

Meetings and Societies

Drugs for the Soul; the Rise of Psychopharmacology

The phrenotropic agents, and conferences about them, have become drugs on the market. Three out of ten prescriptions in this country are now for "tranquilizers," more than a billion meprobamate tablets alone have been ordered by their physicians for 160 million Americans in a little more than a year; hundreds of millions of dollars have been spent; mental hospitals have become quieter and less congested; and the anxiety level of the citizenry has presumably ebbed.

Such dramatic events have aroused great interest—in the public, kept more than adequately informed or misinformed by the mass media; in officials and others concerned with mental health, who are responsible to the public for decisions involving large funds and institutions and subpopulations; in neuropharmacologists and physiological psychologists, who see new tools for clarifying the elements of behavior and relating these to the functional elements of the nervous system; and in psychiatrists of all schools, who find their views shaken or supported by the emphatic re-entry of the brain into the mental arena and the attendant deemphasis of the interpersonal aspects—and this great interest is expressed in the welling of communication.

Even at the professional level (it would be prohibitive to follow the wider lay situation) the reports and meetings, the gossip and symposia and publications, have become prodigious. I personally have been asked to attend well over a dozen special symposia on psychopharmacology in the past year (most of which have or will burst out in monographs), have actually participated in half of them, and have been guilty of organizing one. The two most recent meetings, the Conference on the Evaluation of Pharmacotherapy in Mental Illness held in Washington in late September, which I organized, with the fine support of Jonathan Cole, for the sponsoring groups (USPH, National Institute of Mental Health; National Academy of Sciences-National Research Council;

American Psychiatric Association), and the Conference on Meprobamate and Other Agents Used in Mental Illness held in New York in mid-October, sponsored by the New York Academy of Sciences, which I summarized at the request of the chairmen, James G. Miller and Frank Berger, form the basis of this invited report.

In all conferences, certain general problems receive more or less attention: the psychosocial, administrative-economic, and public health impact of these agents; the mechanisms of action; nomenclature; problems of animal and human experimentation with new agents, especially those with a possible "behavioral toxicity" and expected to produce changes in the nuances of complex behavior; criteria and procedures for valid clinical testing; and, where particular drugs are under consideration, the inevitable question of actual effectiveness and in which human ailments.

The meprobamate conference devoted half a day to "laboratory" studies on the pharmacological action of this and related substances and, especially, on behavioral changes induced by them. No deterioration in vision or in simulated driving resulted from the taking of meprobamate, even when it was taken along with alcohol; imprinting of behavior patterns in ducklings under this drug remained possible for more hours; some differential effect of the agent on conditioned and unconditioned reflexes of several types was affirmed and questioned—with dosage an important factor. The other three half-days were given to clinical reports on the action of meprobamate and comparison drugs in a wide variety of situations: on level of general tension and disturbance in a ward, in anxiety states, for postoperative control, for headaches, on air personnel and disturbed children and senile or chronic psychotics or alcoholics, and for various conditions associated with increased muscle tone. Meprobamate seemed most useful in reducing tension level, whether manifested in motor effects—which seemed especially helped—or in anxiety or in hostility, directed outward or inward. Action on acutely disturbed psychotics was relatively slight;

and considerable argument developed on whether meprobamate should be classed with the tranquilizers or the hypnotics.

The issue of nomenclature is everywhere encountered in this new arena of psychopharmacology. Names not only are needed for communication; they also carry overtones of inference and record the developing attention to and understanding of a subject area. If a given drug is called a tranquilizer, it is likely to be prescribed for disturbed psychotics, to be compared with chlorpromazine or another tranquilizer, and to be regarded in the patient's milieu as a stigma on the taker; if it is called a hypnotic, it is likely to be used on a ten- or twentyfold larger scale, to be compared with barbiturates, and to be accepted as neutrally as is aspirin.

