LETTERS TO THE EDITOR

Scope

Heart welcomes letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

Presentation

Letters should be:

- not more than 600 words and six references in length
- typed in double spacing (fax copies and paper copy only)
- signed by all authors

They may contain short tables or a small figure. **Please send a copy of your letter on disk.** Full instructions to authors appear in the July 1999 issue of *Heart* (page 116).

Management of scorpion sting

EDITOR,—We read with great interest the haemodynamic pattern in patients with scorpion envenomation.[1] We have studied this acute time sensitive medical emergency since 1976 and have tried various regimens including antiscorpion venom.[2] Since the advent of prazosin (1983–84)—an α adrenergic blocker which acts as an antidote to venom—the mortality of scorpion sting victims is less than 1%.[3]

In the pre-prazosin era (1961–83) a fatality rate of 25–30% was reported from western India,[4] acute pulmonary oedema causing death. We were therefore surprised by the 25% mortality reported by Karnad,[1] and that two victims died on the third day of hospitalisation; we has similar findings in 1978–82—that is, before prazosin treatment.[5]

We have reported that the severity of scorpion sting depends on the victim's age, the season, and the time between sting and administration of prazosin. The symptoms following the sting are hypertension, tachycardia, pulmonary oedema, and shock (autonomic storm).[6] We believe that the transport of Karnad's patients to the nearest major hospital contributed to their deaths[5]; seven of eight had acute pulmonary oedema owing to a delay in reaching a tertiary care hospital.[1]

Scorpion venom inhibits angiotensin converting enzyme (ACE), resulting in accumulation of bradykinin, which is implicated in the development of pulmonary oedema and acute reversible pancreatitis.[7] Captopril (an ACE inhibitor) has a similar action resulting in hypotension resistant to dopamine agonists.[1] Bradykinin further enhances noradrenaline (norepinephrine) release by a presynaptic mechanism.[8]

Alpha receptor stimulation plays a major role in the pathogenesis of pulmonary oedema.[9] It causes hyperkalaemia and hyperglycaemia (inhibition of insulin secretions). Angiotensin II stimulates α adrenergic receptors in the myocardium and hypoxia results from coronary spasm as well as accumulation of free fatty acids and free radicals injurious to myocardium leading to cardiac arrhythmias and sudden death.[1]

At a general hospital at Mahad we successfully treated 658 cases of severe scorpion sting with oral rehydration, oral prazosin, and oxygen and aminophylline: 362 (55%) had hypertension, 178 (27%) had pulmonary oedema, 118 (18%) had tachycardia; no patient had lethal arrhythmias. Seventeen patients who died on the way to Mahad had been referred 24 hours after being stung while 13 cases were admitted with multiorgan failure and were moribund and comatose; they died 30–60 minutes after admission despite treatment with dopamine, nitroprusside, oxygen, and insulin–glucose drip. The remaining 56 cases with massive pulmonary oedema recovered after treatment with intravenous sodium nitroprusside.

We travelled throughout western Maharashtra where *Mesobuthus tamulus* scorpion flourish, and taught all peripheral doctors how to treat scorpion sting victims. There has not been any deaths over the past two years due to scorpion sting reported from this region. Moreover, only two patients had massive pulmonary oedema, which was treated with intravenous sodium nitroprusside. Captopril failed to correct haemodynamic abnormalities in two cases who had cardiac arrhythmias.[1] Prazosin treatment would have been life saving in the two patients treated with captopril who died in Karnad's report.[1] As a potent inhibitor of phospodiesterase, prazosin causes accumulation of cGMP, a second messenger of nitric oxide, in vascular endothelium and myocardium, inhibits the formation of inositol triphosphate, and activates venom inhibited calcium dependent potassium channels.

