A Proposal for Multinational Development of New Drugs

Edward D. Frohlich

To provide a closer linkage between the Council for High Blood Pressure Research and Hypertension, Dr. Allyn Mark invited me to initiate a series of commentaries by the council chairman. In this commentary, I suggest new thoughts concerning a very complex, costly, and important area of investigation in the field of hypertension—the development of new pharmacological entities. This discussion may also be applied to other areas of medical care.

Our broad field of hypertension research has been the model for new concepts in clinical and fundamental research: it has introduced formal training in clinical pharmacology; it championed clinical epidemiology and elucidated the concept of the risk factors of disease; it introduced and established the feasibility of multicenter clinical and pharmacological trials; it introduced the role of the heart as more than that of hemodynamic adaptation; it provided to cardiovascular medicine the fundamental molecular mechanisms of hormonal systems for specific therapy; and now it advances the concepts of local humoral autocrine/paracrine and intracrine control of cardiovascular function. Our investigators have made seminal contributions to the area of pharmacology and drug development that have been responsible for a major downturn in cardiovascular morbidity and mortality. Over the past 43 years, our council has maintained its position as the premier investigative organization that has advanced innovative concepts concerning hypertension research through its varied activities within the American Heart Association as well as in liaison with other scientific bodies.

For over 4 decades, the development and release of new antihypertensive agents have paralleled changes in the regulations by the Food and Drug Administration. During these years, the evaluation and approval of new agents have demanded increasingly more complex means to demonstrate their safety and efficacy. This is because our knowledge of diseases and their underlying mechanisms has become more complex, and the questions about chronic illness similarly have become increasingly more complicated. Each of these considerations has contributed to the increased time and costs related to new drug development over and above the costs relative to new technology and, of course, inflation.

In an effort to respond to the narrowing commercial life of these compounds, Congress recently extended the patent life by approximately 3 years. This action, important as it is for industry, provided little incentive to reduce the cost of these agents for our patients. Although 3 years added a significant time to the commercial life of the drug, and hence in amortizing costs, it did not offset other major costs of drug development: the increasingly more costly fundamental and clinical investigations, the need for complicated physiological and pharmacological studies, and the increasingly more sophisticated resources necessary for multicenter clinical trials. These costly expenditures are compounded by the necessity to duplicate these same efforts in every country that has its own regulatory agency for drug approval and monitoring.

Most of the antihypertensive agents are developed by large multinational pharmaceutical firms with independent corporations located in the major countries of the western world. These new pharmacological entities are usually developed in their independent corporate research laboratories. They are then studied in each country in which the parent company desires to open the clinical market. Depending on the number of countries in which these pharmaceutical companies wish to market their compound, there is a proportionate increase in the number of fundamental, clinical, and multicenter studies. The standards vary among nations with respect to the drug approval process; some nations accept certain previous studies and some nations have more or less rigid regulations. Much of the expenditure of time, money, and effort is highly duplicative. A not insignificant, and questionably ethical, part of this duplication is the unnecessary employment of human subjects required by replicated studies in each country.

Address for correspondence: Edward D. Frohlich, MD, Vice President for Academic Affairs, Alton Ochsner Medical Foundation, 1516 Jefferson Highway, New Orleans, LA 70121.
Nevertheless, as communication among individual scientists and nations increases, there will be greater opportunities afforded to bring our mutual needs together. We are all preoccupied with the need to develop new means for cost-effectiveness, cost containment, and curtailment of highly costly duplication of effort and human risk in health-care delivery. Means are available to answer these concerns in new drug development. For example, we hear that it is improper and too costly to develop new pharmacological agents with greater specificity for hypertensive disease, greater safety, and fewer side effects for patients: they will be more costly than presently available medications, and we already have inexpensive and effective antihypertensive drugs. How intellectually wrong, medically unacceptable, and unrealistic for modern medical science.

Proposal: At this time of multinational agreements for trade, finance, and other purposes, I suggest that it is feasible for nations to join forces in the clinical evaluation of new drugs. The model would involve multinational companies and nations with regulatory agencies that have similar commitments. It is possible for the Ministers of Health of our nation and other nations to bring together regulatory officials and industrial representatives to initiate a feasibility and demonstration trial. Questions may arise as to the storage of data for ready review by all concerned, but in these days of orbiting satellites, instant data retrieval should not be a major problem. Another question relates to multinational review of the scientific and medical data for the approval process. This, too, should pose no problem; scientific organizations such as our council (with members from many other nations) have a long experience of working together in peer review of a variety of scientific activities. In the final analysis, as certain companies assume these responsibilities, of necessity others will follow. These advances will eventually force the use of a common international standard for the development of increasingly more sophisticated therapeutic agents of the future.

In conclusion, the time is right for enlightened leadership of academia, industry, and government to join in an innovative program of drug development. With a generation of experience, we should initiate plans for a multinational program to develop and test new agents. Let it begin with the antihypertensive drugs. The time is appropriate with the present development of the European Economic Community and its relation with the United States to consider this proposal. The Council for High Blood Pressure Research of the American Heart Association has a broad international membership of expertise and is without conflict of interest. To this end, our council stands ready to offer its scientific expertise.

(Hypertension 1989; 14: 458–459)
Just what heart researchers have been hoping for.

THE AMERICAN HEART ASSOCIATION PHARMACEUTICAL ROUNDTABLE

The member companies of the AHA Pharmaceutical Roundtable offer new hope for the future of vital cardiovascular research. With their unprecedented commitment of time, expertise and funding, these pharmaceutical leaders have the opportunity to exchange ideas and information relevant to heart research, while also supporting promising projects. Altogether, cardiovascular researchers couldn't hope for a more dedicated circle of friends and supporters.

FOUNDING MEMBERS
Bristol-Myers Company
CIBA-GEIGY Corporation
Genentech, Inc.
Sandoz Pharmaceuticals Corporation
Squibb Corporation
Wyeth-Ayerst Laboratories
Winthrop Pharmaceuticals/Division of Sterling Drug, Inc.

REGULAR MEMBER
Boehringer Ingelheim Pharmaceuticals, Inc.

American Heart Association
A proposal for multinational development of new drugs.
E D Frohlich

*Hypertension*. 1989;14:458-459
doi: 10.1161/01.HYP.14.4.458

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/14/4/458.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Hypertension* is online at:
http://hyper.ahajournals.org/subscriptions/