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BMJ 2003;326:1444-1448
doi:10.1136/bmj.326.7404.1444

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Clinical review

Science, medicine, and the future

American trypanosomiasis (Chagas' disease) and the role of molecular epidemiology in guiding control strategies

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Chagas' disease is a parasitic infection that has far reaching consequences for public health and national economies in Latin America. The latest molecular typing methods may help in developing targeted, effective control programmes

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BMJ 2003;326:1444-8

In terms of public health and economic impact, American trypanosomiasis (Chagas' disease) is the most important parasitic infection in Latin America. More than 10 million people carry the protozoan agent *Trypanosoma cruzi*, which multiplies inside cells, particularly of heart and smooth muscle.¹ In the chronic phase of infection up to 30% of infected people may develop severe abnormalities on the electrocardiogram and chagasic cardiomyopathy.²

Chagas' disease is a complex zoonosis, primarily transmitted by triatomine bugs, which infest poor quality housing. We describe how research in molecular genetics has shown the remarkable genetic diversity of *T cruzi*, and also detected cryptic species of triatomine vector. This insight into the genetic diversity of pathogen and vector helps both to unravel the complexities of transmission cycles and to guide control strategies. Chagas' disease thus provides an example of how molecular epidemiology can be applied to disease control. In addition it is also a model for the role that research collaboration has in stimulating international cooperation, in mobilising political will, and in driving international control programmes.³

Methods

This article draws primarily on recent publications on the molecular genetics of *T cruzi* and triatomine bugs, including unpublished data, and on progress reports on international control programmes, in part through a Latin American triatomine research network (ECLAT, coordinated by C J Schofield).

Transmission

Vectorborne Chagas' disease is transmitted when mucous membranes or abraded skin are exposed to faeces of triatomine bugs that are infected with *T cruzi*. Occasionally adult triatomine bugs contaminate palm juice presses or other foods, causing orally transmitted outbreaks (fig 1).⁴ Blood transfusion is also an important route of infection; blood and organ donors can be screened for *T cruzi* infection by serology.

Summary points

Infection with *Trypanosoma cruzi* is a complex zoonosis, transmitted by many triatomine vector species and sustained by a multitude of mammalian reservoir hosts

Widespread transmission in the wild (silvatic transmission) occurs in palm trees and other animal refuges that are infested with triatomine bugs; domestic transmission occurs where bugs colonise houses

Silvatic and domestic transmission cycles may be separate or overlap

Comparative genetics can resolve the extensive intraspecific diversity of *T cruzi* and can be applied to detect cryptic triatomine species

Unravelling transmission cycles by comparative genetics can guide the design of cost effective and improved control strategies

Congenital infection occurs in a small proportion of newborns from infected mothers.

Epidemiology

The transmission cycles of *T cruzi* are complex (fig 1). More than 130 species of triatomine bug are known⁵; most are confined to the Americas. Most American triatomine species are reported to carry *T cruzi*. Their many wild (silvatic) habitats include palm trees, tree holes, arboreal epiphytes, burrows, rock crevices, or other animal refuges. Transmission cycles of *T cruzi* are enzootic if abundant silvatic transmission occurs but no domestic triatomine colonies exist and only sporadic cases of Chagas' disease occur, usually caused by adult bugs attracted to lights from silvatic habitats (fig 1).⁴

A few triatomine species have adapted to colonise and thrive in houses, where they transmit *T. cruzi* to humans and domestic animals such as dogs, cats, and guinea pigs. *Triatoma infestans*, which is found in the six "southern cone" countries of South America (Argentina, Bolivia, Brazil, Chile, Paraguay, Uruguay) has spread far beyond its initial silvatic habitats and is solely domestic or peridomestic throughout most of its geographic range.³ Other species, such as *Triatoma brasiliensis* in northeastern Brazil, may reinvade houses from adjacent silvatic populations. Domestic and silvatic transmission cycles in a given locality can thus tentatively be considered as separate or overlapping, based on the degree of interaction between them (fig 1).