Thus prazosin reverses both inotropic (hypertension), and hypokinetic (pulmonary oedema, hypotension, tachycardia) phases evoked by scorpion envenoming.[10]

H S BAWASKAR
P H BAWASKAR
Bawaskar Hospital & Research Centre Mahad, Raigad, Maharashtra India 402301

1 Karnad DR. Haemodynamic pattern in patients with scorpion envenomation. *Heart* 1998;**79**:485–9.
2 Bawaskar HS, Bawaskar PH. Envenoming by scorpion and snake (elapidae), their neurotoxins and therapeutics. *Trop Doct.* [In press.]
3 Bawaskar HS, Bawaskar PH. Prazosin in the management of cardiovascular manifestations of scorpion sting [letter]. *Lancet* 1986;i:510–11.
4 Gaitonde BB, Jadhav SS, Bawaskar HS. Pulmonary oedema after scorpion sting [letter]. *Lancet* 1978;i: 445–6.
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6 Bawaskar HS, Bawaskar PH. Stings by red scorpions (Buthotus tamulus) in Maharashtra State, India: a clinical study. *Trans R Soc Trop Med Hyg* 1989;**83**:858–60.
7 Ismail M, Fatani AJY, Dabees TT. Experimental treatment protocols for scorpion envenomation: a review of common therapies and an effect of kallikrein-kinin inhibitors. *Toxicon* 1992;**30**:1257–79.
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9 Freire-Maia L, Campose JA. Pathophysiology and treatment of scorpion poisoning. In: Ownby CL, Odell GV, eds. *Natural toxins*. New York: Pergamon Press, 1988: 139–59.
10 Abroug F, Ayari M, Nauria S, *et al.* Assessment of left ventricular function in severe scorpion envenomation in a combined haemodynamic and echo Doppler study. *Int Care Med* 1995;**21**: 629–35.

EDITOR,—The study by Karnad[1] on the haemodynamic patterns encountered in scorpion envenomation raises important concerns. Karnad claims that the mechanism of pulmonary oedema observed in scorpion envenomation had not previously been established as pulmonary artery wedge pressure (PAWP) had not been measured. However, the haemodynamic mechanism of pulmonary oedema in scorpion envenomation was suggested in animal studies as early as 1980[2] and confirmed by numerous series in human subjects. All of these series performed a haemodynamic study and measured PAWP.[3–5] We are therefore not surprised with Karnad's findings and observe that they are consistent with our previous reports suggesting similar effects of the Indian red scorpion *Mesobuthus tamulus* and the yellow scorpion of North Africa (*Androctonus australis*).

We are particularly concerned by Karnad's interpretation of the haemodynamic records in the envenomated patients and the treatment strategy he suggests. Numerous haemodynamic, echocardiographic, and angioscintigraphic studies have shown that severe scorpion envenomation impairs left and right ventricles to the same extent.[3–5] Echocardiographic studies showed that LV systolic function might be deeply depressed with a mean LV fractional shortening as low as 12%.[3] Regarding the right ventricle, in eight patients we recorded a mean RV ejection fraction of 24%.[5] In fact, severe scorpion envenomation evokes acute heart failure which tends to recover in a few days. The heart failure might be concealed in some patients by the simultaneous hypovolaemia that occurs in envenomated patients as a consequence of vomiting and sweating. Hence, the patterns II, III, and IV described by Karnad should not be regarded differently from the multiple facets of the same and only haemodynamic feature that is the profile of acute heart failure (patterns II and IV) that might be mitigated by simultaneous hypovolaemia (pattern III). Moreover, the three reported patients who had simultaneous hypovolaemia exhibited a worsening in their pulmonary oedema with fluid infusion, suggesting an exaggerated increase in PAWP resulting from altered LV function.

Although attractive from a pathophysiological standpoint, Karnad challenges the usefulness of inotropic drugs and claims that they improve only transiently the circulatory failure observed in scorpion envenomation with no effect on mortality. We are unaware of any study specifically dedicated to address this issue. Nevertheless, owing to the clearly established haemodynamic pattern of severe scorpion envenomation and on the basis of a pathophysiological approach, we and others have usually treated envenomated patients exhibiting pulmonary oedema and/or peripheral circulatory failure with dobutamine. The physiological effects were as expected, those usually observed in the treatment of heart failure: an increase in cardiac output as a consequence of an increase in stroke volume with enhanced LV performance, a substantial decrease in PAWP, and an increase of arterial pressure.[6]

Finally, Karnad suggests that RV failure occurs late in the terminal phase of scorpion envenomation and combines with pre-existing LV failure to produce severe cardiogenic shock. This speculation is not supported by Nouira *et al* who used a modified Swan–Ganz catheter equipped with a fast response thermistance.[5] This study showed that scorpion envenomation evokes simultaneous impairment of the LV as well as the RV, the latter being depressed to the same extent as the former. Infusion of dobutamine enhances RV as well as LV performance.[6]

In conclusion, scorpion envenomation kills thousands of patients in developing coun-

tries. First line clinicians need comprehensive and meaningful insights regarding the pathophysiology and valuable treatments of this dreaded accident. The clearer and simpler the message on this issue the better the effect in daily clinical practice.

