ANNEX B 3282
1516

THE LANCET

Blood Transfusion, Haemophilia, and AIDS

THERE are new anxieties concerning the acquired immunodeficiency syndrome (AIDS), especially in its relation to blood transfusion and the use of plasma derivatives. The role of blood and its products in the transmission of the syndrome is being clarified by the detection of the putative virus called lymphadenopathy-associated virus (LAV) by the French group[1] and human T cell lymphotropic virus III (HTLV III) by the American group.[2] The evidence that HTLV III is the cause of AIDS includes its demonstration in tissues, the high incidence of antibodies to it in patients, and the development of AIDS in infants of apparently healthy antibody-positive mothers. The last observation suggests that the antibodies are not necessarily protective; and in fact they are not neutralising in the presence or absence of complement.[3] In the UK, antibodies to HTLV III were found in less than 1 in 1000 of the general population whereas they were present in almost all the AIDS patients and in about 20% of homosexual males.[4] Although four Australian premature infants contracted the disease from one donation,[5] the chance of AIDS developing after ordinary blood transfusion is very low. About 100 transfusion-associated cases have occurred in the USA, where some three to four million transfusions are given annually—a risk over the past three years of about 1 in 100 000 transfusions. However, the Australian experience illustrates both the risk to the premature immune system and one danger of divided donations.

What has been gained from the virological advances reported in 1984? The main immediate spin-off will be the large-scale development of antibody tests to exclude donors who are HTLV III antibody positive. Already five American commercial firms are competing to provide test kits, and there are confident predictions of success despite a high rate of false positives at present. Clearly, even a true positive test is not diagnostic of AIDS since most people who seroconvert have not acquired the disease. Neither does a positive test necessarily indicate protection or exclude the carrier state, since the antibodies are not neutralising. Presumably also donors may be infective before seroconversion occurs, so that tests for viral antigens will be needed to complete the screen. On p 1418 of this issue Dr Salahuddin and colleagues report on four such antibody-negative carriers. One was the wife of an AIDS patient and another the wife of a patient with AIDS-related complex, and these observations are very pertinent to haemophiliacs at risk. Nevertheless, HTLV III antibody screening and more rigorous donor selection should exclude most of the donors who constitute a risk. The chance of contracting AIDS from ordinary blood transfusion is therefore very small indeed and should become even less as donors are effectively screened. To limit blood donation to females is unnecessary and impracticable.

What of the risk in haemophiliacs? Fifty-two haemophilia-associated cases of AIDS have been reported in the USA (including two in haemophilia B patients and two in patients with other clotting disorders[6]) and three in the UK. The overall prevalence of AIDS in treated American haemophiliacs is about twice that in Europe,[7] but in countries that use factor VIII concentrate from the USA the incidence is likely to increase. Thus Gürtler et al[8] in Germany reported a steadily rising incidence of HTLV III antibody in stored samples from their healthy haemophilic population, from 0% before 1980 to 53% in 1984. In the UK, 32% of healthy haemophiliacs were found to be antibody positive[4] compared with 72% in the USA.[9] In a later American study 94% of treated symptomless patients with haemophilia A were found to be positive during 1984.[10] Since the prevalence of HTLV III antibody in the donor population in the UK is extremely low,[4] the virus was presumably acquired mainly via American concentrate. On p 1444 of this issue Dr Melbye and co-workers provide evidence for this notion. They report that, of Scottish haemophilic patients treated at one centre with domestic factor VIII concentrate only and who had not travelled abroad, none were HTLV III antibody positive whereas in other patients positivity correlated with exposure to American commercial concentrate. However, the prevalence of HTLV III infection in homosexuals and others seems to be increasing rapidly in countries outside the USA[11] and contamination of local blood products must only be a

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matter of time. Dr Melbye's findings must be reconciled with previous observations that this particular Scottish haemophilia population still exhibited the abnormal lymphocyte subsets seen in other haemophilic populations at risk.[12] These observations together with the relative lack of Kaposi's sarcoma in transfusion-associated and haemophilia-associated AIDS are consistent with suggestions[3] that the pathogenesis of AIDS involves something more than infection with HTLV III.

