LSD and the Drug Culture: New Evidence of Hazard

The hallucinogenic effects of lysergic acid diethylamide (LSD) are well documented, but the existence of harmful long-term biochemical effects resulting from its use has been a bone of considerable contention. Many studies have shown, for example, that LSD can cause chromosome damage in cultured human cells, that it can cause birth defects in laboratory animals and humans, and that it is carcinogenic. An equally large number of studies have shown that there is no evidence for such effects, particularly at LSD concentrations that might be encountered in drug abuse.

These conflicting results and the growing body of negative findings have generated an increasing sense of complacency about the hazards of LSD. Two new reports, however, suggest that this complacency may be ill-founded. One report implicates LSD in a greatly increased rate of spontaneous abortions and birth defects among drug abusers. The other suggests that it may disrupt the body's immune system by interfering with the production of antibodies.

The first evidence that LSD might be hazardous was presented in 1967 by Maimon Cohen of the State University of New York at Buffalo. He found that it increased the incidence of chromosome breakage in cultured human leukocytes, although the amount of the increase was not related in a simple manner to either dosage or duration of exposure. Other studies quickly demonstrated a similar effect in leukocytes from patients who admitted to LSD ingestion.

Since Cohen's original report, at least nine other published studies have dealt with the possibility of such damage. Four provided evidence for it; five did not. Recent observers have suggested that the chromosome damage observed in cultured cells might be an artifact of the culturing technique because temperature changes, mechanical stimulation, and a wide variety of chemicals have been shown to increase breakage under such conditions.

Several investigators have also reported an increased incidence of embryo resorptions, stillbirths, and congenital deformities in pregnant mice, rats, hamsters, and primates given LSD early in gestation. These results, however, have been successfully duplicated only for some strains of mice. The conflicting findings have not yet been reconciled, but a likely possibility is that there is a wide variation in individual, strain, and species susceptibility to the effects of LSD.

The possibility that LSD is teratogenic in humans is even more difficult to determine because of problems in separating its effects from those of other chemicals. There have been at least half a dozen reports of birth defects in infants whose fathers or mothers had ingested LSD prior to or during gestation. In each of these cases, however, the LSD was illicitly obtained and it was impossible to determine how much—if any—was ingested and what impurities or substitutes were present. In almost all of these instances, moreover, the parents had been exposed to many other drugs of abuse, further muddying any conclusions that might be drawn.

Abortions and Birth Defects

In the most exhaustive study to date, William H. McGlothlin and David O. Arnold of the University of California, Los Angeles, examined in retrospect 148 pregnancies in which one or both parents had been exposed to pure LSD administered in controlled experiments or in the course of psychotherapy. The rate of spontaneous abortion among those patients (82 percent) exposed only to pure LSD was 15 percent, well within the normal range of 15 to 20 percent. Among the smaller group (18 percent) that had ingested both illicit and pure LSD, the abortion rate was 37 percent; this rate drops to 24 percent, however, if five successive spontaneous abortions by one woman are excluded from the study. Of the combined 120 live births for both groups, there were 14 infants with medical problems, but none of the problems could be attributed definitely to genetic damage.

In a much different study published last December, however, Cecil B. Jacobson of George Washington University School of Medicine, Washington, D.C., and Cheston M. Berlin, now at the Milton S. Hershey Medical Center, Hershey, Pennsylvania, reported on 148 pregnancies in which exposure of the women and their consorts to LSD was ascertained prior to delivery. A much higher incidence of abnormalities was found than had been observed in any previous study.

All the patients, Jacobson and Berlin say, came from a white, middle- to upper-middle-class population. About half the women had adopted a counterculture life style; the rest, though largely in sympathy with this life style, chose to remain in a conventional setting. Although most of the parents studied had experimented with various drugs of abuse, the only common denominators were LSD ingestion and the use of marijuana.

Of the 148 pregnancies observed in this group, 83 resulted in live births; 8 of these 83 infants, nearly 10 percent, had major congenital defects and 2 died after birth. The normal incidence of such defects is less than 1 percent. In about 50 percent of the infants the incidence of chromosome breakage was above normal, but most of this damage mended naturally in the first 3 to 6 months after birth.

There were 65 abortions in the group; 53 were elective and 12 were spontaneous. All of the spontaneous abortions occurred among women who were enrolled in the study during the first 3 months of pregnancy, and the rate of spontaneous abortions in this subgroup was 43 percent. Embryos sufficiently intact for analysis were obtained from 14 of the elective abortions; 4 of the 14 showed gross abnormalities, a much higher number than expected.

Six of the women who had normal births with the first child had a total of eight succeeding pregnancies, four of which terminated with abnormal offspring. And 8 of 12 women attempting to have repeat pregnancies have been unable to conceive for a period of at least 18 months. Despite the limited number of examples, both findings suggest a greater hazard in serial pregnancies.

Jacobson and Berlin were unable to provide a definitive correlation of increased reproductive risk with LSD because most of the parents in the study also ingested other illicit drugs prior to conception. A significant number of the women also suffered from infectious diseases and possible malnutrition during gestation, and both of these conditions have been associated with an in-

creased risk of birth defects. But the uniform use of LSD by patients in the study, they argue, combined with observations of teratogenicity of LSD in animals, supports the suspicion that ingestion of illicit LSD is hazardous to human reproduction. And at the very least, they conclude, it is clear that multiple drug use and the counterculture environment present a very severe hazard to birth.

