of treatment. We suggest that more attention should be directed to evaluating new or old anticonvulsants in newly diagnosed untreated patients.

Finally, our results may have been influenced by the relative lack of associated neuropsychiatric handicaps (table I), which have been shown to be associated with a generally poorer prognosis.[11] On the other hand, although we excluded patients with obviously progressive neurological diseases, our patients are typical of those referred to a neurological clinic and representative of most adult epileptic patients. Further studies of this type should certainly be undertaken in a more brain-damaged population and also in children, in whom epilepsy is so common.

Whether those patients who continue to have seizures despite an optimum blood concentration of one drug will be improved by the addition of another drug is still uncertain. We have not observed any further improvement in the few patients who failed on a single drug but the numbers were too small to draw firm conclusions. In our retrospective study of chronic patients,[6] however, the addition of a second drug was not usually associated with improved control, but when control did improve it was usually associated with an optimum blood level of one of the drugs. It is at least possible, therefore, that polypharmacy is totally unnecessary and we may have to adjust to the idea that some patients will continue to have attacks with one drug instead of continuing to have them, as is usually the case, with multiple drugs. Only further studies will clarify this.

We conclude from our two prospective trials and retrospective study that there is now considerable potential for improving the quality and results of treatment of epileptic patients. In the population we studied polypharmacy appears to be largely unnecessary and most patients can be satisfactorily treated from the beginning with one drug, assisted by blood level monitoring. An added advantage of this policy will be the associated reduction in chronic toxicity and economic costs.

We thank Mr L Vydelingum and Mr M Laundy for the anticonvulsant drug measurements; Miss V Jessop for secretarial help; and the Medical Research Council, Parke Davis, and Ciba Geigy for financial assistance.

Requests for reprints should be addressed to Dr E H Reynolds, University Department of Neurology, Institute of Psychiatry, De Crespigny Park, London SE5.

References

1 Guelen, P J M, Van der Kleijn, E, and Woudstra, U, in *Clinical Pharmacology of Antiepileptic Drugs*, ed H Schneider, *et al*, p 2. Berlin, Springer-Verlag, 1975.
2 Reynolds, E H, *Epilepsia*, 1975, **16**, 319.
3 Sherwin, A L, Robb, J, and Lechter, M, *Archives of Neurology*, 1973, **28**, 178.
4 Lund, L, *Archives of Neurology*, 1974, **31**, 289.
5 Reynolds, E H, Chadwick, D, and Galbraith, A W, *Lancet*, 1976, **1**, 923.
6 Shorvon, S D, and Reynolds, E H, *British Medical Journal*, 1977, **1**, 1635.
7 Kupferberg, H J, *Clinica Chimica Acta*, 1970, **29**, 283.
8 Toseland, P A, Grove, J, and Berry, D J, *Clinica Chimica Acta*, 1972, **38**, 321.
9 Bird, C A K, *et al*, *British Journal of Psychiatry*, 1966, **112**, 737.
10 Simonsen, N, *et al*, *Epilepsia*, 1976, **17**, 169.
11 Rodin, E A, *Prognosis in Epilepsy*. Springfield, Illinois, C C Thomas, 1968.
12 Woodbury, D M, Penry, J K, and Schmidt, R P, (editors), *Antiepileptic Drugs*. New York, Raven Press, 1972.
13 Richens, A, *Drug Treatment of Epilepsy*. London, Henry Kimpton, 1976.
14 Coatsworth, J J, *NINDS Monograph*, No 12, 1971.
15 Gowers, W R, *Epilepsy and Other Chronic Convulsive Disorders*. London, Churchill, 1901.

(*Accepted 21 December 1977*)

Cellular hyperviscosity as a cause of neurological symptoms in leukaemia

F E PRESTON, R J SOKOL, J S LILLEYMAN, D A WINFIELD, E K BLACKBURN

British Medical Journal, 1978, **1**, 476-478

Summary

Six patients with various forms of leukaemia had neurological signs and symptoms associated with an extremely high white blood cell count and increased whole blood (but not plasma) viscosity. All were treated by leucapheresis with an Aminco Celltrifuge. Rapid and complete reversal of all symptoms occurred in three patients and partial recovery in one. One patient died shortly after leucapheresis and another (from cerebral intravascular coagulation) two days later.

It is concluded that a cellular hyperviscosity syndrome may cause neurological dysfunction in patients with extremely high white cell counts, and that leucapheresis, in carefully selected patients, can be an effective method of treatment.

