TABLE III-DISTRIBUTION OF RELIABILITY SCORES FOR RESPONSE
TO QUESTIONS ABOUT SEVERE DIARRHOEAL DISEASE

	Very reliable	Fairly reliable	Unreliable	Total
Cases	131	26	3	160
Controls	135	23	1	159*

*Not recorded for 1 control.

Most of the responses were made with noticeable conviction, and virtually all the reliability scores were within the acceptable range, with similar distribution in cases and controls (table III).

Given consistency in the method of interview and no serious recall bias, the validity (sensitivity and specificity) of the diarrhoea question should have been similar in cases and controls, so that even if it were only a relatively poor diagnostic method, this would not constitute a serious source of bias.

The same arguments apply to the ascertainment of past exposure to heatstroke. The local terms for heatstroke referred to a uniformly serious condition, a "stroke", that was a memorable event, bound to be accompanied by a crisis of dehydration.

The second phenomenon that could have given rise to bias is confounding or mixing of the effects of other possible risk factors that are associated both with severe diarrhoeal disease and also independently with cataract. The possible confounding was controlled by the close matching of cases with controls in respect of a number of key variables, and this in turn resulted in matching for other possible confounders such as sources of water supply and composition of diet.

Close matching for age was of particular importance. In 91% of matched pairs the age difference within pairs was no more than 5 years. In 72% of pairs, the controls were older or of the same age as the cases, and in only 5 pairs (3%) the cases were older by more than 5 years. However, exclusion of these 5 pairs or even all the pairs with cases older than controls had only a very slight effect on the magnitude of the relative risks and virtually no effect on the trend of increasing risk with rising levels of exposure.

The controls could be regarded as a good representative sample of the general non-cataract population in the catchment area. They consisted mainly of patients with refractive errors, viral and other conjunctivitis, lachrymal problems, and minor lid infections—conditions that afflict the general population more or less indiscriminately.

The simple diagnostic method used to categorise patients as cataract cases requires some explanation. The study focused on types of cataract that were clinically important-ie, central lens opacities causing visual impairment. This meant that the comparisons had to be made between patients with visual impairment due to central lens opacities and matched controls who did not have central lens opacities. Therefore, in classifying a patient as a case or possible control, it was neither necessary nor desirable to scrutinise the lens in great detail through a dilated pupil with a slit-lamp microscope. No doubt some of the controls might have had peripheral lens changes. However, their agematched counterparts had much more advanced cataract that caused visual impairment, and the study was designed to evaluate the aetiological determinants of this clinically important difference in cataract development.

Any final inferences from our results must remain subject to the outcome of the other case-control and population-based studies that are in progress in the Raipur district and elsewhere in India. If our findings are shown to reflect a widespread phenomenon, they would indicate an urgent need to devise practical measures to control the incidence and the dehydrating severity of diarrhoeal disease and heatstroke in adults as well as children. This should substantially reduce the incidence of cataract and the need for surgical and optical services for the relief of disability from cataract.

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ISOLATION OF NEW LYMPHOTROPIC RETROVIRUS FROM TWO SIBLINGS WITH HAEMOPHILIA B, ONE WITH AIDS

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Summary A human T-lymphotropic retrovirus was isolated from cultured T lymphocytes from two siblings with haemophilia B. Patient 2 was healthy, but patient 1 had acquired immunodeficiency syndrome. The retrovirus differed from human T-cell leukaemia virus (HTLV) but it was similar to the lymphadenopathyassociated retrovirus (LAV) in its morphology and its major core protein (P25). Both patients had antibodies against LAV and patient 1's retrovirus, detected by an enzyme-linked immunosorbent assay or a radioimmunoprecipitation assay. Seroepidemiological data indicated the transmission of this retrovirus by plasma products.