The uncertainty over names, moreover, reflects ignorance regarding mechanisms. *Phrenotropic* is a noncommittal word saying that there is an action on the mind; and the subgroup *psychosomimetic* is still a descriptive term. Yet, even here, there is an implication of overstimulation of the brain; and the term *tranquilizer*, which more explicitly refers to lessened stimulation (and so covers the opposite subgroup), has satisfied few. Yet the plain fact is that a drug which depresses all neurones or synapses but acts more strongly on the inhibitory than the excitatory ones could evoke the same behavior changes as a drug which stimulates all units but favors the excitatory ones.

New names arise as some situation generates more attention, is more discriminatingly observed, and requires more differentiated communication; but the terminology becomes really sound and analytic only when the bases of the phenomena are understood. Then a genotypic statement supersedes a phenotypic one, and drugs will be classified in terms of established mechanisms of action. For the nervous system, these will probably be in terms of particular neurone groups with recognized quantitative (gradient) differences in metabolism or, more often, qualitative differences, or, perhaps even more frequently, in terms of the patterns in which neurones interact. Knocking out a particular enzyme or cell type would disturb function as would omitting all *e*'s or *t*'s in a paragraph; but altering patterns of interaction could be much more devastating, like pieing the type.

The Washington conference, although it was also concerned with the aforementioned matters, focused on the general problems encountered in evaluation of phrenotropic drugs. The growing public health problem posed here led the National Institute of Mental Health to initiate and finance this project, which was carried out with the National Re-

search Council as administrator and the American Psychiatric Association as co-sponsor. After preliminary conferences at the institute—which defined our concern as primarily with evaluation of the drugs, “Do they act?” rather than with mechanism, “How do they act?” or with the over-all consequences, “What if they act?”—half a dozen work papers were invited and served to guide a formal planning committee. The subject was soon divided into five areas, and appropriate subcommittees were formed to develop them—each with its own consultants and with new work papers. These met for 2 days to formulate and integrate their findings and then reported at plenary sessions to several hundred participants, who further discussed them.

The Subcommittee on Preliminary Screening, Louis Goodman, chairman, considered problems of animal testing—for mode of action, behavioral effects and toxic complications—and the especially vexing ones of human testing prior to releasing a drug for sale and extensive clinical evaluation. Such difficulties as the following were considered: detecting subtle neural alterations in anesthetized animals; devising useful measures of animal behavior; finding valid indicators for a specific drug action on patients (in animals that might lack the anatomical substrate, or normal human beings who might lack the physiological dysfunction, underlying the disease or symptoms requiring relief); using patients to explore new agents and the ethical and legal problems in either giving or withholding a potentially harmful or useful substance.

Three subcommittees concerned directly with clinical testing covered Test Conditions, Alfred Bay, chairman; Patient Selection and Control Problems, John Clausen, chairman; and Evaluation of Change in Treated Patients, Milton Greenblatt, chairman. Under test conditions were considered such matters as actual drug administration and selection of dose, route, timing, repetition, and the like; the use of placebos and the double blind technique; and the halo effect produced by altered attitudes and actions of the persons making the test or by other indirect changes associated with drug administration. The latter is exemplified by different responses when subjects are alone or in groups; by a quieting of non-treated, as well as treated, patients on a ward when the general level of noise and confusion is lowered by a true drug action on treated ones; and by the general finding that the improvement seen when drugs are introduced is often less in therapeutically oriented institutions than in custodially oriented ones, in which the mere increase of active interest in patients has a beneficial effect. The problem of the placebo is surprisingly com-

plex and, despite its name, generates more strife than peace among investigators. Its use demands thought and discrimination, even though the placebo effect is really as simple as Mark Twain's experience when, after tossing in the bed of a hot stuffy room, he hurled a shoe at the window he could not open, inhaled eagerly of the fresh air that entered after the crash, and happily slept—only to find in the morning that he had broken a mirror.

