# CORRESPONDENCE

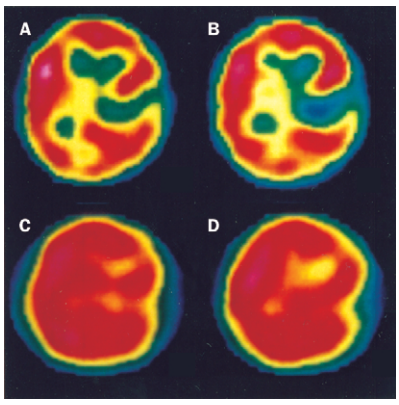
e-mail submissions to correspondence@lancet.com

## Hyperbaric oxygenation for cerebral palsy

Sir—Jean-Paul Collet and colleagues' report (Feb 24, p 582)[1] on the treatment of children with cerebral palsy strongly suggests benefit from increasing the plasma oxygen tension.

Workers in several studies of oxygen treatment for such children have reported benefit from hyperbaric oxygenation, generally 100% at 1·5 atmospheres absolute (ATA), but Collet and colleagues suggest that 1·3 ATA air is as beneficial, except that 1·75 ATA oxygen had more rapid results in a more disabled group of children. As they state, the oxygen level breathing 1·3 ATA air is equivalent to about 28% by mask at 1·0 ATA. If 28% can be shown to be beneficial under controlled conditions, an improved quality of life might be possible for thousands of children with cerebral palsy. However, the earlier use of oxygen therapy in such children may be more beneficial,[2] and hyperoxia might be beneficial for the fetus in utero.[3]

At our centre, about 250 children with cerebral palsy and brain injuries, aged from 6 weeks to 14 years, have been treated with hyperbaric oxygenation at pressures of up to 1·5 ATA in Vickers monoplace chambers. The patients have been used as their own controls. A baseline image taken with single photon emission computed tomography (SPECT) is taken for each patient. Scanning is repeated after the series of hyperbaric treatments. In more than 90% of patients, improvement in blood flow and metabolism has been noted on imaging, accompanied by clinical improvement, especially obvious to the parents.[4] Physical, occupational, and speech therapy are continued during the treatment period and, therefore, the only variable was the administration of hyperbaric oxygenation. As already reported,[5] there is growing evidence from the use of oxygen at increased doses that in certain brain insults there are idling neurons, which are receiving enough oxygen to prevent membrane failure, but not enough to allow the generation of action potentials.




**SPECT axial slice before (A, C) and after (B, D) hyperbaric treatment**

The following case study illustrates the effects, seen on SPECT. A boy aged 3·5 years developed a severe left-hemiparesis after a traumatic birth, with damage to the blood supply to the right hemisphere. The axial view of the baseline before treatment showed severe hypoperfusion in the distribution of the right midcerebral artery (figure). After 77 1 h treatments of hyperbaric oxygenation at 1·5 ATA, the scan was repeated (figure). A striking increase in flow and metabolism can be seen in the right hemisphere. The patient arrived in a wheelchair but by the end of the treatment course although he still had mild weakness on the left side he was able to run.

We suggest that SPECT should be adopted to provide objective evidence of benefit from interventions in brain-injured children.

*R A Neubauer*

Ocean Medical Center, Lauderdale by-the-Sea, FL 33308, USA

1 Collet J-P, Vanasse M, Marois P, et al. Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial. *Lancet* 2001; **357:** 582–86.

2 Machado JJ. Reduction of spasticity, clinically observed in patients with neurological diseases, submitted to hyperbaric oxygen-therapy especially in children with cerebral palsy: transcripts from New Horizons in Hyperbaric Medicine. Annual Meeting of the American College of Hyperbaric Medicine, Orlando, Florida, 1989: 101–10.

3 Sparacia A, Sparacia B. Recenti acquisizioni fisiologiche sull'ossigeno in iperbarismo. *Minerva Anestesiologica* 1991; **57:** 187–204.

4 Neubauer RA. Hyperbaric oxygenation in cerebral palsy and the brain injured child. Proceedings of 3rd EPNS Congress, European Paediatric Neurology Society, Nice, November, 1989: 283–89.

5 Neubauer RA, Gottlieb SF, Kagan RL. Enhancing "idling" neurons. *Lancet* 1990; **335:** 542.

Sir—Hyperbaric treatment is reported by Jean-Paul Collet and colleagues[1] as producing striking improvements in children with cerebral palsy. The improvements were seen in children breathing oxygen at 1·75 ATA, or compressed air at 1·3 ATA, and were still present 3 months later.

This result is remarkable, since drug therapy was withdrawn 6 weeks before the study, and physiotherapy stopped during the treatment and 3-month assessment. The beneficial effects might have been reduced by the unacceptably high rate of ear barotrauma, especially in the oxygen group. Unfortunately a control group was not included, and the investigators claim to be unsure whether the improvements were due to pressure, the additional oxygen, or a participation effect related to the motivation of the parents.

Compressed air at 1·3 ATA increases the plasma oxygen tension from 12·7 kPa (95 mm Hg) to 19·7 kPa (148 mm Hg), and to increase the concentration of such a reactive substrate by 50% is certainly notable. I illustrate the striking effect of similar increases in air pressure with two cases.

A compressed-air worker fainted during decompression after completing an 8 h shift at 2·5 ATA,[2] but recovered quickly. He gradually developed paralysis of the legs overnight, but became symptomfree on recompression. However, symptoms returned during decompression. Over the next 9 days, in the pressure chamber, the patient lost consciousness several times and developed limb paralysis. Small increases in air pressure reversed the symptoms on each occasion.

A girl aged 16 years trekking in Nepal became ataxic during a descent from 3505 m altitude,[3] which is 0·36 atmospheres less than sea-level pressure. She worsened and was

placed in a hyperbaric chamber. After 15 min, pressurised to nearly sea level, she recovered completely. The pressure was maintained for 2 h, but 1 h after decompression she worsened to semiconsciousness. She again recovered on compression and was kept in the chamber for 4 days.

In the compressed-air worker, gas bubbles initiated symptoms, but relapses of neurological decompression sickness are associated with damage to the blood-brain barrier.

In studies of the exercise tolerance of patients with chronic obstructive pulmonary disease taken from Jerusalem to the Dead Sea, workers noted improvements that lasted for 2 weeks after return to the higher altitude.[5]

Oxygen is not a drug and, because it is metabolised, there is no simple dose-response curve. If therapy with 28% oxygen at 1·0 ATA is as effective for children with cerebral palsy as air or oxygen under hyperbaric conditions, many children could benefit. However, these positive results suggest that both hyperbaric air and oxygen therapy can be recommended for such children, since these children had major handicaps, and neurological or neuropsychological status did not worsen.

*Philip B James*

Wolfson Hyperbaric Medicine Unit, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

1 Collett J-P, Varnasse M, Marois P, et al. Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial. *Lancet* 2001; **357:** 582–86.
2 Campbell-Golding F, Griffiths P, Hempleman V, Paton WDM, Walder DN. Decompression sickness during construction of the Dartford tunnel. *Br J Ind Med* 1960; **17:** 167–70.
3 Austin D. Gamow bag for acute mountain sickness. *Lancet* 1998; **351:** 1815.
4 Hills BA, James PB. Microbubble damage to the blood-brain barrier: relevance to decompression sickness. *Undersea Biomed Res* 1991; **18:** 111–16.
5 Kramer MB, Springer C, Berkman N, et al. Rehabilitation of hypoxemic patients with COPD at low altitudes at the Dead Sea, the lowest place on Earth. *Chest* 1998; **113:** 571–75.