Clinical Chagas' disease has a "kaleidoscopic" presentation (fig 2). At the site of exposure to infected bug faeces an initial lesion may occur and *T. cruzi* may multiply locally, giving rise to unilateral conjunctivitis and oedema (Romaña's sign) or to a cutaneous chagoma. However, the initial, acute phase of infection is usually asymptomatic and unrecognised, although trypanosomes may be detectable in blood by microscopy and concentration methods. A reactivated acute phase can occur in immunocompromised people. Both immunocompromised and congenital cases may be associated with meningoencephalitis, which has a poor prognosis.²

Without treatment *T. cruzi* infection is usually lifelong. In the chronic phase of infection parasitaemia is detectable only by intensive blood culture or by xenodiagnosis, which entails feeding laboratory bred triatomines on the patient and later dissecting the bugs to look for acquisition of *T. cruzi*. The chronic phase may be asymptomatic (indeterminate) for life, but heart disease is common, with abnormalities seen on the electrocardiogram (especially right bundle branch block). Aneurysm of the apex of the left ventricle is said to be characteristic for chronic chagasic cardiomyopathy. Chagasic megasyndromes, particularly megaesophagus and megacolon, may occur during the chronic phase (fig 2).⁶ The pathogenesis of the disease is not fully understood: prolonged presence of *T. cruzi* is thought to be important, but neurological damage may occur in the acute phase; autoimmunity may be involved.⁶

Chronic Chagas' disease manifests in markedly different ways in different geographical regions.¹ Chagasic megasyndromes are common in central Brazil and southern South America but rare or absent from endemic regions in northern South America and Central America.^{1,2} Are these differences in the geographical distribution of severe Chagas' disease due to variable genetic susceptibilities of human populations or to differences in virulence of the pathogen, *T. cruzi*? Similarly, is what determines whether a person infected with *T. cruzi* leads a normal healthy life or succumbs to chronic Chagas' disease dependent on the human genotype or the infecting strain of *T. cruzi*?

T. cruzi: one agent of disease or many?

The disparate geographical distribution of severe Chagas' disease as well as the variable response to treatment and diverse biological behaviour in mammals and triatomine bugs have led to the assumption that *T. cruzi* might not be a single entity but a