Selecting of test and control subjects and securing adequate and homogeneous samples present additional problems. There are difficulties in selecting by diagnosis, or symptom, or at random, or as a fixed time sample, or by individual attributes, or even by comparing each patient with his pretreatment self. If male schizophrenics between 35 and 44 years old and ill from 5 to 9 years are desired, the entire 13,000 population of the largest mental hospital of New York State can hardly supply the 440 needed to tell (at the 0.5 and 0.1 *P* levels for the type-I and type-II errors) whether a drug doubles the discharge rate. Certain prognostic indicators may help, for example, the response to previous treatments or tests (as mecholyl), or the marital or educational status, or behavior during psychiatric observation—one study reported a 75-percent successful prognosis based on the initial interview. Since no therapy so far tested over a 5-year period has shown any gross statistical advantage over simple custodial care, either none has been of value or various ones have helped in particular subpopulations; so appropriate selection is as important in avoiding false rejection of a hypothesis (type-I error) as in avoiding false acceptance (type-II error).

The criteria of change now available are largely impressionistic and qualitative and reflect the presently unsatisfactory tools of behavioral science in general. The need is great to forge sharper instruments and to move from simple observation, through observation in planned test situations, objectively judged interviews, validated rating scales and questionnaires, to completely objective tests—of behavior, as in reaction time after a fixed interval warning signal, or in organizing a total situation presented by the PSI apparatus; or of material, as in the esterification of phosphate by erythrocytes or in the chromogens recently found in plasma or urine. With care, group criteria, rather than individual ones, can be used effectively, as in average stay in an institution, discharge (or, better, dischargeability) rates, sick calls, clothes damage, ward noise, and the like; but, if handled carelessly, group data of this kind can seem to tell that the average American is 49-percent male, 13-percent colored, and slightly pregnant!

The fifth subcommittee, on Planning and Coordination, Seymour Kety, chairman, also served as an executive committee. It was concerned with the national picture, with formulating recommendations, and, especially since Congress had responded to a suggestion of the Planning Committee, among other things, with a \$2-million appropriation to further the effective evaluation of new drugs (now administered through the Psychopharmacology Service Center set up in the National Institute of Mental Health), with advising on a program of research in this area. Should one great study be set up for the country—a single \$6.4-million question (on the assumption that brute financial strength can solve any problem, rather like assuming that enough monkeys with typewriters will turn out the *American Journal of Psychiatry*)? Or should local projects be coordinated and assisted, as the VA study of two drugs on their schizophrenic hospital patients, or research on better indicators of change be fostered, or experiments on the mechanism of action be supported—a hundred \$64,000 questions? Should additional publications be encouraged or special conferences for exchange of research results, for agreement on nomenclature, for consideration of ethical and legal problems, and the like? What cooperation could be developed with and among the pharmaceutical companies, the Food and Drug Administration, and other interested groups? How essential is another weapon besides psychotherapy, when fewer than 5000 practicing psychiatrists are available for more than 10 million acute mental patients? Such questions arose and received consideration in many contexts up to that of the plenary sessions of the conference. The formal recommendations finally passed by the Planning Committee, representing the sponsoring institutions, are appended.

I cannot close without touching on the problem of ease and dis-ease or of content and discontent, which was often mentioned and was the theme of Aldous Huxley's address and of part of my summary at the New York Academy conference. There is a basic conflict: in the individual between the desire for experience, with its trials, and for experienceless nirvana; and between individual peace and group progress, or change, if a value direction is denied. Group change, whether as biological or cultural evolution, depends on the contribution of the individual, often attended by extremes of effort or suffering. Prometheus, who brought fire to man and was condemned for his impious act to an unrelenting gnawing of his vital organs, symbolizes this conflict. It is the core of the ethical problem in human drug testing: What risks to the individual are justified

for a potential gain for mankind? When should the good be relinquished in the quest for the better?

