caused even less inconvenience to those treated with it. With neither drug was it necessary to curtail or to arrest the course of treatment as a result of toxic side-effects.

The results of treatment with aureomycin and terramycin therefore appear to me to be encouraging. It seems that treatment with either of the two will sterilize most of the average cases of amoebiasis encountered in practice. But these drugs are not infallible, and I do not think that in achieving the eradication of the infection they give results superior to those obtained with the combined course of treatment used so successfully in this country for many years. They are a most useful addition to the older amoebicides; and their especial value has been evident in those few cases of infection which have proved refractory to repeated courses of treatment with the older accepted amoebicidal drugs. The number of such cases, it is well to remember, is very small, but when encountered such refractory infections have hitherto constituted an apparently insoluble problem. These two antibiotics, when used as a supplement to the older amoebicidal drugs, seem to have provided the extra force necessary to eradicate these peculiarly resistant infections, and I value them accordingly. I would not recommend at present the indiscriminate employment of these antibiotic drugs in the ordinary straightforward case of amoebiasis, if only on the grounds of their considerable cost and their scarcity.

Summary

Two important bacillary infections in the Tropics are bacillary dysentery and cholera. Chemotherapy has not proved of benefit in cholera; it may be that it will not do so in the future in view of the extraordinary acuteness of the condition.

In the bacillary dysenteries sulphaguanidine and its successors, succinylsulphathiazole and phthalylsulphathiazole, are effective and are not prone to cause crystalluria and renal blockage. The absorbable sulphonamides, especially sulphadiazine, are also very effective, but renal obstruction may occur from their use.

Treatment of *Entamoeba histolytica* infection is discussed. The drugs accepted as being specifically amoebicidal include the alkaloids emetine and conessine, certain arsenicals, and the iodo-quinolines. Trials of aureomycin and terramycin show that these antibiotics are useful additions to the range of amoebicidal drugs. Their outstanding value appears to lie in their capacity, when given together with these drugs, to eradicate the extremely refractory infections occasionally met with.

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Burroughs Wellcome and Co. have made a new 16-mm. colour film (with sound) on the life cycle of *Schistosoma mansoni* and its laboratory maintenance entitled "The Human Blood Fluke." The film, which is in two parts each running for 16½ minutes, is intended for doctors, parasitologists, and pharmacologists. After a brief introductory sequence, the life cycle of the trematode is illustrated by living material and animated diagrams. Then follow details of the culture of the vector snail, *Australorbis glabratus*, and of the method of infecting mice with the cercariae. Lastly, the activities of various drugs against the disease in mice are compared. The film may be obtained from the Wellcome Film Library, 183-193, Euston Road, London, N.W.1.

THE CHEMOTHERAPY OF MALARIA AND TRYPANOSOMIASIS*

BY

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Malaria

The three synthetic antimalarials which had the most widespread use in the field until a year or two ago are mepacrine, pamaquin, and proguanil ("atebrin," "plasmoguin," and "paludrine"—as in every other field of chemotherapy, there is a confusing multiplicity of names for the same substance). These three drugs, although still extensively used, may now be regarded as the parent substances of classes of new and more effective drugs.

Mepacrine is of value as a suppressant but has no activity against the tissue stages of the malaria parasite. The closely related 4-aminoquinoline derivatives chloroquine and camoquin are now replacing mepacrine as malaria suppressants. Chloroquine was introduced by the Germans as "resoquin," was developed in America as "aralen," and is also produced in France and Britain as "nivaquine." It is less toxic than mepacrine and does not stain the skin, and it acts a little more rapidly. It is now the drug of choice for the treatment of the malarial attack, although many workers still find a place for quinine in the treatment of the more severe cases (Covell, 1949). A dose of 300 mg. of chloroquine once weekly is enough in most areas for the suppression of malaria; this is the dose which is at present being used among sections of the United Nations Forces in Korea. The related compound camoquin is almost as good as chloroquine, and is being used chiefly in India, Egypt, South America, and the Philippines.

