

Edited by
J. D. Williams and A. M. Geddes

CHEMOTHERAPY

Volume 6

**Parasites, Fungi,
and Viruses**



CHEMOTHERAPY

Volume 6 Parasites, Fungi, and Viruses

Edited by

J.D. Williams

*The London Hospital Medical College
London, U.K.*

and

A.M. Geddes

*East Birmingham Hospital
Birmingham, U.K.*

Plenum Press · New York and London

Library of Congress Cataloging in Publication Data

International Congress of Chemotherapy, 9th, London, 1975.
Parasites, fungi, and viruses.

(Chemotherapy; v. 6)

Includes index.

1. Chemotherapy—Congresses. 2. Anti-infective agents—Congresses. I. Williams, John David, M.D. II. Geddes, Alexander McIntosh. III. Title. IV. Series.
RM260.2.C45 vol. 6 615'.58s [616.9'6'061] 76-1932
ISBN 0-306-38226-1

Proceedings of the Ninth International Congress of Chemotherapy
held in London, July, 1975 will be published in eight volumes,
of which this is volume six.

©1976 Plenum Press, New York
A Division of Plenum Publishing Corporation
227 West 17th Street, New York, N.Y. 10011

United Kingdom edition published by Plenum Press, London
A Division of Plenum Publishing Company, Ltd.
Davis House (4th Floor), 8 Scrubs Lane, Harlesden, London, MW10 6SE, England

All rights reserved

No part of this book may be reproduced, stored in a retrieval system, or transmitted,
in any form or by any means, electronic, mechanical, photocopying, microfilming,
recording, or otherwise, without written permission from the Publisher

Printed in the United States of America

CHEMOTHERAPY

Proceedings of the
9th International Congress of Chemotherapy
held in London, July, 1975

Editorial Committee

K. Hellmann, *Chairman* (Anticancer)
Imperial Cancer Research Fund, London.

A. M. Geddes (Antimicrobial)
East Birmingham Hospital.

J. D. Williams (Antimicrobial)
The London Hospital Medical College.

Congress Organising Committee

W. Brumfitt
K. Hellmann
K.D. Bagshawe
H. Smith
E.J. Stokes
F. Wrigley
J.D. Williams

I. Phillips
M.R.W. Brown
D.G. James
C. Stuart-Harris
R.G. Jacomb
D.T.D. Hughes
T. Connors

H.P. Lambert
P. Turner
A.M. Geddes
D. Armitage
D. Crowther
D.S. Reeves
R.E.O. Williams

International Society of Chemotherapy Executive - to July 1975

P. Malek
C. Grassi
G.H. Werner

H.P. Kuemmerle
Z. Modr
K.H. Spitzzy
P. Rentchnick

H. Ericsson
G.M. Savage
H. Umezawa

Preface

The International Society of Chemotherapy meets every two years to review progress in chemotherapy of infections and of malignant disease. Each meeting gets larger to encompass the extension of chemotherapy into new areas. In some instances, expansion has been rapid, for example in cephalosporins, penicillins and combination chemotherapy of cancer - in others slow, as in the field of parasitology. New problems of resistance and untoward effects arise; reduction of host toxicity without loss of antitumour activity by new substances occupies wide attention. The improved results with cancer chemotherapy, especially in leukaemias, are leading to a greater prevalence of severe infection in patients so treated, pharmacokinetics of drugs in normal and diseased subjects is receiving increasing attention along with related problems of bioavailability and interactions between drugs. Meanwhile the attack on some of the major bacterial infections, such as gonorrhoea and tuberculosis, which were among the first infections to feel the impact of chemotherapy, still continue to be major world problems and are now under attack with new agents and new methods.

From this wide field and the 1,000 papers read at the Congress we have produced Proceedings which reflect the variety and vigour of research in this important field of medicine. It was not possible to include all of the papers presented at the Congress but we have attempted to include most aspects of current progress in chemotherapy.

