PRESIDENTIAL ADDRESS

The Genesis of a Drug

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One of the more pleasant and rewarding aspects of assuming the presidency of an organization such as this is the opportunity to review the past volumes of the Proceedings, to read the presidential addresses of the people who have held this post, and to hope that I may add something—besides length—to the long list of significant talks which have been delivered on this occasion. My own file of Proceedings of the Academy of Science starts with the 1930 volume, the year I joined the organization; thanks to my close association with the late Rev. Julius A. Nieuwland, C.S.C., President of the Academy in 1934, my collection of Proceedings also includes the 1913 and 1914 volumes, also those from 1926, 1927, 1928. Needless to say, I prize this collection; and one of my regrets during the year of my presidency has been the lack of time to peruse these Proceedings more carefully, for there is a great deal of Indiana scientific history in these volumes.

Since my duties in the institution which I represent have been for the past fifteen years more in student administration and teaching than in research, I must rely upon my initial profession, pharmacy, to furnish me with a topic for my talk on this occasion—"The Genesis of a Drug." But I do so with considerable trepidation for the reason that many members of that profession have been or are active members of the Indiana Academy of Science, and maintain a closer association with the day-to-day developments in the medicinals industry than I have been able to do in my present position. In the present-day production of drugs, however, all areas of science and a fair number of the engineering branches are playing important parts to keep us well supplied with the best medicines history has known to date.

Thanks to the excellent cooperation and help of Dr. Will Edington in response to my query about the role of pharmacy in the Academy, I should like to include a bit of interesting history. Since the Academy has never included a pharmacy division, those of us who have become members of the organization did so because of our interests in the work of some other division. Seven Academy presidents have been associated with the Eli Lilly Co.: Stanley Coulter and Robert Hessler in 1896 and 1906, respectively, and both were charter members of the Academy; John S. Wright served in 1905; Severance Burrage in 1914; Eli Lilly in 1938; Horace Powell in 1953; William Daily in 1958.

Other prominent pharmacists who were associated with the Academy at one time or another were Chalmers J. Zufall and Dean Charles B. Jordan, both of beloved memory, and Charles O. Lee, now located at Ohio Northern University; also, Edward W. Koch, Francis E. Bibbins, Harley W. Rhodehamel, Walter A. Jamieson, George H. A. Clowes, Edward H. Niles, Adam H. Fiske, Ralph W. Showalter, and Bert R. Mull. At the risk of omitting names of many good friends, I will refrain from attempting to list all the active Academy members from the Eli Lilly Co., the Pitman-Moore Co., the Mead Johnson Co., and other pharmaceutical

houses in Indiana, and from the faculties of the College of Pharmacy at Purdue and at Butler, but as a fellow pharmacist I welcome them to membership in this organization. It may be of interest to many of you that until 1939 four institutions for the study of pharmacy were in operation in this state. In that year both Valparaiso and Notre Dame discontinued the divisions of pharmacy, leaving Purdue University and the Indianapolis College of Pharmacy—later to become part of Butler University—for the training of pharmacists in the state.

An interesting bit of pharmaceutical history concerns Charles C. Deam (1865-1953), President of the Academy in 1924, who owned and operated a drug store in Bluffton for many years, although he had not received formal training in pharmacy. As pointed out in the memorial by Will Edington and in the summary of his life by Daniel DenUyl, both fascinating reading in the 1953 Proceedings, botany claimed more of his attention than the drug business.

It is a well-known fact that the pharmaceutical industry is intensely competitive. Research is very important in this industry, and in no industry, probably, has it been more productive. The volume of the ethical drug business at the manufacturer's level rose from less than 350 million dollars in 1940 to over $1200 million in 1955; in 1955, 36% of the prescriptions written were for drugs that were not even in the test-tube stage four years before; in that year some 400 new products were introduced as compared with less than 100 in 1940. If I may inject a very brief personal note, one reason why I try to spend a week or two each summer as a pharmacist in the prescription department of a local pharmacy is to learn about the many important new items which are being introduced to the medical profession each year. One needs only to read Aldous Huxley's *Brave New World* and the sequel to it, *Brave New World Revisited* to get at least a fictional picture of the work being done in the field of tranquillizing agents and psychic energizers; a contemplation of what is being done in the highly classified research in chemical warfare centers on "nerve-gas" and "psychogenic agents" provides a more somber note in the tension-laden, cold-war existence in which we are living.

