median nerve) with lesions of the proximal segments (F-wave latency 62-ms on stimulating the tibial nerve at the ankle). There was a pronounced and widespread axonal degeneration, reflected in the small amplitude of the muscle and nerve potentials in nerve conduction velocity studies, and profuse fibrillations or positive sharp waves in muscles at rest on the electromyogram. These findings were compatible with a polyneuritis with severe axonal loss. Subsequent progress has been disappointingly slow, and the patient has been confined to a wheelchair for eight months since the onset.

### Comment

The initial gastrointestinal illness with bloody stools suggested a *Campylobacter* infection; this was confirmed by the high antibody titre and by stool culture, which grew a *Campylobacter* species at high temperatures to identify it as one of the *C coli/C jejuni* group. The subsequent neurological illness was consistent with a clinical diagnosis of the Guillain-Barré syndrome.[1] Though this syndrome may follow a gastrointestinal illness[1 2] an organism is rarely isolated from the stools, though a *Salmonella* species was found in two cases.[3 4] Sixteen cases of Guillain-Barré syndrome occurred after an outbreak of water pollution, in which 5000 people had diarrhoea but no definite causative organism was found.[5] So far as we are aware no case has been reported after *Campylobacter* infection. In our patient the Guillain-Barré syndrome occurred two weeks after the initial infection. This interval is similar to that seen after other gastrointestinal illnesses and suggests that the Guillain-Barré syndrome was triggered by the infection. There is no report of this syndrome occurring with any of the drugs he had received. Since *Campylobacter* infections have been recognised only in recent years, and the organism may be difficult to isolate from the stools, previous cases of *Campylobacter* infection associated with the Guillain-Barré syndrome may have been missed. Serum antibody titres to *Campylobacter* may help to resolve this in future cases of the Guillain-Barré syndrome associated with a gastrointestinal illness.


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# Acquired inhibitor to human factor VIII associated with paraproteinaemia and subsequent development of chronic lymphatic leukaemia

Apparently benign paraproteinaemia is relatively common in the elderly, with a 3% incidence in those over 70 and 12% in those over 80.[1] It is sometimes associated with subsequent development of B-cell lymphoid neoplasm. Acquired inhibitors to factor VIII associated with paraproteinaemia have also been noted in otherwise healthy people (often elderly), in autoimmune diseases, particularly systemic lupus erythematosus, post partum, and in various malignancies.[2]

We describe a case in which a factor VIII inhibitor appeared five years after a paraprotein was noted and in which chronic lymphatic leukaemia developed eight years later.

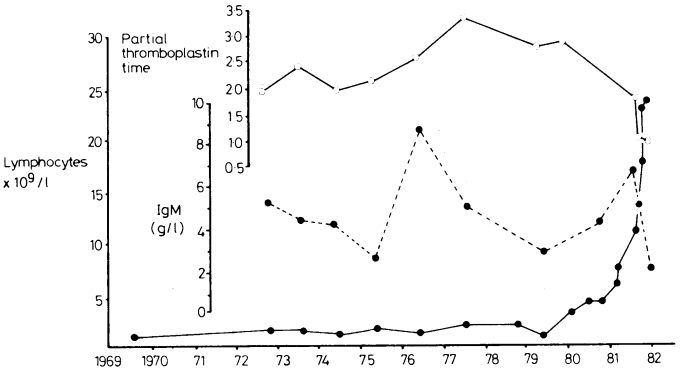
### Case report

A 66-year-old woman presented with bronchial asthma which was eventually controlled with prednisolone 5 mg daily. Incidental findings were a raised erythrocyte sedimentation rate and an IgM paraprotein band. Total IgM was only moderately raised, IgA and IgG values were normal, and no urinary Bence Jones protein was present. Blood count showed 14% eosinophils but was otherwise normal.

Five years later the patient presented with haematuria followed three weeks later by extensive soft-tissue haemorrhage in both arms after minor trauma. Investigations showed partial thromboplastin time 99 s (control 52 s) and whole-blood clotting time 37 min (normal 4-9 min). Prothrombin time, bleeding time, thrombin time, platelet count, and fibrin degradation products were normal. Full blood count showed a normochromic normocytic anaemia, haemoglobin concentration 10 g/dl, white cell count $15 \times 10^9$/l (98% neutrophils, 2% lymphocytes), and a normal platelet count. Factor VIII was undetectable and high-titre inhibitor to factor VIII was present. Antinuclear factor titre was positive at 1/100, $C^4$ concentration was reduced, LE cells were not detected, and all immunoglobulin values had fallen compared with before (IgM 2·9 g/l, IgA 0·6 g/l, IgG 4·2 g/l). (DNA binding was not tested initially but was subsequently found to be normal.

