Summary

A scheme offering unlimited chest x-ray facilities for general practitioners is described. Such a service could be provided in large towns if mass x-ray teams concentrated entirely on examination of general practitioners' cases.

The incidence of minor respiratory symptoms which are agreed by specialists to indicate the need for a chest x-ray film is so high in general practice that if the practitioner accepted the criteria and used the x-ray services available the clinics would be overburdened.

Early pulmonary tuberculosis mimics the symptoms of commoner minor ailments. It is a wolf in sheep's clothing.

These difficulties are well known to general practitioners, but the relatively narrow field of specialist experience has prevented the experts and the medical planners from being fully aware of them.

In general practice pulmonary tuberculosis is often diagnosed only on a "time" basis, after elimination of other causes, as distinct from "instantaneous diagnosis" by x-ray examination.

It may be objected that by offering unlimited x-ray facilities to general practitioners the profligate use of film is encouraged. No evidence of dilution was found to suggest that those doctors who used the scheme intensively had a lower discovery rate than those who x-rayed less often.

Figures are given for the incidence of pulmonary tuberculosis in patients referred with different symptoms or symptom-complexes.

Attention is drawn to the importance of radiological examination of unmarried people of both sexes who present with certain symptoms.

General practitioners must not feel disconcerted when many x-ray examinations yield nothing abnormal. This is the price of early diagnosis. The practitioner should use the miniature chest film with as little hesitation as he uses his stethoscope.

Tribute should be paid to the 183 general practitioners without whose enthusiastic participation the scheme could not have been started. We thank Dr. P. C. Anderson for advice and co-operation in the interpretation of films. We are also much indebted to the staff of the mass x-ray service for their indispensable assistance.

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The Department of Rheumatic Diseases of the West London Hospital has again with great promptness issued its annual report for the preceding year, and as usual it is full of interesting and useful information, including reports of original work. Of the patients who attended for treatment during the year, 33.2% were suffering from osteoarthritis, 12.8% from rheumatoid arthritis, 8.6% from the lumbar disk syndrome, 5.5% from capsulitis of shoulder, 3.2% from cervical disk syndrome, 2.6% from ankylosing spondylitis, 2.1% from psychogenic rheumatism, and 1.7% from gout. In his preface to the report Dr. W. S. C. Copeman, physician in charge of the department, mentions that gold salts are still found to be the most satisfactory single medicinal agent in the treatment of rheumatoid arthritis, and a large clinic, specially for these injections, has been organized. Research has continued into the most effective method of treating rheumatoid arthritis with cortisone and A.C.T.H.

TREATMENT OF BOWEL INFECTIONS OF THE TROPICS*

BY

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Bowel infections are notoriously prevalent in the Tropics, where they cause much morbidity in both the indigenous population and the European personnel serving there. The infections briefly can be divided into: (1) bacillary, (2) protozoal, and (3) helminthic. For most of these there is now available some reasonably effective treatment, and for some there is very effective specific treatment. It is with the specific treatment of a few of them that I propose to deal.

Bacillary Infections

Among the more important of the bacillary infections are the bacillary dysenteries and cholera; and typhoid, in view of the particular damage it causes to the bowel, may be added to them. The bacillary dysenteries and cholera are caused by infections which are localized within the bowel; in the former in the large intestine and in the latter in the small intestine. Typhoid is, of course, a generalized or systemic infection, and I do not propose to consider it as primarily a bowel infection.

The demonstrations by Marshall *et al.* (1941) of the efficacy of sulphaguanidine in the arrest and eradication of acute bacillary dysenteric infections in children in the United States was the beginning of the specific chemotherapy of the bacillary dysenteries. The findings of Marshall and his co-workers were rapidly confirmed by Fairley and Boyd (1943) on troops in the Mediterranean area, where bacillary dysentery had more than decimated the forces during the first world war. The speedy adoption by the British Forces of sulphaguanidine as a specific for the bacillary dysenteries was followed by the virtual disappearance of these diseases as a major cause of morbidity and mortality during the second world war. For a normal adult the dosage is an initial one of 6 g., and this is followed by 3 g. four-hourly, and then eight-hourly for two or three days into convalescence. The drug must not be continued for more than 10 days.