The increased incidence of infectious disease in the women enrolled in the George Washington University study is apparently typical among drug abusers. Other new evidence suggests that this increased susceptibility to disease may result, at least in part, from LSD use. Edward W. Voss, Jr., and his associates at the University of Illinois, Urbana, last month reported that LSD inhibits the production of antibodies by cultured rabbit lymphoid cells.

Voss removed the spleen and lymph nodes from rabbits that had been hyperimmunized to various antigens, and then cultured cells from these organs. He was able to show by appropriate methods that the cultured cells continued to produce antibodies under normal conditions. When the cells are incubated in the presence of small quantities (less than 10 micrograms per milliliter) of LSD or lysergic acid, however, the production of immunoglobulins is almost totally inhibited. The cells remain viable and protein synthesis, which was measured by incorporation of tritiated leucine, continues. But the proteins secreted by the cells show no measurable antibody activity, and are of much lower molecular weight than the expected immunoglobulin (whose molecular weight is about 150,000).

Examination of the secreted proteins shows that the ratio of incorporation of tritiated leucine to incorporation of ^{14}C-labeled tryptophan is much higher than in control cells. Voss thus suggests that the indole alkaloid LSD and its analogs can substitute for the indole amino acid tryptophan in protein synthesis in much the same fashion that the antimicrobial agent puromycin substitutes for tyrosine in many microorganisms. Because LSD does not have the carboxylic acid moiety necessary for formation of a peptide bond, its incorporation leads to premature termination of the growing peptide chain, and thus prevents formation of the whole immunoglobulins. Support for this thesis is provided by the observation that addition to the reaction medium of a large excess of tryptophan—and only of tryptophan—reverses the effect of LSD.

Voss's results are preliminary, however, and their full significance is not yet clear. The only supportive evidence that such an effect might occur in vivo, he says, are limited observations that animals under the influence of LSD show a reduced responsiveness to antigens. Nonetheless, his findings suggest that biochemical damage might be manifested in symptoms other than chromosome damage, or that such damage might occur by a more devious route than was previously suspected.

—THOMAS H. MAUGH II

Additional Reading

1. M. M. Cohen, M. J. Marinello, N. Bach, *Science* **155**, 1417 (1967).
2. W. H. McGlothlin and D. O. Arnold, *Arch. Gen. Psychol.* **24**, 35 (1971).
3. N. I. Dishotsky, W. D. Loughman, R. E. Mogar, W. R. Lipscomb, *Science* **172**, 431 (1971).
4. C. B. Jacobson and C. M. Berlin, *J. Amer. Med. Ass.* **222**, 1367 (1972).
5. E. W. Voss, Jr., J. E. Babb, P. Metzel, J. L. Winkelhake, *Biochem. Biophys. Res. Commun.* **50**, 950 (1973).

Birth Control: Current Technology, Future Prospects

The news about birth control is that there is no news—at least, no news of the imminent availability of methods that differ radically from existing techniques for controlling human fertility. New variations on old themes, however, may offer better efficacy, more convenience, greater freedom from hazardous or uncomfortable side effects, or all of these. Advances in basic research on reproductive physiology also suggest that new techniques may be developed in the future—but a minimum of 10 to 15 years could be required before they are available for routine use.

The "pill," introduced in the early 1960's, did revolutionize birth control technology. Because the oral contraceptives produce virtually 100 percent inhibition of female fertility, their superior efficacy has not been questioned. Nevertheless, reports of side effects that range from the merely uncomfortable —nausea, excess water rentention—to the potentially dangerous—a higher incidence of abnormal blood clots in users —have sparked efforts to formulate oral contraceptives without these disadvantages. One such effort is the "mini-pill," now being marketed by Ortho Pharmaceutical Corporation, Raritan, New Jersey, and by Syntex Corporation, Palo Alto, California.

Oral contraceptives depend on synthetic steroids for their effectiveness. (Synthetic steroids must be used because they are not destroyed by the body's enzymes before they reach their target organs.) The older "pills," which contain both an estrogen and a progestogen, act primarily by inhibiting the monthly release of the egg from the ovary. The "mini-pill," on the other hand, contains only a progestogen in a daily dosage roughly one-third or less that of the other "pills"; the low concentration of progestogen apparently prevents the sperm from reaching the oviducts, where fertilization occurs, by maintaining the mucus at the opening to the uterus in a condition that hinders sperm migration.

Although most of the side effects of the "pill" are associated with the estrogenic component, the Food and Drug Administration (FDA) has warned that not enough data are available at present to determine whether the risks of bloodclotting are indeed lower with the "mini-pill." The FDA points out that a small percentage of the progestogen in the "mini-pill" is actually converted to an estrogen in the body. Moreover, the risk of pregnancy—almost 3 percent—is higher for "mini-pill" users. (A failure rate of 3 percent means that if 100 women use a contraceptive technique for 1 year, 3 of them will become pregnant.)

Other research on steroidal control of female fertility is directed at the design of more convenient methods of drug administration, especially those applicable in areas or countries where conventional medical care is not readily available. Some of these delivery methods use a plastic material impregnated with the contraceptive steroid, usually a progestogen. The plastic can be implanted under the skin or it can be fashioned into a ring that is inserted into the vagina. Depending on the amount of hormone released per day, steroids thus administered act either as ovulation inhibitors or by the same mechanism as the "mini-pills." The vaginal rings are worn