

CORRESPONDENCE

Calcium channel blockers and cardiovascular risk in diabetes

Sir—In their March 7 commentary Marco Pahor and colleagues¹ propose that “the changes in the composition of cellular membranes resulting from diabetes increase the binding of lipophilic drugs such as amlodipine, so diabetic patients may be vulnerable to adverse effects of high doses of calcium antagonists”. In support of this statement they refer to a report by Byington and co-workers² which referenced original research, including findings from our own laboratory. However, the application of this research to the development of a biological mechanism explaining a presumed abnormal membrane accumulation of calcium channel blockers (CCB) in hypertensive diabetic patients is inappropriate.

Pahor and colleagues refer to two separate studies: our laboratory's work³ on the non-specific binding properties of CCB in model membranes of varying cholesterol to phospholipid (C/P) mole ratios, and Mazzanti and co-workers⁴ research on the lipid composition of platelet membranes of diabetic patients. Pahor et al infer from these two reports that lipid composition changes in cellular membranes of diabetic patients would result in a greater membrane accumulation of CCB.

We found that the C/P mole ratio influences the packing constraints of the phospholipid bilayer, thereby affecting the membrane partitioning of CCB. In model membranes that contain up to 37.5 mol % total cholesterol, we found an inverse relation between the C/P mole ratio and the extent of CCB accumulation.³ These experiments did not involve intact biological membranes, and the membrane binding of CCB was not correlated with their pharmacological potency.

In relating the binding work done in our laboratory with a putative excessive accumulation of CCB in cellular membranes of diabetic patients, Pahor et al cite the biochemical findings of

Mazzanti and colleagues,⁴ which showed changes in the platelet membranes of diabetic patients. These membranes exhibited an increase in total phospholipid content and membrane fluidity, neither of which has been evaluated as a factor in CCB membrane partitioning experiments. Furthermore, the membrane C/P mole ratio, a known key modulator of CCB membrane binding,³ did not differ significantly between diabetic patients (39 mol %) and controls (40 mol %).

Pahor and colleagues have previously published work which makes no reference to the work of Mazzanti's laboratory.⁵ Rather, they cited a hyperglycaemic rat model, in which a temporary decrease was recorded in the C/P mole ratio of erythrocyte membranes after insulin withdrawal. Pahor and colleagues did not mention that the cholesterol content of these cells was spontaneously restored to the control level within days while still in the hyperglycaemic state, and also after insulin treatment.

There is no consistency in the available data on the biochemical composition of cellular membranes of diabetic patients, and, hence, there is no rationale for an increased accumulation of CCB in these membranes. Moreover, the assumption that changes in blood cell lipid composition would be reproduced in vascular contractile cells, the target for CCB, has not been substantiated. Any biological mechanism crafted to rationalise potential harmful effects of this widely used class of drugs must be based on an accurate and complete review of scientific publications.

*R Preston Mason, Pamela E Mason

Department of Biochemistry, MCP-Hahnemann School of Medicine, Allegheny University of the Health Sciences, Pittsburgh, PA 1512, USA

- 1 Pahor M, Psaty BM, Furberg CD. Treatment of hypertensive patients with diabetes. *Lancet* 1998; **351**: 689–90.
- 2 Byington RP, Craven TE, Furberg CD,

Pahor M. Isradipine, raised glycosylated haemoglobin, and risk of cardiovascular events. *Lancet* 1997; **350**: 1075–76.

- 3 Mason RP, Moisey DM, Shajenko L. Cholesterol alters the binding of Ca²⁺ channel blockers to the membrane lipid bilayer. *Mol Pharmacol* 1992; **41**: 315–21.
- 4 Mazzanti L, Rabini RA, Faloia E, Fumelli P, Bertoli E, de Pirro R. Altered cellular Ca²⁺ and Na⁺ transport in diabetes mellitus. *Diabetes* 1990; **39**: 850–54.
- 5 Pahor M, Kritchevsky SB, Zuccala G, Guralnik JM. Diabetes and risk of adverse events with calcium antagonists. *Diabetes Care* 1998; **21**: 193–94.

Sir—In their commentary,¹ Marco Pahor and colleagues once again seem to exaggerate concerns about the use of calcium-channel blockers, leaving the impression that this group of agents is bad for diabetic patients.

In the FACET² study the reported difference between the effect of the calcium-channel blocker and the ACE inhibitor on cardiovascular events was not significant once the data were correctly adjusted for multiple comparisons. However, it seems reasonable to conclude that these results are compatible with the belief (already held by most physicians) that ACE inhibitors are preferable for hypertension management in diabetic patients. Nevertheless, since the combination of amlodipine and fosinopril seemed more effective in terms of reducing cardiovascular events than either amlodipine or fosinopril alone, it seems most unlikely that calcium-channel blockers are bad for diabetic hypertensives.

The decision to stop part of the ABCD³ study seems eccentric. There were two groups of diabetics in this trial—arbitrarily defined as normotensives and hypertensives—treated with either nisoldipine or enalapril. There were five secondary endpoints, one of which—cardiovascular events—included 13 possible types and combinations of events such as heart failure, stroke, myocardial infarction (MI), &c. Thus, including the primary endpoint, the 13 types of

cardiovascular event and the four other secondary endpoints in each half of the study, there were 36 types of event that were potentially open to comparison. Chance would predict two of any such comparisons to be significantly different. In published data³ two of the possible 36 types of events (non-fatal MIs and combined fatal and non-fatal MI) differed significantly between the calcium-channel blocker and ACE treated groups in the hypertensive half of the study. Presumably no such differences or trends were apparent in the normotensives, otherwise that part of the study would also have been stopped early.

Nevertheless, the ABCD findings were compatible with the FACET study in suggesting that ACE inhibitors are preferable for treatment of hypertension in diabetics, but not that calcium-channel blockers are bad for such patients.

These purist or technical criticisms of the interpretation of the study results notwithstanding, the findings of these two sets of subgroup analyses on secondary endpoints in small studies should be put in the full context of the evidence. First, current medical practice recommends aggressive blood pressure lowering in hypertensive diabetics. This reduction is unlikely to be achieved in most patients by ACE inhibition alone; calcium-channel blockers are effective lowering agents and the FACET study suggests that, if anything, they may be a reasonable add-on group to ACE inhibitors. Second, putting aside potentially flawed observational data⁴ large randomised outcome trials have now clearly shown substantial benefits in stroke and coronary events associated with the use of calcium-channel blockers in elderly hypertensives.⁵

Interim analysis (unpublished) of diabetic patients randomised to calcium-channel blockers in the ALLHAT study has not resulted in the premature termination of that limb of the trial, which provides further reassurance that there is no sign of an adverse effect of these agents. I therefore believe that ACE inhibitors are probably the drug of choice for diabetic patients with hypertension, but that when further blood-pressure lowering is necessary, calcium-channel blockers are a reasonable choice of add-on agent.

N R Poulter

Cardiovascular Studies Unit, Department of Clinical Pharmacology, Imperial College School of Medicine, St Mary's Hospital, London W2 1PG, UK

1 Pahor M, Psaty B, Furberg C. Treatment of

hypertensive patients with diabetes. *Lancet* 1998; **351**: 689–90.

- 2 Tatti P, Pahor M, Byington RB, DiMauro P, Guarisco R, Stollo F. Outcome results of the fosinopril versus amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998; **21**: 597–603.
- 3 Estacio RO, Jeffers BW, Hiatt WR, Biggi SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular events in patients with non-insulin dependent diabetes and hypertension. *New Engl J Med* 1998; **338**: 645–52.
- 4 Lindberg G, Binge K, Ransam J, Rastam L, Melander A. Use of calcium channel blockers and risk of suicide: ecological findings confirmed in population-based cohort study. *BMJ* 1998; **316**: 11–15.
- 5 Staessen JA, Fagard F, Thijs I, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **350**: 757–64.

Authors' reply

Sir—Evidence from three randomised trials and supportive data from several observational studies have documented a particularly evident excess risk of cardiovascular events associated with the use of calcium antagonists compared with other agents among hypertensive patients with diabetes or prediabetes.¹ The findings are strong and consistent, with relative risk ratios ranging between 2 and 7. Our hypothesis of a magnified pharmacological effect of calcium antagonists among diabetic patients is based on the observation in the calcium antagonist group of FACET and MIDAS that patients who had an event had a paradoxically greater blood pressure reduction than those without events (M Pahor, presentation at the American Society of Hypertension meeting, 1998). The theory that changes in composition of the membrane lipid bilayer might result in toxic sequelae of calcium antagonists was, in fact, proposed by Mason and co-workers early in 1997.²

The independent Data and Safety Monitoring Board, advisory to the National Institutes of Health, reviewed the data of ABCD, concluded that the increased number of cardiovascular events in the nisoldipine group was alarming, and took the prudent action to recommend early termination of the hypertensive arm of the trial.³ Even after adjustment for the 38 comparisons suggested by N R Poulter, the seven-fold difference in risk of acute myocardial infarction was striking and statistically significant in favour of enalapril compared with nisoldipine ($p < 0.001$). The results for all cardiovascular events in ABCD were in the same direction. These results replicate the published findings

with fosinopril and amlodipine in FACET.⁴

The nitendipine versus placebo comparison in Syst-Eur provides no information on the relative risk/benefit of calcium antagonists versus other agents.⁵ A large number of patients were lost to follow-up compared with the number of primary events (237 patients lost *vs* 124 strokes), and the case-fatality rates for stroke and heart failure in the control group were very high (27.3% and 20.4%). In SHEP, which had a similar sample size and twice the duration of follow-up, only ten patients were lost, and strokes occurred in 262 patients. The case-fatality rates for stroke and heart failure in the SHEP control group were 8.9% and 6.4%. These large differences in case-fatality rates among the controls suggest that either certain European centres may have failed to identify non-fatal events or that compared with the care provided to the SHEP participants, the medical care among certain clinical centres in Syst-Eur may have been suboptimum. In any case, the case-fatality differences raise questions as to what extent the findings of Syst-Eur are generalisable.

