Severe acute respiratory syndrome coronavirus and viral mimicry

Sir—Viruses have evolved various strategies to counteract host-cell processes, notably our immune responses toward their invasion. Oleszak and colleagues1 reported that the spike proteins of coronaviruses, particularly the mouse hepatitis virus, bovine coronavirus, and transmissible gastroenteritis virus, display Fc gamma receptor activity. Such molecular mimicry of components of our own immune system may even have a role in viral pathogenicity. This phenomenon, if shown to be true with the severe acute respiratory syndrome (SARS) virus, could help to explain why seemingly healthy individuals with active immune responses make up a large proportion of the patients who die from SARS. This mimicry of the Fc receptor might result in binding of non-specific IgG to virus or virus-infected cells, which would then inhibit neutralisation by virus-specific IgG because of steric hindrance. Such mimicry might also protect infected cells from antibody-dependent cell-mediated cytotoxicity and complement neutralisation.

Antibody-dependent enhancement of infection has been described for certain viruses, including the feline infectious peritonitis virus (FIPV), which is a coronavirus.2 Such enhancement involves the binding of virus-antibody complexes to Fc or complement receptors on the surface of monocytes or macrophages, resulting in virus uptake via receptor-mediated endocytosis, instead of neutralising the infection. With FIPV, antibody-dependent enhancement is mediated by specific sites on the spike protein.3 Whether the SARS virus exhibits such properties needs to be investigated.

Viruses affect the occurrence or course of certain autoimmune diseases. Talbot and colleagues4 have suggested that molecular mimicry between part of the human coronavirus (HCV) 229E and myelin basic protein of the central nervous system might contribute to the pathogenesis of multiple sclerosis. Autoreactive T cells specific to myelin components are cross-reactive with HCV 229E, and coronavirus-like particles have been isolated from patients with multiple sclerosis.4 We need to be vigilant as to whether the SARS virus (and vaccine) would also have such mimicry.

Funding source: Agency for Science Technology and Research of Singapore, and The National University of Singapore.

*Fook Tim Chew, Su Yin Ong, Choy Leong Hew
Department of Biological Sciences, National University of Singapore, Science Drive 4, Singapore 117543 (e-mail: dbscf@nus.edu.sg)


Diagnosis of tuberculosis

Sir—Katie Ewer and colleagues (April 5, p 1168)5 confirm what colleagues in veterinary science have previously shown, although none of their reports were referenced. In 1991, Wood and colleagues6 wrote that interferon-γ production can be used as an indicator for exposure to tuberculosis in cattle and hence provide an alternative diagnostic assay for tuberculosis. Several groups7–9 have also reported, as long ago as 1997, that the use of highly specific antigens, such as the 6 kDa early secretory antigen target (ESAT-6), further improves the specificity of the assay and discriminates between infected animals and those vaccinated with BCG.

The particular assay for interferon-γ production (enzyme-linked immunospot, ELISPOT) used by Ewer and colleagues,6 although elegant, might not be practical as a routine diagnostic test. The labour-intensive need to isolate lymphocytes and the need to have access to sophisticated equipment greatly limits ELISPOT’s usefulness and undoubtedly makes it an expensive procedure for routine use. To avoid these constraints and to create a viable diagnostic alternative to the tuberculin skin test, the preference has been to use simple whole-blood cultures and well-established ELISA technology to measure interferon-γ production. Such an assay system has been extensively validated and is routinely used as a diagnostic test in cattle and primates, and has also gained approval from the US Food and Drug Administration for use in human beings.1

The use of tuberculosis-specific antigens in both the whole blood interferon-γ test and the ELISPOT method has obvious benefits for improved specificity. In cattle, commensurate sensitivity between the two test methods was observed when cocktails of ESAT-6 and peptides from a 10 kDa culture filtrate protein (CFP-10) were compared as antigens. However, it is noteworthy that the amount of ESAT-6–specific interferon-γ measured by ELISA, but not the frequency of responding cells (ELISPOT), correlated positively with the degree of pathology after infection with Mycobacterium bovis.4

The effect of skin testing on boosting subsequent interferon-γ responses has also been shown by several groups,2,3 although this issue was not discussed by Ewer and colleagues.1 The finding that a previous tuberculin test will boost a subsequent interferon-γ response is now being used in New Zealand, with the interferon-γ assay replacing the comparative skin test in cattle.1 The fact that the children in Ewer and colleagues’ study had a Heaf test 1–2 months before being tested with ELISPOT would have had an effect on the results of this study, even allowing for the fact that tuberculosis-specific antigens were used. Therefore, whether the ELISPOT assay will have a similar sensitivity for the diagnosis of latent tuberculosis in individuals who have not had a recent skin test is yet to be established.

