Reviews in Medicine

Tropical medicine

G.C. Cook

Department of Clinical Sciences, Hospital for Tropical Diseases, St. Pancras Way, London NW1 0PE, UK

Introduction

Most disease in tropical and subtropical countries either has an infective basis or is a manifestation of the infection–malnutrition cycle. Many of these diseases, such as schistosomiasis, trypanosomiasis, leishmaniasis and filariasis, have clearly circumscribed geographical areas of distribution; others, such as malaria and the intestinal helminthiases and protozoan infections are far more widely spread. Some of the relevant bacterial and a few viral infections have already been covered in this series of review articles.¹ Some regional reviews are also available; for example, a succinct account of endemic diseases prevalent in the Middle-east was produced during the recent Arabian Gulf conflict.² Not all disease in tropical countries has an infective basis. Hypertension, atherosclerosis and diabetes mellitus are examples of diseases the prevalence of which is rapidly increasing, especially in urbanized communities. They can no longer be classified as diseases of ‘westernized’ or industrialized societies and they too have already received attention in this series of review articles. The present overview concentrates on parasitic – both protozoan and helminthic – and, to a lesser extent, viral and bacterial infections. The major objective is to highlight evolving areas, notably in diagnostic techniques and recent advances in management.

Some general problems in tropical countries

Apart from infection, the most obvious overt clinical problem in the tropics is malnutrition. This is not a new problem. Even in pre-colonial Africa devastating famines occurred not infrequently;³ kwashiorkor is certainly not, therefore, a modern problem! Despite a vast amount of research, many aspects of kwashiorkor, not least its precise

aetiology, remain enigmatic. This also applies to the nature of the oedema which is an important component in this clinical syndrome.⁴ The importance of early malnutrition in the production of long-term structural and metabolic deficits also remains unclear.⁵ Whilst an impairment in growth and mental development seem well established, the precise nature of these relationships is unclear.⁶ It has recently been reiterated that the ‘.... potential importance of micronutrient deficiencies such as deficiency of vitamin A among children with malnutrition seems to have been eclipsed by emphases on body composition and considerations of dietary energy and protein’.⁷ Furthermore, it now seems highly probable that the overall importance of vitamin A deficiency in the aetiology of infections, including childhood measles, pneumonia and persistent diarrhoea has been seriously underplayed.^{7,8} It is also the cause of much blindness in the developing countries.⁹

Inequalities in the availability of foodstuffs is largely a consequence of poverty, the situation in much of Africa being good testimony to this shortcoming.¹⁰ As has recently been pointed out, the ‘.... alleviation of poverty can only come from changes in social outlook which lead to alterations in the internal economy of a country and these changes can be effected only by the people themselves.’¹⁰ The major limiting factor at present seems to be a breakdown in food distribution rather than overall production. However, with population expansion proceeding at its present rate, an absolute shortage of foodstuffs seems inevitable. Coupled with food shortages, scarcity of fresh water seems a certain problem in much of Africa unless realistic solutions are soon forthcoming.¹¹ One estimate is that water shortage now threatens two-thirds of the African population. Lack of water impedes economic progress, leads to all manner of infective disease, and in times of drought imperils the survival of entire communities.

Healthwise, some barbaric local practices per-

Correspondence: G.C. Cook, M.D., D.Sc., F.L.S., F.R.C.P., F.R.A.C.P.

sist; one such is the dangerous and abhorrent technique of female circumcision.¹² This continues to be carried out in 28 African countries, by various groups in the Middle-east, Far-east, and by many of the descendents of west African slaves in Brazil. This custom incidentally is carried out wherever practising people have settled – including Europe, America and Australia.

What can be done to remedy the rapidly deteriorating situation?

Possible measures to bring about an improvement in the health of the populations of the developing countries – most of whom live in the tropics – can best be divided into macro- and micro-policies. In the latter, health care at a primary and tertiary level clearly has a significant impact. The major problem here is that the correct balance between the two seems impossible to achieve. Large scale immunisation is an attractive strategy for improving the health of residents in tropical countries;¹³ it ‘prevents illness and death through a small number of contacts with the health services; it is highly cost-effective; and its effects are long term’. Since 1974, this arena has been dominated by the Expanded Programme on Immunisation (EPI) under the auspices of the World Health Organization (WHO). After the Alma Ata conference of 1978, EPI declared a commitment to integrate services into primary health care, and the diseases (and vaccines) chosen were: tuberculosis (BCG), diphtheria, pertussis and tetanus (DPT), poliomyelitis (oral polio vaccine), and measles. Clearly there are major omissions in this programme, and potential prophylactic strategies for other lethal infections must be introduced: hepatitis B (HBV), respiratory tract infections (pneumococcal infection and *Haemophilus influenzae*), diarrhoeal disease (newer vaccines for rotavirus, typhoid and cholera), and *Plasmodium falciparum* malaria.¹³

A further example of a flawed policy concerns the WHO’s ‘essential drugs concept’ which originated in the 1970s.¹⁴ The list was drawn up in order that governments of developing countries could ‘rationalise their requirements for drugs by selecting a limited number which could be matched to assessed national health needs’. This stimulated international competition and initially brought prices down significantly. But the Action Programme on Essential Drugs which was established in 1981 has emphasized the plight of 1.3–2.5 billion of the world’s population who remain today without regular access to the most basic drugs at primary health care level.

At a tertiary care level, debate continues on the role of ‘centres of excellence’ for curative medicine and the training of medical personnel at all levels.

This also applies to the more sophisticated techniques used in investigation; are endoscopy and ultrasonography, for example, cost-effective procedures which should be adopted by developing countries?¹⁵ The consensus seems to be that the latter, at least, is justified in certain centres and is especially applicable to the diagnosis of hepatic lesions,^{16,17} and in the practice of obstetrics. The type of training required by medical practitioners in tropical countries has recently been highlighted during a controversial correspondence surrounding the possible setting up of Chairs of Tropical Surgery in the UK and other European countries.^{18,19} The obvious lack of appropriate case-material in these countries has to be balanced against the difficulties involved in an adequate and appropriate training in a developing country. Some will maintain that when a level of excellence has been achieved in a doctor or paramedical from a developed country, adaptation to the local scenario is by no means difficult.

Is there anything which can usefully be achieved, however, at a ‘macro’ level? Regrettably, foreign aid to developing countries decreased during the 1980s;²⁰ Britain’s contribution fell from more than £2 billion to under £1.6 billion in real terms! Unless new approaches are forthcoming, when viewed in the light of the economic crisis in Africa, continued expansion and improvement of health care will prove impossible. There is a shortage of imported drugs, migration of skilled health workers, and private practice is escalating. The present situation is exacerbated by the on-going acquired immunodeficiency syndrome (AIDS) crisis (especially in Africa) and the relentless increase in population size (in which Asia and southern America are principally affected); the latter results both from a lack of private family planning policies, and also longer survival.²¹ The human population has, in fact, expanded 5-fold in the past 150 years. If the birth rate does not fall, and with an ever increasing pressure on the world’s resources, in the presence of a rapidly deteriorating environment – the death rate will inevitably rise again.²³ Ultimately a plateau will be achieved when birth and death rates reach an equilibrium, but the present situation is that the birth rate remains high while the death rate is falling! So serious is the problem of overall growth in the world’s population, that King²³ has recently concluded, somewhat controversially, that ‘such measures as oral rehydration should not be introduced on a public health scale, since they increase the man-years of human misery, ultimately from starvation’. Although vast numbers of people actually want smaller families, and this applies even to the poor and illiterate, family planning strategies (other than abortion) are either not being adequately supported or implemented, or are still violently opposed.²² Unless an element of

reality is introduced in order to solve this equation, a sustainable global economy in biological terms will never be achieved and the world as we know it will cease to exist.²³ Unfortunately, the 'childhood survival hypothesis', championed, amongst others, by UNICEF, has failed.²² In Jordan for example, infant mortality has fallen significantly but fertility has not. It seems clear therefore that the attempted solution must now be jettisoned.

Malaria: prophylaxis and management

Plasmodium falciparum remains the most important parasitic infection of the tropics and subtropics and is responsible for countless billions of deaths. The most important complication is cerebral involvement. The precise mechanism(s) by which erythrocytes parasitized by mature *P. falciparum* trophozoites adhere to the cerebral capillaries is presently the subject of a great deal of research.²⁴

The other three species of *Plasmodium* affecting humans are of lesser consequence. Acute mortality is very unusual despite the fact that they cause significant morbidity and, occasionally, massive splenomegaly (hyperreactive malarious splenomegaly) and nephrotic syndrome (from *P. malariae* infection). However, malaria remains to this day a world-wide scourge on a vast scale.²⁵ No traveller to a malarious region of the world can afford to be complacent. In Britain, the last decade has seen an overall increase in annually reported cases of malaria of over 50%, and *P. falciparum* has increased from one-fifth to one-third of these.²⁶ In diagnosis there is presently no simple short-cut to replace the diligent examination of thin and thick blood films. New methods of biotechnology will doubtless ultimately make confirmation of this disease a simpler exercise.²⁷⁻²⁹

Prophylaxis for *P. falciparum* infection

The modern era of chemoprophylaxis began in the 1920s and '30s with the synthesis of several compounds which subsequently became widely used.^{25,30} For various reasons the development of new agents has failed to keep pace with demand. Many strains of the *P. falciparum* parasite have developed significant inherent resistance to the currently used drugs, and some second-line chemoprophylactics, especially when used in combination, have caused an unacceptably high rate of side effects, including many fatalities.³¹ As a result, older advice that avoidance of mosquito-bite is the safest line of prophylaxis, is once again dominating the scene.³¹ Mosquito-repellents, impregnation of bednets and clothing, and spraying of living accommodation with insecticide, are widely recommended. Because many large towns and cities in

malarious areas are largely free of the disease it is sometimes safer for the traveller to avoid chemoprophylactic agents and instead to treat an acute febrile illness with pyrimethamine and sulphadoxine ('Fansidar') or quinine. There is good evidence that, even when recommended, chemoprophylactic agents are poorly understood and compliance is unsatisfactory.³²

Recommendations regarding chemoprophylaxis are at present therefore difficult and have changed frequently during the last few years.^{30,31,33} Chloroquine-resistant strains of *P. falciparum* are commonplace in south-east Asia, northern South America, and east and central and, to a rapidly growing extent, west Africa. The distribution of resistance to other chemoprophylactic agents, including the dihydrofolate reductase (DHFR) inhibitors, is poorly documented. Table I summarizes advice currently given in Britain. Most centres in the USA offer different guidelines, and recent WHO recommendations include the abandonment of maloprim and its substitution with mefloquine in south-east Asia, Papua New Guinea and Africa; others would suggest doxycycline, which is strictly contraindicated in young children and pregnant women, as an alternative.