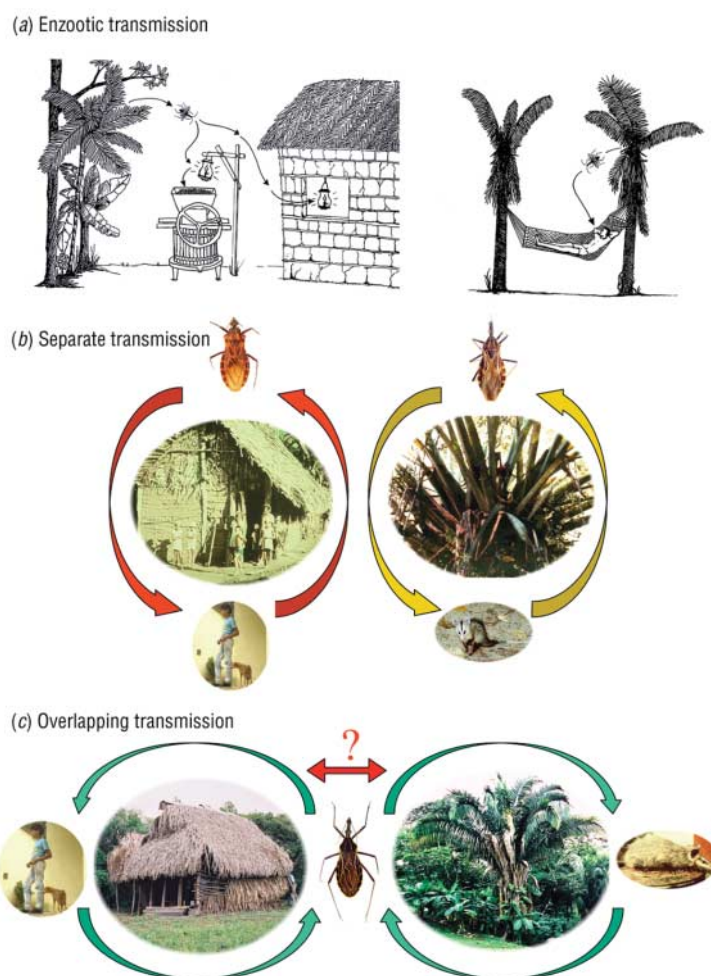


Fig 1 Transmission cycles of *Trypanosoma cruzi*. (a) Enzootic transmission in the Amazon rainforest: no domestic colonies of triatomine bugs exist, but infrequent, sporadic cases of Chagas' disease may occur due to adult bugs flying to palm presses or houses, or when the triatomine species *Rhodnius brethesi* attacks workers sleeping in the forest to harvest piassaba palms. (b) An example of separate silvatic and domestic transmission cycles in Bahia state, Brazil: left, houses are infested by the triatomine bug *Panstrongylus megistus*; right, bromeliad epiphytes, refuges of the opossum (*Didelphis albiventris*), are infested by the triatomine bug *Triatoma tibiamaculata*. *T. cruzi* II is found in the domestic cycle and *T. cruzi* I in the silvatic cycle. (c) An example of overlapping silvatic and domestic transmission cycles in parts of Venezuela: the triatomine genus *Rhodnius* has several similar species; *R. prolixus* may infest both houses and palms. Molecular analysis of triatomine vectors and *T. cruzi* isolates shows where silvatic and domestic cycles are linked, which influences the design of control programmes (reproduced with permission from James Patterson)

heterogeneous complex of organisms.¹ Both biochemical comparisons (phenotyping) and DNA comparisons (genotyping) have shown that *T. cruzi* is a remarkably diverse species. Intraspecific heterogeneity was first conclusively shown by phenotyping *T. cruzi* isolates by their isoenzyme profiles. In a classic study in Bahia state, Brazil, two very different strains of *T. cruzi* were isolated.⁷ One strain, named *T. cruzi* zymodeme II, was exclusive to the domestic transmission cycle. The other, *T. cruzi* zymodeme I, was exclusive to the nearby silvatic cycle. The domestic and silvatic *T. cruzi* strains were distinct by 11 of 18 enzymes—more than distinguished, well recognised, separate species of *Leishmania*. Different triatomine species sustained the two separate transmission cycles. In contrast, research in Venezuela showed that zymodeme I occurred there in both the domestic and silvatic transmission cycles,⁸

which implies that in some localities the local domestic triatomine vector (*Rhodnius prolixus*) might be moving between infested palm trees and houses. This formed the basis of the important concept that typing of *T. cruzi* strains can act as an indicator of whether a link exists between domestic and silvatic transmission cycles.

A plethora of molecular methods has since been applied to genotyping *T. cruzi* strains by analysing DNA polymorphisms. Methods include genetic fingerprinting by random amplification of polymorphic DNA (RAPD), comparing the sequences of mini-exon genes and intergenic ribosomal spacers or other DNA targets, and comparing the sizes of microsatellites. Based on all these methods two principal subdivisions of *T. cruzi* have been designated by international consensus.⁹ These subdivisions are named *T. cruzi* I, corresponding with zymodeme I, and *T. cruzi* II, incorporating zymodeme II. Up to five subgroups of *T. cruzi* II have been recognised, named *T. cruzi* IIa to IIe.¹⁰

The question arises whether the great diversity of *T. cruzi* is in part due to genetic recombination between isolates. This is an important question because a capacity for genetic exchange could facilitate the spread of virulent strains and drug resistant genotypes. Population genetics has been used to search for recombination by examining allele frequencies in natural populations of *T. cruzi*. Random mating (panmixia) can be looked for by using the Hardy-Weinberg test, or conversely departure from panmixia can be detected by using linkage disequilibrium tests. These methods have been applied to field isolates from dispersed geographical regions. The results indicate that *T. cruzi* is predominantly propagated clonally, without genetic exchange.¹⁰ Nevertheless, isoenzyme profiles typical of hybrid strains were noted long ago for the *T. cruzi* sub-

groups IIc and IIe.¹¹ Phylogenetics analysis based on DNA sequence data has recently confirmed that strains *T. cruzi* IIc and IIe are probably derived by hybridisation of strains similar to IIb with IIc or IIa.¹²

Does *T. cruzi* have an active capacity for genetic exchange? With the aid of genetic transformation and drug resistant markers to select recombinants, *T. cruzi* I hybrids have recently been produced experimentally,⁹ proving that *T. cruzi* is still capable of genetic exchange. Hybrids, recovered from the mammalian stage of the life cycle, seem to result from fusion, followed by loss of genetic material (genome erosion), probably in conjunction with some homologous recombination. In the malaria parasite (*Plasmodium*) genetic exchange is an obligatory part of its life cycle, whereas in *T. cruzi* it is not. Neither does *T. cruzi* have quite the same genetic exchange as African trypanosomes, which is thought to occur in the salivary glands of tsetse flies.¹³ Nevertheless, the implications of genetic hybridisation in *T. cruzi* are profound, allowing recombination across greater genetic distances than mendelian inheritance and potentially facilitating rapid speciation and evolution, possibly with adaptation to new hosts.