Pamaquin is not an outstanding schizonticide, and is of little value alone in the acute malarial attack. However, it has the property of killing the tissue forms of *Plasmodium vivax*. It has to be used with caution because of its toxic side-effects. Closely related 8-aminoquinoline derivatives have been prepared and tested in the United States; the best of them so far are pentamquine, isopentamquine, and primaquine. Primaquine is the primary amine corresponding to pamaquin, and is the best and least toxic of this series of drugs (Edgcomb *et al.*, 1950). It is now being used for the eradication of tissue forms of *P. vivax* in home-going United States Service men from Korea. When the men embark they are given a large dose (1 g.) of chloroquine to deal with any asexual parasites, and then a course of 15 mg. of primaquine daily for 14 days on the voyage home. This appears to be reducing very greatly the incidence of relapses of benign tertian malaria. The treatment therefore reduces the chances of re-establishing endemic foci of the disease in areas of the United States where anopheles mosquitoes capable of transmitting it still flourish (Public Health Reports, 1952). Even with primaquine, care is necessary because toxic side-effects occur in dark-skinned people.

Proguanil

Proguanil, which belongs to an entirely different class of chemical compound, has proved to be a very useful malaria suppressant, and in spite of the fact that inadequate treat-

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ment may give rise to resistant strains of malaria, there is little evidence of its having done so in most countries in which the drug has been used for the last six or seven years. A notable exception is Malaya, where Field and Edeson (1949) have found a gradually increasing resistance to proguanil treatment among the cases of overt malaria which are admitted to hospital. Resistance is caused by inadequate suppressant dosage, and is induced in the trophozoites but not in the tissue forms of the parasite (Cooper *et al.*, 1950). There is little chance of developing drug-resistance if sufficiently large and regular doses of proguanil are taken to suppress the blood parasites effectively, and, in any case, proguanil-fast strains are not resistant to mepacrine or chloroquine. Proguanil is a causal prophylactic against *P. falciparum*; it has some action upon the tissue forms of *P. vivax*, but is not a certain cure in every case.

It has been known for several years that proguanil itself has very little activity *in vitro* upon laboratory malaria parasites, but that serum from an animal treated with proguanil is active. This work suggests that the drug is changed in some way in the body of the host to produce an active metabolite. The nature of this metabolite was recently discovered by the workers at the laboratories of the Imperial Chemical Industries (Carrington *et al.*, 1951). It is formed by the cyclization of the biguanide chain of proguanil to form a diamino-dihydrotriazine derivative, which is about a hundred times as active as the parent substance in laboratory malaria infections. The introduction of a second chlorine atom into proguanil or into the triazine derivative produces even more active compounds which are at present undergoing clinical trial.

Pyrimethamine

Before the discovery of the metabolite of proguanil, Hitchings and his colleagues in the United States had been investigating the properties of diaminopyrimidine derivatives as antagonists of folic acid in cultures of bacteria. They found that proguanil was also a folic acid antagonist, and made the suggestion that diaminopyrimidines might therefore show antimalarial activity (Falco *et al.*, 1949). This was found to be the case, and a thorough investigation of a series of nearly 300 related compounds (Falco *et al.*, 1951) resulted in the introduction of a new antimalarial pyrimethamine ("daraprim"; "B.W. 50-63"). This drug has a chemical structure which resembles the metabolite of proguanil, and is somewhat more active against laboratory malaria infections. Clinical trials have been in progress in many parts of the world during the last 18 months, and the new drug appears to have considerable promise, especially as a malaria suppressant. A single dose of 5 mg. of pyrimethamine banished asexual parasites of *P. falciparum* and *P. malariae* from the blood of Lagos schoolchildren (Archibald, 1951). A weekly dose of 25 mg., given to all members of an isolated population in the Belgian Congo at the beginning of the rainy season, reduced the parasite rate in the people to zero after 15 doses, and the sporozoite rate in trapped anopheles mosquitoes to a very low level. Transmission of malaria was virtually at a standstill at the time of the year when it would have been expected to be proceeding at a very high rate (Vincke, 1952). Vincke is hopeful that courses of treatment with pyrimethamine may bring about a great reduction in malaria transmission over wide areas. In the treatment of the malarial attack, pyrimethamine has similar properties to proguanil, and has been found by most observers to be less rapidly effective than chloroquine.

Increasing attention is being given all over the world to the control of malaria by means of drugs, insecticides, and hygienic measures. In some areas notable progress has already been made in reducing the vast morbidity and mortality due to the disease, which was so vividly portrayed by Shortt (1951).

