Edited by

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CHEMOTHERAPY

Volume 6

Parasites, Fungi, and Viruses

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CHEMOTHERAPY

Proceedings of the
9th International Congress of Chemotherapy
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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.

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Contents

WHAT ARE THE PROBLEMS IN TROPICAL INFECTIONS?

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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.

Neglact 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 socities 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 pharmaceutic 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 Melarsopral 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 clounds.

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 problesm 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

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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 Leithead 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, spirochaetaemia 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

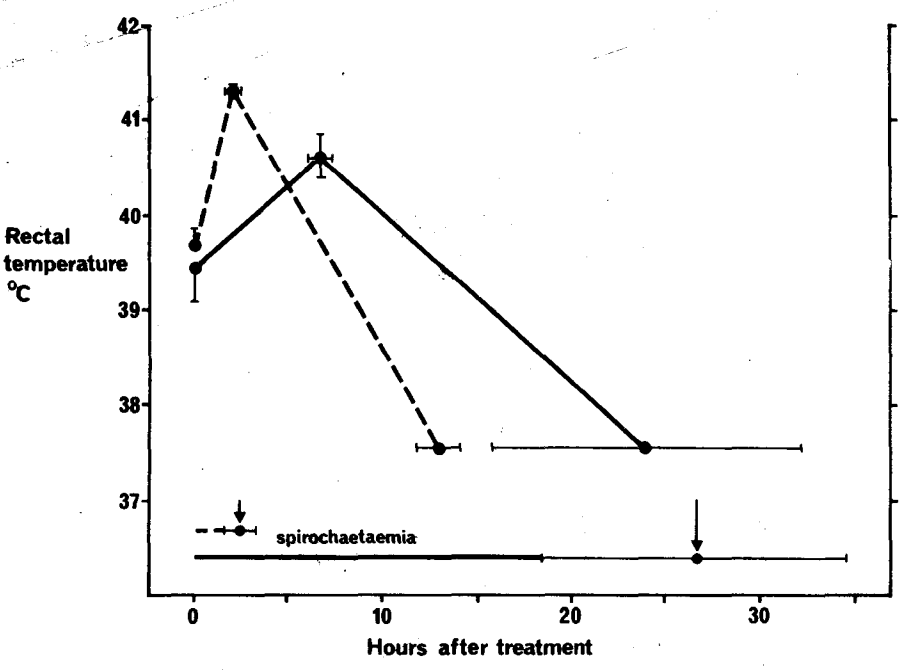

Fig. 1 Course of fever and persistence of spirochaetaemia in six patients treated with tetracycline (dashed line) and six treated with PAM (solid line). (Mean ± 1 standard error).

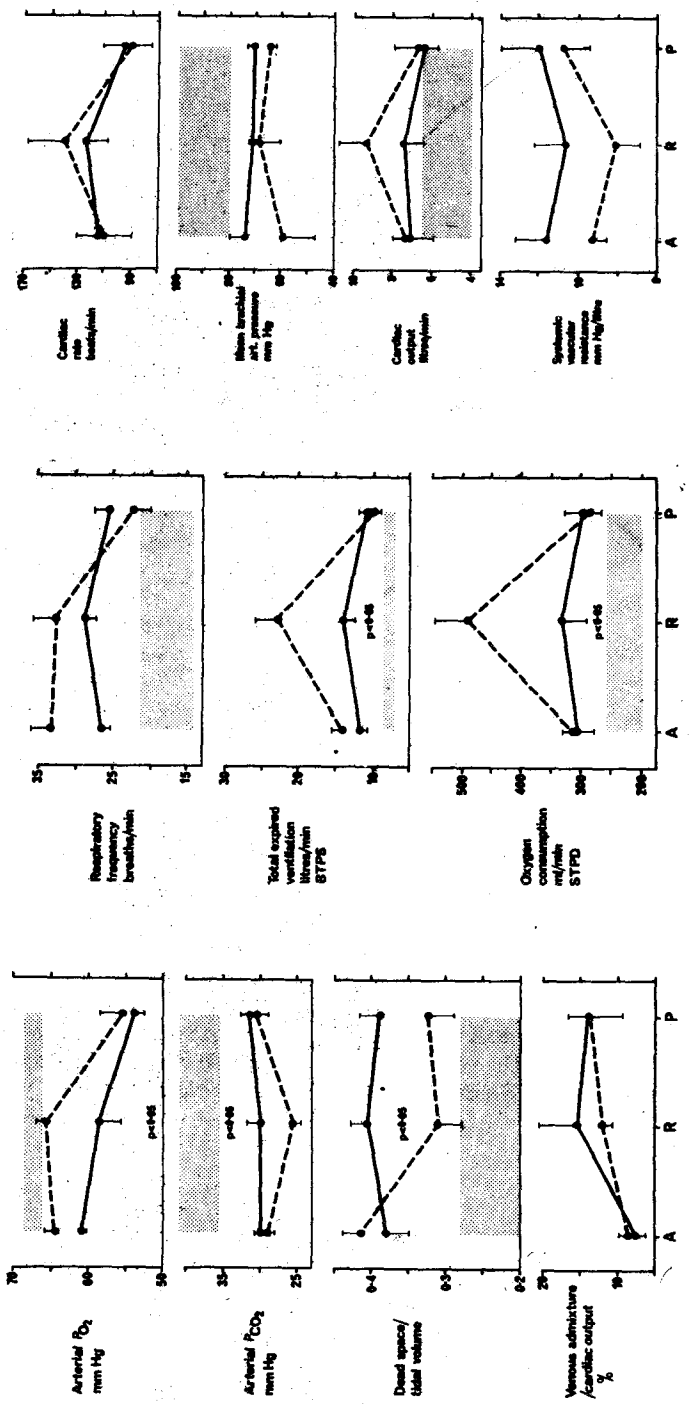

Fig. 2 Physiological changes in the two groups of patients (see caption to Fig. 1). On the abscissa, A indicates values before treatment, R at the peak of the reaction and P, 24 hours after treatment. Shaded areas represent normal values at an altitude of 2,250 metres. (Mean ± 1 tandard deviation).