We thank the authors of these communications for their cooperation in enabling the Proceedings to be available at the earliest possible date. The method of preparation does not allow for uniformity of typefaces and presentation of the material and we hope that the blemishes of language and typographical errors do not detract from the understanding of the reader and the importance of the Proceedings.

K. HELLMANN, Imperial Cancer Research Fund
A. M. GEDDES, East Birmingham Hospital
J. D. WILLIAMS, The London Hospital Medical College

Contents

What Are the Problems in Tropical Infections?	1
A. Bryceson	
Epidemic Diseases	3
D. A. Warrell, P. L. Perine, and D. W. Krause	
Progress Achieved in the Chemotherapy of Soil- Transmitted Helminths	11
F. Arfaa and I. Farahmandian	
The Treatment of Chloroquine-Resistant Falciparum Malaria	23
A. P. Hall	
The Role of University Research Departments in the Development of Antiparasitic Chemotherapy	29
W. Peters	
Current Problems in the Chemotherapy of Parasitic Diseases - The Role of the Pharmaceutical Industry	35
O. D. Standen	
New Nitroimidazoles with a Chemotherapeutic Activity	43
E. Winkelmann and W. Raether	
New 5-Nitroimidazoles with Antiprotozoal Activity: Effect of Hoe 088 (Pirinidazole)	45
W. Raether and E. Winkelmann	
Pharmacokinetic and Metabolic Studies with Ornidazole in Man. Comparison with Metronidazole	49
D. E. Schwartz and F. Jeunet	
The Diagnosis and Treatment of Lambliasis	61
W. Altorfer	

Treatment of Giardiasis with a Single Oral Dose of Tinidazole	65
T. Pettersson	
A Rural Study in Tanzania of the Chemosuppressant Activity of Various Regimes of Co-Trimoxazole or Chloroquine in Subjects with <u>P. falciparum</u> Parasitaemia	69
Th. J. Goosen, M. A. L. Goosen, and A. J. Salter	
Results of the Anti- <u>T. cruzi</u> Activity of Ro 07-1051 in Man	79
J. A. Cerisola, C. A. Barclay, H. Lugones, and O. Ledesma	
The Efficiency of Metronidazole "Flagyl" Against <u>Trypanosoma evansi</u> In Vivo	87
A. M. Mandour and A. M. Abd-El Rahman	
Emericid (31 559 R.P.): A New Anticoccidial	91
F. Benazet, J. R. Cartier, J. Florent, C. Johnson, J. Lunel, and D. Mancy	
Efficiency of Levamisole "Ketrax" on Some Nematode Infections in Assiut Province	97
A. M. Mandour and L. A. M. Omran	
Review of Amphotericin B	105
J. E. Bennett	
Polyenes: Actions and Prospects	111
D. Kerridge and N. J. Russell	
Review of Imidazole Group	117
R. J. Holt	
Mode of Action and Resistance to 5-Fluorocytosine	127
J. Schönebeck	
Combination of Amphotericin B and 5-Fluorocytosine	137
A. Polak and H. J. Scholer	
Combined Flucytosine - Amphotericin B Treatment of Cryptococcosis	143
J. P. Utz, I. L. Garriques, M. A. Sande, J. F. Warner, G. L. Mandell, R. F. McGehee, R. J. Duma, and S. Shadomy	