It is inappropriate to speculate on the confidential interim analysis in ALLHAT. Enrolment was just completed and extreme group differences would be required to stop the trial at this early stage. Since treatment differences in FACET and ABCD started to appear after 1–2 years of follow-up and became significant only after several years, conclusive data from ALLHAT on risk/benefit may not be available in the next 3–4 years. Therefore, it is prudent at this time to use low-dose diuretics and ACE inhibitors as first-line agents in hypertensive patients with diabetes.

*Marco Pahor, Bruce M Psaty, Curt D Furberg

*Department of Preventive Medicine, University of Tennessee, Memphis, TN 38105, USA; Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, WA; and Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC

- 1 Pahor M, Furberg CD, Psaty BM. Treatment of hypertensive patients with diabetes. *Lancet* 1998; **351**: 689–90.
- 2 Mason RP, Rubin RT, Mason PE, Tulenko TN. Molecular mechanisms underlying the effects of cholesterol on neuronal cell membrane function and drug-membrane interaction. In: Hillbrand M, Spitz RT, eds. *Lipids, health and behaviour*, first ed. Washington DC: American Psychological Association, 1997: 127–38.
- 3 Estacio RO, Jeffers BW, Hiatt WR, Biggi SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular events in patients with non-insulin-dependent diabetes and

hypertension. *N Engl J Med* 1998; **338**: 645–52.

- 4 Tatti P, Pahor M, Byington RP, et al. Outcome results of the fosinopril versus amlodipine cardiovascular events randomized trial in patients with hypertension and NIDDM. *Diabetes Care* 1998; **21**: 597–603.
- 5 Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **350**: 757–64.

Internet access to patients' records

See Commentary page 1751

Sir—The University of Washington Academic Medical Centers (AMCs) in Seattle constitute a unique resource in the Pacific Northwest of the USA. Their facilities include the only tertiary-care hospital, level-one trauma centre, and medical school available in the five contiguous states of Washington, Wyoming, Alaska, Montana, and Idaho (WWAMI)—an area equal to 27% of the US landmass.¹ Consistent with this regional mission, the construction of a large relational repository known as the Medical Information Networked Database (MIND) was undertaken in 1989. Its goal was to make both clinical and reference information available in real-time to providers of primary and secondary care in the University of Washington's far-flung referral base.

MIND initially used interfaces with legacy registration, billing, pharmacy, laboratory, radiology, pathology, and transcription computing systems to generate text of patients' records that were viewable on the AMCs' local area network. In late 1995, however, clinical informaticists began to collaboratively design a graphical HTML front end to the MIND repository, to make its contents accessible over the Internet with standard browsers such as Netscape Navigator or Microsoft's Internet Explorer. Security for this information tool, christened MINDscape, was provided by Secure Socket Layer technology, and a custom database application that authenticated users, managed passwords, and logged all accesses to the system. Faculty and residents also signed confidentiality agreements and patients were given the opportunity to ask that their computerised records be accessible only in case of medical emergency.²

The University of Washington customer service liaisons had been working with a cardiology group and a multispecialty practice on Puget Sound, just west of Seattle, and a large multispecialty clinic across the Cascade

Mountains to the east. Physicians expressed increasing frustration over the continued inability to obtain procedure notes and discharge summaries before seeing patients who had returned home for follow-up care. In response, physicians at these three clinics became the first community providers to be given access to MINDscape in Spring, 1997, which enabled them to view the records of their identified patients under the pilot program U-link. Dictated procedure notes, for example, could now be read on-line as they were transcribed, well before the receipt of hard copies.

To date, 44 referring physicians have been enrolled in the pilot. With the support of conveniently integrated materials, such as PubMed¹ (the National Library of Medicine's web-based literature citation and retrieval system) and a University of Washington developed Federated Drug Reference,³ the physicians have followed the care of 1290 patients admitted to hospital in Seattle. Some have done so from as far away as Ketchikan, Alaska—a distance of 1074 km.*

Access to MINDscape, which currently stores the records of 404 000 patients, will soon be more widely offered to WWAMI physicians who can supply their own personal computer and an Internet-service provider. One satisfied user took advantage of the e-mail feedback to developers and commented, "I think the MINDscape system will be the most significant change in how we practice here that we have seen in the last decade". Another user said, "this is the best thing since sliced bread". Hyperbole aside, we believe that the Internet will have an important role in the routine conduct of medical commerce.

*Representative print-screens are available from the authors or *The Lancet*, on request.

*H I Goldberg, P Tarczy-Hornoch, K Stephens, E B Larson, J P LoGerfo

*Department of Medicine, University of Washington, Harborview Medical Center, Seattle, WA 98104, USA; and IAIMS Program, Health Sciences Libraries and Medical Centers Information Systems, University of Washington, Seattle

- 1 Schwarz MR. The WAMI program: a progress report (Medical Education). *West J Med* 1979; **130**: 384–90.
- 2 Tarczy-Hornoch P, Kwan-Gett TS, Fouche L, et al. Meeting clinician information needs by integrating access to the medical records and knowledge resources via the web. *Proc AIMI Annu Fall Symp Suppl* 1997: 809–13.
- 3 Ketchell DS, Ibrahim KN, Murri NA, et al. Architecture for the Federated Drug Reference in a managed care environment. *Proc AIMI Annu Fall Symp Suppl* 1996; 413–17.

Acellular pertussis vaccines: progress but déjà vu

Sir—The correspondents on pertussis vaccines (Feb 28, p 677)¹ all overlook the major advance in our understanding of acellular pertussis vaccines provided by the Swedish trial² on which they comment. The outstanding feature of that trial was its correlation of prophylactic efficacies with laboratory markers. It also involved a large group of infants, and cases of pertussis infection during the 3-year study were confirmed reliably, by bacterial culture.

In the Swedish trial whole-cell vaccine was compared with three acellular vaccines containing two, three, and five, components (A2, A3, A5). Whole-cell vaccines had the highest efficacy against pertussis infection. A5 was better than A3, which in turn was better than A2. But efficacy was not related to the number of components, as your correspondents suggest,¹ so much as to their nature. Titres of antibody to pertussis toxin and to filamentous haemagglutinin were not related to efficacy; and A3, A5, and whole-cell vaccine produced the same titres of antipertactin, although they differed significantly in efficacy. Two further components (fimbriae 2 and 3) were included in A5, and only antifimbrial antibodies showed clear correlation with efficacy.

So, which components are necessary? Could the excessive cost of acellular vaccine¹ be reduced by excluding what is superfluous? The Swedish results kindle a sense of déjà vu, because they accord with the protective efficacies of some early whole-cell vaccines—vaccines without agglutinin 2 (Agg2) did not protect children against serotype 1,2 infection in Australia and Finland, and vaccines without Agg3 did not protect against type 1,3 infection in Britain, Canada, Israel, Poland, USA, and the former USSR.³ Hence, WHO recommends that the vaccine should contain these major agglutinogens to produce vaccines with very high efficacy.

Although there is broad agreement that Agg2 is fimbrial, the nature of Agg3 is controversial: some believe it to be fimbrial, others that type 1,3 cells are non-fimbriate and that Agg3 is on the surface of the cell wall.⁴ Thus, the nature of the fimbria-3 component of the A5 vaccine in the Swedish study is unclear. Unfortunately, serum samples in that study were not assayed for anti-fimbriae 2 and 3 separately, nor were the serotypes of the bacterial cultures assessed.

We therefore agree with E Miller et al¹ that further costly trials are needed if the remaining questions about acellular pertussis vaccine are to be answered. But we would add that such trials should be held in one country where type 1,2 predominates and in another with a prevalence of type 1,3. Also, serum samples should be assayed for agglutinins 2 and 3 separately, because of their known protective roles,³ and any strains cultured from vaccinated children should be serotyped. Meanwhile, we support the sound advice of a recent WHO report on the Expanded Programme on Immunisation; "whole-cell pertussis vaccine should remain the mainstay of national immunisation programmes".⁵

*Noel W Preston, Ruth C Matthews

Pertussis Reference Laboratory, University Department of Medical Microbiology, Clinical Sciences Building, MRI, Manchester M13 9WL, UK

- 1 Miller E, Eskola J, Hurley S, Bennet J, Gust I, Poland GA. Issues about pertussis vaccines. *Lancet* 1998; **351**: 677-79.
- 2 Olin P, Rasmussen F, Gustafsson L, Hallander HO, Heijbel H. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccine compared with whole-cell pertussis vaccine. *Lancet* 1997; **350**: 1569-77.
- 3 Preston NW. Importance of agglutinin content in vaccines for inducing protection. In: Manclark CR (ed), Proceedings of an informal consultation on the World Health Organization requirements for diphtheria, tetanus, pertussis and combined vaccines. DHHS publication no (FDA) 91-1174. Bethesda: United States Public Health, 1991.
- 4 Preston NW, Zorgani AA, Carter EJ. Location of the three major agglutinogens of *Bordetella pertussis* by immunoelectronmicroscopy. *J Med Microbiol* 1990; **32**: 63-68.
- 5 WHO. Report of European Advisory Group on EPI. EUR/ICP/CMD5 01 01 06. Copenhagen: WHO, 1997

Micronutrient deficiencies and protein-energy malnutrition

Sir—Before 1980, most attention given to nutrition in developing countries focused on protein-energy malnutrition (PEM). The culmination of this attention was the era of multisectoral nutrition planning in the 1970s. In retrospect, those of us who pursued multisectoral planning met with disappointment, partly because of the mainly nutriocentric lens through which we viewed development, and partly because some of us did not pay adequate attention to the underlying socioeconomic and political determinants of malnutrition.