F ABROUG
S NOUIRA
S ELATROUS
ICU CHU F Bourguiba, 5000 Monastir, Tunisia

1 Karnad DR. Haemodynamic patterns in patients with scorpion envenomation. *Heart* 1998;**79**:485–9.
2 Gueron M, Adolph RJ, Grupp IL, *et al*. Hemodynamic and myocardial consequence of scorpion venom. *Am J Cardiol* 1980;**45**:979–86.
3 Abroug F, Boujdaria R, Belghith M, *et al*. Cardiac dysfunction and pulmonary edema following scorpion envenomation. *Chest* 1991; **100**:1057–9.
4 Abroug F, Ayari M, Nouira S, *et al*. Assessment of left ventricular function in severe scorpion envenomation: combined hemodynamic and echo Doppler study. *Intensive Care Med* 1995; **21**:629–35.
5 Nouira S, Abroug F, Haguiga H, *et al*. Right ventricular dysfunction following severe scorpion envenomation. *Chest* 1995;**108**:682–7.
6 El Atrous S, Nouira S, Besbres-Ouames L, *et al*. *Chest*. [In press.]

These letters were shown to the author, who replies as follows:

The efforts of Bawaskar and Bawaskar in popularising prazosin treatment in western India are truly commendable, and the effect on mortality following scorpion envenomation is impressive. They cite their personal experience of 658 patients treated with prazosin, of whom only 30 (4.5%) died. They had previously reported 526 patients treated with prazosin up to 1992; in this series 28 patients (5%) died.[1] They are surprised that two of the eight patients reported in my paper died. However, it must be understood that as the objective of my paper was to describe haemodynamic patterns, only eight patients in whom detailed serial haemodynamic data were available were reported; these cases are not the entire experience of our unit with captopril in scorpion envenomation.

In India, scorpion envenomation occurs almost exclusively in rural areas, and is particularly common in the coastal regions of western India where Dr Bawaskar's hospital is located. Patients stung by scorpions are likely to consult local doctors first, especially if envenomation is mild, explaining why 18% of patients had tachycardia alone and 55% had hypertension. Pulmonary oedema, resulting from more severe envenomation, was seen in 27% of patients. In contrast, our experience is from a tertiary referral centre in Bombay. Most patients treated in our unit were referred from rural areas 80 to 150 km away, 6–36 hours after the sting. Moreover, these patients had not improved despite receiving treatment at primary care centres. Consequent to this referral pattern, a greater proportion of our patients had severe envenomation and presented late—18 of 31 patients treated in our unit with captopril in the past 10 years had pulmonary oedema with hypotension. Four patients (all had severe pulmonary oedema with hypotension) died. In Dr Bawaskar's series, 178 patients with pulmonary oedema were treated with prazosin and 30 (17%) died. This is not significantly different from the 22% mortality in our experience with captopril.

I agree with Abroug and colleagues that patterns II, III, and IV described in my paper are facets of the same underlying abnormality. For this reason, they were all grouped under the category of predominant myocardial effects. Haemodynamic abnormalities in patterns II and III differ only in terms of the patients' fluid balance, but the clinical features of the two patterns were so different as to need separate discussion. Pattern II is characterised by severe pulmonary oedema and mild or no hypotension. Pattern III is seen in dehydrated patients and manifests as severe hypotension, with little or no pulmonary oedema.

Abroug *et al* have, in a previous study, shown that left ventricular ejection fraction measured by echocardiography was severely depressed (26%) following scorpion envenomation. They showed a threefold improvement to 75% during recovery.[2] In another study, they assessed right ventricular function using a pulmonary artery catheter; right ventricular ejection fraction was 24% following envenomation and improved to 39% during recovery.[3] Unfortunately simultaneous right and left ventricular functions have not been studied.

Our patients with pattern II showed severely raised PAWP and subnormal left ventricular stroke work index, while right ventricular stroke work index and right atrial pressures were normal, suggesting that the left ventricle was more severely affected than the right. In pattern IV, however, left as well as right ventricular stroke work indices were severely depressed and both PAWP and right atrial pressures were grossly raised suggesting that at this stage right ventricular function was also severely deranged.