CONTENTS

xi

The Tissue Culture Study of Antifungal Agents and Their Morphological Changes on Yeast and Yeast-Like Fungi	157
A. Uetsuka, S. Satoh, M. Itoh, N. Okazaki, Y. Ohno, and K. Yoshimura	
Miconazole Plasma Levels in Healthy Subjects and in Patients with Impaired Renal Function	165
J. Boelaert, R. Daneels, and H. Van Landuyt, and J. Symoens	
In Vitro Studies with Miconazole and Miconazole Nitrate	171
S. Shadomy and L. Paxton	
Clinical Studies with Clotrimazole: Pharmacokinetics, Efficacy, Tolerance	179
H. Weuta	
Oral Clotrimazole in the Treatment of Fungal Infection . . .	183
R. Y. Cartwright	
Clotrimazole (Canesten) Therapy of Fungal Keratitis	189
D. B. Jones, B. R. Jones, and N. M. Robinson	
Replication of Picornaviruses	199
F. Brown	
Molecular Biology of Influenza Virus Replication and Points of Action of Inhibitors	203
J. S. Oxford	
Metalloenzymes: A New Focus for Antiviral Drug Design? . . .	209
D. D. Perrin	
Inhibition of Influenza Virus Replication by 2-deoxy-2,3- dehydro-n-trifluoroacetylneuraminic Acid (FANA) . . .	215
J. L. Schulman and P. Palese	
Virus Specified Enzymes in Herpes Simplex Virus- Infected Cells	219
J. H. Subak-Sharpe and J. Hay	
Studies with IBT-Resistant and IBT-Dependent Mutants of Vaccinia Virus to Clarify the Mechanism of the Antipox Activity	227
E. Katz, E. Margalith, B. Winer, H. Felix, and N. Goldblum	

The Role of Cell-Mediated Immunity in the Therapeutic Action of Isoprinosine of Viral Disease Processes	235
A. J. Glasky, G. E. Friebertshauer, J. W. Holker, R. A. Settineri, and T. Ginsberg	
Bonaphton - A New Antiviral Chemotherapeutic Drug	239
G. N. Pershin, N. S. Bogdanova, I. S. Nikolaeva, A. N. Grinev, G. Ya. Uretskaya, and N. V. Arkhangelskaya	
Chemotherapeutic Activity of Bonaphton in Herpetic Keratitis in Rabbits	247
N. S. Bogdanova, I. S. Nikolayeva, S. M. Kutchak, and G. N. Pershin	
Effect of Ribavirin on Influenza Virus Infection in Ferrets	253
K. P. Schofield, C. W. Potter, J. P. Phair, J. S. Oxford, and R. Jennings	
I. C. I. 73602 - A Potent Anti-Rhinovirus Compound	271
D. L. Swallow, R. A. Bucknall, W. E. Stanier, A. Hutchinson, and H. Gaskin	
Assessment of Some Antirhinovirus Compounds in Tissue Culture and Against Experimental Challenge in Volunteers	277
S. E. Reed and D. A. J. Tyrrell	
The Potential of Nucleosides as Antiviral Agents	279
R. W. Sidwell, L. B. Allen, J. H. Huffman, J. T. Witkowski, P. D. Cook, R. L. Tolman, G. R. Revankar, L. N. Simon, and R. K. Robins	
Bichlorinated Pyrimidines as Possible Antiviral Agents	295
P. La Colla, M. A. Marcialis, O. Flore, A. Firinu, A. Garzia, and B. Loddio	
Experimental Chemotherapy of Arbovirus Infections	303
A. N. Fomina and A. K. Schubladze	
The Use of Lung Weight Changes for Evaluating the Activity of Drugs Against Influenza Infections in the Mouse	307
M. F. Beeson and M. R. Boyd	
In Vivo Topical Activity of the Interferon Inducer BRL 5907 and Ribavirin in Ferrets Infected with Influenza Virus	313
M. R. Boyd and M. F. Beeson	