### *Authors' reply*

Sir—We compared hyperbaric oxygen treatment with sham hyperbaric oxygen treatment (slightly pressurised room air) to improve children with cerebral palsy. Our conclusion was that the global improvements in the two treatment groups might be related to the context of the intervention and the selection of motivated parents. A possible effect of increased pressure cannot be ruled out because of the slight increase in partial arterial pressure of oxygen; nevertheless, the same increase in blood oxygen can be reached by simple mask administration of 28% fractional inspiration oxygen without increased pressure, which needs to be assessed before it can be recommended.

Therefore, hyperbaric oxygen treatment is not necessary to improve cerebral palsy in children. As R A Neubauer acknowledges, this finding is good news, because children will not have to face the risk related to hyperbaric oxygen treatment therapy[1] and the family will not have to support the costs.

The cases presented by Neubauer do not provide scientific results but are simple anecdotal reports of changes in SPECT tomography under exposure to hyperbaric oxygen treatment. This change is not surprising with hyperbaric oxygen treatment, since oxygen is such a reactive substrate, as P B James notes. In the report of one such case,[2] Neubauer says clearly that many variables must be taken into account besides grey-matter metabolism. We agree, including the complex interaction between mind and body as an independent factor.[3]

We think that these observations should be used to generate hypotheses only. Their presentation to the public (patients or family) is inappropriate for two reasons: with our degree of knowledge, relation of the changes in the brain image to the sole effect of increased partial arterial pressure of oxygen is impossible; more importantly, no causal association can be made between the changes in the brain image and the clinical improvement that is especially obvious to the parents.

The two cases presented by James deal with the health difficulties caused by changes in atmospheric pressure: case one is an accident due to rapid decompression, case two is the report of a severe case of acute mountain sickness (caused by low atmospheric pressure in altitude). Treatment was successful in the two patients, as expected. However, the cases do not relate at all to the situation of children with cerebral palsy, and no extrapolation can be made between the two situations.

The two letters illustrate the confusion that prevails in the domain of hyperbaric treatment, for which scientific evidence is lacking, leading clinicians to rely on anecdotal evidence.

Among four references presented by Neubauer only one is an article (reference 3) published in a national journal; two are references of meeting presentations (references 1 and 4), and one is a letter (reference 5). Our study is the first randomised controlled trial in this field, and our results show that hyperbaric oxygen treatment is not better than sham therapy. On the other hand there is evidence of many possible side-effects after hyperbaric oxygen therapy.[4]

**J P Collet, M Lassonde, S D Tremblay, J Lacroix, A Majnemer*

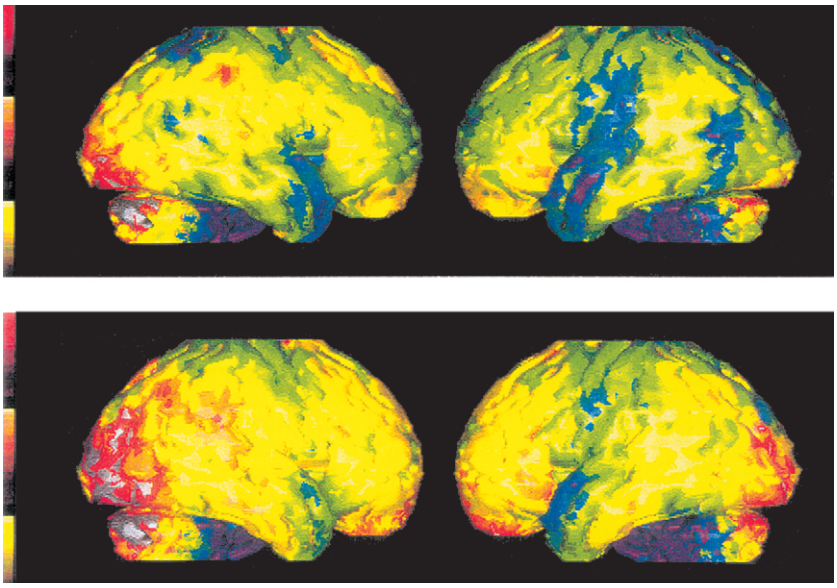
*Randomised Clinical Trial Unit, Jewish General Hospital (SMBD), Department of Epidemiology, and School of Physical and Occupational Therapy, McGill University, 3755 Côte Sainte Catherine, Montreal, QC H3T 1E2, Canada; Paediatric Neurology Department, Sainte-Justine Hospital, Montreal; Psychology Department, University of Montreal; and Centre Hospitalier Hôtel-Dieu de Lévis, Lévis

1 Nuthall G, Seear M, Lepwsky M, Wensley, Skippen S, Hukin J. Hyperbaric oxygen therapy for cerebral palsy: two complications of treatment. *Pediatrics* 2000; **106:** e80.
2 Neubauer RA, Gottlieb SF, Kagan RL. Enhancing "idling" neurons. *Lancet* 1990; **335:** 542.
3 Damasio AR. Human emotions and the mind-body problem: science of mind-body interaction—an exploration of integrative mechanisms. Washington: National Institutes of Health, 2001.
4 Tibbles P, Edelsberg J. Hyperbaric oxygen therapy. *N Engl J Med* 1996; **334:** 1642–48.

Sir—Jean-Paul Collet and colleagues[1] conclude that hyperbaric oxygen does not improve the condition of children with cerebral palsy compared with those exposed to slightly pressurised air. Nevertheless, they wonder whether improvement is due to slightly pressurised air rather than a bias from study participation.

We treated eight adults with toxic encephalopathy (impaired brain function secondary to exposure to pesticides, solvents, and other neurotoxic compounds). Patients were given ten daily treatment sessions of 1 h each, with 1·32 ATA and an oxygen concentration of 24% (mild treatment). As done by Collet and colleagues, we measured attention and reaction time by use of a test of variables of attention. However, we added SPECT brain scanning before and after hyperbaric oxygen therapy to objectively assess results.[2–4]

The figure shows three-dimensional displays of SPECT of the cerebral hemispheres of a representative patient before and after treatment with mild therapy. Our computer program makes a regional quantitative comparison of an individual's scan



**SPECT scan of child's brain before and after mild hyberbaric therapy**
Top=before therapy, bottom=after.

with a group of more than 20 controls. The baseline impairment of perfusion moved into the normal yellow zone after treatment.

All eight patients improved significantly after only ten sessions of mild therapy. General wellbeing and variables of attention also improved.[5]

We conclude that mild hyperbaric oxygen therapy can be effective in improving SPECT as well as attention and reaction times. Therefore, the beneficial effect in patients described by Collet and colleagues is probably related to the beneficial effects of slightly pressurised air rather than to the act of participating in the study.