Huxley was concerned lest man, in possession of agents that can bring tranquility, would drug himself into inertia, and he pointed out that all the natural "depressant" drugs were exploited from prehistory—alcoholic drinks, opium, hashish, and the like. But the same is true for the "excitant" drugs—coffee, tea, maté—and, indeed, the dominant drink of each civilization where it is available is "the cup that cheers but not inebriates." There is some "elan vital" in all creatures, and this divine unrest is maximal in man. Here we leave science for the humanities and religion and yield to the poets. But between Swinburne and Untermeyer, I would here agree with the lesser poet and subscribe to the second of these verses:

From too much love of living,
From hope and fear set free,
We thank with brief thanksgiving
Whatever Gods may be
That no life lives forever;
That dead men rise up never;
That even the weariest river
Winds somewhere safe to sea.
[From "The Garden of Proserpine"]

From compromise and things half-done,
Keep me, with stern and stubborn pride;
And when, at last, the fight is won,
God, keep me still unsatisfied.

[From "Prayer"]

Appendix. The following recommendations have been formally passed by the Committee on Planning and Coordination of the Conference on the Evaluation of Pharmacotherapy in Mental Illness.

1) It is recommended that the funds allocated to the Psychopharmacology Research Center [now the Psychopharmacology Service Center] be used to support further basic research, the development of research methodology, the institution of pilot drug evaluation studies and the coordination of cooperative research programs.

2) It is recommended that the Psychopharmacology Research Center arrange a conference of selected investigators and representatives of the pharmaceutical industry to discuss and attempt to arrive at minimum criteria of effectiveness and toxicity in the evaluation of drugs for clinical trial. This proposed conference should consider the ways in which their suggested criteria might be applied in practice. It is also recommended that special attention be given by the pharmaceutical industry, the Food & Drug Administration, investigators and physicians to possible untoward effects of drugs on behavior and mental function.

3) It is recommended that the Psychopharmacology Research Center un-

dertake to improve communication in this and related fields by the preparation or support of annotated bibliographies, reviews, news letters and appropriate conferences. It is further recommended that attention be given to the problem of providing financially adequate fellowship support to the graduate student, early post-doctoral or early post-residency levels to provide interdisciplinary training for men in psychiatry or the relevant basic sciences who wish to prepare themselves for a research career in psychopharmacology. It is felt that at present it is difficult for men at the early post-doctoral level to obtain support adequate to encourage them to become competent in more than one discipline.

R. W. GERARD

*Mental Health Research Institute,
University of Michigan, Ann Arbor*

ONR Decennial Symposium

An opportunity for Navy scientists to review the work of their colleagues in Navy laboratories will occur 26–27 Mar., when the Office of Naval Research holds a symposium on "A decade of basic and applied science in the Navy." The symposium will be held as part of ONR's Decennial Year.

Scientific personnel from all Navy laboratories will participate. Papers to be presented will deal both with research which has had significant application in the Naval establishment and with that which has contributed to basic science. Invitations to the symposium will be sent to scientists and other interested personnel of the military services and other government research groups and to selected members of the scientific press.

AGPA Report

The American Group Psychotherapy Association has announced the publication of a 44-page abstract covering its 14th annual convention, which took place in January 1957. This comprehensive survey may be purchased for \$1 from AGPA, Room 300, 345 E. 46 St., New York, N.Y.

Venereal Disease Symposium

The eighth annual Symposium on Recent Advances in the Study of Venereal Diseases will be held in the auditorium of the Department of Health, Education, and Welfare, Washington, D.C., on 24–25 Apr. The sessions are open to all interested physicians and workers in allied professions. Hundreds of participants from all parts of the country attend this

meeting annually to exchange the latest available information. Topics to be discussed will cover many aspects of venereal disease control, including basic and clinical research, serology, epidemiology, treatment, program operation, and professional education.

Society Elections

■ National Geographic Society: pres., Melville Bell Grosvenor; v. pres. and sec., Thomas W. McKnew; treas., Robert V. Fleming.