Introduction

THE occurrence of acquired immunodeficiency syndrome (AIDS) in haemophiliac patients¹ strongly suggests transmission of the disorder by blood products, such as concentrates of factor VIII or factor IX. The aetiology of AIDS remains unknown but epidemiological studies suggest that it may be related to a transmissible agent. Two human T-lymphotropic retroviruses have been considered as possible agents. The human T-cell leukaemia virus (HTLV) has been isolated from the lymphocytes of some AIDS patients.² Antibodies against the surface antigens of a T-cell

line infected with HTLV have been found in such patients³ and HTLV-related sequences were detected in lymphocyte DNA from two patients.⁴ A second human T-lymphotropic virus, lymphadenopathy-associated virus (LAV), has been isolated from cultured lymph-node T lymphocytes of a homosexual man with lymphadenopathy.⁵ Both viruses have distinct morphology, and their major core proteins are not antigenically related. LAV may specifically infect the T4-positive lymphocyte subset,⁶ a subpopulation of lymphocytes which is reduced in AIDS. Finally, a similar retrovirus, immunodeficiency-associated virus (IDAV), has been isolated from a homosexual man with AIDS.⁶ We now report the isolation of a lymphotropic retrovirus from cultured T lymphocytes of two siblings with haemophilia B.

Case-reports

Patient 1

A 13-year-old White boy with severe haemophilia B (factor IX clotting activity levels below 1% of normal) was referred to the paediatric department because of fever persisting for 3 months. The patient had a history of haemorrhages, including splenic and renal haematomas. He was treated with infusions of factor IX concentrate (PPSB [Prothrombin proconvertin factor II and IX]) prepared according to Soulier et al7 and obtained from the plasma of volunteer blood donors (Centre National de Transfusion Sanguine [CNTS]). In April, 1980, during a holiday in Austria, he also received three preparations ('Bibulin') derived mainly from plasma collected in the USA (Immuno). Self-infusion on request was required almost weekly (1500, 800, and 700 units of factor IX per kg per year in 1980, 1981, and 1982). Circulating anticoagulant to antihaemophilic factor was never detected and the patient never received other blood products. In 1972, a hepatitis B virus infection was followed by persistently high levels of liver enzymes and the presence of hepatitis B surface and e antigens. In 1978, hepatosplenomegaly was noted. Patient 1 also had clinical and serological symptoms of hepatitis A infection in July, 1980, associated with transient and severe pancytopenia with hypoplastic bone marrow. In 1981, histology of the liver showed features typical of chronic active hepatitis without cirrhosis, associated with an important focal lymphocyte infiltration of the portal tracts. In 1982, antibodies against hepatitis Be appeared for the first time. Lymphopenia did not occur before January, 1983.

During the first quarter of 1983, an episode of persistent fever, oral thrush, lymphadenopathy with hepatosplenomegaly, and a weight loss of 4 kg occurred. Seroconversion to *Toxoplasma gondii* with the presence of specific IgM antibody was observed in an indirect immunofluorescence test (1:1250 IU). No antibodies to cytomegalovirus (by ELISA; enzyme-linked immunosorbent assay), to herpesvirus or adenovirus (complement-fixation test), or to Epstein-Barr virus (immunofluorescence) were detected. No virus was recovered from blood, urine, or stools. The platelet counts were between 60 and 100×10^9 /l. High levels of serum alpha-interferon (32 IU/ml) partly (50%) inactivated by pH2 treatment were observed in July, 1983. 3 months later, the titre had risen to 320 IU/ml with 75% inactivation at pH2.

The patient had been treated with spiramycin alone for 3 months. Lymphadenopathy disappeared but recurrent fever and asthenia persisted. An improvement was obtained with the combination of pyrimethamine and sulphadiazine, but this treatment had to be discontinued because of a severe cutaneous reaction. In July, 1983, seizures occurred; a computed tomographic scan of the brain revealed four low-density lesions with a lucent aspect on contrast injection, suggesting toxoplasma abscesses. (The computed tomographic scan had been normal in May, 1983.) Reinstitution of treatment resulted in clinical improvement and another scan showed that the lesions had become smaller and were no longer lucent.