*Gunnar Heuser, J Michael Uszler

*NeuroMed and NeuroTox Associates, Agoura Hills, CA 91301, USA; and Department of Nuclear Medicine, Santa Monica-UCLA, Santa Monica, CA
(email: gheuser@ucla.edu)

1 Collet J-P, Vanasse M, Marois P, et al. Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial. *Lancet* 2001; **357:** 582–86.
2 Neubauer RA. Cerebral palsy and the brain injured child: 26th Annual Meeting of the European Underwater and Baromedical Society on Diving and Hyperbaric Medicine, Malta, Sept 14–17, 2000.
3 Neubauer RA, Gottlieb SF, Kagan RL. Enhancing "idling" neurons. *Lancet* 1990; **335:** 542.
4 Neubauer RA, Uszler J, James P. Hyperbaric oxygenation: the recoverable brain in certain pediatric patients: 8th International Child Neurology Congress, Ljubljana, Slovenia, Sept 13–18, 1998.
5 Heuscr G, Heuser S, Aguilera O, Rodelander D, Amoun K. Hyperbaric oxygen (HBO) treatment for impaired brain function: 8th Intemational Congress on Anti-Aging and Biomedical Technology, Las Vegas, CA, Dec 15–17, 2000.

## Sentinel node biopsy in breast cancer

Sir—Axillary lymph node dissection (ALND) in operable breast cancer provides an accurate way of staging the disease.[1] Since popularity of screening has increased, most women do not harbour axillary metastasis in which ALND can be avoided. Sentinel-node biopsy has, therefore, gained rapid popularity because the technique can predict the presence of metastasis in the downstream lymph nodes.[2]

Sentinel-node biopsy, however, has a certain learning curve[2] but is ultimately successful in identifying the first station lymph node or nodes in 85–90% of patients.[3,4] The false-negative outcome varies from 4% to 13% of metastatic lymph nodes that will be left untreated in the axilla.

The technique involves the use of radioisotopes and an expensive probe to detect radioactivity. Surprisingly, despite the so-called targeted nature of the technique with blue dye and radio-guided dissection, the number of lymph nodes removed in studies has ranged from one to eight.[3,4] A similar number of nodes is dissected from the first level of axilla if an axillary node sampling is done.[5] Axillary-node sampling has the advantage of having a 100% yield and a sensitivity of 97%, compared with 85–90% for the sentinel-node biopsy.[5] Furthermore, axillary-node sampling is a simple procedure, does not require radioisotopes or expensive gadgetry, and has no false-negative rates during the learning curve.

We have come to the conclusion that sentinel node biopsy is expensive and is driven by lure for technology and fashion, and has little advantage over axillary-node sampling in predicting a negative axilla. A study should be done to compare morbidity for this technique with that for sentinel-node biopsy before it becomes routine practice, at least in less-developed countries.

*R A Badwe, I Mittra

*Tata Memorial Hospital, Parel, Mumbai, 400012 India
(email: tmho3@bom2.vsnl.net.in)

1 Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival: a Bayesian meta-analysis. *Ann Surg Oncol* 1999; **6:** 109–16.
2 Orr-RK; Hoehn-JL; Col NF,. The learning curve for sentinel node biopsy in breast cancer: practical considerations. *Arch Surg* 1999; **134:** 764–67.3 McMasters KM, Giuliano AE, Ross MI, et al. Sentinel lymph-node biopsy for breast cancer: not yet the standard of care. *N Engl J Med* 1998; **339:** 990–95.
4 Tafra L, Lannin DR, Swanson MS, et al Muilti-centre trial of sentinel node biopsy for breast cancer using technetium sulphur colloid and isosulphan blue dye. *Ann Surg* 2001; **233:** 51–59.
5 Ahlgren J, Liljegren G, Holmberg L, Berg J. Five node biopsy of the axilla an alternative to sentinel node biopsy in operable breast cancer results from a prospective trial. *Eur J Cancer* 2000; **36:** (suppl 5): S98 (abstr 274).

## Trafficking of lacrimal aquaporin-5 in Sjögren's syndrome

Sir—In their report on the distribution of aquaporin-5 in lacrimal glands of patients with Sjögren's syndrome, Kazuo Tsubota and colleagues (March 3, p 688)[1] reveal new morphological features of the syndrome but do not reflect other workers' observations.

Tsubota and colleagues describe an altered immunohistochemical distribution of aquaporin-5 in Sjögren's tissues, with an absence of aquaporin-5-immunoreactivity at the apical membrane and diffuse cytoplasmatic staining, contrary to the biospy samples of the other groups who detected similar concentrations of aquaporin-5 protein. This finding provides new insights to the mechanisms underlying Sjögren's syndrome and substantially underlines an extensive study by Steinfeld and colleagues.[2] They showed an expression of aquaporin-5 mainly confined to the basal membranes of salivary glands of patients with Sjögren's syndrome contrary to an apical expression in control tissues.

Although Tsubota and colleagues come to the conclusion that these data suggest a selective defect for trafficking of aquaporin-5 in Sjögren's syndrome

with an unknown mechansim, Nguyen and colleagues[3] earlier suggested that the dysregulation of water channels within Sjögren's syndrome might be based on autoimmune antibodies to M3 receptors. The humoral immune response and the targeting of this muscarinergic M3 cell-surface signal transduction receptor may negatively affect the secretory response through a translocation of aquaporins.

Contrary to these morphological findings, which support the idea that dimished lacrimation in Sjögren's syndrome may be due to the absence of membrane-bound aquaporin-5, functional studies of Moore and colleagues,[4] in which knockout mice were used, provided direct evidence against an essential role for aquaporins in lacrimal gland fluid secretion.

*David A Groneberg, Alexander Gerber, Axel Fischer

University Hospital Charité, Allergy and Immunology Research Group, Humboldt University, D-13353 Berlin, Germany
(e-mail: david.groneberg@charite.de)

1 Tsubota K, Hirai S, King LS, Agre P, Ishida N. Defective cellular trafficking of lacrimal gland aquaporin-5 in Sjögren's syndrome. *Lancet* 2001; **357:** 688–89.
2 Steinfeld S, Cogan E, King LS, Agre P, Kiss R, Delporte C. Abnormal distribution of aquaporin-5 water channel protein in salivary glands from Sjogren's syndrome patients. *Lab Invest* 2001; **81:** 143–48.
3 Nguyen KH, Brayer J, Cha S, et al. Evidence for antimuscarinic acetylcholine receptor antibody-mediated secretory dysfunction in nod mice. *Arthritis Rheum* 2000; **43:** 2297–306.
4 Moore M, Ma T, Yang B, Verkman AS. Tear secretion by lacrimal glands in transgenic mice lacking water channels AQP1, AQP3, AQP4 and AQP5. *Exp Eye Res* 2000; **70:** 557–62.

### *Authors' reply*

Sir—We agree with David Groneberg and colleagues that our findings of altered aquaporin-5 trafficking in the lacrimal gland of Japanese patients with Sjögren's syndrome are consistent with Steinfeld and colleagues' findings. Additionally, our findings of preserved distribution of the basolateral sodium-potassium-ATPase and apical sodium channels in Sjögren's syndrome patients, coupled with the observation of normal concentrations of aquaporin-5 protein expression, strongly suggest that the defect is at least fairly specific to aquaporin-5 trafficking.

Groneberg and colleagues offer that the mechanism of this trafficking defect, rather than being unknown, was suggested by Nguyen and colleagues, in a study of the role of antibodies to the M3-muscarinic receptor in a mouse model of Sjögren's syndrome. Although that study provides interesting information about a potential role for antibodies to M3, the findings on aquaporin distribution are not definitive or straightforward. The basis for their observation was analysis of aquaporin expression in protein immunoblots of crude plasma membrane preparations from mouse submandibular glands after exposure to antibodies to M3 and carbachol. No direct observations of aquaporin distribution were provided to confirm the suggested difference in distribution. Of greater concern, however, is the fact that their immunoblots were done with antibodies to aquaporin-1, which is present in endothelial but not epithelial cells in the salivary (or lacrimal) glands. We question, therefore, which cells are represented in the immunoblots, and whether the findings provide any insight into the aquaporin trafficking defect.