Effects of Pyrimidine Derivatives on RNA Dependent RNA Polymerase of Mengovirus Infected FL Cells	319
E. M. Tonew and B. Fahlbusch	
"In Vivo" Depression of Either Endotoxin or Virus- Induced Interferons by Rifampicin and Rifamycin Derivatives	327
E. Ronda, M. L. Alonso, and I. Barasoain	
Investigations upon the Mode of Action of Compound 48/80 on ss DNA of Phage ϕ X174	333
R. Dennin	
Anti-Herpes Simplex Virus (HSV) Effect of Amphotericin B Methyl Ester In Vivo	339
H. Shiota, B. R. Jones, and C. P. Schaffner	
Comparative Drug Trial in Cholera	347
A. F. B. Mabadeje	
Trimethoprim Resistance of Pathogenic Organisms Previous to Common Clinical Use of Sulprim [®]	353
S. Ortel	
Susceptibility of Chloramphenicol-Resistant Strains of <u>Salmonella typhi</u> to Trimethoprim/ Sulfamethoxazole	359
M. B. Bushby and S. R. M. Bushby	
Activity of Trimethoprim and Sulphonamides Against <u>Pseudomonas aeruginosa</u>	365
D. Gray and J. M. T. Hamilton-Miller	
Microbiological and Clinical Studies with Co-Trimoxazole	369
M. Aguirre, J. M. Alés, F. Lahoz, and R. Vela	
Cotrimoxazole as an All-Purpose Antibacterial Agent	373
J. C. Gould and B. Watt	
Treatment of Human Brucellosis with Doxycycline and Trimethoprim-Sulfonamide	379
L. Telegdy and J. Kéri	
Trimethoprim/Sulfamethoxazole Synergy and Prostatitis	383
S. R. M. Bushby and M. B. Bushby	

The Concentration of Sulphamethoxazole and Trimethoprim in Human Prostate Gland	389
W. Oosterlinck, R. Defoort, and G. Renders	
Long-Term Treatment with the Combination SMZ/TMP in Children with Urinary Tract Infections	395
L. B. Hahn and C. A. Barclay	
Long-Term Low-Dosage Co-Trimoxazole in the Management of Urinary Tract Infection in Children	403
J. M. Smellie, R. N. Grüneberg, A. Leahey, and W. S. Atkin	
A Double-Blind Study of Sulfamethoxazole- Trimethoprim vs. Its Components in Chronic Urinary Tract Infections	409
C. Demos, J. Pinderhughes, and M. Oakes	
A New Combination of Trimethoprim and a Sulphonamide (Sulphadiazine) in Urinary Tract Infections, a Double-Blind Study	415
A. Lövestad, B. Gästrin, and R. Lundström	
Comparative Clinical Trial of Parenteral Co-Trimoxazole in Major Respiratory Infections:	421
M. Janousek, L. Corbeel, and P. Stenier	
List of Contributors	433

WHAT ARE THE PROBLEMS IN TROPICAL INFECTIONS?

Anthony Bryceson

Hospital for Tropical Diseases

London, U.K.

Our forefathers had quinine, mercury and tartar emetic; smallpox and typhoid vaccines and diphtheria antitoxin. The epidemiology of sleeping sickness, Chagas disease, leishmaniasis, onchocerciasis, schistosomiasis, plague and yellow fever was unknown. We have certainly come a long way since then. Vaccine has the upper hand of yellow fever, smallpox, measles. Vector control has gone a long way in some areas to combat malaria and sleeping sickness. Education and sanitation are diminishing the terrors of schistosomiasis, plague, cholera and typhus. Chemotherapy is biting slowly into the mass of leprosy and tuberculosis - and some of the more recent successes attributable to chemotherapy will be presented in the middle section. But one of the scourges has gone and each one still represents either a continuing pool of misery and debility or a threat of another decimating epidemic. We have no cause for complacency.

Indeed we have cause for very great concern, because in some fields progress has halted and to this we intend to draw your attention. This is a heavy task because this has to deal with problems of 7/10ths of the world's population.