Patient 2

The 17-year-old brother of patient 1 also has haemophilia B. He

had a history of repeated spontaneous haemarthroses and intramuscular haematomas. He received PPSB preparations from CNTS and in April, 1980, two infusions from Immuno (680, 480, 525 units factor IX per kg per year, in 1980, 1981, and 1982). Circulating anticoagulant to antihaemophiliac factor was never found and blood transfusion had not been required since 1977. In July, 1980, he contracted a hepatitis A infection associated with a severe and central transient pancytopenia. In 1983, a symptomless hepatitis B infection was detected only by the presence of antibodies against hepatitis B core antigen with no surface antigen. Alphainterferon was not detectable in his serum (<2 IU/ml). Apart from symptoms related to haemophilia, clinical examination was normal.

The parents are healthy and do not belong to any group known to be at high risk of AIDS. $^{8\text{-}10}$

Methods

Immunological Evaluation

Mononuclear cells were isolated on a 'Ficoll-Hypaque' gradient and analysed for markers of T and B lymphocytes. Monoclonal antibodies specific for T lymphocytes or T-cell subsets (OKT3, OKT4, and OKT8; Ortho, Raritan, New Jersey) were used in an indirect fluorescence test. B lymphocytes were revealed by rhodamine-labelled F(ab)'2 fragments of anti-heavy chans revealing surface immunoglobulins. The other immunological tests were done as previously—proliferative response to mitogens, antigens, and to irradiated allogeneic cells (mixed leucocyte reaction),¹¹ generation of plasma cells in cultures stimulated with pokeweed mitogen,¹² and natural killer activity.¹³

Virus Isolation

Materials.—Blood leucocytes were separated by ficoll (Pharmacia) gradient centrifugation. T cells were stimulated by phytohaemagglutinin for 3 days. The medium was then removed and the cells were cultured in RPMI 1640 medium supplemented with 10% fetal calf serum, 10% T-cell growth factor, $2 \mu g/ml$ 'Polybren' (Sigma), and 0 · 1% anti-human alpha-interferon sheep serum (a 1:10⁵ dilution of this preparation neutralises 7 IU alpha-interferon). The medium was changed twice a week.

Virus detection.—Cell-free supernatants were harvested twice a week and the reverse transcriptase activities of 1 ml samples were determined.⁵

Virus propagation.—Lymphocytes from a healthy adult donor were stimulated with phytohaemagglutinin. After 3 days the medium was removed and the cells were resuspended in the supernatant of virus-producing lymphocytes (5000 cpm reverse transcriptase activity for 10^6 cells). 1 h later, the cell concentration was adjusted to 10^6 /ml. The viral production was followed every 3 days by measuring the reverse transcriptase activity of the supernatant.

Virus purification.—The virus was concentrated either by ultracentrifugation or by 10% polyethyleneglycol 6000 precipitation. Concentrated virus was then banded to equilibrium in a 20-60% sucrose gradient. This procedure was used for preparation of disrupted virus for ELISA. For protein analysis, the virus was purified by ultracentrifugation in a linear 'Nycodenz' gradient (35-5%) (Nyegaard, Oslo) for 2 h at 45 000 rpm. The reverse transcriptase activity of each fraction of the gradient was determined.

Virus characterisation.—Two previously described methods,⁵ electron microscopy and radioimmunoprecipitation assay, were used to identify the virus. Furthermore, an ELISA, using purified viral antigens obtained from LAV or IDAV, was done. Briefly, antigens were disrupted in 0.5% sodium dodecyl sulphate at 37° C for 15 min, and the prediluted sera (1:40) were tested against viral antigens and a crude cytoplasmic extract of uninfected lymphocytes from the same donor as control. The specifically fixed IgG were revealed by a peroxidase-conjugated antibody against human serum IgG. The enzymic reaction was carried out with orthophenylene diamine as substrate. An ELISA ('Biotech' kit) was also used for the detection of anti-HTLV antibodies.

