dependency unit might permit improved care and provide an acceptably economic option owing to reduced complications, earlier discharges, and reduced use of intensive care facilities.

A study of substantial proportions is needed to examine this question, which could have major implications for the organisation of postoperative care. The continuing study of the trauma unit at Staffordshire Royal Infirmary has set a precedent for such research. Similar foresight applied to the question of provision of postoperative care might permit a major and widespread advance in a relatively neglected part of the perioperative period.

ALAN M COHEN
Senior registrar

Department of Anaesthetics,
Bristol BS7 9QJ

- 1 Lunn JN. Recovery from anaesthesia. *BMJ* 1994;308:804. (26 March.)
- 2 Association of Anaesthetists of Great Britain and Ireland. *Immediate postanaesthetic recovery*. London: AAGBI, 1993.
- 3 Knill RL. Clinical research in anaesthesia. Past accomplishments and a future horizon. *Anaesthesia* 1990;45:563-5.
- 4 Mangano DT. Perioperative cardiac morbidity. *Anesthesiology* 1990;72:153-84.
- 5 Association of Anaesthetists of Great Britain and Ireland. *The high dependency unit—acute care in the future*. London: AAGBI, 1991.

Arthritis as a complication of intravesical BCG vaccine

EDITOR,—In their editorial on treating superficial bladder cancer with intravesical BCG vaccine¹ Neeraj Sharma and Stephen Prescott do not mention the important, though rare, complication of arthritis.^{2,4} We describe a case of asymmetric oligoarthritis in a patient treated with intravesical BCG vaccine.

After an episode of painless haematuria in April 1992 a 40 year old man was diagnosed as having a moderately differentiated transitional cell carcinoma of the bladder. At cystoscopy all visible tumour was resected. Repeat cystoscopy, however, showed recurrence, with the development of extensive satellite lesions. A six week course of weekly treatment with intravesical BCG vaccine was started in November. The first three instillations were each followed by influenza-like symptoms, which responded to antipyretic agents. After the fourth treatment he developed fever (38°C), bilateral conjunctivitis, periorbital oedema, and arthralgia of the left shoulder. Over the next two days his right fourth toe, right knee, both ankles, and right fourth proximal interphalangeal joint became painful, tender, and swollen.

Laboratory investigations showed a normal full blood count, but the C reactive protein concentration and erythrocyte sedimentation rate were 180 mg/l and 84 mm in the first hour respectively. Blood and urine cultures yielded negative results. A chest x ray film was normal. Isoniazid and prednisolone 30 mg were started. No clinical improvement was observed.

Further serological investigations excluded infective causes of reactive arthritis. A test for rheumatoid factor yielded a negative result and serum uric acid concentration was normal, but he was positive for HLA B-27. The isoniazid was stopped and prednisolone withdrawn, and diclofenac was started. He improved progressively and with regular physiotherapy returned to full mobility within a month.

The incidence of arthralgia after intravesical instillation of BCG vaccine is quoted to be 0.5-1% of treated patients.^{3,4} Bilaterally symmetric polyarthritis affecting the hands, wrists, and knees generally develops a few days to five months after the first instillation.² Further instillations aggravate the arthritis. Laboratory investigations yield non-specific findings, and examination of synovial

fluid or a synovial biopsy specimen does not show infection with the Calmette-Guérin bacillus. Because of the absence of diagnostic tests, attention to the sequence of events in history taking is of paramount importance.

The pathophysiology of this condition is believed to be a reactive immunogenic response to the BCG antigen, the same response that is essential for BCG vaccine's therapeutic effect on the bladder cancer. As immunotherapy with BCG vaccine becomes more commonly used more cases of this new form of reactive arthritis are likely to occur.

MARK DEVLIN
Senior house officer
ATUL DEODHAR
Research registrar
MARTIN DAVIS
Consultant

Duke of Cornwall Rheumatology Unit,
Royal Cornwall Hospital (City),
Truro TR1 2HZ

- 1 Sharma N, Prescott S. BCG vaccine in superficial bladder cancer. *BCG* 1994;308:801-2. (20 March.)
- 2 Goupille P, Soutif D, Valat JP. Arthritis after Calmette-Guérin bacillus immunotherapy for bladder cancer. *J Rheumatol* 1992;19:1825-6.
- 3 Lamm DL, van der Meijden ADPM, Morales A, Brosman AS, Catalona WJ, Herr HW, et al. Incidence and treatment of complications of bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. *J Urol* 1992;147:596-600.
- 4 Torisu M, Miyahara T, Shinohara N, Ohsato K, Sonosaki H. A new side effect of BCG immunotherapy. BCG-induced arthritis in man. *Cancer Immunol Immunother* 1978;5:77-83.