CSL manufactures diagnostic products based on interferon-γ technology.

*P R Wood, S L Jones
CSL Animal Health, Parkville, Victoria 3052, Australia (e-mail: Paul.Wood@csil.com.au)
Sir—The test described by Katie Ewer and colleagues1 has great potential as an alternative to the tuberculin test. But, what is really needed is a test able to detect active tuberculosis in children. Little emphasis is placed on the management of childhood tuberculosis in national tuberculosis control programmes that incorporate the WHO DOT (directly observed therapy) strategy; too much importance is given to sputum-smear positivity. Diagnosis on the basis of positive sputum smears is rarely possible in developing countries, where costly investigations are impractical.

Sathish Agadi
Department of Paediatrics, Karnataka Institute of Medical Sciences, Vidyanagar, Hubli 580022, India
(e-mail: agadisathish@hotmail.com)


Sir—Katie Ewer and colleagues1 suggest that an ELISPOT test based on ESAT-6 and peptides from CFP-10 could improve tuberculosis control. Screening of contacts is undertaken to detect and prevent new cases of tuberculosis. Ewer and co-workers mention that there were 69 secondary cases of tuberculosis, nine of whom were culture-positive, seven with an identical strain. Were these cases of tuberculosis and others2 have suggested that patients with tuberculosis produce less interferon γ in response to ESAT-6 than contacts.

The gold standard for assessment of latent tuberculosis infection is the later development of disease, which is estimated as a 10% lifetime risk for those with a positive tuberculin skin test or 1-68% at 2 years or longer in those who do not receive preventive treatment.3 If the ELISPOT test were used to focus preventive treatment, then 31 participants in the study would have been spared chemoprophylaxis, but a further 27 would have needed treatment. The new test is therefore not better than tuberculin skin testing, unless some of the 27 with a positive ELISPOT but negative tuberculin skin test develop tuberculosis. Furthermore, 80% of healthy residents of Mumbai, India have a positive ELISPOT, and preventive treatment cannot possibly be given to such a large section of the population.4

To improve tuberculosis control, a test that can identify those contacts who will develop infectious tuberculosis or at least limit the unnecessary use of preventive treatment is needed. The ELISPOT test as described does not fulfil such criteria.

Graham H Bothamley
North East London TB Network, Homerton University Hospital, London E9 6SR, UK (e-mail: graham.bothamley@homerton.nhs.uk)


Sir—We recognise P Wood and colleagues’5 veterinary research on diagnosis of tuberculosis in cattle, and their valuable contribution to bovine tuberculosis infection in non-HIV infected persons. Evidence-Based Med 1999; July/August: 122. We doubt its usefulness in cattle, but since it has significant cross-reactivity with previous BCG vaccination, we are unsure about its clinical usefulness in diagnosis of latent Mycobacterium tuberculosis infection in healthy urban Indians. J Infect Dis 2001; 183: 469–77.

Authors’ reply

Sir—We support P Wood and colleagues’5 veterinary research on diagnosis of tuberculosis in cattle, and their valuable contribution to bovine tuberculosis infection in non-HIV infected persons.6 Evidence-Based Med 1999; July/August: 122.

P Wood and Jones may be unfamiliar with the ELISPOT technique, since it is not especially labour intensive, depends on no sophisticated equipment, and is robust. Only a centrifuge, an incubator, and a microscope are needed, and our collaborations with colleagues in resource-poor countries—India, Zimbabwe, South Africa, Zambia, and Turkey—have enrolled more than 2000 participants without technical difficulties.
Preliminary results from ongoing studies with sequential tuberculin skin tests and ELISPOT assays indicate that ELISPOT is not boosted by previous tuberculin skin tests (unpublished data).

We appreciate Satish Agadi's cogent reminder that diagnosis of tuberculosis in children remains woefully inadequate, especially in resource-poor settings. We are heartened to hear about early promise shown by the glutaraldehyde coagulation test. We prospectively assessed the clinical usefulness of ELISPOT for diagnosis of active tuberculosis in 293 children with a high HIV-1 seroprevalence in rural Africa, and will report results shortly.