Abroug *et al* mention that they have been using dobutamine in scorpion envenomation with good results. Their patients also received antivenom, which is not available in India. It may be possible that antivenom favourably alters the response to inotropic catecholamines. The experience of Bawaskar and Bawaskar suggests that inotropic treatment given to patients who have not received antivenom does not decrease mortality. Although no controlled studies exist, studies using historical controls treated conventionally, including inotropic drugs, have shown that vasodilators are beneficial in the treatment of cardiovascular manifestations of scorpion envenomation.[1 4 5] Vasodilators like prazosin, calcium channel blockers, ACE inhibitors, and sodium nitroprusside have been used.[1 4 5] However, whether any one of them is superior has not been studied. Currently available evidence indicates that these are equally effective and the suggestion that prazosin may have been effective in patients who did not improve with captopril as suggested by Bawaskar can only be considered speculative.

1 Bawaskar HS, Bawaskar PH. Treatment of envenoming by Mesobuthus tamulus (Indian red scorpion). *Trans R Soc Trop Med Hyg* 1992;**86**:459.
2 Abroug F, Ayari M, Nouira S, *et al*. Assessment of left ventricular function in severe scorpion envenomation. *Intensive Care Med* 1995;**21**: 629–35.
3 Nouira S, Abroug F, Haguiga H, *et al*. Right ventricular dysfunction following scorpion envnomation. *Chest* 1995;**108**:682–7.
4 Karnad DR, Deo AM, Apte NM, *et al*. Captopril for correcting diuretic-induced hypotension in pulmonary oedema after scorpion sting. *BMJ* 1989;**298**:1430–1.
5 Gueron M, Sofer S. Vasodilators and calcium blocking agents as treatment of cardiovascular manifestations of human scorpion envenomation. *Toxicon* 1990;**28**:127–8.

Is BNP ready for use in clinical practice?

EDITOR,—Richards *et al* suggest that brain natriuretic peptide (BNP) measured 24–96 hours after acute myocardial infarction (AMI) is a powerful, independent prognostic indicator for subsequent development of left ventricular failure and death.[1]

In their multivariate analysis the site (anterior *v* inferior) and type (Q wave *v* non-Q wave) of infarction do not appear to have been included. The important prognostic value of these indicators has been established.[2 3] One might expect the anterior infarcts (39% of their study population) to demonstrate greater left ventricular dysfunction, higher BNP concentrations, and a poorer prognosis than the inferior infarcts (51%). A similar relation may exist between type of infarct and outcome, although figures for each type are not given. It would be interesting to see whether BNP is still a powerful prognostic variable if site and type of AMI were included in their analysis.

Two further confounding variables that may have weakened the association between BNP and outcome are the timings of the radionuclide ventriculography and blood sampling (1–4 days after AMI). Assessment of ventricular function in the first 24–48 hours after AMI can lead to an overestimation of damage due to the phenomenon of myocardial stunning.[4] The time course of BNP shows a peak at 16 hours followed by a significant decline in the next 48–72 hours.[5] A narrower and standardised time window for ventriculography and venesection may have improved the correlations.

It would have been useful to know the area under their receiver operating characteristic (ROC) curve for BNP, which is highly relevant in assessing the true value of a test.[6] They demonstrated a negative predictive value of 100% for BNP at a threshold of 20 pmol/l, but they used different thresholds for looking at the sensitivity and specificity and predictive power for left ventricular ejection fraction and left ventricular failure (25 and 33 pmol/l, respectively). Although these values were derived from their ROC analyses, it is difficult to envisage how a BNP result should then be interpreted in clinical practice.

If the additional prognostic value of BNP is confirmed once site and type of infarct are incorporated into their analysis, then its precise role still needs to be clarified. Measurement of BNP after AMI is unlikely to reduce the need for imaging of ventricular function because of its poor positive predictive value. Its potential use may lie in its ability to identify a high risk population in whom some sort of intervention is feasible before development of "clinical end points". However, at present, there is no evidence to suggest that treating a high plasma BNP in the presence of a normal ejection fraction improves outcome. Clearly this should be an area for further investigation.