The reaction of many was to pull strongly in the opposite direction, one which has been labelled nutrition isolationism, and, indeed, there were attractive candidates. New understanding about the effects of micronutrient deficiencies, particularly vitamin A and iodine, and improved technologies and logistics for the delivery of micronutrients (massive dose supplements and fortification) made possible important and attractive achievements within a short time.

Accordingly, many of us have pursued these micronutrient interventions, in some cases with remarkable success, and can take some pride in these accomplishments. This success notwithstanding, it is clear that we have, all too often, neglected the over-riding issue of inadequate calorie intake and its determinants which continue to take such an enormous toll on vulnerable populations.

We know more today about how to address PEM through food security, nutritional care of women and children, and public-health interventions than we did 20 years ago. But the attention of the nutrition community and the resources of donors are more attracted by the glamour of micronutrients, a largely technical and often top-down solution (as close to a quick fix magic bullet as we are likely to get in this field), than by the politically sensitive business of poverty alleviation, people's empowerment, and equity, necessary to ensure that mothers and children have access to health and educational services and adequate food to eat.

In India, micronutrient deficiencies deserve serious attention. At the same time, however, the poorest three deciles of the population consume only 1681 adult equivalent calories daily, whereas 78% of Indian children suffer from undernutrition. Both issues are unacceptable, but they need to be kept in proper perspective.

At a recent meeting of African nutrition experts, representatives of one country with disturbingly high rates of moderate and severe malnutrition listed 16 nutrition research priorities, 13 of which were micronutrient related. The list, however, hardly reflects the most urgent nutrition needs of African countries.

All too often, governments and donors have concluded that they can check off their concern and attention to nutrition by launching a micronutrient or an isolated breastfeeding project, while ignoring the challenges of PEM that so seriously affect the ultimate welfare of women and children, as well as long-term development processes.

The challenge that we face is not only to maintain our momentum in support of micronutrient interventions, but also to redress the imbalance, and the relative neglect of PEM and food insecurity which usually require a different set of interventions. Our hope in the years to come is that the technical skills and partnerships that have driven salt iodisation and supplementation programmes for vitamin A and iron can be coupled with the political acumen that has sparked successful social-mobilisation movements to bring about the substantial reductions in global undernutrition we all desire.

Claudio Schuftan, V Ramalingaswami,
*F James Levinson

Hanoi, Vietnam; New Delhi, India; and *School of Nutrition Science and Policy, Tufts University, Medford, MA 02155, USA

HIV-1 transmission through artificial insemination

Sir—B Matz and co-workers (March 7, p 728)¹ report a 35-year-old female health worker who developed HIV-1 infection after artificial insemination with fresh sperm. The rest of the donated semen was frozen and used for further inseminations 1-4 months after donation until the donor's HIV-1 seroconversion was detected.

We tested this donor, 12 women inseminated with his frozen sperm, and four of their partners for HIV-1 infection. We measured HIV-1 antibodies, HIV-1 p24 antigen, proviral HIV-1 DNA in peripheral blood mononuclear cells, and HIV-1 titre. A serum sample collected from the donor 136 days after sperm donation was positive for HIV-1 antibodies by ELISA. Reactivity was confirmed by HIV-1 immunoblot. HIV-1 titre was 8.4×10^3 copies/mL. No viraemia, antigenaemia, or seroconversion could be detected in any of the recipients or their partners 1-3 months after insemination, which indicates that only the woman inseminated with fresh sperm acquired HIV-1, whereas those who received frozen semen did not show any signs of the HIV-1 infection during follow-up. The HIV-1 titre was high enough to transmit infection only in the fresh semen. Cryopreservation of the sperm probably led to a decline in viral titre, thus preventing 12 women from becoming infected with HIV-1.

Gynaecologists should be discouraged from the use of fresh

sperm. There should be a mandatory quarantine storage and, even more important, the semen should not be used until the donor is retested for HIV-1 6 months after the donation, and proven to be HIV-1 antibody negative.²

R S Ross, M Elgas, *M Roggendorf

Institute of Virology, Essen University Hospital, D-45122 Essen, Germany, (e-mail: roggendorf@uni-essen.de)

- 1 Matz B, Kupfer B, Ko Y, et al. HIV-1 infection by artificial insemination. *Lancet* 1998; **351**: 728.
- 2 Centers for Disease Control and Prevention. Semen banking, organ and tissue transplantation, and HIV antibody testing. *MMWR Morb Mortal Wkly Rep* 1988; **37**: 57-58.

Isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection

Sir—We question the use of short-course rifampicin and pyrazinamide for tuberculosis prevention in developing countries that Neal Halsey and colleagues (March 14, p 786)¹ report. The use of such a regimen outside a research setting, without a careful investigation to exclude active tuberculosis, without supervised treatment, without home visits, and without incentives such as the monthly nutrition supplements could lead to rifampicin resistance.

With the increasing tuberculosis burden in developing countries this is a risk we cannot take. Even in regions with a high HIV-1 seroprevalence, the traditional tuberculosis-control strategies—improving compliance with short-course rifampicin regimens, directly observed treatment, and improved case finding—should remain the cornerstone of control programmes. Community-wide screening for HIV-1 followed by tuberculosis prophylaxis could even be counter productive because it may increase stigmatisation, is costly, and will certainly overstretch poor health-care delivery systems.

A rifampicin and pyrazinamide tuberculosis regimen for individuals with HIV-1 infection in developed countries is also questionable, because the use of rifampicin is contraindicated in people treated with protease inhibitors.²

*R Colebunders, E Florence

Department of Clinical Sciences, Institute of Tropical Medicine, B2000 Antwerp, Belgium

- 1 Halsey NA, Coberly JS, Desormeaux J, et

al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. *Lancet* 1998; **351**: 786-91.

- 2 Centers for Disease Control and Prevention. Clinical update. Impact of HIV protease inhibitors on the treatment of HIV-infected tuberculosis patients with rifampicin. *MMWR* 1996; **45**: 921-25.

Increase of allergy in East Germany

Sir—Erika von Mutius and colleagues (March 21, p 862)¹ report that the prevalence of positive skinprick tests (SPT) and allergic rhinitis increased between 1991-92 and 1995-96 in East German schoolchildren.

We did a similar study in three rural areas 100 km from Leipzig in 1992-93 with 769 children aged 5-7 years (response rate 84.0%) and in 1995-96 with 725 children of the same age-group (response rate of 74.6%).² Because of difficulties with the standardisation of the Stallergènes multitest device used in von Mutius' study with insufficient quality-control information from the manufacturer, visible colour differences and variable radioallergosorbent-test (RAST) inhibition between different precoated batches,³ we decided to use a serum RAST test for the cross-sectional comparisons. All frozen serum samples were analysed at the end of the second survey by the CAP-FEIA system for specific IgE with the same reagents (table). SPT and RAST seem to be interchangeable for a diagnosis of allergic diseases, whereas individual specific serum concentration of IgE may not always correspond to SPT reactivity.⁴

Physician-diagnosed asthma did not increase significantly, but there was a significant increase in the prevalence of any physician-diagnosed allergic diseases. However, we found no

	1992/93	1995/96
Physician diagnoses (ever)		
Asthma	2.9	4.1
Any allergy	10.1	16.5*
Hay fever	2.8	2.6
Bronchitis	56.6	41.8*
Allergy symptoms (last year)		
Conjunctivitis	6.1	6.4
Sneezing	6.8	8.6
Running nose	8.6	10.2
RAST sensitisation (at examination)†		
Dust mite (der p1)	8.8	9.1
Cat	3.7	4.4
Grass pollen	15.4	14.0
Birch pollen	5.7	6.8
Cladosporium	3.1	2.9
At least one allergen	22.1	20.3

Prevalence in % (number of children/those with data).

*p<0.001. †RAST class ≥ 2 (0.70 kU/L) used. Similar results were obtained for RAST class ≥ 1 (0.35 kU/L).

Allergy in East Germany

increase in hay fever, allergic symptoms, or serum markers. Thus, we believe that a real increase in the prevalence of allergic diseases is unlikely at the moment. The observed increase in the prevalence in physician-diagnosed allergic diseases seems more likely to be due to changes in physicians diagnostic patterns and the increased awareness of the public about allergic diseases. Heinrich and colleagues⁵ have also reported a similar effect of increased self-reported prevalence of allergic rhinitis in East German adults.