The associations of the subdivisions of *T. cruzi* strains with natural hosts and vectors are not yet fully defined; in particular the hosts of some *T. cruzi* II subgroups are unresolved. However, separate evolutionary histories have been proposed for *T. cruzi* I (associated with the vector tribe *Rhodnini*, the marsupial opossum *Didelphis*, and the palm tree habitat) and *T. cruzi* II (associated with the vector tribe *Triatomini* and terrestrial mammals).¹⁴

From an epidemiological viewpoint it is striking that *T. cruzi* II is the agent of Chagas' disease in the southern cone countries of South America, where megasyndromes occur, whereas *T. cruzi* I is endemic in northern South America and Central America, where chronic Chagas' disease is said to be more benign. Furthermore, the hybrid strains *T. cruzi* IIc and IIe are particularly prevalent among communities in some endemic regions of the southern cone countries of South America.¹¹

Identifying cryptic vector species and intraspecific variation

Designing control campaigns for triatomine bugs depends on understanding whether recurrent infestations are due to residual domestic populations that survive spraying with insecticides or to reinvasion of bugs from silvatic habitats (see below). It is essential therefore to be able to identify domestic and silvatic triatomine species and populations accurately. Morphology, including dimensions and colour, has been used for classic triatomine taxonomy.⁵ Unfortunately, the size and colour of triatomines seem to evolve rapidly, giving smaller domestic populations or camouflaged colour morphs of the same species. Conversely, some valid species are very similar and are often confused, notably those in the genus *Rhodnius*. Two new approaches have been developed to identify cryptic triatomine species. The first entails size free comparisons of morphological landmark configurations, known as geometric morphometrics or Procrustes analysis (Procrustes of Greek mythology either stretched or surgically trimmed guests to fit his bed

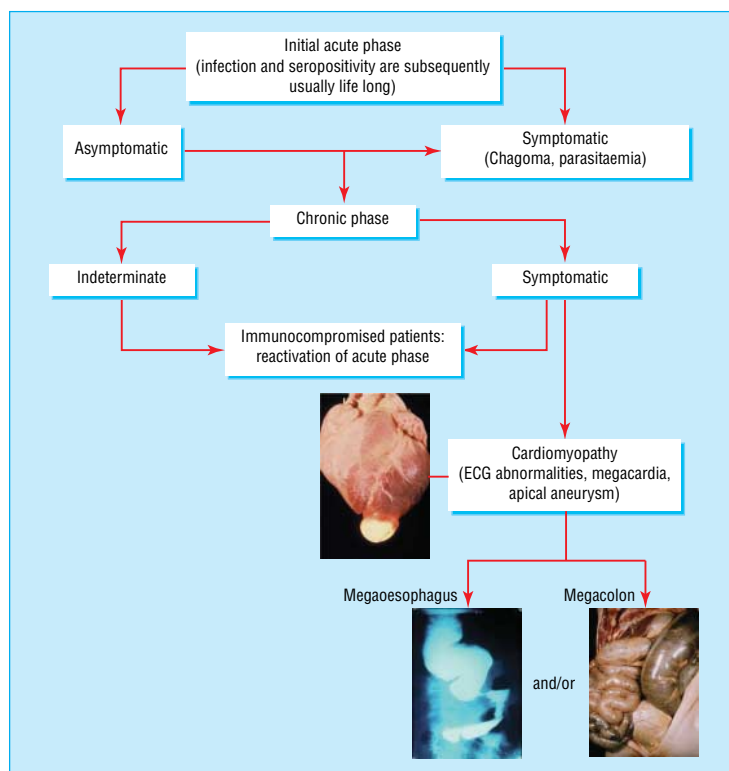


Fig 2 Chagas' disease: clinical phases (reproduced with permission from James Patterson)

precisely).¹⁵ The second approach is to analyse genetic diversity directly by sequencing both mitochondrial (maternally inherited) and nuclear genes.¹⁶