University Department of Haematology, Royal Infirmary, Sheffield S6 3DA
F E PRESTON, MD, MRCPATH, consultant haematologist
J S LILLEYMAN, MB, MRCP, consultant haematologist
E K BLACKBURN, MD, FRCPATH, professor associate

Regional Blood Transfusion Centre, Sheffield
R J SOKOL, MB, MRCPATH, deputy director and consultant

Department of Haematology, Derbyshire Royal Infirmary, Derby
D A WINFIELD, MRCP, MRCPATH, consultant haematologist

Introduction

The hyperviscosity syndrome is a symptom complex of neurological dysfunction, visual disturbances, and a haemorrhagic tendency caused by increased blood viscosity. It is classically associated with Waldenström's macroglobulinaemia, and is a more recently recognised complication of myelomatosis—in both cases the symptoms resulting from increased plasma viscosity produced by the abnormal circulating paraprotein.[1 2] Generally, however, the packed cell volume is the most important factor affecting blood viscosity, and the symptoms resulting from abnormal viscosity in polycythaemia vera are well recognised. Though white blood cells on the other hand normally contribute little to whole blood viscosity, patients with leukaemia may develop the hyperviscosity syndrome as a direct consequence of a grossly raised white blood cell count. We report studies on six patients and the results of treating them with leucapheresis.

Patients and methods

The six patients, seen by us between November 1976 and March 1977, had various forms of leukaemia—chronic lymphocytic (CLL) in three cases and myelogenous in three (one each of acute myeloblastic (AML), chronic granulocytic (CGL), and transformed chronic granulocytic leukaemia). They presented with the same clinical features as patients with the hyperviscosity syndrome of the paraproteinaemias, including profound lethargy, unsteady gait, visual disturbances, and coma; two patients also had bilateral retinal haemorrhages not associated with profound thrombocytopenia or a coagulation abnormality (see table). Three patients complained of bilateral hearing loss which preceded coma by 48 hours in one case. Apart from the retinal haemorrhages, none displayed clinical evidence of a generalised bleeding tendency.

VISCOSITY AND MEAN WHITE CELL VOLUME

Whole blood viscosity was measured with a Wells-Brookfield microviscometer at two rates of shear, 23 and 230 s^{-1}—23 s^{-1} being thought to reflect conditions in large vessels and 230 s^{-1} conditions in capillaries. To eliminate the effect of the packed cell volume (PCV) on serially measured blood viscosities, we converted results to a PCV of 0·45.

Since the patients had extremely high white cell counts (WCC) the mean white cell volume (MWCV) could be calculated from the formula

$$\frac{\text{PWCV}}{\text{WCC}\ (10^9/l)} \times 10^6 fl(\mu m^3),$$ where PWCV = packed white cell volume.

Results of viscosity studies

The viscosity of the whole blood, but not plasma, measured at both rates of shear, was increased in all six patients. Serial measurements (fig 1) show that for a given increment in white cell count there is a significantly greater increase in whole blood viscosity in the patients with myeloid leukaemias than in those with lymphoid leukaemias. The MWCVs were 180-337 fl in the patients with lymphoid leukaemias and 731-923 fl in the patients with myeloid leukaemias.

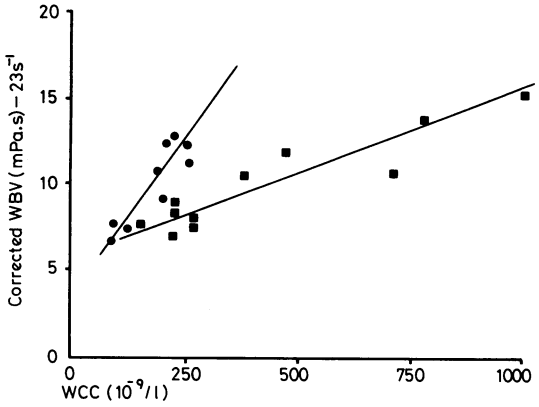

FIG 1—Relationship between PRCV-corrected whole blood viscosity and total white cell count obtained by multiple sampling in patients with acute myelogenous leukaemia (●) and chronic lymphocytic leukaemia (■).

Treatment

All patients were treated by leucapheresis with an Aminco continuous-flow blood cell separator, heparin being used as anticoagulant and dextran 150 to facilitate leucocyte separation.

CLINICAL RESPONSES

Clinical responses were excellent in three patients, satisfactory in one, and poor in two. One patient (case 3) who had been extremely lethargic and drowsy before leucapheresis was discharged symptom-free two days later. Another (case 5) could hear normal speech after treatment, whereas she had been almost stone deaf before; and a third (case 4) recovered normal gait 24 hours after leucapheresis and no longer complained of recurrent blurring of vision. There was no improvement in the auditory acuity of the fourth patient (case 5), but her gait, which had been definitely ataxic, returned to normal two days later. Two patients died after leucapheresis. One (case 1) was comatose when treated and died shortly afterwards without recovering consciousness; although leucapheresis greatly reduced her whole blood viscosity, it did not restore it to normal. The general condition of the other patient (case 2) improved for about 18 hours after leucapheresis, but he then rapidly lost consciousness and died shortly after starting chemotherapy. Just before his death there was haematological evidence of intravascular coagulation, which was confirmed by histological examination of the brain. This complication of chemotherapy in acute leukaemia is attributed to the release of thromboplasmins from damaged blast cells.[3]

HAEMATOLOGICAL RESPONSES

Leucapheresis led to a considerable fall in the total white cell count of all patients, accompanied by a parallel reduction in blood viscosity (fig 2). The white cell harvest data showed that 108-494 $\times 10^{10}$ white cells were removed from each patient.