Graham Bothamley reminds us that patients with active tuberculosis produce less interferon-γ than tuberculosis contacts. This fact does not adversely affect ELISPOT results, since diagnostic sensitivity was 96% in adults with culture-confirmed active tuberculosis in the UK1 and 92% in HIV-1-positive adults with smear-positive pulmonary tuberculosis in Zambia.2 In the school outbreak, 30 of 545 children tested with ELISPOT had been given a diagnosis of active tuberculosis; 27 (90%) of these were ELISPOT positive. The three ELISPOT-negative children did not have a bacteriological diagnosis, but were presumptively diagnosed on the basis of positive tuberculin skin tests and suggestive chest radiography.

Of the 535 students who were tested with ELISPOT and a tuberculin skin test, 153 had positive tuberculin skin tests, of whom 32 (21%) were ELISPOT-negative, which suggests, as explained in the article, that these were probably false-positive skin test results. Thus, ELISPOT would have lessened the use of unnecessary chemoprophylaxis by 21%, which we consider to be a significant advantage.

Bothamley asks whether ELISPOT-positive contacts subsequently develop active tuberculosis. Because of the long incubation period of tuberculosis, this important question will take many years to answer. However, we have begun to address it, by following up ELISPOT-positive contacts in all our ongoing studies internationally.

Finally, Bothamley notes that through use of ELISPOT in regions with a high tuberculosis burden we have shown a high prevalence of latent tuberculosis infection in adults (80% in Mumbai3 and 69% in Lusaka).4 He seems to agree that although preventive treatment of latent infection is important for tuberculosis control in low-prevalence countries,5 it is not appropriate in high-burden countries,6 where improving treatment of active tuberculosis remains the priority. However, better diagnosis of tuberculosis infection could help tuberculosis control in high-burden countries in three ways: by improving diagnosis in children and in HIV-1-positive people,7 and by enhancing epidemiological surveys to assess the effect of tuberculosis control measures.8

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**West Nile virus and blood donors**

Sir—During the past 2 years, the West Nile virus epidemic has emerged as a major public-health concern in North America. Although the infection is symptomless in most instances, it can cause mild symptoms and be responsible for encephalitis or meningitis in individuals with some degree of immunodeficiency, including elderly people. In 2002, more than 200 deaths associated with West Nile virus were reported in the USA.

Until recently, the virus was considered transmissible to human beings exclusively by mosquito bites. However, the rapidly expanding North American epidemic has revealed that the virus could also be transmitted by organ transplantation and by transfusion of blood or blood components. Such transmission can only take place in the initial window of infection during which fairly high degrees of viraemia are observed. After 2–3 weeks post-contact, IgM and IgG antibodies are produced that make the virus no longer infectious and ultimately lead to recovery.

Since most infected individuals remain symptomfree they are eligible as blood donors. Similar to hepatitis C virus, West Nile virus can be inactivated by solvent-detergent treatment to prevent contamination of plasma derivatives. However, transmission of the virus by cellular blood products has been reported.9 To prevent further contamination of cellular blood products, the US Food and Drug Administration has decided to implement nucleic acid testing of the virus in blood banks from July, 2003.10

Occasional and limited outbreaks of West Nile virus have been reported in horses and in people in Europe.11 In the aftermath of the epidemic in Tuscan horses in 1998, no clinical cases were reported in human beings, although...
about 4% of individuals in close contact with these animals seroconverted (L Nicoletti, personal communication). The virus is, therefore, considered endemic. This case seems to be true even in the UK, where West Nile virus was previously thought to be absent.2 Western Europe is not in an epidemic situation, the likelihood of widespread infection is small, and specific nucleic acid testing of stored blood is, therefore, not justified.

However, during the 2–3 weeks after a potential mosquito bite, blood taken from individuals travelling from an epidemic area such as the USA or Canada should be considered at risk of contamination. Hence, we suggest that North Americans travelling to Europe and Europeans returning from North America, in particular during spring to autumn, should be excluded from blood donation. Since the duration of viraemia in West Nile virus infection is short, this exclusion period should be transient (no longer than 2 months).

In the UK, only about 8% of adults (eligible as blood donors) travel to North America every year, so the effect on blood banks would be negligible; about 0·7–1·3% decrease in donors. Furthermore, though about 3 million North Americans visit the UK every year, few are expected to become blood donors. In the rest of Western Europe, these figures should be much lower.


5 Creek PD, Crowcroft NS, Brown DW. West Nile virus and the threat to the UK. Commun Dis Public Health 2002; 5: 138–43.

Frozen blood

Sir—Lawrence Goodnough and colleagues (Jan 11, p 161)1 provide a look into the future of transfusion medicine, and their ideas could be applied as a model for national blood programmes for many years. They describe new technology, which makes possible extended use of post-mortem frozen red cells that have been stored for many years. The Review contains information showing, to the specialist, that there are severe limitations on the practical applications of frozen blood, but the authors do not connect adequately the two ideas for the reader.