Neglect then, is the first problem and ignorance among our own profession. Take onchocerciasis for example. This year 300,000 adult males, the breadwinners of their families and the backbone of the societies will be blind of this disease, and next year the same number and the year after too. What have we to offer? Two weeks' course of tablets which cause devastating reaction and 6 weeks of injections which cause nephritis. A clinical and logistic impossibility. There has been no advance since Suramin was introduced exactly 50 years ago. Ernst Friedheim, whose solo efforts deserve

more praise than the whole of the pharmaceutical industry, did introduce a new arsenical, but unfortunately there were a few deaths and it was dropped. Not one University Department or Pharmaceutical Company is showing the slightest interest in this devastating disease.

It is very difficult to develop any new chemotherapeutic agent now. The criteria laid down by W.H.O., Food and Drug Administration and the Committee of Safety of Medicines for example, are so strict that they have virtually stopped progress in certain parasitic diseases. What a mercy we had arsenic and antimony before these Committees were born, for we still use both. Costs too, inhibit progress. We have no new drug for sleeping sickness since Melarsoprol was introduced full 30 years ago; and the facts are such now that it is not worth the while a pharmaceutical company to develop a drug even if a promising lead were offered. For even if the drug was given to every patient with the disease in Africa, that company would still not cover its development costs. These very important, perhaps the most important and ever lowering problems of cost and development are aired in the last section, and you will be pleased to hear that there is at last a chink in the clouds.

Even the best drug is no good if you cannot deliver it to the patient, and in Africa, Asia and South America, the problems of space and time and their practical expression - communications - pose problems which we paleo- and neo-artic citizens constantly fail to appreciate.

There is a prevalent myth that tropical infections are all due to "parasites" (i.e. big parasites - the protozoa and helminths). They are not. It is, however, under the steady burden of these big parasites that the battle against the little parasites is fought, and it is becoming increasingly clear that the one drastically lowers resistance to the other. The annual mortality of meningococcal meningitis in Northern Nigeria makes this point.

EPIDEMIC DISEASES

D.A. Warrell, P.L. Perine and D.W. Krause

Radcliffe Infirmary, Oxford OX2 6HE, U.K. and U.S.
Naval Medical Research Unit No 5, P.O. Box 1014
Addis Ababa, Ethiopia

The chemotherapy of epidemic diseases in tropical countries poses important practical problems which tend to be underestimated in those western countries where patients can be admitted to hospital, precisely diagnosed and given the drug appropriate to the sensitivity of the infecting organisms.

1. Particular social and environmental conditions may give rise to mixed epidemics of clinically-similar diseases spread by the same vector. Since laboratory facilities may be very limited and immediate confirmation of diagnosis impossible, it is important to consider drugs which are active against both infections, even though they may not be the first choice for either infection alone (e.g. chloramphenicol for bacterial meningitis : doxycycline for relapsing fever and typhus).
2. In the rush of an epidemic it may be impossible to admit patients for prolonged, supervised, courses of chemotherapy. The use of single dose long acting preparations has great advantages in this situation, provided that relapses can be prevented (e.g. doxycycline for relapsing fever and typhus).
3. Drugs effective in killing organisms may endanger the patient's life by causing complications such as Jarisch-Herxheimer type reactions (J-HR) (e.g. relapsing fever and plague).
4. Chemoprophylaxis and the treatment of carriers are important in those infections in which immunisation is not an entirely adequate method of protecting the population. Mass therapy creates problems which include encouragement of the emergence of resistant strains and significant incidence of unpleasant side effects (e.g. meningococcal meningitis).

These problems are illustrated by considering recent progress in the chemotherapy of four important epidemic diseases : louse-borne

relapsing fever (LBRF), louse-borne typhus (LBT), meningococcal meningitis and plague.

