NEW WAYS WITH HALLUCINOGENS

Of the various endogenous toxins postulated as causes of schizophrenia, none has had a more lasting appeal than the one proposed by Osmond and Smythies. They pointed out that the potent hallucinogen mescaline (trimethoxyphenylethylamine) had structural similarity to some natural catecholamine derivatives, and the production of a mescaline-like substance by metabolic aberration might be the cause of schizophrenia. At first, attention centred on adrenochrome, and although this possibility was pursued diligently by some it has found little empirical support. In 1962 Friedhoff and van Winkle reported the presence of a "pink spot" in the urine of schizophrenic patients and they later identified it as dimethoxyphenylethylamine (D.M.P.E.A.). This substance, which differs by only one methoxy group from mescaline, evoked much interest. Unfortunately further experiments, with dietary control, failed to confirm the finding and, although a Liverpool survey demonstrated preponderance of pink spots among schizophrenic patients compared with normal controls, the techniques used probably measured phenothiazines as well as the pink spot. The validity of its presence in schizophrenia remains to be conclusively demonstrated. Moreover, D.M.P.E.A. was found to have no psychotomimetic effect.

Nevertheless, preoccupation with the methoxy structure of mescaline persists and is reflected in a search for abnormal methylation (producing such groups) or failure of normal demethylation (converting methoxy to hydroxy) which in this context supposedly inactivates (although the converse holds for natural products). A different approach has lately been adopted by Shulgin et al. They collected over 40 derivatives of phenylethylamine or α-methylphenylethylamine (amphetamine), the bulk being in the second category. All these substances were then tested in volunteers and, using mescaline as a reference compound, Shulgin et al. estimated the psychotomimetic potency of each in terms of mescaline units (dose of mescaline divided by equivalent dose of the compound). This potency was then examined in relation to chemical structure. The amphetamine derivatives were by far the most potent. As amphetamine is not a natural product of the body Shulgin et al. infer that the resistance of such derivatives to monoamine-oxidase suggests that the endogenous toxin is similarly protected from monoamine-oxidase, perhaps by formation in the synaptic cleft. As for methoxy groups, those in an ortho or para position enhance activity, while meta substituents decrease it. Three methoxy groups are optimum and two or four less potent; a substituent at the 4-position gives stability and a 4-methyl group greatly increases activity. It was also possible to deduce, by way of much chemical sophistication, the paths by which indoles (which may also be potent psychotomimetics) can be formed. The most important result of this approach, however, is that Shulgin et al. were able to predict two candidates for the role of endogenous toxin. The first is 3, 4-dimethoxyphenylethanolamine which (if it occurred as a normal intermediary) would be rapidly demethylated to normetanephrine. Failure of such demethylation could produce a psychotic state. The second structure proposed is 2-hydroxy-4, 5-dimethoxyphenylethanolamine, which could be formed if the enzyme converting tyrosine to homogentisic acid could also act on dopa and if the product was methylated.

This work is an encouraging departure from the way most research is conducted in this area. The findings are based exclusively on human data in which individual variations have been reduced, as far as possible, by comparing as many hallucinogens as possible in the same subject and by the use of a reference hallucinogen, mescaline. The experiments are also novel in the use of the "double conscious" technique of Alles; and, perhaps most important of all, there is the courage to make predictions on the basis of a detailed analysis of structure, psychotomimetic potency, and knowledge of naturally occurring processes.

To many the toxic hypothesis of schizophrenia, particularly the variant postulating a methoxylated endogenous hallucinogen, is a dead duck. Such critics point out that seventeen years of intensive research have produced little that stands up to critical evaluation. They would also argue that "model psychoses" induced by hallucinogens are irrelevant to schizophrenia; and they may hope to endorse their view by finding in the work of Shulgin et al. questionable details, such as the use of "effective dose" (a mean of the threshold dose capable of accurate assessment and the maximum dose where variability must be considerable). Nevertheless two clearly testable predictions emerge which can be examined thoroughly—a welcome departure from the many unhelpful generalisations of the past.

TOPICAL STEROIDS IN CHILDREN

The application of steroid-containing preparations to the skin of patients with widespread skin disease may produce varying degrees of pituitary-adrenal suppression, especially when occlusive dressings are used. The return to normal is rapid after treatment is stopped. Steroid therapy has an important place in the management of childhood dermatoses, and on p. 485 Dr. Feiwel and his colleagues record evidence suggesting that adrenal function was suppressed in 8 out of 19 infants and young children with eczema, who were treated as outpatients with topical steroids without dressings. 12 of these children had already been treated with other potent steroids by their family doctor. All received betamethasone-17-valerate cream during the investigation. The main side-effect of steroid therapy in children is retardation of growth; but no association has been reported between topical preparations and growth retardation. Dr. Feiwel and his associates suggest, however, that percutaneous absorption of steroids should be considered as a possible cause in any disturbance of general health in a child being treated in this way.