BNP and its prohormone derivative (N-terminal proBNP) offer exciting prospects for non-invasive assessment of myocardial function and outcome following infarction. Richards *et al* have clearly demonstrated the prognostic superiority of BNP over other neurohormonal markers thus supporting their initial hypothesis. Their concluding statement, however, suggesting that plasma BNP "could reasonably be included in the routine clinical workup of a patient following myocardial infarction" seems premature.[1]

K KHAN
Clinical Research Fellow,
Department of Medicine & Therapeutics,
Clinical Sciences Building, Leicester Royal Infirmary
Leicester LE2 7LX, UK
kmk2@le.ac.uk

1 Richards AM, Nicholls MG, Yandle TG, *et al*. Neuroendocrine prediction of left ventricular function and heart failure after myocardial infarction. *Heart* 1999;**81**:114–20.
2 Molstad P. Prognostic significance of type and location of a first myocardial infarction. *J Intern Med* 1993;**233**:393–9.
3 Hands ME, Lloyd BL, Robinson JS, *et al*. Prognostic significance of electrocardiographic site of infarction after correction for enzymatic size of infarction. *Circulation* 1986;**73**:885–91.
4 Marwick TH. The viable myocardium: epidemiology, detection, and clinical implications. *Lancet* 1998;**351**:815–19.
5 Mizuno Y, Yasue H, Oshima S, *et al*. Effects of angiotensin converting enzyme inhibitor on plasma B-type natriuretic peptide levels in patients with acute myocardial infarction. *Journal of Cardiac Failure* 1997;**4**:287–93.
6 Hanley JA, McNeill BJ. The meaning and use of the area under a receiver operator characteristic (ROC) curve. *Radiology* 1982;**143**:29–36.

This letter was shown to the authors, who reply as follows:

Dr Khan's letter raises a number of interesting points. First, when the site of myocardial infarction (anterior or inferior) is included in multivariate analysis of data reported in our recently published paper, plasma BNP remains an independent prognostic indicator for both death and development of heart failure. This is not surprising as division of patients according to inferior or anterior site of infarction creates crude categories, which both include a broad spectrum of injury from mild to very severe. In contrast, plasma BNP is a continuous variable and is related to the severity of cardiac injury across the entire group. This finding is also predictable in view of the fact that already published reports have indicated BNP has prognostic power independent of left ventricular ejection fraction (LVEF).[1 2] LVEF acts as a common indicator of degree of severity of injury regardless of site of infarction.

Dr Khan also comments on a potential weakening of the association between BNP and outcome (although the context suggests he means LVEF rather than morbid or mortal outcomes) due to the timing of radionuclide ventriculography and blood sampling. We find a similar correlation between early postinfarction BNP(1–4 days) and both early (1–4 days) and late (3–5 months) radionuclide ventriculography.[1] In addition, repeat BNP measurements at four months (unpublished data) continued to show a similarly strong correlation, albeit with an offset regression due to mean BNP falling somewhat from early postinfarction concentrations. In other words, a similar correlation is observed between BNP and ejection fraction regardless of early or late measurements of either variable. This suggests that the time window involved is not overly important provided reference data are established to allow for the systematic fall in plasma BNP over the months after infarction. However, multivariate analyses show that BNP and left ventricular ejection fraction are *independent* predictors of death or later heart failure following myocardial infarction, and their independent nature implies their correlation will not be overly strong. The association of BNP with prognosis may well reflect the influence on plasma BNP concentrations of diastolic dysfunction and left ventricular mass as well as systolic function.[3 4] For these reasons efforts to alter measurement method or timing simply to improve the correlation of BNP with LVEF are likely to be unproductive.

The statement by Dr Khan "The time course of BNP shows a peak at 16 hours followed by a significant decline in the next 48–72 hours" does not take into account the conflicting nature of the literature. The pattern of BNP change is dependent on the severity of infarction, the exact nature of the BNP assay employed, and its degree of cross reactivity with pro-BNP 1–108 or its N-terminal deleted metabolites.[5–8] In our hands the time profile shows a plateau between 24 and 72 hours and hence our election of a 1–4 day sampling window.

Dr Khan's comment that it is "difficult to envisage how a BNP result should then be interpreted in clinical practice" is disingenuous. Our published paper clearly points out that plasma BNP of less than twofold the upper limit normal within 1–4 days postinfarction has 100% negative predictive value for an ejection fraction of < 40% four months after MI. Our report also makes it very clear that the positive predictive value for BNP above this level is very weak (that is, BNP above the normal range within the early postinfarct period is a weak predictor of reduced LVEF), and we do **not** recommend the routine use of plasma BNP as a substitute for measurement of left ventricular ejection fraction. However, the *prognostic* value of BNP is strong and, at the very least, early postinfarct BNP measurements will allow better risk stratification and therefore better targeting of surveillance in the follow up period.