In the medium term, blood-donor selection by publicity, more searching questions at donor sessions, and serological testing should go some way towards exclusion of at-risk groups. However, experience with hepatitis B suggests that additional measures will be needed, because with products that are pooled from over 5000 donations even one HTLV III infected donation has contaminated a whole batch. Since HTLV III is relatively heat-labile,[6] heat treatment of concentrates (as developed for serum hepatitis) is a step that could rapidly be introduced. Alcohol precipitation and pasteurisation are used successfully for sterilisation of albumin, but treatment of protein to retain complex functions such as those of blood coagulation is more difficult. β-propiolactone and ultraviolet light have been used successfully to sterilise factor IX with regard to hepatitis[13] but these techniques inactivate factor VIII for therapeutic use and their effectiveness against LAV is unproven.[14] Dry heat, designed to conserve about 85% of the factor VIII, has been used for the first generation of heat-treated concentrates. In the UK unheated large-pool concentrates, even those prepared from voluntary donations, have transmitted non-A, non-B hepatitis,[15] and we learn that a first-generation dry heated concentrate has also transmitted the disease (Mannucci PM, unpublished). There are no published data concerning the transmission of hepatitis by concentrates heated in solution in the presence of stabilisers but the loss of factor VIII (and hence the cost) is probably much increased. Thus although dry heat shows promise of inactivating HTLV III in factor VIII concentrates, such concentrates are not necessarily sterile. Their clinical efficacy vis-à-vis AIDS and seroconversion remains to be studied in previously unexposed patients. Meanwhile the serious nature of AIDS justifies a pragmatic approach, and it is reasonable to switch to heat-treated factor VIII concentrate for haemophilia A. The position regarding heat-treatment of factor IX concentrate is less clear. HTLV III antibody and lymphocyte changes in haemophilia B seem to be less common than in haemophilia A[16,18] although AIDS is still occurring.[7] The effect of heat treatment on thrombogenicity of factor IX concentrate is unknown, but heat-treated factor IX is available commercially.

The National Hemophilia Foundation of the USA has lately examined the options, including the possible use of pharmacological means of raising factor VIII such as desmopressin (DDAVP).[17] Cryoprecipitate (or fresh frozen plasma for haemophilia B) prepared from a small number of donors is recommended for the treatment of children under 4 years of age and newly diagnosed patients but the large volumes have proved troublesome in small children. In the UK heated domestic concentrate should be more acceptable, though it may still involve a risk of non-A, non-B hepatitis. DDAVP is effective only in mildly affected patients with haemophilia A and von Willebrand's disease[17] but is an attractive option in this group who are at high risk of infection from concentrates. Extensive use of frozen cryoprecipitate prepared from selected plasma exchange donations, as suggested by McLeod and Scott,[18] is probably impracticable on a large scale and the material would not be as acceptable for home treatment as dried standardised heated concentrates. The aim of plasma fractionators should thus be to prepare factor concentrates from non-infected donors and to ensure sterility before use. For England and Wales a new blood products factory should be in operation in 1986 and Scotland is already self-sufficient, but the ability to provide all the products needed will depend upon increasing the supply of plasma at regional level. This will demand a reassessment of regional financing for plasma procurement, a requirement made all the more urgent by the AIDS crisis. Meanwhile, additional funds will be needed to purchase heat-treated concentrate. It would be indefensible to allow prescription and home use of material known to be at risk from HTLV III when apparently safer preparations are available.

These developments re-emphasise the need for adequately staffed centralised haemophilia facilities at which management and follow-up can rigidly be controlled; perhaps decentralisation has already gone too far. The safety considerations extend beyond haemophilia. All blood products must be reassessed in the light of these events. Hyperimmune globulin for hepatitis B and cytomegalovirus infection is derived from an AIDS-risk population but the preparative procedures used for this, for ordinary immunoglobulin, and for antithrombin III may well inactivate HTLV III. On the other hand, plasminogen, fibrinogen, and other pooled blood and human tissue products must be regarded as potential hazards until

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proved otherwise. Ethical questions are raised by HTLV antibody testing of blood donors and haemophiliacs. An unenviable task will be the counselling of people with positive results—a task made all the more necessary by the detection of virus in semen and saliva and the findings reported by Dr Salahuddin and colleagues in this issue.