The new system offers the first practical option for increasing blood reserves, because it makes possible a 2-week post-mortem shelf-life for frozen cells.1 However, donor-deferral questions remain an important method for increasing transfusion safety.1 A medical history must be obtained—as the first defence against unwitting carriers of transfusion-transmitted disease—before every unit of blood is collected. Information cannot be obtained retrospectively, and blood already in storage becomes worthless when new screening questions become part of the history list.1

Rotation of stock in a frozen red cell reserve would prevent obsolescence, but could double the cost of blood to recipients. Use of existing blood component stocks to anticipate an expected new regulation is unethical and poor public policy. This point was shown in France after the AIDS crisis in charges of involuntary manslaughter and imprisonment for the highest government officials.2

Additions to donor-deferral questions are an ongoing event, and therefore make impossible large-scale application of long-term storage for frozen red cells. After the Sept 11, 2001, terrorist attacks, 500 000 donations in a magnificent public response overloaded the blood supply chain. None of that blood was needed by the victims, and much became outdated in the liquid state. The American Red Cross froze almost 10 000 units.3 Then the Food and Drug Administration (FDA) placed new restrictions in October, 2002, on the time prospective donors had spent in Europe, as added protection against potential transfusion-transmitted variant Creutzfeldt-Jakob disease.4 Blood already in the freezer became unusable. As late as February, 2003, a 6-month deferral was applied by the FDA to prospective donors taking dutasteride for benign prostate hyperplasia for fear that drug transfer by transfusion to a pregnant recipient could have teratogenic results.4

50 years of research into frozen blood have resulted finally in a practical method. However, other events were happening in the blood-supply system, and practical frozen blood storage has arrived too late for large-scale application. All elements in a review such as that by Goodnough and colleagues need to be assessed for change before planning the future, and in this case, that is true of transfusion medicine of the future.

Paul J Schmidt
Department of Pathology University of South Florida, 913 Mooring Circle, Tampa, FL 33602, USA
(e-mail: pauljschmidt@hotmail.com)


Cost of medical education in the USA

Sir—From Robert A Schwartz’s Correspondence letter (Jan 18, p 264)1 about the exorbitant application fees indirectly charged by the Association of American Medical Colleges, one would be tempted to suggest that the acronym AAMC could equally stand for An Awfully Mercenary Crew. In addition to the figures quoted for application to medical school and to residency programmes, there are also the costs of the Step 1 and Step 2 examinations, taken during medical school, which are a prerequisite for gaining entry to the application system. These rather tortuous 8–9 h computer-based tests weigh in at the hefty cost of US$420 each for those taking the examination in the USA, with costs for foreign graduates rising to US$800–900. Add this price to the numbers already cited by Schwartz, and it is not hard to see why many young US doctors spend their formative years in practice saddled with enormous debt.

Sarah Walsh
Cork University Hospital, Wilton, Cork, Republic of Ireland
(e-mail: sawalsh@eircom.net)

Syndromic STI and behaviour-change interventions in Uganda

Sir—The sexually transmitted infection (STI) and behaviour-change intervention study in Masaka, Uganda, by A Kamali and colleagues (Feb 22, p 645) found that, despite reductions in the prevalence of gonorrhoea and high-titre syphilis, HIV-1 incidence did not decrease. Policy makers might therefore conclude that STI activities should be downplayed despite the authors’ assertion that HIV-1 transmission is facilitated by STIs. If some of the hard-won advances in STI/HIV-1 prevention and control are not to be lost, convincing explanations are needed to account for these findings.

Despite the decrease in laboratory-diagnosed gonorrhoea and high-titre syphilis in the STI intervention group, the study also found no reduction in reported genital ulcers or urethral discharge in the past year. These STI syndromes reflect HIV-1 risk at individual and community levels, and are important indicators by which to assess HIV-1 prevention interventions. In this community, the question arises whether the laboratory STI test results reflect the true STI burden in the community, or whether other unrecognised factors led to an underestimation of the prevalence of STIs with high relevance to HIV-1 transmission.

Although the STI intervention group used syndromic management along standard guidelines,1 this approach has limitations. First, in this community where genital herpetic is the commonest cause of genital ulcers, the algorithm for this disorder recommends treatment for genital ulcers and chancroid, but makes no mention of genital herpetic. Most individuals with genital herpetic would therefore receive little benefit from this approach. Indeed, this experience could dissuade them from attending again if they had recurrences of genital herpes or even syphilis or chancroid.

