Meetings

Antidepressant Drugs

The therapeutic efficacy of several of the tricyclic antidepressants, of which imipramine is the prototype, has been fairly well established in a number of clinical investigations. The tricyclic antidepressants are known to potentiate the effects of norepinephrine in many physiological systems; this action in the brain has been suggested as the cause of the antidepressant activity of these compounds. The effects of the tricyclic antidepressants on the metabolism of norepinephrine and other catecholamines, or the interactions of these antidepressants with other drugs which alter norepinephrine metabolism, was the major focus of an International Symposium on Antidepressant Drugs held at the Istituto di Ricerche Farmacologiche "Mario Negri," Milan, Italy, 25–27 April 1966. This interdisciplinary symposium, organized by S. Garattini and A. Leonardi (Italy), was attended by over 170 scientists from 17 nations.

J. Glowinski (France) reported that the uptake of H^3-norepinephrine injected into brain through the lateral ventricle was inhibited by the tricyclic antidepressant desmethylimipramine and the stimulant amphetamine; these drugs did not alter the uptake of H^3-dopamine. Since reuptake into the adrenergic neuron may be a major means of inactivation of norepinephrine discharged from the nerve, this finding may be of considerable physiological significance and may account for the potentiation of norepinephrine by these drugs. In stressed rats, N. Matussek (Germany) found that behavioral changes were correlated with the uptake of H^3-norepinephrine into the midbrain, but not with the uptake of C^{14}-serotonin or with levels of endogenous norepinephrine or serotonin. N. H. Neff and E. Costa (United States) reported that, in rat brain, desmethylimipramine and protriptyline increased the turnover of brain norepinephrine without changing the turnover of dopamine. Chlorpromazine, a tranquilizer, in contrast, did not change the rate of the turnover of norepinephrine.

The imipramine-like antidepressants counteract the hypothermia induced by reserpine, a drug which depletes norepinephrine [S. Garattini and A. Jori (Italy)]. Garattini suggested that this interaction between imipramine-like drugs and reserpine involved adrenergic neurons. Imipramine-like drugs potentiated the hyperthermia induced by norepinephrine, whereas the hyperthermic effect induced by desmethylimipramine in animals pretreated with reserpine was antagonized by adrenergic blocking agents or inhibitors of norepinephrine synthesis.

E. B. Sigg (United States) proposed the hypothesis that cranial parasympathetic outflow is modulated by norepinephrine. An increase in parasympathetic efferent impulses occurred after depletion of norepinephrine by reserpine or alpha-methyl-*p*-tyrosine, a drug which blocks norepinephrine synthesis. In contrast, parasympathetic outflow was decreased when excess norepinephrine was induced by administration of the precursor dihydroxyphenylalanine to cats pretreated with an inhibitor of monoamine oxidase, an enzyme which metabolically inactivates catecholamines.

G. M. Everett (United States) described an unusually effective pharmacological screening test for antidepressant drugs. This procedure measures potentiation by the antidepressant drug of the behavioral effects produced by dihydroxyphenylalanine in animals pretreated with a monoamine oxidase inhibitor. Catecholamines at brain receptors may account for the observed activity.

The effects of various psychoactive drugs on brain self-stimulation was reported by L. Stein (United States). When electrodes are implanted in certain brain areas, animals will perform tasks, such as lever pressing, without external rewards, in order to obtain electrical stimulation of brain through the implanted electrodes. Drugs that facilitated self-stimulation (amphetamine or alpha-methyl-*m*-tyrosine) rapidly release brain norepinephrine. However, inhibitory drugs deplete norepinephrine (reserpine) or block adrenergic receptors (chlorpromazine). It was hypothesized that noradrenergic neuronal systems were involved in the phenomenon of self-stimulation and that this experimental model may be of heuristic value in understanding the pathophysiology of affective disorders in man.

J. J. Schildkraut (United States) reported on norepinephrine metabolism in patients with affective disorders. Decrease in the urinary excretion of 3-methoxy-4-hydroxymandelic acid (VMA), the major metabolite of norepinephrine, was observed during treatment with imipramine or a monoamine oxidase inhibitor. These changes in VMA excretion indicate drug-induced alterations in norepinephrine metabolism. However, VMA excretion does not necessarily reflect the physiological utilization of norepinephrine. Further changes in the excretion of normetanephrine, the metabolite which may reflect noradrenergic activity, however, were associated with changes in clinical state. A gradual rise in normetanephrine excretion occurred during the period of definitive clinical improvement in depressed patients treated with imipramine. These and other findings suggested that increasing noradrenergic activity might characterize the period of clinical improvement from depression and that noradrenergic activity may be decreased in retarded depressions and increased in hypomania.

