quate resources to undertake a screening programme and routine contact tracing. This becomes particularly difficult in the large institutions, which appear to offer favourable conditions for the spread of *Mycobacterium tuberculosis*. There is now a greater emphasis on health education within the program, and public awareness about the mode of transmission and symptoms seems to be increasing. This will hopefully go some way to improve the situation. There is still much work to be done and tuberculosis control remains an enormous challenge to the Tibetan community.

CONCLUSION

In my short time in Dharamsala I was uniquely privileged to be allowed into the exiled community and to observe the problems they encountered while living in India. They present a tale of enduring hardship coupled with a tenacity for preserving their unique, deep-seated religious and cultural identity. Having emerged from their mountain home they have entered a vastly foreign world. They seem to have embraced our own concept of allopathic medicine and yet retain their own traditional practices in a truly complementary way. The prevalent health problems remain the diseases of poverty, and there is a recognition of the huge task that is required to overcome them. The future for Tibetans is as precarious as it is uncertain. Walking the political tightrope between their masters in China and their hosts in exile is a difficult and dangerous journey. If and when the hard-line approach from Beijing relaxes and Tibet returns to autonomy there will then be the mammoth task of shaping a health programme not in exile but at home.

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PROTECTING TRAVELLERS FROM TROPICAL DISEASES: THE PRESENT POSITION AND FUTURE PROSPECTS

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This paper was written after returning from the fourth meeting in Mexico in 1995 of the International Society for Travel Medicine (ISTM) attended by 900 participants.

Malaria

No significant changes in recommendations for prophylaxis were reported, although since ICTM3 in Paris there has been a move towards more uniform recommendation of mefloquine. There is now a greater acceptance that the rate of adverse effects (AE) is higher for mefloquine than for chloroquine; this in contrast to the results of large retrospective studies published in 1993 which found virtually no difference between chloroquine and mefloquine. Retrospective and prospective studies may lack sensitivity for AE depending on the questions asked and time lapse between the timing of the questionnaire and onset of AE.

In a short term study of Spanish tourists the rate of dizziness, anxiety and insomnia was about twice as great on mefloquine (18 per cent) compared to chloroquine (8 per cent). A British retrospective study examined AE in over 1,000 mefloquine users. The incidence of severe neuropsychiatric symptoms was about 1:170, far higher than the 1:10,000 previously quoted for prophylactic use, compared to zero for chloroquine plus proguanil. Dissociation from reality was the most prominent symptom in severe cases.

Pharmacological studies have not found that AEs correlate with plasma levels. Hearing, postural control and vestibular function did not show any abnormality in ten healthy volunteers given mefloquine 250 mg weekly for 16 weeks, even though some experienced AE. A double blind crossover trial of weekly mefloquine in trainee pilots detected no impairment of performance, although there was a low incidence of sleep related AE. Older travellers tend to have less AE than young adults. There was a report of a patient who had several episodes of paranoid psychosis on mefloquine but only in association with heavy (600 ml of whisky) alcohol consumption. After he ceased his weekly binges he had no further problems. The relationship of mefloquine AE to alcohol needs further study as many tourists increase alcohol intake during vacation.

Multi-drug resistance seems to be increasing in Papua New Guinea with 15 per cent of falciparum cases resistant to quinine, 27 per cent resistance to mefloquine and 31 per cent to halofantrine. These drugs are structurally similar and cross resistance was expected.

Mefloquine seems to be tolerated better in children than in young adults, and the prohibition on the use of mefloquine in children under 15 kg can be viewed flexibly, although with no liquid formulation, compliance with tablets limits its use. Break through malaria during or following mefloquine prophylaxis with its long half life, is likely to lead to both more frequent late recrudescence, and malaria with low parasitaemia. There is some evidence that this is occurring.

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The use of tetracycline as an adjunct to quinine in children was discussed. A paediatrician who treats Rocky Mountain Spotted Fever in children observed that the staining effect on teeth is dose dependent and should not occur at total doses of <8 g or an equivalent dose of doxycycline. Tetracycline should not be withheld in children if there is a strong clinical indication. For radical cure of falciparum malaria in pregnancy, where tetracyclines would most definitely be contra-indicated, quinine plus clindamycin is an alternative that has not been much utilised in the UK. In the USA quinine is not freely available and quinidine is the main anti-falciparum agent of choice.

A Swedish group has delineated the relationship between chloroquine levels in whole blood and adverse effects. In general there was little relationship between AE and whole blood concentrations except for changes in visual accommodation. This was of interest to me as I had recently seen a traveller in my clinic who had stopped chloroquine because he felt his vision was deteriorating.

Doxycycline is being used more widely. Although there is good experience with 50 mg daily long term use in acne, the safety of 100 mg daily long term remains to be established; its major drawback is the need for daily administration and poor resultant compliance. Interest grows in azithromycin as a prophylactic but data is sparse at the moment.