Recommendations for special groups, including pregnant women, infants, immunosuppressed patients, and Africans and Asians returning to their countries of birth, are complex.^{30,31} All pregnant women should be advised against travel to an infected region, or alternatively removal from one, if this is possible.

The value of antimicrobial agents requires further evaluation. Doxycycline (100 mg daily) has proved effective in Thailand.^{33,34} However, it is not widely recommended and has certain contraindications as already described. Chronic riboflavin deficiency has been shown to produce antimalarial effects^{30,35,36} and work is underway to investigate inhibitors of riboflavin metabolism. Whichever chemoprophylactic agent, or combination of agents, is chosen, it must always be appreciated that protection is never 100%.

Work on malaria vaccines has been in progress for some years; research in several laboratories is targeted at sporozoite, merozoite and gametocyte vaccines.^{31,37-40} However, many problems remain, and some of these have recently been highlighted.⁴¹ When it is eventually available, a *P. falciparum* vaccine will obviously not protect against infection with the other *Plasmodium* sp. At present these are nearly always sensitive to chloroquine, but not always to the DHFR inhibitors.

Treatment of *P. falciparum* infection^{31,42,43}

Until recently the chemotherapeutic agent of choice was chloroquine, and this remains the best agent if, or when, parasite sensitivity to it can be

Table I Widely used guidelines in *P. falciparum* chemoprophylaxis for British travellers

	Geographical areas	Regimen
(i)	No evidence of chloroquine or DHFR*-inhibitor resistance (Mediterranean and Middle-east)	Proguanil 100–200 mg daily, or chloroquine 300 mg weekly
(ii)	Widespread chloroquine resistance (including east, west and central Africa)	Proguanil 200 mg daily and chloroquine 300 mg weekly
(iii)	Widespread chloroquine resistance and regimen (ii) apparently ineffective (south-east Asia, the Pacific, and Papua New Guinea)	Maloprim [†] 1 tablet weekly and chloroquine 300 mg weekly, or mefloquine 1 tablet weekly

*Dihydrofolate reductase inhibitors, e.g. proguanil ('Paludrine') and pyrimethamine ('Daraprim'). [†]Maloprim = pyrimethamine 12.5 mg + dapsone 100 mg (single tablet).

ascertained. Regrettably, there are very few such areas left (Table I). In practice, it is obviously incorrect to gamble on parasite sensitivity in a life-threatening disease and, therefore, the vast majority of physicians now always use quinine when treating *P. falciparum* infections in travellers. In some areas, such as Thailand, partial resistance to this agent is a problem. Chloroquine remains the drug of choice in infection with the three other species of *Plasmodium*; but if there is initial doubt concerning identification of the infective species, quinine therapy should be instituted. Chloroquine is also usually effective in treating individuals in malaria-endemic areas who have partial immunity to the infection.

Table II summarizes quinine and chloroquine recommendations for use in treatment. Opinions differ on the optimal dose of quinine; some physicians recommend that a 'loading dose' (20 mg/kg) should be given during the first 4-hour period to achieve a high initial blood concentration.⁴⁴ This certainly seems wise in severe infections. When administered 8-hourly, signs and/or symptoms of toxicity occasionally appear³¹ and reduction to 12-hourly dosage is then necessary. The mere presence of tinnitus can usually be equated with a satisfactory blood concentration. Hypoglycaemia is an important side-effect especially during late pregnancy. Chloroquine given intravenously occasionally produces hypotension and other cardiovascular side-effects. 'Fansidar' is slower in action than either quinine or chloroquine, and should not be used alone in a severe infection.

The major chemotherapeutic agents are partly effective in most *P. falciparum* infections as, if it exists, chloroquine resistance is rarely complete,

and partial quinine resistance⁴⁵ is still localized geographically. However, other approaches are sometimes required.³¹ Mefloquine hydrochloride can be given as a 15 mg/kg (base) single dose or preferably in 2 divided doses.⁴⁴ However, resistance has been widely reported,^{46,47} and administration with 'Fansidar' in a combination regimen has been used successfully. Objections to this latter regimen have been made, largely on pharmacokinetic grounds. The sesquiterpene lactone, artemisinin (Qinghaosu), isolated from the wormwood plant *Artemisia annua* L, and for long used in China as a febrifuge, has recently received widespread attention^{43,48–50} but is still only rarely available outside China. It acts more rapidly than mefloquine, and its mode of action is unique. As well as tetracycline and doxycycline, clindamycin has been shown to have a place in the chemotherapy of *P. falciparum* infection.^{43,51,52} Sulphonamides and co-trimoxazole also possess anti-plasmodial properties, but all the antimicrobials have a relatively weak action and are not recommended alone. In addition, other 4-aminoquinolines, including dichlorquinazine⁵³ and pyronaridine,^{43,54} have been subjected to *in vitro* studies. The phenanthrene methanols, the most promising of which are halofantrine and enproline, have undergone clinical trial.^{43,55} In Thailand, recent evidence indicates that, following widespread reduction in chloroquine usage, strains of *P. falciparum* sensitive to this compound are rapidly re-emerging.⁵⁶

A patient with a high *P. falciparum* parasitaemia (>10%) possesses a potentially lethal infection, and requires first-class management, preferably in an intensive therapy unit and by a physician with special expertise of malaria.³¹ Cerebral involvement and extra-cardiac pulmonary oedema are

Table II Chemotherapeutic regimens for a *P. falciparum* infection

Agent	(during first 8 h)	Subsequent dose	Duration (days)
Quinine* (300 mg quinine sulphate/ tablet; 300 mg quinine dihydrochloride/ml)	10–20 mg/kg	10 mg/kg (maximum 600 mg) 8-hourly†	5–7
Chloroquine sulphate* (150 mg base/tablet; 40 mg/ml)	10 mg/kg	5 mg/kg after 6 h, followed by 5 mg/kg on subsequent 2 days	3
'Fansidar' (pyrimethamine 25 mg + sulphadoxine 500 mg)	3 tablets		1
Mefloquine ('Lariam')	0.75 g at 12-hour intervals		1

*The intravenous route should always be used in severely ill patients. †Some cautious physicians with an exaggerated concern for side effects use quinine 12-hourly, throughout. It should always be appreciated, however, that *P. falciparum* is a life-threatening disease, and presence of signs of minor toxicity, such as tinnitus, do not, in themselves, justify a lower dose regimen.

very important complications.²⁴ The role of exchange blood transfusion is presently unclear. It seems unlikely that it has a significant effect on parasitised erythrocytes sequestered in the cerebral capillaries, but it might remove certain mediators such as tumour necrosis factor and various metabolites. At present this procedure should probably be reserved for those with a parasitaemia more than 50% in the absence of complications, and more than 10% when cerebral involvement, pulmonary, renal, or haemostatic complications are present.^{24,57} In a developing country context the possibility of introducing infections, not least human immunodeficiency virus (HIV), hepatitis B and C viruses, probably outweigh the potential advantages of this technique.⁵⁷ Especially careful management of a *P. falciparum* infection is required during the last trimester of pregnancy; although quinine occasionally produces problems, these are usually of secondary importance to its life-saving properties.

In *P. vivax* and *P. ovale* infections, the exo-erythrocytic^{58,59} cycle can only be eliminated by adding primaquine to the therapeutic regimen, after the glucose-6-phosphate dehydrogenase concentration has been checked. The usual dose is 7.5 mg twice daily for 14 days, but should be higher in south-east Asia and the Pacific region.^{24,31}

Other important systemic parasitoses

Hydatidosis, an important canine-zoonosis,⁶⁰ is caused by infection with the cestode parasites *Echinococcus granulosus* and *E. multilocularis*. The disease is present wherever man exists in close

proximity to sheep and dogs.²⁴ The most important organ to be involved is the liver. Cysticercosis results from infection with the larval stage of *Taenia solium*, the porcine tapeworm.²⁴ Central nervous system involvement produces the most serious manifestations of infection.⁶¹ The emphasis in this section will be upon diagnosis and management of these two important parasitoses which exist not only in the tropics, but in many temperate zones, also.