■ American Documentation Institute: pres., James W. Perry, Western Reserve University; pres.-elect, Herman H. Henkle, John Crerar Library; past pres., Joseph Hilsenrath, National Bureau of Standards; treas., Kenneth L. Fagerhaugh, Carnegie Institute of Technology; sec., Charles G. LaHood, Jr., Library of Congress, Washington 25, D.C. Representative to the AAAS Council is Milton O. Lee.

■ Southeast Branch, Alaska Division of the AAAS: pres., Leo M. Thompson, Alaska Department of Health; v. pres., Russell C. McGregor, U.S. Forest Service; sec.-treas., Dorothy J. Phelps, Department of Library Services, Alaska Office Building, Juneau.

Forthcoming Events

March

1–2. American Physical Soc., Norman, Okla. (K. K. Darrow, Columbia Univ., New York 27.)

1–3. National Wildlife Federation, annual, Washington, D.C. (C. H. Callison, 232 Carroll St., NW, Washington 12.)

2. Air Pollution and Its Control, 5th annual symp., Staten Island, N.Y. (N. Colosi, Dept. of Bacteriology and Public Health, Wagner College, Staten Island 1.)

3–6. American Inst. of Chemical Engineers, White Sulphur Springs, W.Va. (F. J. Van Antwerpen, AIChE, 25 W. 45 St., New York 36.)

3–9. American Soc. of Photogrammetry, 23rd annual, joint with American Cong. on Surveying and Mapping, 17th annual, Washington, D.C. (C. E. Palmer, ASP, 1515 Massachusetts Ave., NW, Washington 5.)

4. Wildlife Soc., annual, Washington, D.C. (D. L. Leedy, Fish and Wildlife Service, Dept. of the Interior, Washington 25.)

4–6. National Biophysics Conf., Columbus, Ohio. (H. P. Schwan, School of Medicine, Univ. of Pennsylvania, Philadelphia 4.)

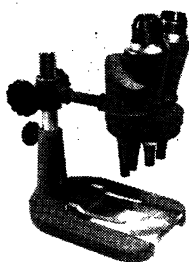
4–6. North American Wildlife Conf., 22nd, Washington, D.C. (Wildlife Management Inst., 709 Wire Bldg., Washington 5.)

4–8. Analytical Chemistry and Applied

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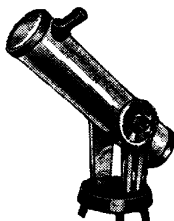
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Spectroscopy, Pittsburgh, Pa. (L. M. Melnick, U.S. Steel Corp., Applied Research Lab., Monroeville, Pa.)

7-9. American Orthopsychiatric Assoc., 34th annual, Chicago, Ill. (M. F. Langer, AOA, 1790 Broadway, New York 19.)

7-9. Biometric Soc., Eastern North American Region, Washington, D.C. (A. M. Dutton, Box 287, Sta. 3, Rochester, N.Y.)

7-9. Fundamental Cancer Research, 11th annual symp., Houston, Tex. (L. Dmochowski, M. D. Anderson Hospital, Texas Medical Center, Houston 25.)

7-9. Optical Soc. of America, semianual, New York, N.Y. (S. S. Ballard, Scripps Inst. of Oceanography, San Diego 52, Calif.)

10-16. Nuclear Engineering and Science Cong., 2nd, Philadelphia, Pa. (Engineers Joint Council, 29 W. 39 St., New York 18.)

11-15. National Assoc. of Corrosion Engineers, 13th annual, St. Louis, Mo. (R. T. Effinger, Shell Oil Co., Deer Park Refinery, Houston, Tex.)

11-18. Pakistan Assoc. for the Advancement of Science, 9th annual conf., Peshawar, West Pakistan. (B. Ahmad, PAAS, University Institute of Chemistry, The Mall, Lahore, Pakistan.)

12-13. Cellular and Humoral Aspects of the Hypersensitive States, symp., New York, N.Y. (A. M. Pappenheimer, Jr., Dept. of Microbiology, New York Univ., College of Medicine, 550 First Ave., New York 16.)