Halofantrine has fallen from its privileged position as an effective and convenient standby treatment due to high rates of resistance to safe doses in parts of SE Asia (only 50–60 per cent effective) and cardiotoxicity. Five per cent of males and 15 per cent of females have a QT interval of >0·44 and in these individuals the QT lengthening potential of halofantrine is unsafe, ventricular arrhythmias becoming more common when the QT interval exceeds 0·55. It still has a role for Africa if the QT interval is normal, but British authorities no longer recommend its use for self treatment.

The increasing failures of commonly used prophylactics has prompted a search for alternatives and primaquine is being evaluated in Papua New Guinea as a causal prophylactic (acting against hepatic schizonts) and gives about 85 per cent protection against plasmodium. The falciparium doses needed are high, 0·5 mg/kg/day, adding up to about 40 mg for an adult as compared to the normal anti-vivax hypnozoite dose of 15 mg daily. A primaquine analogue developed in the USA looks promising, is close to Phase III trials, and probably about 5 years away from marketing. Its huge advantage, if safe enough as a prophylactic, would be interruption of transmission through its anti-gametocidal effect.

For malaria diagnosis PCR is emerging as a useful tool for detecting mixed infestations where the parasitaemia of the secondary organism is below the detection sensitivity of blood slide microscopy.

Vaccines

Smith Kline Beecham move closer to releasing an oral enterotoxigenic *E coli* (ETEC) vaccine which should give on average about 70 per cent protection for the 40 per cent travellers diarrhoea caused by ETEC organisms. The oral killed cholera B subunit whole cell vaccine provides short lasting protection against ETEC disease via cross reactivity with ETEC heat labile toxin, but does not protect against ETEC producing heat stable toxin. A formalin killed ETEC vaccine seems to overcome these difficulties and combined with the oral cholera B subunit vaccine, the ETEC immunogenic effect seems to be enhanced.

Merck Sharp & Dohme are close to releasing VAQTA, a highly purified formalin inactivated alum adjuvant Hepatitis A vaccine which they hope will give fewer side effects than competitive vaccines and even higher levels of protection. They have been able to eradicate almost all traces of the human fibroblasts in which the vaccine is cultured, virtually eradicating immune responses to histocompatibility antigens. HAVRIX is now licensed in the USA and has an excellent safety record. Ten cases of neurological adverse effects have been reported after huge worldwide use but in nine of these there was simultaneous administration of one or more other vaccines which might have been responsible.

Pasteur Mérieux also have a Hepatitis A vaccine under trial which gives a more rapid onset of seroconversion than HAVRIX, 93 per cent and 76 per cent respectively at two weeks; the Swiss Serum Institute also have a candidate vaccine. New data now confirms that delaying the second dose of HAVRIX to 12 months gives a 27 per cent higher mean titre of anti-HAV IgG at 24 months.

The advantages of combined vaccines are obvious from a traveller's perspective. The new Merieux Dip/Tet vaccine is already available, and another being investigated is HAVRIX/Typhim Vi. With this no increase in AE has been seen and immunogenicity for anti-HAV is enhanced, particularly after the second HAVRIX booster. The immunogenic potential of this combination for typhoid is being assessed.

Accelerated regimes for Engerix B have been assessed for travellers who need rapid immunity. A 0, 7 and 21 day regime more rapidly induces surface antibody than a 0, 14 and 28 day regime and both give an adequate plateau of HBsAb during the first year that can then be boosted by a further dose at 12 months.

Japanese B encephalitis vaccine, released in the USA two years ago, has as its main AE facial oedema and generalised urticaria, present in 0·1 per cent and 1 per cent respectively in an analysis of the effects of the first 15,000 doses. Concern about the teratogenic potential of yellow fever vaccine persists, and it is contraindicated in infants younger than 4 months in whom it may cause encephalitis. British recommendations are to avoid it in infants under one year. Tick borne encephalitis vaccine has a limited role, although one million of the 7 million population in Austria have now been vaccinated. The risk has been calculated at 1 case per 381,000 person months of exposure. Short term high risk persons may consider the use of alternative TBE immune globulin, available at airport clinics in Europe.

Dengue fever occasionally leads to encephalopathy, hepatic damage and cardiomyopathy, and the well recognised dengue shock syndrome (DSS) which may occur without prior infection with another serotype. Prior infection enhances infectivity by providing non-neutralising antibody to bond with the virus which then penetrates mononuclear cells more easily. Danger signs of DSS include intense and persistent abdominal pain, the transition of fever to hypothermia and increasing somnolence. Treatment comprises vigorous fluid replacement with no demonstrable benefit from steroids or platelet transfusions. Tetravalent dengue vaccine field trials have now started.

Enteric and other bacterial infections

The problem of antibiotic resistance has been enhanced by travel. Some shigella organisms in Africa are resistant to all anti-microbials except quinolones and the development of resistance to this antibiotic group could mark the end of the road for anti-microbials in this group of bacteria. Deaths from *S. dysenteriae* in Africa

in 1991 were 200,000. For enteric organisms short antibiotic courses apply less selection pressure than longer courses. Similarly in Western settings vancomycin resistance is spreading and some *Staph aureus* is now virtually untreatable.