Although the AIDS crisis is worsening, silver linings can be discerned in the clouds. The main causal virus seems to have been identified and, although there will be difficulties (eg, because of the lack of total protection by antibody), a vaccine will probably be developed. In addition several drugs active against reverse transcriptase, the virus, or serious secondary pathogens such as cytomegalovirus are under study including suramin, inosine pranobex, phosphonoformate, and ribavirin,[19-22] as well as immunorestorative agents. Meanwhile we must not forget that by far the commonest cause of haemophilic death is bleeding.

Q Fever: Antigens and Vaccines

Q FEVER is a disease of worldwide importance,[1] most notably as an occupational hazard in people exposed to infected cattle, sheep, or goats.[2] Nevertheless, the frequency of clinical Q fever in certain occupational groups varies from place to place, and unexplained outbreaks sometimes occur in the general population.[3] These sporadic outbreaks are presumably the result of airborne infection from an unrecognised source; exposure to infected milk from cows or goats may also be responsible for some cases.[4] On p 1447 of this issue Dr Kosatsky describes a Q fever outbreak in which the parturient family cat was a probable source of infection.

While Q fever vaccines have been available for some years, prophylaxis has been largely restricted to laboratory workers. Vaccination is commonly held to be effective but has a reputation for causing unpleasant reactions.[5] Early Q fever vaccines (Smadel vaccines) given to laboratory workers in the 1940s and 1950s undoubtedly caused some local and systemic reactions but a clear distinction was not always made between trivial effects at the inoculation site (eg, erythema, transient induration, tenderness) and more serious complications such as persistent masses, abscesses, and fistulas. Benenson[6] then reported that serious reactions were related to frequency of revaccination, and he also showed that local reactions were more apt to arise when Q fever complement fixing (CF) antibody was present before injection. Prevaccination screening for immunity or hypersensitivity was subsequently introduced.[7] Diluted vaccine was inoculated intradermally and only non-reactors were vaccinated, with the result that the frequency of reactions diminished. Development of modern, inactivated, whole-cell Q fever vaccines stems from the discovery by Stoker and Fiset[8] of antigenic phase variation in *Coxiella burneti*. When the organism is isolated from infected animals or man it has a surface antigen (phase 1) with some important biological properties.[9] If an isolate is passaged serially in chick embryo yolk sac, phase 1 organisms are gradually replaced by organisms lacking phase 1 antigen (phase 2). Inactivated vaccines made from purified *C burneti* in phase 1 are much more potent than comparable phase 2 vaccines.[10]

Interest in vaccine prophylaxis for certain occupational groups was rekindled in the 1970s by outbreaks of Q fever in research institutes and medical schools where pregnant sheep were used as laboratory animals, and more recently by sharp increases in Q fever in Australian abattoirs that had started slaughtering feral goats. On p 1411 Professor Marmion and his colleagues report the results of a South Australian trial with low dose (30 μg) inactivated, whole cell, Henzerling strain phase 1 vaccine in more than 1600 abattoir workers. Seroconversion of 50–60% was achieved, as judged by antibody tests of medium sensitivity, and no cases of Q fever were observed in vaccinated subjects who had time to acquire immunity after vaccination before they were exposed to natural infection.

This evidence of protection is encouraging but several questions remain unanswered. How long does protection last and are booster doses required? Single-dose vaccination regimens have been used in staff at the Rocky Mountain Laboratory for many years with no Q fever cases among vaccinees, suggesting that immunity is long-lasting. In abattoirs or other high-risk environments, protection given initially to the new recruit by vaccine might well be boosted by periodic natural exposure, without clinical illness; longer term investigations are needed to verify this. It is important to establish which markers are valid indicators of immunity after vaccination. Antibody tests vary considerably in sensitivity, and this complicates their use as an index of vaccine efficacy. Moreover, immunity does not depend on antibody alone;[8,11] there are strong indications that the outcome of *C burnetii*/macrophage interactions is central to the pathogenesis of Q fever and to immunity to the

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equally applicable, or better? Current pilot studies suggest that they probably are, provided that cheaper gene probes and methods for their labelling can be developed. This is a very important problem because as the high mortality rate in the first year of life due to malnutrition and infection is controlled in these countries, genetic diseases will pose an increasingly serious problem; there are already an estimated 700 000 severely affected children in Thailand for example.