*Joachim Heinrich, Matthias Wjst

Institut für Epidemiologie, GSF Forschungszentrum für Umwelt und Gesundheit, D-85764 Neuherberg, Germany (e-mail: joachim.heinrich@gsf.de)

- 1 von Mutius E, Weiland SK, Firtzsch C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998; **351**: 862-66.
- 2 Wjst M, Trepka MJ, Wellmann J, Heinrich J, Stiller-Winkler R, Wichmann HE. Serum immunoglobulin level and skin prick test response. *Eur J Med Res* 1997; **2**: 177-81.
- 3 Wjst M, Reitmeir P, Dold S, et al. Road traffic and adverse respiratory health effects of children. *BMJ* 1993; **307**: 596-600.
- 4 Kelso JM, Sodhi N, Gosselin VA, Yunginger JW. Diagnostic performance characteristics of the standard Phadebas RAST, modified RAST, and Pharmacia CAP system versus skin testing. *Clin Exp Allergy* 1990; **20**: 175-79.
- 5 Heinrich J, Richter K, Magnussen H, Wichmann HE. Is the prevalence of atopic diseases in East and West Germany already converging? *Eur J Epidemiol* 1998; **14**: 239-45.

Sir—Many studies have been done to analyse the increasing prevalence of atopic diseases, but a satisfactory explanation still has not been found. On the basis of a recent cross-sectional study of schoolchildren from East Germany, Erika von Mutius and co-workers¹ present some interesting data. They claim that the development of atopic sensitisation and hay fever is affected by environmental factors that occur after infancy. However, the study's methods merit further discussion and the investigators' conclusions cannot be absolutely confirmed.

To understand the potential effects of variables that affect the prevalence of atopic disorders, a prospective cohort study would be most suitable.² The study by von Mutius and co-workers is limited because of the two different study populations with different sample sizes. Furthermore, they provide no information about the, possibly increasing, prevalence of hay fever in schoolchildren from West Germany during the observation periods. These baseline data would make it possible to

assess the effect of western environmental factors.

A fundamental criticism of the study by von Mutius concerns the diagnostic procedure used to investigate time trends in atopic diseases, such as hay fever. The skinprick tests they use reflect the immediate skin reactivity in sensitised individuals, which is affected by several factors. For sensitisation and the elicitation phase, an important factor is the immunological response induced by the presence of pollen allergens in the environment. This particular response fluctuates seasonally^{3,4} and annually,^{4,5} and is strongest during the time of peak pollination.^{3,5} Therefore, it is essential to relate the rates of positive skinprick tests in different surveys to corresponding pollen counts. To correctly interpret the presented data, pollen counts for hazel and birch during the survey periods, including probable time periods of sensitisation, varied by a factor 6 and 14, respectively. Pollination is a more likely reason for the observed changes than the claimed attribution to lifestyle, especially given the short time between the two surveys. This hypothesis is strengthened by the fact that, as stated by the investigators, the prevalence of allergic asthma and sensitisation to animal dander have not increased in the observation period.

*B Kränke, S M John, H J Schwanitz

*Department of Dermatology, University of Graz, A-8036, Austria; and Department of Dermatology, University of Osnabrück, Osnabrück, Germany

- 1 von Mutius E, Weiland SK, Fritsch C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998; **351**: 862–66.
- 2 Kuehr J, Frischer T, Karmaus W, et al. Early childhood risk factors for sensitization at school age. *J Allergy Clin Immunol* 1992; **90**: 358–63.
- 3 Haahntela T, Jokela H. Influence on the pollen season on immediate skin test reactivity to common allergens. *Allergy* 1980; **35**: 15–21.
- 4 Sato K, Nakazawa T, Sahashi N, Kochibe N. Yearly and seasonal changes of specific IgE to Japanese cedar pollen in a young population. *Ann Allergy Asthma Immunol* 1997; **79**: 57–61.
- 5 Frei T, Oertmann C, Bergmann K. Comparison of pollen data and pollen-associated oral allergy syndrome. *Allergologie* 1998; **21**: 98–104.

Authors' reply

Sir—Joachim Heinrich and Matthias Wjst present interesting data on repeated prevalence surveys in three rural areas in East Germany which seem to contrast with our findings. They suggest that a diagnostic shift may explain the observed increase in the prevalence of hay fever in Leipzig and

express concerns about the validity of the Stallergènes multitest device. However, they do not provide evidence to support their concerns and the reference given does not refer to the standardisation and validity of this multitest device.

Our data do not indicate that these methodological issues have distorted our findings. The reproducibility of skinprick test results with multitest devices is high.^{1,2} Furthermore, blood samples that we collected from the children in 1995–96 in Leipzig allow the comparison of skin-test reactivity measured by the Stallergènes multitest device with specific serum concentration of IgE against a panel of aeroallergens measured by RAST (n=1045). Positive skinprick test reactions were closely related to specific serum IgE concentrations (sensitivity 73·0%, specificity 87·5% with serum IgE concentrations above 0·7 kU/L as standard). In addition to the Leipzig survey, we also measured specific serum IgE concentrations in a random sample of schoolchildren of the same age-group in 1995–96 in Munich by the same method (RAST, n=1285). We were, thus, able to calculate the expected prevalence of skin-test reactivity in Munich in 1995–96 by direct standardisation with four categories of specific IgE. The calculated estimate (35·4%) is similar to the prevalence observed in Munich in 1989–90 (36·7%), when we used the Stallergènes multitest device in schoolchildren of the same age-group to assess atopic sensitisation (n=4451).³ This finding provides further indirect evidence for the validity of the method, suggesting a similar association between skinprick test results and specific serum IgE concentration in both surveys. Finally, the proportion of skin-test positive results in children with hay fever hardly changed between the study periods (77·8% in 1991–92 and 79·5% in 1995–96), which argues against a change in diagnostic habits in Leipzig.

The populations studied by Heinrich and Wjst differ from ours in several respects. The children lived in rural areas and the time between study periods was shorter than between our surveys in Leipzig. This consistent relation between atopic sensitisation and hay fever accords with our findings and also argues against changes in diagnostic labelling of hay fever. Finally, Heinrich and Wjst studied children of a younger age-group who have been shown to have a lower prevalence of hay fever and atopy.⁴

B Kränke and colleagues in turn propose that changes in pollination over the study period may explain our

findings of an increased prevalence of atopic sensitisation rather than changes in lifestyle. Although we agree that skin-test reactivity of sensitised individuals varies slightly with allergen exposure, it seems unlikely that changes in the prevalence of skin-test positivity on a population level of such a magnitude as observed in Leipzig can be explained by variation in pollen counts. The concomitant observed increase in the sensitisation to house-dust-mite allergens lends support to this view.

*Erika von Mutius, Stephan K Weiland, Heinrich Duhme, Ulrich Keil, Christian Fritsch

*University Children's Hospital, D-80337 München, Germany; Institute of Epidemiology and Social Medicine, University of Münster, Münster; and University Children's Hospital, Leipzig

- 1 Illi S, Garcia-Marcos L, Hernando V, Guillen JJ, Liese A, von Mutius E. Reproducibility of skin prick test results in epidemiological studies: a comparison of two devices. *Allergy* 1998; **53**: 353–58.
- 2 Berkowitz RB, Tinkelman DG, Lutz C, Crummie A, Smith K. Evaluation of the multi-test device for immediate hypersensitivity skin testing. *J Allergy Clin Immunol* 1992; **90**: 979–85.
- 3 von Mutius E, Martinez FD, Fritsch C, Nicolai T, Reitmeir P, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994; **149**: 358–64.
- 4 Aberg N, Engstrom I. Natural history of allergic diseases in children. *Acta Paediatr Scand* 1990; **79**: 206–11.

NIH follow-up study of women with augmentation mammoplasty: Investigator replies

Sir—Patricia Clark and others (May 2, p 1358)¹ pose questions and concerns about our Followup Study of Women with Augmentation Mammoplasty. Some reflect their unfamiliarity with the study as designed, including our approach to identify study participants, which did not involve recruitment from plaintiff lawyers or advocacy groups. We believe that the best forum for answering their questions and concerns will be within the context of the discussion of the study results. We are currently analysing data from this large and complex study, and will disseminate results as soon as methodological and scientific issues have been thoroughly addressed.

Louise A Brinton

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20892, USA

- 1 Clark P, Garbe E, Habbick B, et al. Questions on breast implants study. *Lancet* 1998 **351**: 1358–59.

Gammow bag for acute mountain sickness

Sir—On a trekking trip to the Himalayas, one of my trekking party developed sudden and striking acute mountain sickness. The patient was a previously healthy 16-year-old woman. The group had acclimatised well after taking 2 weeks to reach Namche Bazaar (3505 m).

We were trekking at 3505 m when it began to snow and became very cold, so we decided to retreat downhill. The patient then told me she had felt unwell since early morning. She had a Glasgow Coma Score (GCS) of 15/15, but was cold and dehydrated. After rehydration and warmer clothing we continued downhill. During the trip back she became progressively more unwell—she was ataxic with a GCS of 13/15—we then carried her, but she continued to deteriorate. When we reached the tea house where we were staying she had a GCS of 7/15 with papilloedema. I treated her in our Gammow bag (an airtight tube, pressurised with a foot pump that increases the ambient pressure, the equivalent of a quick descent), and after 15 min she had completely recovered. Treatment was continued for 2 h. At this time she was conscious, appropriate, and oriented, but 1 h after treatment she deteriorated to GCS 8/15. Once more I treated her in the bag for 6 h and began intravenous dexamethasone 4 mg every 6 h.

Over the next 4 days, a similar pattern evolved—recovery in the bag and deterioration outside. I kept her in the Gammow bag for 4 days apart from food and toilet stops. Once in Namche, we flew back to Kathmandu by helicopter where we had no further problems. In New Zealand she was examined by a neurologist who could find no abnormality. Computed tomography was done, but the scan was normal. Others have described similar cases in which small tumours of the fourth ventricle are found on computed-tomography scan and a small amount of cerebral oedema causes cerebrospinal-fluid outflow obstruction.