When sulphaguanidine was in short supply other sulphonamides, notably sulphapyridine, had been tried and been found also to be specific in the arrest of these infections. Their use in such a dehydrating febrile disease in a hot climate not uncommonly led to crystalluria and renal obstruction; where facilities were not immediately available to relieve this by ureteral lavage, deaths followed from uraemia. As a result the use of the freely absorbable and diffusible sulphonamides in the treatment of the bacillary dysenteries was discouraged among the British Forces, and the comparatively non-absorbable sulphaguanidine was adopted as the standard specific drug. Sulphaguanidine was followed in due course by other compounds with similar properties, of which succinylsulphathiazole and phthalylsulphathiazole are those most used. These are said to be even more effectively bacteriostatic than is sulphaguanidine, and in civil practice they now largely replace the sulphaguanidine of the war years. They are used in similar dosage.

The Americans have been less averse to the employment of the absorbable sulphonamides for the treatment of the bacillary dysenteries than are the British. There is some agreement that sulphadiazine is the most therapeutically

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effective sulphonamide for the treatment of the bacillary dysenteries. But those advocating its use emphasize the need for correcting dehydration and alkalinizing the urine before beginning treatment with it. There can be little doubt that at least under field conditions it is preferable to adhere to the British practice of using sulphaguanidine, succinylsulphathiazole, or phthalylsulphathiazole for treating cases of bacillary dysentery in all cases except under the stress of emergency. When sulphadiazine is used the dosage employed is up to 8 g. daily, in divided doses at four-hour intervals.

During the recent war years there was little evidence of the development of sulphonamide resistance by strains of the organisms causing bacillary dysentery. But Hardy (1946), in America, has recorded the development, by a strain of Flexner Z, of resistance to sulphadiazine. This development occurred in an institution for mentally defective children, in which successive cases of bacillary dysentery due to this organism were treated with subcurative doses of sulphadiazine, with the result that eventually this strain became completely refractory to the drug, and the course of the disease in the patients treated with it late in the epidemic was unchecked.

Hardy and Halbert (1948) treated a number of these children with streptomycin by the mouth. Given by this route streptomycin is not absorbed, and so it does not cause the toxic side-effects associated with its parenteral administration. They found that streptomycin was therapeutically beneficial in bacillary dysentery, but nevertheless it was much inferior to the sulphonamides; its only virtue in this connexion therefore seems to lie in its use in cases of infection with sulphonamide-resistant organisms, if these ever become prominent.

Cholera is an epidemic disease which ravages many parts of the East, and its effective treatment has so far been palliative along physiological lines. While claims have at various times been made that a number of drugs, in particular certain sulphonamides, act specifically in terminating the infection, none of these has withstood the test of time. Indeed, Lahiri (1951) indicates that, so far, the chemotherapeutic treatment of cases of cholera has proved detrimental to the patient rather than beneficial. In a fulminating infection of this kind, in which the vibrios multiply at incredible speed to a prodigious number throughout an extremely brief incubation period, it may well be that chemotherapy could only be employed too late to expect any benefit from it; and, apart from chemoprophylaxis, a specific drug treatment for the destruction of the organisms will not prove to be of value.

Protozoal Infections

The most important and geographically widespread of these is infection with *Entamoeba histolytica*; but, in addition, as localized infections of the intestine which may or may not cause clinical manifestations of their presence, there are lamblia (giardiasis), trichomoniasis, and the much less common balantidiosis. Certain generalized protozoal infections such as kala-azar may secondarily implicate the bowel; but these hardly fall within our compass, and their treatment is that of the generalized infection.

Amoebiasis and amoebic dysentery (the terms are not synonymous) occur all over the world, and their precise relationship is uncertain. Hoare (1950) discussed the evidence for and against the view that all *E. histolytica* infections of man are pathologically active; he concluded that the parasite can and does live in the bowel commensally at times. If his opinion, which I share, is accepted, it can be argued that even in those persons who suffer from unmistakable relapsing attacks of amoebic dysentery the parasite may alternate between pathogenicity and commensalism. In view of its ubiquity it obviously is impracticable to detect, much less to attempt to sterilize, every case of infection with this parasite among the human populations of both the temperate and the tropical zones of the world. But nevertheless, rightly or wrongly, most clinicians feel it

desirable, when circumstances allow, to sterilize of their infections persons found to be harbouring large cyst-producing races of the parasite, particularly if these persons have returned to temperate climates from a visit to the Tropics.

Infections with strains producing small cysts (below 10 μ in diameter) may be ignored in the absence of any convincing clinical manifestations to the contrary. To me it seems entirely unwarrantable, as is the practice of certain workers, more particularly in France and in the United States, to ascribe to an *E. histolytica* bowel infection an apparently limitless range of indeterminate symptoms remote from the abdomen; this especially when the patients have never been outside the moderate temperate zones, and have never even suffered from bowel troubles that could reasonably be attributed to the intestinal parasitization. One's credulity is stretched beyond the limit when anything from headache and visual disturbances to sexual disorders and rheumatoid arthritis have been ascribed to an otherwise symptomless *E. histolytica* infection solely on the grounds that specific treatment of the latter allegedly relieved these troubles.