The most important and insightful part of Dr Khan's letter addresses the possible potential for BNP together with ejection fraction to identify high risk populations in whom some sort of intervention is feasible before development of "clinical end points". He states correctly that at present "there is no evidence to suggest that treating a high plasma BNP in the presence of a normal ejection fraction improves outcome". In a manuscript now in preparation, the Christchurch Group is able to report follow up data on over 500 MI patients with a mean follow up period of approximately two years. This group has been divided according to both plasma BNP and radionuclide LVEF. Notably, over 20% of the group have an early postinfarct LVEF in excess of 40% but a concomitant BNP of over 25 pmol/l (2.5 times the upper limit of normal). This subgroup has a significantly greater risk of mortality and of developing heart failure than the group with LVEF above 40% and plasma BNP < 25 pmol/l. Furthermore, in patients who have ejection fractions below the 40% threshold but BNP < 25 pmol/l, there is very little increase in risk of either death or heart failure over two years compared with that group with low BNP concentrations and high ejection fraction. In other words, reduction in ejection fraction only predicts increased morbidity or mortality in the presence of neurohormonal activation as indicated by raised plasma BNP. Our findings concur with data from colleagues in Sweden and Norway (T Omland, C Hall, personal communication), and it is becoming clear that a randomised controlled trial of treatment in asymptomatic patients with LVEF > 40% but clear neurohumoral activation should be done.

1 Richards AM, Nicholls MG, Yandle TG, *et al*. Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction. *Heart* 1999;**81**:114–20.
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3 Yu CM, Sanderson JE, Shum IOL, *et al*. Diastolic dysfunction and natriuretic peptides in systolic heart failure. Higher ANP and BNP levels are associated with the restrictive filling pattern. *Eur Heart J* 1996;**17**:1694–702.
4 Cheung BMY. Plasma concentration of brain natriuretic peptide is related to diastolic function in hypertension. *Clin Exper Pharmacol Physiol* 1997;**24**:966–8.
5 Yandle TG, Richards AM, Gilbert A, *et al*. Assay of brain natriuretic peptide (BNP) in human plasma: evidence for high molecular weight BNP as a major plasma component in heart failure. *J Clin Endocrinol Metab* 1993;**76**:832–8.
6 Mukoyama M, Nakao K, Obata K, *et al*. Augmented secretion of brain natriuretic peptide in acute myocardial infarction. *Biochem Biophys Res Commun* 1991;**180**:431–6.
7 Nagaya N, Nishikimi T, Goto Y, *et al*. Plasma brain natriuretic peptide is a biochemical marker for the prediction of progressive ventricular remodeling after acute myocardial infarction. *Am Heart J* 1998;**135**:21–8.
8 Foy SG, Crozier IG, Richards AM, *et al*. Neurohormonal changes after acute myocardial infarction: relationships with haemodynamic indices and effects of ACE inhibition. *Eur Heart J* 1995;**16**:770–8.

Transfusion associated graft versus host disease

EDITOR,—Ahya *et al* reported a case of transfusion associated graft versus host disease (TA-GVHD) in a non-immunocompromised patient resulting from blood transfusion after coronary artery bypass grafting (CABG).[1] They concluded that this devastating complication of transfusion is probably underreported. There is no doubt that diagnosing this condition needs a high index of suspicion because its manifestations can be seen in other more common conditions such as septicaemia. Moreover, histological diagnosis needs specialist expertise in tissue typing.

We report another patient with TA-GVHD acquired following elective four-vessel CABG and perioperative transfusion of a total of six units of blood. A 68 year old man was admitted three weeks after surgery with a seven day history of skin rash, breathlessness, cough, and expectoration of brown sputum. He had an extensive erythrodermic maculopapular eruption, oral thrush, tachycardia, hypotension, bilateral chest crepitations, and mild hepatomegaly. His condition worsened progressively with development of profound pancytopenia, disseminated intravascular coagulation, metabolic acidosis, hepatitis, and acute renal failure. His bone marrow was aplastic and skin biopsy showed monocytic infiltration with cellular apoptosis supporting the clinical diagnosis of TA-GVHD. Treatment with high dose steroids, ciclosporin, and OKT3 was initiated, but despite maximum support he died within seven days of readmission.