13-15. Society of Exploration Geophysicists, 10th annual midwestern, Fort Worth, Tex. (G. A. Grimm, Tide Water Associated Oil Co., Box 2131, Midland, Tex.)

14. Effect of Radiation on Foods, Assoc. of Vitamin Chemists, Chicago, Ill. (M. Freed, Dawe's Laboratories, Inc., 4800 S. Richmond St., Chicago 32.)

15. Fats in Human Nutrition, AMA symp., New Orleans, La. (Council on Foods and Nutrition, American Medical Assoc., 535 North Dearborn, Chicago 10, Ill.)

18-21. Institute of Radio Engineers, natl. convention, New York, N.Y. (B. Warriner, IRE, 1 E. 79 St., New York 21.)

19-21. American Meteorological Soc., 151st national, Chicago, Ill. (K. C. Spengler, AMS, 3 Joy St., Boston 8, Mass.)

20-22. National Health Forum, Cincinnati, Ohio. (National Health Council, 1790 Broadway, New York 19.)

20-23. National Science Teachers Assoc., annual, Cleveland, Ohio. (R. H. Carleton, NSTA, 1201 16 St., NW, Washington 6.)

21-23. American Physical Soc., Philadelphia, Pa. (K. K. Darrow, APS, Columbia Univ., New York 27, N.Y.)

21-23. International Assoc. for Dental Research, annual, Atlantic City, N.J. (D. Y. Burrill, 129 E. Broadway, Louisville 2, Ky.)

21-23. Michigan Acad. of Science, Arts and Letters, annual, Detroit, Mich. (R. F. Haugh, Dept. of English, Univ. of Michigan, Ann Arbor.)

(See issue of 18 January for comprehensive list)

EQUIPMENT NEWS

All inquiries concerning items listed here should be addressed to Science, Room 604, 11 W. 42 St., New York 36, N.Y. Include the name(s) of the manufacturer(s) and the department number(s).

■ VISCOSIMETER has a temperature range from 0° to -65°F. The unit utilizes mechanical refrigeration, and temperature is controlled by an adjustable hydraulic thermostat. The stainless-steel working chamber, which has 6 in. of insulation, is large enough to accommodate several Kinematic tubes. The stirrer is air-driven. (Labline, Inc., Dept. S138)

■ LABORATORY REACTOR operates at a 5-watt power level and produces a flux of 10⁸ neutrons/cm² sec. The core is a 1-ft stainless-steel sphere that holds about 4 gal of enriched uranyl sulfate in water solution. The unit is 8 ft high and 8 ft in diameter; about 6 mo are required for installation. (Atomics International, Dept. S139)

■ RECORDING SPECTROPHOTOMETERS are described in a new catalog. The specifications of two models of Cary instruments designed for use in the visible, infrared, and ultraviolet regions are given. (Applied Physics Corp., Dept. S141)

■ SCALER with five decade units is designed as a general-purpose nuclear-counting instrument. Five plug-in decade units, plus a 100,000th-unit indicator, permit a direct count up to 199,999 without the use of external registers. Over-all resolution time is 1.0 μsec per pulse pair. A pulse-height control allows the sensitivity to be varied, and a single control lever starts, stops, and resets the count and time. (Technical Associates, Dept. S142)

■ INDUCTION FURNACE is designed for analyzing hydrogen in titanium and zirconium metals as well as in metal hydrides. The furnace burns the sample in a stream of oxygen, converting the hydrogen and oxygen into water, which is then weighed in a gravimetric bulb. The unit utilizes standard tank oxygen, which is run through a heated sample in a bath of molten iron. (Laboratory Equipment Corp., Dept. S143)

■ GRATING MONOCHROMATERS covering the range between 220 and 2800 mμ are described in a new bulletin. Three units, for use in the ultraviolet, visible, and infrared regions, are listed. The units can be used as light sources in microscopic studies whenever monochromatic light is desirable. (Farrand Optical Co., Dept. S144)