Two Stages of Treatment

There are two stages in the treatment of an intestinal *E. histolytica* infection, and these are sharply distinct. First, there is the treatment of an acute attack of amoebic dysentery; secondly, as a sequel, there is the eradication of the bowel infection with the parasite. In addition to these, treatment in some cases may be necessary for an extra-intestinal infection with the parasite, such as an amoebic abscess of the liver.

For the treatment of an acute attack of amoebic dysentery emetine hydrochloride in doses of 1 gr. (65 mg.) given intramuscularly daily for a few days, is still unequalled. It has been stated that emetine is a dangerously toxic drug and that it always affects the heart. Its dangers have been grossly exaggerated. If a patient is kept in bed during the treatment and the drug is not given recklessly and in needlessly excessive dosage its dangers can with safety be completely ignored in ordinary practice. From three to six daily doses of the drug is all that is necessary to stop an acute attack of dysentery.

While emetine will unfailingly bring an acute attack of amoebic dysentery rapidly to an end, usually it will not sterilize the bowel of the infection, however unwisely the drug may be pushed or the course of treatment with it be prolonged. During the last few years some French workers have been pressing the claims of conessine, the active principle of kurchi bark, as a drug superior to emetine in the treatment of amoebic dysentery. Dispassionate observers studying the literature on the subject cannot fail to be unfavourably impressed by the unquestionable toxic side-effects of conessine treatment. Whereas emetine may affect the heart, conessine most certainly affects the head; indeed, it can cause very grave mental disorder, with maniacal symptoms, in persons unusually susceptible to the drug. The use of kurchi, or conessine, has almost been abandoned in India, where its employment over many years has largely been on the score of its ready availability there, and so its cheapness. There seem to me to be no adequate grounds for reviving it when emetine can be used; and, recently, informed French opinion appears increasingly to support this view.

When the acute attack of dysentery is controlled the next measure is to eradicate the basic intestinal infection before relapse of the dysentery can occur. For this, emetine by itself is ineffective, but a large number of compounds of extraordinarily divergent constitution have been advocated as effective specifics to achieve this end. Broadly, they may be classified as (a) compounds which contain emetine, of which E.B.I. (emetine and bismuth iodide) is the most generally used; (b) arsenicals, such as acetarsol, carbarsone, and the more recent milibis (a combination of arsenic and bismuth); (c) the iodo-oxyquinolines, such as "chinfofon,"

iodochlorhydroxyquin, and di-iodohydroxyquinoline; and very recently (*d*) the antibiotics, of which aureomycin and terramycin so far have proved the most effective.

Differences of Opinion

The claims put forward for any one of these drugs range in a remarkable manner from extreme optimism to extreme pessimism; and so the literature on them, in addition to being voluminous, is very confusing. After studying and attempting to analyse it, I find that the statements made by a large number of authors, writing of their experiences with them, are quite irreconcilable. One is driven to the conclusion that many of their statements are based on a lack of knowledge of the normal and possible courses of an *E. histolytica* infection and of the procedures necessary to determine its presence or absence. It seems to me that the most common cause of the confusion is a failure to examine efficiently for parasites an adequate number of specimens of stool after completion of a course of treatment with the drug under test. It should be common knowledge, as it is an unquestionable fact, that the number of parasites voided in the stools fluctuates from day to day and from week to week; often they are so scanty that none can be found for days on end.

From a considerable personal experience, I suggest that it is most unwise to infer that a person is free from *E. histolytica* infection of the bowel until at least ten or a dozen daily specimens of stool have been found to be free from parasites by a skilful technician regularly engaged in such examination. Even under such conditions, very occasionally a case of infection may escape notice; so, ideally, these serial examinations should be repeated at three-monthly intervals over a period of up to a year. While these standards obviously can but rarely be applied in ordinary medical practice, nevertheless adherence to them before statements are made about the efficacy of new and speculative amoebicides would do much to lessen the extravagance and inaccuracy of many claims and to obviate the resultant confusion in an already redundant literature.