Hydatidosis

Localization of the cyst (usually hepatic) is by radiography, ultrasonography, and/or computed tomographic (CT)-scanning. However, these techniques are not always as accurate as some investigators have claimed,⁶² and the result is occasionally suggestive of an erroneous diagnosis. Eosinophilia is inconstant and serological tests have, until recently, lacked specificity and sensitivity. However, the ELISA now has an important place in diagnosis, especially when antibody against 'Arc-5' (a genus-specific antigen isolated from unilocular hydatid cyst fluid) is used.²⁴ Recently, an immunoblot assay using an *E. granulosus* antigen of 8 kDa molecular weight has given 100% specificity in the diagnosis of hepatic hydatidosis.⁶⁴ Furthermore, cyst-fluid obtained by ultrasound-guided aspiration can be subjected to cytological verification or an ELISA technique.⁶²

Management was formerly surgical, usually after prior injection of the cyst with hypertonic saline, silver nitrate, or 0.1% cetrimide. The benzimidazole group of compounds has been widely used for 'medical' management over the last decade

and is still undergoing evaluation.^{24,63} Mebendazole was the first chemotherapeutic agent to be used,⁶⁵ but the most effective compound to date is undoubtedly albendazole.⁶⁶⁻⁶⁸ There is now excellent evidence indicating that, provided an adequate concentration is attained within the cyst, it is scolicidal.^{66,67,69} Albendazole is also effective as a chemotherapeutic agent in inoperable cases and for prevention of intra-abdominal spread, prior to surgery.^{68,70} Horton⁶⁸ has recently reviewed the outcome of a large series of infected patients who were given albendazole chemotherapy, mostly 800 mg daily in cycles of 28 days separated by 14 days, during an approximately 5-year period. Of 253 infected patients, 72 (28%) were considered cured, 129 (51%) improved, 46 (18%) unchanged and 6 (2%) worse off. Forty-seven patients underwent surgery after treatment and in only 5 (11%) were cysts still viable. Experience with *E. multilocularis* infection was limited, but of 35 who were treated, 2 were cured, 4 improved, the disease had stabilized in 25, and 4 had worsened. Side-effects of albendazole were uncommon.

When surgical intervention is necessary, albendazole should be administered pre-operatively; an experimental study using gerbils has demonstrated that a delay in chemotherapy until 15 days after peritoneal inoculation of protoscoleces diminishes this advantageous effect.⁷¹ Cyst viability following chemotherapy can be assessed by the ELISA,⁷² specific IgG, and CT-scanning; complete cyst calcification usually signifies a successful outcome.

Praziquantel alone, and in combination with albendazole, has undergone extensive study in rats and gerbils infected with *E. multilocularis*.^{73,74} It is an active protoscolicidal agent, but is less active than albendazole in the inhibition of cyst growth. Recently, praziquantel has been subjected to clinical trial, but its efficacy is currently impossible to evaluate; there is no doubt however, that this compound, when present at an adequate concentration, is a very active protoscolicidal agent.⁷⁵ However, a recent *in vitro* study has indicated that praziquantel is probably inferior in this respect to albendazole sulphoxide.⁷⁴ There is currently an urgent need for large multicentre trials to accurately assess the role of albendazole⁷⁶ and praziquantel. Combination regimens using albendazole + praziquantel seem effective when either of these agents has failed when used alone.^{24,77} Some cases will probably always require surgery, but only after prior albendazole and/or praziquantel treatment.

Neurocysticercosis

A history of exposure to an endemic area, even 30 years or more previously, is important diagnostically. In such an area, neurocysticercosis is the

most common cause of epilepsy in young adults. Family and friends, as well as the patient, occasionally have a current infection with *Taenia solium* and faecal examination may then reveal eggs. The entire body-surface should be palpated for subcutaneous and intramuscular nodules; a high 'index of suspicion' in an individual known to have been at risk is very important.⁷⁸ Definitive diagnosis is dependent on histological examination of a cysticercal cyst, which if situated subcutaneously can be excised under local anaesthesia. The fluid-filled opaque 'bladder' (1 to 70 mm in diameter) contains a single, solid, white sphere (the scolex). A translucent membrane with a central 'milk spot' is characteristic; if alive, the parasite may evaginate its head and neck, or it may be induced to do so by immersion in hot saline.

In children, a skull-radiograph often shows sutural diastasis. However, the 'hallmark' of neurocysticercosis radiologically consists of multiple elliptiform intracranial calcifications; a central calcified scolex surrounded by a calcified cyst is pathognomonic.⁷⁹ Calcification does not, however, usually occur until at least 3 years after infection and often very much later. In one study, intracranial calcifications were found in 36% of cases within 10 years of the presumed date of infection, but 97% already had calcification in skeletal muscles. CT-scanning may reveal non-calcified cysts, and this is the most valuable radiological procedure.⁷⁹⁻⁸³ It is also of value in the widely disseminated form of the disease. When present in the ventricles, contrast-enhancement is usually necessary because cyst and cerebrospinal fluid absorption values are similar. The CT patterns of neurocysticercosis have been recently reviewed.⁸⁴ A report from South Africa documents a close correlation between appearances on nuclear magnetic resonance (NMR) imaging and histopathological features,⁸⁵ the excellent degree of resolution allowed visualization of larval protoscoleces.

Although an eosinophilia is sometimes present, this is of little or no value diagnostically.^{79,80} The finding of *T. solium* eggs in a faecal specimen is, overall, an unusual finding. Cerebrospinal fluid (CSF) pressure is occasionally elevated.⁷⁹ A pleocytosis of 5 to 500 cells or more, with either a lymphocyte or eosinophil predominance is inconstant.^{79,80} Protein changes are non-specific; total protein and IgG may sometimes be elevated.⁷⁹ A very low glucose concentration apparently carries a bad prognosis.⁸⁰ Surgical biopsy is sometimes necessary for a definitive diagnosis.⁷⁹

Immunodiagnosis, formerly unreliable,⁸⁶ is becoming increasingly sensitive and specific.⁷⁸ Widely divergent sensitivity of serodiagnostic tests depend not only on the technique, but also the characteristics of the patient population(s) and cyst viability.⁸⁷ Limited evidence suggests that antigen derived

from cysticercal fluid possesses far greater reactivity than that from the cyst-wall.⁸⁸ An indirect haemagglutination test has proved useful, but negative results certainly do not rule out active infection.^{79,89}

An ELISA with sensitivity which varied between 61% and 79% was documented in 1982,^{86,90} but cross-reactions with hydatid and schistosomal infections, proved troublesome. A group in Mexico considered that serological tests for neurocysticercosis still lacked reliability.⁹¹ However, when antigen from *Cysticercus cellulosae* fluid is available, the ELISA now produces results which are both sensitive and specific.⁸⁸ Experience with serum and cerebrospinal fluid testing using an ELISA designed to detect IgG antibodies against *C. cellulosae* and *T. solium* antigens has been reported from Columbia,⁹² Mexico,^{86,93,94} Durban, South Africa⁹⁵ and Brazil.⁹⁶ The sensitivity and specificity rates are of the order 85–90%.

Until 1979 the only form of management for this disease was surgical,⁸⁹ since when chemotherapy has produced generally encouraging results.⁷⁸ Experimental work demonstrated that praziquantel can destroy the tegument along the whole pseudostrobila and the scolex of the related species – *C. fasciolaris*.⁹⁷ Assessment of the efficacy of chemotherapy can be evaluated *in vivo* by CT-scanning in conjunction with serial measurement of serum antibody titres against cysticercal antigen.^{89,98,99} Early clinical trials gave satisfactory results in 172 out of 192 cases of neurocysticercosis.⁹⁸ In Mexico, 26 patients were treated with 50 mg praziquantel/kg daily for 15 days; after 3 months all had improved clinically and 13 were asymptomatic.⁹⁹

The most frequent 'inflammatory' problem with praziquantel has been the CSF reaction syndrome, characterized by fever, headaches, meningismus, and exacerbation of many of the neurological symptoms of the disease. It is considered to be caused by a local reaction to dead and dying larvae, possibly analogous to the Jarisch-Herxheimer reaction. Simultaneous administration of corticosteroids has produced encouraging results in prevention and/or attenuation of this reaction.^{82,100–102} A large group of 141 patients with neurocysticercosis treated with praziquantel, half of whom also received prednisolone, has been reported;¹⁰³ 75 of them were asymptomatic after 5 years and the cysts or nodules had either disappeared or had calcified, while 35 showed both clinical and radiological improvement. However, intraventricular cysts in 5 of them had to be removed surgically, and 31 were unchanged or had actually worsened.

Although still controversial, nearly all physicians now favour the addition of a corticosteroid 'cover' to reduce the incidence of the CSF reaction syndrome.^{104,105} Del Brutto and Sotelo,⁸⁴ however,

consider that dexamethasone should only be given when intracranial hypertension develops during therapy as there is evidence that simultaneous administration of a corticosteroid significantly reduces the plasma praziquantel concentration. Another group of physicians considers that praziquantel administration without corticosteroids becomes increasingly hazardous as neurocysticercosis becomes progressively severe.¹⁰⁵

Recently, albendazole has been used in 7 patients with neurocysticercosis;¹⁰⁶ when treatment was begun, 157 cysts were delineated by CT-scanning and at 3 months after treatment this had reduced to 22. In a prospective, controlled and randomized study, albendazole has been compared with praziquantel in 20 patients;⁸³ after 3 months, 76% and 73% cyst-remission rates, demonstrated by CT-scanning, were recorded in those treated with a single course of albendazole and praziquantel respectively. However, an exacerbation of neurological lesions, similar to that after praziquantel, has been documented and simultaneous corticosteroid administration is then necessary.⁸⁴ Albendazole has been combined with dextrochloropheniramine in a clinical trial at São Paulo, Brazil;¹⁰⁷ this combination produced promising results, but it is unclear whether it has any advantages over albendazole when given alone. Limited use of flubendazole, another benzimidazole compound, has been documented.⁸⁰ A further potentially useful chemotherapeutic agent is metrifonate. In certain situations, especially when CSF pressure is significantly raised, surgery is, however, still the major line of treatment.^{79,80,84,103,106}

Intestinal parasitoses

Helminths

For the most part, diagnosis of these infections, which are extremely common in the developing countries and occur in travellers to them, remains dependent on the demonstration of eggs in a faecal sample. Serology has little or no part in diagnosis. The introduction of the benzimidazoles, praziquantel, and ivermectin, has revolutionized chemotherapy of these infections; this subject has recently been reviewed in the *Postgraduate Medical Journal*.¹⁰⁸ However, the serious problem of cost remains; with the exception of ivermectin, which is currently being provided free by the manufacturer, but specifically for use in onchocerciasis, all of these compounds are expensive. But provided financial constraints allow, none of the human intestinal nematode, cestode, or trematode infections can now be regarded as untreatable.