Trypanosomiasis

In the field of trypanosomiasis there have also been considerable advances in the last few years. The problem of treatment of human trypanosomiasis is threefold—the treat-

ment of early cases, the treatment of advanced cases with involvement of the central nervous system, and prophylaxis. Early cases often respond satisfactorily to treatment with suramin ("Bayer 205," "antrypol") or pentamidine. Pentamidine is the least toxic and most effective trypanocide of the series of aromatic diamidines which were synthesized by Ewins and his colleagues at the laboratories of May and Baker. This work was a continuation of the studies upon long-chain diamidines carried out by King, Lourie, and Warrington Yorke. Pentamidine is very effective in the early stages of the disease, but it does not penetrate to the nervous tissue; it is therefore useless by itself for the treatment of advanced cases. Late cases are still treated with the arsenical drug tryparsamide, often together with pentamidine, and in many areas tryparsamide is still the mainstay of treatment.

Unfortunately, resistant strains of trypanosome are being encountered in some localities, especially in the Belgian Congo. It is therefore fortunate that a new series of potent arsenic derivatives has been introduced by Friedheim (1939, 1948, 1949). These are the melaminyl compounds, melarsen, melarsen oxide, and mel B. Perhaps the most promising of this series is mel B, which is a compound of melarsen oxide with dimercaprol ("B.A.L."), and which is less toxic than melarsen oxide itself. This substance is now manufactured by Rhône-Poulenc under the name of "arsobal." It is proving effective in the treatment of advanced cases even if they have failed to respond to tryparsamide, and a single dose is often enough to cure an early case of trypanosomiasis. The drug is not without its dangers, and some trouble has been encountered in the chemical preparation of batches which are uniform in toxicity. It is therefore essential that all batches of the drug which are manufactured should be controlled by biological tests similar to those laid down for the organic arsenicals used in the treatment of syphilis (Lourie, 1951). Toxic effects such as arsenical encephalopathy can be controlled by giving additional doses of dimercaprol until the arsenic has been excreted. Melaminyl arsenical derivatives produce resistant strains of trypanosome if insufficient drug is given, and these strains are also cross-resistant to all other arsenical drugs, including tryparsamide (Friedheim, 1951).

Another arsenical drug introduced in recent years is butarsen, which was selected for clinical trial after a great deal of careful laboratory work by Eagle (1945). Unfortunately butarsen is active only against early trypanosome infections, and is of no use when the central nervous system is involved. The drug is also of some value in the acute stage of South American trypanosomiasis caused by *Trypanosoma cruzi*.

For the prophylaxis of populations exposed to the risk of trypanosomiasis pentamidine is used. An injection will protect for a period of 4 to 12 months. However, it is very important that a full survey of the population should be made before the first dose is given, because some individuals are likely to be harbouring the disease already. Unless these are treated adequately with a full course of drugs, the infection may become cryptic and trypanosomes continue to live in nervous tissue without ever appearing in the blood or lymph-node juice. The opportunity for curing such patients easily will then have been missed.

Cattle Trypanosomiasis

Shortt (1951) has stated that he considers "the trypanosomes affecting man's domestic animals to be far and away more important [than human trypanosomiasis] when the whole picture is looked at in perspective." This is because animal trypanosomiasis denies at least a quarter of the land surface of Africa to all domestic animals except poultry. A number of drugs have been introduced during the last 10 years which give reason to hope that in the future it may be possible to utilize at least the marginal areas of the tsetse belts for the grazing of cattle, and it is already possible to transfer cattle through fly country from one safe area to another, under cover of a protective injection of a drug.

