plus 5 U regular insulin, 50 mmol NaCl, and 80 mmol KCl. On admission, blood tests showed the following abnormal values: white cell count $2 \cdot 5 \times 10^9$/l; K^+ 2·8 mmol/l, HCO_3^- 18 mmol/l; urea 1·0 mmol/l; ketone bodies ++; prothrombin time 50% with factors VII and X 22%, factor II 48%, and factor V 100%; IgA 3·2 g/l (152% of normal); and haptoglobin 0·2 g/l (24% of normal). The patient was fed intravenously for 3 days and left the hospital after 6 days, able to feed himself by mouth. Some gait instability persisted for one month and occasional dizziness for three months.

The three other fasters became increasingly reluctant, from the 34th to 36th day onwards, to drink more than a litre of water a day; their preference was for a brand with high salt and bicarbonate content. They complained of myalgia and feeling the cold. A rapid increase in tiredness, syncopal episodes, and the development of psychic lability meant that two fasters could not meet the Press on day 38. On Sept 12, the members of the alliance Fast for Life—mainly the respondents of the fasters and the fasters themselves—decided that fasting would be terminated in Paris and elsewhere by the 40th day, despite failure to achieve their objectives. Apart from sinus bradycardia and an increase in muscle wasting, clinical examination revealed no particular changes during these last few days. The blood picture and serum electrolytes remained unremarkable and on the electrocardiograms T waves and QT intervals remained within normal ranges.

Refeeding was extremely cautious for the first week, intake being restricted to boiled or raw unsalted vegetables. The fasters resumed their ordinary work on days 60–75, and within three months regained 95% of their original weight.

DISCUSSION

Total fasting in these normal non-obese adults seemed fairly well tolerated up to 18% weight loss, and was compatible with sedentary activities. There is no certainty, however, that our observations are applicable to other fasters. Repeated episodes of fasting augment the ability to endure food deprivation;[11] furthermore, in contrast to most hunger-strikers these four subjects had prepared themselves over several months and, aside from their grief as it became apparent that the protest would not achieve its goal, they had good living conditions and strong psychological support from their sympathisers.

Weight loss of 18–20% represented a turning-point at which ingestion of liquid became tedious, gastric intolerance developed, muscles became weak, and mental alertness waned. The main source of calories at this stage of starvation is fat; and, in theory, 20% weight loss is far from total depletion of adipose tissue.[12] We suppose that the abrupt transition from wellbeing to feebleness is due to some failure of metabolic adaptation, with or without deficiencies of essential elements; these observations add force to the view[11] that the supply of calories is not the prime limiting factor in survival.

What of the role of physicians in this episode? Between the medical team and the fasters and their respondents a trusting relationship developed, as indicated by the fasters' compliance with the physicians' minor practical recommendations and by their ready acceptance of the strongly expressed view of the senior physician (an active peace-worker and atheist) on the value of their lives and the worthlessness of proceeding further. Did the company of physicians, whose profession symbolises preservation of life, progressively sap the fasters' determination and lead them to believe that their cause would be better served by continued life than by death from inanition? Although the presence of the medical team led to timely hospital care in one instance, we do not know whether it influenced the decision of the other participants. One element in the dynamics of such a demonstration relates to the psychological pressure by which supporters compel the fasters to persevere in their efforts; success—measured usually in terms of media coverage—depends primarily on the performance of a few front runners. A medical presence may perhaps, in this context, provide a life-oriented counterforce.

The actions and views expressed by the authors may not represent those of their respective departments.