Second, before the trial started, single-dose oral treatment for gonorrhoea—the commonest cause of urethral discharge in Africa—would not have been available in this community. However, drugs donated to community studies often find their way to local drug sellers. If men with urethral discharge could get access to a simple treatment such as single-dose ciprofloxacin, they would not have to attend a clinic and would not be classified as a gonorrhoea case. Third, there was no reduction in infection with Chlamydia spp. Syndromic management algorithms usually advise that treatment be given for concomitant chlamydial infection whenever a syndrome needing gonorrhoea treatment is diagnosed, and a decrease in chlamydial infection would be expected if gonorrhoea were reduced.

The study also showed that a behavioural intervention targeting this rural community was not effective. Perhaps this finding was not so surprising. In any significant HIV-1 epidemic, targeting of core groups is likely to have the most effect, but this rural intervention did not try to target high-risk individuals. The study has again shown the difficulties in identifying the best ways of delivering STI care to key individuals at high risk of HIV-1 transmission, in particular those with genital ulcers.1,3

Nigel O’Farrell
Pasteur Suite, Infection and Immunity, Ealing Hospital, London UB1 3HW, UK (e-mail: ofarrell@postmaster.co.uk)


Sir—A Kamali and colleagues1 describe the results of a study of syndromic STI management for HIV-1 prevention in Uganda. They found that provision of high-quality syndromic STI management resulted in a significant reduction in gonorrhoea prevalence and a marginally significant reduction in syphilis incidence, but did not affect the incidence of herpetic simplex type 2, Chlamydia trachomatis infection, or HIV-1.

In an accompanying Commentary, Judith Stephenson and Frances Cowan2 postulate that the low incidence of HIV-1 reducing the study’s power and a secular trend of declining HIV-1 incidence might have accounted for the failure of this effort to produce a significant effect. However, the findings imply that, given the fairly small proportion of STI-attributable HIV-1 infections in these populations, population-level STI treatment might not be a very efficient means of preventing HIV-1.

On the other hand, the findings do not invalidate STI screening or treatment as an important component of HIV-1 prevention programmes, in particular among high-risk groups. Previous research1 has shown an intervention including STI screening and treatment of prostitutes to be effective at lowering HIV-1 incidence in this high-risk population. After accounting for increased condom use, the STI treatment intervention seemed to exert an independent effect. Focusing on high-risk groups is logically more effective than population-wide efforts because: (1) the increased likelihood of disease increases the power of research to detect an effect; (2) fewer high-risk individuals have to be screened or treated to cure one case of STI; (3) the lower number needed to treat means that more frequent screening can be done without incurring high costs; and (4) prevention of one case of STI or HIV-1 in this population can potentially prevent many secondary cases, since high-risk individuals who are highly sexually active have the opportunity to spread infection to many others.

A final advantage of frequent, targeted screening is that, by contrast with syndromic management, it will shorten the duration of asymptomatic as well as symptomatic STIs. Detection of asymptomatic infections is vital, since they represent a large proportion of STIs overall, and are unlikely to be addressed by syndromic management alone.

In short, population-wide syndromic STI management efforts might or might not be efficient in the prevention of HIV-1, but more intensive STI screening and treatment programmes targeted at high-risk groups are likely to be effective. Over time, such efforts can substantially decrease HIV-1 incidence at lower cost than less intensive population-wide approaches.

Joshua R Mann, Mary B Adam

*University of South Carolina School of Medicine, Columbia, SC 29208, USA (JRM); and Department of Pediatrics, University of Arizona College of Medicine, Tucson, AZ, USA (MBA) (e-mail: joshua.mann@palmettohealth.org)


Sir—A Kamali and colleagues1 begin the abstract of their report with the assertion that behavioural interventions are one of the two main methods used to prevent HIV-1 in developing countries. Yet this statement is contradicted by evidence presented elsewhere in their article.

The behavioural interventions they tested in their community-based randomised controlled trial did not have an effect on HIV-1 incidence. However, there is persuasive evidence that Ugandans have successfully assimilated scientific knowledge about how HIV-1 is transmitted, have used this knowledge to change high-risk sexual practices, and have enjoyed the expected pronounced fall in disease incidence; which is encouraging news. In important respects, this situation reflects the English experience of the first wave of the HIV-1 epidemic in the early 1980s.