Moore and colleagues measured tearing in a single mouse strain with deletions of aquaporin genes, including aquaporin-5, and noted no difference in basal or stimulated tear formation between wild-type and knockout mice. We do not mean to discount these observations; however, we believe caution must be exercised in extrapolating from them. Striking strain differences in mice are well established for a wide array of pathophysiological processes, which potentially complicates analysis of transgenic animals. Study of different strains, or generations of back-crossing might be required to establish phenotypes. More importantly, we believe it is premature to definitively extrapolate from findings in a single mouse strain to human pathophysiology. Even within the limited scope of aquaporin biology, examples of species differences are clearly emerging. One example comes from the assessment of rare aquaporin-1-null human beings, in whom the renal consequences of aquaporin-1 deficiency are very different from those seen in aquaporin-1-null mice.[1]

We believe that the observation of altered aquaporin-5 trafficking in human beings with Sjögren's syndrome is compelling, and is made more so by the finding of a similar alteration in aquaporin-5 distribution in two populations who are geographically and ethnically distinct. Although differences in aquaporin function between lacrimal and salivary glands may exist, definitive functional assessment in human beings is not available, and inferences drawn across species may not be correct. We believe that our statement that decreased tearing may be due to the absence of apical aquaporin-5 is an honest prediction based upon our experimental findings.

*Kazuo Tsubota, Shinichiro Hirai, Landon S King, Peter Agre, Naruhiro Ishida

Department of Ophthalmology, Tokyo Dental College, 5-11-13 Sugano, Ichikawa-shi, Chiba 272-8513, Japan
(e-mail: tsubota@tdc.ac.jp)

1 Choi, MC, King, LS, Fernandez, PC, Cartron, PC, Agre, P. Urinary concentrating defect in aquaporin-1 null individuals. *J Am Soc Nephrol* 2000.

## Review of diagnosis and treatment manual

Sir—I was disappointed with Laragh Gollogly's (March 17, p 893)[1] review of the book *Diagnosis and Treatment* by Keith and Ginny Birrell.

She identifies the readership incorrectly. The manual states that it is intended to upgrade the skills of primary-health-care workers, such as medical assistants, nurses, health aides and village healthworkers in less-developed countries. They are not doctors but make diagnoses and prescribe medicines, which is reality in many less-developed countries. The book is not for doctors, although it will be of use to them in the training of junior members of their team. The manual seeks to improve medical care at community level by upgrading the clinical and prescribing skills of health workers. By not correctly identifying the readership, Gollogly misses the point of the manual.

Gollogly takes particular issue with the simple language used. This book is written for people whose first language is not English. Many staff may have hardly used any books in their training. The information is basic and simply expressed; it may not be eloquent, but it is correct. While she cannot make up her mind about whether the book's directness is refreshing or not, Gollogly overlooks the fact that the approach is relevant for this readership.

Nowhere does the book advocate eliciting fracture crepitus. Advice in the book is tailored to the reality of treatment opportunities in less-developed countries. To select just one example scrutinised in the review—oral rehydration salts (ORS) used to treat shock on the way to hospital. Doctors and medical students in more-developed countries might be surprised to learn that the essential drug kits for primary-health-care units in poorer countries do not include intravenous fluids or cannulae. ORS are an effective method of fluid replacement in this situation. The list goes on.

The book's content was reviewed by more than 45 eminent health workers in poor countries. I do not doubt that the manual is a valuable and unique contribution to increasing the skills and capacity of district and village level primary care in such countries. I strongly recommend it to staff struggling to improve care with limited resources.

It goes someway to replace Maurice King's *Primary Child Care*, which has been widely used for training and has not been available for 4 years.

*David Morley*

Department of Tropical Child Health, University of London, Harpenden AL5 1BN, UK

1 Gollogly L. Molasses in the tropics: Diagnosis and Treatment. *Lancet* 2001; **357:** 893.

## *Helicobacter pylori*: the story continues

Sir—Pim Allen's March 3 news item (p 694)[1] on the work of Robin Warren and Barry Marshall reminds us of similar efforts by Frank Gorham, a Missouri physician, in trying to understand peptic ulcer disease.

Gorham[2] began using bismuth in 1930 to treat peptic ulcers in patients whose disease would not heal under normal ulcer management. In these patients, he noted encouraging results. Since bismuth had known antisyphilitic properties, he postulated that an organism thriving in an acid medium was "a possible factor of chronicity, if not an etiological factor, in peptic ulcer."[2]

At the same time, E V Cowdry and colleagues[3] at the Washington University School of Medicine, USA, were studying an unidentified so-called spirochete in the stomachs of rhesus monkeys. Being familiar with Cowdry's research, Gorham forwarded stomach samples to Cowdry for analysis. In turn, Cowdry's preliminary findings led a colleague, James Doenges,[4] to undertake a more comprehensive study.

Through examination of 242 human stomachs removed at necropsy, Doenges[4] reported 43% to be positive for the spirochete. Although infections were mainly characteristic of *H pylori*, in several cases the bacteria matched the description of the related *H heilmannii*. Unfortunately, Doenges could not make a consistent association between *H pylori* and any specific lesion. In a later study by Freeberg and Barron, they noted that in the absence of ulceration, spirochetes were rarely found; yet, overall they concluded that any evidence of pathogenic significance was lacking.[2] Although so close to an understanding of the cause and treatment of this disease, these inconclusive results thwarted further progress. Conclusive proof of an association was not identified until the revitalisation of this research by Warren and Marshall.

After more than a century since the first observation of *H pylori* in the human stomach by Salomon,[5] and although many clinical applications of this discovery have been developed, we believe that this story is far from over.

**S A Hoption Cann, J P van Netten, C van Netten*

*Special Development Laboratory, Royal Jubilee Hospital, Victoria, BC V8R 1J8, Canada; Department of Biology, University of Victoria, Victoria; and Department of Health Care and Epidemiology, University of British Columbia, Vancouver
(e-mail: cann@medscape.com)

1 Allen P. What's the story *H pylori*? *Lancet* 2001; **357:** 694.
2 Freeberg AS, Barron LE. The presence of spirochetes in human gastric mucosa. *Am J Dig Dis* 1940; **7:** 443–45.
3 Cowdry EV, Scott GH. Effect on monkeys of small doses of concentrated preparation of viosterol. *Arch Pathol* 1936; **22:** 1–23.
4 Doenges JL. Spirochetes in gastric glands of Macacus rhesus and humans without definite history of related disease. *Arch Pathol* 1939; **27:** 469–77.
5 Salomon H. Ueber das Spirillum des Saugetiermagens und sein Verhalten zu den Belegzellen. *Centralbl Bakt* 1896; **19:** 433.

Sir—The association of *H pylori* with gastritis described in your March 3 news item[1] was first published in 1975 by Steer,[2] although his bacteriology associate cultured only pseudomonas.

In 1981 in Western Australia, I was Head of the Royal Perth Hospital Microbiology Department when Marshall, then a junior doctor not in my Department, asked for my help to culture these bacteria in a series of 100 patients. Although he had no research money, I agreed. If Marshall had been a junior doctor in the USA with no research money, would he have received such cooperation?