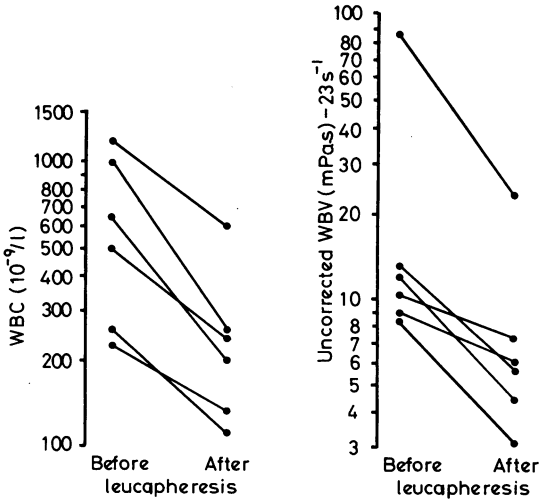

FIG 2—Effect of leucapheresis on total white cell count and whole blood viscosity in patients with leukaemia.

Clinical and haematological features of six patients with leukaemia and the hyperviscosity syndrome before leucapheresis

Case No	Age and Sex	Diagnosis	Presenting features	Hb (g/dl)	WBC (10^9/l)	Platelets (10^9/l)	WBV(mPa.s)—230s^{-1}		WBV(mPa.s)—23s^{-1}	
							Uncorrected	PCV-corrected (normal <4.0)	Uncorrected	PCV-corrected (normal <7·0)
1	43 F	CGL	Unsteady gait, deafness, coma	8·2	1288	90	>10·0	>10·0	85·0	>85·0
2	39 M	AML	Profound lethargy, headaches	6·6	260	95	5·9	7·5	8·4	12·3
3	23 M	Transformed CGL	Drowsiness, profound lethargy, headaches	9·1	233	71	7·0	8·0	10·5	12·7
4	55 M	CLL	Blurring of vision, unsteady gait	10·5	500	110	5·8	6·6	9·9	11·7
5	70 F	CLL	Bilateral deafness, profound lethargy	11·1	647	74	6·4	6·8	9·0	10·1
6	83 F	CLL	Bilateral deafness, unsteady gait	8·4	1000	45	8·5	9·5	12·3	14·6

Discussion

Although white blood cells normally make little contribution to the viscosity of the blood, it has been suggested that granulocytes have a greater effect on it than whole blood viscosity measurements indicate.[4] Increased concentrations of white cells moreover may greatly influence the viscosity of packed red cells.[5] Several workers have shown the high intrinsic viscosity of white blood cells,[5 6] and it has been suggested that some of the clinical features of chronic granulocytic leukaemia may result from the effects on viscosity of the increased white cell mass.[7] Our data suggest that this may be true of several morphological types of leukaemia.

Neurological symptoms are not uncommon in patients with leukaemia. They can be produced by leukaemic infiltration into the central nervous system and haemorrhage, and some are accentuated by the electrolyte imbalance found particularly in acute myeloblastic leukaemia and the blast crisis of chronic granulocytic leukaemia. Nevertheless, our patients showed clinical features that were identical, apart from the absence of severe haemorrhage, with those that are common in Waldenström's macroglobinaemia, including auditory and visual disturbances, abnormalities of gait, and alterations of consciousness. The fact that leucapheresis could rapidly abolish them is evidence that in leukaemia also these symptoms and signs may be explained solely by increased blood viscosity; and indeed the clinical responses, excellent in three cases and partial in a fourth, were associated with appreciable falls in total white blood count and whole blood viscosity.

Neurological symptoms seemed to occur at lower white cell counts in patients with myeloid leukaemias, and we found that a given increment in the white cell count of these patients produced a greater rise in blood viscosity than a similar increase in lymphocytes. Cell size is almost certainly an important factor, though probably not the only one; and the MWCVs were indeed appreciably greater in the myelogenous than the lymphoid group.

Leucapheresis is an extremely effective method for removing large numbers of circulating white cells and therefore alleviates the symptoms caused by the associated hyperviscosity. As it is not a procedure without hazard, patients should be carefully selected.