Results

Patient 1's serum IgG levels were raised without monoclonal protein on immunoelectrophoresis (table I). Isohaemagglutinin (anti-B) and antibody formation after sensitisation to Bordetella pertussis, to poliovirus, and to tetanus toxoid were slightly lower than normal. The Coombs' test was negative. Rheumatoid factors and antinuclear antibodies were not detected. In contrast, this patient had a severe cell-mediated immunodeficiency; he had no skin-test reactivity to phytohaemagglutinin and antigens (purified protein derivative, 'Candidin', and tetanus toxoid). Lymphopenia with a profound reduction in OKT4-positive lymphocytes was observed (table I). T-lymphocyte functions were greatly impaired: proliferative responses to phytohaemagglutinin and to allogeneic cells were very low, and despite the documented toxoplasmosis, there was no proliferative response to toxoplasma antigen. The generation of plasma cells in cultures stimulated with pokeweed mitogen was also abolished. The natural killer activity was normal at different effector:target ratios.



Fig 1—Time course of virus production by cultured T lymphocytes from patient 1.

Day 0 is when culture was started, July, 1983. Solid line=reverse transcriptase activity; broken line=cell concentration.

	Patient 1		
_	March 1983	June 1983	Normal values (mean±SD or range)
Serum immunoglobulins (g/l):		•	
IgG	38	20	10.5-14.9
IgA	1.16	4	1.16-2.28
IgM	$1 \cdot 26$	1.50	0.88-1.72
Isohaemagglutinin titre	NT	1:8	>1:32
Delayed type skin reactivity	Absent	Absent	
Total lymphocytes (/µl)	1400	600	>1500
SIg + lymphocytes (%)		8	$10 \cdot 2 \pm 3 \cdot 7$
T3+ cells (%)	84	58	77·5±9·9
T4+ cells (%)	9	4	$49 \cdot 3 \pm 3 \cdot 2$
T8+ cells (%)	79	48	$31 \cdot 4 \pm 4 \cdot 7$
Prohferative response* (%)			
PHA	8	7	90±50
Toxoplasma antigens	1.5	1.6	>5
Allogeneic cells+		3	14 ± 8
Natural killer activity			
(ratio 50:1) (%)			
Spontaneous	NT	35	60 ± 16
Interferon-activated	NT	85	80 ± 20
PWM-induced plasma cells	NT	0	200 ± 80

TABLE I-IMMUNOLOGICAL STUDIES

NT=not tested; SIg=surface immunoglobulin;

PHA = phytohaemagglutinin; PWM = pokeweed mitogen.

*In cpm $\times 10^{-3}$.

+Mixed leucocyte reaction.





Fig 2—Ultrathin sections under electron microscopy of lymphocytes from a healthy donor (A and B) infected with $IDAV_2$ and from patient 1 (C).

A=immature budding particles; B=mature particles with eccentric dense core; C=patient 1.

In patient 2 serum levels of immunoglobulins were normal. The absolute and relative numbers of OKT4-positive and OKT8-positive lymphocytes, as well as the proliferative response to mitogens and to allogeneic cells, were in the normal range.

In all three experiments done (May, July, and September, 1983), reverse transcriptase activity was detected in the lymphocyte supernatant of patient 1 as early as day 5 to day 7 of culture. Fig 1 shows the time course of reverse transcriptase activity. The reverse-transcriptase-positive supernatant was used to infect lymphocytes from normal individuals, and the same pattern of reverse-transcriptase activity was observed. The virus produced was further characterised and was named immunodeficiency-associated virus (IDAV₂). No continuous lines could be obtained after viral infection.

The reverse-transcriptase activity showed a preference for poly-A-oligo-dT12-18 and poly-C-oligo-dG12-18 over poly-dA-oligo-dT-12-18, a feature which usually distinguishes retroviral enzymes from cellular DNA polymerases. The maximum activity was obtained with Mg^{2+} over Mn^{2+} with poly-A-oligo-dT as template primer as previously described for human retroviruses such as HTLV or LAV.⁵ DNA polymerase activity with poly-A-oligo-dT12-18 peaked at a density of $1 \cdot 16$ g/ml, which is characteristic of retroviruses. In nycodenz gradients, the density of the virus was $1 \cdot 10 - 1 \cdot 11$ g/ml, similar to that of murine leukaemia virus.