But in a world in which millions of children die each year of starvation, the major medical application of recombinant DNA technology should be via improving world food supplies (see Dr Swaminathan's review, Dec 8) and for developing vaccines and diagnostic agents for parasitic and infectious diseases which, together with malnutrition, still look like being the main killers of the 21st century.

One of the major challenges arising from the development of biotechnology is how to persuade the governments and biotechnology industries of the developed countries that the problems of the Third World are worth tackling. Their present track records suggest that they will wish to confine their energies to diseases of western society where the financial rewards are greatest. It is sobering to reflect that if we were to develop a malaria vaccine over the next year or two it might be very difficult to find a biotechnology company to produce and market it. The first question they will ask is who will pay for the product; the answer is not obvious.

Broader Implications of Human Molecular Biology

The advent of recombinant DNA technology has raised the expectation that, as we gradually gain control over our genome, we may be able to modify the human phenotype more or less as we please. Already we have been regaled by television accounts of potential parents wandering around gene supermarkets stocking up their trolleys with genes that they would like to see expressed in their children, and fears of positive eugenics, with overtones of Nazi Germany, have been raised again—fears put into more sensible context by Professor Rose (Dec 15). There is no doubt that biological determinism is having a major impact on sociobiology and that the uncertain science which underlies this philosophy has already provided a convenient peg on which a few less balanced political groups have hung their views on how society should be regulated. But the fact is that we do not have the faintest idea about the nature of the complex interactions of genome and environment that underlie human behaviour. Indeed it is debatable whether we shall ever be able to adequately define love, greed, or jealousy, let alone the final movement of the "Jupiter" symphony, in terms of a DNA sequence. Perhaps in the long term our exploration of the human genome will provide some real insights into why we are what we are but it would be unwise to pin our hopes for the future on this expectation. In the meantime we must exploit the extraordinary medical possibilities of the new DNA technology, and try to ensure that our increasing knowledge of the human genome is not used prematurely to provide a basis for ill-conceived sociobiological theory and political extremism.

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Public Health

HTLV-III SEROPOSITIVITY IN EUROPEAN HAEMOPHILIACS EXPOSED TO FACTOR VIII CONCENTRATE IMPORTED FROM THE USA

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Summary 77 Scottish haemophiliacs and 22 Danish haemophiliacs were serologically tested for antibodies to human T-cell leukaemia virus III (HTLV-III). Since 1979 the Scottish patients had been treated largely with factor VIII concentrate produced in Scotland, whereas all but 2 of the Danish patients had received both locally prepared concentrate and commercial concentrate made from US donor material. 15·6% of Scottish and 59·1% of Danish haemophiliacs were antibody positive ($p<0·001$). None of 11 haemophiliacs not treated in the period 1979–84 was seropositive. 2 (6·7%) of 30 subjects who had been treated with locally produced concentrate only were antibody positive, compared with 23 (39·7%) of 58 subjects who had been treated with commercial concentrate. Among 52 users of both commercially and locally produced factor VIII concentrate, seropositivity was directly correlated with the consumption of commercial concentrate ($p<0·001$) but not locally produced material. These data indicate that European haemophiliacs were exposed to HTLV-III via some factor VIII concentrates obtained from the USA.

