* 10 Shattuck Street, Boston, Massachusetts 02115.

RADIOMIMETIC PROPERTIES OF LSD

DURING the past four decades of extensive exploration in the field of cytogenetics, spontaneous and induced gene and chromosome mutations have, invariably, been shown to be detrimental to cell and organism. Because of the development of atomic energy and the growing need for pharmacologic testing, it became necessary to add mammalian species and cell cultures (including human derivatives) to the growing list of experimental models. Radiation and drug safety limits, tests for teratogenic effects and other precautions and regulations continue to be revised in the overall effort to guard against hazards of overexposure to potential mutagenic and carcinogenic agents.

Currently, direct observations on chromosomes of cultured peripheral lymphocytes have aided immensely in updating of the designs of human safeguards previously based on applications of data obtained on lesser organisms. The simplicity of the cultured lymphocyte technic encourages the periodic monitoring of patients and has no ill-effects. This feature has been invaluable in determining the status of abnormal chromosomes that have persisted for many years in some patients exposed accidentally to radiation. The same procedure is presently revealing some startling events of considerable importance in users of hallucinogenic drugs.

At this very moment, moral and social points of view proposing regulations and enforcement of the law to halt the indiscriminate use of psychotomimetic drugs are being amplified by the discovery and confirmation of elevated frequencies of chromosome breaks induced by LSD in patients and offspring of mothers who had previously ingested single or multiple doses of the drug (page 1043 of this issue). In their report on the cytogenetic consequence of LSD on the "user" Cohen, Hirschhorn and Frosch call attention to several detrimental features (fetal wastage, malignant tumors and congenital malformations) presently attributed to, or associated with, syndromes known to be gene and chromosome related.

The stability and effectiveness of LSD in continuing to produce chromosome damage many weeks after its ingestion indicate this drug to be highly radiomimetic[1] – a vital observation, which may bear upon the interpretations of other disciplines. A preliminary comparison can be made of the chromosome-breakage frequencies reported to occur after use of LSD or similar products with those obtained in both plant and animal cells exposed to varying amounts of radiation.[2] The comparison suggests that the average LSD "user" may experience somatic mutations and cell depletion at rates equivalent to a dose of 25-50 R per day of chronic whole-body gamma radiation.

When chromosomes are broken or rearranged by drugs and radiation most abnormal cells are elimi-

nated immediately because of the accompanying dominant lethal effects. However, there are a number of kinds of aberration, such as reciprocal translocations, which are capable of persisting from cell to cell and generation to generation. Progression and infinite growth of experimental tumors and cell cultures are distinctly associated with the onset of atypical forms and numbers of chromosomes.

With radiomimetic properties of LSD persisting from many weeks after ingestion, and the occurrence of chromosome breaks suspected of being augmented synergistically when other drugs are ingested, the probability that more sensitive tissues and cell types, such as spermatogonia, may be damaged heavily merits immediate investigation. Recent confirmations of the teratogenic effects of LSD and related drugs in rodent fetuses[3] point to the need for a concentrated effort to investigate the remaining unknowns, notably genetic defects and production of viable congenital malformations.

The time has come to stress the negative attributes of psychotomimetic drugs, as well as the positive value and role of the peripheral leukocyte technic in approaching these matters. "Users," old and new, must reconsider their personal thoughts about drugs in general. Their decision today may very well be reflected by the biologic fitness of the next generation.

References

1. Sax, K., and Sax, H. J. Radiomimetic beverages, drugs, and mutagens. *Proc. Nat. Acad. Sc.* **55**:1431, 1966.
2. Bender, M. A. X-ray-induced chromosome aberrations in mammalian cells *in vivo* and *in vitro*. In *Immediate and Low Level Effects of Ionizing Radiation*. 103-18. Edited by A. Buzzati-Traverse. 381 pp. London: Taylor and Francis, 1960.
3. Geber, W. F. Congenital malformations induced by mescaline, lysergic acid diethylamide, and bromolysergic acid in hamster. *Science* **158**:265, 1967.

LIMITATIONS IN DIAGNOSTIC STUDY

The interesting article by Melby et al. in this issue of the *Journal* again raises the question of the use of highly sophisticated or "research" technics in the clinical practice of medicine. The precise and highly technical data obtained on the 7 patients with adrenal adenomas producing primary hyperaldosteronism serve not only to confirm the diagnosis but also to help localize the lesion. With the variety of technics available, however, each physician and institution must ask, "How far do we go in obtaining detailed information about a patient before therapy or operation?" The answer may be that the more experienced physician can often make the diagnosis with a high degree of reliability and with the aid of fewer tests. This conclusion should not suggest that the patient should be delivered to the surgeon with any doubt remaining about the diagnosis. In the diagnosis and therapy of hyperaldosteronism, as in most endocrine conditions that are responsive to surgery, it is the first duty of the internist to make a definitive diagnosis. It is certainly not wise to expect a surgeon to decide at operation whether a small adenoma is or is not functional. Because of this, it is extremely helpful if overactive tissue can be accurately localized before operation.

Since it is unlikely that many institutions will be able to develop the technical skill to carry out studies of the type done by Melby and his co-workers, many patients presumably will continue to be treated surgically without the benefit of an aldosterone determination in adrenal-vein plasma. The alternative is to refer patients with questionable diagnoses or those with complicating conditions making extensive exploration inadvisable to medical centers that have the necessary capability. Every technical advance with its emphasis on ultraskill underlines the need for equitable regional planning of hospital services.

PROSTAGLANDINS

It is approximately thirty years since Blalock and Levy noted the antihypertensive action of the so-called "untouched" kidney in experimental hypertension due to unilateral renal-artery narrowing and since Grollman, Williams and Harrison described an extract of whole kidney that produced a sustained lowering of arterial pressure in animals with experimental renal hypertension. In the interim a great number of workers have contributed to these parallel physiologic and chemical approaches to the role of the normal kidney in protecting against the hypertensive state. As reviewed by Dr. Lee elsewhere in this issue, these two approaches may be unified with the recent identification of prostaglandins in mammalian renal medulla. For the uninitiated in the field of prostaglandins, a splendid review of the classic work of the Swedish investigators by Prof. Bergström is available.[1] Without this experience it is fair to say that American investigators, working with kidney extracts, would still be struggling to make the final identification of the vasoactive lipid extractable from renal medulla. A description of the lipid nature and similarity of this extract to the seminal-vesicle prostaglandins of the Swedish workers was first published in 1964.[2]

Although the prostaglandins and, specifically, "medullin" may, in fact, be the mediators of the "antihypertensive function" of the kidney, several words of caution are in order. In the first place, whereas Lee et al[3] and Hickler and his associates[4] believed that they had identified the important renomedullary vasodepressor lipid as "prostaglandin A_2," recent work suggests that the major agent is in the "hydrated form" of prostaglandin A_2 – that is, prostaglandin E_2, the dehydration perhaps to a greater or lesser extent representing a product of the extraction procedures.[5] The term "medullin," then, may be superfluous on two counts: it is not the chief vasodepressor lipid present; and according to