Before 1938 the only substance of any value in the treatment of *Trypanosoma congolense* and *T. vivax* infections in

cattle was tartar emetic. The Germans introduced "surfen C," which was effective but toxic, and shortly afterwards Walls synthesized the first of the phenanthridinium compounds (Browning *et al.*, 1938), which have since been widely used for the treatment of *T. congolense* and *T. vivax* infections. The most effective substance of this series was, until recently, dimidium. Unfortunately this drug has a severe locally irritant action, and sometimes produces damage to the liver, which may lead to a condition resembling photosensitization of the skin, appearing five to six weeks after the dose. In 1949 "antrycide" was introduced, and it looked for a time as though at last an effective remedy had been found, both for the treatment of infected cattle and for the prophylaxis of animals grazing in fly areas (Davey, 1950). "Antrycide" is a very good drug, but, like all other chemotherapeutic substances, it has its limitations. It produces toxic side-effects in ill-fed animals, and in areas of heavy fly density an injection of antrycide prophylactic will protect only for a period of two months (Unsworth, 1951). In the wilder parts of Africa it is not possible to give protective inoculations at short intervals, and antrycide prophylactic does not exert its action for long enough to make it very suitable for use in this way. However, for the purpose of grazing animals for limited periods in marginal territory, and for the passage of cattle through the fly belts on their way to market, the drug has very real uses (Unsworth and Birkett, 1952). Antrycide-resistance is easy to produce, and resistant strains of trypanosome are cross-resistant to the phenanthridinium compounds.

A new phenanthridinium compound has recently been prepared and tested by workers in the laboratories of Boots at Nottingham. This is "ethidium," which has an ethyl group instead of a methyl group associated with the quaternary nitrogen atom (Watkins and Woolfe, 1952). Ethidium is claimed to be less toxic and more active than dimidium, and preliminary trials in the field have been encouraging. A number of other phenanthridinium derivatives are still undergoing trial, and a trypanocidal cinnoline compound is soon to be tested in the field (Lourie *et al.*, 1951). The frequency with which new organic compounds are being presented for trial in the field gives promise that it may not be long before cattle trypanosomiasis is brought under control. Investigations are also being made upon the breeding of races of cattle which show increased natural tolerance to the disease, and it may be that this method, and not the injection of chemical poisons, will prove to be the real answer to the establishment of cattle in the tsetse areas.

Summary

Developments in the chemotherapy of malaria are discussed, together with the qualities of the various anti-malarial drugs.

The treatment of human trypanosomiasis and the question of mass prophylaxis are surveyed.

The importance of the treatment of cattle trypanosomiasis is emphasized, and the value of new drugs used for this purpose is assessed.

Mention is made of the employment of antrycide as a short-term prophylactic in cattle.

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SUCCESSFUL LACTATION IN ADDISON'S DISEASE

BY

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Successful pregnancy in a woman suffering from Addison's disease has often been reported, but successful lactation would seem to be a rare event. It is therefore thought worth while to report a case in which delivery of a healthy infant was followed by the establishment of successful breast-feeding.

Literature

A search of the literature since replacement therapy has been used has shown several reports of successful pregnancy; in some of these no mention is made of lactation, in others slight congestion of the breasts was noted a few days after delivery, and in yet others attempts at breast-feeding were not permitted. Fitzpatrick (1922) reported the successful delivery of a patient in whom Addison's disease had been diagnosed during the pregnancy; he did not, however, mention lactation. At the same time he reported 11 cases from the literature in which Addison's disease had complicated either pregnancy or the puerperium, but in none of which both mother and infant had survived. A further case of successful delivery was reported by Perkins (1932), but breast-feeding was said not to have been permitted. Maranon (1936), in a review of sexual function in 169 cases of Addison's disease, 88 of them women, stated that pregnancy was less likely to occur in those suffering from Addison's disease, but that when it did occur death of the woman during pregnancy or soon after delivery was not uncommon. He agreed with the opinion expressed by Rowntree and Snell (1931) that in most women suffering from Addison's disease mammary atrophy occurred, and that this was the reason why breast-feeding of the infant was not possible.

Galloway *et al.* (1940) reported the successful delivery of a full-term infant in a case in which the pregnancy had been complicated by an acute suprarenal insufficiency. Van Zwanenberg (1945) reported two cases in which symptoms of Addison's disease occurred during pregnancy; one of these patients died during the fourth month following hysterotomy and sterilization, while the second responded to "eucortone" therapy and a live child was obtained. In this case the infant was not put to the breast and no attempt was made to inhibit lactation, but, except for some hardening of the breasts on the third and fourth days of the puerperium, there were no signs of lactation. The case of a woman suffering from Addison's disease who had two successful pregnancies was reported by Leonard Simpson (1946). He suggested that lactation might have occurred if treatment had been different, cortical extract containing the carbohydrate factor being used instead of deoxycortone.