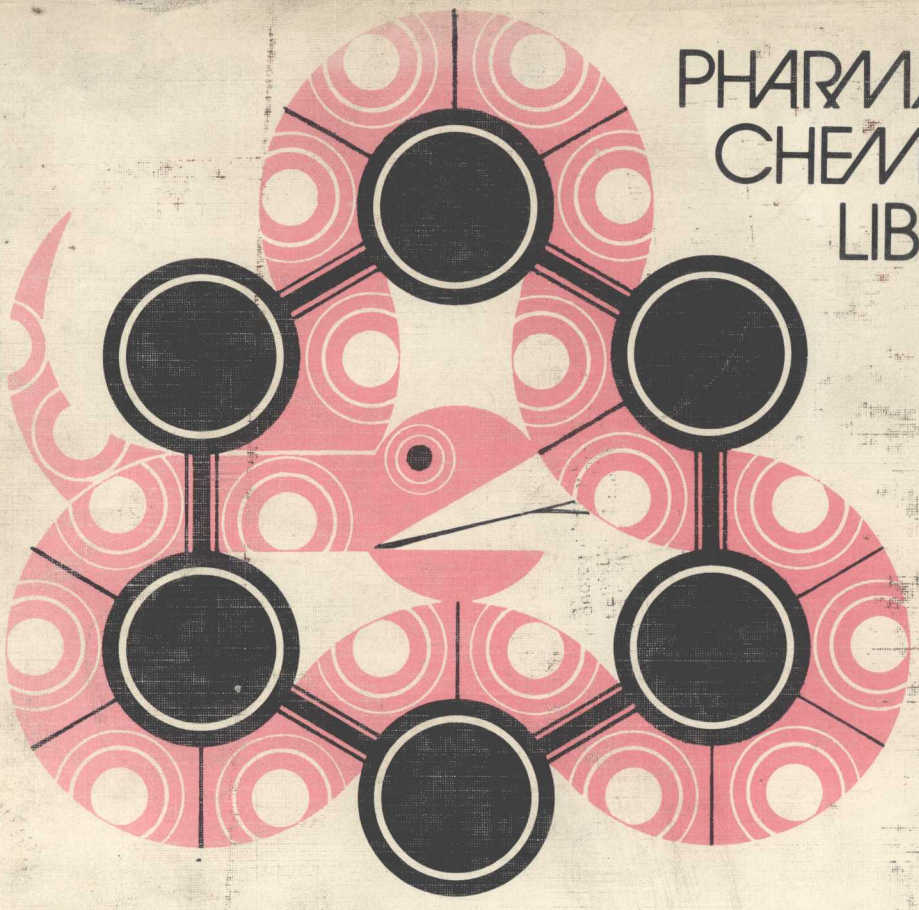

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STRATEGY IN DRUG RESEARCH

EDITED BY

J. A. KEVERLING BUISMAN

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Editors: W.Th. Nauta and R.F. Rekker

Volume 4

STRATEGY IN DRUG RESEARCH

Proceedings of the second IUPAC-IUPHAR Symposium held in Noordwijkerhout (The Netherlands), August 25–28, 1981

Edited by

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c/o Duphar BV, Weesp, The Netherlands

ELSEVIER SCIENTIFIC PUBLISHING COMPANY
Amsterdam – Oxford – New York 1982

ELSEVIER SCIENTIFIC PUBLISHING COMPANY
Molenwerf 1
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

Distributors for the United States and Canada:

ELSEVIER SCIENCE PUBLISHING COMPANY INC.
52, Vanderbilt Avenue
New York, NY 10017

Cover design by Dr. C. van der Stelt

Library of Congress Cataloging in Publication Data
Main entry under title:

Strategy in drug research.

