- 5 Jacobs S, Ostfeld A. An epidemiological review of the mortality of bereavement. *Psychosom Med* 1977;39:344-57.
- 6 Clayton P. Mortality and morbidity in the first year of widowhood. *Arch Gen Psychiatry* 1974;30:747-50.
- 7 Gerber I, Wiener A, Battin D, Arkin AM. Brief therapy to the aged bereaved. In: Schoenberg B, Gerber I, Wiener A, Kutscher AH, Peretz D, Carr AC, eds. *Bereavement: its psychosocial aspects*. New York: Columbia University Press, 1975:310-33.
- 8 Ward AWM. Mortality of bereavement. *Br Med J* 1976;i:700-2.
- 9 McNeill DN. *Mortality among the widowed in Connecticut*. Yale University: New Haven MPH essay, 1973.
- 10 Niemi T. The mortality of male old-age pensioners following spouse's death. *Scand J Soc Med* 1979;7:115-7.
- 11 Young M, Benjamin B, Wallis C. The mortality of widowers. *Lancet* 1963;ii:454-6.
- 12 Rees WD, Lutkins SG. Mortality of bereavement. *Br Med J* 1967;iv:13-6.
- 13 Parkes CM, Benjamin B, Fitzgerald RG. Broken heart: A statistical study of increased mortality among widowers. *Br Med J* 1969;i:740-3.
- 14 Bowling A, Benjamin B. Mortality after bereavement: a follow-up study of a sample of elderly widowed people. *Biology and Society* 1985;2:197-203.
- 15 Helsing KJ, Szklo M. Mortality after bereavement. *Am J Epidemiol* 1981;114:41-52.
- 16 Cox PR, Ford JR. The mortality of widows shortly after widowhood. *Lancet* 1964;i:163-4.
- 17 Kraus AS, Lilienfeld AM. Some epidemiological aspects of the high mortality rate in the young widowed group. *J Chronic Dis* 1959;10:207-17.
- 18 Mellström D, Nilsson A, Oden A, Rindgren A, Svanborg A. Mortality among the widowed in Sweden. *Scand J Soc Med* 1982;10:33-41.
- 19 McMahon B, Pugh TF. Suicide in the widowed. *Am J Epidemiol* 1965;81:23-31.
- 20 Frankel F, Smith D. Conjugal bereavement amongst the Huli people of Papua New Guinea. *Br J Psychiatry* 1982;141:302-5.
- 21 Jones DR, Goldblatt PO, Leon DA. Bereavement and cancer: some data on deaths of spouses from the longitudinal study of Office of Population Censuses and Surveys. *Br Med J* 1984;289:461-4.
- 22 Lynch JJ. *The broken heart*. New York: Basic Books, 1977.
- 23 Parkes CM, Brown RJ. Health after bereavement: A controlled study of young Boston widows and widowers. *Psychosom Med* 1972;34:449-61.
- 24 Maddison DC, Viola A. The health of widows in the year following bereavement. *J Psychosom Res* 1968;12:297-306.
- 25 Ciccio A. On mortality in husbands and wives. *Hum Biol* 1940;12:508-31.
- 26 Helsing KJ, Comstock GW, Szklo M. Causes of death in a widowed population. *Am J Epidemiol* 1982;116:524-33.
- 27 Horwitz O, Weber J. Aegteskabelig stilling og dødelighed. *Ugeskr Laeger* 1973;135:1089-104.
- 28 Koskenvuo M, Kaprio J, Kesaniemi A, Sarna S. Differences in mortality from ischaemic heart disease by marital status and social class. *J Chronic Dis* 1980;33:95-106.
- 29 Schmale AH, Iker H. Hopelessness as a predictor of cervical carcinoma. *Soc Sci Med* 1978;27:95-100.
- 30 Frederick JF. Physiological reactions induced by grief. *Omega* 1971;2:71-5.
- 31 Hofer M, Wolff C, Friedman S, Mason JW. A psychoendocrine study of bereavement. *Psychosom Med* 1977;39:481-504.
- 32 Bartrop RW, Lazarus L, Luckhurst E, Kiloh LG, Penny R. Depressed lymphocyte function after bereavement. *Lancet* 1977;ii:834-6.
- 33 Schleifer SJ, Keller SE, Camerino M, Thornton JC, Stein M. Suppression of lymphocyte stimulation following bereavement. *JAMA* 1983;250:374-7.
- 34 Cox T, Mackay C. Psychosocial factors and psychophysiological mechanisms in the aetiology and development of cancers. *Soc Sci Med* 1982;16:381-96.
- 35 Stein M, Schiavi RC, Camerino M. Influence of brain and behaviour on the immune system. *Science* 1976;191:435-40.
- 36 Rowland KF. Environmental events predicting death for the elderly. *Psychol Bull* 1977;84:349-72.
- 37 Helsing KJ, Szklo M, Comstock GW. Factors associated with mortality after widowhood. *Am J Public Health* 1981;71:802-9.
- 38 Parkes CM. Bereavement counselling: does it work? *Br Med J* 1980;281:3-6.
- 39 Parkes CM. *Bereavement. Studies of grief in adult life*. Harmondsworth: Penguin, 1986.