To date she has remained well, though has not ventured back to

altitude. The cause of such fulminant cerebral oedema at a moderate altitude after good acclimatisation is unclear. This case illustrates that a Gammow bag may be lifesaving and that it can be used for lengthy periods.

David Austin

Intensive Care Unit, Waikato Hospital,
Private Bag 3200, Hamilton, New Zealand

Human-milk lactadherin in protection against rotavirus

Sir—David Newburg and colleagues (April 18, p 1160)¹ show that potential protection against rotavirus is associated with the glycoprotein lactadherin in human milk. *The Lancet* press release of this report says this “may eventually lead to the development of a new therapeutic agent that could be taken as a tablet by new mothers in order to protect their babies from childhood diseases”. *The Lancet* makes a fundamental error in interpretation—any such therapeutic agent would need to be taken orally by the baby and not the mother.

Journalists and media channels frequently rely on research article summaries, particularly when the content of a paper is technical. Journals such as *The Lancet* are regarded as expert sources of information. This story has now spread far and wide, even local newspapers such as *The Cairns Post* have printed it.²

We wish to highlight three important factors that could have affected the results reported by Newburg and co-workers—breastmilk sampling, degree of breastfeeding, and weaning.

Sampling of breastmilk is important yet receives less than four lines in the paper. The investigators say, “The entire milk content of one breast was collected by breast pump between 0800 h and 1200 h”, which is a technical impossibility and a common misconception. Lactation is a dynamic process and the breast is not merely a container that can be emptied. In a lactating woman, right and left breasts can work independently and produce milk of consistently different quantity and fat content (mucin and lactadherin are found in the fat globule membrane). We suggest that use of the same breast in each woman each time could give rise to less individual variations over time in concentrations of lactadherin. The type of breast pump used (manual, electric, or battery-powered pump) was not described. The type of pump used, the frequency and length of time for

expression of milk, the expertise of the user, and the hormonal response during pumping will all affect quantity and fat content.³ Pumped milk is also likely to differ from milk obtained by a feeding baby.⁴ We sincerely hope that the mothers were not attached to the breast pump for the full 4 h, which would be pretty uncomfortable!

The investigators use a non-standard measure of breastfeeding status which they call degree of breastfeeding, calculated as the percentage of feedings in the past 24 h that was breastmilk. This measure does not make sense to us. A baby who has six breastfeeds and six other feeds will have the same ratio as one that has one breastfeed and one other feed, yet many have ingested a much bigger volume of breastmilk. A decreasing frequency of breastfeeds is associated with higher concentrations of immunoglobulin, possibly as a protective effect as exposure to other foods and fluids increases. Thus, frequency is important. A better measure would be the number of breastfeeds in the previous 24 h.

Weaning is not defined in the paper, an important omission. Definitions range from the introduction of foods other than breastmilk or breastmilk substitutes to the end of lactation. Since there is no recognised and agreed definition of weaning, it is inadvisable to use it in research without clarification.

Another point is whether freezing or long-term storage would affect the concentrations of lactadherin. Newburg and co-workers also state that the groups of infants with symptomless and symptomatic infections had a similar profile in terms of sex, yet there are more girls with rotavirus infection than boys (22 vs 9). Does this mean that the study enrolled a much bigger group of female than male infants? If so, we think this point is worth reporting.

Finally, we hope that the international rush to identify and synthesise the many active components of breastmilk will not obscure reality—even the best breastmilk substitute in the world will never be the real thing.

*Mary E Black, Debbie Armstrong

*Department of Social and Preventive Medicine, North Queensland Clinical School, University of Queensland, PO Box 1103, Cairns, Queensland 4870, Australia; and Maternity Unit, Cairns Base Hospital, Queensland, Australia

1 Newburg DS, Peterson JA, Ruiz-Palacios GM, et al. Role of human-milk lactadherin in protection against symptomatic rotavirus infection. *Lancet* 1998; 351: 1160–64.

2 Ross E. Breastmilk breakthrough. *Cairns Post*, April 18, 1998.



Gammow bag

- 3 Hartman PE, Rattigan S, Saint L, et al. Variation in the yield and composition of human milk. *Ox Rev Reprod Biol* 1985; 7: 118–67.
- 4 Zoppou C, Barry SI, Mercer GN. Dynamics of human milk extraction: a comparative study of breast feeding and breast pumping. *Bull Math Biol* 1997; 59: 953–73.

Authors' reply

Sir—In our article we conclude that protection against rotaviral diarrhoea by human breastmilk is associated with lactadherin, a glycoprotein. Speculation that our findings “may eventually lead to the development of a new therapeutic agent that could be taken as a tablet by new mothers in order to protect their [breastfed] babies from childhood diseases” is reasonable, and not a “fundamental error” by *The Lancet*. Eventually, an agent with homology to lactadherin might be developed for prophylactic use against rotavirus in infants; to predict its most promising route of administration is premature. Mary Black and Debbie Armstrong may question the press release publicising this speculation, rather than reissuing the call to breastfeed, but our discovery of new beneficial components of breastmilk should not be construed as promoting breastmilk substitutes. That notwithstanding, infants whose mothers elect not to breastfeed also deserve to have the best possible protection from disease.

We agree that proper sampling of breastmilk is important; emptying a breast of its stored milk is based upon fundamental physiology and established sampling techniques,¹ not misconception. For our nurses of 10–18 years' experience, pumping the contents of a lactating breast has never been “a technical impossibility”. The 10–20 min pumping procedure was done between 0800 h and 1200 h to provide flexibility to mother and nurse while ensuring standardised collection time. Participation in these studies never compromises and usually augments the comfort and care of a mother and her infant. We accepted the substitution of “breast pump” for “Egnell breast pump (SMB)” by *The Lancet* editors, since previous publications describe our methods.^{2,3}

“Percentage of feedings that are breastmilk”, far from “non-standard”, is part of international recommendations for categorising the degree of breastfeeding⁴ and was chosen precisely because it is independent of feeding frequency and total feeding volume. All methods that measure exposure to human milk have limitations. For “number of breastfeeds per 24 h”, exclusively breastfed infants

may be fed from four to 12 times daily, yet receive the same quantity of milk and protective factors. We have not observed an association between number of breastmilk feedings per day and degree of protection or variation in milk content (eg, rotavirus antibody or lactadherin concentrations).

Although the literary sense of “weaning” includes “withdrawal by degrees” (*Webster's New World Dictionary*), we used the word as a standard medical term, meaning, “to deprive permanently of breastmilk and nourish with other food” (*Stedman's Medical Dictionary*). The recommended standard practice of gradual introduction of solid foods starting from month 4–6 of breastfeeding is distinct from weaning.

Freezing alters the distribution of lactadherin between the cream and skim fractions of milk, a factor controlled for in our study. Neither freezing per se nor long-term storage in the frozen state seem to affect total lactadherin concentrations or activity.

As reported, the sex distribution between symptom groups are similar (31% vs 27% male). In this cohort, girls tended to be breastfed longer than boys and, therefore, had more opportunity to become infected during breastfeeding. The distribution of nine boys and 22 girls in the total infected group is not significantly different from chance at the 95% CI.

We are resolved to continue our efforts to support breastfeeding through basic research, clinical research, and direct intervention as part of our commitment toward the health of all infants.

David S Newburg, on behalf of all investigators

*Shriver Center for Medical Retardation, Waltham, MA 02254, USA; and Harvard Medical School, Boston

- Jensen RG, Bitman J, Wood L, Hamosh M, Clandinen MT, Clark RM. Methods for the sampling and analysis of human milk lipids. In: Jensen RG, Neville MC, eds. *Human lactation: milk components and methodologies*. New York: Plenum Press, 1985.
- Hayani KC, Guerrero ML, Ruiz-Palacios GM, Gomez HF, Cleary TG. Evidence for long-term memory of the mucosal immune system: milk secretory immunoglobulin A against *Shigella* lipopolysaccharides. *J Clin Microbiol* 1991; 29: 2599–603.
- Hayani KC, Guerrero ML, Morrow AL, et al. Concentration of milk secretory immunoglobulin A against *Shigella* virulence plasmid-associated antigens as a predictor of symptom status in *Shigella*-infected breastfed infants. *J Pediatr* 1992; 121: 852–56.
- Armstrong HC. International recommendations for consistent breastfeeding definitions. *J Hum Lact* 1991; 7: 51–54.

The viable myocardium

Sir—We question the aetiology of hibernating myocardium, as reported in Thomas Marwick's review (March 14, p 815).¹ Hibernating myocardium was thought to be a state of persistently impaired left-ventricular function due to a chronic reduction in resting myocardial blood flow.² There is now evidence that resting myocardial blood flow to hibernating myocardium is within normal limits in most patients.³

If resting myocardial blood flow is not reduced, one must therefore postulate an alternative trigger for hibernation that is still a consequence of coronary artery disease and ischaemia. Acute ischaemia can lead to left-ventricular dysfunction that extends into the postischaemic period, despite the restoration of normal flow, myocardial stunning. We believe that repetitive episodes of a disorder known as myocardial stunning may lead to hibernating myocardium. A model of chronic ischaemic left-ventricular dysfunction has been developed in which resting myocardial blood flow is normal. In this porcine model with a progressive coronary artery occlusion, repetitive and cumulative stunning after repetitive ischaemic episodes led to a chronic reduction in ventricular function in the presence of normal resting blood flow. Camici and colleagues,² postulated that patients with coronary artery disease may behave, pathophysiologically, in a similar way to this model.