INTRODUCTION

HAEMOPHILIACS are at increased risk of the acquired immunodeficiency syndrome (AIDS).[1,2] In the United States this risk group comprises 1% of all diagnosed cases of AIDS, whereas in Europe, at the beginning of 1984, 8 (2·5%) of 314 cases had been reported among haemophiliacs.[3] AIDS is believed to be transmitted via the clotting-factor preparations used by these patients,[4–6] and antibodies to the probable causal agent(s), human T-cell leukaemia virus III (HTLV-III) or lymphadenopathy-associated virus, have been sought in haemophiliacs. Initial prevalence studies revealed a high prevalence of antibodies to these viruses in European[7] and American haemophiliacs[8] (and Goedert JJ, Sarngadharan MG, Eyster ME, et al, unpublished). We have compared HTLV-III antibody prevalences in two populations of haemophiliacs—Scottish patients who mainly use factor VIII concentrate of local origin, and Danish patients who use both imported and locally manufactured concentrates.

MATERIALS AND METHODS

Blood was taken from Danish haemophiliacs in Aarhus, during routine health evaluation in April, 1984; and plasma was kept at −70°C until testing. Detailed information was available on the

mount and origin of factor VIII or IX used by each patient since 979. Similar data were obtained on Scottish haemophiliacs nrolled in the Regional Haemophilia Reference Centre, Glasgow. llood was taken from these patients between December, 1983, and uly, 1984.

Antibody to HTLV-III was measured by an enzyme-linked mmunosorbent assay[9] in which disrupted whole virus (HTLV-II-H9)[10] was the substrate. Samples were run in duplicate and a known negative control was run eight times on each microtitre plate, the results for each being averaged. Sample results were compared with negative control results through the ratio of the two values.[11] Antibody was recorded as present if the ratio between sample and background was >5·0, and as borderline if the ratio was between 3·0 and 5·0. Tests for significance (χ squared and Wilcoxon-Mann-Whitney W test[12,13]) compare antibody-positive with antibody-negative persons, persons with borderline ratios being excluded.

RESULTS

Patient with AIDS

35-year-old Scottish haemophilia A patient with no other S risk factors had since 1979 been treated exclusively with US manufactured factor VIII concentrate in high dosage. In his last 7 months, he had malaise, anorexia, weight loss, intermittent fever, lymphadenopathy, and night sweats. There were persistent herpetic lesions of the lips and oral cavity, and also candidiasis of the mouth and anus. Latterly he complained of dysphagia and central sternal pain. He was HTLV-III seropositive, lymphopenic, and moderately thrombocytopenic, and had reduced responses to several mitogens. T helper cell numbers were reduced, as was the helper/suppressor ratio (May, 1984, 0·64; July, 1984, 0·29). In September, 1984, he was admitted to hospital with streptococcal septicaemia and he died in late October with *Pneumocystis carinii* pneumonia.

Healthy Haemophiliacs

22 Danish haemophiliacs (mean age, 22·8 yr, range 12–46) and 77 Scottish haemophiliacs (mean 34·9 yr, range 13–72) were enrolled. 12 (57%) of 21 Danish haemophilia A patients had antibodies against HTLV-III, as did a single haemophilia B patient (total, 59% positive; table I). Between 1979 and 84 antibody-positive subjects with haemophilia A had ived significantly ($p<0·05$) larger quantities of factor

TABLE I—HTLV-III SEROPOSITIVITY IN HEALTHY SCOTTISH AND DANISH HAEMOPHILIACS

	Total tested	HTLV-III antibody positive (%)
Scotland		
No treatment	11	0 (0·0)
Local	28	2 (7·1)
Commercial	4	1 (25·0)
Both	34	9 (26·5)
Total	77	12 (15·6)
Denmark:		
Local	2	0 (0·0)
Commercial	1	1 (100·0)
Both	19	12 (63·2)
Total	22	13 (59·1)
Both countries:		
No treatment	11	0 (0·0)
Local	30	2 (6·7)
Commercial	5	2 (40·0)
Both	53*	21 (39·6)
Total	99	25 (25·3)

*Detailed information on use of factor VIII concentrate missing on 1 subject (see figure).

TABLE II—MEAN UNITS OF LOCAL AND COMMERCIAL FACTOR VIII CONCENTRATE USED BY SEROPOSITIVE AND SERONEGATIVE HAEMOPHILIA A PATIENTS, 1979–84

	HTLV-III antibody		
	Positive	Negative	P*
Scottish			
Local	202·700	98·700	>0·05
Commercial	144·900	9·100	<0·001
Danish			
Local	164·500	144·200	>0·05
Commercial	499·800	51·800	<0·05

*Wilcoxon-Mann-Whitney (W) test.