(Pharmacochemistry library ; v. 4)
Organized by the Medicinal Chemistry Division of the Royal Netherlands Chemical Society under the sponsorship of the International Union of Pure and Applied Chemistry, Commission on Medicinal Chemistry, and others.
Includes index.
1. Pharmaceutical research--Congresses. 2. Structure -activity relationship (Pharmacology) I. Keverling Buisman, J. A. (Jan Anne) II. International Union of Pure and Applied Chemistry. Commission on Medicinal Chemistry. III. International Union of Pharmacology. IV. Series. [DNLM: 1. Pharmacology--Congresses. 2. Research--Methods--Congresses. W1 PH272L v.4 / QV 20 5 I92 1981s]
RS122.S77 615'.1'072 81-19476
ISBN 0-444-42053-3 (v. 4) AACR2

ISBN 0-444-42053-3 (Vol. 4)
ISBN 0-444-41564-5 (Series)

Printed in The Netherlands

Preface

The second Noordwijkerhout IUPAC-IUPHAR Symposium "Strategy in Drug Research" was organized by the Medicinal Chemistry Division of the Royal Netherlands Chemical Society under the sponsorship of the International Union of Pure and Applied Chemistry (IUPAC) (Commission on Medicinal Chemistry), the International Union of Pharmacology (IUPHAR), the European Federation for Medicinal Chemistry (EFMC), the Fédération Internationale Pharmaceutique (FIP) and the Royal Netherlands Association for the Advancement of Pharmacy (KNMP).

As for the first symposium in this new series it was the aim of the organizers of the meeting to intensify the dialogue between the two major groups of scientists active in the field of medicinal chemistry, the chemists and the pharmacologists.

The symposium was held during the period of August 25-28, 1981 in Congress Centre Leeuwenhorst in Noordwijkerhout, the Netherlands; 275 participants from 25 countries came to Noordwijkerhout.

The topic "Strategy in Drug Research" was chosen because such strategies can be based upon both chemical and biological findings. Within the subjects : Receptor Studies and Research Strategy; Lessons from Enzyme Chemistry; Toxicological Parameters as a Lead; Pharmacokinetics as a Starting Point; Biological Measurements, Methods and Data Handling; 14 lectures had been chosen as examples for the respective fields which gave together with $\pm$ 45 posters a good overview of the actual state of affairs. Interesting results of the designing of 'better' molecules, being the central aspect in the broad field of medicinal chemistry, on basis of receptor studies, theoretical considerations in enzyme mechanisms, toxicological and pharmacokinetic studies as well as on molecular pharmacological investigations were presented. Much emphasis was put on the need for reliable biological parameters in all studies aiming at the design of new molecules.

In the opening lecture special attention was called to drug research strategy for tropical diseases. According to professor Ariëns, in his concluding remarks the pharmacologists and the chemists meet at the receptor level - the receptor being defined broadly -; they should therefore also discuss at this meetingpoint, he said. It is clear that in modern medicinal chemistry, results can only be expected when this discussion takes place in a language understandable for all participants to it. In this respect the symposium "Strategy in Drug Research" contributed in a very positive way.

The proceedings include the full texts of all lectures presented, as well of the four presented during the satellite symposium "The value of predictions in Structure-Activity Analysis", during which symposium the predictive merits of QSAR studies have been amplified.

H. Timmerman
Chairman Organizing Committee

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J.A. Keverling Buisman (Editor), *Strategy in Drug Research*

DRUGS FOR DEVELOPING COUNTRIES

ADETOKUNBO O. LUCAS, M.D., Director
UNDP/WORLD BANK/WHO Special Programme for
Research and Training in Tropical Diseases

ABSTRACT

Tropical parasitic infections remain major public health problems in many developing countries. Efforts to control some of these diseases have been hampered by a number of factors both medical and managerial. One specific constraint is the lack of drugs which can be suitably applied in largescale control programmes in the endemic countries. Such drugs should be highly effective, safe, and simple to apply in the field.

