REVIEW OF REVIEWS[1]

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Increasing specialization threatens to break the unity of pharmacology as a significant biomedical discipline. Specialization in depth may be very helpful in organizing reseach in obtaining grants, and in getting important new bits of pharmacological and toxicological knowledge. Yet, it disturbs the balanced picture of pharmacology, especially for its satisfactory teaching to students in health professional schools.

This increasing specialization in pharmacological research has stimulated the publication of many new journals for reporting the new findings in such special areas as applied pharmacology, biochemical pharmacology, clinical pharmacology, molecular pharmacology, and toxicology. Who can keep up with the overwhelming flood of new ideas and new data in pharmacology as a whole? For myself, I have long argued that competent review articles can aid in holding the discipline together. All, no matter how specialized in individual research, may profit from noting the general advance continually being made in our knowledge of the interactions of chemical compounds with living material, organized as it is from molecules to ecologies. This general view of pharmacology is increasingly necessary in teaching health professional students, and it is best maintained by familiarity with competent analytical and critical summaries.

These comments are offered in apology for continuing to make an effort to call attention to significant reviews and summaries of current pharmacological knowledge. Such reviews are increasing greatly in number and in unsuspected places of publication. While *Pharmacological Reviews* and *Annual Review of Pharmacology* remain indispensable, many excellent reviews of pharmacological information appear in various biomedical periodicals, in symposia, in monographs, and in compilations of the "Recent Advances" variety.

The current situation in pharmacology is confused by much popular clamor over drug names and prices, and by the unfortunate bureaucratic regulations of the Food and Drug Administration. These seem certain to interfere with laboratory and clinical study of drugs, new or old, if merely by weight of red-tape, forms, applications, and reports, necessary if one is to avoid the unpleasant harassment of Federal agents. Both Modell (52) and Visscher (68) have protested vigorously. A significant issue is whether evaluation of drugs is to continue to be a matter for scientific and clinical judgment and agreement.

[1] The survey of the literature pertaining to this review was concluded in July 1967.

On the other hand, pharmaceutical manufacturers, even the best, continue to insult the intelligence of members of the health professions with their specious and over-expensive advertising. They continue to hide necessary knowledge (such as what the drug actually is, chemically) behind ballyhooed trade-marked names, seeming to be ashamed to use their company name for assurance of the quality of their product. At the same time, some dealers masquerade under false respectability by offering sub-standard drugs under "generic" names. As Kreig (42) emphasizes, there is a large black market for sub-standard drugs with forged labels and containers, with evidence of mobster backing in this kind of drug racketeering.

General

Ariens and his colleagues (2) continue to explore molecular bases for drug action, noting that agonists and antagonists often interact with different but related receptor sites. They suggest the probability of receptor reserves. Drug-receptor interactions are also considered in depth in the third volume of *Advances in Drug Research*, edited by Harper & Simmonds (29). New methods of analysis of drug-receptor interactions are described, as well as tolerance and physical dependence in relation to receptors. Autoradiographic techniques are discussed, as well as the use of β-alkylamines in the differentiation of receptors. Both adrenergic and cholinergic mechanisms are examined. A notable feature of the discussion is a reminder of the limitations of molecular pharmacology. This consideration of receptors continues the discussion begun the year before, in which there were reviews of adrenergic receptors of catecholamines, muscarinic receptors, and receptor analysis with 2-halogeno-ethylamines.

An important review, covering many Russian reports, was made by Khromov-Borisov & Michelson (37) on the disposition of cholinoreceptors of locomotor muscles and their changes in the course of evolution. The notion developed of anionic points on the receptors on the post-ganglionic membranes corresponding to the internitrogen distance in decamethonium (about 14 Å, or C-10 structure), or in other highly potent myorelaxants with greater internitrogen distances (about 20 Å, or C-16 structure). Electron shifts in the cationic heads are discussed, and a tetrameric arrangement of receptor subunits is suggested. Data suggest that in the course of evolution, the C-16 structure appeared first, with the C-10 structure coming later.

Burns (6) chaired a symposium on drug interactions, in which it was noted that some drugs, such as phenobarbital, can increase the activity of liver microsomal enzymes to speed the metabolism of other drugs, such as steroids. Various examples of synergism were described, as between pyrazine and thiazide diuretics.

Seeman (59) reviewed membrane stabilization by drugs, with special reference to tranquilizers, steroids, and anesthetics. In a careful analysis of 395 articles on drug action in relation to membrane lipids, Cuthbert (9) concluded that there is no adequate theory of drug action on membranes.

LaSalle (46), noting only seven reports, comments on the paucity of information on sex differences in response to drugs. With reference to 118 reports, Yaffe (75) examined various aspects of perinatal pharmacology. Wagner (72) reviewed the use of computers in analysis of pharmacological data, and in model-making in pharmacokinetics. A discussion of immunotolerance to simple chemicals was made by DeWeck & Frey (11).