Combined Use of Drugs

It has been the practice of British workers to combine the use of a number of the amoebicidal drugs over a period of two or three weeks when attempting to eradicate a bowel infection with *E. histolytica*. On the whole, in my opinion this practice has been thoroughly justified by the results. Some drugs, such as emetine, are absorbed from the bowel when given by mouth, and so presumably exert their action when conveyed systemically to parasites situated in the tissues of the bowel wall. Others, such as the iodo-oxy-quinolines, are not absorbed to any appreciable extent; so presumably they exert their action locally within the lumen of the bowel on the parasites with which they actually come into contact. That emetine, when given by mouth, is absorbed from the gut, and therefore cannot be regarded as exerting its action locally, is evident by the cerebral nausea which rapidly follows its liberation within the bowel from good-quality enteric-coated tablets.

As an example of the second mode of action, may I cite the case of a man suffering from a very chronic form of true relapsing dysentery. He was given 16 tablets (nearly 3.5 g.) of di-iodohydroxyquinoline daily for three months, during which his stools were examined daily. No parasites at all were seen during this time, but after the drug was stopped they reappeared in the stools in large numbers within 48 hours. This suggests that the drug does destroy the amoebae with which it comes into contact within the lumen of the bowel, and so prevents their encystment and passage to the exterior in the stools. But under such circumstances the absence of parasites from the stools is not evidence of freedom from infection of the bowel; this is merely masked by the drug while it is being taken.

Within the last few years the antibiotics, particularly aureomycin and terramycin, have received much attention

as therapeutic agents in infections with *E. histolytica*. The initial claim, which was based on an inadequate number of cases and insufficiently exacting standards of examination, was that aureomycin cured 100% of such intestinal infection. With further study by other workers this claim has been modified to a 50 to 80% cure rate. Terramycin has been stated to be at least as effective as is aureomycin and even less toxic; the general opinion is that it also will eradicate at least 70 to 80% of intestinal infections with *E. histolytica*. But Schneider (1951) has stated that though terramycin, like aureomycin, produces a satisfactory immediate clinical and parasitological response in intestinal amoebiasis, its effect is purely transitory, as clinical and parasitological relapse follow its use. Of 35 patients with amoebic dysentery, treated by Schneider with 2 g. of terramycin daily for 10 to 15 days, all relapsed parasitologically, and many clinically, within a few weeks of completing the treatment. Furthermore, he states that the drug was not always well tolerated, and in one of his cases it caused a marked rash.

Personal Observations on Aureomycin and Terramycin

In view of these remarkable discrepancies I venture to put forward some observations of my own on the uses of aureomycin and of terramycin in intestinal amoebiasis and amoebic dysentery. These are founded on the treatment of ex-members of the Forces with aureomycin or with terramycin, and their subsequent study and periodic re-examination over periods of at least three months and in some cases up to two years.

The treatment in each of these cases consisted in the administration of 0.5 g. of aureomycin by mouth six-hourly for 10 days, with no other accompanying drug treatment. Of 27 men treated with aureomycin, 23 were considered to be sterilized of their *E. histolytica* infections. Of the four cases which were not cured, in one case parasites were seen irregularly in the stools actually throughout the course of treatment; from the stools of the other three cases parasites were absent after the fourth or fifth day of treatment, but they reappeared within a week or two of its completion. Two of these four cases of failure to cure were those of men suffering from severe relapsing dysentery who had repeatedly been treated for some years with a remarkable and varied assortment of the usually accepted amoebicidal drugs: they were examples of the very refractory type of infection encountered from time to time. The subsequent re-treatment of all these four men with yet another combined course of amoebicidal drugs, and also a further course of aureomycin given concurrently with it, resulted in their successful sterilization as judged by regular re-examination over periods of from one to two years.

Forty-nine similar patients were treated with a comparable dosage of terramycin (0.5 g. six-hourly for 10 days); 46 of these 49 were considered to be cured by it. In one of the three cases of failure, parasites recurred in the stools irregularly during the treatment; in the case of the other two parasitological relapse followed within a week or two of treatment. Two of these three men were then cured by a combined three-weeks course of amoebicidal drugs given concurrently with terramycin. A third, after the initial unsuccessful terramycin treatment, was given a course of aureomycin alone; this failed to cure him. He then had a combined course of amoebicidal drugs without any antibiotic, which also failed. This combined course was repeated with the addition of aureomycin, and again it failed; but its repetition with terramycin instead of aureomycin resulted in the eradication of the infection, as judged by careful re-examination at three-monthly intervals for more than two years.

In no case was there any serious complaint of toxic side-effects from aureomycin or terramycin treatment in the dosages employed (20 g. over 10 days). Aureomycin not uncommonly caused a minor degree of gastro-intestinal upset, and occasionally a mild anal pruritus which in one or two instances persisted for some weeks. Terramycin

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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