Rhodnius prolixus, the most notorious domestic vector in Venezuela,¹⁷ Colombia, and Central America, illustrates the application of the molecular approach. *R. prolixus* is virtually indistinguishable from the species *R. robustus*. DNA sequencing has now shown that *R. robustus*, formerly of controversial status, is not only a valid species but probably encompasses several cryptic species with different geographical distributions.^{16 18} So far colonies of *R. robustus* have been reported only from silvatic habitats, although adult bugs occasionally fly into houses. None of the silvatic populations of *R. robustus* are yet proved to replenish the domestic transmission cycle. In contrast, the same molecular approach indicates that *R. prolixus* can be found in both domestic and silvatic habitats, at least in parts of Venezuela, and therefore it may well reinvade houses from infested palm trees.

Morphometrics and comparisons of DNA sequences can also be used to explore wider relations between triatomine species by phylogenetics analysis, although morphometric phylogenetics has limited scope. Molecular clocks based on rates of change in DNA sequences can date when triatomine tribes diverged. A new molecular clock for the insects implies that the tribe *Rhodnini* diverged up to 90 million years ago, about the time when palm trees evolved.¹⁹

Programmes to control Chagas' disease

The costs of coping with the public health burden of chronic Chagas' disease are enormous, as a result of the morbidity, mortality, hospitalisation, drug treatment of arrhythmias, provision of pacemakers, and surgery. There is no vaccine, and none is likely because the role of autoimmunity in pathogenesis is under dispute. No prophylactic drugs exist, and treatment for infection with benznidazole,² although potentially life saving in the acute phase, entails prolonged administration and side effects and is not guaranteed to eliminate *T. cruzi*. However, the availability of comparatively low cost and proved interventions to prevent transmission, in the form of spraying houses infested with bugs and screening blood and organ donors, provided indisputable economic justification for establishing control campaigns.³ Preventing transmission is therefore an excellent investment for the governments of the countries of Latin America where *T. cruzi* is endemic.

Unlike the tsetse fly vectors of African trypanosomiasis, triatomine bugs do not fly to hosts to take a blood meal. The threat from triatomine bugs arises because some species colonise houses in large numbers, feeding from humans, domestic mammals, and chickens (although the latter are not susceptible to *T. cruzi*, they are an important blood source). *T. infestans* is the domestic vector of Chagas' disease in the vast southern cone region of South America. Surprisingly, silvatic *T. infestans* is known only from central Bolivia³ and from parts of the Chaco region of South America. This fact has prompted the idea that a united international campaign to spray houses infested with *T. infestans* could eliminate the species from almost its

entire geographical range. The southern cone programme was born from this idea.³

The control methods used in the programme are simple³: spraying houses and domestic animal shelters with residual pyrethroid insecticide to kill triatomines and serological screening of blood donors to stop transmission by blood transfusion. Spraying programmes are carefully designed, with preparatory, attack, and surveillance or consolidation stages. Health education and participation of communities are vital to surveillance for persistent bug infestations. Serological surveys of children born after the control programme started track down pockets where vectors remain and detect cases of congenital transmission. Long term planning and commitment to the programme have helped to prevent diversion of resources.

The success of the southern cone programme is unequivocal. Uruguay was certified free of transmission in 1997, Chile in 1999, central and southern Brazil in 2001, four provinces of Argentina in 2002, and one department of Paraguay in 2003. This success has been dependent on the strength of the public health based and economic arguments for controlling transmission, the availability of proved interventions, the shared public health problem, shared political will, adequate political stability, unequivocal support by health ministries, allocation of resources, and concurrent action across national boundaries. The early stages of the initiative were driven by a common purpose emerging from research conferences, and by the vigour of key individuals and networks of collaboration.³ Sustainability will be dependent on: unimpeded resources; continued surveillance to consolidate control and avoid resurgence, and on international monitoring and accurate public reporting of progress. The southern cone programme shows what can be achieved if disease control transcends national boundaries. It has been suggested that similar principles could be adopted to combat African trypanosomiasis.²⁰

The southern cone initiative has spawned three others: an Andean Pact control programme (Venezuela, Colombia, Peru, Ecuador), a Central American control programme, and a surveillance programme to protect the Amazon basin from incursion by domestic triatomines.^{4 21} The simple southern cone principle of eliminating vectors may be directly transposable to parts of the range of *Triatoma dimidiata* (Ecuador, Peru) and *Rhodnius ecuadoriensis* (northern Peru), where these bugs seem to be confined to houses.