Protozoa

With the possible exception of the coccidia, *Giardia lamblia* remains the most common protozoan to inhabit the human small-intestine; the spectrum of disease in both children and adults ranges from the asymptomatic state to travellers' diarrhoea, and one of severe steatorrhoea and weight-loss. Diagnosis continues to depend upon visualization of the trophozoite in the duodenal or jejunal fluid or biopsy, or cyst in a faecal sample.¹⁰⁹ Serological diagnosis has contributed little; serum IgG remains elevated for months or years after infection and is usually increased in an individual resident in an endemic area. A specific serum anti-*Giardia*-IgM response – which is short-lived – can, however, sometimes be used to differentiate a present from a past infection. Detection of specific *Giardia*-antigen in a faecal sample has now been carried out in several laboratories, but is not yet, however, in routine diagnostic use. Countercurrent immunoelectrophoresis (CIE) or ELISA are usually used; a *Giardia* antigen-capture ELISA has given a sensitivity of 90%. Recently, a *Giardia lamblia*-specific antigen (65000 M_r) (GSA 65) has been identified in faecal samples in infected individuals, this also being detected by CIE. The highly specific DNA-probes which are increasingly being introduced for enteric infections will doubtless eventually improve diagnosis of this cosmopolitan protozoan infection. Management continues to be dominated by the 5-nitroimidazole compounds – metronidazole and tinidazole.^{24,109}

The most important of the common colorectal protozoan infections, by far, is *Entamoeba histolytica*. In diagnosis, using a faecal sample, differentiation from other intestinal protozoa is important.^{24,110} Shigellosis produces a clinical picture which is often similar and this diagnosis must obviously be excluded.^{111,112} Visualizing trophozoites in a *fresh* faecal sample, or rectal scraping or biopsy is the surest means of diagnosis; ingestion of the host's erythrocytes is characteristic. *E. histolytica* trophozoites can occasionally be detected in liver 'pus', and an indirect fluorescent antibody technique has been applied.¹¹³ Although first developed in 1925, *in vitro* faecal culture remains primarily an investigative technique.

Immunological tests for *E. histolytica* infection have been reviewed and their value in epidemiological surveys assessed.²⁴ The immunofluorescent antibody test (IFAT) is of considerable value in severe invasive amoebiasis; however, even in this situation, some 5% or more of results are negative in the early, acute stage of an hepatic 'abscess'. In amoebic colitis, although up to 75% of cases give positive results, the titre is usually much lower than it is in invasive disease involving the liver. A rapidly

performed indirect haemagglutination test for serodiagnosis has been documented. An ELISA designed to detect circulating immune complexes of *E. histolytica* proteins as a diagnostic test in hepatic amoebiasis has been reported¹¹⁴ but it is important to recognize that immunosuppression can give rise to false-negative results. A CIE and cellulose acetate precipitation (CAE) test are of value in the diagnosis of acute disease in that they become positive much earlier, and remain positive for a far shorter time than the IFAT. Detection of *E. histolytica* antigen in faecal material using an ELISA has also been reported.^{115,116} A technique utilizing immunofluorescence with monoclonal antibodies to separate pathogenic from non-pathogenic *E. histolytica* might prove useful in clinical management.¹¹⁷

There appear to be genomic DNA differences between pathogenic and non-pathogenic *E. histolytica*.¹¹⁸ Unfortunately, the isoenzyme technique used to identify the subspecies takes several days to perform and is of little or no value in clinical medicine; it will, however, continue to be valuable in epidemiological work.¹¹⁹ Ultrasonography and CT-scanning are extremely valuable techniques for localizing hepatic abscesses, and for differentiating them from other intrahepatic space-occupying lesions. When aspiration is carried out (see below), it can be performed under ultrasonographic control.

Mortality rate from invasive amoebiasis fell from more than 80% during the nineteenth century to around 10–20% in the early 1970s, and to 2% after the introduction of metronidazole. Treatment of amoebic colitis is now usually straightforward: 800 mg metronidazole three times a day is given orally for 5–10 days. Recently, tinidazole, 2 g daily for 3 days, has also been used, but evidence of cure, using controlled trials, is far less extensive. Ornidazole is also effective; success rates of up to 94% have been achieved.

Whether or not amoebic colitis can proceed to inflammatory bowel disease (IBD) is debated. Misdiagnosis of amoebic colitis as IBD, followed by subsequent corticosteroid therapy can be followed by a fatal outcome.²⁴ Perforation – although a rare event – can complicate amoebic colitis, with the production of amoebic peritonitis;¹²⁰ there may be diffusion of *Entamoeba histolytica* from a 'blotting-paper'-like colon, peritoneal perforation (especially in the rectosigmoid or caecal regions), perforation to the retroperitoneal tissues, or leaking into a confined space resulting in a pericolic abscess or internal intestinal fistula. Management consists of gastric suction and intravenous fluid replacement; metronidazole – 800 mg 8 hourly for 10 days preferably by the intravenous route – and a broad-spectrum antibiotic should be started immediately.

Because the colon is extremely friable, laparotomy is usually best avoided;¹²¹ overall mortality is of the order of 50%, and after surgery often close to 100%! Two recent reports have documented the results of surgical intervention in 15 patients with fulminant amoebic colitis.^{122,123} It seems likely from this limited evidence that when the diagnosis is made *before* surgery and metronidazole started immediately, surgical resection can be beneficial. An amoeboma of the colon or rectum can easily be mistaken for a colorectal carcinoma.¹²⁴ When doubt exists, a course of metronidazole should be given and resolution usually occurs within one week.

Aspiration of a liver 'abscess' is indicated only when a large abscess(es) is present in a sick patient, or the abscess impinges upon a vital organ such as the pericardium.¹²⁴ A recent controlled trial in India has clearly demonstrated that in an uncomplicated case routine aspiration is *not* indicated.¹²⁵ Resolution of an amoebic abscess can be assessed by ultrasonography or CT-scanning; it is very slow, but this is entirely consistent with successful chemotherapy.¹²⁶

Spontaneous perforation of an amoebic liver 'abscess' (especially into the pericardial cavity) is a serious complication;¹²⁰ Ken *et al.*¹²⁷ recommend wider use of catheter drainage of perforated abscesses, whilst Singh *et al.*¹²⁸ advise a similar technique for apparent drug resistant abscesses.

When available, diloxanide furoate ('Furamide'), 500 mg 8 hourly for 10 days, should *always* follow the 5-nitroimidazole compound. Diloxanide is an excellent luminal amoebicide, whereas both metronidazole and tinidazole have relatively weak activity on the cyst-stage.²⁴ Numerous examples exist of a second amoebic liver abscess(es) arising when a full course of metronidazole has not been followed by diloxanide.

Should all *E. histolytica* cyst-carriers be treated? In a Western country where diloxanide is available the answer must at present be *yes*. If determination of specific zymodemes becomes available,¹²⁹⁻¹³¹ individuals harbouring non-invasive zymodemes need not perhaps receive diloxanide, a view which has however been challenged.¹³² The situation in Third World countries is different, as diloxanide is frequently not readily available.¹³³ A study in India has suggested that the cyst-carrier state usually resolves spontaneously.¹³⁴ *E. histolytica* infections are common in male homosexuals, but nearly all seem to belong to non-invasive zymodemes.^{135,136} Some workers have concluded that the cyst-carrier state in homosexual men can be safely left untreated,¹³⁶ but caution is surely required.¹³⁷

AIDS-associated intestinal parasitic infections

Although the range of opportunistic parasites involved is similar, their prevalence tends to differ in patients suffering from AIDS in a tropical country compared with a temperate one.^{24,138} For example, *Pneumocystis carinii* seems to be less common in tropical Africa perhaps because patients usually succumb first to a more virulent organism, such as *Mycobacterium* sp. or *Salmonella* sp. The small-intestinal coccidia are of very great importance because they contribute to severe watery diarrhoea, malnutrition and weight-loss (the 'slim-disease' of Uganda). The two other major systemic parasitoses – *P. carinii* and *Toxoplasma gondii*¹³⁸ – are dealt with elsewhere in this series of review articles.