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Occasional Survey

ACQUIRED IMMUNODEFICIENCY SYNDROME AND OTHER POSSIBLE IMMUNOLOGICAL DISORDERS IN EUROPEAN HAEMOPHILIACS

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Summary A questionnaire concerning the occurrence of acquired immunodeficiency syndrome (AIDS) and possible related clinical syndromes in treated haemophiliacs was sent to directors of 201 European haemophilia centres. 135 replies were received from eighteen countries, covering 8928 patients with haemophilia A, 1889 with haemophilia B, and 2330 with von Willebrand's disease treated with blood products per year; 8 cases of AIDS were identified, one of which was in a patient with haemophilia B; 7 suffered from infections and 1 from pleomorphic non-Hodgkin's lymphoma. 3 other patients with lymphoma were recorded. The median age was 20 years with range 12–57 years and 3 were aged 14 years or less; 3 of the patients had died. 179 patients with other possible immunological disorders were recorded including 86 with lymphadenopathy but 70 of these occurred at one centre. At least 48 patients with thrombocytopenia were identified, suggesting that this condition is more common in treated haemophiliacs than is "idiopathic thrombocytopenic purpura" in the general population. None of the abnormalities could be related to use of any particular type of factor VIII concentrates. These results, together with 3 cases of AIDS previously reported and

not returned in this study, point to an incidence of 11 cases in 13 000 treated haemophiliacs.

INTRODUCTION

THE features of the acquired immunodeficiency syndrome (AIDS) include opportunist infections such as *Pneumocystis carinii* pneumonia and oesophageal candidiasis and tumours such as Kaposi's sarcoma and non-Hodgkin's lymphoma. There is associated evidence of impaired T cell mediated immunity and, sometimes, abnormal B cell antibody responses. Other symptoms or signs arise, such as weight loss, diarrhoea, lymphadenopathy, and thrombocytopenia and these are usually referred to as AIDS-related features.

AIDS is thought to be due to passage of a transmissible agent, although a non-infective aetiology has not definitely been excluded.[1] The infective theory is supported by the observation of unusual opportunistic infections[2] and thrombocytopenia[3] in haemophilic patients treated with coagulation factor concentrates. In addition, 18 cases of AIDS have been reported from the USA following transfusion of ordinary blood products into recipients who were not otherwise at risk, and in each case so far studied in detail an at-risk donor has been identified.[4] A recent assessment of AIDS in haemophilia documents 21 patients in the USA (19 haemophilia A, 2 haemophilia B).[12] There are about 20 000 haemophiliacs in the USA, so the incidence of AIDS in haemophilia there is about 1/1000, but if, as in the UK,[5] only about 50% of patients need treatment in any year,[5] the incidence in treated haemophilia is probably about 2/1000. About 30% of otherwise healthy patients with haemophilia A who have received treatment with factor VIII concentrate have abnormal T cell markers.

Most of the information concerning the incidence of AIDS in haemophilia has come from North America.[2] Only a handful of patients have been reported from Europe although factor VIII concentrates prepared from American blood are widely used there. Thus 2 cases have occurred in the UK,[6] 3 (1 fatal) from Seville in Spain,[7] and 1 from France.[13] This report presents the results of a survey of the prevalence of AIDS and "AIDS-related complex" in European haemophiliacs.

METHODS

A simple questionnaire was sent to the directors of haemophilia centres in 18 European countries as listed in the World Federation of Hemophilia (WFH) Guide for Travelling Hemophiliacs. The questionnaire was dispatched at the beginning of December, 1983, and the deadline for receipt was given as Jan 20, 1984. It was divided into two parts. The first solicited information about the number of patients at risk (ie, patients with haemophilia A and B and von Willebrand's disease treated per annum, eg, in 1982); the types of treatment used; and recent changes of treatment policy. The second sought information on the number and details of patients with AIDS and possible AIDS-related features. The clinical criteria for diagnosis of AIDS broadly followed the Centers for Disease Control criteria; possible AIDS-related features included thrombocytopenia, granulocytopenia, haemolytic anaemia, lymphadenopathy, unexplained weight loss, fever, and immunological abnormalities (eg, of T cells). In addition, information on other risk factors such as homosexuality or intravenous drug addiction was sought.