One of the problems confronting the health agencies today is the critical attitude of the general public toward the cost of medical care, one facet of which involves the allegedly high cost of drugs for the prevention, cure, or diagnosis of disease, and the alleviation of symptoms. An impartial analysis of, and a sober reflection on the benefits of modern medication, however, reveal some interesting facts. In terms of per capita costs, annual spending for drugs moved from about $10 in 1948 to $19 in 1958, according to the Department of Commerce. Much of this increase is not due to higher prices; it comes about because people buy more drugs. Production of vitamins gained 239% in the decade 1948-1958, and today many vitamin preparations are bought voluntarily without prescription.

Understandably, some drugs when first introduced, do cost a lot, but industry can point to many sharp cuts in prices over the years. The Eli Lilly Company, for example, cites a 95% reduction in the cost of insulin to the diabetic since 1923, all this in the face of raw material costs that are double those of 1923, and wage costs that are five times higher than in 1923. Many examples from other companies in more recent drug inno-

vations can be cited. Merck's introductory price for cortisone in 1949 was $200 per gram; by 1952 the price had dropped to $20.00 per gram—a 90% reduction—without the pressure of competition. Lederle has pointed out that the price of its broad-spectrum antibiotic, Aureomycin, dropped 65% within a year of its introduction.

Actually, today's drugs are a bargain; deaths from diphtheria have declined 96% since 1944, pneumonia 24%, tuberculosis 80%, scarlet fever and strep throat 90%, and whooping cough 93%. The average length of stay in general hospitals today is nine days (in 1935 it was 15 days); and since 1900, twenty years have been added to the life expectancy of Americans.

The production of a new drug constitutes what might be termed the creative stage, one of three in the path of human progress: 1) the adoptive, 2) the adaptive, 3) the creative. In the adoptive stage a crude drug may find its way into empirical use in medicine. Because of a bitter taste or objectionable odor, or for other reasons, an enterprising chemist or pharmacist may isolate the active principle into a concentrated form to facilitate the administration of the drug; this constitutes the adaptive stage. Finally, the scientist proceeds to analyze the product, to synthesize it in the laboratory, and then, as the final step in the creative stage, to prepare compounds with the same action, but which may have no close chemical relationship with the natural product. The story of cinchona bark, then of quinine, and finally of the synthetic antimalarials, illustrates this interesting sequence in the production of drugs.

The genesis of a drug or new product development is a long, tedious, complex pathway more frequently beset with failures than with successes, some of which may be short-lived. Those who have read the fascinating story of Ehrlich's magic bullet, arsphenamine, know that 605 compounds were made and tested against syphilis before the 606th showed promise. Research on antimalarials has produced 14,000 drugs, of which only a few, possibly a dozen, have been found to be satisfactory; fortunately, the pharmacological testing has pointed to many other uses for some of these compounds. Of the many hundreds of antispasmodic drugs, only a few are widely used; more than 5,000 analgesics have been discovered, but not more than a dozen are commonly used. A team of 55 scientists spent two and a half years screening 100,000 soil samples at a cost of $4 million; only 76 showed organisms with antibiotic activity.

To many persons unfamiliar with new product development, serendipity appears to be an important factor in the production of a new drug. To those of us who have been in contact with scientific research, however, sound fundamental training, the ability to plan a problem, and the good common sense to recognize the big break which may come his way, still remain as prime factors in the success of a scientist to produce a new compound.

In the development of a new drug, ten important steps may have to be taken; from start to finish, this may involve a period of eight or nine months to many years, and constitutes an ever-increasing challenge to the pharmaceutical industry. I should like to comment briefly on each of these ten steps.

1) The original impetus may arise in very diverse areas of scientific investigations. A graduate student whose work is being subsidized by a grant from a pharmaceutical house in a university laboratory may initiate the work on a particular compound; within ear-shot of a chemist at a scientific meeting a physician may express a wistful hope for a new drug to help him in a baffling case; or a researcher on a world tour may observe the effects of a crude drug which may well warrant further investigation. Only the limitations of human ingenuity and planning can affect this initial step toward new products.

2) If the initial plan warrants further investigation, the research committee of the company next considers the feasibility of the research on the particular compound or compounds in question. Expense, consumer acceptance, and availability of raw materials are only a few of the factors which must be considered in this step. It is remarkable, I think, that in 1959 the drug industry spent $200 million for research and development, but came up with fewer than 50 new drugs. In the past decade one company has spent $100 million and has marketed some 70 new products. Another company in 10 years has spent $111 million, another $36 million. These amounts represent between 8 and 9% of total industry sales, far above the levels of most other industries.

3) If the research committee decides favorably on the proposed research, the work involved is assigned to the various divisions of the organization. The pattern of competition which has developed within the past few years between the pharmaceutical companies to maintain their positions in the high-powered promotion race makes it imperative that the people involved in this step are conscientious, responsible group leaders who can gear their divisions to meet deadlines and to interlock their duties with those of other groups to produce the intermediates and the final product. Those of us who teach the sciences and who counsel the young folks who may enter these industries are challenged to foster in them these personal attributes of initiative, cooperation, and responsibility—all this in addition to giving them a sound scientific background.