Ultrathin sections of patient 1's lymphocytes and of invitro-infected lymphocytes from a normal donor showed immature particles with a dense crescent budding at the cell surface and mature particles with a small dense eccentric core in the extracellular spaces (fig 2). The morphology of these particles was similar to that seen in preparations of T lymphocytes infected with LAV.⁵

³⁵S-methionine-labelled virus was purified to compare the viral proteins of IDAV₂ with those of LAV. The fractions corresponding to the peak of reverse transcriptase activity were analysed by polyacrylamide gel electrophoresis. A protein of molecular weight 25 000 (P25) was observed in fractions 5 and 6 of both IDAV₂ and LAV (fig 3), corresponding to the peak of reverse transcriptase activity. The radioimmunoprecipitation assay showed that P25 was recognised by serum from a patient with LAV but not by goat serum specifically raised to HTLV P-24 (fig 4). Patient 1's serum recognised P25 from LAV (fig 4).

Antibodies against LAV were detected by ELISA in patient 1's serum obtained at different times. The titres fell from



Fig 3—Polyacrylamide gel (12.5%) electrophoresis of ³³Smethionine-labelled proteins from purified virus.





Lanes 1 and 2: P25 protein from patient 1 virus; serum from LAV patient (1) and serum from patient 1 (2) Lanes 3-6: P25 protein from LAV; serum from patient 1 (4), serum from LAV patient (5), serum from healthy donors (3,6) Lanes 7-9: P25 protein from IDAV;; serum from patient 2 (7), serum from father (8), and mother (9).

June, 1981, to May, 1983 (table II). No patient serum sample was available before June, 1981. The available samples were also positive for antibodies against $IDAV_2$ (1:40) but negative against HTLV.

In all three experiments (July, August, and September, 1983), reverse transcriptase activity was also detected in the culture supernatant of patient 2's lymphocytes. The activity followed the same pattern as seen in patient 1 and had the same ionic requirements and template primer specificities, but it reached levels 5-6 times higher. On electron microscopy the morphology of the viral particles was similar to that in patient 1. The P25 of IDAV₂was recognised by patient 2's serum (fig 4). By ELISA his serum contained antibodies (1:160) against LAV (table II) and IDAV₂, but not against HTLV.

In January, 1984, no antibodies to LAV could be detected in patient 1's serum. In that month patient 2 was still healthy but his T4/T8 ratio had fallen to 0.20 without lymphopenia.

No virus was found in cultured T lymphocytes from either parent. However, the father's T lymphocytes could be infected by LAV. No antibodies against LAV and HTLV were found in the parent's serum samples (table II).

TABLE II-SERUM ANTIBODY TITRES TO LAV AND HTLV BY ELISA

_	Date	LAV	HTLV
Patient 1	June, 1981*	1:160	<1:20
	Feb, 1982	1:320	<1:20
	Feb, 1983	1:80	<1:20
	May, 1983	1:40	<1:20
Patient 2	Feb, 1983	1:160	<1:20
	May, 1983*	1:160	<1:20
Father	May, 1983	<1:40	<1:20
Mother	May, 1983	<1:40	<1:20

*Positive titres (1:40) against IDAV₂ (isolated from patient 1 lymphocytes) **Discussion**

Our findings are consistent with the hypothesis that retroviruses such as that found in our patients can be transmitted by way of plasma products. The two patients who had received factor IX preparations of similar origin had specific antibodies to $IDAV_2$, whereas their parents did not. Moreover, the virus infection could be transmitted in vitro to lymphocytes from healthy donors. This retrovirus can be transmitted by blood products of apparently healthy volunteer donors. The exact origin of the contaminating plasma (French or American) could not be traced, since we had no serum samples from patient 1 before June, 1981, by which time he was already seropositive for the virus. The fall in LAV antibodies at the time of AIDS occurrence is important, since it may explain why antibodies to retrovirus are not detected in all AIDS cases. The search for antibodies against IDAV₂ in the haemophiliac population is under way, so that we can compare the incidence of this retrovirus infection with that of HTLV infection. A significant proportion of some haemophiliac groups in the USA have antibodies to HTLV-associated membrane antigens.¹⁴