Although TA-GVHD does occur in immunocompetent individuals who had blood transfusion for other reasons, it is more frequent following cardiopulmonary bypass surgery. This type of major surgery appears to induce a transient immunodeficiency state, the mechanism of which is poorly understood and is likely to be multifactorial. Stress of surgery, use of fresh blood with more viable lymphocytes, immunosuppressive effect of multiple transfusions, and transient reduction of interleukin 2 production and mitogenic lymphocyte transformation following

cardiopulmonary bypass may all cause a degree of immune dysfunction.[2–5] If the donor's blood happens to be homozygous for one of the recipient's major HLA types, this transient immune dysfunction may facilitate donor's lymphocyte engraftment and development of TA-GVHD.

We emphasise the relation of this highly dangerous condition with cardiopulmonary bypass surgery. One can only speculate as to the nature of this association.

M H GHREW
T RINGROSE
D YOUNG
T PETO
Nuffield Department of Medicine, John Radcliffe Hospital, Oxford OX3 9DU, UK

1 Ahya R, Douglas JG, Watson HG. Transfusion associated graft versus host disease. *Heart* 1998;**80**:299–300.
2 Williamson LM. Transfusion associated graft versus host disease and its prevention. *Heart* 1998;**80**:211–12.
3 Vogelsang GB, Hopkins J. Transfusion associated graft versus host disease in non-immunocompromised hosts. *Transfusion* 1990; **30**:101–3.
4 Manno CS, Hedberg KW, Kim HC, *et al*. Comparison of the hemostatic effects of fresh whole blood and components after open heart surgery in children. *Blood* 1991;**77**:930–6.
5 Kenzo Y, Akio M. High risk of transfusion-associated graft versus host disease with nonirradiated allogenic blood transfusion in cardiac surgery. *Transfusion* 1998;**38**:1117–18.

This letter was shown to the authors, who reply as follows:

Ghrew *et al* report a patient with TA-GVHD following elective four-vessel CABG and perioperative transfusion of six units of blood. It would be interesting to know in this case about the freshness of the transfused blood and whether shared haplotypes between the donor(s) and recipient was a feature in addition to the transient immunomodulatory effect of cardiopulmonary bypass.

The Oxford report re-emphasises that TA-GVHD as a complication of cardiopulmonary bypass surgery is seen in Europe. The association was first made in Japan, where the reported frequency of one way matching or sharing HLA haplotype in a non-first degree relative ranges from 1:312 to 1:874 and, probably as a result, more than 200 cases of TA-GVHD have been reported in immunocompetent individuals.[1] Greater HLA diversity probably accounts for the reduced incidence in immunocompetent white patients, but it is clear that shared haplotype is not the sole requirement for the development of TA-GVHD after cardiopulmonary bypass. This is supported by data from the USA where in the caucasian population the most common haplotype is HLA A1, B8, DRB1*03 with a reported frequency of 6.6%.[2] Given this haplotype frequency, 0.05% of the transfusions in this population would be expected to result in a one way HLA match. If shared haplotype was the sole requirement for the development of TA-GVHD then around 1500 cases might be expected each year. The reported frequency is well below this (less than 10 reports in total of which we are aware). Several explanations for this can be offered.

First the transfused units may contain an insufficient number of immunocompetent lymphocytes; second, some recipients may be able to destroy the donor lymphocytes on the basis of subtype differences in the class 1 or other minor histocompatiblity antigens between the donor and recipient.[3] Finally, it is possible, and quite likely, that some cases have remained unrecognised and unreported.

We hope that our publication in *Heart* of two cases of TA-GVHD after cardiac surgery will heighten awareness of this complication of transfusion, and result in full investigation and reporting of all suspected cases to SHOT (serious hazards of transfusion). It is necessary to establish the true incidence of TA-GVHD in cardiac surgery so that cost–benefit analysis and informed review of guidelines on the irradiation of cellular blood products for this indication can be completed.