Marwick describes myocardial stunning as important in three clinical settings (myocardial infarction, angioplasty, and coronary surgery), and acknowledges that recurrent episodes of ischaemia and therefore stunning may occur. We believe that this explanation is crucial in the pathophysiology of hibernating myocardium. Myocardial stunning occurs after exercise in patients with coronary artery disease.⁴ Repetitive episodes of exercise-induced ischaemia can lead to cumulative and lengthy left-ventricular dysfunction, thought to be due to myocardial stunning in man.⁵ Normally, changes in myocardial-oxygen demand are met by alterations in myocardial blood flow by means of the coronary flow reserve.

In patients with coronary artery disease, this is abolished for stenoses greater than 80% of the luminal diameter.² Increases in cardiac work cannot be met by an increase in myocardial blood flow, which leads to ischaemia that may not be associated with angina. These episodes can lead to repetitive episodes of myocardial stunning which culminate in a state of chronic left-ventricular dysfunction, as

in hibernating myocardium. This dysfunction can be reversed with revascularisation by restoring the coronary flow reserve. In such patients, we now have evidence not only of an improvement in ejection fraction but also in exercise capacity and quality of life scores.

Edward Barnes, David Dutka, R J C Hall,
*P G Camici

Department of Cardiology and *MRC Cyclotron Unit, Hammersmith Hospital, Imperial College School of Medicine, London W12 0NN, UK

- 1 Marwick TH. The viable myocardium: epidemiology, detection, and clinical implications. *Lancet* 1998; **341**: 815–19.
- 2 Camici PG, Wijns W, Borgers M, et al. Pathophysiological mechanisms of chronic reversible left ventricular dysfunction due to coronary artery disease (hibernating myocardium). *Circulation* 1997; **96**: 1–10.
- 3 Camici PG, Rimoldi O. Resting myocardial blood flow in patients with hibernating myocardium quantified by positron emission tomography. *Basic Res Cardiol* 1997; **92** (suppl 2): 6–8.
- 4 Ambrosio G, Betocchi S, Pace L, et al. Prolonged impairment of regional contractile function after resolution of exercise-induced angina. *Circulation* 1996; **94**: 2455–64.
- 5 Rinaldi CA, Linka AZ, Mansani ND, Saunders H, Hall RJC. Repetitive episodes of exercise-induced myocardial stunning produce cumulative left ventricular dysfunction. *Eur Heart J* 1996; **17**(suppl): 452 (abstr).

Costs of stenting for acute myocardial infarction

Sir—The role of stenting for acute myocardial infarction (AMI) has been investigated in randomised trials.¹ Preliminary results seem promising, and stenting may overcome some of the limitations of primary angioplasty therapy for AMI.² We have recently completed the initial phase of a randomised trial of stenting versus balloon angioplasty for AMI.³ On theoretical grounds, stenting may be costeffective in various settings,⁴ but so far there are no published data on the actual costs and costeffectiveness of stenting for AMI.

We have completed 12 months of follow-up in our randomised trial, including initial in-hospital and follow-up costs. We calculated costs by counting the numbers of hospital days and procedures, as previously described.⁵ Results are shown in the table. Our data show that, at least in the setting of a Dutch (non-academic) hospital with an existing infrastructure for angioplasty and stenting, there is no difference in costs after 1 year between balloon angioplasty and stenting for AMI. Although the initial in-hospital costs of stenting are higher, this is

	Balloon (n=115)	Stent (n=112)
In-hospital costs		
Hospital stay	5000	5400
Angioplasties	9000	9000
Stents	365	2304
Additional balloons	104	161
IABP	196	349
Re-PTCA	500	103
CABG	157	161
Total costs	15 322	17 508
Follow-up at 1 year		
Re-MI	443	45
Second angioplasty	1739	2033
Re-PTCA	1607	412
CABG	2996	1420
Total costs	6785	3910
Total costs at 1 year	22 107	21 418

re-MI=recurrent myocardial infarction; IABP=intra-aortic balloon pumping; PTCA=percutaneous coronary angioplasty; CABG=coronary bypass surgery. All costs are per patient.

Costs per patient (Dfl) of coronary stenting versus balloon angioplasty for acute myocardial infarction

compensated by the lower costs during follow-up, which makes stenting a good investment.

Arnoud W J van 't Hof,
Harry Suryapranata, Menko-Jan de Boer,
Jan C A Hoorntje, *Felix Zijlstra

Department of Cardiology, De Weezenlanden Hospital, 8011 JW Zwolle, Netherlands

- 1 Steinhilbl SR, Topol EJ. Stenting for acute myocardial infarction. *Lancet* 1997; **350**: 532–33.
- 2 Weaver WD, Simes RJ, Betriu A, et al, for the Primary Coronary Angioplasty versus Thrombolysis Collaboration Group. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative overview. *JAMA* 1997; **278**: 2093–98.
- 3 Suryapranata H, van 't Hof AWJ, Hoorntje JCA, De Boer MJ, Zijlstra F. A randomized comparison of primary stenting with primary balloon angioplasty in acute myocardial infarction. *Circulation* (in press).
- 4 Lieu TA, Gurley RJ, Lundstrom RJ, et al. Projected cost-effectiveness of primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1997; **30**: 1741–50.
- 5 Zijlstra F, de Boer MJ, Beukema WP, et al. Mortality, reinfarction, left ventricular ejection fraction and costs following reperfusion therapies for acute myocardial infarction. *Eur Heart J* 1996; **17**: 382–87.

Coronary microvascular spasm and angina pectoris

Sir—Mashahiro Mohri and colleagues (April 18, p 1165)¹ postulate coronary microvascular spasm, and not just reduced vasodilating capacity, as a cause of chest pain in a subgroup of patients with microvascular angina (syndrome X). In his accompanying commentary J C Kaski² discusses the aetiopathogenesis of syndrome X. Investigations with intravascular ultrasound show the anatomical and

physiological heterogeneity of syndrome X, which ranges from normal coronary arteries to vessels with intimal thickening and atheromatous plaque.³ There have been suggestions that some patients with this syndrome may not have cardiac disease at all. Microvascular angina is essentially a benign disorder, but has adverse effects on the quality of life, employment, and increased use of health-care resources. Potts and Bass⁴ found that two-thirds of patients with chest pain and normal coronary arteries predominantly have a psychiatric disorder. Cardiac syndrome X and the metabolic syndrome X (an epidemiological association between insulin resistance, atheroma, dyslipidaemia, and hypertension) might have more in common than the chance of their common sobriquet.

An issue that Kaski does not address is the difficulty in managing these patients. The symptoms are persistent and most patients continue to have chest pain that leads to repeated hospital admissions and cardiac catheterisations. In patients with syndrome X in whom ischaemia can be confirmed, a trial of antianginal agents (nitrates and β -blockers) is logical, but the response to this therapy is often poor.⁵ Calcium-channel antagonists decrease the frequency and severity of angina and improve exercise tolerance in some patients. Oestrogen deficiency is one of the mechanisms responsible for abnormal microvascular responses in syndrome X, so oestrogen would seem a treatment option for postmenopausal women with the syndrome; however, its clinical effectiveness is not known. Imipramine has been reported to be helpful in some patients; isolated cases of therapeutic benefit have been reported with oral aminophylline and angiotensin-converting enzyme inhibitors in some patients.

*Shahid A Kausar, Sue Adams

Princess Margaret Hospital, Swindon, Wiltshire SN1 4JU, UK

- 1 Mohri M, Koyanagi M, Egashira K, et al. Angina pectoris caused by coronary microvascular spasm. *Lancet* 1998; **351**: 1165–69.
- 2 Kaski JC. Chest pain and normal coronary arteriograms: role of "microvascular" spasm. *Lancet* 1998; **351**: 1144–45.
- 3 Wiederman JG, Schwartz A, Apfelbaum M, et al. Anatomic and physiologic heterogeneity in patients with syndrome X—an intravascular ultrasound study. *J Am Coll Cardiol* 1995; **25**: 131.
- 4 Potts SG, Bass CM. Psychological morbidity in patients with chest pain and normal or near normal coronary arteries—a long term follow up study. *Psychol Med* 1995; **25**: 339.
- 5 Cannon RO III. The sensitive heart: a syndrome of abnormal cardiac pain perception. *JAMA* 1995; **273**: 883.

N-methyl-(R)-salsolinol and Parkinson's disease

Sir—Manfred Gerlach and colleagues, in their March 21 commentary,¹ leave the mistaken impression that MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which is known to induce a Parkinson-like syndrome via destruction of dopaminergic neurons in the substantia nigra, is produced during the illicit synthesis of heroin. This is, fortunately, not so, and heroin users, who already have many health threats to contend with, need not also fear the onset of Parkinson's.

MPTP first made its appearance in California in 1982, where it caused Parkinson's in four intravenous drug users trying out what they described as new heroin.² MPTP seems to have resulted from an inept attempt to synthesise a designer drug—1-methyl-4-phenyl-4-propionoxypiperidine (MPPP). MPPP (prodine) has the structure of pethidine (meperidine, Demerol) with the ester functionality reversed. It had been made previously (without MPTP contamination) by Hoffmann-LaRoche chemists in 1947.³ After the tragic incident in California, workers at the Research Triangle Institute repeated the Hoffmann-LaRoche synthesis and found no traces of the (pro)neurotoxin MPTP.⁴ The underground California chemist of 1982 must have inadvertently heated the MPPP (or its alcohol precursor) to dryness under highly acid conditions, when either will decompose to MPTP.

