Brain natriuretic peptide in Chagas' disease: further insights

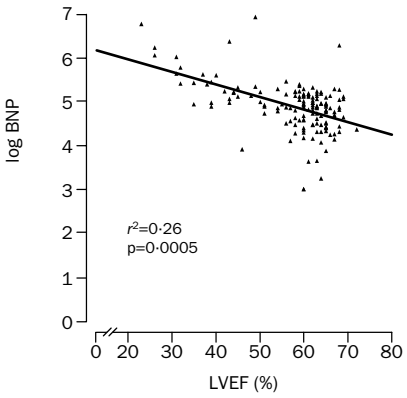
Sir—We cannot agree with Thomas Walther and colleagues'[1] criticisms (May 3, p 1567) of our study,[2] which showed that measurement of concentrations of brain natriuretic peptide (BNP) can accurately detect left ventricular (LV) dysfunction in individuals with Chagas' disease.

BNP is a new and evolving diagnostic method, and different techniques for its measurement are available. The wide variation in normal reference values[3] is an established feature of BNP measurement, and widely different cutoff points for the detection of LV dysfunction have been reported.[4] The high concentrations of BNP measured in our study were related to the different measurement method we used.

All patients were submitted to a strict screening protocol and normal values of LV ejection fraction (LVEF) and diastolic dimension were reported for controls;[2] as a consequence, patients with heart failure were excluded. We measured all samples in the same assay to avoid interassay variations. From the iodination of tyr^0-BNP to purification by high performance liquid chromatography and radioimmunoassay, using antibody and standards purchased from Peninsula, all steps were undertaken in the laboratory following an established procedure and supervised by AMR, an experienced researcher in the specialty of natriuretic peptides.

We studied consecutive patients with Chagas' disease with various degrees of LVEF depression, and observed a progressive rise in the logarithmically transformed BNP concentrations with decreasing LVEF (figure). The 40% cutoff point of LVEF was arbitrarily defined to identify those patients that might benefit from drugs, such as β blockers and angiotensin-converting enzyme inhibitors. Since most patients with Chagas' disease in our clinic-based sample had normal LVEF, they outnumbered those with slightly depressed LVEF. We did not aim to assess whether patients with minor reductions of LVEF could have raised BNP values.

Walther and colleagues based their criticisms on a small sample study that has not been published in complete form in a peer-reviewed journal. A look at their figure suggests



Correlation between BNP concentration (natural log) and LVEF in patients with Chagas' disease
Data from reference 2.

that patients were not consecutively recruited and that they were actually clustered into two groups: one with normal LVEF greater than 55%, and the other with LVEF of less than 45%. Walther and co-workers used this uneven and biased group of 22 patients with LVEF of greater than 40% to contest our findings, which were obtained with an almost seven-fold larger sample of consecutive patients. Based on the results of only three patients with raised BNP values and LVEF between 40% and 45%, they argued that "a rise is to be expected in this group". A possible cause for the raised BNP concentrations in their patients would be the calculation of LVEF by the Teichholz method, which overestimates the real LVEF in individuals with Chagas' disease because of abnormal LV geometry. In their sample, BNP concentrations were clearly not normally distributed (the SE in group 2 was 33 times higher than that in controls), but statistical analysis was entirely based on parametric methods, such as linear regression and analysis of variance.

Despite these methodological and statistical errors, their correspondence reinforces the potential value of BNP measurement in Chagas' disease, raising some important issues—eg, the ideal cutoff points.

We have reproduced our results (unpublished data) in a validation sample of patients with Chagas' disease, measuring BNP with a commercial kit (Triage, Biosite, San Diego, CA, USA). Further studies should indicate how BNP measurement can be incorporated in a cost-effective way into the diagnostic approach to the patient with Chagas' disease.

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Asia-Pacific and the millennium health targets

Sir—In his news item about the United Nations (UN) report, *Promoting the Millennium Development Goals in Asia and the Pacific: Meeting the challenges of Poverty reduction*, Khabir Ahmad (June 14, p 2056)[1] warns that millennium health targets may not be met. Such a wake-up call should be welcomed by those of us concerned with health development.

The report's analysis of the goal of combating HIV/AIDS, malaria, and other diseases, reveals that the UN perceives there has been some encouraging progress in Asia-Pacific and they even suggest that this particular goal may be achieved.[2] Not surprisingly, the importance of these diseases has seemingly been downplayed in subsequent discussions of policy priorities. Can this be justified? Take the cases of HIV/AIDS and tuberculosis. The optimism of the UN report about these disease in Asia-Pacific rests on assumptions about the existing effective strategy to fight tuberculosis and success stories in combating AIDS.