In the initial HIV-1 epidemic in England (as reconstructed by back projection2) incidence rose sharply from 1981 to reach a peak in 1983, and then fell by 80% from peak levels by 1985. Formal mass campaigns aimed at discouraging high-risk sexual practices did not begin until 1986.3 The evolution of the incidence of HIV-1 since 1986 would suggest that formal behavioural interventions have had little additional effect. England thus also experienced success without interventions. As in Uganda, this success was nevertheless dependent on scientific knowledge of how the infection was transmitted (in the UK mainly among homosexual men, in Uganda mainly among heterosexual individuals). As in Uganda, the channels by which this new knowledge reached the groups most at risk will have mostly lain outside the formal health services, coming instead from, for example, the mass media and formal and informal communication networks.

These experiences delineate two views of public health: the interventionist view, in which the public only enjoy the fruits of science when they are ministered directly to them by the intrusive activities of professionals; and an alternative, less technocratic view, which values the advance of science no less, but which seeks to realise its benefits by creative engagements with all relevant forms of social organisation, and not just by professionally controlled interventions. Unfortunately, those who value science seem often to distrust democracy, and vice versa.

The course of the HIV-1 epidemics in Uganda and England carries a message consistent with experience in the control of many other major diseases: maximum benefit from public-health endeavours has mostly come from creative combinations of science and civic engagement.

*John Powles, Nicholas Day

*Department of Public Health and Primary Care, Institute of Public Health, Robinson Way, Cambridge CB2 2SR, UK (JP); and Strangeways Research Laboratory, University of Cambridge, Cambridge (ND)

(e-mail: jwp11@cam.ac.uk)


Roth spots obscure the picture

Sir—Peter Tong and Risa Ozaki’s Clinical picture (Feb 22, p 689)4 could mislead some readers. Retinal bleeding of the type shown, called white-centred retinal haemorrhage, was noted by Roth in infective endocarditis.2 However, Roth made the mistake of attributing the white centres to septic emboli. As Ling and James3 have described, retinal haemorrhages with a white centre are now thought to represent acute systemic insults to homoeostasis, which cause retinal-capillary rupture. Thus, the term Roth spots is less widely used.4,5 Identical haemorrhages can occur, for example, in shaken baby syndrome but are rarely called Roth spots.3 Diabetes can cause this type of retinal haemorrhage as correctly suggested by Tong and Ozaki. Acute, substantial changes in body homoeostasis, such as rapid changes in blood glucose, could cause these bleeds.1 Yet Tong and Ozaki provide no evidence that the inner blood-retina barrier of their patient was disturbed by diabetes to such an extent that it could cause this type of retinal bleeding.

In their patient, the cause of the bleeding retina was unremarkable. The patient was weak, malnourished, and also had thrombocytopenia, which became fatal when she died of intracranial haemorrhage. Infective endocarditis was excluded, and myelodysplastic syndrome causing anaemia and thrombocytopenia diagnosed. Haematological malignant diseases are known to cause this type of retinal bleeding.6 However, severe anaemia and thrombocytopenia are also classic and common causes of such retinal bleeding.4–6 Indeed, severe anaemia is a textbook cause of retinal haemorrhages with a white centre.7 The suggested association made by Tong and Ozaki with diabetes is thus most unlikely for this patient. Unlike thrombocytopenia, severe anaemia, and infective endocarditis, diabetes remains an extremely rare cause for this type of retinal bleeding.

Farhan H Zaidi

*Department of Ophthalmology, Faculty of Medicine, Imperial College London, London W6 8RF, UK; and The Western Eye Hospital, London (e-mail: fhz12@hotmail.com)


Authors’ reply

Sir—Farhan Zaidi has mistaken the message of our Clinical picture. We clearly stated that we made a diagnosis of myelodysplastic syndrome, which is the most likely cause of the Roth spots in our patient. Subacute presentation with non-specific symptoms of fever, tiredness, visual disturbance, and Roth spots does not necessarily imply bacterial endocarditis. Roth spots were initially regarded as a pathognomonic feature of subacute bacterial endocarditis.8 Other conditions in which Roth spots occur include leukaemia, anaemia, trauma, intracranial haemorrhage, and anoxia.9 As suggested by Zaidi, the pathogenesis of Roth spots is unclear. Fibrin fibrilae were identified in white-centred haemorrhages.2 The rupture of retinal capillaries may lead to formation of a platelet-fibrin thrombus. White-centred haemorrhage is not a common finding in myelodysplastic syndrome, although it is a common feature in acute leukaemia.1 Catalano and colleagues2 noted that in 5% of patients with diabetic retinopathy, multiple white-centred haemorrhages were associated with microaneurysms.