Neither MPPP nor MPTP has been present in any street drug since the 1982 incident, although several industrial chemists have since contracted Parkinson's through careless exposure to large batches of MPTP.⁵

Daniel M Perrine

Department of Chemistry, Loyola College in Maryland, Baltimore, MD 21210, USA

- Gerlach M, Koutsilieri E, Riederer P. N-methyl-(R)-salsolinol and its relevance to Parkinson's disease. *Lancet* 1998; **351**: 850–51.
- Langston JW, Ballard P. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 1983; **219**: 979–80.
- Ziering A, Berger L, Heineman SD, Lee J. Piperidine derivatives, part III: 4-arylpiperidines. *J Org Chem* 1947; **894**–903.
- Carroll FI, Brine GA. 4-Phenylpiperidine analgesics, fentanyl and fentanyl analogues: methods of synthesis. In: Klein M, Sapienza F, et al, eds. *Clandestinely produced drugs, analogues and precursors:*

problems and solutions. US: Washington Drug Enforcement Administration, 1989: 67–90.

- Langston JW, Ballard PA. Parkinson's disease in a chemist working with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *N Engl J Med* 1983; **309**: 310.

Butyrylcholinesterase K: an association with dementia with Lewy bodies

Sir—C Russ and colleagues (March 21, p 881)¹ fail to find an association of butyrylcholinesterase K allele (BChE-K) in Alzheimer's disease (AD), after the suggestion that the BChE-K frequency was raised in this condition, particularly in those carrying the apolipoprotein E (APO E) $\epsilon 4$ allele.² Dementia with Lewy bodies is the second most common cause of dementia after AD,³ and in some studies has been classified as AD.

Dementia with Lewy bodies shows a fluctuating course, and hallucinations are a common feature. Extrapyraxidal movement disorder is also present in a proportion of cases and, as with Parkinson's disease, a distinguishing pathological feature is the presence of Lewy bodies, especially in multiple cortical sites. We have genotyped a series of cases of AD, dementia with Lewy bodies, Parkinson's disease, and age-matched controls for the BChE-K variant, since dementia with Lewy bodies shows similar features to the other two conditions, and may share common genetic determinants. All cases and controls were clinically and neuropathologically diagnosed by standard criteria³ and were matched for age. BChE-K and APO E genotyping was done as previously described.^{4,5} The χ^2 -test was used to analyse data for the frequency of the K variant and K-variant homozygosity compared with age-matched controls.

No increase in the BChE-K allele frequency was seen between the AD cases and controls, or between dementia with Lewy bodies or Parkinson's disease cases (table). An increased number of BChE-K-variant homozygous individuals was noted in dementia with Lewy bodies ($p=0.028$),

and Parkinson's ($p=0.051$) groups compared with controls but not in the AD group ($p=0.24$). No alteration in the allele frequency for BChE-K was recorded when stratifying for the effect of the APO E $\epsilon 4$ allele (data not shown).

Our findings lend support to those of Russ and colleagues by showing no association of BChE-K with AD. The finding that about 8% of the dementia with Lewy bodies and parkinson populations seem to be homozygous for BChE-K, may have a bearing on the suggestion that patients with dementia with Lewy bodies are more likely to respond to cholinergic therapy than are AD cases (I G McKeith, unpublished). Such cases may have reduced cholinesterase activity because the BChE-K variant has 30% less catalytic activity than normal cholinesterase, and, if so, administration of cholinesterase inhibitors would be expected to have greater effect in raising central nervous system acetylcholine in BChE-K homozygotes. Screening at the BChE locus for polymorphisms with reduced activity may therefore be used to predict individuals who will have a good response to cholinergic therapy before treatment.

A B Singleton, A M Gibson,
J A Edwardson, I G McKeith,
*C M Morris

*MRC Neurochemical Pathology Unit, Institute for the Health of the Elderly, and Department of Old Age Psychiatry, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, UK

- Russ C, Powell J, Lovestone S, Holmes C. K variant of butyrylcholinesterase and late-onset Alzheimer's disease. *Lancet* 1998; **351**: 881.
- Lehman D J, Johnston C, Smith AD. Synergy between the genes for butyrylcholinesterase K variant and apolipoprotein E4 in late onset confirmed Alzheimer's disease. *Hum Mol Genet* 1997 **6**: 1933–1936
- McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB International Workshop. *Neurology* 1996; **47**: 1113–24.
- Jensen FS, Nielsen LR, Schwartz M. Detection of the plasma cholinesterase K variant by PCR using an amplification-created restriction site. *Hum Hered* 1996; **46**: 26–31.
- Wenham PR, Price WH, Blundell G. Apolipoprotein E genotyping by one stage PCR. *Lancet* 1991; **337**: 1158–59.

	BChE-K frequency			
	BChE-K	WT/WT	WT/K	K/K
Control (88)	0.20	0.61 (54)	0.38 (33)	0.01 (1)
AD (103)	0.20	0.64 (66)	0.32 (33)	0.04 (4)
DLB (59)	0.26	0.56 (33)	0.36 (21)	0.09 (5)*
PD (39)	0.23	0.62 (24)	0.31 (12)	0.08 (3)†

Numbers in parentheses indicate the number of cases studied; * $p<0.05$; † $p=0.05$.

Allele frequency of the butyrylcholinesterase gene K variant in Alzheimer's disease, dementia with Lewy bodies (DLB); and Parkinson's disease (PD)

Harm reduction and needle exchange programmes

Sir—It is profoundly troubling that Sandra Bennett (March 14, p 839)¹ cites as “telling indications of the failure of needle exchange programmes” (NEPs) the deaths of two proponents of NEPs from an alleged drug overdose. One of the two individuals she names was John Watters, Director of the Urban Health Study. Personally and professionally, Watters was a committed and tireless researcher whose life’s work reflected his passionate belief that public-health interventions and the search for knowledge had to be extended to those from whom society and the medical community often turned away. His contributions to HIV prevention and drug abuse research included not only evaluation of different harm reduction strategies such as street-based education,² but also the development of innovative methods for community-based sampling of a difficult to access and often hidden population. These studies included the finding that users of NEPs were less likely to engage in syringe sharing,³ a risk factor for HIV infection among injection drug users.

Many publications and several major reports support the belief that NEPs do not promote drug abuse in a community, are associated with a reduction in high-risk drug practices, and are likely to reduce the risk of HIV infection. Contrary to Bennett’s speculations, studies indicate that NEPs are not associated with an increased risk of hepatitis C⁴ or with an increase in the number of discarded needles.⁵ The contention that Baltimore, MD (one of many metropolitan areas throughout the world with an NEP), has a high mortality rate hardly proves that one factor is causally related to the other.

Identifying the most effective ways to reduce HIV transmission among injection drug users throughout the world is a critical public health priority. Evidence concerning the potential harm as well as the benefit of NEPs needs to be rigorously examined and openly debated. However, lowering the level of this debate to personal innuendo and insinuation is not the way to go. The preventable death of any individual, whether well known or forgotten, is a tragedy. Exploiting these tragedies to score debating points cheapens us all.

Alan R Lifson

Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN 55454, USA

1 Bennett SS. Needle-exchange programmes in the USA. *Lancet* 1998; **351**: 839.

2 Watters JK, Downing M, Case P, Lorvick J, Cheng YT, Fergusson B. AIDS prevention

for intravenous drug users in the community: street-based education and risk behaviour. *Am J Comm Psych* 1990; **18**: 587–96.

- 3 Watters JK, Estilo MJ, Clark GL, Lorvick J. Syringe and needle exchange as HIV/AIDS prevention for injection drug users. *JAMA* 1994; **271**: 115–20.
- 4 Hagan H, Des Jarlais DC, Friedman SR, Purchase D, Alter MJ. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *Am J Publ Health* 1995; **85**: 1531–37.
- 5 Oliver KJ, Friedman SR, Maynard H, Magnuson L, Des Jarlais DC. Impact of a needle exchange program on potentially infectious syringes in public places. *J Acquir Immune Defic Syndr* 1992; **5**: 534–35.

Author’s reply

Sir—It is tragic enough when someone decides to try an illicit substance and becomes addicted, but it is even more distressing when the user is a physician, a person whom the population relies on to be wise, honest, compassionate, and law abiding. Although Alan Lifson recites a number of Watters’ contributions, the fact remains that Watters died of a heroin overdose.

Like Watters, many of the leaders of the movement to legalise psychoactive and addictive drugs for personal recreational use are professionals, who perhaps seek to justify, sanctify, and exonerate their own illegal and dangerous involvement with illicit drugs.

Several studies have shown that even a small amount of cocaine can cause a fatal cardiac episode.^{1,2} In 1980, Lester Grinspoon of Harvard, an outspoken supporter of legalisation, wrote that “used no more than two or three times a week, cocaine creates no serious problems”,³ and in 1988 that cocaine is “a relatively safe, nonaddicting euphoriant agent”, and dismissed the idea of cocaine dependence as “moralistic exaggerations”.⁴ There is no doubt that such misleading and unscientific rhetoric, published in prestigious medical journals and repeated on university campuses across the USA, played an important part in the explosion of cocaine use and related deaths. Government-endorsed needle-exchange programmes will give the same message—ie, that it is okay to do it if you do it carefully.