The central technical strategy for tuberculosis control has been case detection and treatment. To control tuberculosis, high rates of case detection and treatment need to be achieved. Up to 2002, the case-

detection rates of the high-burden countries in the region have been low, with Thailand and Vietnam being the only exceptions.[3] In the case of Indonesia, for example, a country with a population of 213·6 million unevenly distributed across up to 13 667 islands, increasing case detection from the current rate of 21% to the required level of 70% will need tremendous efforts. These efforts may well be obstructed by insufficient leadership in primary care, weak staffing, inadequate financial management at provincial and district levels, and limited involvement of public hospitals and private practitioners.

Despite well documented and successful HIV-prevention programmes in a few countries, the HIV/AIDS epidemic continues to spread in Asia and the Pacific.[4] Moreover, without wishing to detract from the achievements of Cambodia and Thailand, recent developments show that success might be relative. Despite well funded, comprehensive programmes, one in every 100 people in Thailand is infected with HIV, and AIDS has become the leading cause of death in that country.

Now is hardly the time to divert much-needed political commitment for confronting the major microbial killers. The diluted sense of urgency about tackling these diseases in the UN report's sections on policy discussion can be attributed to flawed assumptions underlying the progress analysis. HIV/AIDS and tuberculosis pose clear and present danger to development in the Asia-Pacific region. The UN's high-profile report is making its way toward the desks of the policy makers in the region. The public-health community has the duty to set the record straight and protect public-health interests.

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Ötzi had a wound on his right hand

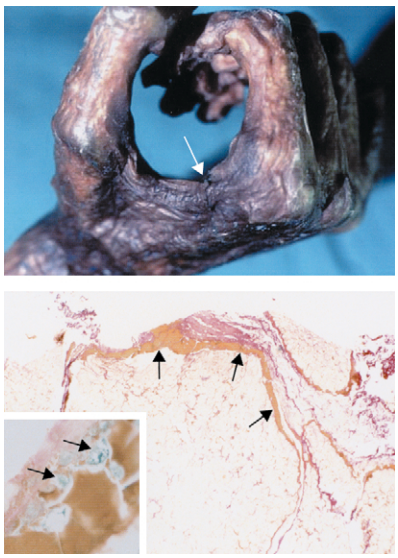
Sir—Many have assumed[1] that the c5300 year-old mummy of the Tyrolean Iceman, Ötzi, has given up all of its secrets. However, here we present new histological and biochemical evidence, which suggests that a few days before his death Ötzi sustained an injury on his right hand.

When the iceman was found in September, 1991, his mummified body was damaged in various places during removal from the ice. Furthermore, the body sustained several injuries that could have arisen after death as the mummy became encased in the glacier. Apart from these injuries, a re-examination[2] of thoracic CT scans provided evidence for a presumably intravital arrow injury; a point on the iceman's back has been identified as the point of entry. This finding indicates that Ötzi died from a lethal assault.

One of us (EEV) has carefully re-examined the mummy since these findings came to light and detected an irregularly shaped 3·7 cm long, deep stab wound on Ötzi's right hand, extending from the palm to the back of the hand between the thumb and index finger (figure). The wound margins are wavy and dark brown. Macromorphologically we could not ascertain whether this wound arose during life. We therefore rehydrated a small tissue sample from that site for histological analysis, including histochemical staining for haemosiderin deposits (on Prussian blue stains). The results showed well preserved dermal collagen fibres and subcutaneous fat with slight adipocere formation (in accordance with previous observations[3]). The fat tissue additionally revealed cord-like inclusions of an amorphous, autofluorescing material with isolated focal haemosiderin pigment droplets in Prussian blue staining (figure). On histology and high-resolution scanning force microscopy, no intact erythrocytes were identified.

To confirm our observations, we isolated the amorphous material by laser-based microdissection,[4] dissolved in a minute amount of phosphate-buffered saline, and tested for the presence of haemoglobin. The Guaiac-based test provided a faint, but positive, result, confirming the presence of a blood clot.

Our findings indicate that the Iceman sustained a stab wound to the right hand. Since forensic medical practise suggests that macrophages that contain haemosiderin develop between 3 and 8 days after injury,[5] we believe that the wound was inflicted a few days before his death. We do not yet know if the skin wound happened simultaneously or shortly after Ötzi was hit by the arrow, but if so this finding would suggest that he survived the attack for a few days.



Ötzi's right hand
Upper: macroscopic view of stab wound (arrow). Lower: histological features of the wound, showing an amorphous material between collagen fibres and fat tissue (arrows); original magnification ×100. Inset: small haemosiderin deposits (arrows); original magnification ×450.

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DEPARTMENT OF ERROR

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