LOUSE-BORNE RELAPSING FEVER

The main endemic focus of LBRF is in the Ethiopian highlands where there may be 100,000 cases per year (Bryceson et al. 1970) and there have been recent reports of epidemics in adjacent Sudan (Abdalla 1969; Perine and Reynolds 1974). Various antibiotics are highly effective in eliminating Borrelia recurrentis spirochaetes from the blood, but, unfortunately, a severe J-HR usually results (Parry, Bryceson and Leithhead 1967) and may kill the patient as a result of hyperthermia or hypotension (Warrell et al. 1970). Tetracycline eliminates spirochaetes within 2-3 hours but invariably causes a J-HR which is not prevented by cortico-steroid. Slow release penicillins seem less likely to cause a reaction, but eliminate spirochaetes more slowly and may allow relapses. (Rijkels 1970; Knaack et al. 1972)

In Addis Ababa, Ethiopia, a group of 12 male patients (ages 18-38 years) with proven LBRF were randomly allocated for treatment with either pyrrolidino-methyl-tetracycline (Reverin, Hoechst, 275mg intravenously) or procaine penicillin with aluminium monostearate (PAM) (Specia-Paris 600,000 units intramuscularly). This dose of PAM was found to be very effective against syphilis and yaws and to produce therapeutic blood levels of penicillin for at least four days (Ovčinnikov and Korbut 1965; Hume and Facio 1956).

Physiological measurements were made before treatment, near the peak of the febrile response and 24 hours after treatment. Temperature, electrocardiogram and intravascular blood pressures were monitored continuously and the patients closely observed throughout.

The two groups were comparable before treatment. Spirochaetes were eliminated much more rapidly by tetracycline (Fig. 1). After PAM, spirochaetemia and fever persisted for up to 48 hours, whereas spontaneous crisis with disappearance of spirochaetes was observed in five out of 19 patients who were admitted overnight for treatment the next day. In the tetracycline-treated group peak temperature was higher, occurred sooner and was always associated with rigors, whereas only one of the PAM-treated patients had rigors. At the peak of the febrile response and 24 hours after treatment there was no significant difference between the groups in cardiac or respiratory rates, pulmonary venous admixture, cardiac output, mean brachial artery pressure, systemic vascular resistance and arterial pH. There were significant differences ($P < 0.05$) at the peak of the reaction in total expired ventilation, oxygen consumption, arterial PO_2 and PCO_2 and dead space : tidal volume ratio. (Fig. 2) These were consistent with a greater respiratory stimulus in the tetracycline treated group, perhaps related to higher body temperature and the added

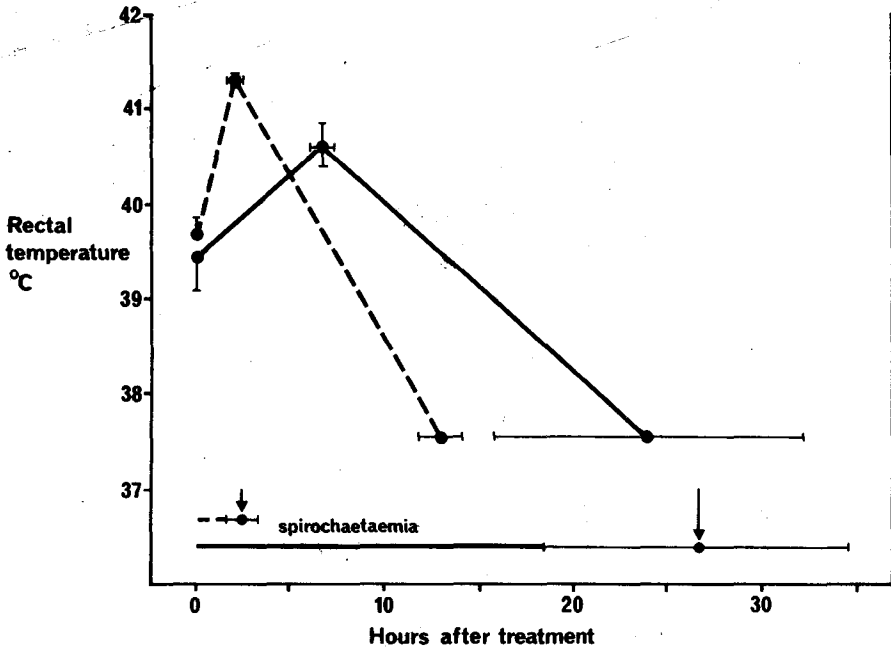


Fig. 1 Course of fever and persistence of spirochaetaemia in six patients treated with tetracycline (dashed line) and six treated with PAM (solid line). (Mean \pm 1 standard error).