References

1 Fahey, J L, Barth, W F, and Solomon, A, *Journal of the American Medical Association*, 1965, **192**, 464.
2 Tuddenham, E G D, *et al*, *British Journal of Haematology*, 1974, **27**, 65.
3 Leavey, R A, Benham, K S, and Brodsky, I, *Cancer*, 1970, **26**, 142.
4 Adell, R, Skalag, R, and Braemash, P I, *Blut*, 1970, **21**, 91.
5 Dintenfass, L, *Experimental and Molecular Pathology*, 1965, **4**, 597.
6 Palmer, A A, *Quarterly Journal of Experimental Physiology*, 1959, **44**, 149.
7 Wintrobe, M M, *Clinical Haematology*, 7th edn. Philadelphia, Lea and Feburger, 1974.

(*Accepted 20 October 1977*)

SHORT REPORTS

Mycoplasmal (ureaplasma) septic arthritis in hypogammaglobulinaemia

Patients with primary hypogammaglobulinaemia commonly suffer from bacterial infections of the respiratory tract and occasionally develop bacterial meningitis or arthritis. They also tend to develop atypical and chronic *Mycoplasma pneumoniae* lung infections,[1] although no other organs have previously seemed to be susceptible. We describe here the isolation of mycoplasmas of the species *Ureaplasma urealyticum* from the septic joint of a patient with primary hypogammaglobulinaemia.

Results of immunological and microbiological investigations

Investigations	Results
Immunology	
White blood count ($\times 10^{-9}$/l)	9
Lymphocytes ($\times 10^{-9}$/l)	1·365
Polymorphs ($\times 10^{-9}$/l)	6·188
B lymphocytes (surface Ig)	Absent
T lymphocytes (E rosettes) (%)	66
Lymphocyte transformation (phytohaemagglutinin)	Normal
Dinitrochlorobenzene contact sensitivity	Positive
IgG (g/l)	3
IgA (g/l)	<0·02
IgM (g/l)	<0·10
Microbiology	
No of ureaplasmas isolated (in urea-containing medium[5])*:	
Synovial fluid:	
16 April	?
19 April†	10/0·2 ml
21 April	$\geqslant 10^3$/0·2 ml
Throat swab:	
20 April	$\geqslant 10^3$
24 May	10^4
16 September	10^3

*All were sensitive to $\geqslant$0·1 mg/l of rolitetracycline, doxycycline, minocycline, and spectinomycin and were resistant to $\leqslant$250 mg/l of erythromycin, gentamicin, streptomycin, and clindamycin.
†Specimen frozen before testing.

Case report

The patient, a dental student born in 1957, had no relevant family history. Hypogammaglobulinaemia was diagnosed at 3 years of age after some chest infections the preceding year. He received weekly gammaglobulin injections and remained in relatively good health until he was 14, when he developed a painful swollen right ankle after a sprain. Resolution took 12 weeks and left a fibrous arthrodesis despite treatment with penicillin, cloxacillin, kanamycin, and co-trimoxazole. He remained well until, at the age of 18, he developed a painful swollen left knee after a fall. Operation showed a torn medial meniscus and generalised synovial inflammation. Fever and a large knee joint effusion developed postoperatively. Fluid from the joint was purulent but no bacteria were grown. He was given oral tetracycline and cloxacillin and discharged in a plaster cast 10 days later when apyrexial. A few days afterwards he was readmitted with fever and swelling of the knee, and "sterile" purulent fluid was again aspirated. Gentamicin, carbenicillin, and cloxacillin were given intravenously for the next two weeks without effect.

After referral to Northwick Park Hospital ureaplasmas were sought for the first time and found in three separate joint aspirates (see table). The organisms were sensitive to tetracycline. Intravenous rolitetracycline (350 mg 12 hourly) was started and the joint was continuously aspirated via a Redivac vacuum drain for five days. He became apyrexial within 24 hours and his knee became less painful. A two-month course of oral doxycycline (200 mg three times a day) was substituted two weeks later and the patient was discharged nine weeks after the initial injury. Three months later he was walking without aids.

Comment

We know of only one other case of hypogammaglobulinaemia in which a ureaplasma was isolated from a septic joint (M Stukey *et al*, personal communication). The origin of infection in our patient was probably the throat (see table), and the arthritis four years earlier was probably caused by a similar organism. It is curious that the throat organisms persisted despite their known in-vitro sensitivity to tetracyclines. This is in contrast to the ease of eliminating ureaplasmas from the genital tract but in keeping with the difficulty experienced with *M pneumoniae* infections of the respiratory tract.[2]

The organisms isolated from this patient were probably not laboratory contaminants because they were found in synovial fluids on three occasions. They were strains of *U urealyticum* since they caused colour changes only in medium containing urea, produced characteristically small colonies on agar medium; were sensitive to