The chemistry, biological effects, and pharmacology, as well as clinical applications of dimethyl sulfoxide (DMSO) were carefully reviewed in an international symposium, the proceedings of which were edited by Laudahn & Gertich (47). Some 395 reports were edited. An analysis was made of over 9,000 patients receiving the drug. Helpful results were reported in about three-fourths, with no evidence of eye injury or other serious untoward effects. A large symposium covering similar material and with similar findings was edited by me (48).

Biochemical Pharmacology

Specific biochemical aspects of pharmacology are being increasingly emphasized. It may be unwise, however, to rely too greatly on biochemical concepts and terminology in trying to explain mechanisms of drug interactions with living material. Yet, it would be mutually helpful for biochemists and pharmacologists to explore such interactions in cooperation.

Witkop (73) offered a concise but conventional review, with 30 references, on the role of biochemistry in drug design. He emphasized that nature is a unity and not departmentalized, no matter how much specialists may wish otherwise. His comments included such items as control of enzyme action, biopolymer cleavage, modification of nucleotides, biosynthesis and metabolism of amines and amino-acids, and norepinephrine release.

An extensive survey, using 313 references, was made by Fox & Fox (21), of drug effects on spermatogenesis. It appears that testosterones inhibit the activity of the anterior pituitary and reduce binding between histone and DNA in prostates. Steroidal androgens of the 17-2 hydroxyprogesterone type inhibit spermatogenesis and engage in competitive blocking of androgen receptors. Many cytotoxic compounds inhibit spermatogenesis. Nitrogen mustards are more effective in insects than in mammals. Other spermatogenic inhibitors include triethylene melamine, methylmethane and dimethane sulphonates, dinitropyrroles, methyl hydrazines, and bis(dichloracetyl) diamines. Kihlman (39) describes damaging effects of chemicals on chromosomes and discusses mitotic inhibitors and chromosome breaking agents.

With 516 references, Kiese (38) considered mechanisms of ferrihemoglobin transformation under the influence of aromatic amines and nitrates. Lande & Lerner (44) reviewed the biochemistry of melanotropic agents, with reference to 129 reports, identifying a melanotropin as a basic acetyl-tridecapeptide-amide. Xanthines are melanin dispersing agents, and sodium and calcium ions are involved.

The transport function of plasma proteins was considered in a sym-

posium edited by Desgrez & De Traverse (10). In a review of botulinal, tetanal, and enterostaphlococcal toxins, by Lamann & Carr (43), it was concluded that selective receptors for these agents exist in the central and autonomic nervous systems. Langh (45) opened a short symposium on renin, angiotensin, aldosterone, and hormonal regulation of arterial blood pressure and salt balance. Perutz (54) summarized a symposium on lysozymes and their enzymatic cleavages of various substrates including glucosides. Strominger and associates (64) described penicillin-sensitive enzyme reactions involving peptidoglycon transpeptidase and *d*-alanine carboxy peptidase. A helpful review of pharmacologically active peptides, with 165 references, was made by Ungar (65). He discussed the role of oxytocin, vasopressin, angiotensin and plasma kinins in osmoregulation, parturition, lactation, homeostasis, shock, inflammation, and pain.

Nervous System

Von Euler (70) with 42 references, reviewed the uptake, storage, and release of catecholamines in adrenergic neurons. The metabolism of norepinephrine in the central nervous system was surveyed, with 321 references, by Glowinski & Baldessarini (25), together with a review of the action of drugs on central norepinephrine and of the inhibition of its catabolic enzymes. Valdman (66) edited a comprehensive survey of drug action on synaptic transmission in different brain structures. This provides much data on the effects of neurotropic drugs on pontine respiratory and vasomotor centers.

Antidepressant drugs were well considered in a Milan symposium edited by Garattini & Dukes (24), with special attention paid to metabolic and biochemical effects, methods of evaluation, and clinical use. Gyermek (28) reviewed the pharmacology of imipramine and related antidepressants. Caffey and colleagues (7), using 83 references, compiled a sharp concise review of antipsychotic, antianxiety, and antidepressant drugs.

The general pharmacology of psychopharmacological agents, including tranquilizing and antidepressant drugs, was reviewed by Von Brücke & Hornykiewicz (69). Gordon (27) continued the editing of a general survey of psychopharmacological agents with extensive bibliographies in phenothiazines and meprobamate-like compounds. A detailed series of reports on pharmacological-psychiatric combination therapy was edited by Petrilowitsch & Kranz (55). The interactions of drugs with placebos in controlling pain and anxiety were explored by Dinnerstein, Lowenthal & Blitz (12), who found that subjective, contextual, and suggestive factors are operative. Using 140 references, Schildkraut & Kety (58) reviewed the relation between brain biogenic amines and emotions and the effects thereon of various drugs, including lithium salts.