Recent interest in human coccidia is by no means confined to immunodeficient persons and those with AIDS however. It has recently become clear that some coccidia, at least, are causatively important in the self-limiting diarrhoea of infants and children as well as in the diarrhoea suffered by immunocompetent travellers. The clinical importance of the intestinal coccidia varies geographically. As with certain systemic protozoan parasites they are more prevalent in many Third World countries compared with most industrialized ones.^{139,140}

The small-intestinal coccidia have a history dating back several million years. From their haematogenous *Plasmodium* sp., the causative agents of malaria, originated.^{24,141} Their life-cycles, which are complex and have still not been satisfactorily unravelled, vary from species to species.¹⁴²⁻¹⁴⁵ In some instances, light and electron microscopical studies are currently open to different interpretations.¹⁴² Absence of mitochondria in *Cryptosporidium* sp. brings it perhaps into line with intraluminal protozoa including *Giardia lamblia*; on the other hand, *Isospora belli* which does possess these organelles has points in common with other intracytoplasmic enterocytic parasites.¹⁴² Development of *Cryptosporidium* sp. in cell culture has been described.¹⁴¹

Overall, most known facts about coccidia relate to *Cryptosporidium* sp., although even here it is still unclear whether or not more than one species exists.^{24,142} This genus infects a wide range of animal species, including reptiles, fish, birds, and mammals ranging from rodents and household pets to farm animals, especially calves.^{143,144} Despite its great antiquity and widespread distribution (identification in mice dates back to 1907), it required AIDS to bring it to prominence in a human context. Heavy infections associated with protracted diarrhoea, severe malabsorption and weight-loss, are an especial problem with AIDS in Africa.¹⁴⁶ After initial recognition, it rapidly

became clear that routine faecal staining-methods completely failed to identify this and other coccidia. Either a modified Ziehl-Neelsen or Kinyoun acid-fast technique is, however, satisfactory.^{141,142} There are now extensive data incriminating this organism, and other coccidia also, in acute diarrhoeal disease in both Western, and Third World^{147,148} countries, especially in indigenous children, but also in adult travellers suffering from travellers' diarrhoea.¹⁴⁹ There have been outbreaks in day-care-centres in the USA and Canada.¹⁴⁴ Up to 13% of acute diarrhoeal episodes in Third World paediatric practice¹⁴⁴ have been attributed to cryptosporidiosis. Limited evidence indicates that breast-feeding gives some protection.¹⁵⁰ Apart from AIDS, the infection is also important in immunocompromized states such as those resulting from lymphoma, leukaemia and cytotoxic therapy.^{141,142}

Until recently, cryptosporidiosis was considered to be a zoonotic disease; indeed, the first recorded human case involved a 3 year old girl who lived on a farm.¹⁴¹ However, within the past 5 years, person-to-person transmission and infection from contaminated food and water^{151,152} have become increasingly apparent. Airborne and perinatal routes of infection have also been suggested recently.¹⁴¹ The potential reservoir for human infection must be vast. The organism is widely spread in the animal kingdom, and oocysts are stable in excreta and are resistant to many chemical agents.¹⁴¹ While *I. belli* infections arise largely from oocysts ingested in contaminated food and water,¹⁵³ *Sarcocystis hominis* infection usually originates from ingestion of bradyzoites in raw beef or pork especially cardiac and oesophageal muscle; person-to-person transmission is probably unusual.

Clinical manifestations of a coccidial infection vary greatly between the immune-intact and the immunocompromized person. In the former, cryptosporidial infection produces self-limiting diarrhoea of 2–14 days duration. The incubation period of 4 to 14 days may include an 'influenza-like' illness and low-grade fever.^{24,141} Abdominal discomfort, anorexia, nausea, vomiting and mild weight-loss are additional features. In travellers, in particular, the clinical syndrome resembles very closely that caused by *Giardia lamblia* infection with which it may coexist.¹⁵⁴ In the immunocompromized host, the resultant small-intestinal diarrhoea may be torrential with 1 to 15 litres of fluid being passed daily for many weeks or months. This is often accompanied by malabsorption with grossly deranged absorption tests.¹⁴⁶ It is important to appreciate that HIV-1 and HIV-2 can both produce enterocyte damage – HIV-enteropathy in the absence of an opportunistic organism (see below). Fever may be a feature, and death a certain

sequel.

Disease caused by *I. belli* is, in most respects, similar, the incubation period in the immunointact being approximately 1 week. Oocysts may be recovered from faecal samples for 9 to 15 days after infection. One estimate is that 15% of AIDS sufferers in Haiti are infected with *I. belli*.¹⁵³ In *Sarcocystis hominis* infection, diarrhoea and abdominal pain usually begin 14 to 18 days after infection. Overwhelming evidence now exists that *Microsporidium* sp. is a significant opportunistic infecting organism in AIDS.^{155,156} Other intestinal opportunistic infections are often present in association with coccidia.¹⁵⁷

In AIDS, *Cryptosporidium* sp. may involve any part of the gastrointestinal tract, including the biliary system.¹⁴¹ Histological appearances closely resemble those of idiopathic sclerosing cholangitis.¹⁴⁴ Multisystem involvement has been recorded, as has infection with *I. belli* which included a chronic granulomatous response in mesenteric and tracheobronchial lymph glands.¹⁵⁸

Diagnosis of coccidial infections is by detection of oocysts in faecal samples by means of appropriate staining techniques, as described above. An indirect fluorescent antibody procedure¹⁵⁹ and a monoclonal technique¹⁶⁰ for detecting oocysts in faeces have given encouraging results. Serum antibody to *Cryptosporidium* sp. has been detected by use of an indirect immunofluorescence technique (IIFT).^{161,162}

Chemotherapy for coccidiosis is not indicated in those whose immune response is intact. Infection is self-limiting in them, but oral rehydration may be required in the acute phase of the illness. Shedding of oocysts continues for 8 to 50 (mean 12–14) days,¹⁴¹ a carrier-state and relapse seem to be very unusual. When the immune response is impaired as in AIDS, chemotherapy is badly needed, but ineffective. In cryptosporidiosis, the macrolide antibiotic, spiramycin^{141,163,164} is the only chemotherapeutic agent which apparently has any value. Even when treatment is temporarily successful, recurrence is usual in those with AIDS. Many other lines of treatment have been attempted, but with very limited success. The value of azidothymidine (AZT) is so far unclear.¹⁶⁵ Hyperimmune bovine colostrum has been given orally but results to date are contradictory.^{166–168} Treatment of an *I. belli* infection in the immunosuppressed is more satisfactory – with furazolidone, or trimethoprim and sulphamethoxazole.^{141,153,164} Despite improvement in clinical symptomatology, there is little evidence that metronidazole or primaquine are effective in eliminating *Microsporidium* sp.¹⁵⁶ *Blastocystis hominis* infection, which some investigators persist in regarding as merely commensal^{169,170} in immunosuppressed persons, respond to metronidazole.^{171–173}

Diseases with localized geographical distributions

Schistosomiasis

One estimate is that 200 million people in 74 developing countries are affected by this helminthic parasitosis first described by Theodor Bilharz in 1852.¹⁷⁴ It seems likely that only malaria has a more important effect on socioeconomic factors and health.

The range of clinical presentation is broad. Infection can continue for 30 years and more.¹⁷⁵ While many cases are asymptomatic, fatal haematemeses – from bleeding oesophageal varices, and ascites (in the hepatosplenic form of *S. mansoni* and *S. japonicum*), and chronic urinary obstruction, pyelonephritis, and squamous carcinoma of the bladder (in *S. haematobium* infection) form the tip of an iceberg. The most common presenting features are terminal haematuria, usually associated with dysuria (*S. haematobium*), and intermittent diarrhoea which is occasionally bloody (*S. mansoni* and *S. japonicum*). Any organ can be involved but central nervous system involvement can present a particularly serious clinical problem. Pulmonary involvement has been recorded.¹⁷⁶ Acute schistosomiasis (Katayama fever)¹⁷⁷ presents 3–6 weeks after an initial infection, with a febrile illness, hepatosplenomegaly and frequently a giant urticarial rash. There may be no parasitological or serological evidence of infection at presentation, these becoming positive some days later. Immunological mechanisms^{178–180} are important in the clearance of immature schistosomulae. Whilst IgE can mediate damage to the parasite, there is only limited evidence that it affects host protection. However, in the Gambia, an age-related decline in the severity of reinfection after treatment with praziquantel in the first 2 decades of life, is associated with a high IgE concentration.¹⁸¹ Production of both IgE and IgG4, which is elevated in younger patients, are stimulated by interleukin 4. The importance of these observations in the quest for a vaccine is debatable.

Diagnosis of the disease is dependent upon the detection of characteristic eggs in urine, a faecal sample, or bladder, liver or rectal biopsy; concentration techniques are valuable in urinary and colonic infections. Serologically, the ELISA now gives very high ($\geq 95\%$) sensitivity and specificity. However, this is of only very limited value in the assessment of cure, because after successful treatment, it does not become negative for 2–3 years. Ultrasonography is of value in the diagnosis of pipistem fibrosis. An intravenous urogram and/or cystoscopy are usually required to adequately assess urinary tract involvement. In patients with *S. mansoni* liver disease, the hepatitis B surface antigen (HBsAg) carrier state is up to 4 to 5 times

more common than in the uninfected population;^{182,183} this association has not, however been established in *S. japonicum* infection.

The last decade has seen very important advances in chemotherapy of schistosomiasis.¹⁰⁸ Praziquantel has received widespread assessment – especially in *S. mansoni* infection.^{24,184} As well as arresting progression of disease, an actual reduction of hepatosplenomegaly and portal hypertension has been documented.^{185–187} When compared with oxamniquine, another newer agent,¹⁸⁸ in *S. mansoni* infections, it is generally superior, although oxamniquine has a place in management as it is cheaper. In *S. haematobium* infection, praziquantel is preferred, but metrifphonate^{189,190} is cheaper and is widely used in developing countries. In acute schistosomiasis, chemotherapy should either be delayed until after the initial phase has passed, or preferably given under a corticosteroid cover.¹⁷⁷

Attempts at snail eradication have been made in several countries and have almost invariably met with a lack of overall success. Education of indigenous populations is of paramount importance in disease prevention.