Hyperplastic anaemia and parvovirus infection

Acute episodes of erythroid hypoplasia causing anaemia of rapid onset and a low reticulocyte count have been recognised as a complication of chronic congenital haemolytic anaemia for many years. Patients with red cell enzyme or membrane defects or with haemoglobinopathies are equally susceptible. These episodes typically occur in children (but not infants) and may affect more than one family member, with a modal interval of nine days between the index and subsequent cases.¹ The illness usually ends after 10-12 days and does not recur. In areas with a high prevalence of sickle cell disease outbreaks occur at three to five year intervals.²

Such epidemiological evidence suggests that the cause of these crises is a single infective agent, probably a virus. This notion is supported by the prodromal symptoms reminiscent of a virus infection and the accumulating evidence of associated human parvovirus infection. Virus antigen has been detected during crises in a few patients with sickle cell disease³ and hereditary spherocytosis.⁴ The more common detection of specific class IgM antibodies to human parvovirus has provided evidence of a recent infection in patients presenting in crisis.^{4,5}

The human parvovirus is a small (20-25 nm) DNA virus, and infection in an otherwise healthy individual results in a mild febrile illness.⁶ The same infection in some children probably results in erythema infectiosum (fifth disease),⁷ when there is an associated rash; adult patients frequently complain of arthralgia. The antigen was first detected in the serum of healthy blood donors,⁸ and the high frequency (30%) of specific antibody to the virus in the serum of unselected young adults shows that the infection is readily transmitted and causes subclinical illness in most cases.

Normal human erythroid colony growth has been inhibited in vitro (without complement mediation) by adding sera containing virus antigen,⁹ and this is neutralised by adding convalescent serum containing antibody to human parvovirus. The target cell is a late erythroid progenitor¹⁰; granulocyte-macrophage colony growth is largely unaffected. Erythroid suppression together with a shortened red cell lifespan will produce a serious effect, whereas in those without haemolysis it produces only a subclinical fall in the

haemoglobin concentration. Measures that prolong the red cell lifespan, such as splenectomy in hereditary spherocytosis or recent blood transfusion in sickle cell disease,¹¹ may protect against the abrupt cessation of red cell production.

Human parvovirus infection is not known to be associated with the more familiar severe aplastic anaemia that causes pancytopenia and has a very poor prognosis. In half of British cases a cause is identified—usually an idiosyncratic reaction to a drug. The only known infective causes are, rarely, non-A non-B hepatitis¹² and, even more rarely, infectious mononucleosis.¹³ In addition to the patients with haemolytic anaemia many of those infected with parvovirus (either as sporadic cases⁶ or as contacts of patients with aplastic crises of haemolytic anaemia⁴) have a transient leucopenia and thrombocytopenia—but this seems to be entirely benign and not specific for this virus.¹⁴

Patients with severe aplastic anaemia do not have evidence of recent human parvovirus infection,¹⁰ nor is the frequency of IgG antibody to human parvovirus higher than in a normal population. These observations do not entirely exclude the parvovirus as a cause. Inquiry about infections should be included in the investigation of patients with severe aplastic anaemia in addition to the usual search for previous exposure to drugs and toxins. Modern DNA technology may eventually help to identify the role of virus infection in idiopathic aplastic anaemia.

