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 corrections to authors appear in the July 1999 issue of Heart (page 116).

Management of scorpion sting

EDITOR,—We read with great interest the haemodynamic records in the envenomated patients and the treatment strategy he suggested for severe scorpion envenomation. In our study 20% of the patients had pulmonary oedema which was treated with intravenous sodium nitroprusside. Captopril failed to correct haemodynamic abnormalities in two cases who had cardiac arrhythmias. Bawaskar et al.9 implied that two patients would have been alive saving in the two patients treated with captopril who died in Karnad’s report.1 As a potent inhibitor of phosphodiesterase, prazosin causes accumulation of cGMP, a second messenger of nitric oxide, in vascular endothelium and myocardium, inhibits the formation of inositol triphosphate, and acts as an antidote to venom—the morbidity of scorpion sting victims is less than 1%.6

In the pre-prazosin era (1961–83) a fatality rate of 25–30% was reported from western India,7 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 have similar findings in 1978–82—that is, before prazosin treatment.8

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 (autoimmune storm).9 We believe that the transport of Karnad’s patients to the nearest major hospital took 12–24 hours. We have reported8 that seven of eight had acute pulmonary oedema owing to a delay in reaching a tertiary care hospital.10 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.11 Captopril (an ACE inhibitor) has a similar action resulting in hypotension resistant to dopamine agonists.11 Bradykinin further enhances noradrenaline (norepinephrine) release by a presynaptic mechanism.11

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 radicals and free radicals injurious to myocardium leading to cardiac arrhythmias and sudden death.12

At a general hospital at Mahad we successfully treated 658 cases of severe scorpion sting with oral rehydration, oral prazosin, and oxygen and umbramine: 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 furosemide-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 flourishes, 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. It is possible that two patients would have been alive saving in the two patients treated with captopril who died in Karnad’s report.9 We believe that the transport of Karnad’s patients to the nearest major hospital took 12–24 hours. We have reported8 that seven of eight had acute pulmonary oedema owing to a delay in reaching a tertiary care hospital.10 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.11 Captopril (an ACE inhibitor) has a similar action resulting in hypotension resistant to dopamine agonists.11 Bradykinin further enhances noradrenaline (norepinephrine) release by a presynaptic mechanism.11

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In the 24-hour period following the sting with oral rehydration, oral prazosin, and fluid infusion, suggesting an exaggerated increase in PAWP resulting from altered LV function. Although attractive from a pathophysiological standpoint, Karnad challenges the usefulness of introtopic 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 addressing this issue. Nevertheless, owing to the clearly established haemodynamic pattern of severe scorpion envenomation and on the basis of a pathophysiological approach, we have previously 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.10

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 thermistor. 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.12

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

2 Bawaskar HS, Bawaskar PH. Envenoming by scorpion bite: clinical features and management of their neurotoxins and therapeutics. Trop Doct. [In press.]
7 Ismail M, Faniou AJY, Dabees TT. Experimental treatment protocols for scorpion envenomation: reversal of common therapies and an effect of kalikrein-kinin inhibitors. Toxicon 1999;35:1257–70.

EDITOR,—The study by Karnad 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 and confirmed by numerous series in human subjects. All of these series performed a haemodynamic study and PAWP was 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 suggested for severe scorpion envenomation. Experimental evidence to support ELITE. Lancet 1998;i:634–6.
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 38 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 died. This is not significantly different from the 22% mortality in our series. 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 (31%). 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 echocardiographic study 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. The time course of BNP shows a peak at 16 hours followed by a significant decline in the next 48–72 hours.

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. They demonstrated a negative predictive value of 100% for BNP at a threshold of 50 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 what the 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 the analysis, the question of whether a high plasma BNP in the presence of a normal or low 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 that support their initial hypothesis. Their concluding statement, however, suggests that when using the routine clinical model of a patient following myocardial infarction" seems premature.


6 Hanley JA, McNeill BJ. The meaning and use of the area under a receiver operating 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 recent 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 underlying 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). 

In our letter we pointed 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 possible use of 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 is the addressing 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 a significantly increased 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 neurohumoral 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.

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18 Hanley JA, McNeill BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29–36.


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 during 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 sepsis or infection. 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, bleeding, cough and expectoration of brown sputum. He had an extensive erythromedocrine maculopapular eruption, oral thrush, tachycardia, hypotension and general 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 mononuclear 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 more frequent following cardiac pulmonary 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 in interleukin 2 potentiates the genetic lymphocyte transformation following


cardiopulmonary bypass may all cause a degree of immune dysfunction. 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.

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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 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 25% of cases of TA-GVHD have been reported in immunocompetent individuals. 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%. Given this haplotype frequency, 0.05% of the transfusions in this population would be expected to result in a one way 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 histocompatibility antigens between the donor and recipient. 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.


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 complications, 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 Eisenmenger’s complex)
• 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 conditions from complex congenital heart disease including tricuspid atresia with Fontan operation (1.3%), single ventricle with total cavopulmonary connection (TCPV) (1%), complex pulmonary atresia with right ventricular outflow tract reconstruction (2.6%), sepatated 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 TCPV 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 collars, 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.

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