The proliferation of needle exchanges as a factor in the death rate in Baltimore was only postulated, but it certainly cannot be disregarded. However, a flyer from the Baltimore City needle exchange states “This program is free and confidential. No identification is needed. There is no minimum age requirement. All that is needed is a desire to live healthier”.⁵ If health and safety were truly a concern of those using injection drugs, then their own personal vial of bleach would be a cheap, easy, and confidential way to

avoid HIV contaminated needles, and the use of condoms could prevent sexual transmission of the disease. But many of those using NEPs use them mainly as a resource for finding a supply of drugs, and share needles anyway.

Lifson would do well to look carefully at the Canadian studies on needle exchange and the explosion of drug addiction in those cities in which needle exchange programmes have been entrenched. If saving lives is the goal, needle exchange is not the answer.

Sandra S Bennett

Northwest Center for Health and Safety, PO Box 5853, Portland, OR 97228, USA

- 1 Libershtson RR. Sudden death from cardiac causes in children and young adults. *N Engl J Med* 1996; **334**: 1043.
- 2 Morris DC. Cocaine heart disease. *Hospital Pract* 1991; **26**: 83–92.
- 3 Grinspoon L, Bakalar JB. Drug dependence: non-narcotic agents. In: Kaplan HI, Freedman AM, Sidock BJ, eds. *Comprehensive textbook of psychiatry*, 3rd edn. Maryland: Williams and Wilkins, 1980.
- 4 Gawin FH, Ellinwood EH Jr. Cocaine and other stimulants. *N Engl J Med* 1988; **318**: 1173–82.
- 5 Baltimore City Needle Exchange (April 1–30), 1998.

Sir—In her response¹ to your Jan 10 editorial² urging the lifting of the federal ban on funding for needle-exchange programmes (NEP) in the USA, Sandra Bennett suggests that overdoses among injection-drug users (IDUs) could result from NEP use. Although there is some debate about the causes of fatal drug overdose,³ it is possible to explore whether there is an association between NEP use and non-fatal overdoses. To do this, we examined cross-sectional data collected by the Urban Health Study from 1114 street-recruited, active IDUs in six San Francisco Bay Area communities in 1997.

Study participants were asked to report if they had ever overdosed, how many times they had overdosed, and the month and year when they last overdosed. Of the 1114 respondents, 469 (42%) reported that they had overdosed, 137 of whom overdosed in 1996 or 1997 (referred to hereafter as recent overdose). IDUs who reported that the syringe exchange was their usual source of syringes in the past 6 months and who also reported use of the NEP in the 30 days before interview were classified as NEP users. In our respondents, NEP users were less likely than non-users to report recent overdose (10.9% vs 14.3%, $p < 0.09$).

To assess whether the absence of an association between recent overdose and NEP use was due to confounding by other factors, we used multiple logistic regression. Included in the regression model were factors previously associated

with overdose (sex, years of injection, alcohol use in the past week, frequency of injection, frequency of heroin injection, and the use of various drugs in the past 30 days). In this model, NEP use was not significantly associated with increased likelihood of recent overdose (adjusted odds ratio 0.73 [95% CI 0.50–1.07]). Indeed, there was a trend towards a protective effect against overdose.

No studies to date have found an association between NEP use and increased drug use at the individual or community levels, nor have they been found to foster the use of injection drugs.⁴ Drug overdose is a leading cause of morbidity and mortality among IDUs and is worthy of prevention interventions in its own right. In our sample, 12.3% of respondents reported a recent overdose. We support the increased use of overdose-prevention strategies, such as expansion of the capacity and diversity of drug treatment, distribution of naloxone to heroin users, and heroin prescription for long-term, treatment-adverse IDUs.

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**Ricky N Bluthenthal, Alex H Kral, Jennifer Lorvick, Elizabeth A Erringer, Brian R Edlin*

University of California, Urban Health Study, Institute for Health Policy Studies, School of Medicine, Box 1304, San Francisco, CA 94143, USA

- 1 Bennett SS. Needle exchange programmes in the USA. *Lancet* 1998; **351**: 839.
- 2 Editorial. Needle-exchange programmes in USA: time to act now. *Lancet* 1998; **351**: 75.
- 3 Darke S, Zador D. Fatal heroin "overdose" a review. *Addiction* 1996; **91**: 1765–72.
- 4 Normand J, Vlahov D, Moses L, eds. Preventing HIV transmission: the role of sterile needles and bleach. Washington, DC: National Academy Press, 1995.

Water hyacinths

Sir—Water hyacinth (*Eichornia crassipes*) has been in Africa much longer than Paul Epstein indicates in his Feb 21 news item (p 577).¹ According to Ken Harley, of the Commonwealth Scientific and Industrial Research Organisation in Australia, it arrived in Egypt in the 1890s, in South Africa in 1910, and was in the Congo River in 1952.² Cardiff-trained Timothy Stamps, the present Minister of Health in Zimbabwe, encountered water hyacinths when he was appointed to the Ministry of Health in Salisbury, Rhodesia, in 1968. Water hyacinths later caused a national emergency when a glacier of weed swept over the Lake Chivero dam and

threatened road and rail links to Bulawayo. As this weed has spread around Africa, each country seems to have gone through the same cycle of despair and agitation by fishermen, followed by government attempts at physical removal and chemical control, which ended with a realisation that the only sustainable action is to introduce biological control with pests from the country of origin.

The main lesson for the future is to start the latter at an early stage because of the time taken for the insects to multiply. From a public-health point of view, control of water hyacinth frequently leads to outbreaks of blue-green algae. As Elder and colleagues³ earlier pointed out, these present a wide range of health risks. Another point that is often glossed over is the fact that outbreaks of water weed are invariably preceded by a build up of nutrients in the water, usually as a result of pollution from industries or sewage.

**Theresa Watts, Ronald Watts*

Ngwelezane Hospital, P/Bag X20021, Empangeni 3880, South Africa

- 1 Epstein P. Weeds bring disease to the east African waterways. *Lancet* 1997; **351**: 577.
- 2 Harley K. Control of Africa's floating water weeds. Commonwealth Science Council. CSC(93) AGT-18 PR 295, London: CSC, 1993.
- 3 Elder GH, Hunter PR, Codd GA. Hazardous freshwater cyanobacteria. *Lancet* 1993; **341**: 1519–20.

Botulinum toxin, a historical note

Sir—*The Lancet* and other journals have published on the therapeutic use of type A neurotoxin of *Clostridium botulinum*. Therapeutic chemodenervation in conditions caused by focal hypercontractions of skeletal muscles (such as strabismus, hemifacial spasm, and focal dystonias) was pioneered by Scott.¹ However, botulinum toxin inhibits the release of acetylcholine not only at the motor nerve terminal but also at the cholinergic parasympathetic and sympathetic terminals, producing autonomic symptoms, and the toxin has been successfully used to treat over contraction of smooth muscles (eg, achalasia)² or dysfunction of the autonomic nervous system such as palmar or axillary hyperhidrosis.³

An accurate description of botulinum-toxin-induced autonomic failure was published 175 years ago by the German physician and poet Justinus Kerner (1786–1862) (figure). Kerner also developed the idea of a possible therapeutic use. He published the earliest systematic clinical descriptions of foodborne botulism in 1817⁴ and later



Justinus Kerner, aged 69

Oil painting by Julius Hamel, c 1855.

published two monographs. He thought that a toxic substance in sausages, which he called "fatty acid", was responsible for the clinical features of botulism. His second monograph⁵ reviewed 155 cases of poisoned patients and precisely described the autonomic dysfunctions: "The tear fluid disappears, the gullet becomes a dead and motionless tube; in all mucous cavities of the human machine the secretion of the normal mucus stands still, from the largest, the stomach, to the tear duct and the excretory ducts of the lingual glands. No saliva is secreted. No drop of wetness is felt in the mouth . . .".

Chapter 8, entitled "About the fatty acid as a possible therapeutic drug", suggested the therapeutic use of botulinum toxin not only in muscular hypercontractions ("in such doses that its action could be restricted to the sphere of the sympathetic nervous system only") but also in conditions with hyperhidrosis and hypersalivation.

Kerner conceded that what he had written about the "fatty acid" as a therapeutic agent "belongs to the realm of hypotheses and may be confirmed or disproved by observations in the future". It is fascinating to see his vision being validated over the past 20 years of clinical research.

Frank J Erbguth

Department of Neurology, University of Erlangen-Nuremberg, D-91054 Erlangen, Germany

- 1 Scott AB. Botulinum toxin injection of eye muscles to correct strabismus. *Trans Am Ophthalmol Soc* 1981; **79**: 734–70.
- 2 Pasricha PJ, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kaloo AN. Intraspinal botulinum toxin for the treatment of achalasia. *N Engl J Med* 1995; **322**: 774–78.
- 3 Naumann M, Flachenecker P, Brocker EB, Toyka KV, Reiners K. Botulinum toxin for palmar hyperhidrosis. *Lancet* 1997; **349**: 252.
- 4 Kerner J. Vergiftung durch verdorbene Würste. *Tübinger Blätt Naturwissenschaften Arzneymkunde* 1817; **3**: 1–25.
- 5 Kerner J. Das Fettgift oder die Fettsäure und ihre Wirkungen auf den thierischen Organismus ein Beytrag zur Untersuchung des in verdorbenen Würsten giftig wirkenden Stoffes. Stuttgart, Tübingen: Cotta, 1822.