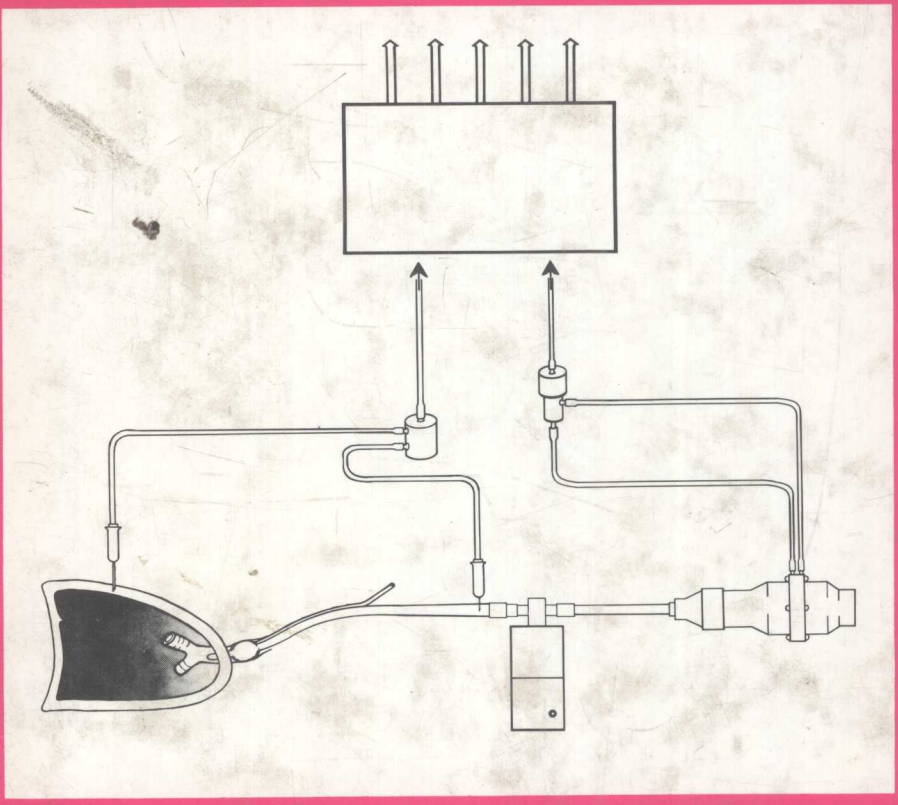
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 5

New Drugs

DISCOVERY AND DEVELOPMENT



edited by Alan A. Rubin

New Drugs

Discovery and Development

edited by

ALAN A. RUBIN

Vice President-Research
Endo Laboratories, Inc.
Garden City, New York

MARCEL DEKKER, INC.

New York • Basel

Library of Congress Cataloging in Publication Data

Rubin, Alan A
New drugs.

(Drugs and the pharmaceutical sciences ; v. 5)
Includes indexes.
1. Pharmaceutical research. 2. Drugs. I. Title.
RS122.R8 615'.1'072 77-16084
ISBN 0-8247-6634-2

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

New Drugs

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PREFACE

The 1972 publication Search for New Drugs (Volume 6, Medicinal Research Series) was authored predominantly by university researchers. Its compilation represented an attempt to communicate to investigators in the field of drug research some of the more promising academic approaches to new drug discovery and evaluation.

The present volume is also concerned with the search for new drugs, but from the vantage point of the industrial researcher. All of the contributors to this volume conduct their research in pharmaceutical company settings. Their requirements for the screening and evaluation of potential drug candidates are basically similar to those of the academician insofar as predictive validity and reliability of test methods are concerned. But the industrial researcher is also accountable for high screening capacity, cost effectiveness and judicious manpower allocation. The appropriate combination of these scientific and economic components forms the basis of successful industrial research.

The nine subjects covered in this volume were selected for their broad appeal and include four on the central nervous system (major and minor tranquilizers, antidepressants, and analgesics), three on the cardiovascular system (antianginals, antiarrhytmics, and antihypertensives) and one each on allergy and arthritis. The authors have presented their personal views of (1) the advantages and shortcomings of current drug evaluation methodology, (2) the profile of an ideal drug, and (3) possible future developments in their respective areas of expertise.