Gangliosides and the Guillain-Barré syndrome

EDITOR,—Various authors criticised our report on Guillain-Barré syndrome after gangliosides.¹ Francesco Grigoletto computed the cases of the syndrome expected by chance alone according to age specific frequencies of therapeutic cycles of gangliosides.² Without defining "therapeutic cycle" he concluded that our 24 cases were equal to the number expected by chance in Italy. However, to obtain this result he considered one month after gangliosides were given as the period at risk, whereas we considered only the first three weeks and excluded cases with later onset. Applied to our three week interval, Grigoletto's calculations yield 17 cases expected by chance, appreciably less than our 25.

J C Sampson and M G Fiori misleadingly state that our 5.6 cases per year "represent a yearly incidence of 0.2/100 000"—but this is a three week incidence, the yearly incidence being 3.5/100 000. They further argue against comparing the incidence of Guillain-Barré syndrome in the normal population with that in patients treated with gangliosides, "that is, patients with neuropathy." However, only two of our cases had received gangliosides—for eight and for 10 days—for "neuropathy," unilateral Bell's palsy, a highly improbable presentation of the syndrome with this time course. These authors speculate that low back and (unilateral) sciatic pain represented initial manifestations of unrecognised Guillain-Barré syndrome, leading to protopathic bias. Ropper and Shahani noted that pain was "invariably bilateral" in Guillain-Barré syndrome³; when it was the presenting symptom, weakness followed within five days, a shorter interval than in our patients. That "several reports have described measurable effects of ganglioside treatment in controlled clinical trials" does not disprove our statement that "no well designed clinical trial has convincingly shown their efficacy."

Marino Massarotti and Rita Matano suggest protopathic bias for patients who "already had clinical manifestations of a paretic condition" and those with pathological signs identifiable "as pathogenic features."⁴ However, paretic conditions were unrelated to our patients' subse-

quent symptoms, and we discussed the low prevalence of prodromal infections in our group.¹ Admittedly, our opinion on the risk to benefit ratio for gangliosides is a personal one, and we are not surprised that Fidia's representatives disagree. Yet our opinion is shared by the German health authorities, who withdrew gangliosides in 1989. Gangliosides have not been marketed in Scandinavia, Britain, or the United States, where drug regulatory standards are more stringent, and the European Committee for Proprietary Medicine Products recommended their suspension. Finally, we would like to reassure Massarotti and Matano that our report on Guillain-Barré syndrome after gangliosides was not intended to disparage the research studies performed at Fidia's laboratories.

GIANLUCA LANDI
Neurologist
ALFONSO CICCONE
Neurologist

Ospedale Policlinico,
20122 Milan,
Italy

ROBERTO D'ALESSANDRO
Neurologist

Policlinico S Orsola
Bologna

BRUNO CURRÒ DOSSI
Neurologist

Ospedale degli Infermi
Rimini

STEFANO RICCI
Neurologist

Ospedale Policlinico
Perugia

ISABELLA LAURA SIMONE
Neurologist

Istituto di Clinica delle Malattie Nervose e Mentali,
Università di Bari,
Bari

- 1 Landi G, D'Alessandro R, Currò Dossi B, Ricci S, Simone IL, Ciccone A. Guillain-Barré syndrome after exogenous gangliosides in Italy. *BMJ* 1993;307:1463-4.
- 2 Grigoletto F. Gangliosides and the Guillain-Barré syndrome: apparent association is a coincidence. *BMJ* 1994;308:653-4. (5 March.)
- 3 Samson JC, Fiori MG. Gangliosides and the Guillain-Barré syndrome: no causal link. *BMJ* 1994;308:653. (5 March.)
- 4 Ropper AH, Shahani BT. Pain in the Guillain-Barré syndrome. *Arch Neurol* 1984;41:511-4.
- 5 Massarotti M, Matano R. Gangliosides and the Guillain Barré syndrome: science supports the use of gangliosides. *BMJ* 1994;308:654. (5 March.)

Insurance against injury in clinical trials

EDITOR,—Recent correspondence has considered the issue of insurance against injury for participants in clinical trials.^{1,2} In the Netherlands many hospitals are not insured against injury that occurs during clinical trials not sponsored by a pharmaceutical company. If a complication occurred the patient's health insurance company might decide that, because the patient had voluntarily consented to a procedure that was not medically necessary, the company need not cover the financial consequences. This is undesirable, especially because legislation to make coverage of research mandatory is expected. To avoid discussions over whether a procedure during a study was done as part of research or for reasons of care I consider it to be mandatory that the research liability insurance policy and the professional liability insurance policy should originate from the same company. A research policy should provide cover for more than liability: it should also cover financial claims after a complication of a procedure that was performed correctly (risk coverage).

As the number of complications that occur during research is unknown, insurance companies are not eager to offer cover. In studies, procedures are often more stringently defined and patients are healthier than is the case in the real world. Perhaps pharmaceutical companies could help in calculating the average risk of a patient incurring injury