This problem has been tackled by the World Health Organization in collaboration with scientists and institutions all over the world, including the pharmaceutical industry. A Special Programme for Research and Training in Tropical Diseases, co-sponsored by the United Nations Development Programme (UNDP), the World Bank, and the World Health Organization (WHO), is seeking new and improved tools for the control of six major tropical diseases - malaria, schistosomiasis, filariasis (including onchocerciasis), trypanosomiasis (both African and the American form called Chagas' disease), leishmaniasis and leprosy. The scientific programme is planned and executed by multidisciplinary groups of scientists. The research programme ranges from metabolic studies of the parasite and the screening of candidate compounds, to clinical evaluation and field trials. Existing drugs are being re-examined and innovative drug delivery systems are being sought.

The issue of drugs for developing countries resolves itself into two separate problems. The first concerns the availability to the people of developing countries, especially to the most needy, of those drugs which are already in general use. This issue is being tackled by the Essential Drug Programme of the World Health Organization which, in collaboration with governments, is examining the various problems associated with the manufacture, purchase and distribution of a basic list of drugs required by the health services of each country.

The second issue concerns the need for new and improved drugs required to deal with diseases which are common in, and mostly peculiar to, the developing countries in the tropics. In dealing with this question, it is important to understand the basis for the geographical distribution of these diseases which are highly endemic in the tropics. Some diseases acquired this distribution in historical times, being cosmopolitan with no special predilection for the tropics until relatively recently. Through the inevitable pressures of development, and in particular, the improvement in environmental sanitation and personal hygiene, these diseases have retreated from the developed countries and are now found mostly in developing countries. Thus epidemics of cholera, for example, no longer occur in developed countries, while they remain a persistent menace in developing countries. The distribution of cholera is now mainly tropical, but its global distribution in earlier times shows that the tropical environment was not a prerequisite for its occurrence. Many such examples can be cited - plague, tuberculosis, and so on. These diseases can be seen as being tropical in the historical perspective.

There is another group of diseases for which the tropical climate plays a significant role in their occurrence and distribution. Some, of these, like African trypanosomiasis, onchocerciasis and other filariases, are clearly diseases of warm climates with no possibility of sustained transmission in colder climates. In other cases, such as malaria, minimal transmission did occur in some countries with temperate climate, but because of the biological requirements of the parasite and its vector, the infection had a tenuous hold in these areas. The intensity of transmission graduates from this low level in cold, hypoendemic areas to the wet tropics where the disease is hyperendemic to holoendemic. In parts of tropical Africa, for example, the transmission of malaria is intense,

occurring at a rate which is several thousand fold the critical level required to sustain transmission.

In this paper, I will specifically examine the second question - the search for new and improved drugs for the control of tropical parasitic and infectious diseases.

What is the role of drugs in the control of these diseases? In the treatment of infected persons, drugs may prove life-saving in severe cases or, in less seriously ill patients, they may relieve symptoms, arrest and reverse pathological processes. In the public health context, drugs may have an impact on transmission by reducing or eliminating the reservoir of infection in man or, when used prophylactically, by protection of the susceptible persons in the population. The limitations of drugs in the control of these diseases are well recognized; they have been emphasized almost to the point of exaggerating the limitations and underestimating the value of the rational use of drugs in the control of tropical and parasitic diseases. What must be emphasized is that drugs must be used in association with other measures - environmental sanitation and modification of human behaviour - to enhance the impact of chemotherapy and perhaps render the gains more permanent. Without doubt, drugs are useful, even essential, elements in the armamentarium of weapons against tropical diseases.

In response to the call for intensification of research and development in this area, there has been much debate and discussion, and the authorities in this field are apparently divided into two dissenting camps. Some point to the wide variety of anti-parasitic and other anti-infective agents which have been introduced into the pharmacoepia in recent years: piperazine, tetramisole and mebendazole for the treatment of intestinal helminths; niridazole, metrifonate, oxamniquine, and praziquantel for schistosomiasis, and so on.

Whilst welcoming the discovery and duly acknowledging the value of these new drugs, the other camp draws attention to areas of need. For some of the tropical diseases there is a clear need for safe and effective remedies; the available drugs are judged inadequate to meet the needs of programmes for the control of these diseases in endemic areas of the tropics. Authorities differ, not so much on fundamental issues, but rather on emphasis. The first group favours a pragmatic approach, emphasizing the need to apply vigorously the available drugs in

association with other measures in the control of these diseases. The second group, no less practical, draws attention to the limitations of some of these drugs, especially in situations where such limitations constitute a significant constraint on control programmes. In such cases, there is a clear indication for research aimed at the development of new drugs or new formulations of existing ones.

