Networks for pain

To the editor — Patrick Wall's *News & Views* discussing the articles on dorsal horn and dorsal column nuclear neurons, and nerve growth factor and the synthetic protein trkA-IgG (*Nature Medicine* 1, 740–741; 1995) suggests that medical information about the brain still lives in the nineteenth century.

When I left the Skin Senses Laboratory in Tallahassee, Florida, in 1971, the hostile schools of Specificists and Spatiotemporal Patternists were a hoary joke; John Paul Nafe, the formal founder of spatiotemporal pattern theory, had died in 1969, while even Ainsley Iggo was admitting that some somatosensory pathways to the brain could be less private than others. Yet Wall is still having to do battle with windmills while exaggerating the case against C fibres, lamina one of the spinal cord, and ventral me-

dial nucleus of thalamus. Surely no neuroscientist any longer doubts the existence of both primary afferent and central neural 'preferences' for conveying nociceptive information, nor of thalamocorticothalamic re-entrant signalling whose possibly noise-enhanced and sometimes almost-periodic oscillatory behaviour may become our "conscious comment" (William James, 1870–80)?

Your readers may require a supreme act of faith before visiting a neurologist, in this, the Decade of the Brain. They should have been taught some thirty years ago that the ventrolateral quadrant maneuvers by neurosurgeons are only transiently effective for the relief of pain because those 'pathways' are not 'private' to sensoriperceptual pain, but just a rather preferential route for nociceptive signalling. The biological nervous

system is a neural network, not a nineteenth century telegraph machine.

HILTON STOWELL

140 C South Jefferson

Milledgeville, Georgia 31061-3420, USA

Wall replies — How much I wish you were right that I fight windmills and that the telegraph machine is no longer an acceptable analogy for a sensory system. However, recent work describing "A thalamic nucleus specific for pain and temperature" (*Nature* 372, 22–29; 1994) presents the nineteenth century triumphant.

PATRICK WALL

United Medical and Dental Schools

St. Thomas's Campus

London, SE1 7EH, UK

Clinical trials: Testing the hypothesis

Holmberg and Baum in their defence of clinical trials as scientific method in medicine invoke Popper and the mandatory requirement for hypothesis testing'. An axiomatic hypothesis of their own is that clinical trials methodology provides the only reliable mechanism by which hypotheses leading to improved medical treatment may be tested. As a corollary, clinical trials confer scientific method on therapeutic medicine and should be the major route of medical progress in areas where they are applied. This hypothesis is testable.

In oncology, progress is recognized to have occurred in specific areas over the last three decades. In 1988 a study funded by the US National Cancer Institute² highlighted four areas in which it was considered that definite clinical progress had been made (bone marrow transplantation, radiotherapy of prostatic carcinoma, treatment of acute lymphoblastic leukaemia, treatment of Wilms' tumour). Other recent examples are treatment of Hodgkin's lymphoma, testicular teratoma, choriocarcinoma and osteosarcoma and the introduction of treatment methodologies or agents (linear

accelerators in radiotherapy, platinum drugs in chemotherapy) recognized as advances. Citation analysis could now be carried out to plot the progress of these innovations and to identify the role played by randomized controlled clinical trials. The null hypothesis is that critical papers catalysing the introduction of superior treatment procedures *do not* depend on the results of rigorously controlled trials.

It is not *a priori* obvious that clinical trials provide the sole route to medical progress. Alternative mechanisms are easily envisaged, including the 'wildfire' route (treatment advances so obviously superior that the new approach 'spreads like wildfire'), multiple incremental upgrade (innumerable small improvements with cumulative benefit) and deductions made on the basis of comparisons with historical data (including case control studies and 'serial audit'). Intuitively, it seems plausible that clinical trials methodology is well suited to identifying small improvements in treating common conditions but is not the optimal search procedure in all clinical situations. Dramatically superior treatments may best be found by multiple parallel searches with reduced emphasis on fine-tuned statistical rigour. Consideration of competing strategies of treatment advance is muted by the present dominance of trials methodology; however, it is not clear that this hegemony is firmly based.

Hypothesis testing may help.

T. E. WHELDON

Departments of Radiation Oncology and Clinical Physics

University of Glasgow and West Glasgow

Hospitals University NHS Trust

CRC Beatson Laboratories

Glasgow G61 1BD, UK

A. BARRETT

Department of Radiation Oncology

University of Glasgow and West Glasgow

Hospitals University NHS Trust

Beatson Oncology Centre

Western Infirmary

Glasgow G11 6NT, UK

Baum & Holmberg reply — It was never our intention to state that the randomized controlled trial was the only method for testing biological hypotheses in clinical medicine. Our commentary was meant to be a robust defence against the constant, hostile and ill-informed criticism against scientific method in clinical medicine.

If you have a condition with a predictable natural history and a therapy which is a spectacular advance, then observational techniques with historical controls may be sufficient and we acknowledge many of the examples cited by Wheldon and Barrett. In contrast, if you have a chronic disease with an unpredictable natural history where