Vector control is less straightforward for species with both silvatic and domestic populations such as *R. prolixus* and *T. brasiliensis*. In this context molecular methods, by determining the distribution of *T. cruzi* and triatomine genotypes, can define whether interaction occurs between domestic and silvatic transmission cycles. In principle this molecular epidemiological approach, in conjunction with ecological data, will allow estimation of the risk that houses will be reinvaded after spraying. In localities at risk of reinvasion control strategies can then be modified—for example, by repeating spraying or more frequent surveillance, or by devising some tactic—such as spraying palm trees—to attack triatomines in silvatic foci. Where these modifications are not necessary the cost of control will be lower.

Future challenges

- Distinguishing cryptic triatomine species and devising simple methods of identification
- Mapping where reinvasion from silvatic transmission cycles is a problem for control of Chagas' disease
- Designing improved interventions to combat reinvasion
- Developing a non-toxic, oral drug to eliminate *T. cruzi* infection from chronic carriers
- Proving whether distinct *T. cruzi* strains cause benign and severe chronic Chagas' disease, and if so, determining which genes encode pathogenicity
- Following the Chagas' disease model, to establish more international initiatives to control infectious diseases

The way ahead

The prospects for control of Chagas' disease are good. The elimination of domestic vector populations will continue if the flow of resources and political will can be sustained. It is now clear that molecular genetics of *T. cruzi* and its vectors can be used to identify areas where silvatic and domestic transmission cycles overlap, which helps to measure the risk of reinvasion. Modified control strategies will be devised to deal with such localities. New centres of domestic transmission might arise in the Amazon basin, but hopefully they will be detected rapidly and the bug colonies destroyed.⁴ In addition, new trypanocidal drugs are desperately needed for the treatment of *T. cruzi* infection,²² not only to save lives in the acute phase but also to eliminate the vast reservoir of infection in the human population of Latin America. The great hope, as with other pathogens, is that sequencing the *T. cruzi* genome will identify new drug targets present in the parasite but not in the host. Comparative genomics of virulent and avirulent *T. cruzi* strains may identify genes that are associated with pathogenicity and lead to prognostic indicators. Assuming that resources are adequate, individuals carrying strains associated with a poor prognosis could then be given intensive chemotherapy. Above all, the success of control strategies for Chagas' disease must encourage more governments around the world to establish international cooperation for the regional control of infectious diseases.

We thank J Patterson and S Fitzpatrick for comments on the manuscript, J S Patterson for preparing figure 1, and J S de Oliveira for the images in figure 2.

Contributors: MAM prepared the manuscript in collaboration with MDF and ARdeA, in particular to check the context and relevance to endemic areas in Venezuela and the southern cone countries of South America. MAM is the guarantor.

Funding: Wellcome Trust project grant for collaboration between United Kingdom, Venezuela, and Paraguay.

Competing interests: None declared.

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Inappropriate prophylaxis for long haul flights

Take a holiday to Kenya and a fit and healthy 56 year old woman who had never taken non-steroidal anti-inflammatory drugs or aspirin. Add advice from a friend to take aspirin to minimise the risk of deep vein thrombosis. Take one aspirin on the outward bound journey and two within 36 hours of return.

Result? Well, predictably coffee ground vomiting and melaena stool five days after return, with a haemoglobin concentration of 69 g/l when admitted to hospital five days later. The patient required a 5 unit blood transfusion, and endoscopy confirmed an

ulcer in the duodenum. Incidentally, she was also infected with *Helicobacter pylori*.

She made an uneventful recovery, had helicobacter eradication therapy, and was warned not to take aspirin in the future.

I suspect we are in for many more such patients and worry about the consequences should the bleed occur in a remote area of the world during a holiday.

Tina Diggory *locum consultant in gastroenterology, Hull Royal Infirmary*