TABLE III—HTLV-III SEROPOSITIVITY IN HEALTHY HAEMOPHILIA A AND B PATIENTS

	Total tested	HTLV-III positive (%)
Scotland		
Haemophilia A	62	11 (17·7)
Haemophilia B	15	1 (6·7)
Denmark		
Haemophilia A	21	12 (57·1)
Haemophilia B	1	1 (100·0)

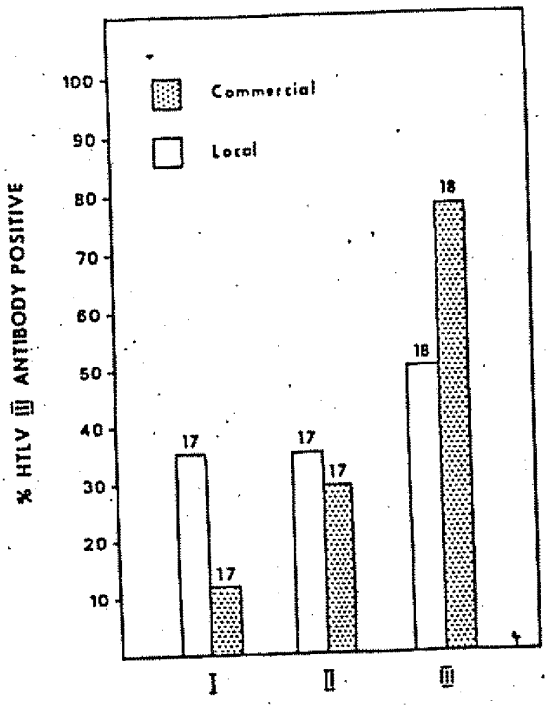
VIII concentrate made from US donor material (mean 498·8 units) than antibody-negative subjects (mean 83·8 units). There was no statistical difference between the amounts of locally manufactured concentrate used in the two groups (table II). The 2 subjects who had not received factor concentrate made from US donor material in the period 1979–84 were both seronegative, whereas the seropositive haemophilia B patient had used only US manufactured factor IX concentrate.

In Scotland, 11 (18%) of 62 haemophilia A patients and 1 (7%) of 15 haemophilia B patients were HTLV-III positive (tables I and III). All but 2 of the seropositive subjects were known to have received commercial factor concentrate in the period 1979–84: one had travelled yearly throughout Europe and could have received unrecorded treatment; the other was a citizen of Pakistan who often visited his home country. Seropositive haemophilia patients had received more commercial clotting factor concentrate than seronegative subjects ($p<0·001$), whereas there was no statistical difference between the two groups in use of local products.

As shown in table I, 40% of subjects receiving commercial factor concentrate either alone or in combination with local products had antibodies against HTLV-III, compared with 6·7% of those recorded as receiving only local products. HTLV-III seropositivity was more common in persons more exposed to commercially produced factor VIII (figure). The proportion with antibody rose from 11·8% among subjects in the bottom third of commercial product use to 29·4% in the middle third and 77·8% in the top third (trend analysis, $p<0·001$). In contrast, no significant difference in seropositivity was observed between groups classified according to their use of locally produced factor VIII concentrate.

DISCUSSION

Since 1982, almost all treatment in Glasgow has been with locally produced factor concentrate. Therefore exposure to the HTLV-III antigen is likely to have taken place among Scottish patients before then. In line with this observation are data from another study showing that some American haemophiliacs were infected as far back as in 1979 (Goedert JJ, unpublished). Clinical AIDS in an American citizen can



Percentage HTLV-III seropositivity among 52 haemophiliacs distributed into thirds according to use of both commercially and locally produced factor VIII concentrate.