My deputy, Pearman, supervised the microbiology technicians. Among the first 34 samples, gram stain revealed spiral bacteria in six, but despite variations of media and incubation temperatures, these bacteria were not cultured because incubation was limited to 48 h (after which contaminants frequently covered the plates). Longer times of incubation were about to be attempted when the 35th culture was left during the Australian Easter holiday of 5 days; and that culture contained a pure growth of *H pylori*—stomach acid must have killed any contaminants.

The colonies showed only curved organisms with gram stain, not spirals as seen in the smears, and Marshall doubted whether we had grown the correct organism. Subsequent samples were incubated for at 4–5 days, and 11 isolations were achieved. Annear, senior scientist in my department, maintained these cultures; and from his hanging-drop preparations Armstrong produced electron-micrographs.

In 1983, I went on sabbatical leave and Marshall moved to Fremantle Hospital, from where he wrote the first description of the culture. In his letter he stated "We have cultured the bacteria . . ." and this has been repeated by him and nearly all other writers subsequently.[3] So perhaps it is not strange that at the time of his 1995 Lasker award, Marshall wrote that the histopathologist Warren and he "together embarked on an attempt to culture the organisms" . . . "We tried many different culture media".[4] This story must have been told to *The Lancet* feature writer.

The genus name *Helicobacter* was not introduced by Marshall or Warren. From 1984, I started in my hospital department basic bacteriology research on what was then called *Campylobacter pyloridis* that led to its first culture in liquid medium, the first reliable serology test for infection, and the first evidence of genomic variation in *H pylori*, &c. In 1989, I published the new genus name helicobacter[5] (in the required technical journal, which is not found on MEDLINE). The extensive bacteriological justification required for this new genus included contributions from colleagues in Queensland, Australia and England, UK.

Certainly Marshall was the first to challenge clinicians to accept *H pylori* as an essential but insufficient cause of peptic ulcer. However, bacteriology input was essential from the beginning.

*Stewart Goodwin*

Department of Gastroenterology, St George's Hospital Medical School, London SW17 0RE, UK
(e-mail: stewart@pylori.demon.co.uk)

1 Allen P. What's the story *H pylori*? *Lancet* 2001; **357**: 694.
2 Steer H. Ultrastructure of cell migration through the gastric epithelium and its relationship to bacteria. *J Clin Pathol* 1975; **28:** 639–46.
3 Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; **1:** 12731–34.
4 Marshall BJ. The Albert Lasker Medical research Award. *Helicobacter pylori*: the etiologic agent for peptic ulcer. *JAMA* 1995; **274:** 1064–06.
5 Goodwin CS, Armstrong JA, Chilvers T, et al. Transfer of *Campylobacter pylori* and *Campylobacter mustelae* to *Helicobacter* gen. nov. as *Helicobacter pylori* comb. nov. and *Helicobacter mustelae* comb. nov. respectively. *Int J Syst Bacteriol* 1989; **39**: 397–405.

## Thyroid function tests

Sir—In the otherwise excellent review of thyroid function tests by Colin Dayan (Feb 24, p 619),[1] the pattern of thyroid function tests described for the iodine deficiency disorders (IDD) is not entirely correct.

The pattern described by Dayan—raised thyrotropin (TSH), low free T4 or T3—is rarely encountered, and is typical only of the most severe IDD with thyroid failure and myxoedematous cretinism.[2] The more usual patterns in severe, moderate, or mild IDD are characterised by raised thyrotropin concentration normal or supranormal T3, and low T4; or, more commonly, slightly raised thyrotropin concentration with normal T3 and T4 concentrations (subclinical hypothyroidism).[2–4] Furthermore, in many areas of endemic goitre and moderate to severe IDD, all three tests (thyrotropin, T3, and T4) are within the normal range.[5]

*Michael Zimmermann*

Laboratory for Human Nutrition, Swiss Federal Institute of Technology Zürich, PO Box 474, CH-8803 Rüschlikon, Switzerland

1 Dayan CM. Interpretation of thyroid function tests. *Lancet* 2001; **357:** 619–24.
2 Delange FM. Iodine deficiency. In: Braverman LE, Utiger RD, eds. Wemer and Ingbar's the thyroid, 8th edn. Philadelphia: Lippincott Williams and Wilkins, 2000: 295–316.
3 Chopra IJ, Hershman JM, Hornabrook RW. Serum thyroid hormone and thyrotropin levels in subjects from endemic goiter regions of New Guinea. *J Clin Endocrinol Metab* 1975; **40:** 326–33.
4 Delange F, Hershman JM, Ermans AM. Relationship between the serum thyrotropin level, the prevalence of goiter and the pattern of iodine metabolism in Idjwi island. *J Clin Endocrinol Metab* 1971; **33:** 261–68.
5 Zimmermann MB, Adou P, Zeder C, Torresani T, Hurrell RF. Persistence of goiter despite oral iodine supplementation in goitrous children with iron deficiency anemia in the Côte d'Ivoire. *Am J Clin Nutr* 2000; **71:** 88–93.

Sir—Colin Dayan's interpretation of thyroid function tests[1] is a model of clarity and deals with every eventuality that can occur on first seeing a patient with a thyroid disorder.

Probably, thyroid function tests are done at least 50 times more commonly to assess thyroxine dose than to diagnose thyroid dysfunction. Dayan did not address this feature of the subject except for his important reminder that in patients who adhere to treatment, thyroxine might not be absorbed when small-bowel disease is present or cholestyramine and some other drugs are given concurrently.

Every qualifying medical student knows that thyrotoxicosis can cause atrial fibrillation or osteoporosis and makes the illogical extrapolation that a patient given a dose of thyroxine that suppresses or brings the serum thyroxine concentration to higher than the reference range is receiving too much replacement. It is excusable for doctors to believe that if the serum thyroxine concentration is higher than the so-called normal range that the dose of thyroxine should be decreased. In fact, the thyroxine is replacing the thyroxine and tri-iodothyronine, which is produced by a normal gland. The only function of doing a thyroxine estimation is to confirm that the patient is taking the thyroxine and that it is being absorbed. Serum thyroxine concentration, if raised, confirms that the thyroxine replacement dose is inadequate but a suppressed concentration does not necessarily show that the dose is too high. Serum T3 must be kept within the normal range.

Before the days of hormone assays, hypothyroid patients received about double the average dose of thyroxine given today, but did not develop osteoporosis or atrial fibrillation. Doses should be judged clinically rather than be governed by misinterpreted hormone results.

*P B S Fowler*

Shirley Holms 4 South Park Drive, Gerrards Cross, Buckingharmshire SL9 8JH, UK

1 Dayan CM. Interpretation of thyroid function tests. *Lancet* 2001; **357:** 619–24.

Sir—Colin Dayan[1] says his review of thyroid function tests is a guide for the general physician. He is right if he means the hospital internist, who sees patients with a high probability of previous disease. However, if he means the family physician, who sees patients with a low prevalence of disease, he only pays lip service to his conclusion that a test has to be applied to the right individual at the right time. As previous probability decreases, so does the predictive power of a test: more positive tests only mean more false positive results.[2]

Our laboratory manages a blood-drawing service. 2 years ago we did a study to understand our family physicians' prescribing practices. 209 clients were selected casually in the service, to whom thyroid function tests had been prescribed. 86 of them had never had thyroid tests before; 47 admitted no symptom suggestive of thyroid disease, and two-thirds had a request for a complete thyroid package (free tri-iodothyronine, free thyroxine, and thyrotropin). Five of 47 people had positive results, two with raised thyrotropin only (presumably subclinical hypothyroidism), and three with isolated raised free tri-iodothyronine. These last three were followed up; their physicians requested new measurements of free tri-iodothryonine for all of them (one was tested three times to be sure). All further results were lower than the upper reference range.

