Letters to the Editor

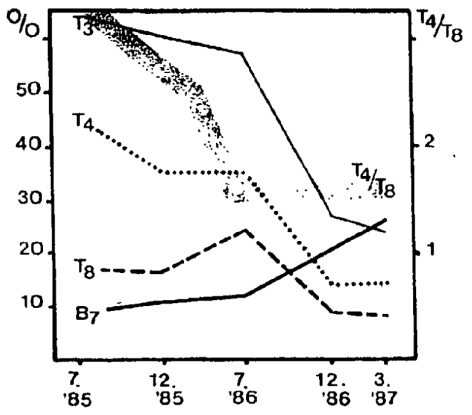
PERSISTENT FATIGUE AND DEPRESSION IN PATIENT WITH ANTIBODY TO HUMAN B-LYMPHOTROPIC VIRUS

SIR,—In October, 1986, a new virus was described in *Science*.[1,2] It was isolated from patients with "chronic infectious mononucleosis-like syndrome" or premalignant and malignant lymphoproliferative diseases. Antibody titres were sporadically positive in healthy volunteers and in HIV-positive AIDS patients without lymphoma.[3]

Epidemics of this unusual disease were recorded in the United States (Lake Tahoe area and Nevada).[4-6] The virus was identified as a herpesvirus without antigenic cross-reactivity or DNA-probe cross-hybridisation with other viruses (Epstein-Barr [EBV], cytomegalovirus [CMV], *Herpes simplex* [HSV], varicella-zoster). The new virus has been tentatively named human B-lymphotropic virus (HBLV). We have seen a patient with antibody to HBLV and unusual clinical symptoms.

A 54-year-old man sought medical attention because of a persistent sore throat, fatigue, depression, and anxiety (occasionally with suicidal tendencies). About 4 weeks before the onset of his illness in July, 1985, he had had sexual contact with a woman who, as he later learned, was admitted to a neurological clinic. He was worried about AIDS. He did not belong to any risk group for HIV infection and denied drug or alcohol abuse. His medical history consisted of appendicectomy in childhood, toxoplasmosis (1975), tonsillitis and herpes labialis and genitalis (1981), and non-specific colitis (1983).

The symptoms of his illness were recurrent tonsillitis, persistent sore throat and stomatitis, recurrent aphthous stomatitis, night sweats, fatigue and malaise, recurrent arthritic pain, diarrhoea, and depression. He was moderately overweight and had mild cervical lymphadenopathy but no hepatosplenomegaly. Clinical examination confirmed bilateral sinusitis, pharyngitis, chronic tonsillitis, and non-specific diffuse stomatitis; there was no candida infection. Other organ systems were unremarkable. White cell count 5000–7000/μl (27–39% lymphocytes); platelets 293–360 × 10^3/μl; serum proteins 7·8 g/dl (13·5–17·8% gammaglobulins); liver enzymes normal; C-reactive protein 10 mg/dl. He was seronegative for HIV-1 and HIV-2 and for a wide screen of other bacterial and protozoal pathogens. Serological studies for EBV, HSV 1 and 2, CMV, hepatitis B, and toxoplasmosis indicated previous, but currently inactive, infection, with the following titres: EBV VCA IgG 64 (IgM and IgA zero), EA zero, EBNA 8; CMV IgG 32, IgM 8; HSV-1 IgG 256–512, IgM 8; HSV-2 IgG 512, IgM 8; hepatitis A IgG +; anti-HBs +, anti-HBc +, HBs negative; toxoplasma 40 (IgG 64, IgM zero).



Serial lymphocyte subtype monitoring in HBLV-positive patient with chronic fatigue syndrome.

Serum samples were tested on HBLV-infected human cord blood mononuclear cells by immunofluorescent assay (IFA)[1] and a titre above 40 IgG was found.

Peripheral blood lymphocytes were classified by fluorescent activated cell sorting ('Spectrum III'; Ortho) with 'Orthimmune' antisera (figure). Immature T-lymphocytes did not exceed 2·9% and NK-cells 17·0%.

The patient continues to complain of mild cervical lymphadenopathy, fatigue, sore throat, and mild-to-moderate depression.