The course of clinically evident parvovirus infection is benign, and, although many patients require red cell transfusion, there are no recently reported deaths. Whether parvovirus contributes to the more serious, though rare, severe aplastic anaemia, remains speculative. Although aplastic crises are rare in temperate areas, in areas where sickle cell disease is common about 10% of patients with sickle cell disease will suffer a crisis before the age of 15 years. It should be possible to produce a vaccine to protect against this self limiting disease in high risk groups.

D P BENTLEY

Consultant Haematologist,
Llandough Hospital,
Penarth,
South Glamorgan CF6 1XX

BMJ 1986;293:836-837
 Copyright 1986 by British Medical Journal
 0959-6551/86/0000-0836\$05.00
 Printed in Great Britain
 All rights reserved
 No part of this publication may be reproduced without permission from the British Medical Journal

- 1 Mortimer PP. Hypothesis: the aplastic crisis of hereditary spherocytosis is due to a single transmissible agent. *J Clin Pathol* 1983;36:445-8.
- 2 Serjeant GR, Mason K, Topley JM, et al. Outbreak of aplastic crises in sickle cell anaemia associated with parvovirus-like agent. *Lancet* 1981;ii:595-7.
- 3 Pattison JR, Jones SE, Hodgson J, et al. Parvovirus infections and hypoplastic crisis in sickle-cell anaemia. *Lancet* 1981;i:664-5.
- 4 Kelleher JF, Luban NLC, Mortimer PP, Kamimura T. Human serum "parvovirus": a specific cause of aplastic crisis in children with hereditary spherocytosis. *J Pediatr* 1983;102:720-2.
- 5 Lefrere JJ, Courouce A-M, Girot R, Bertrand Y, Soulier J-P. Six cases of hereditary spherocytosis revealed by human parvovirus infection. *Br J Haematol* 1986;62:653-8.
- 6 Shneerson JM, Mortimer PP, Vandervelde EM. Febrile illness due to a parvovirus. *Br Med J* 1980;280:1580.
- 7 Anderson MJ, Jones SE, Fisher-Hoch SP, et al. Human parvovirus, the cause of erythema infectiosum (fifth disease)? *Lancet* 1983;i:1378.

- 8 Cossart YE, Field AM, Cant B, Widdows D. Parvovirus-like particles in human sera. *Lancet* 1975;ii:72-3.
- 9 Mortimer PP, Humphries RK, Moore JG, Purcell RH, Young NS. A human parvovirus-like virus inhibits haematopoietic colony formation in vitro. *Nature* 1983;302:426-9.
- 10 Young NS, Mortimer PP, Moore JG, Humphries RK. Characterisation of a virus that causes transient aplastic crisis. *J Clin Invest* 1984;73:224-30.
- 11 Anderson MJ, Davis LR, Hodgson J, et al. Occurrence of infection with a parvovirus-like agent in children with sickle cell anaemia during a two-year period. *J Clin Pathol* 1982;35:744-9.
- 12 Zeldis JB, Dienstag JL, Gale RP. Aplastic anaemia and non-A, non-B hepatitis. *Am J Med* 1983;74:64-8.
- 13 Lazarus KH, Baehner RL. Aplastic anaemia complicating infectious mononucleosis: a case report and review of the literature. *Pediatrics* 1981;67:907-10.
- 14 Lewis SM, Gordon-Smith EC. Aplastic and dysplastic anaemias. In: Hardisty RM, Weatherall DJ, eds. *Blood and its disorders*. 2nd ed. Oxford: Blackwell Scientific Publications, 1982: 1229-68.

Normal pressure hydrocephalus

In 1965 Raymond Adams and his coworkers described a new clinical syndrome of dementia with psychomotor retardation, unsteadiness of gait, and urinary incontinence. It was of insidious onset and associated with a characteristic pneumoencephalographic appearance of ventricular enlargement with an absence of air over the cerebral cortex owing to subarachnoid obstruction but with normal pressure in the cerebrospinal fluid on lumbar puncture. Patients showed clinical improvement after cerebrospinal fluid shunt procedures.^{1,2}