The obvious conclusion is, when tests that patients do not need are prescribed, the results will only bring trouble. When previous probability of having a disease with abnormal free tri-iodothyronine or free thyroxine is low, as in people with no indication of thyroid disease, physicians should limit themselves to thyrotropin testing only. If previous probability is higher, then patients should be offered all the tests they need, with a skilled interpretation such as that offered by Dayan.

**Pietro Alfonsi, Vincenzo Iannuzzi*

Patologia Clinica 1, Ospedale S Chiara, 38100 Trento, Italy

1 Dayan CM. Interpretation of thyroid function tests. *Lancet* 2001; **357:** 619–24.
2 O'Reilly DS. Thyroid function tests: time for reassessment. *BMJ* 2000; **320:** 1322–24.

## Risk of colorectal cancer after breast cancer

Sir—Craig Newschaffer and colleagues (March 17, p 837)[1] mention that the European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE) "concluded that the risk increase associated with breast-cancer history was similar to that conferred by having a first-degree relative with colorectal cancer". This statement constitutes a misinterpretation of the work of EPAGE.

By use of the RAND appropriateness method,[2] the expert panel assessed the appropriateness of 309 clinical indications for colonoscopy. In a series of 37 indications about screening for colorectal cancer in non-symptomatic patients, the appropriateness of use of colonoscopy was assessed according to four explicit degrees of risk for developing colorectal cancer (baseline, slight, moderate, or high).[3] Slight risk included the following situations: colorectal cancer in one first-degree relative or in two second-degree relatives, adenomatous polyp in one first-degree relative, history of breast, or ovarian or endometrium cancer in the patient or in a first-degree relative. However, the relative increase of the risk of developing colorectal cancer is not thought similar for all these disorders. The rationale for grouping

disorders in four ordinal risk categories was based on estimates of relative risks of developing colorectal cancer. Expansion of the number of risk categories would have increased considerably the number of clinical scenarios.

Furthermore, although the terms and definitions used by EPAGE were reviewed by panel members, they are not formally a result of the panel process. The results consist of the assessment of appropriateness of indications for colonoscopy in 309 clinically specific scenarios by nationally recognised experts, based on published evidence and their clinical judgment. These results can be seen on a dedicated website.[4]

In addition, the non-inclusion of a history of a previous breast cancer in the slight risk category is unlikely to have changed the judgments of appropriateness made by panellists, since they probably referred to other more meaningful situations in this risk category, such as colorectal cancer in relatives. The indications to use colonoscopy for colorectal-cancer screening were most frequently judged inappropriate or uncertain in patients with a slight increased risk for colorectal cancer.

One key feature of quality guidelines is regular updating. The literature review on which EPAGE appropriateness criteria are based is periodically updated; definitions and criteria are modified accordingly and submitted anew to the panel members. The evidence provided by Newschaffer and colleagues will be included in the next update of the literature review.

Finally, the exhaustive guidelines endorsed by at least eight US national societies (including the American Cancer Society and most gastroenterology associations) also mention that a previous breast cancer was deemed a risk factor for subsequent colorectal cancer.[5]

*Bernard Burnand, Jean-Jacques Gonvers, John-Paul Vader, Florian Froehlich

*Institute of Social and Preventive Medicine and Medical Outpatient Clinic, Department of Community Medicine and Community Health, University of Lausanne, Lausanne CH-1005, Switzerland
(e-mail: Bernard.Burnand@inst.hospvd.ch)

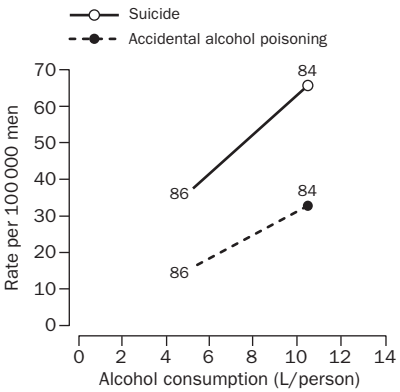
1 Newschaffer CJ, Topham A, Herzberg T, Weiner S, Weinberg DS. Risk of colorectal cancer after breast cancer. *Lancet* 2001; **357:** 837–40.
2 Vader JP, Burnand B, Froehlich F, Dubois RW, Bochud M, Gonvers JJ. The European Panel on Appropriateness of Gastrointestinal Endoscopy (EPAGE): project and methods. *Endoscopy* 1999; **31:** 572–78.
3 Burnand B, Bochud M, Froehlich F, Dubois RW, Vader JP, Gonvers JJ. Appropriateness of colonoscopy: screening for colorectal cancer in asymptomatic individuals. *Endoscopy* 1999; **31:** 673–83.
4 European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE). www.epage.ch
5 Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 1997; **112:** 594–642.

## Changes in life expectancy in Russia

Sir—Vladimir Shkolnikov and colleagues (March 24, p 917)[1] interpret the striking decline in mortality among men and women aged 25–60 years, after the break up of the Soviet Union, as being due to the decrease of 19% in mean alcohol consumption between 1994 and 1998.

We have shown a positive correlation between decreasing alcohol consumption and falling mortality from suicide, violent causes of death, and accidental alcohol poisoning, which supports Shkolnikov and colleagues' interpretation.[2–4] In all 15 republics of the former Soviet Union, suicide rates decline significantly for people aged 15 years and older. For the whole Union of Soviet Socialist Republics (USSR), the decrease was 34·0% (38·8% for men, 17·6% for women) in 1984–88, when a restrictive alcohol policy was introduced. The corresponding proportions for Russia alone were 35·7% (40·2% and 19·1%). Mortality among men from suicide, violent death, and alcohol intoxication were much higher than those among women, but mortality decreased for both sexes.

Alcohol consumption, expressed as L absolute alcohol per person per year, measured by sales statistics (a measure with shortcomings in its method), fell by 40–52% in the Slavic republics and 46–53% in the Baltic republics in 1984–88.[2]




**Suicide and accidental alcohol poisoning rates and consumption of alcohol in Russia in 1984–86**
Rates are per 100 000 population.

Regression analysis with alcohol consumption as the independent variable and suicide rates and violent death rates as dependent variables have revealed that suicide and alcohol consumption were positively correlated, as were violent death and alcohol consumption, in all 15 republics. Mortality due to alcohol intoxication also sharp decreased sharply between 1984 and 1988.

The reliability of statistics on suicide and other violent deaths in the Slavic and Baltic republics of the former USSR has been shown by quantitative and qualitative analyses to be good. Analyses show also that statistical fluctuations during the period studied cannot be explained by systematic changes in the issue of death certificates and encoding of causes of death.[4]

We noted a striking fall in suicide rates for men and women aged 25–54 years. This finding tallies well with those of Shkolnikov and colleagues. This age-group seems to be sensitive to sudden social, economic and labour-market changes, since they are bringing up children and caring for elderly relatives.[5]

However, the influence of social, economic, and political factors, and especially feelings of hope, on this exceptional decrease in suicide and other violent causes of death cannot be excluded. Changes in life expectancy are attributable not only to changes in the frequency of excessive drinking. People consume or abuse alcohol because of their ambient psychosocial conditions. Alcohol can exert a protective effect when consumed in small amounts per week, but is a hazard to health and life when used as a coping mechanism in situations when hope, trust and belief in the future are lacking.