The specifications of the ideal drugs for controlling these diseases are dictated by a number of important features of the diseases and the environment in which they occur. Often a high proportion of the community is affected or at risk and therefore control measures must be suitable for large-scale application in the field rather than in hospitals. In view of the shortage of highly trained personnel in most of the affected areas, the ideal drug would be safe enough to permit its administration without supervision by highly trained personnel. It should be effective in producing clinical improvement of disease in the affected individual; and in the context of control, it should also be capable of making a significant impact on transmission. Since these diseases most commonly affect the poor rather than the affluent, the ideal drug must be reasonably cheap so that the governments and the people in most need of it can afford it. In summary, the ideal drug for dealing with each of these tropical diseases should be highly effective, safe, simple to apply and cheap. These specifications are highly demanding, but should be retained as the ultimate goal, and as the yardstick for monitoring progress.

One major effort aimed at intensifying the search for such drugs was initiated by the World Health Organization and co-sponsored by the United Nations Development Programme (UNDP) and the World Bank.

The Special Programme has two interdependent objectives.

1) Development of new and improved tools to control tropical diseases - to develop new preventive, diagnostic, therapeutic and vector control methods specifically suited to prevent, treat and control selected tropical diseases in the countries most affected by them. The new methods must be susceptible to implementation:

- at a cost that can be borne by developing countries;
- requiring minimal skills or specialized supervision; and

- in a manner which allows their integration into the health services, especially the primary health care systems of developing countries.

2) The second objective is the strengthening of biomedical research capability in the countries most affected by tropical diseases, through training in biomedical sciences and various forms of institutional support. Biomedical research capability in tropical countries must be strengthened because major activities in the specification, development and testing of new tools must occur in the tropical countries where the diseases are endemic, to ensure that these tools are effective in controlling the target diseases in these countries.

The six diseases initially included in the scope of the Special Programme are: malaria, schistosomiasis, filariasis, trypanosomiasis (both African sleeping sickness and the American form called Chagas' disease), leishmaniasis and leprosy.

Criteria for selection of the diseases included:

- impact of the disease as a public health problem;
- the absence of satisfactory methods for control of the disease in prevailing circumstances of the tropical countries;
- the presence of research opportunities leading to improved control methods.

The activities of the Programme are directed towards development of any practical tool needed to solve the problems of the selected diseases. Development is focused on drugs, vaccines, methods for biological control of vectors, and diagnostic tests which are simple to perform.

The research and development component of the Programme is therefore concentrated on:

- chemotherapy and chemoprophylaxis,
- immunotherapy and immunoprophylaxis,
- biological control of vectors,
- diagnostic aspects, especially immunodiagnosis

The research is focused upon specific objectives and involves investigators from all relevant areas of the biomedical, physical and social sciences.

Since several major problems requiring research apply to most or all of the six diseases, in addition to disease components, the Programme includes components on epidemiology and operational research, vector control, socio-economic and biomedical research.

Epidemiology and operational research serve to provide the basis for the specifications of the required tools and to assess their effectiveness. The research therefore ranges from the most sophisticated laboratory investigations to the use of simple diagnostic tests in the field. The research and development interlinks with related sectors such as nutrition, economics and education.

Each component is developed under the guidance and with the participation of multidisciplinary groups of scientists organized into a number of Scientific Working Groups, each with clearly defined research goals.

These Scientific Working Groups (SWGs) are the modus operandi of the Programme's research and development activities. An SWG comprises all the scientists who plan and/or carry out research on a specific aspect of the Programme. Members of the Group define the research objectives, devise a strategic plan to achieve them, carry out the research according to the plan, and review the plan and the research as the work progresses. The Steering Committee of a Scientific Working Group manages and guides the Group's activities towards the objectives.