From the beginning the aetiology and pathophysiology of the condition have been difficult to understand, and they are probably multifactorial. It has been described after head injury,^{2,5} subarachnoid haemorrhage,^{3,5-7} intracranial surgery,⁸ cerebrovascular disease,⁹⁻¹¹ meningo-encephalitis,^{1,3,4,9} and in association with a brainstem glioma,¹² third ventricular cyst,¹ cerebellar haemangioblastoma,¹³ aqueduct stenosis,⁵ and third ventricular compression from an ectatic basilar artery.^{14,15} In perhaps as many as half of all cases there is no obvious cause. The factor common to all of these conditions is impairment of outflow and resorption of cerebrospinal fluid; this leads to a rise of the intraventricular pressure, which diminishes as the ventricles distend.^{2,16,17} Neurological signs and symptoms are produced by a combination of mechanical stretching of periventricular fibre pathways,¹⁸ of parenchymal brain disturbance as a result of diminished cerebral blood flow and reduced metabolism,^{8,19-21} and of periventricular oedema from transependymal flow of cerebrospinal fluid.²⁰⁻²³ Cerebrospinal fluid diversion procedures, usually ventriculoatrial or ventriculoperitoneal shunts with valves which open at low pressures, have reversed these abnormalities and produced clinical improvement in some highly selected patients—as many as two thirds in some series.^{3,7,9,24-31}

It is, however, difficult on clinical grounds alone to select patients who will benefit from shunt procedures and to distinguish them from those with dementia due to irreversible causes such as Alzheimer's disease or multiple cerebral infarcts. Several investigations have been used. The first was pneumoencephalography with some specific diagnostic measures.^{1,2,32,33} Computed tomography is now the preferred imaging method,³⁴⁻³⁶ and it may be combined with metrizamide cisternography.³⁷⁻³⁹ Investigations which determine the absorption and flow characteristics of cerebrospinal fluid have included radionuclide encephalography and cisternography,^{5,40-42} estimation of blood radionuclide concentrations,⁴³ lumbar saline infusion tests, and monitoring of

intracranial pressure.^{7,17,31,44-46} Despite or because of this multiplicity of tests there has not been general agreement about which factors best predict a successful outcome from shunting, either singly or in combination, and their prognostic value has been questioned.^{3,7,23-25,27,28,30,31,47}

If surgery was free of risk it might be a reasonable proposition to carry out a cerebrospinal fluid diversionary procedure on any demented patient with ataxia and urinary incontinence and large ventricles on computed tomography. In practice, however, complications—shunt infection, subdural haematoma and effusion, epileptic seizures, and shunt malfunction—occur in about one third of patients (range 9%-44%),^{3,24,25,27,31,47} and such a policy would inevitably lead to operations being done on many patients with Alzheimer's disease and other irreversible brain degenerations and parenchymal damage who could not hope to improve. More recent studies of cerebral blood flow and metabolism have shown that the regional flow, volume, and metabolism are reduced in patients with normal pressure hydrocephalus, particularly in the frontal, temporal, and basal ganglia areas. If the ventricular pressure and size are reduced the clinical state improves and there has been an accompanying improvement in these factors in most but not all reports.^{20,21,48-53} These techniques are not, however, sufficiently sensitive yet to differentiate reliably between normal pressure hydrocephalus and Alzheimer's disease and other forms of dementia.

Changes in Alzheimer's disease are detectable by positron emission tomography⁵⁴—decreased cortical blood flow and regional metabolism for glucose and oxygen in frontal, temporal, and parietal regions. A recent report by Jagust *et al*, using positron emission tomography with labelled fluoro-deoxyglucose to map cerebral glucose metabolism, showed global cerebral hypometabolism in three patients with normal pressure hydrocephalus; this could be distinguished from the bilateral temporoparietal hypometabolism seen in Alzheimer's disease.⁵⁵ The apparent paradox of global metabolic disturbance in normal pressure hydrocephalus with positron emission tomography, whereas blood flow studies usually show focal reduction, has not been explained. Positron emission tomography is an expensive, technically complex, and time consuming technique, available in only a few centres world wide. Possibly metabolic analogues of positron emitters may be synthesised and labelled with γ emitters to allow single photon tomographic studies to be undertaken—and this should be possible in most departments of nuclear medicine. Preliminary results in Alzheimer's disease are encouraging.⁵⁶ Such studies are in a very early