1966

APPROACHES TO RATIONAL DRUG DESIGN*

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In expressing my appreciation for the 1966 Rho Chi Lecture Award, I want to emphasize the singular characteristic which has made membership in Rho Chi a memorable honor. It has been not only high academic performance reflected in high undergraduate course grades, but the degree of enthusiasm which has driven the members to leadership achievement. This enthusiasm stems from the vision of an ever-brighter and expanding future of the science, art and profession of pharmacy. In turn, this progressive expansion depends directly upon the discovery of novel therapeutic agents with greater effectiveness, fewer side reactions, and a wider margin of safety. In order to attain these goals, hundreds of thousands of new compounds must be tested biologically by competent investigators. The major and minor activities of the drugs must be carefully observed in vitro and in vivo, and their mode of action at the molecular level studied. If necessary, analogs of the "lead" compound must be prepared by guide lines that permit rationalization of drug design with a minimum of effort. Not all these rather lofty goals are easily reached; also, they constitute only approachers to exacting clinical trials and the inevitable set-backs that occur with every drug. After a drug has been introduced into medical use it usually unfolds disadvantages which become significant only in the statistical evaluation of large-scale clinical observations.

Opposed to the wish for new drugs held by the patient and the medical and pharmaceutical professions is the fear of regulatory governmental agencies and of uninformed groups such as the churches and politicians, that an expanded armamentarium spells the possibility of an overabundance of potentially dangerous drugs. There is only one way to avoid dangerous drugs, namely, to abolish all drugs. Danger from drug use and abuse will always be at hand because no chemical has only one biological action. It is generally assumed that all drugs inhibit enzymes, and as far as has been observed, never just one single enzyme. If in turn physiological aberrations from normal conditions are caused by imbalances in the rate of operation of enzymes, any multiple interference with enzymatic reaction rates will give rise to side effects - which may occasionally lead to toxic or damaging symptoms. Abuses are beyond the province of the medicinal scientist. Drug abuses arise from pathological, morbid sociological and psychiatric premises which lead to abuses of anything, not just drugs. In relation to the total benefits obtained from therapeutic agents, the percentage of drugs sidetracked into illegal or pathogenic channels has remained very small. Even though criminal and sociopathological sequences of drug abuses may be disturbing, especially to segments of the population which are bent on ferreting out any trouble, they cannot be cited as arguments that drugs should not be used at all, or only under the most desperate circumstances.

More weighty may be questions about the proliferation of psychopharmacological agents, especially tranquilizers, in conditions other than a correction of a severe psychiatric disorder. It has been argued that a certain amount of anxiety is necessary for the desire for achievement, for inventive and progressive attitudes, and for the civilized striving for improvements in human life. As Shakespeare (The Merchant of Venice, Act I, Scene I) put it "Why should a man whose blood is warm within, sit like his grandsire, cut in alabaster?" One could contemplate permitting only those drugs to be used which provide therapy in severe neurotic or psychotic episodes. However, it will be difficult to condemn any given drug since individual idiosyncrasies and genetic indispositions may make a drug highly effective for a given patient while the same agent may be relatively ineffective in a majority of patients. It would be unwise to deprive any minority of individuals of a beneficial agent just because others do not require this drug frequently.

* The Annual Rho Chi Lecture, Dallas, Texas, April 1966

In all science, understanding of fundamental processes is necessary if the full practically applicable potential of these basic reactions is to be exploited. The search for new drugs has not yet taken this recognized pathway, largely because of the as yet insuperable difficulties of dealing with minute details of macromolecular reagents in the living cell. The pressing need for new drugs has forced medicine men of primitive tribal peoples, and sophisticated medicinal scientists of our age, to choose new agents empirically. A number of time-honored empirical methods are being pursued, and it may be well to consider them in a projection of future progress in drug discovery. Since pharmacy is vitally interested in the practical utilization of drugs, this aspect will be stressed.

The revival of interest in therapeutically active natural products stems from the discovery of the tranquilizing and depressor properties of reserpine in 1952. This event initiated a decade of random screening of ten thousands of botanical specimens; a few pharmacologically interesting compounds were discovered in these searches, but medicine has provided almost nothing from this effort. Only two or three new naturally occurring drugs have been introduced into clinical use based on this work, a yield so infinitesimally low that the practical value of random botanical screening must be questioned seriously. A refinement of the method consists of selecting plants on the basis of medicinal folklore but this too has proved essentially unrewarding when one adds up its practical results.

As a purely scientific side product, natural products work has given a tremendous impetus to structural-analytical organic chemistry and to the application of spectroscopy to molecular science. It is to be hoped that the knowledge thus gained will shorten the time needed to explore such very complicated natural products as biologically active proteins, enzymes, and polynucleotides. It should also not be denied that the twisted and unorthodox chemical structures found among pharmacologically active waste products of plant metabolism have given us leads in novel structural areas in which to search for improvements in the form of potential medicinal agents. This has perhaps been the most important contribution of natural products chemistry to medicinal science.

There are a few natural products which lie outside of this critique. They are vitamins, hormones and other compounds of a priori established therapeutic activity which have been studied chemically, have been synthesized inexpensively, and have thus enabled the physician to use them widely in his practice.

The screening of soil samples for antibiotics has also remained an inordinately low-yield operation. On the whole, the random screening of synthetic chemicals has done a little better, although certainly not much better. The condition for any screening program is the application to a well-working and meaningful biological test which gives a measure of promise of carrying over into the human pathology it is meant to represent in the laboratory. These conditions have been fulfilled best in the case of pathogenic infections in laboratory animals, and indeed the respective screening programs have yielded a number of highly effective drugs (bacteremias, tuberculosis, malaria). The huge tumor screening programs have been much less successful percentagewise, as measured by the number of drugs applicable to human malignancies. Here the test methods have not stood the criteria given above. The equally vast screening of psychopharmacological agents in mice, rats, pigeons and monkeys has been even more harassing to the participating pharmacologists: tests geared to learned behavior of animals do not easily reflect the activity of a chemical in modifying human mental aberrations with their multiple physiological causes which in turn are affected by environmental factors.

After a "lead" structure has once been discovered, one finds often that the first compound is seldom the therapeutically best representative of that structural type. This necessitates a program of developing the optimal drug in the series by molecular modification. This term has been as much maligned as it has been praised. Criticism of molecular modification has come chiefly from a congressional committee

investigating the practices of the American pharmaceutical industry; praise has been heaped on molecular modification as the chief and most successful method of selecting a superior drug from dozens of congeners, and of applying keen pharmacologic observations as guide lines for additional chemical work.

Both praise and criticism have had some justification. Many drug firms eye appreciatively the success of a given major drug and are not above trying to capture a percentage of such a lucrative market. This is done often by altering the lead structure in a minor way (replacing dimethylamino groups by diethylamino groups, introducing a small alkyl in an unstrategic position, etc.) without changing the overall character of the structure and of its action. The dozens of available antihistaminic drugs, progestin-types, sympathomimetics, etc., are examples of such modifications. However, even such obvious "me-too" changes may be defended on therapeutic grounds. No two compounds have entirely the same range of activities, and even the most similar ones differ in the extent of side actions, behavior toward resistant or otherwise genetically caused conditions, and the response of the individual toward any drug. The small structural difference between benzylpenicillin and benzyloxypenicillin, and the different action of these agents on resistant cocci may be quoted as an example for the justification of any molecular modification.

There are two intellectually more stimulating facets of molecular modification. First, one can often predict from the chemical and physical properties of a "lead" compound what structural changes might do to its reactivity. Thus polar groups can be strengthened or weakened, the electron distribution can be influenced, and the shape of the molecule can be changed predictably. If such changes will conceivably improve the medicinal properties of the "lead" compound, modifications on purely chemical grounds will be beneficial. The rules governing such changes have been lumped together in the concept of bioisosterism.

If a compound is deactivated prematurely by biological variation, the introduction of sterically hindering groups may protect it from metabolic destruction; alternately a hindered analog may block enzymes which ordinarily would dispose of the active compound, and the latter will thus be given a chance to unfold its action at its bioreceptors.

The most interesting stimulus for molecular modification arises from observations of side actions during the laboratory studies or therapeutic use of a drug. By patient and extensive structural manipulation it is quite often possible to deemphasize the original therapeutic action of a compound and to bring a side action decisively to the fore. An example for this sequence may be found among the bacteriostatic sulfonamides which, during wide therapeutic use, exhibited minor natriuretic and hypoglycemic side actions. Progressive molecular modification succeeded in suppressing chemotherapeutic activity and to enhance diuretic (azetazolamide, chlorthiazide) and later antidiabetic (tolbutamide) properties.

Truly scientific drug design with a minimal rate of disappointing failures is still in its infancy, although this infant has grown only very slowly in its 30 years of biochemically nurtured life. It is still beset with heavy remnants of empiricism, because we have learned so very little about the active sites of enzymes and bioreceptors at which a drug must act (but how?) as a prelude to symptomatically observable biological effects. Some progress has been made by cutting drug design loose from accidentally found "lead" structures, and modifying instead the chemical structure of a metabolite (vitamin, hormone, peptide, saccharide, nucleotide, etc.) with which the drug is to interfere in some way. By designing molecules which would interfere with the biosynthesis or the biochemical utilization of such metabolites, a wide range of competitive, reversible, non-reversible and non-competitive metabolite antagonists have been devised. Although many such compounds do indeed inhibit the proper metabolite or enzyme system in simple, often artificial, environments, most of them fail to perform their task in vivo. It is clear that we know too little about membrane permeabilities, difficulties in drug transport, absorption at the desired place, and the compound's side-tracking at therapeutically meaningless and undesirable tissues. Finally, our ideas of the interaction of a drug at the active site depend largely on interpretations of drug-enzyme kinetics. The suggestion that many metabolites may shape enzyme molecules to fit their structural and electronic requirements, and that drugs may perturb this shaping of the active site, has not had fruitful practical consequences in drug design as yet.

It is clear that the future of purposeful and defendable drug design depends on strengthening the organic and biochemical basis of the interaction of drugs with cell chemicals. Without such long-range fundamental work medicinal science will remain an empirical art. The graduate schools of colleges of pharmacy are the logical institutions for such studies. In such schools there can be free interplay between organic and physical chemists, pharmacologists, biochemists and microbiologists. Neither the graduate schools of chemistry nor research units in medical schools command all these disciplines under one roof. Moreover, the natural emphasis on fundamental studies in the universities provides an additional proper setting for such work. The generous grant support by Health Agencies of the Federal Government, and the absence of financial pressure to produce a profitable drug as it is always present in the industry, lend further support for a strengthening in the graduate schools of pharmaceutical sciences. Members of Rho Chi who have shown leadership qualities as a prerequisite to their election, should devote time and energy to put these blueprints of drug science into practice.

Dr. Alfred Burger (center) Professor of Chemistry, University of Virginia, recipient of the 1966 Rho Chi Award, is shown above with Dr. John G. Adams (l.) Chairman of the Award Committee, and President Edward J. Rowe (r.) at the Dallas meeting of Rho Chi Society.