Recognised pathogens were found in 46 per cent of US students who had diarrhoea while visiting Mexico, ETEC comprised 63 per cent of the total, with shigella in second place at 21 per cent and salmonella third at 6 per cent. An extensive survey of potable water samples in Greece showed no evidence of *0157 E. coli* suggesting that this form of *E. coli* is not transmitted through water contamination. The preferred treatment for travellers diarrhoea is loperamide plus quinolone. Zalderide, a calmodulin inhibitor with gastro-intestinal anti-secretory properties was as effective as loperamide. Cyclospora is now a recognised cause of prolonged diarrhoea in Nepal and other countries. In a trial of cotrimoxazole after seven days only 6 per cent were shedding cylcospora in the treated group compared to 88 per cent in the placebo group.

Miscellaneous

An assault is a major health risk for long term expatriates and risk factors have been examined in US Peace Corps Volunteers (PCV). Thirty one per cent were aggravated (weapon used or hospitalisation required), 31 per cent were simple assault, 17 per cent were completed or attempted rape and 21 per cent were other sexual assaults. Single PCVs were 4 times more likely to be assaulted than were married, men 6 times more likely to be injured than women and injury was more likely in those who had misused alcohol. Most sexual assaults involved single white women and resistance (particularly vigorous verbal protest) decreased the likelihood of completed rape by about seven times. A minority but high proportion of rapes were preventable and due to risk increasing behaviour, for instance walking home alone late at night.

The potential for pulmonary emboli arising from cramped seats on long over night flights was emphasised by five cases of the economy class syndrome. Ages ranged from 25 to 75 but four were under 40 and one died. As a World Traveller Class BA passenger I took 300 mg soluble aspirin on both main flights. A poster documented the stability of paracetamol at high ambient temperatures and a 35 per cent degradation of aspirin after 30 days at 50°C.

Liverpool tropical physicians reported two unusual cases of Lake Malawi acquired *S haematobium* manifesting with Katayama fever. Rectal biopsies to exclude the possibility of combined *S haematobium* and *S mansoni* infestation were apparently not performed. Researchers at the London Hospital for Tropical Diseases reported contrasting sensitivity of serum schistosomal ELISA, for *S mansoni* 94 per cent and *S haematobium* 63 per cent. The relationship of false negatives to the probable timing of infection was not clarified. *S haematobium* sometimes has an extended seronegative window and some of the apparent seronegatives might have seroconverted later if further specimens had been performed. One third of PCVs swimming in Lake Malawi are infected.

The Medical Advisory Service for Travellers Abroad group (MASTA) reported on toxicology and efficacy studies for their non-DEET eucalyptus extracted Mosiguard Natural insect repellant. It appears to be comparable to DEET both for insect repellant activity, duration of action and to be safe.

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ANTIRETROVIRAL THERAPY: A REVIEW

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Human immunodeficiency virus (HIV) infection represents a global pandemic. The World Health Organisation has estimated that over 18·5 million adults and 1·5 million children are now infected with over 4·5 million cases of acquired immunodeficiency syndrome (AIDS).[1] Significant progress has been made in understanding the biology of HIV and the pathogenesis of the resulting disease. Clinical evidence suggests that treatment with antiretrovirals can delay progression of the disease and prolong survival[2,3] but development of new treatments have been hampered by drug resistance, treatment intolerance and the limited validity of available surrogate markers for assessing disease progression.

HIV is a retrovirus consisting of a protein core surrounded by a lipid envelope. There are two types of HIV, 1 and 2, and although both types are known to cause AIDS, infection with HIV-1 is more common in Western Europe, Australasia and the United States of America. HIV possesses a diploid single stranded RNA genome comprising genes common to all retroviruses; *gag, pol* and *env*. In addition, HIV-1 contains unique extra genes, including *tat, rev* and *nef* which act as regulators of replication. Embedded in the lipid envelope of the virus is the glycoprotein gp 120 which binds preferentially to CD4 molecules. CD4 molecules are present most commonly on T4 lymphocytes but also occur on macrophages, monocytes and dendritic cells which may also be infected with HIV.

After binding with CD4 receptors the virus fuses with the cellular membrane releasing its core proteins and viral RNA into the cytoplasm. A virion associated enzyme, reverse transcriptase (RT), catalyses the synthesis of a double stranded DNA copy using the viral RNA genome as a template. The DNA is subsequently incorporated into the host genome by viral integrase. Here it results in the synthesis of new viral particles by repeated transcription into RNA. HIV protease is responsible for post-translational processing of polyproteins into the structural proteins and enzymes of the mature virus. Hence, by understanding the life-cycle of HIV, potential targets for anti-HIV therapeutic agents have been identified.

HIV attachment

Agents that bind to either viral gp120 or host CD4 molecules are able to disrupt binding of the virus to the host cell. Agents such as recombinant soluble CD4 (rsCD4) and other CD4 analogues have been devised to bond to viral and cellular gp120, and many of these agents have significant antiretroviral activity *in vitro*,[4–6] although their effects *in vivo* are less clear.[7]

HIV penetration and uncoating

The aromatic polycyclic diones, hypericin and pseudohypericin to prevent penetration and uncoating of HIV-1 in the presence of visible light illumination.[8] The clinical relevance of this interaction remains unclear.