Alan A. Rubin

CONTRIBUTORS

NEETI R. BOHIDAR, Department of Biometrics Research, Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania

JOHN R. CUMMINGS, Department of Pharmacology, Ayerst Research Laboratories, Montreal, Quebec, Canada

BERNARD DUBNICK,* Department of Pharmacology, Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Ann Arbor, Michigan

STEWART J. EHRREICH,† Department of Pharmacology, Schering Corporation, Bloomfield, New Jersey

WILLIAM H. FUNDERBURK, Department of Pharmacology, A. H. Robins Company, Richmond, Virginia

RALPH E. GILES,‡ Department of Pharmacology, Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Ann Arbor, Michigan

FRANCIS R. GRANAT, Department of Biochemistry, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey

DAVID J. HERZIG, Department of Pharmacology, Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Ann Arbor, Michigan

*Present affiliation: Cardiovascular and Central Nervous System Research Section, Lederle Laboratories, Pearl River, New York

†Present affiliation: Division of Cardio-Renal Drug Products, Food and Drug Administration, Rockville, Maryland

‡Present affiliation: Biomedical Research Department, ICI Americas, Inc., Wilmington, Delaware

DAVID N. JOHNSON, Department of Pharmacology, A. H. Robins Company, Richmond, Virginia

ALLAN D. RUDZIK, CNS Research, The Upjohn Company, Kalamazoo, Michigan

JEFFREY K. SAELENS, Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey

DEWEY H. SMITH, JR., Pharmaceuticals Division, E. I. du Pont de Nemours & Company, Inc., Stine Laboratory, Newark, Delaware

JOHN M. STUMP, Pharmaceuticals Division, E. I. du Pont de Nemours & Company, Inc., Stine Laboratory, Newark, Delaware

C. GORDON VAN ARMAN,* Department of Pharmacology, Merck Institute for Therapeutic Research, Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania

VERNON G. VERNIER, Pharmaceuticals Division, E. I. du Pont de Nemours & Company, Inc., Stine Laboratory, Newark, Delaware

*Present affiliation: Department of Biological Research, Wyeth Laboratories, Radnor, Pennsylvania

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Chapter 1

ANTIARTHRITICS

C. Gordon Van Arman and Neeti R. Bohidar

Merck Institute for Therapeutic Research and Biometrics
Merck Sharp and Dohme Research Laboratories
West Point, Pennsylvania

I. INTRODUCTION

The main reason many pharmaceutical companies have had frustrating experiences in the clinical trials of their new drugs is insufficient and inadequate laboratory research.

In this chapter there is a particular philosophy of how to go about choosing a better antiarthritic drug from the abundance of compounds available for testing. Some of the assays described will become outdated within a few years because of the rapid succession of new findings about the arthritic diseases, but the basic principles of how to set up an assay can hardly change. It is not the purpose of this chapter to compare in detail the many new drug candidates that are either now in clinical trial or proposed for it by pharmaceutical companies, because most of these drugs will prove to be of temporary interest only. Nor is it appropriate here to enter into a discussion of the most fundamental aspects of arthritis, with comparisons of various theories. Some of the theories now rampant are not worth the trouble to consider; some, on the other hand, are at least partly correct, but whether or not they are makes little or no practical difference at this time. The gap between our present concepts of arthritis and the ultimate reality is surely so vast that the current theories do not help the research worker whose job is merely to find a better drug than we currently have.

In the laboratory phase of the search for any kind of drug, the first requirements for an assay are validity and reliability, in that order.

A. Validity

Validity for a human disease requires that drugs proved effective clinically should be effective in the laboratory model, that drugs effective in the model should be effective clinically, that drugs not effective clinically should not be effective in the model, and that drugs inactive in the laboratory should not be active in the clinic.[1] These requirements may seem clear and simple, but for inflammatory diseases they cannot be met at present. The model need not ostensibly resemble the clinical disease; generally, models have some points of similarity with a clinical disease, but many dissimilarities. There is no single test in vivo or in vitro that correlates well with clinical experience in the arthritic diseases over a number of different chemical structures.

With regard to chemical structure of drugs, we are forced to rely on assays that have apparent validity for some kinds of structure but not for others, even with respect to a single disease entity. The various arthritic diseases are different from one another not only in their clinical

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[1]The term accuracy as customarily used for chemical assays means the same as validity here.

manifestations but also in their responses to drugs. It is important, therefore, to consider carefully the details of a particular disease, for example rheumatoid arthritis, or another, such as ankylosing spondylitis, when one is attempting either to set up a laboratory model or to choose one from the literature.

Validity depends also on which species, sometimes even which strain within a species, of animal is tested, and on the details of the particular test being used with that strain. We conclude that one cannot entirely trust any single laboratory assay alone, nor even several, to forecast quantitative results in the arthritis clinic. The assays described herein have nevertheless shown good correlation thus far with clinical results in general, for several of the most common arthritic diseases.

B. Reliability

Reliability is much easier to measure. Here we mean merely how reproducible a given assay method or treatment is in the laboratory.[2] If an assay has high variability, it also has low reliability. Once the appropriate data are in hand, sophisticated means of measuring reliability can be used with the calculators now available, and are rapid and simple. For any new drug, an investigator no longer has much excuse for failing to show the dose-response line, the slope of the dose-response line, the confidence limits at certain doses, the potency with respect to a standard, and the confidence limits of this relative potency. Certain essential terms are defined in the section on statistical concepts. When a routine assay, especially a new one, is running continuously, it is advisable, or even essential, to submit one or two standard drugs at irregular intervals, in such a way that the identity of the drug is not known to any person in direct contact with the assay. With suitable explanations given well beforehand, there will be no reason for the laboratory workers to feel that they are being examined; it is the method itself on trial, and good laboratory workers welcome such trials as proof not only of the reliability of the method but also of their skill.