Number of subjects tested is at top of each column. Use: I = lowest, II = middle, III = highest. Trend analysis: local, not significant: commercial, $p<0.001$

be traced back to 1978, so the virus must have been present in the United States before this date. In 1981, 9% of Danish homosexual men had antibodies against HTLV-III and seropositivity was most strongly correlated with travel to the United States and especially to New York City.[14] These and other[3,15] observations suggest that, in terms of prevalence of HTLV-III antibodies and incidence of AIDS, European homosexuals are 1–2 years behind those in the United States. However, the prevalence rates of HTLV-III antibodies in Danish haemophiliacs are similar to those in American haemophiliacs, probably because of the use of US plasma products. Furthermore, the estimated incidence of AIDS among American haemophiliacs, 1–2 per thousand, is very close to that in European haemophiliacs (1 per thousand).[16]

Our findings suggest that HTLV-III was distributed through haemophiliac populations by factor VIII concentrate made from US donor material. Although a high proportion of patients exposed to such products were seropositive, the effects on their health remain to be clarified. Both HTLV-III and lymphadenopathy-associated virus have been isolated from haemophiliacs with AIDS.[17,18] Furthermore, mouse type C retroviruses have proved to withstand the procedures used for factor VIII concentration;[18] however, lymphadenopathy-associated virus is labile under certain circumstances.[20] In addition, most factor preparations are stored for months at 4°C before use, and this might inactivate the virus while preserving its immunogenicity.

People in groups at high risk of AIDS are now asked to exclude themselves as donors; this should reduce the risk from future batches of factor concentrates. However, until viral contamination can be completely eliminated it seems desirable to treat newly diagnosed haemophilic children with concentrates from donors living in low-risk areas.

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"Viewing medicine as a battle too often reduces the patient to an object—a fragile boat, a rudderless frigate, a hapless barge of statistical misfortune tossed upon the stormy seas of illness. The doctor, in turn, views his responsibilities as a naval skirmish—a confrontation to be prepared for, fought, and won. The patient in this perspective is entirely passive. He hopes only to be saved. The doctor sends in his armada and tries to occupy disease's strategic islands; or occasionally he has to retreat. What he does not do is relate well to his patient. The family of the patient is also relegated to the role of helpless bystander . . . With distressing regularity, families are excluded from any substantive involvement with the physician . . . They hover compliantly in the background while physicians, medicine's gladiators, unsheathe their swords and do battle with disease. What a waste of powerful, and potentially healing, resources!"—DAVID E. REISER and DAVID H. ROSEN. Medicine as a human experience. Baltimore: University Park Press. 1984: 139.

HOUSEHOLD OUTBREAK OF Q-FEVER PNEUMONIA RELATED TO A PARTURIENT CAT

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Summary An outbreak of febrile respiratory disease occurred over 11 days among thirteen adults in Nova Scotia, all members of an extended family and their friends. Signs of illness included bradycardia at the same time as fever, palatal petechiae, and rapidly enlarging bilateral pulmonary infiltrates. Ten of the patients had a four-fold rise in antibody to phase-2 Q-fever antigen as determined by complement fixation on acute and 4-week-convalescent serum samples. Six children of the extended family for whom a four-fold titre rise was shown had slight or no disease. Investigations showed that the illness related to having entered the home of four of the patients on 1 of 2 consecutive days. On the first day the family cat, subsequently found to have antibody to Q fever, gave birth to kittens which she nursed in a basket kept inside the entry way. Q fever has been associated with parturient cattle, sheep, and goats but family pets, particularly cats, have not previously been implicated in human illness.

INTRODUCTION

THE manifestations of Q-fever infection vary from flu-like illness through acute multifocal pneumonia to chronic endocarditis.[1] Outbreaks of Q fever have been reported in occupational settings among abattoir workers,[2] animal laboratory assistants,[3] and soldiers in an endemic area,[4] but household outbreaks have received little attention. In spring, 1982, an outbreak of pneumonia among adults associated with a small house in rural Nova Scotia was related to Q fever. I report here clinical and epidemiological features of the outbreak.