HBLV antibody titres in healthy individuals in the United States are below 20, and the frequency of seropositivity is about 12%.[3] A role for HBLV infection in chronic fatigue syndrome has been discussed by Barnes[4] and Strauss.[5] In our patient, slowly rising B-lymphocytes (figure) and gammaglobulins can be consistent with B-cell stimulation by a lymphotropic virus similar to EBV. We are culturing cells in an attempt to isolate the virus. This patient may have HBLV-related disease; if so this would be the first evidence for the presence of this virus in Europe.

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TESTING BLOOD DONORS FOR NON-A, NON-B HEPATITIS: IRRATIONAL, PERHAPS, BUT INESCAPABLE

SIR,—In three letters in *The Lancet* Dr Anderson, Dr Gillon, and Dr Dow and their colleagues (April 18, p 912; June 13, p 1366) point out weaknesses in the arguments which have been used to support the introduction of blood donor screening to reduce transfusion-transmitted non-A, non-B hepatitis (NANBH), using alanine aminotransferase (ALT) and hepatitis B core antibody (anti-HBc) as surrogate markers. All three letters suggest that the UK transfusion services should not start donor screening until prospective controlled studies have been done in the UK to find out how many cases of post-transfusion hepatitis would be prevented. No large study to answer this critical question has yet been presented, and we agree that the size of the benefit to be gained from surrogate testing cannot be accurately established without such a study. However, the time for this study has already passed. Starting now will give us an answer in 3–4 years—and that is probably 3 to 4 years too late. The introduction of surrogate marker testing for NANBH is now virtually inescapable, for three reasons:

(1) In 1988 European legislation on strict product liability comes into force in the UK. If harm should come to the recipient of a therapeutic product, the producer will be held liable unless he can demonstrate that he used all known methods and information to avoid the risk. Under these rules a patient who contracted NANBH via transfusion of blood or a blood product would have a claim against the supplier if it was shown to come from a donor who had not been tested for both raised ALT and anti-HBc.

(2) Although we all hope that pooled plasma fractions will soon be made safe by heating or other antiviral treatment, these processes remain to be validated in large-scale trials. Meantime, even if surrogate marker screening would only modestly reduce the level of

TABLE I—SURROGATE MARKER SCREENING TO REDUCE NANBH: COSTS AND BENEFITS IN THE UK*

Patients transfused per year in UK	600 000
Number contracting NANBH	15 000 (2·5%)
Number who survive more than 2 yr after transfusion (50% die of underlying disease)	7500
Number who acquire chronic NANBH (50% of those infected and surviving 2 yr or more)	3750
Number who progress to cirrhosis (10% of those with chronic NANBH)	375
Number prevented by screening programme (30%)	125
Cost of screening programme (£2 per test, 2·3 million donations)†	£4600 000
Cost per case of cirrhosis prevented	*£37 000*

*Calculations exclude consideration of fractionated plasma products in expectation that heat or chemical processes are likely in near future to remove risk of virus transmission.
†This costing, and those in table II, represent direct testing costs only; costs of counselling, replacing lost donors, and so on have not been included.

infectivity in these products, many would argue that some improvement is better than none.

(3) The UK transfusion services, although the major suppliers of blood and blood products in this country, cannot afford to ignore the wishes of consumers to be supplied with "non-A, non-B tested" products, even if it is believed that the real benefit in safety which is offered to the patient is marginal. Commercial suppliers will not be slow to point out that their products are made from tested plasma and must therefore be safer. Clinicians and patients can hardly be blamed for taking note of this message. And this argument may be applied equally to whole blood, red blood cells, platelets, and plasma. What better marketing ploy for a private blood bank than to emphasise that its donors are tested to exclude hepatitis using the standards applied in the United States, Germany, and France? The local NHS blood supplier will have trouble shrugging off accusations of providing a second-class product.

It is also worth taking a second look at the assumption that surrogate marker testing is necessarily a "bad buy" in comparison with the tests that are accepted as essential to prevent other transfusion-transmitted infections. Table I shows a calculation to illustrate the cost of surrogate testing to prevent one case of cirrhosis due to transfusion-transmitted NANBH. This should be compared with the cost of HIV antibody testing to prevent one case of transfusion-transmitted AIDS. Alternatively, one could compare the costs of the present practice of routinely hepatitis B testing all repeat blood donors (in whom the prevalence of infection is predictably very low). Table II shows how these testing costs relate to the gains in recipient safety. These calculations suggest that, even if the underlying assumptions are varied quite widely, the cost of preventing morbidity by surrogate marker testing for NANBH may be no greater, and could be less, than those which are accepted for established screening programmes.