201 forms were sent and 135 replies were received in time for analysis. As a measure of the completeness of the survey an attempt was made to assess the expected prevalence of treated haemophilia in the various countries and compare this with the numbers reported. In the UK there is a nationwide system of designated haemophilia centres each one of which sends detailed yearly statistics to a collating office at Oxford. There is reason to believe that the treatment of the great majority of British haemophiliacs is recorded by the haemophilia centres so that the number of patients treated annually is known. Although only 54 of the 107 UK haemophilia centres are listed in the WFH guide, these represent the larger centres and many of the other centres, to which a questionnaire was not sent, treat fewer than 10 patients a year. From the national figures for all UK centres for 1982 the prevalence of treated haemophilia A in the UK was estimated at 40·2 per million population (table I). In any one year a similar number of registered patients with haemophilia A and B, mainly those who are mildly affected, are not treated so that the total prevalence of haemophilia in the UK is about 80 per million. The expected prevalences for treated haemophilia in each European country were calculated from these UK figures. Although this method requires assumptions about gene frequencies and intensity of treatment which may not be correct it at least gives some idea of the completeness of the survey and, possibly, the relative prevalences of treated haemophilia in different countries. Thus it can be calculated that, although the smaller UK centres were not included in the survey, data on 88% of treated UK haemophilia A patients were received (table I). Similarly, data on 105% of the estimated number of treated Swiss patients were reported (data not shown), indicating that coverage of Switzerland was probably complete and that the prevalence of treated haemophilia (ie, mainly severe forms) in Switzerland is similar to that in the UK. On the other hand, data from some other countries seemed less complete, either because the gene frequencies are lower than in the UK or, more likely, because the WFH guide is incomplete. Thus only 5 centres were indicated in Italy and the guide did not include centres in Naples or Rome.

Table I gives data on completeness of the survey. Over 13 000 treated patients were covered in a population of 367 million. The high figure for von Willebrand's disease is due to the higher prevalence of the condition in Scandinavia than in the UK. Underreporting in the UK and the other European countries seems unlikely from comparison with related data.[8] The survey therefore covered about 65% of European patients with treated haemophilia A and B and von Willebrand's disease.

RESULTS

The number of patients reviewed and the abnormalities reported are listed in tables II and III. 8 patients were recorded by respondents as meeting the criteria of AIDS (7 with opportunist infections and 1 with non-Hodgkin's lymphoma). 3 further patients were reported with lymphoma. Of the AIDS patients, 1 had other risk factors—namely, homosexuality and drug abuse. It is noteworthy that 1 had haemophilia B; and patient 8, from Portugal, had been treated only with cryoprecipitate and fresh frozen plasma. The median age of the AIDS patients was 20 years and 3 had died. There were no reports of Kaposi's sarcoma.

179 patients were reported to have had other abnormalities. 48 had thrombocytopenia, 6 had granulocytopenia, and 86

TABLE I—COMPLETENESS OF SURVEY: % EXPECTED PREVALENCE TREATED HAEMOPHILIA REFERRED TO UK PREVALENCE

	Total population ($\times 10^6$)	Questionnaire reported haemophilia			Expected haemophilia from UK prevalence			% expected prevalence reported		
		A	B	vW/d	A	B	vW/d	A	B	vW/d
UK	56	1979	317	289	2251	284	272	88	83	106
All countries	367	8928	1889	2330	14 700	2495	1761	61	76	132

TABLE II—CLINICAL DISORDERS

Country	ITP	Granulocytopenia	Lymphadenopathy	Other/unspecified	Type of concentration used
UK	17	5	6	10	Mixed
W Germany	15	—	—	8	Mixed
Spain	6	—	70	3	Mainly imported
France	2	—	3	8	Local*
Austria	2	—	2	1	Mixed
Italy	3	—	1	—	Mixed
Netherlands	—	—	—	6	Local*
Switzerland	—	—	—	1	Local*
Sweden	—	1	3	1	Mixed
Greece	1	—	1	—	Imported and local
Portugal	2	—	—	—	Local cryo
Norway	—	—	—	1	Local*
	48	6	86†	39	

None reported from Yugoslavia, Cyprus, Finland*, Denmark*, Belgium, Hungary.
*Mainly local concentrates used.
†3 patients with lymphoma not classified as AIDS also reported.