Although the exact role of such retroviruses in the pathogenesis of AIDS remains to be determined, our data are consistent with their involvement. First, the isolated retroviruses are similar, if not identical, to that described in a homosexual man with lymphadenopathy.⁵ We have isolated the same type of retrovirus from cultured lymphocytes from several patients with AIDS, including a homosexual man with Kaposi sarcoma, a Haiitian man,⁶ and a Zaïrian woman. No virus was isolated from healthy donor lymphocytes cultured under the same conditions. Secondly, seroepidemiological investigations indicate that antibodies against the P25 protein of this group of viruses are widely distributed in the population at risk of AIDS⁶ (and unpublished). Thirdly, such viruses display strict tropism for the OKT4-positive (helper) subset of T lymphocytes and cannot replicate in the OKT8positive subset⁶ (and D. Klatzmann et al, unpublished). Preliminary data indicate that the viruses have no transforming activity on human T lymphocytes. No continuous lines could be raised after in-vitro infection and, in every experiment, virus production ceased at about the same time as cell replication declined. A slight cytopathic effect (cell fusion and early arrest of cell growth) was observed in some instances but is so far not reproducible.

If this hypothesis is correct, an outstanding question is why patient 2 was infected with the same or a similar retrovirus, without any sign of AIDS. It has been postulated that the primary event of T-lymphotropic retrovirus infection, often inapparent, must be followed by immunogenic stimulation to bring about AIDS.6 Many antigenic stimuli, such as HBV infection (chronic hepatitis in patient 1) or frequent infusions of plasma products, may elicit T-cell proliferation, including that of lymphocytes with latent infections. This activation could trigger viral expression in these lymphocytes and therefore increase diffusion of the virus in the population of helper T cells. In this respect, we must emphasise that patient 2 received fewer infusions and had a symptomless hepatitis B infection. It is therefore possible that the virus production observed in his cultured lymphocytes was a consequence of artificial activation and did not take place in vivo. Other factors, such as the age of the patient when infected and genetic constitution, may also explain the lack of immunodeficiency in patient 2. Molecular probes for this type of lymphotropic retrovirus would help to confirm whether or not the viruses have a central role in the occurrence of AIDS. Definite evidence will require an animal model in which such viruses could induce a disease similar to AIDS

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BLOOD-PRESSURE RESPONSE TO MODERATE SODIUM RESTRICTION AND TO POTASSIUM SUPPLEMENTATION IN MILD ESSENTIAL HYPERTENSION

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Summary To determine whether moderate restriction

of dietary sodium content or supplementation of potassium intake reduces blood-pressure in patients with mild essential hypertension, twelve patients were put on

mild essential hypertension, twelve patients were put on three different diets-a control diet (180 mmol sodium/day), a sodium restricted diet (80 mmol/day), and a potassium supplemented diet (200 mmol potassium/day). Each diet was taken for at least 4 weeks and the sequence of the regimens was randomised. At the completion of each regimen intraarterial pressure was recorded continuously, and vasoactive hormones were measured hourly, for 24 h, under standardised conditions, in hospital. Compared with the control diet, sodium restriction was associated with lower blood-pressure readings in seven patients, higher levels in five, and an overall reduction in mean pressures of only $4 \cdot 0/3 \cdot 0$ mm Hg (not significant). Individual differences in blood-pressure between these two diets correlated closely with concomitant differences in plasma renin activity (r=0.75). Potassium supplementation also resulted in variable changes in arterial pressure, and the mean difference in pressure recordings $(0 \cdot 1/0 \cdot 8 \text{ mm Hg})$ was insignificant. The results show that moderate restriction of sodium intake or supplementation of dietary potassium has variable effects on arterial pressure in individuals with mild essential hypertension, and that overall the blood-pressure changes

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