Filariasis

This group of nematode infections comprises lymphatic filariasis (*Wuchereria bancrofti* and *Brugia malayi*), tropical pulmonary eosinophilia, *Onchocerca volvulus* ('river blindness'), *Dracunculus medinensis* (guinea-worm), and *Loa loa* infection.^{24,191,192} The adult worms live for many years, during which time they produce large numbers of immature larvae which are the infective stage which is transmitted to the insect vector.

Lymphatic filariasis Elephantiasis is a disease of great antiquity; it was described in early Persian and Indian texts and is probably depicted in the thirteenth century *Mappa Mundi*, at Hereford Cathedral;¹⁹³ it is possible, however, that the latter might refer to podoconiosis – a non-parasitic form of elephantiasis caused by the penetration of silica particles through the soles of the feet into the lower limb lymphatics.¹⁹⁴ Manson first demonstrated the causative organism ('*Filaria sanguinis hominis*') in mosquitoes in 1877.¹⁹⁵ Orchitis, epididymitis and hydrocele are important clinical manifestations. The only presenting feature (which may be recurrent) consists of localized pain, tenderness, swelling, erythema and adenolymphangitis involving one or other limb. The classical signs, which include elephantiasis and chyluria, resulting from lymphatic obstruction, usually appear about 10 years after the initial infection.

Diagnosis is by detection of microfilariae in a nocturnal blood sample, chylous urine or hydro-

cele fluid. Serology is not specific for the individual filariasis and there is cross-reaction with strongyloidiasis. Diethylcarbamazine (DEC) remains the major chemotherapeutic agent;²⁴ although it exerts a lethal effect on microfilariae it has a more limited effect on the adult worms and has no effect on established obstructive lymphatic features. Ivermectin (see below) is undoubtedly inferior to DEC.^{196,197} Metrifiponate is also a good microfilaricide.

Tropical pulmonary eosinophilia This pulmonary disease, which results from dense parenchymal eosinophilia, occurs most frequently in southern India and Sri Lanka.²⁴ There is usually a striking elevation of the peripheral blood eosinophil concentration (usually $> 3.0 \times 10^9/l$), strongly positive filarial serology, and an absence of microfilariae in peripheral blood. Dyspnoea, wheezing, and a paroxysmal cough are most marked nocturnally; there is little sputum production. Serum IgE is elevated. There is a profound immunological response to filarial infection in the lower respiratory tract and these filaria-specific antibodies play an important role in the pathogenesis of this disease.¹⁹⁸ Most cases are caused by animal filariae, especially *B. pahangi*. Response to DEC is rapid, but corticosteroid cover is advisable, because the extent of antigen release is often substantial.

Onchocerciasis *Onchocerca volvulus* is transmitted by black flies (the *Simulium damnosum* – complex). Ophthalmic and skin involvement are the most prominent features. The microfilariae, which after several months of active life die with the production of inflammatory lesions which subsequently fibrose, cause significant tissue damage; the adult worms – which can form nodules which may be subcutaneous – are essentially benign. The microfilariae produce an eosinophilic response often exacerbated by DEC administration, and granuloma formation.

The type and distribution of the dermatological lesions vary in different geographical locations.²⁴ The ophthalmic lesions include: presence of microfilariae in the anterior chamber (slit-lamp examination is valuable), punctate keratitis, sclerosing keratitis, anterior uveitis, choroidoretinitis, optic neuritis and atrophy, and glaucoma. Diagnosis is made by microscopical examination of skin-snips which are taken from standard sites.

Both DEC and ivermectin are microfilaricidal¹⁹⁹ and neither has much effect on adult worms. Ivermectin has proved safe in pregnancy²⁰⁰ and is effective as a microfilaricidal agent.^{201–203} This should be given at yearly intervals;¹⁰⁸ ophthalmic complications are certainly less than with DEC. In west Africa and South America, serious side-effects are rare, and seem to be limited to those with a very

high level of infection.^{204–206} A higher prevalence has been reported in travellers from the UK²⁰⁷ and USA.²⁰⁸ Ivermectin is being widely distributed in west Africa.²⁰⁹ Recently, amocarzine has produced a 73% adult worm death-rate 4 months after treatment.²¹⁰ Clearly further trials are required.

Dracunculiasis Guinea worm infection causes a great deal of morbidity in endemic areas – west Africa, western India and Pakistan, and to a lesser extent the Middle-east. The global incidence is estimated at 5–10 million cases annually. A recent report from Nigeria, documents the high prevalence of permanent disability resulting from the infection.²¹¹ This accounts for a substantial burden on rural communities in endemic areas. The major problem is one of secondary bacterial infection which usually involves the knee or ankle joint with the production of cellulitis and osteomyelitis. The traditional form of management, still in use, is to wind the adult worm – a few cm daily – around a matchstick as it emerges from the cutaneous lesion. Chemotherapy remains unsatisfactory.¹⁰⁸ A recent report indicates that 3% chlortetracycline ointment when applied during the emergence of the adult from the subcutaneous tissues promotes expulsion of the worm, thus preventing secondary infection, and kills the larva during shedding, thus reducing transmission of the disease.²¹² This observation clearly requires confirmation. Eradication of the infection is a plausible possibility and the WHO has given priority to preventive strategies.^{213,214}

Loaiasis *Loa loa* is conveyed by tabanid flies and is localized to the rain forest regions of west and central Africa. It is the most trivial of the human filariases. The clinical manifestations are soft tissue (subcutaneous) swellings – ‘Calabar swellings’, and the worms may be seen subconjunctivally.²¹⁵ Meningoencephalitis is a rare manifestation. Treatment is with DEC. Ivermectin has been used, but results are conflicting.^{24,216}

Trypanosomiasis

African trypanosomiasis The two forms of this disease are caused by *Trypanosoma brucei* sp. *T. b. rhodesiense*, which is a zoonotic disease, is localized to east and central Africa, and *T. b. gambiense*, for which man is the sole reservoir, to west Africa. The vector is the tsetse fly (*Glossina* sp.). There are 6000–25000 new cases annually. Traditionally chemotherapy is with suramin or one of the pentamidines, followed by melarsoprol or nitrofurazone when CNS involvement is present. However, all of these agents are potentially toxic²¹⁷ but corticosteroid significantly reduces the prevalence of melarsoprol encephalitis in *T. b. gambiense* infection.^{24,215} Recently, α -difluoromethylornithine

(eflornithine, DFMO), which has been shown to block ornithine decarboxylase, an enzyme necessary for polyamide formation required for reproduction of trypanosomes, has been widely tested in west Africa in *T. b. gambiense* infections.^{219–221} It seems to be safe and effective, but has to be given intravenously. A trial of nifurtimox has been undertaken in *T. b. gambiense* infection in Zaire.²²² Meanwhile molecular biological studies on *T. b. brucei* sp. continue.^{223,224}

South-American trypanosomiasis (Chagas' disease) *T. cruzi* infection, which is conveyed by reduviid bugs affects an estimated 20 million people in southern and central America; it is confined to rural areas. Congenital transmission and introduction via a blood transfusion are other routes of infection. Cardiac complications can occur in both early and late cases, after infection. Late in the disease, mega-oesophagus and mega-colon which result from parasympathetic denervation can ensue. Diagnosis is by detection of *T. cruzi* in peripheral blood samples in the early stages of disease; in later cases it is very difficult; xenodiagnosis is of value. Nifurtimox and benznidazole are now well established chemotherapeutic agents in the early phase of disease.^{24,217,225,226} *In vitro* work indicates that clomipramine affects the motility of *T. cruzi*.²²⁷ In longstanding chronic disease, symptomatic treatment is all that can be offered.

Leishmaniasis

Visceral leishmaniasis (kala azar) This systemic infection is caused by one or other of the subspecies of *Leishmania donovani*, and is characterized by a febrile illness with hepatosplenomegaly, weight-loss, anaemia, leucopenia and polyclonal hypergammaglobulinaemia.²⁴ It is transmitted to man, (after an incubation of 2–6 months) by the sandfly, and possesses several animal reservoirs. The endemic areas are southern Europe and the Mediterranean littoral and islands, Middle-east, central Asia, northern China, the Indian subcontinent, sub-Saharan Africa, and much of South America. Host factors are important in infection.²²⁸ Visceral leishmaniasis is an 'opportunistic' infection in patients infected with HIV-1 and HIV-2.

During the last few years a great deal of work has been carried out on the molecular biology of *Leishmania* sp;²²⁴ molecular probes have been developed to detect leishmanial DNA; this is valuable in diagnosis and also in differentiating the different strains of the parasite. The disease is often complicated by bacterial²²⁹ and tuberculous^{230,231} pneumonia. Renal amyloidosis is an occasional sequel. Post-kala azar dermal leishmaniasis is a tiresome complication in India, and occasionally Africa and China. It has recently been recorded in

Sudan in the absence of active visceral leishmaniasis.²³² Diagnosis is by detection of amastigotes in a bone marrow or splenic puncture specimen; the latter gives a higher yield of positive results. The IFAT (which uses promastigotes as antigen) is positive in about 95% of cases; recently, an ELISA has also proved equally valuable. The leishmania skin test becomes positive in around 90% of patients between 6 weeks and one year after recovery.