1 Takahashi K, Juji T, Miyazaki H. Post transfusion graft versus host disease occurring in non-immunosuppressed patients in Japan. *Transfus Sci* 1991;**12**:281–9.
2 Tsuji K, Aizawa M, Sasazuki T, eds. HLA 1991. *Proceedings of the eleventh international histocompatibility workshop and conference*, New York. Oxford: Oxford University Press, 1991:1145.
3 Goulmy E, Schipper R, Pool J, *et al*. Mismatches of minor histocompatibility antigens between HLA-identical donors and recipients and the development of graft-versus host disease after bone marrow transplantation. *N Engl J Med* 1996;**334**:281–5.

Outpatient clinics for adults with congenital heart disease

EDITOR,—We agree with the views expressed by Gatzoulis *et al* concerning the need for dedicated clinics for adults with congenital heart disease.[1] We started such a clinic in 1993. Initially this was once a month, becoming semimonthly in 1995 and weekly in 1999. The clinic is in a district general hospital serving a population of 650 000, and the initial numbers may have been present because of the early work of Bill Oliver in establishing catheter facilities on this site and the link with Great Ormond Street visiting cardiologists. One of us also runs a paediatric clinic and the other has experience in adult congenital heart disease.

Forty three per cent of our 260 patients are male, and 25% of the patients have septal defects (both atrial and ventricular). As uncomplicated, closed defects are not followed up all these patients have additional lesions or residual sequelae of the original repair.

- 12% have had a tetralogy of Fallot repaired
- 11.5% have bicuspid aortic valves
- 8.7% have had a coarctation repaired
- 11% have cyanotic heart disease (5% with the Eisenmenger reaction)
- 5% have left ventricular outflow tract abnormalities
- 5% have transposition of the great arteries—all of whom have had the Mustard repair
- 12.1% of patients have Marfan's syndrome (although patients with Marfan's are also seen in general clinics).

The remaining 9.9% have various condition from complex congenital heart disease including tricuspid atresia with Fontan operation (1.3%), single ventricle with total cavopulmonary connection (TCPC) (1%), complex pulmonary atresia with right ventricular outflow tract reconstruction (2.6%), septated double outlet ventricles (2.6%) to abnormal AV valves (mitral clefts and Ebstein's anomaly) (2.1%), corrected transposition, pulmonary valve and pulmonary branch stenoses.

- 33.6% have had no previous interventions
- 58.5% have had a single surgical repair of which 10.9% have had one or more reoperations
- 7.9% have had palliative procedures only.

There have been a few patients with complex cyanotic heart disease who we have referred for their first operative intervention in their 20s, including TCPC in a patient with single ventricle, and right ventricular outflow tract reconstruction in a patient with complex pulmonary atresia.

- 2.1% have had catheter interventions such as dilatation of aortopulmonary collaterals, coil obliteration of residual shunts, etc
- 2.1% have had pacemaker implantations.

One patient has already been transplanted (atrial septal defect and restrictive cardiomyopathy), three are waiting (two heart–lung and one heart transplant), and one died on the waiting list.

We use transoesophageal echocardiography and magnetic resonance imaging in selected patients in addition to the more routine use of echocardiography, ECGs, Holter monitoring, and exercise testing. Very complicated cases are usually sent to a tertiary centre for catheterisation, with whom we have a close liaison; indeed in some cases the patient care is shared and discussion of difficult problems in other cases is helpful. The patients do seem to value a dedicated clinic in their local hospital, particularly when given the time to discuss contraception, employment, insurance, housing, inheritance, and pregnancy.

New patients transferred from the paediatric service are also introduced to the GUCH (grown up congenital heart) association, which has newsletters, helplines, and area meetings. We try to maintain an emergency slot for patients if they become worried about symptoms. "At risk" pregnancies are also supervised within the clinic, with close liaison with obstetricians and anaesthetists. Fetal echocardiography is performed at 20 weeks. We would concur with Gatzoulis *et al* that structured transitional requirements for these patients must be introduced so that they are not lost to follow up when the leave the paediatric service and, as we hope we have shown, a dedicated clinic within a region does fulfil a need, a point purchasers may care to note.

L J FREEMAN
A J PAGE
Department of Cardiology, Norfolk and Norwich Health Care Trust, Brunswick Road, Norwich, Norfolk NR1 3SR, UK

1 Gatzoulis MA, Hechter S, Siu SC, *et al*. Outpatient clinics for adults with congenital heart disease: increasing workload and evolving patterns of referral. *Heart* 1999;**81**:57–61.