Our patient had neither leukaemia nor diabetic retinopathy. Diabetes mellitus is, however, associated with endothelial dysfunction and coagulopathy. The presence of diabetes mellitus may have increased the fragility of the retinal capillaries, thereby increasing the tendency to form Roth spots. Although Roth spots may...
be an occasional finding in diabetic retinopathy, a preponderance of such haemorrhages in the absence of typical features of retinopathy should alert clinicians to other possibilities.

*Peter Tong, Risa Ozaki
Division of Endocrinology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong (e-mail: ptong@cuhk.edu.hk)

2 Falcone PM, Larsson WI. Roth spots seen on ophthalmoscopy: diseases with which they may be associated. Cone Med 1995; 59: 271–73.

We investigated whether international representation in psychiatric publications has increased or decreased in the past decade. We undertook a retrospective study of publications in four leading generalist psychiatry journals from various parts of the world (British Journal of Psychiatry, American Journal of Psychiatry, Acta Psychiatrica Scandinavica, and Australian and New Zealand Journal of Psychiatry) for two 2-year periods, 1991–92 and 2001–02. For all research articles (including preliminary and brief reports), we recorded the country of origin of the author to whom corresponding should be sent and calculated the frequency of representation of each country. We then compared the two time periods.

The table shows that, although all four regional journals had an expected bias toward publishing articles from their geographical region, there was a shift in the distribution of contributor region between 1991–92 and 2001–02. In the American Journal of Psychiatry, the proportion of research articles authored by groups in the USA decreased whereas contributions from Europe and the rest of the world increased. Similarly, in Acta Psychiatrica Scandinavica, the proportion of research articles by Scandinavian authors decreased and representation from the rest of Europe and the USA increased. The Australian and New Zealand Journal of Psychiatry showed a slight decrease in frequency of publications from local authors, from 88% to 86%, and a corresponding increase in reports from Europe and the USA. By contrast, the proportion of articles by UK authors in the British Journal of Psychiatry was higher in 2001–02 than in 1991–92, whereas the proportion from North America was lower.

In this era of globalisation, should international representation in major generalist psychiatric journals show such diverse trends? To address such disparities we need to understand whether this trend arises because of differences in submission rates or editorial process.

Lisa A Catapano, *David J Castle
Harvard Medical School, Boston, MA, USA (LAC); and *Mental Health Research Institute and University of Melbourne, Melbourne, Australia (DJC)
(e-mail: dcastle@mhri.edu.au)

1 Saxena S, Levav I, Mautik P, Saraceno B. How international are the editorial boards of leading psychiatric journals? Lancet 2003; 361: 609.

How international are psychiatry journals?

Sir—Shekhar Saxena and colleagues have documented the under-representation of developing countries on the editorial and advisory boards of ten leading psychiatry journals.1 Their report followed other work that showed a lack of international representation in publications in major psychiatric journals.2,3 For example, Patel and Sumathipala1 reported that in six leading European and American psychiatric journals from 1996 to 1998, only 6% of the articles were written by authors from countries outside of Western Europe, North America, and Australia/New Zealand. Furthermore, of the three journals for which submission records were obtained, all had significantly decreased rates of acceptance for submitted papers from these countries.2

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Regional distribution of research publications in four leading psychiatry journals

Acute myocardial infarction

Sir—The important role of vitamins in the treatment and secondary prevention of coronary artery disease is largely ignored by Eric Boersma and colleagues (March 8, p 847)1 in their otherwise excellent Seminar on acute myocardial infarction.

There is objective evidence for the efficacy of folic acid, vitamin B12, and pyridoxine in reduction of the rates of restenosis and revascularisation after coronary angioplasty.2 Furthermore, nicotinic acid, when added to simvastatin therapy, greatly reduces the number of clinical end points in patients with coronary disease, and low HDL and normal LDL cholesterol concentrations.3 These simple, low cost, and safe interventions should be routine in appropriate patients.

William Tormey
Department of Chemical Pathology, Beaumont Hospital, Dublin 9, Ireland (e-mail: william.tormey@beaumont.ie)


For personal use. Only reproduce with permission from The Lancet Publishing Group.
Sir—The Lancet is a scholarly journal, representing evidence-based medicine, and the Seminar on acute myocardial infarction provides a comprehensive overview of the results of recent studies into the disease. However, Eric Boersma and colleagues do not adequately address ways in which patients are managed.