*Danuta Wasserman, Airi Vdmik

*Institute for Psychosocial Medicine, Karolinska Institute; National Swedish Centre for Suicide Research and Prevention of Mental Ill Health, Granits Väg 4, Box 230; 171177 Stockholm, Sweden; and Tartu University, Tallin, Estonia

1 Shkolnikov V, McKee M, Leon DA. Changes in life expectancy in Russia in the mid-1990s. *Lancet* 2001: **357:** 917–21.
2 Wasserman D, Värnik A, Eklund G. Male suicides and alcohol consumption in the former USSR. *Acta Psychiatr Scand* 1994: **89:** 306–13.
3 Värnik A, Wasserman D, Dankowicz M, Eklund G. Marked decrease in suicide among men and women in the former USSR during *perestroika*. *Acta Psychiatr Scand* 1998: **98** (suppl 394)**:** 13–19.
4 Wasserman D, Värnik A. Reliability of statistics on violent death and suicide in the former USSR. *Acta Psychiatr Scand* 1998: **98** (suppl 394)**:** 34–41.
5 Wasserman D, Vdmik A. *Perestroika* in the former USSR: histroy's most effective suicide prevention programme for men. In: Wasserman D, ed. Suicide: an unnecessary death. London: Martin Dunitz, 2001: 253–57.

## The fourth disease, 1900–1881, RIP

Sir—We strongly disagree with Martin Weisse's (Jan 27, p 299) [1] repetition of Powell's proposal that the fourth disease was a toxin-producing staphylococcal infection. We were workers involved in the description of staphylococcal scalded skin syndrome[2] and the work generally thought to disprove the existence of fourth disease.[2]

The existence of the fourth disease was seemingly laid to rest a decade ago, and should have been buried 120 years ago: it never existed.[2] To Weisse's rhetorical question "Is it a separate exanthum [sic]?" we respond with an unequivocal no: fourth disease was not staphylococcal scalded skin syndrome (SSSS) or any staphylococcal syndrome. It was a collection of misdiagnoses of rubella and scarlet fever seen in school outbreaks.[3,4] These misdiagnoses arose because physicians did not fully appreciate the variable and overlapping spectra of childhood exanthems.

We encourage readers who question these carefully researched conclusions to look at reference 3 and its citations, and to consider the following: SSSS (excluding localised bullous impetigo) uncommonly occurs beyond infancy and early childhood because antibody to staphylococcal exfoliative toxin is highly prevalent by then; school outbreaks of SSSS do not occur; most children with SSSS have foci of staphylococcal infection, unlike those with fourth disease; patients with SSSS have more extensive skin loss and denuding than the typically mild flaking described for fourth disease; and deaths from SSSS in otherwise healthy children are almost unheard of, whereas the more than 10% fatality in the scarlet fever-like fourth disease cases was typical of scarlet fever at the time.[3]

Data linking fourth disease to misdiagnosed rubella and scarlet fever are extensive and include the construction, by use of original 1896/1900 line lists, of epidemic curves for fourth disease that were specific for the various predominant characteristics of the observed exanthems.[3] These curves show that most of the 1896 cases Weisse discusses occurred in four cleanly separated epidemic waves, exactly 2 weeks apart—a classic pattern for rubella but unheard of for SSSS. To support SSSS, Weisse emphasises clinical observations, such as one describing tender skin. The attaching of specific meanings to single historically observed symptoms such as skin tenderness or sensitivity is problematic.[3] Rarely noted in fourth disease, skin sensitivity can hardly be taken to be a distinguishing symptom of a pseudosyndrome subsuming at least two other misdiagnosed exanthems, especially since it was also described for scarlet fever.[5]

All remaining clinical issues raised by Weisse were dealt with in the 1991 publication.[3] SSSS is highly inconsistent with many of the key features of fourth disease, but scarlet fever and rubella are not. The weight of evidence is still overwhelming: fourth disease never existed. All cases are explained clinically and epidemiologically by misdiagnosed scarlet fever (described in 1641) or rubella (established in 1881).

*David M Morens, Alan R Katz, Marian E Melish

*National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20815, USA; and John A Burns School of Medicine, University of Hawaii, Honolulu, Hawaii

1 Weisse ME. The fourth disease, 1900-2000. *Lancet* 2001; **357:** 299–301.
2 Melish ME, Glasgow LA. Staphylococcal scalded skin syndrome: the expanded clinical syndrome. *J Pediatr* 1971; **78:** 958–67.
3 Morens DM, Katz AR. The "fourth disease" of childhood: reevaluation of a nonexistent disease. *Am J Epidemiol* 1991; **134:** 628–40.
4 Dukes C. On the confusion of two different diseases under the name of rubella (rose-rash). *Lancet* 1900; **2:** 89–94.
5 Frank J-P. Scarlatine. In: Frank J-P. Traité de médecine-pratique: nouvelle édition—tome premier, genre II. Paris: J-B Baillière, 1842: 250–61.

### *Author's reply*

Sir—David Morens and colleagues state that fourth disease was not SSSS or any staphylococcal syndrome and detail the disorder's inconsistency with the bullous form of SSSS. I agree with several of the distinctions they make between these two syndromes.

The expanded spectrum of SSSS was described in two early reports[1,2] as having several forms, including Ritter's disease, generalised bullous disease in older children (of which the most severe cases were formerly called toxic epidermal necrolysis), bullous impetigo, and staphylococcal scarlet fever. I used the generic term SSSS, since the clinical spectrum of fourth disease spans more than one of these clinical forms. I maintain that there is compelling evidence that fourth disease is most consistent with staphylococcal toxin disease, especially staphylococcal scarlet fever. My panel 3 shows that there are important discrepancies between fourth disease, rubella, and scarlet fever, and many similarities between SSSS and fourth disease.

Morens and colleagues comment that school outbreaks of SSSS are not reported. That staphylococcal scarlet fever (SSF), with or without bullae, can arise in clusters is supported by reports of family outbreaks,[1,3] one of which had a periodicity of 3 weeks between infections,[1] similar to that of fourth disease. Morens and colleagues further state that most children with SSSS have focal infection and fourth disease patients do not. With SSF, the form of SSSS most similar to Dukes' descriptions, focal infection was noted in only one of the 22 cases documented in three reports.[1–3] As opposed to patients with generalised bullous disease, patients with SSF do not have extensive skin loss, but instead have peeling, as is reported with fourth disease. Finally, the toxins and immunology of SSF seem to be different than the generalised bullous form of SSSS,[4] and we can only guess at the seroprevalence of antibodies against the various staphylococcal toxins a century ago.

I agree that interested parties should assess their reference, but I suggest revisiting Dukes' original report in light of arguments I put forward in my report. Not everyone feels that the fourth disease was laid to rest 10 years ago. Students of history can consider the evidence and make up their own minds.

*Martin E Weisse*

Department of Paediatrics, West Virginia University, PO Box 9124, Morgantown, WV 26506, USA

1 Margileth AM. Scalded skin syndrome: diagnosis, differential diagnosis, and management of 42 children. *South Med J* 1975; **68:** 447–54.
2 Melish ME, Glasgow LA. Staphylococcal scalded skin syndrome: the expanded clinical syndrome. *J Pediatr* 1971; **78:** 958–67.
3 Ladhani S, Newsom T. Familial outbreak of staphylococcal scalded skin syndrome. *Pediatr Infect Dis J* 2000; **19:** 578–79.
4 Lina G, Gillet Y, Vandenesch F, Jones ME, Floret D, Etienne J. Toxin involvement in staphylococcal scalded skin syndrome. *Clin Infect Dis* 1997; **25:** 1369–73.