TABLE III—AIDS IN EUROPEAN HAEMOPHILIACS

Patient	Diagnosis	Country	Age	Alive/dead	Infection	Tumour
1*	A	W Germany	28	a	Candida	—
2	A	Spain	26	d	Candida, herpes, CMV	—
3	A	Spain	14	a	—	Pleomorphic non-Hodgkin's
4	B	France	12	a	Toxoplasma	—
5	A	Austria	?	a	Candida	—
6	A	UK	57	d	Candida, *P carinii*	—
7	A	UK	20	a	Candida, *P carinii*, herpes	—
8	A	Portugal	12	d	*P carinii*, candida, CMV, cryptosporidiosis, herpes, TB	—

*Homosexual, drugs.

had lymphadenopathy (though 70 of these were from one centre in Spain). 39 were said to have other or unspecified abnormalities and some of these could have been thrombocytopenia, granulocytopenia, or lymphadenopathy so that the figures for these must be regarded as minimum estimates. Data on in-vitro lymphocyte tests were too fragmentary to be of epidemiological value. Of the 179 patients, 8 were homosexuals and 5 were drug addicts.

An attempt was made to relate the abnormalities to the type of factor therapy—domestic or imported—but it was not possible to relate the development of thrombocytopenia &c to any particular type of concentrate.

Information was also sought on changes of attitudes to treatment. Of 135 respondents 40 admitted to a recent change of clinical practice presumably due to the development of AIDS in treated haemophiliacs. Among these 40 the changes were as follows: stopped using US material, 7; reduced US material, 23; increased use of cryoprecipitate, 26; increased use of FFP, 8; stopped prophylaxis, 4; stopped elective surgery, 5; advised curtailment of activities, 11; and increased use of heat-treated concentrate, 4. A high proportion of haemophilia physicians in some countries (eg, Netherlands and Sweden) had changed their practice but overall about two-thirds had made no changes.

DISCUSSION

The occurrence of AIDS in haemophilic patients in the USA is usually attributed to the presence of an infective agent in factor VIII or IX concentrates. Since identical concentrates prepared from imported American plasma are widely used in certain European countries, it is possible that cases of AIDS will arise in haemophiliacs in these countries also. Even if the pathogenesis of AIDS involves a non-infective component such as protein load, the prevalence of the condition in European haemophiliacs is still of interest.

To date few European cases have been reported. 2 British cases were reported to the Centre for Disease Surveillance and Control in London[6,9,10] and 3 cases were reported from Seville in Spain.[7] The present report covers an estimated 65% of treated patients from 18 countries. 8 patients had been classified by their own physicians as having AIDS. In addition, information covering the 3 cases previously reported from Spain[7] was not returned in the present survey so that if these are included the total of reported European cases is 11, giving an incidence of about 1 per 1000 treated haemophiliacs. The median age of the patients in the present survey was 20 years and it is noteworthy that at least 3 of the patients were 14 years old or less. The tendency of AIDS to be more prevalent in older patients, noted by Evatt et al[2] in American haemophiliacs, was not apparent. 1 of the patients in the present survey had pleomorphic non-Hodgkin's lymphoma and 3 other patients with lymphoma were also reported.

The most important data concerning other possible immunological complications of haemophilia or its treatment relates to thrombocytopenia. At least 48 cases were reported. In Sweden the average yearly incidence of idiopathic thrombocytopenia (ITP) is about 3 per 100 000.[11] Although one should not extrapolate from incidences to prevalences, the findings suggest that ITP is more common in treated haemophilia than in the general population. Thrombocytopenia has been reported previously in haemophilia[3] but its relation to AIDS is doubtful. Conceivably it could represent an abnormal B lymphocyte response associated with impairment of self-recognition. Some cases may result from infection or from the presence of immune complexes.