Acute myocardial infarction is a form of acute myocardial ischaemia. Identification and management of individuals with early acute myocardial ischaemia could prevent infarction altogether, a fact not made clear in the Seminar. Boersma and colleagues do not discuss systems of care set up to shift management from individuals with heart attacks to those with early stage, reversible myocardial ischaemia.

In the USA, chest-pain centres are becoming more and more common. These centres deal with patients who have chest pain, and stratify them into various risk groups managed with appropriate protocols. Observation units within the centres identify patients with low probability of ischaemic disease. These units are effective in reducing the frequency of discharge from hospital of patients with missed myocardial infarction, as well as in reducing the number of inappropriate admissions. Such measures are very cost effective and have brought about reimbursement from the Centers for Medicare and Medicaid Services (Health Care Finance Administration).

The paradigm shift in the way individuals are managed arises when individuals with chest pain can be divided into those at high and low risk of myocardial infarction, thereby opening the door for the hospital’s cardiac outreach programme, which alerts the public about the early warning symptoms of myocardial ischaemia before infarction (prodromal unstable angina).

In their final sentence, Boersma and colleagues state that “the time of symptom onset to treatment of 2·7 h, as recorded in clinical trials in the beginning of the 1990s (GUSTO-I), has remained unchanged”. Though possibly true, if one intercepts before a person has a heart attack, fewer people will be affected by this statistic.

Raymond D Bahr
Paul Dudley White Coronary Care System, St Agnes Health Care, Coronary Care Administration, 900 Canton Avenue, Box 043, Baltimore, MD 21229, USA
(e-mail: cbrown1@STAGNES.ORG)

CORRESPONDENCE

Sir—Eric Boersma and colleagues have highlighted the challenge of effective implementation of preventive action in treatment of survivors of acute myocardial infarction. Although their comprehensive work refers to secondary prevention measures, including use of prophylactic drugs, they fail to identify the importance of cardiac rehabilitation or how long-term treatment schedules might be implemented.

The benefits of cardiac rehabilitation in patients who survive a heart attack have been confirmed in a Cochrane review. Growing evidence shows the benefits of nurse-led clinics in patients with coronary heart disease. Our experience is that when such primary-care-based clinics are integrated with cardiac rehabilitation programmes, it is possible to achieve improvements in secondary prevention outcome measures advocated by EUROASPIRE II.

*Hasnain Dalal, Philip Evans, Tony Mourant, John Campbell, Denis Pereira Gray
*Lower Lemon Street Surgery, Truro TR1 2LZ, UK (HD); Sahlgrenska University Hospital, Gothenburg (TM); Peninsula Medical School, Exeter (PE); Royal Cornwall Hospital, Truro (TM); Peninsula Medical School, Exeter, UK (JC); and University of Exeter, Exeter (DPG)
(e-mail: hmdalal@doctors.net.uk)


Management of severe malnutrition: facilitating learning

Sir—Child malnutrition is a major public-health problem in developing countries. The management of protein energy malnutrition (PEM) by careful assessment, appropriate treatment, and rehabilitation, using standard protocols that are easy to follow, reduces morbidity and mortality.

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While teaching the guidelines of PEM management to medical students and health workers, we noted that learners often seemed confused, being unable to provide the correct sequence of answers to the questions posed during the assessment phase of the course. We therefore developed mnemonics to help them remember the correct sequence of treatment, rehabilitation, and follow-up of severely malnourished children, as described in the standard WHO guidelines.

To facilitate learning, mnemonics must be simple, meaningful, and pleasant besides being catchy and pertinent to the topic.

Successful initial management of malnutrition depends on frequent, careful clinical assessment and anticipation of common problems so they can be prevented, or recognised and treated at an early stage. The principal tasks during initial treatment are to detect, treat, and prevent common and life-threatening complications. Thus, severely malnourished children have to be SHIELDED (treated or prevented) against:

S—Sugar deficiency—ie, hypoglycaemia
H—Hypothermia
I—Infection and septic shock
E1—Electrolyte imbalance
DE—Dehydration
D—Deficiencies of iron, vitamins, and other micronutrients.

Dietary therapy and social aspects are important components during rehabilitation and follow-up. Dietary management is divided into initial feeding in the sick and anorexic child followed by energy dense dietary formulas before switching to home-based foods. Thus, malnourished children need BEST dietary management:

B—Beginning of feeding
E—Energy dense feeding
S—Stimulation of emotional and sensorial development
T—Transfer to home-based diets before discharge or transfer to nutritional rehabilitation centers.

*Deheraj Shah, Piyush Gupta
Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India
(e-mail: shahdeheraj@hotmail.com)


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