The well established chemotherapeutic agent is sodium stibogluconate;²⁴ pentamidine, amphotericin B, and allopurinol (usually combined with an antimonial compound) have also been used. Recently, interferon- γ has been added to pentavalent antimony chemotherapy in disease which was unresponsive to the latter agent; 6 out of 8 responded well.^{233,234} Evidence has also been produced that this form of management might be valuable in recurrent or resistant kala azar in the HIV-infected individual.²³⁵ An alternative agent is pentamidine; amphotericin B and allopurinol have also been used, the latter mainly in conjunction with a pentavalent antimonial compound. Ketoconazole has given encouraging results.^{236,237}

Cutaneous leishmaniasis Old world lesions, which are well-circumscribed and either nodular or ulcerative, are caused by *Leishmania tropica*, *L. major* and *L. aethiopica*.²⁴ The areas involved are the Mediterranean littoral, Middle-east, western part of the Indian subcontinent, and sub-Saharan Africa. The clinical manifestations depend on the strain of the parasite; lesions may be simple or multiple and satellite lesions are common. Mucocutaneous disease is unusual. A recent case, contracted in Spain, was caused by the most common enzyme variant of *Leishmania infantum*.²³⁸ In Iran and Iraq, a very chronic form – *leishmaniasis recidivans*, and in Ethiopia – *disseminated cutaneous leishmaniasis*, which possesses immunological similarities with lepromatous leprosy, are variants of this disease.

As with kala azar, sodium stibogluconate is the usual chemotherapeutic agent. Ketoconazole has given encouraging results (see above). Recently γ -interferon has been used. Topical treatment may be effective;²³⁹ for further details see ref. 24. A combination vaccine consisting of live BCG and killed leishmania promastigotes, proved of value in Venezuela. It is of low cost and applicable to primary health services in rural areas.²⁴⁰ Molecular biological approaches to *L. major* infection have been reported.²²⁴

Mucocutaneous leishmaniasis This disease is caused by *L. mexicana* or *L. braziliensis* and is largely restricted to South America; mucocutaneous lesions involving the mouth, nose, and

pharynx (espundia) can result from infection by the latter organism. Travellers can be affected.²⁴¹ A new clinical variant, caused by *L. donovani chagasi* has recently been reported from Honduras.²⁴² The incubation period is from a few weeks to several months. Chronic lesions can destroy the nasal septum, palate, lips, pharynx, and larynx. Diagnosis is similar to that in Old World disease but because the organisms are present at lower concentration, a more generous aspirate or biopsy is required.

Systemic chemotherapy is always indicated because mucocutaneous disease is an unpleasant complication. Pentavalent antimony compounds are usually used.²⁴³ Intradermal interferon- γ has proved effective in *L. braziliensis* infection, although results to date are less good than in Old World disease. Amphotericin B and nifurtimox have also been used with success. The relative importance of reactivation and reinfection in the recurrence of *L. braziliensis* lesions has recently been addressed.²⁴⁴ Reinfection by closely related organisms seems to be an important problem.

Some virus diseases

Although viruses account for morbidity and mortality rates in the tropics and subtropics on a vast scale, there are regrettably very few laboratories in those countries which are equipped to deal with this important area. The scene is, however, now largely dominated by the HIV-1 and HIV-2 retroviruses – especially in Africa; these diseases are covered elsewhere in this series of reviews.

HIV-1 and HIV-2

The origin of these viruses remains the subject of considerable controversy. The consensus of opinion places the initial focus in Africa,^{245–247} the viruses having close similarities with simian retroviruses, and possibly in the chimpanzee population of west Africa.^{246,247} However the method by which they entered *Homo sapiens* is hotly debated. Could it have been present for very many generations in isolated communities in rural areas, and the introduction of some feature of modern society, such as syringes and hypodermic needles, allowed its more widespread transmission?^{246,248} Or has it very recently entered the human population?²⁴⁸ The recent report of HIV-1 infection in a British sailor who died in Manchester, England, in 1959 does nothing to resolve the controversy.²⁴⁹

Whether or not the site of origin of the viruses can now be proved remains doubtful, but there can be no doubt that the HIV-AIDS pandemic is sweeping across sub-Saharan Africa,^{250–254} Southern America^{255,256} and Asia.²⁵⁷ There are

significant differences in the distribution of HIV-1 and HIV-2; the former is less common in west Africa, and the latter remains so far unusual in Uganda.²⁵⁸ Whether condoms should be widely available in developing countries, including the Philippines,²⁵⁹ evokes passionate views – especially within the Roman Catholic Church.²⁶⁰ Travellers to the tropics and subtropics must be advised of the risk of infection;²⁶¹ this is now at least as important as a correct prescription for malaria chemoprophylaxis drugs. Criteria for a clinical definition of AIDS in Africa have proved surprisingly difficult to delineate,^{262–264} especially in children.

An especial problem in Africa and other tropical countries is that intestinal absorption of precious nutrients is compromised, not only by the causative viruses,^{265,266} but by several opportunistic infections: *Cryptosporidium* sp., *Isospora belli*, *Sarcocystis hominis* and *Microsporidium* sp.²⁶⁷ *Pneumocystis carinii* is, however, less commonly found in AIDS sufferers in Africa than in temperate zones (see above). Tuberculosis and other mycobacterial infections contribute other major opportunistic events in AIDS throughout the African continent.^{268–271} There have been suggestions that leprosy is an AIDS-associated infection; however data remain scanty and this must remain *sub judice*.²⁶⁹

Viral hepatitis

Hepatitis A (HAV) remains a common hazard for travellers throughout tropical countries. Those with lack of evidence of infection in the past, and without detectable HAV antibody should receive prophylaxis in the form of immunoglobulin.^{272,273} Subclinical infection with HAV is a relatively common event; in American Peace Corps workers who were maintained on a routine prophylactic immunoglobulin regimen, serum markers of HAV were present in 15 (5%) out of 298 before proceeding to a tropical country, and 72 (14%) out of 529 after 12 months service.²⁷⁴

Hepatitis B (HBV) infection remains a major problem throughout developing countries and accounts not only for acute morbidity and mortality, but also for a colossal amount of chronic liver disease including chronic active hepatitis, macronodular cirrhosis, and hepatocellular carcinoma.²⁷⁵ HBV infection is arguably therefore, the most widespread chronic viral infection affecting *Homo sapiens*. The Medical Research Council's Unit at Fajara, The Gambia, is presently conducting a longitudinal study to assess the effect of vaccination on development of chronic liver disease.²⁷⁶ Despite an 89% decay in antibody concentration over the first 2 years, vaccination was 97% effective in preventing chronic infection; a few 'breakthrough infections' were associated with low initial antibody responses and chronic mater-

nal carriage of HBV. Efforts are currently being made to add HBV vaccine to diphtheria, tetanus and pertussis as a tetraivalent vaccine at Witwatersrand, South Africa.²⁷⁷ When chronic sequelae have developed, the only agent to have a role in management is interferon- α ; however, it is effective in only 30–40% of patients and should only be used in those most likely to benefit.^{278,279} There are significant ethnic differences in response; Chinese patients do not respond to this agent.²⁷⁸

Hepatitis C (HCV) is now known to produce all of the various complications attributable to HBV – including hepatocellular carcinoma. It is too early to know exactly what proportion of cases of chronic liver disease, including hepatocellular carcinoma,^{280,281} in tropical countries are a direct result of HCV infection. Preliminary studies indicate that the prevalence of HCV in some parts of Africa, including Uganda, is low.²⁸²

Other viruses with a propensity for the tropical environment

The tropics abound in viral diseases, accounts of which are to be found in standard texts on tropical medicine.^{283,284}

The authoritative history of work on the most classical of 'slow virus' infections – Kuru – in Papua New Guinea, has now been produced,²⁸⁵ although the disease is now merely of historical interest. Human T cell-leukaemia virus (HTLV-1) infection on the other hand is known to be widely distributed in tropical countries, although most of the early work came from Jamaica.²⁸⁶ The major classical manifestations are tropical spastic paraparesis and T-cell lymphoma, the latter frequently associated with a *Strongyloides stercoralis* infection.²⁴ The infection is widely spread in the Melanesian²⁸⁷ population, Brazil,²⁸⁸ and in Japan. Recently, an association with polymyositis has been documented in Jamaica.²⁸⁶ A plea has been made for the routine screening of blood for transfusion for HTLV-1; this will probably come about in the course of time, but the case presently seems less pressing than that for HCV testing.²⁸⁹

Although now an unusual infection in developed countries as a result of widespread vaccination campaigns, poliomyelitis still afflicts a high proportion of some developing country populations. As recently as 1977, for example, a study on the prevalence of lameness in Ghanaian children gave a figure of 7 per 1000;²⁹⁰ from 'lameness surveys' the WHO has calculated a rate of 250,000 new cases of poliomyelitis annually in developing countries. It is one of the WHO's objectives to eliminate the infection by the year 2000 by vaccination programmes. In a critical analysis of the anatomical distribution of the neurological deficit in individuals with a diagnosis of poliomyelitis,²⁹⁰ the inference is

that either the infection in the tropics is fundamentally different from the classical disease,²⁹¹ or that the diagnosis is often incorrect. These authors suggest that some cases, at least, are a result of diplegia which is acquired as a birth injury. If this is in fact the case, the result of massive vaccination campaigns are certain to be accompanied by disappointments.