Individual Scientific Working Groups are formed according to needs identified by the Programme's Scientific and Technical Advisory Committee (STAC).

The SWG mechanism for research implies clear goals and precise steps to achieve them, assembled into a time-related strategic plan of action. To develop such a plan and operate an SWG, the scientists must describe:

(1) the detailed objective(s) of the SWG, e.g. the specifications for a malaria vaccine applicable and effective in rural areas;

(2) the current state of the art in relation to the objective(s);

(3) the problems which remain to be solved, i.e. the gaps in knowledge;

(4) the possible research approaches and disciplines which may solve these problems, as well as the feasibility, sequence and cost of the activities, or projects, in each line of research;

(5) a clear strategic plan including each research approach and its line(s) of research, leading towards the final objectives.

One of the major objectives of the Special Programme is to develop and apply appropriate and effective tools for control of the tropical diseases in the affected countries. This goal predicates that the research and development operations cover the entire spectrum of activities required to fill the gaps in

knowledge between the current stage of development of these tools and their actual application in the field. These activities will vary, for example, from research into the molecular structure and functions of parasite cell membranes as an early step in vaccine development, to clinical and operational research involving the application of a new or modified chemotherapeutic agent in a rural tropical setting.

Experience over the past four years of the operation of the Programme has confirmed the value of the SWG mechanism. The SWGs involve the participation of scientists from a wide variety of disciplines including:

1. Immunology
2. Biochemstry
3. Molecular Biology
4. Genetics
5. Pharmacology
6. Epidemiology
7. Behavioural Sciences
8. Vector Ecology

Together with experts in parasitology, tropical medicine and tropical public health, these scientists plan, implement and evaluate the scientific programme. For some of the scientists, this activity represents their first involvement with tropical parasitic diseases. They bring to bear on these age-old problems fresh minds, new perspectives and innovative approaches to their solution.

The chemotherapy section of the working group on each disease is using the same basic strategy: re-examination of the existing drugs, with research aimed at improving their performance in control programmes, and a search for new drugs.

There is reason to hope that the usefulness of the existing drugs can be enhanced by suitable modifications of formulations and dosage. One obvious improvement would be the production of long-acting formulations which would make single-dose applications feasible. Another area of improvement would be revision of dosages to optimize efficacy and minimize toxicity. For some of these drugs, the dosage schedules had been determined by trial and error without the guidance through pharmaco-kinetic studies. Such studies are now being undertaken, and it is hoped that these would provide useful clues for improving the performance of the existing drugs.

The development of new drugs is being tackled using the traditional approach of screening compounds that are identified on the basis of various leads and

taking the promising agents through the standard phased testing in man. In addition, aspects of the biology of the parasite are being studied in the hope of identifying metabolic pathways which have features peculiar to the parasite. Such metabolic quirks are possible targets for custom-made chemotherapeutic approaches. The possibility of obtaining more precise targetting of drugs is also being explored by the use of liposomes, lysosomotropic agents and antibody-drug complexes

Some concrete examples will illustrate the approaches that are being made.

Malaria

The emergence of strains of Plasmodium falciparum which are resistant to 4-aminoquinolines, and some other drugs in common use, is a most challenging problem. In order to define the dimensions and the dynamics of the problem, the programme has sponsored projects on the detection and monitoring of drug resistance. Kits for testing the sensitivity of P. falciparum in vitro are being supplied to scientists and institutions in endemic areas. In vivo tests are also being conducted parallel with the in vitro assessment. Alternative drug regimes are being tested in areas where the parasite is proving resistant to standard treatment schemes. Studies aimed at the elucidation of the mechanisms of the action of chloroquine suggest that selective binding of the drug to products of haemoglobin digestion may be an important factor in its schizonticidal activity. It has been suggested that the process of selective binding differs in the sensitive strains as compared with those resistant to chloroquine.