4) During the fourth step, the preparation and purification of the intermediates and the final product, many other problems worthy of investigation may arise; these can be referred back to the committee on research for consideration.

5) The next step involves the pharmacological testing of the compound or compounds for animal toxicity so that a rough idea of their therapeutic index in various species can be determined. To insure safety, extensive testing in animals must be undertaken to establish potency, toxicity, and contraindications. At this stage many companies are compelled to write off tremendous sums already invested, because the compounds are too toxic to warrant further investigation. It is at this stage that the "arm-chair" research of the chemist or pharmacologist may or may not prove to be fruitful.

6) Assuming that the screening and toxicity testing uncovers some promising compounds for specific indications, the production schedule must move out of the pilot-plant stage into large-scale production. This may involve top-level decisions by the company to build plants for the

production of the basic chemicals in order to guarantee an uninterrupted supply of intermediates in the synthesis of the finished compounds. Two examples worthy of note include the construction of the malonic ester plant at the Eli Lilly Company to provide this important intermediate in the production of their barbiturate compounds, and more recently the construction of the citric acid plant at the Miles Laboratories to guarantee plenty of this product for their effervescent aspirin compound, and also to permit the company to become competitive in the sale of this chemical. Large-scale production may introduce problems for which the chemical engineer, the electrical engineer, the civil engineer, and the mechanical engineer must provide the answers.

7) After large quantities of material become available, additional toxicity and pharmacological studies must be conducted. If the drugs pass all of these tests with flying colors, the whole trial process must be repeated with the compound in various mixtures, this in order to determine the toxicity of the solvents or various adjuvants. The sulfa tragedy in the late thirties might have been prevented if toxicological studies had been conducted on the various ethylene glycol derivatives used as solvents. It is a sad commentary that this tragedy was the prod which impelled Congress to take action on the revision of the Pure Food and Drug Act of 1906.

8) The eighth step involves the clinical testing of the product. If the drug has satisfactorily passed all of the previous tests, the whole trial process must be repeated in the clinics under carefully controlled and observed conditions. In the development of one of the new oral drugs for treatment of diabetes, more than one million patient-days went into the clinical program alone. For this step the cooperation of health and welfare agencies is of utmost importance; clinical testing may take years, although the pressure on every company to match the promotional effort of the less responsible companies has created a situation which is being scrutinized carefully by the Food and Drug Administration.

9) Before a drug can be offered to the medical profession, the results of the experimental tests must gain the acceptance of the Food and Drug Administration. Most companies, too, prize the acquisition of the seal of the acceptance of the Council on Pharmacy and Chemistry of the American Medical Association for their products.

Undoubtedly many of you have been following the newer developments which have resulted from the recent Labor-Health, Education and Welfare Appropriation Act. The FDA has been able to increase the number of plant inspections per year, although the officials maintain that the proportion of the thousands of shipments annually which are inspected is not large enough to give a reliable index of the quantity of substandard drugs which the FDA ought to be keeping off the market. Also, the FDA has been able to increase the number of samples tested for adulteration and misbranding as a further protection of consumers against health hazards and economic cheats. In the field of radiological health, the FDA has been able to begin the ground work for an expansion of its monitoring of radiation levels in a great variety of foodstuffs.

In order to maintain proper rapport with the Food and Drug Administration, the pharmaceutical houses must maintain legal staffs to insure proper compliance with food and drug regulations; this, by the way, is

another area of endeavor for those people who have a sound scientific background and a real interest in the legal profession.

10) Even prior to the completion of the initial steps, the sales department begins the task of marketing the product. Work begins at once on one of the trickiest steps of product evolution: the search for a name or often two names—trade and generic. Marketing research steps in to make a preliminary survey of the current market, the pricing, the competitive products, the package sizes and all the other factors which enter into the total marketing picture. Pharmaceutical research will be called in to develop suitable dosage forms—whether tablet, capsule, parenteral or topical or perhaps, eventually, all four. The advertising and promotional program is blueprinted and carefully studied and reviewed. From this will come the plans for the monies to be expended for journal advertising, for direct mail, for sampling and for introduction notices to wholesalers, retailers, and hospitals.

In spite of all the careful planning on the part of the pharmaceutical houses, surveys shows that out of seven new products which reach the druggists' shelves, four are not successful, two show some kind of profit, and one makes a real contribution.

Unquestionably, the genesis of a drug—new product development—is a continuing challenge to scientific research.