C. Sensitivity

Sensitivity is a concept that is different from both validity and reliability. The degree of response to the total amount of standard drug defines the sensitivity. For example, the dog's knee-joint assay described herein is quite sensitive on the basis of milligrams per kilogram of body weight, but because a dog weighs about 10 kg, and several dogs are needed to establish an ED50, the total amount of indomethacin required is several dozen

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[2]The term precision as customarily used for chemical assays means the same as reliability here.

milligrams, or a few grams of aspirin. By our present definition based on total amount, this assay must therefore be considered not sensitive. If we use indomethacin as a standard for the five other assays described herein, the antipyretic assay (yeast fever) is the most sensitive, because less compound is required (about 2 mg) for 50% inhibition in a group of rats. There are many other assays sometimes called antiinflammatory that are much more sensitive: as an example, the inhibition of prostaglandin synthetase in vitro, for which indomethacin has a half-inhibitory concentration of 0.09 μg/ml, enough to perform the assay [1]. In screening methods, it is economical to have good sensitivity, but in fact it is usually not necessary. The main criterion should be validity, which at present one cannot guarantee in any assay. The one characteristic an assay must have is a known reliability.

D. Correlations among Assays

Every biological assay method responds better to certain drugs than to others. Assay methods may be identical or different in respect to the rank order that they assign within a common list of several standard drugs. For example, carrageenan-induced foot edema in the rat gives a rank order for five drugs identical with that found by urate-induced knee-joint inflammation in the dog [2]. In contrast, meclofenamic acid is more active than indomethacin against ultraviolet-induced skin erythema and yeast fever but less active against cotton pellet granuloma [3]. In the mouse ear assay, certain compounds such as ethacrynic acid are more active than indomethacin, but are practically devoid of any effects against carrageenan foot edema in the rat. Any assay in vivo depends on a delicate and complicated network of cellular, humoral, neural, biochemical, and other phenomena. It is prudent, therefore, to withhold conclusions about whether any assay depends on exactly the same phenomena as some other. Among the six assays described in this chapter, there have occurred some astonishing examples of drugs active in one but not in another.

E. Tests In Vitro Compared with Tests In Vivo

Many and various are the tests in vitro used as clues to drugs for the arthritic diseases. There are methods using complement fixation, red-cell stabilization, platelet aggregation, the Boyden chamber for cellular migration, uncoupling of oxidative phosphorylation, the Mizushima method for protein denaturation, von Kaulla's fibrinolysis, acceleration of sulfhydryl exchange, displacement of protein-bound uric acid, and many others. In general, tests in vitro may be done more quickly, cheaply, and easily than those in vivo. Swingle [4] gives references for these and other in vitro

methods, and correctly remarks that if one is going to collect irrelevant data, he may just as well do it rapidly. Tests in vitro are more likely to be valid in a series of compounds within which a prototype has been unequivocally demonstrated by other means. Furthermore, actions found in vitro may shed light upon the fundamental mechanisms relevant in vivo. Great skepticism must be used, however, and should be relented only when proof has been developed in vivo.

The foregoing comments have merely exemplified certain considerations that one should have clearly in mind before choosing which assays to use in the development of a drug. There are many other factors in the choice, and these will vary from one laboratory to another. The assays to be described here are shown merely as examples, and have been selected because they have wide applicability, and use normal laboratory species and relatively simple equipment. There are many variations of these assays presented in the literature, and there are many other methods greatly different, with particular, good reasons for their use. At present it is still necessary to have a number of assays for the selection of a drug candidate, and some of those presented here would appear essential. However, no laboratory can hope to compete in today's market without the ability to handle the statistical matters discussed in the following section.

II. STATISTICAL CONCEPTS

If the reader is not acquainted with the concepts used here, he can find better expositions in the first five chapters of the book by Finney [5]. A full understanding of the details would best be achieved by consulting a trained statistician. Here we shall merely outline the simpler tools of the pharmacologist's trade used in assay work.

The validity of laboratory assays for predicting clinical results could perhaps be quantitatively determined, but in actual practice hardly ever will be, because of the risk and cost of clinical trials. Instead, under the best conditions, the pharmacologist will carefully and laboriously select only a very few compounds by using at least five or six assay methods. These compounds will be the best he can find among perhaps thousands. After toxicology studies, still fewer of these compounds will survive to enter clinical trials. Under such conditions, certain laboratories have had a very high degree of clinical success. There have been too few published failures to allow evaluation of the comparative validity of the methods used to select these failures. At present there seems no way, therefore, in which one could measure statistically the clinical validity of any given antiinflammatory laboratory assay.

Instead, we shall describe the reliability and related measurements for six laboratory assays: