only on urinalysis. Of rather more concern, and not considered, is the carcinogenic potential of cyclophosphamide in long term treatment.[3 4]

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[2] Cooperating Clinics of America. A controlled trial of cyclophosphamide in rheumatoid arthritis. *N Engl J Med* 1970;**283**:883-9.
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***We sent a copy of this letter to the authors, who reply below.—ED, *BMJ*.

SIR,—In our article we reported the first three cases of a longer series. In the period 20 October 1981 to March 1983 a total of 11 patients started treatment with cyclophosphamide. All had erosive classic rheumatoid arthritis; eight were seropositive, three were seronegative.

Before the study 11 had received penicillamine, 10 azathioprine, nine gold, six chloroquine, five low dose prednisone, and one levamisole. These drugs were withdrawn either because of side effects or because the patients did not respond to the treatment.

Cyclophosphamide was offered only to those patients who showed severe radiological progression. Informed consent was obtained from all.

Four patients were given methylprednisolone pulse treatment in the initial phase, and three patients took prednisone in a daily dose of 5-10 mg before starting cyclophosphamide. Six patients were given oral cyclophosphamide, 100 mg/day, for one to three months. Otherwise dosage (ranging from 100 to 300 mg every four days) was individual, depending on body weight, side effects (especially leucopenia), and response. Intermittent treatment was continued for three to 20 months.

After a mean of 6·5 months (range two to 13 months) all 11 patients responded to the treatment with a decrease in morning stiffness, articular index,[1] erythrocyte sedimentation rate, haptoglobin, IgG, and thrombocytes and a rise in haemoglobin (table).

Five patients met the American Rheumatism Association criteria for full remission,[2 3] among them the three patients reported. For the remaining six the disease was suppressed but not in remission. The question of remission versus suppression after cyclophosphamide treatment has been discussed elsewhere.[3]

Clinical and serological variables in 11 patients with rheumatoid arthritis before and after treatment with cyclophosphamide

	Before treatment	After treatment
Erythrocyte sedimentation rate (mm in first hour (Westergren))	78	27*
Haemoglobin (g/dl) (normal 11·3-15·0)	11·4	12·2*
Haptoglobin (g/l) (normal 0·3-2·8)	5·1	2·3*
IgG (g/l) (normal 6-13)	14	10*
Leucocytes ($\times 10^9$/l)	5·2	4*
Thrombocytes ($\times 10^8$/l)	360	220*
Articular index (ref 2)	14	4*
Morning stiffness (minutes)	144	22*

*Wilcoxon's test: $p < 0.01$.

Leucopenia occurred in five patients but resolved after the dose was reduced. Cyclophosphamide was stopped in two patients who in a quiet phase of their disease developed severe leucopenia; disease activity was still suppressed after 10 and 12 months, respectively. Nausea on the day of medication and a slight loss of hair both occurred in two patients. None of the patients displayed urinary symptoms including haematuria (urine microscopy is carried out every three weeks for all patients receiving cyclophosphamide).

A reduction of 62-75% was achieved in the three patients who took prednisone. Side effects were not fewer and the response to treatment was not better in those patients who received low dose prednisone or methylprednisolone pulse treatment.

Radiological examination in October 1983 of the three patients reported in our paper showed no progression since the start of cyclophosphamide treatment.

We have found no evidence of cancer in the patients. The risk of developing neoplasia seems to some degree to be dose dependent.[4] Our intermittent regimen is distinguished by the average daily dose (0·7-1·0 mg/kg) being lower than that usually required to achieve suppression of the disease.[5-7]

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[1] Mørk Hansen T, Keiding S, Lilholt Lauritzen S, Mantorpe R, *et al.* Clinical assessment of disease activity in rheumatoid arthritis. *Scand J Rheumatol* 1979;**8**:101-5.
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Postviral neurological syndromes

SIR,—In his leading article Dr Peter O Behan (24 September, p 853) states that epidemic myalgic encephalomyelitis has been recognised for over 50 years, that most patients have increased IgG antibodies to Coxsackie viruses, and that some with chronic symptoms and signs show increases in specific IgM antibodies. Yet in a previous article Dr Behan lists many outbreaks of the syndrome, from 1950 to 1977, affecting over 3500 cases, and states that tests for Coxsackie viruses have always proved negative.[1]

I am interested to know why Coxsackie virus were never detected in those previous epidemics. Does this mean that Coxsackie viruses have in recent years become more virulent to produce a more severe, chronic, and sometimes devastating neurological syndrome than hitherto? If so, there is an urgent need for increased awareness and vigilance among practitioners that the Coxsackie viruses can behave in this way, contrary to the reassuring statements in many up to date medical and virological textbooks. There is as yet no specific treatment for this syndrome, but Ramsay points out there is much evidence that early rest is extremely important in preventing chronic disease.[2] Thus, pending further research, patients with atypical, severe, recurrent or persisting neuropsychiatric symptoms associated with Coxsackie infections should surely be strongly advised to rest completely.

Early recognition may be difficult, as patients' symptoms may fluctuate greatly in the initial stages, and the doctor may "play them down" or, worse still simply not believe them. Routine bedside neurological examination usually gives negative results, but careful palpation over muscles often shows minute, fixed foci of acute tenderness.[2] Furthermore, if the patient is asked to walk a reasonable distance—for example, up several flights of stairs or round the hospital grounds—abnormalities of gait may become increasingly apparent and may be accompanied by emotional lability of organic type. With respect to diagnosis, how sensitive, specific, and reliable is the IgM antibody test, and would Dr Behan recommend its routine use serially to predict those patients at particular risk of developing a chronic syndrome?

Finally, could this apparently new behaviour of the Coxsackie virus be an artefact, due, say, to better laboratory techniques, and are the cases being picked up in Glasgow and Oxford a local phenomenon, or have such cases been described recently in other countries? Or is there some other explanation as to why Coxsackie viruses were never detected in the epidemics Dr Behan describes in his 1980 article?

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[1] Behan PO. Epidemic myalgic encephalomyelitis. *The Practitioner* 1980;**224**:805-7.
[2] Ramsay AM. *Myalgic encephalomyelitis: a baffling syndrome with a tragic aftermath.* Stanford-le-Hope, Essex: Myalgic Encephalomyelitis Association, 1982.

***We sent a copy of this letter to Dr Behan, who replies below.—ED, *BMJ*.

SIR,—Dr Hughson raises important points concerning myalgic encephalitis. The tests we used to detect IgG antibodies to Coxsackie viruses were not available at the time of the previous outbreaks. They were introduced in Glasgow in 1966 and are simplified microneutralisation procedures, now used routinely in the detection of antibodies to all six types of group B virus.

Samples from the London outbreak are still held and it will be important to test them using this technique, together with the enzyme-linked immunosorbent assay method for detecting IgM Coxsackie antibodies. It is still too early to know how specific, sensitive, and reliable the enzyme-linked immunosorbent assay test is. In children it is probably specific for Coxsackie virus antibodies, but in adults cross reactivity between enteroviruses may be a problem. We need further experience with this test before drawing any firm conclusions. Our studies of large numbers of patients, however, using the neutralisation test for IgG antibodies and the enzyme-linked immuno-