TABLE II—COSTS AND BENEFITS OF HIV ANTIBODY TESTING AND HEPATITIS B REPEAT DONOR TESTING

HIV antibody testing	
Prevalence of anti-HIV positive donors	1/50 000
AIDS cases resulting if no donor testing, on assumption that each donation is processed into two products (eg, red cells and plasma) and that both are transfused to recipients in whom AIDS develops	2 per 50 000 donors
Cost of testing per donation	£2
Cost per AIDS case prevented	*£50 000*
Hepatitis B repeat donor testing	
Prevalence of HBsAg positive repeat donors	1/41 000[1]
Chronic hepatitis B cases resulting if no repeat donor testing, on assumption that each donation is processed and transfused to 2 recipients and that 10% of recipients die or acquire chronic hepatitis B	0·2 cases per 41 000 donations
Cost of testing per donation	£2
Cost per death or case of chronic hepatitis B prevented	*£410 000*

Looking at these three factors—producer's liability, competition, and value for money—we suggest that the decision which has to be made is when rather than whether the UK transfusion services follow the lead of the United States and other European countries in donor screening.

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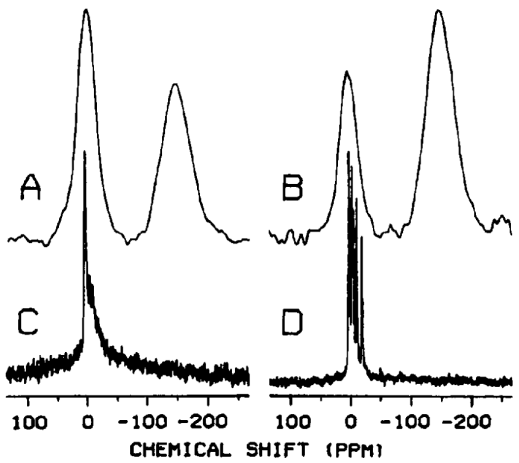
IN VIVO ^{31}P NMR SPECTROSCOPY FOR EVALUATION OF OSTEOPOROSIS

SIR,—Osteoporosis is a major cause of illness in the elderly but progress towards its prevention has been impeded by lack of a full understanding of the underlying causes and by the absence of a method for monitoring osteoporosis not only for early diagnosis but also to evaluate treatment. Current methods based on bone mineral content are not recommended for large-scale use,[1,2] and procedure that is similar, cheaper, and safer in respect of radiation exposure is needed.

The mineral content of samples of bone can be measured by ^{31}P nuclear magnetic resonance (NMR) spectroscopy without "magic angle" sample spinning.[3,4] Since ^{31}P NMR measures mineral content within a selected volume without concern for the geometry of the bone, the assay can be done in parts of the body that pose problems for absorptimetric techniques (eg, wrist). No ionising radiation is involved with ^{31}P NMR. We now have succeeded in recording in vivo ^{31}P NMR spectra of the bones in human fingers and wrist (figure, A and B). The resonance at a chemical shift of 0 ppm arises from apatite; that at −150 ppm is from the quantitative reference standard, KPF_6.[3,4]

The contribution of soft tissue such as marrow and skeletal muscle to the ^{31}P NMR spectra of human fingers and wrist is small. As ^{31}P NMR spectra of freshly excised canine marrow and skeletal muscle (C and D) shows, only the narrow resonances from



In vivo ^{31}P NMR spectra of (A) human fingers and (B) human wrist and in vitro spectra of freshly excised (C) marrow from within canine femur and (D) skeletal muscle from around canine femur.

Spectra recorded with a Nicolet NT-150 spectrometer at 3·5 T (60·7 MHz).[3,4] (A) and (B) were recorded with home-built probes of 55 mm and 75 mm internal diameter, respectively, whereas a Nicolet 20 mm high-resolution probe was used for (C) and (D). Acquisition time was 5 ms in (A) and (B) and 168 ms in (C) and (D). Chemical shifts are given in parts per million from 85% H_3PO_4.