of learning. While forced guidance may, none of the tested drugs or electric shock therapy has "cured" rats once fixated behaviour became established. At high doses (1 mg/kg) LSD_{25} blocks goal-directed behaviour. Chlorpromazine, reserpine and meprobamate suppress avoidance and reduce escape. In higher dosages, they also slow down learning and depress approach behaviour. Before establishment of fixation, i.e. during the training period, high doses of tranquilizers prevent fixation in 20–35 per cent of cases. Barbiturates in doses sufficient to affect avoidance interfere with motor behaviour. MOA inhibitors and related agents (iproniazid, amphetamine, Tofranil and Catron) quicken the approach reactions and, in high doses, increase the rate of avoidance behaviour, but do not significantly affect fixation. Chlordiazapoxide (Librium) differs from previous drugs. Although it induces docility, it shortens reaction time of both avoidance and approach to a greater degree than MAO inhibitors. The behaviour becomes very variable, and Librium given during training period prevents fixation in 50 per cent of the rats. Moreover, Librium fosters learning and the effects of guidance and reduces latency times, while most of these were inhibited by chlorpromazine. Thus, although Librium affects fixation prophylactically in greater percentage of cases than other drugs employed, it does not cure established fixation.

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48 On Mechanism of the Antidepressant Action of Imipramine. F. SULSER and B. B. BRODIE (U.S.A.).

The potent antidepressant effect of the iminodibenzyl derivative imipramine is clinically established. Pharmacologically, the drug exerts weak chlorpromazine-like actions in normal animals and men. None of the screening procedures currently used would suggest this drug to be an antidepressant drug. The antidepressant action of imipramine becomes dramatically evident in studies which show that it prevents in rats and dogs the depression (chronic pretreatment) and increased central parasympathetic activity (single dose) evoked by reserpine or a synthetic benzoquinolizine (RO-4 1284). However, imipramine does not prevent the action of chlorpromazine. Studies of the physiological disposition of imipramine indicate that the drug acts through a metabolic product, monomethyl norimipramine. This compound is much more active in blocking reserpine or RO-4 1284; furthermore, it shows, in contrast to imipramine, no delay in its action. It not only prevents the action of reserpine or RO-4 1284 but actually reverses it, the animals displaying considerable hyperactivity. Neither imipramine nor its metabolite block monoamine oxidase; they do not increase levels of brain serotonin and norepinephrine or prevent reserpine and RO-4 1284 from releasing brain amines. The possibility that imipramine or its metabolite reveal their antidepressant action by blocking free serotonin will be discussed.

49 Unusual Central Depressant Properties of a New Piperidine Compound. T. B. O'DELL, M. D. NAPOLI and J. H. MIRSKY (U.S.A.).

One approach to the study of the complexities of the central nervous system and its functions is through the use of new pharmacodynamic tools. Such tools might be developed by the investigation of properties of new compounds having novel or unusual chemical structures. Analysis of the responses obtained with novel compounds, coupled with known actions of standard drugs, could well provide new leads toward a better understanding of the functioning of the central nervous system.

A series of new piperidine derivatives has been investigated using a battery of standard pharmacological testing procedures. An unusual combination of effects on the central nervous system has been revealed from these studies. One compound, in particular, 4-(3-indolylethyl)-1-phenethylpiperidine hydrochloride demonstrated strong analgesic activity comparable to that found with morphine, and could also produce a tranquilizing effect which resembled that produced by reserpine. These effects could be separated dose-wise with analgesic activity being apparent at doses below those required to induce the tranquilization responses. True sedative effects (i.e. sleep) could not be induced regardless of the magnitude of the dose administered. The duration of these responses, especially the tranquilizing action, was very prolonged and was a function of the dose employed. Thus, compared to the actions on the central nervous system of known drugs, this new compound appears to possess a unique combination of properties.

50 Influence of a New Group of Tranquillizers, Derivatives of Dibenzosuberene, on the Central Nervous System. Z. VOTAVA, J. METYŠOVÁ and M. SOUŠKOVÁ (Czechoslovakia).

In the group of 16 new dibenzosuberane and dibenzosuberene analogues of chlorprothixene, interesting correlations between the chemical structure and pharmacological effect on the central nervous system were found. Tests on prolongation of thiopental anaesthesia, rotating rod, depression of the body temperatures, anti-pentazol action and tentative conditioned reflexes revealed that the double bond in the middle ring of dibenzosuberane increased the tranquillizing activity. Further rise of the activity was produced by the introduction of chlorine in the position two of the cycle. The most promising drugs of this type were chloroheptadiene and chloroheptatriene.