## Context and health outcomes

Sir—Zelda di Blasi and colleagues (March 10, p 757)[1] report on their systematic review of studies in which workers have assessed the effects of doctor-patient interactions on the outcome of care. They show that physicians who adopt a warm, friendly, and reassuring manner are more effective at interacting with patients than those who keep consultations formal and do not offer reassurance.

Di Blasi and colleagues emphasise a triple meaning of the notion of context in medicine. First, because they did a systematic review, through which studies are placed in the context of other relevant research. Second, the investigators broaden the term non-specific effects to context effects, instead of just illuminating the black box of the

physician-patient encounter. A non-specific approach allows many effects and issues to be taken into consideration in such encounters, such as patients' health beliefs, opinions on medicine in general, and on diseases or interventions in particular, as well as the complexity of various sociocultural effects. All these factors contribute to the third meaning, the overall context of medicine.[2]

For many decades, and far beyond, the nature of the effects of interventions in health care have been subject to debate.[3,4] It has been difficult to penetrate as far as the core of this issue. Studies done to assess the application of non-specific interventions in general practice are not available. To investigate how frequently family physicians use non-specific interventions, we did a prevalence study.[5] 48 Flemish family physicians each registered 50 consecutive office encounters; we assessed 2320 consultations. We classified non-specific management as any intervention based on a low degree of certainty of the diagnosis or on a low degree of causality between the diagnosis and the proposed management. Characteristics of doctors, patients, and encounters were collected.

Our data suggest that non-specific interventions were used in 40% of all patients' encounters. We noted that some characteristics of the doctors and patients affected the intervention used. An important predicting variable for non-specific clinical management was related to the encounter—ie, a low degree of certainty about the diagnosis led to non-specific interventions.

Di Blasi and colleagues conclude that context effects, although probably small, can affect outcomes. This finding is encouraging for doctors trying to have positive encounters with their patients. At last this systematic review should be a call for research with good quality methods in primary health care to enable other meta-analyses to be done in the future.

*Etienne Vermeire, Dirk Avonts, Paul Van Royen, Frank Buntinx, Joke Denekens,

*Centrum voor Huisart Sgenceskunde UIA, 2610 Wilrijk, Belgium; University of Antwerp, Belgium; Academic Centre for General Practice, University of Leuven, Belgium; and University of Maastricht, Netherlands
(e-mail: etienne.vermeire@usa.ua.ac.be)

1 Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context effects on health outcomes: a systematic review. *Lancet* 2001; **357:** 757–62.
2 van Weel C. Examination of context of medicine. *Lancet* 2001; **357:** 733.
3 Kienle GS, Kiene H. Placebo effect and placebo concept: a critical methodological and conceptual analysis of reports on the magnitude of the placebo effect. *Alternate Ther Health Med* 1996; **2:** 39–35.
4 Adler HM, Van Buren OH. The doctor patient relationship revisited. *Ann Intern Med* 1973; **78:** 595–99.
5 Vermeire E, Buntinx F, Van der Auwera J-C, Avonts D, Van Royen P, Denekens J. Non-specific interventions of Flemish general practitioners : an analysis. *Huisarts Nu* 2000; **5:** 202–09.

Sir—In their analysis of context on health outcomes, Zelda di Blasi and colleagues[1] note inconsistency in the effects of emotional and congnitive care. This study is important since it shows the limitations of modern science: the confident assumption that the world can be understood by a reduction into its component parts; and the application of rule based methods that assume a linear relation between cause and effect.

The science of complex adaptive systems recognises a world in which events are directed by the non-linear interaction of many parts.[2] This new approach infers a limit to predictability that emphasises the importance of the interaction between agents in a system and not the outcomes of this process. An outcome is seen as something learned, which leads to a decision to take certain actions in the knowledge that such action will generally lead not to an issue being solved, but to a new situation in which the whole interactive process can begin again. Organisational action is never that of the active autonomous individual but always occurs in a relation that people have with each other.

These interactions organise themselves with reference to themselves into emergent processes of relating at the next point in time on the basis of the historically evolved identities without knowing in advance how the system is going to evolve, or even understanding the current system as a whole. The communication is not digital, algorithmic, or processed, but is arranged as narrative and propositional themes that organise the response of those individuals in their being and doing.[3] The focus is on the primacy of the rich interactions, not the outcome.

The unsuccessful application of meta-analysis to the complex non-linear interaction of interpersonal relations reflects the limitations of modern medical science. It is time to move on.

*David Kernick*

St Thomas Health Centre, Cowick Street, Exeter EX4 1HJ, UK

1 Blasi Z, Harkness E, Ernst E, et al. Influence of context effects on health outcomes: a systematic review. *Lancet* 2001; **357:** 757–62.
2 Cilliers P. Complexity and postmodernism. London: Routledge Press, 1998.
3 Stacey R. Strategic management and organisational dynamics: the challenge of complexity. London: Pearson Education, 2000.

## Experiments with insulin

Sir—Making time to read *The Lancet* is an objective I cannot achieve every week, but which is often extremely rewarding when I can. I was so rewarded by the report by E Gale's Feb 3 Commentary.[1]

Gale referred to a paper by Heubner and colleagues,[2] which reminded me of the account of an experiment that I heard of in 1950 when I started work at the Pharmacotherapeutic Laboratory in Amsterdam. The unit had been led by Ernst Laqueur until his death in 1947 (with an intermission during World War II when he had to hide for the German Occupation authorities because of his Jewish descent). The story was told to me by A Kemp, a young technician who had worked for many decades under Laqueur.

Shortly after the first paper by Banting and Best on insulin, Laqueur was visited by Heubner, who had a theory that a satisfactory response from insulin should be possible after sublingual administration, which would avoid the need for injection. Laqueur accepted Heubner's offer to be an experimental subject and Heubner was installed on the sofa in Laqueur's room. A blood sample was taken and given to Kemp to measure the blood glucose, after which insulin was administered under Heubner's tongue.

At that time it took at least 30 min to measure blood sugar concentration. When Kemp came back in the room Heubner was lying on the sofa very quietly, pale and sweating. Kemp rushed to get the syringe filled with glucose solution that had been prepared beforehand just in case of hypoglycaemia. However when Heubner realised what was going to happen he raised his arm to ward off the injection and said with a weak voice "*Nein, nicht spritzen, dies ist viel zu interessant*!" ("No, don't inject, this is much too interesting!"). A blood sample was taken for blood-sugar measurement and the glucose injection was given intravenously. 30 min later, the second blood sugar measurement showed a perfectly normal value, with no indication of hypoglycaemia.

*Jacob van Noordwijk*
Taveernelaan 15, NL-3735 KA, Bosch en Duin, Netherlands

1 Gale EAM. Two cheers for inhaled insulin. *Lancet* 2001; **357:** 324–25.
2 Heubner W, de Jongh SE, Laquer E. Über Inhalation von Insulin. *Klin Wochensch* 1924; **51:** 2342–43.

## DEPARTMENT OF ERROR

*Pulmonary hypersensitivity reaction induced by efavirenz*—In this Research letter by G M N Behrens and colleagues (May 12, p 1503), the dose of efavirenz described in the fourth paragraph, third sentence, should have been 600 mg once daily.