Newer anesthetics were surveyed with 227 references by Dobkin & Su (13), with special attention to halothane, methoxyflurane, halopropane, and intravenous agents. With 250 references, Dundee (18) reviewed the clinical pharmacology of general anesthetics, discussing uptake, distribution, and

factors contributing to untoward effects. Using 361 references, Bromage (5) surveyed the complex process of epidural analgesia involving the passage of local anesthetics.

In an analysis of tranquilizers for the management of alcoholics, Benor & Ditman (4) conclude that benzodiazephines are the drugs of choice in treating acute alcoholism, but that no drugs are useful in chronic alcoholism. Freinkel & Arky (22) reviewed the actions of alcohol on human carbohydrate metabolism, and Goldberg (26) summarized behavioral effects of alcohol in humans. Mendelson (50) edited the symposium on alcoholism in which these reviews appeared, including Russell & Van Bruggen's review on pathways of ethanol metabolism (57), Von Wartburg & Papenberg's on alcohol dehydrogenase (71), and Isselbacher's on the interrelationships of alcohol and lipid metabolism in the liver (32).

Of miscellaneous interest in central nervous system pharmacology, Flexner, Flexner & Roberts (20) reviewed their work on the use of antibiotics to study memory stages in mice in order to indicate molecular events which sustain memory. Kinross-Wright (40) summarized the current status of phenothiazines. Wood and associates (74) gave a computer review of reports on the clinical effectiveness of antimotion-sickness drugs, with an overall effectiveness of 70.6 per cent for antihistamines, 50.1 per cent for belladonnas, 44.9 per cent for phenothiazines, and 64 per cent for dextroamphetamine. A critical bibliographic review of salicylates was made by the Smiths (63).

Endocrinology

Oral contraceptives are attracting wide interest. A symposium on their social and medical aspects was edited by Dukes (17). Drill (16) offered a concise review of the chemical, biological, and clinical facts reported in regard to them; and Hertz & Bailar (30) evaluated the risks of using estrogen-progesterone combinations for contraception.

A full survey of neuroendocrinology was edited by Martin & Ganong (48). Murnaghan & Talalay (53) recounted the long struggle of J. J. Abel (1857–1938) with crystalline insulin. A clear and concise review of oral hypoglycemic agents (60) was made by Seidenstricker & Hamwi (1913–1967). This is a model of what clinical pharmacologists can do to aid practicing physicians.

Dorrington & Munro (15) reviewed 102 reports on the long-acting thyroid stimulator which may be an antibody and is not of pituitary origin. Kenny (36) chaired a symposium on thyrocalcitonin, a peptide thyroid hormone which removes calcium from blood and inhibits bone resorption.

Miscellaneous

Cardiovascular.—A reevaluation of quinidine was offered by Kay (35). In reviewing the effects of drugs on human pulmonary circulation, Dollery & Glazier (14) note that serotonin does not cause a rise in pulmonary vascular

pressure, but that angiotensin and bretylium tosylate do. Hodge & Dornhorst (31) briefly assess the clinical value of vasoconstrictors.

Heavy metals.—In reviewing the role of arsenicals in biology, Frost (23) notes that they counteract selenium toxicity, and aid in stabilization of bones and teeth. Mena and colleagues (49) survey chronic manganese poisoning, and note extrapyramidal tract involvement with prolonged turnover. Mertz (51), in discussing the biological role of chromium, indicates that it is needed for glucose metabolism. Prasad (56) suggests that zinc may be needed to protect RNA from RNase, and reports growth retardation when there is a deficiency.

Toxicity.—Baker & Scott (3) edited the 1966 Prague Conference on the neurotoxicity of various drugs. Antopol and his colleagues (1) discussed the place of pathologists in evaluating potentially toxic substances. Chu (8), with 143 references, reviews reactivators of cholinesterase inhibition as antidotes for poisoning by organophosphorus insecticides. Shelley (62), using 194 references, surveys renal injury from phenacetin, and concludes that it is rare and may be due to the anti-inflammatory element in the mixtures sold or to contamination with 4-chloro-acetanilide.

General miscellany.—With 258 references, Buffoni (5a) reviewed mammalian intracellular enzymes, giving special attention to plasma benzylamine oxidase and the factors affecting enzyme activity in plasma and tissues, and to histaminase. A considerable discussion on the chemistry, metabolism, and biological implications of conjugations of glucuronic acid was edited by Dutton (19). The clinical pharmacology of drugs influencing uric acid production and excretion was reviewed by Krakoff (41). Jellinek (33) surveyed the relation of chemical carcinogens to steroid metabolism. A useful summary of clinical experiences with long-acting sulfonamides in urinary tract infections was made by Seneca (61).

In Prospect

Patterns of review articles in pharmacology shift with changes in research interest and involvement. Currently, emphasis seems to be on molecular aspects of basic pharmacology on the one hand, and on clinical pharmacology on the other. Perhaps, in years to come, there may be a more balanced pattern of pharmacological study over the whole range of organizational levels of living material from molecules to ecologies.

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