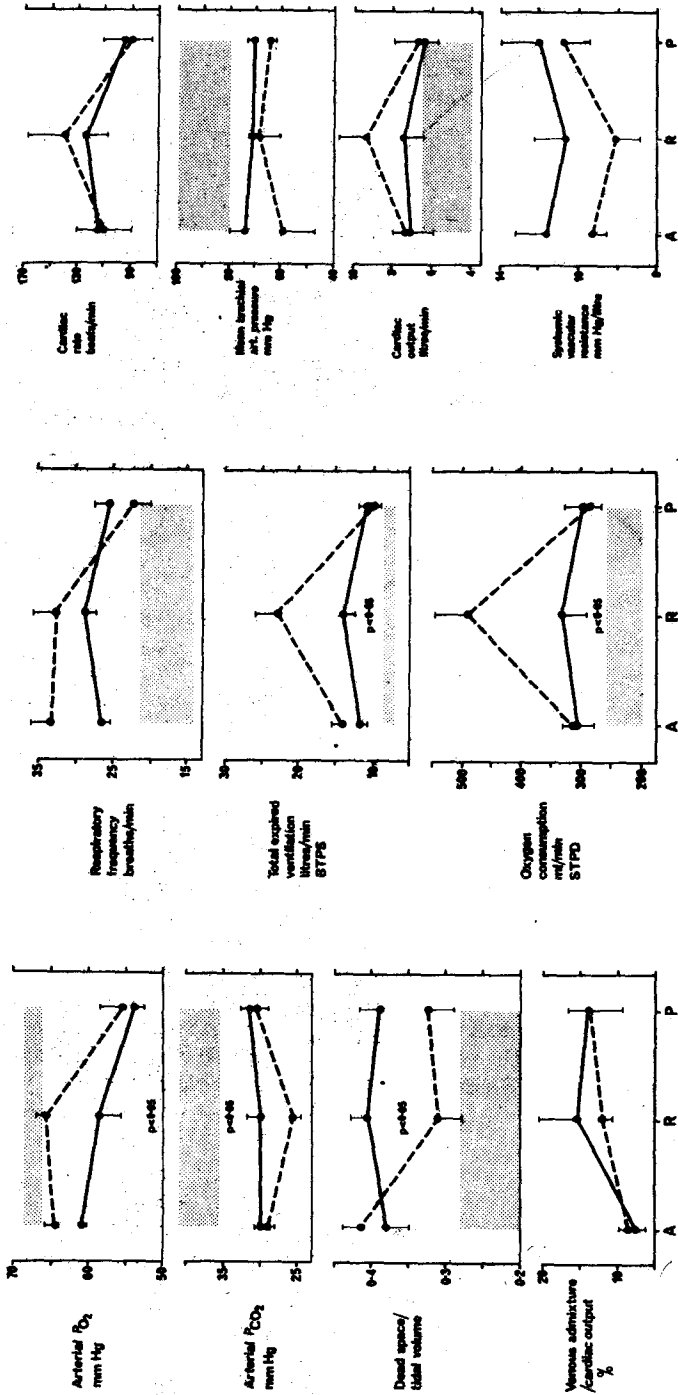


Fig. 2 Physiological changes in the two groups of patients (see caption to Fig. 1). On the abscissa, A indicates values before treatment, R at the peak of the reaction and P, 24 hours after treatment. Shaded areas represent normal values at an altitude of 2,250 metres. (Mean \pm 1 standard deviation).