A relation of AIDS and the other reported disorders to transfusion of imported blood products was not established. Most patients with von Willebrand's disease are treated with locally produced cryoprecipitate and patients with haemophilia B are often treated with domestic factor IX concentrates so that the most likely culprit is imported factor VIII. However, the French patient with haemophilia B was exposed to US concentrate.[13] It is noteworthy that no haemophilic patient with AIDS definitely related to transfusion of blood products was reported from Germany (including the Bonn centre), where very large amounts of American factor VIII concentrates have been used for many years, whereas the Portuguese patient with AIDS had apparently been treated only with cryoprecipitate and fresh frozen plasma. Therefore the role of American concentrates in the causation of AIDS in European haemophiliacs must be regarded as unproven. 23 of 135 haemophilia physicians in Europe had reduced their prescribing of American blood products and only 7 had stopped using them altogether. In view of the immense benefits that haemophiliacs have derived from treatment[10] physicians are naturally reluctant to abandon these agents, with their hypothetical dangers, in the absence of alternative concentrates which have been proven safer. This attitude may change as information accrues, and haemophilia treatment needs to be monitored world-wide.

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Epidemiology

LESSONS FROM THE STUDY OF IMMIGRANT MORTALITY

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THE disease patterns of immigrants are influenced by the environments of the original and new countries and by the process of migration. Study of these patterns by means of mortality statistics contributes to understanding of health and disease, provided that the assumptions underlying mortality studies are accepted.[1] Mortality is an indicator of morbidity and thereby of the health status of a community. Mortality rates are generally very stable and changes are gentle rather than erratic. Cause-specific mortality rates, and their variations over time and by place are largely a product of environment, historically determined style of life (eg, diet, smoking, alcohol, family size, fertility, social interactions), and genetics. Some of these factors act early in life and their effects endure—eg, the effects of age at menarche and age at first birth on breast cancer and the effects of age when smoking began on lung cancer. Others may act also in adult life—eg, the effects of diet and smoking on ischaemic heart disease. Cancers may have initiators that act early in life and promoters that act later.

At the time of migration the disease pattern of migrants, if they are a randomly selected group, should reflect that in the country of origin. After migration the effect of the new environment should gradually be seen on those diseases for which the rates are not solely determined by early exposure. However, migration is not random. The selection of migrants influences health and disease risks, although this effect is likely to disappear with time and in the second generation.

We have completed a systematic review of causes of death among immigrant groups in England and Wales.[2] Mortality rates were compared with rates both in the countries of origin and in England and Wales overall. The examples given here illustrate the general influences on mortality but also point to particular health needs that require attention by health services.

METHODS

Estimates of the populations at risk came from the 1971 census, which recorded country of birth of people present in England and Wales on census day. For the purpose of this study, anyone not born in England and Wales was considered an immigrant. Deaths occurring in the 3 years 1970–72 formed the numerator for calculating mortality ratios. Causes of death were coded according to the 8th Revision of the International Classification of Diseases. Death certificates were classified according to country of birth as listed on the registration document.

Although immigrants from the Indian subcontinent include people from all parts of India, Pakistan, Bangladesh, and Sri Lanka who may have differing mortality patterns, we had to consider them together. Analysis from the OPCS longitudinal study of a 1% sample of the census[3] showed that of deaths in people described as born in Pakistan at the census, 19% were said at death to have been born in India, thus underestimating death rates in Pakistanis. We therefore considered only the combined category, Indian subcontinent. Similar misclassification applied to "immigrants" from Northern Ireland, so we combined Eire, Northern Ireland, and "Ireland—part not stated" into the category Ireland.

For immigrants from the Indian subcontinent, death certificates for 1970–72 were classified from names into ethnic "Indian" and ethnic "British". For this analysis proportional mortality ratios (PMRs) were calculated separately for men and women with all deaths in England and Wales as standard. This is an age-adjusted indicator of the proportion of all deaths in each ethnic group due to a specific cause.

For all other analyses by country of birth, and by social class and country of birth, standardised mortality ratios (SMRs) were calculated with England and Wales death rates as standard. SMRs were calculated for original countries with the same standard.

Tests of statistical significance were not used in the report[2] because a very large number of comparisons were made, some of