SUBJECTS AND METHODS

Jordan Bay is a village of lobster and in-shore fishermen, 200 km south of Halifax, Nova Scotia, Canada. Homes are modest, and extended families strong. Hospital and medical care is provided at Roseway Hospital, Shelburne. Between April 26 and May 6, 1982, thirteen adults (aged 20–75 years) from Jordan Bay and the nearby area presented to Roseway Hospital with fever and respiratory symptoms. They were four members of family A living in a single Jordan Bay house, seven relatives living in six other houses 25 m to 5 km away, and two family friends. Nine patients were admitted to the hospital.

A case of "Jordan Bay fever" was defined as fever (>38°C) and chest tightness or cough among persons who lived in or visited the home of family A during April, 1982. Cases of Jordan Bay fever were sought among persons identified as having visited home A during April and among their families and neighbours. We identified three children in the extended family A who had had fevers during May, but no other subjects meeting the case definition were found.

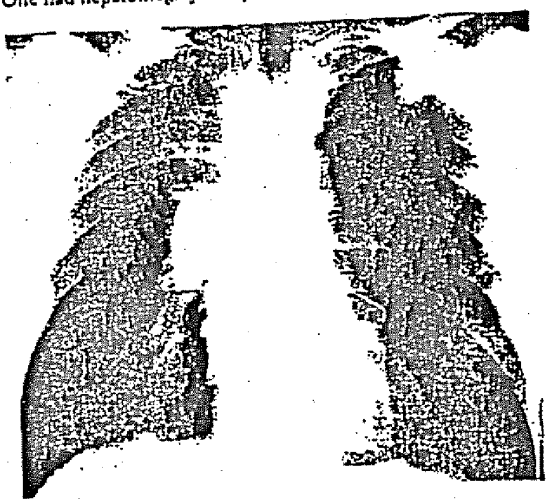
I carried out a standard evaluation, including medical history, physical examination, and laboratory and radiological examination of each patient. A questionnaire was designed to obtain information about the nature and duration of illness, secondary spread, and possible modes of spread. It was administered (during the second week of May) to people who had entered the home of family A during April, to neighbours living within 0·25 km, and to household contacts of the thirteen identified cases.

Serum samples were taken during acute illness from the thirteen cases and at the same time from six children and nine well adult members of their households (seven of whom had entered home A during April) and seven hospital nurses who attended the admitted patients. Repeat samples were taken 4 weeks later. Acute-phase and 4-week-convalescent serum samples were taken from five Roseway Hospital patients who had pneumonia in April or May but were not associated with Jordan Bay. In late May, a single serum sample was taken from six adults who had visited home A in April but had not been unwell, and from nine family pets belonging to the patients. Serum samples from the cases were tested against various antigens, and other serum samples were tested by complement fixation against the phase-2 Q-fever antigen.

RESULTS

Presenting symptoms among the thirteen adult Jordan Bay fever patients included malaise (all thirteen patients), anorexia (thirteen), chills (twelve), cough (twelve), squeezing sensation in the chest (eleven), headache (eleven), myalgia (eleven), ageusia (ten), coryza (nine), diarrhoea (eight), and vomiting (six). Other clinical findings are summarised in the table. Patients 1, 3–7, 9, 10, and 12 were admitted to hospital. The case of a 38-year-old lobster fisherman (4E) is illustrative. On April 27 a squeezing sensation developed below both shoulders with pain worse on inspiration. He noted chills, frontal headache, general myalgia, malaise, and coryza several hours later and non-productive cough the next day. He was admitted to the hospital on May 1. Blood cultures and sputum grew no bacteria. Admission chest X-ray showed three ill-defined bilateral pulmonary infiltrates with gradual enlargement and consolidation on a follow-up X-ray 3 days later (see figure).

Insufficient information was available to characterise the illness in case 11E. Patient 6A presented with headache, fever, and disorientation. The initial impression was meningoencephalitis; after 24 h of penicillin therapy he had recovered completely. While an X-ray of his chest showed no localised disease, those of eleven others revealed the atypical pneumonia pattern as described in 4E. All patients had basal chest crepitations. Splenomegaly was not seen in any patient. One had hepatomegaly. No patient had a skin rash. Punctate



Chest X-ray of case 4E 8 days after onset of illness.

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