Mefloquine, a new drug which was discovered by the Walter Reed Army Institute of Research (WRAIR) is in process of development in collaboration with industry. Phases I and II clinical trials have been completed and more extensive supervised field trials are now planned for the near future.

The Scientific Working Group on the Chemotherapy of Malaria is actively pursuing other approaches in the search for better anti-malarial drugs. In collaboration with Chinese scientists, the group has promoted research on Qing Hao Su, a traditional remedy derived from the plant Artemesia annua. The active principle of this plant is a novel compound in anti-malarial chemotherapy. Chinese scientists have tested the parent compound and a number of chemical derivatives have shown to be more potent in their anti-malarial action.

Anti-malarial drugs with long-lasting action could greatly simplify the logistics of drug distribution in mass campaigns. The Group are approaching this question from two main directions. Using the existing technology for producing longacting formulations of drugs, they have been investigating this approach using existing anti-malarial drugs. For example, more effective and less toxic formulations of primaquine are being developed by covalently linking the drug to the hepatotropic carrier, asialofetuin or by using some of its aminoacyl derivatives. In addition, the Group funded research which led to the design of a biological screen specifically designed to identify compounds which have long-acting anti-malarial action.

Metabolic studies on Plasmodium falciparum have been greatly facilitated by the landmark discovery by Dr. William Trager of a method for the continuous in vitro culture of the parasite. Intensive effort is now being applied in the study of the energy metabolism of the parasite, its lipid metabolism with particular reference to its membranes, its nitrogen metabolism in relation to the digestion of host haemoglobin and so on. In all these studies, there is a search for metabolic pathways and requirements, which differ significantly from those of the mammalian host, as possible targets for drug action.

Filariasis

Of the various forms of filariasis, river blindness, the disease caused by infection with Onchocerca volvulus, has the most serious effect on the population. Furthermore, the existing drugs for the treatment of this infection are inadequate. The highest priority has been accorded to the development of a new drug, especially one which is capable of killing the adult worms of Onchocerca volvulus in man. The only macrofilaricide in use against this infection is suramin - a drug which tends to provoke dangerous side effects; furthermore, it has to be administered intravenously over a six-week period.

Whilst the search for a new drug continues, the Group are concerned about improving the use of existing filaricides. They are anxious to determine the safest and the most practical schedules for the immediate treatment of patients who are at risk of blindness from ocular onchocerciasis. They are looking for methods of reducing the damage resulting from the inflammatory response to the dying worms.

The Onchocerciasis Control Programme (OCP) has carried out field trials which indicated that a smaller dose than is normally prescribed remains effective, but is better tolerated than the standard course. Pharmacological studies of suramin are being carried out so as to further refine its use and to provide leads for the development of new drugs related to the parent compound. Similar studies are being done on diethylcarbamazine (DEC); the drug is microfilaricidal in this infection, i.e. it has no significant effect on the adult worms. Furthermore, it provokes unpleasant side effects. Evidence has been produced suggesting that the excretion of DEC is significantly affected by the pH of the urine. Further study of this phenomenon may guide the use of the drug in future.

With regard to the search for a new macrofilaricidal drug, the activities of a network of screening laboratories is being coordinated by the Programme. The biological screens extend from small animal models which serve as the primary and secondary screens, to the cattle screen (O.gibsoni, O. gutturosa) which so far is the most valid screen for predicting macrofilaricidal activity in man. This screen has indicated that mebendazole in combination with l-tetramisole has embryostatic action, and these findings are now being confirmed in man. Meanwhile, the search continues for truly macrofilaricidal compounds.

The other diseases within the Programme are being tackled in a similar manner. Steps are being taken in each case to re-examine the currently available drugs and seeks ways of optimizing their use in the field. New drug development is being undertaken in collaboration with other agencies, including the pharmaceutical industry. In those cases where industry has undertaken initiatives to develop new drugs, the Programme has collaborated by assisting in the clinical and field evaluation of the new compounds. Where there is little evidence of such interest, the Programme has taken the initiative to promote relevant activity. In these endeavours, the Programme also seeks the collaboration of the pharmaceutical sector.