Prednisolone 30 mg daily produced no improvement. Cyclophosphamide was added but discontinued after two months as bruising and bleeding persisted. Between 1973 and 1978 prednisolone 2·5 mg daily was continued for her asthma. Her course was punctuated by recurrent haemarthroses, haematomas, epistaxes, and on one occasion by life-threatening retropharyngeal bleeding, which responded to intensive plasmapheresis and cryoprecipitate treatment.

In 1979 herpes zoster developed, followed by widespread varicella. The blood count was normal, haemoglobin concentration 13·0 g/dl, white cell count $7{\cdot}4 \times 10^9$/l (76% neutrophils, 16% lymphocytes, 8% monocytes), and platelet count $270 \times 10^9$/l. Analysis of the surface membrane showed a normal total lymphocyte count with normal proportions of T and B lymphocytes and no evidence of monoclonal expansion, but there was gross impairment of lymphocyte transformation in response to pokeweed mitogen and phytohaemagglutinin. The lymphocyte count rose exponentially from 1980 and results of surface-marker analysis in 1981 were typical of chronic lymphatic leukaemia,[3] showing monoclonal expansion of B cells bearing IgM and IgD surface immunoglobulins with lambda light chains and rosette formation with mouse erythrocytes. The total IgM concentration had fallen to 2·0 g/l, the IgA value remained low at 0·25 g/l, and IgG was normal at 7·85 g/l. There had been no bleeding episodes since August 1980, the partial thromboplastin time was normal, and no factor VIII inhibitor was detectable. At no time was lymphadenopathy, splenomegaly, or other clinical features of chronic lymphatic leukaemia present. The chart shows the changes in lymphocyte count, IgM concentration, and partial thromboplastin time during 1969 to 1982.




Changes in lymphocyte count (●——●), IgM concentration (●- - - -●), and partial thromboplastin time (○ —— ○) during 1969-82.

### Comment

Acquired factor VIII inhibitor has been reported in association with non-Hodgkin's lymphoma[4] and myeloma[5] but not with chronic lymphatic leukaemia. In our patient the temporal sequence was reversed; overt chronic lymphatic leukaemia occurred many years after the presenting illness and its appearance seemed to parallel an improvement in her coagulopathy.

The relation between the various immune phenomena are intriguing and the question remains whether the monoclonal IgM, presence of autoantibodies, and impaired lymphocyte transformation represented early signs of occult chronic lymphatic leukaemia or whether their presence in some way predisposed to the eventual emergence of a clone of malignant lymphocytes. This case demonstrates well the prolonged time course and variability of B-cell malignancy and its associated phenomena.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# Serum and cyst concentrations of mebendazole and flubendazole in hydatid disease

Since Bekhti *et al*[1] described the successful treatment of four patients with hydatid cysts by mebendazole there have been many other reports of its successful use, but widespread scepticism remains. Several months often elapse before there is any noticeable improvement in patients, and doses of up to 200 mg/kg have been used. Serious side effects are rare, though haemopoietic depression and transient rise of transaminase activities have occurred, and fever is relatively common in the first few days of treatment.[2] Osborne[3] could not detect mebendazole in venous blood or cyst fluid of his patient; Bryceson,[4] however, reported serum concentrations of 20-160 μg/l. We measured mebendazole concentration in the serum of seven patients and from the fluid of six cysts (five patients).

## Patients, methods, and results

Seven patients with active hydatid disease were studied; all were being treated with mebendazole 50 mg/kg/day in divided doses, and five were undergoing elective surgery. It has been recommended that mebendazole is taken with meals, as concomitant fat ingestion may improve its poor absorption. In the two patients not undergoing operation the last dose of mebendazole was given with food; in the remaining patients the last dose before sampling was given before operation without food. All patients had been treated for one week before sampling. Samples of serum and cyst fluid were taken four hours after drug ingestion (during operation in five patients undergoing surgery). The serum and cyst fluid was frozen and transported to Belgium for measurement of drug concentrations. The technique used antibody to mebendazole produced in rabbits by repeated injection of the mebendazole derivative chemically coupled to bovine serum albumin.[5] This method allows assay of plasma concentrations of mebendazole as low as 100 ng/l. Serum concentrations were mostly between 10 and 20 μg/l, and cyst concentrations were even lower, on average being below 1 μg/l (see table).