The therapeutic efficacy of lithium salts in the treatment of mania was well documented by M. Schou (Denmark). In preliminary studies, J. J. Schildkraut reported that he and his colleagues found lithium to cause a shift in the metabolism of H^3-norepinephrine in rat brain, in a direction opposite to that seen with stimulants or antidepressants.

The findings summarized here and many other studies presented at the symposium supported the thesis that the tricyclic antidepressants may alter the metabolism of norepinephrine and suggested that this may, in part, account for their clinical antidepressant activity. Although the effects of the psychoactive drugs on noradrenergic mechanisms were particularly emphasized during the symposium, peripheral

and central anticholinergic effects of many of these compounds were also reported.

A number of investigators discussed the clinical results obtained with various therapies involving antidepressant drugs. In an extensive multicentered comparative study of the therapeutic efficacy of electroconvulsive therapy (ECT) and antidepressant drugs, M. Shepherd (England) found imipramine to be significantly better than placebo but less effective than ECT. Phenelzine, a monoamine oxidase inhibitor, was found to be no better than placebo, but questions were raised concerning the dosage of phenelzine used in the study.

D. R. Gander (England) presented data suggesting the clinical value of combined administration of monoamine oxidase inhibitors and tricyclic antidepressants in patients refractory to other treatments. Although other reports had warned of the risks of administering these drugs in combination, in this study, Gander found no difference in the nature or frequency of side effects (except for weight increase) from those seen with a single antidepressant. P. Dick (Switzerland) reported favorable clinical responses in some patients when tetrabenazine (a catecholamine-releasing agent) was added to the therapeutic regimen of patients refractory to treatment with a tricyclic antidepressant alone.

The formal presentations concluded with an inspired address by R. Kuhn (Switzerland) who, less than 10 years before, had discovered imipramine to be clinically effective in the treatment of depression. After reviewing much of the progress in the field during the past decade, Kuhn indicated that he was now studying the clinical effects of a drug which promised to be an even more effective and specific antidepressant than imipramine.

On the day after the formal program had ended, a selected group of participants gathered for a period of discussion. In the informality of this unprogrammed session many of the barriers to interdisciplinary communication were overcome. Considerable light was shed on many relevant conceptual and semantic problems which separate the various disciplines. It was the consensus of the participants that such discussions could contribute significantly to future research and to our ultimate understanding of the mechanism of the action of antidepressant drugs.

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Forthcoming Events

December

12–14. **Air Pollution**, natl. conf., Washington, D.C. (A. C. Stern, Div. of Air Pollution, U.S. Public Health Service, Washington, D.C. 20201)

12–17. **History of Oceanography**, intern. congr., Monte Carlo. (R. Novella, Villa Girasole, 16, boulevard de Suisse, Monaco)

14–16. **Fluid Logic and Amplification**, 2nd intern. conf., Cranfield, England. (H. Stephens, British Hydromechanics Research Assoc., South Rd., Harlow, Essex, England)

15–16. International **Brain Research** Organization, central council and executive committee, mtg., Paris, France. (UNESCO, Pl. de Fontenoy, Paris 7)

16–18. American **Psychoanalytic** Assoc., fall mtg., New York, N. Y. (American Psychoanalytic Assoc., 1 E. 57 St., New York 10022)

19–20. British **Biophysical** Soc., winter mtg., London, England. (W. Gratzer, Biophysics Dept., King's College, 26 Drury Lane, London W.C.2)

19–21. **Acceleration Biology**, Sunnydale, Calif. (Univ. of California Extension, Berkeley 94720)

26–31. **American Assoc. for the Advancement of Science**, annual, Washington, D.C. (R. L. Taylor, AAAS, 1515 Massachusetts Ave., NW, Washington, D.C. 20005)

In addition to the 20 sections of the Association and five AAAS committees, the following organizations have arranged sessions at the AAAS annual meeting 26–31 December in Washington, D.C.

Mathematics

American Mathematical Soc. (E. Pitcher, Lehigh Univ., Bethlehem, Pa.)

Association for Computing Machinery (D. Leiti, Heliodyne Corp., Rosslyn, Va.)

National Council of Teachers of Mathematics (J. Gates, 1201 16 St., NW, Washington, D.C.)

Society for Industrial and Applied Mathematics (J. H. Griesmer, I.B.M., T. J. Watson Research Center, Yorktown Heights, N.Y.)

Physics

American Astronautical Soc. (S. F. Singer, Univ. of Miami, Coral Gables, Fla.)

American Meteorological Soc. (J. E. Masterson, Natl. Center for Atmospheric Research, Greenbelt, Md.)

Harvard Project Physics (F. J. Rutherford, Harvard Univ., Cambridge, Mass.)