Dengue remains a major viral infection in tropical countries – most notably in south-east Asia. Although it produces a severe acute illness, the infection is self-limiting in the African and American tropics, but may fall into the dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) category in south-east Asian children. Four distinct but significantly related serotypes exist, but only that associated with DHF/DSS is characterized by an increased vascular permeability and abnormal haemostasis.²⁹²

The fact that yellow fever still remains endemic over most of tropical Africa and southern America has recently been emphasized by the report of a Spanish woman who, despite an adequate immunization programme, contracted yellow fever in west Africa.²⁹³ Whilst Lassa fever, which is endemic in west Africa, has departed from the headlines in the popular press, there has recently been news of an Ebola-like infection in a non-endemic area. This filo-virus has been isolated in cynomolgus macaque monkeys imported into quarantine facilities in the USA from the Philippines.^{294,295} When a serological survey of people exposed to cynomolgus monkeys was made in the Philippines, 12 (6%) out of 186 people proved positive;²⁹⁵ since none of these reported a significant illness, the authors concluded that the infection there does not represent 'an immediate public health menace on the scale of the [1976] African Ebola virus'.

Since the elimination of smallpox in 1977, several other pox viruses have come under surveillance. The most important of these is the monkeypox virus. This virus is very closely related antigenically to smallpox and infection was formerly prevented by smallpox vaccination. It is localized so far to the rain forests of west and central Africa.²⁹⁶ The disease produces an exanthem which is identical to that produced by smallpox, but differs from that disease in that lymphadenopathy is a usual accompaniment. The mortality rate in children is around 10–20%. Despite initial fears that the disease would spread in the wake of the discontinuation of smallpox vaccination, WHO surveillance indicates that these were unjustified.

Haemorrhagic fever complicating a renal syndrome (HFRS) is a serious public health problem in China. Efforts are currently being made to develop a satisfactory inactivated vaccine.²⁹⁷ This disease is, incidentally, widely spread in eastern Europe²⁹⁸ and is increasing in incidence. Several

rodent species have been implicated in its transmission.

Rickettsial infections

Ticks, and less often mites, serve as the vectors and natural hosts for the spotted fever group of rickettsioses; natural reservoirs of infection exist in various species of animals including rabbits, ground squirrels, and mice.²⁹⁹ The disease entities are: Rocky Mountain spotted fever (*Rickettsia rickettsii*), Mediterranean spotted fever (*R. conorii*),³⁰⁰ north Asian rick typhus (*R. sibirica*), Queensland tick typhus (*R. australis*), rickettsialpox (*R. akari*), and oriental spotted fever (*R. japonica*).^{283,284} There is good evidence that the global incidence of these infections is increasing, usually in subtropical countries, but the reason for this is unclear. An increased awareness by physicians, combined with improved diagnostic facilities seems relevant, but some consider that global warming might have increased tick and mite activity.³⁰¹

This group of infections, like African tick typhus characterized by its typical eschar, is becoming an increasing problem in travellers, who may present with an undiagnosed fever. After an incubation period of 3–4 days, a typical presentation includes: headache, fever, a maculopapular or petechial rash, which is usually generalized, and often involves the palms and soles – with or without lymphadenopathy.^{283,284} An eschar is common in all except *Rickettsia rickettsii* infection. A diffuse vasculitis involving skin, subcutaneous tissue and almost any other organ is an important complication; the role of rickettsial endotoxin in the pathogenesis of this event is unclear. The differential diagnoses are considerable: meningococcal septicaemia, measles, rubella, typhoid, infectious mononucleosis, secondary syphilis, and leptospirosis.²⁹⁹ Unfortunately, serological results only become available during convalescence; isolation of rickettsia is time consuming and the techniques are carried out by only a few reference laboratories. However, in the acute phase of disease, immunofluorescence-staining of a cutaneous biopsy-specimen taken from the rash or eschar, will produce evidence of rickettsia. The Weil-Felix reaction is neither sensitive nor specific. Before tetracycline and chloramphenicol were introduced the mortality rate in *Rickettsia rickettsii* infection was 20%; it remains too high – at around 6%.²⁹⁹ Chemotherapy should be initiated early.

Some bacterial infections

Cholera

This remains the archetypal small-intestinal infection; secretory (watery) diarrhoea is the 'hallmark'. Far from being eliminated, this ancient disease is currently producing enormous morbidity and mortality in Asia, Africa and, most recently, Southern America.

Vaccination with inactivated (dead) vibrios gives limited protection³⁰² but an inactivated oral vaccine^{303,304} and a live attenuated strain (CVD 103-HgR) are likely to be available for adult travellers in the near future.^{305,306} Significant progress is being made towards an effective oral bivalent cholera/typhoid vaccine.³⁰⁷ Overall, vaccines have, to date, proved disappointing. Despite the World Health Organization recommendation that cholera vaccination should *not* be compulsory, a very small minority of countries continues demanding vaccination before entry.

Treatment was revolutionized by the introduction of oral rehydration regimens.^{308–310} The enterocyte Na-glucose carrier system is not affected by cAMP, and thus glucose and glycine stimulated membrane transport takes place normally. Sachets of pre-prepared glucose/electrolyte solutions³¹¹ can be obtained commercially by all travellers to the tropics. The place for antibiotics such as tetracycline in management remains unchanged; although the length of time over which *V. cholerae* is excreted is reduced, resistant strains rapidly emerge, rendering them of little or no use in an epidemic.

Enteritis necroticans

This acute small-intestinal infection (also known as 'pig-bel' disease) is caused by the β -toxin of heat sensitive type C strains of *C. perfringens*; it is a far more severe illness than food-poisoning caused by that organism.^{124,312} The disease has been reported from a number of tropical countries, most notably Papua New Guinea,^{124,312–315} but also Uganda, Thailand,³¹⁶ the Solomon Islands,³¹⁷ and Singapore. A similar disease, termed 'Darmbrand' was recognized in Germany at the end of World War II (1939–1945); the disease probably has a much wider distribution when searched for.^{124,313,318–320}

Although adults can be affected, children are more severely involved, and mortality rate is high. In Papua New Guinea, the disease is most common in the Highlands and has been associated with pig feasts at which partly cooked meat is handled under unhygienic conditions and eaten over subsequent days and weeks.^{313,315,319} The disease seems to have an association with malnutrition and trypsin-inhibitors in the staple diet.³¹³ A low concentration

of digestive proteases in the small-intestinal lumen, which may allow the clostridial toxin to initiate the disease, has been suggested as being important in pathogenesis. Severity of the disease varies from acute diarrhoea, to a severe dysenteric-like illness with extensive necrosis of the small,^{313,316,320} and, to a lesser extent, large intestine.³²¹

Specific immunization with *C. perfringens* type C has been shown to give significant protection.^{313,322} Treatment of the disease is initially with fluid replacement. Chloramphenicol or tetracycline are indicated and type-C gas-gangrene serum should also be administered. If there is no improvement, a laparotomy is indicated³²³ as resection of necrotic intestine may sometimes be necessary. Mortality rate can be as high as 80%. Long-term sequelae include: stricture-formation, fistulae and a mal-absorption state.³¹²

Typhoid (enteric) fever

The clinical features of this infection are well known¹²⁴ and the role of vaccination in prevention has been reviewed.^{324–326} New oral vaccines, in particular the attenuated oral Ty21a vaccine, are undergoing clinical trial and encouraging results have been reported from Egypt and Chile.^{326–328} Other vaccines include: auxotrophic *S. typhi* mutant (strain 541Ty), and parentally administered purified Vi polysaccharide of *S. typhi*,^{326,329} the latter has proved valuable in field trials in Nepal and South Africa.³²⁵ *S. paratyphi A* remains, however, an important cause of enteric fever in travellers, and an effective vaccine should be sought.³³⁰ Efforts are being made to develop an effective oral bivalent typhoid/cholera vaccine.³⁰⁷ Basic precautions with food and drinking water together with fresh fruit

and vegetables, as for travellers' diarrhoea and HAV infection, are of great importance.

General measures in management have been described³³¹ and satisfactory chemotherapy for *S. typhi* and other enteric infections has been reviewed.³³² The most widely used and cheapest antibiotic is chloramphenicol,^{331–334} 3–4 g daily reduced to 2 g daily after defervescence for 14 days in an adult. Co-trimoxazole,³³⁵ amoxycillin,³³⁵ and ampicillin³³⁶ are also effective.³³¹ However, resistance to all of these agents, especially chloramphenicol, is now commonplace^{337,338} – especially in the Indian subcontinent^{339,340} and some other Third World countries. Most cases of enteric fever in the UK occur in travellers to the Indian subcontinent (especially Pakistan), the Mediterranean littoral or the Middle East;³⁴¹ this high degree of 'resistance' is therefore a source of concern. Trimethoprim, norfloxacin,³⁴² ciprofloxacin, ceftriaxone,³⁴³ furazolidone, and mecillinam have also been used, but controlled evidence for their efficacy is scanty.

Haemorrhage should be treated by blood transfusion; surgery is occasionally required to arrest localized bleeding.³⁴⁴ Although a controversial issue,^{120,345} perforation should in most cases be treated surgically.^{346–348} Conservative management is sometimes recommended but with either regimen mortality rates are high.³⁴⁸

Ideally, 6 negative faecal and 3 negative urine cultures are required before a patient can be declared free of the disease. In the carrier state, amoxycillin (2 g three times daily for 28 days) gives good results; ciprofloxacin (750 mg orally twice daily)³⁴⁹ and norfloxacin (400 mg twice daily)³⁵⁰ for 28 days have also given good results. Ciprofloxacin has proved effective in eradication of salmonella infection in food handlers.³⁵¹

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