*Serum and cyst concentrations of mebendazole in seven patients studied*

| Case No | Site of cyst | Serum concentration (μg/l) | Cyst concentration (μg/l) |
|---|---|---|---|
| 1 | Hepatic | 37·2 | 0·7 |
| 2 | Hepatic | 14·5 | 0·4, 0·7 |
| 3 | Hepatic | 13·7 | |
| 4 | Hepatic | 25·8 | |
| 5 | Hepatic* | 84 | 14·5 |
| 6 | Splenic | 9·9 | 1·6 |
| 7 | Pulmonary | 13·4 | 1·2 |

*Non-paracytic cyst.

One patient (case No 5) with very high serum and cyst concentrations in fact had a simple hepatic cyst that was misdiagnosed as a hydatid.

Flubendazole is a related benzimidazole compound that is available as a sterile suspension and thus would seem to have an advantage over oral mebendazole, which is extremely insoluble and is thus poorly absorbed. This suspension was administered subcutaneously to 10 white female rats at 100 mg/kg/day at various intervals. The rats were exsanguinated four hours after dose, and flubendazole concentrations measured using technique as described for mebendazole. At one week a concentration of only 2·2 μg/l was achieved rising to 6·4 μg/l after two weeks, 13·4 μg/l after three, and 12·4 μg/l after four. The gradual rise in flubendazole concentration is due to the slow release of the drug from the injected suspension, which is known to occur over at least five days. This is considerably different from the pharmacokinetics of orally administered mebendazole, the half life of which is around four hours.

## Comment

Though this is a small study, the serum concentrations of flubendazole achieved are not encouraging. The use of subcutaneous or intramuscular flubendazole in man would seem unlikely to offer an improvement over the use of oral mebendazole. Mebendazole penetrates large hepatic and pulmonary cysts in man, though in very small quantities. An improved formulation of these compounds that could provide higher serum and cyst concentrations is at present under active investigation.

We are grateful to Mr L D Abrams, Professor P Bevan, Mr V Brookes, Mr J G Gray, Mr D J Oakland, Mr H B Ross, and Dr J Wood for allowing us to study their patients. We also acknowledge the help of Dr J Heykants and his colleagues (Janssen, Beerse, Belgium) who assayed the samples.

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# Localised chondrocalcinosis in unstable joints

Deposition of calcium pyrophosphate dihydrate crystals in articular cartilage (chondrocalcinosis) is a common, age-related phenomenon. Although a few cases are familial and some are caused by metabolic disorders such as hyperparathyroidism, most are sporadic, idiopathic cases in the elderly.[1] Deposits may be asymptomatic but are commonly associated with attacks of crystal synovitis (pseudogout) or chronic joint damage (pyrophosphate arthropathy).[2]

The causes of sporadic chondrocalcinosis are unknown and the nature of its association with arthritis unclear. It is widely believed that a generalised abnormality predisposes to crystal deposition and that the crystals then cause the joint disease.[3] We describe four patients who developed localised chondrocalcinosis in previously damaged, unstable joints.

## Case reports

*Case 1*—A 37-year-old woman had injured her left knee, rupturing the anterior cruciate ligament, when aged 16. From the age of 28 she had suffered repeated attacks of synovitis of the left knee. The synovial fluid contained numerous crystals typical of calcium pyrophosphate dihydrate on polarised light microscopy, and a radiographic joint survey showed linear chondrocalcinosis in the menisci of the left knee. There was no family history of arthritis, and metabolic screening for the known associations of chondrocalcinosis yielded negative results.

*Case 2*—A 48-year-old man with peroneal muscular atrophy, causing instability of the ankles, presented with acute synovitis of his right ankle. Synovial fluid was aspirated and contained pyrophosphate crystals. Radiographic screening showed chondrocalcinosis in both ankles and mid-tarsal joints but nowhere else. His other joints remained clinically normal; there was no family history of arthritis and no metabolic abnormality to account for the chrondrocalcinosis.

*Case 3*—A 36-year-old woman presented with pain at the base of her