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The epidemiology and transmission of AIDS: a hypothesis linking behavioural and biological determinants to time, person and place

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Abstract

Epidemiologically, the Acquired Immune Deficiency Syndrome, AIDS, is transmitted and distributed in the USA and Europe almost entirely in well-defined subsets of populations engaging in, or subjected to, the effects of behaviours which carry high risks of genital and systemic infections. The persons predominantly affected are those engaging in promiscuous homosexual and bisexual activity, regular use of addictive drugs, and their sexual and recreational partners. In such persons and in subsets of populations with corresponding life-styles, the risk of AIDS increases by orders of magnitude. Because of continuity of risk behaviour and of associated indicator infections, the incidence of AIDS over 3–5 year periods is predictable to within 10% of actual totals of registered cases in the USA and UK. Secondary transmission of AIDS beyond these groups is minimal or, in many locations, absent. There is no indication of appreciable spread by heterosexual transmission to the general population.

The Human Immunodeficiency Virus, HIV, is transmissible to some extent in general populations, and more so among promiscuous persons. It may cause viraemia, lymphadenopathy and latent infection (HIV disease) in anyone. In persons engaging in risk behaviours which themselves alter or suppress immune responses, it can interact with MHC, antibodies to other organisms and to semen, and other allogenic antigens to initiate a programmed death of CD4 lymphocytes and other defensive cells, as in graft-host rejections. This occurs also in haemophiliacs receiving transfusions of blood products, and is more pronounced in persons with reactive HLA haplotypes. The susceptibility of particular subsets of populations to AIDS is thereby largely explained. But these changes occur in the absence of HIV, and so do Kaposi's sarcoma, lymphadenopathies and opportunistic infections which are regarded as main indicators of AIDS. The hypothesis that HIV-1 can do all this by itself and thereby cause AIDS is falsifiable on biological as well as epidemiological grounds.

An alternative hypothesis is proposed, linking the incidence of AIDS to the evolution of contemporary risk behaviour in particular communities and locations in the USA, UK and probably in most of Europe. It does not pretend to explain the reported incidence of AIDS in Africa and other developing regions where data are insufficient to provide validation of the pattern of disease and contributory variables.

The immediate, practical implication of this alternative hypothesis is that existing programmes for the control of AIDS are wrongly orientated, extremely wasteful of effort and expenditure, and in some respects harmful.

Introduction

In 1984, a US Secretary of State announced that a retrovirus then named HTLV3, isolated from one patient in Paris, was the unique cause of loss of immunity in a severe infectious disorder first described in 1981 in some homosexual men and drug addicts admitted with unusual symptoms to hospital in New York City and California. Since then, there has been a world-wide consensus in medical science and beyond that this retrovirus, renamed HIV-1, and its innumerable variants are the unique cause of a more complex and extending range of disorders classified and repeatedly re-classfied as the Acquired Immune Deficiency Syndrome, AIDS. When this consensus was challenged by P.H. Duesberg in 1987 (see below), R.C. Gallo, the chief proponent of the claim for HTLV3, and leaders of the consensus replied in a Forum reported by

Table 1. Predictions of new cases and cumulative totals of AIDS in 1991 and 1992 in England and Wales by different methods.

Mathematical methods with references[a–d]	Predictions for years: 1991	1992	1982–92
High predictions[a]			
Exponential	6240	10700	24640
Wilkie: actuarial	6380	9152	24341
Day: Weibull	5160	8080	20582
Center for Disease Control	6273	10308	25618
Healy: extrapolation	8474	15440	34077
Middle of the range[a]			
US growth model	3950	4800	16270
Wilkie: actuarial	3067	37 70	13361
Anderson*	3030–3940	3810–4950	12010–15190
Cox: model for planning	2950	3600	12750
Royal Society Symposium, 1989[b]			
Day et al: back projection		737–3538	5101–12103
Wilkie: actuarial		3490–12097	13000–27000
Ishan: various		2272–2420	10950–11794
Low predictions:			
Public Health Lab Service, 1990	1090–2400	—	—
Stewart: regression**[c,d]	1254	1457	6101
Total of registered cases	1275	1418	6929

[a] See reference: Dept. of Health and the Welsh Office, 1988.
[b] See reference: Cox DR, Anderson RM, Hillier HC (eds). Phil Trans R Soc London (B) 1989; 325; 37–187.
[c] See reference: Stewart GT. Soc of Public Health, Official Handbook 1992-93.
[d] See reference: Lancet, 1993; 341; 898.
*From a model of transmission in homosexual men, proportionally adjusted to allow for heterosexual transmission.
** Rolling average, incidence/time; coefficient of correlation, $r > 0.9$.

Science Magazine (1988;241;514) that the 'Strongest evidence that HIV causes AIDS' came less from isolates of the virus itself than from prospective epidemiology. Having been engaged in epidemiological work which suggests the reverse, I then began a long struggle to persuade the immense epidemiological sector of the consensus that this assertion, no less than the microbiological evidence of causation of AIDS by HIV, merited reconsideration.

When Duesberg challenged the HIV hypothesis in 1987, the epidemiological evidence depended essentially upon a correlation between antibodies to HIV and a diagnosis of AIDS. This was a circular argument since, after 1984, sero-positivity to HIV mandated a diagnosis of AIDS in patients with a scheduled range of diseases, whether or not they were in risk groups. In 1989, a formidable defence of the epidemiological consensus was presented by the Royal Society of London in a Symposium (Cox, Anderson & Hillier, 1989) of invited papers which analysed the epidemic of AIDS to date in the UK and made predictions about its incidence through 1992. These analyses and predictions, like those of a preceding official Report (UK Dept. of Health and the Welsh Office, 1988), rested upon assumptions not only that HIV was the essential cause of AIDS in all its forms but also that all who were sero-positive would get AIDS which would then cause epidemics of tens of thousands of cases by heterosexual transmission in the general population of the UK.

The assumption that HIV would spread by heterosexual transmission was, to a limited extent, correct but predictions of similar spread of AIDS, as in the London Declaration of 1988, from the WHO (Mann, 1989; Sato, Chin & Mann, 1989) and by the Advisory Committee on Dangerous Pathogens (1990) were numerically exaggerated (Table 1), as were actuarial and other projections used for planning and estimates of spread

Table 2. Cumulative total of registered cases of AIDS in the United Kingdom (UK) and New York City (NYC) from 1982 to April 1994.

Presumed mode of transmission	UK population 57,000,000 male	female	NYC population 7,324,711 male	female
Sexual intercourse				
between males	6735 (86% of 7813)		23869 (50% of 47299)	
do plus IDU*	144		1926	
between male and female**	587	446 (5% of 8407)	203	3254 (6% of 57769)
do high risk	28	82	n/a	n/a
do abroad	503	324	n/a	n/a
do within UK	56	40	n/a	
Injecting drug users*	347	148	21301	7216
Subtotals	7813 (93%)	594 (7%)	47299 (82%)	10470 (18%)
Totals	8407		57769	
Mother to infant***	61	66	1246	
Blood or transplant	435	69	214	101
Undetermined	105	18	3267	1287
Subtotals	8414	747		
Totals (incidence of AIDS/10,000 population)	9161 (1.6)		63884 (87.2)	

*Injecting drug users.
**Includes injecting drug users as sexual partners.
***Including twins. Of 1198 mothers, 1170 (98%) were in high risk groups, 28 (2%) unknown.
n/a: Information not available after 1992 because of revision of CDC/WHO classification; see text.
Sources of data: UK: AIDS/HIV surveillance (Public Health Laboratory Service).
NYC: AIDS surveillance updates. (City Health Dept.).

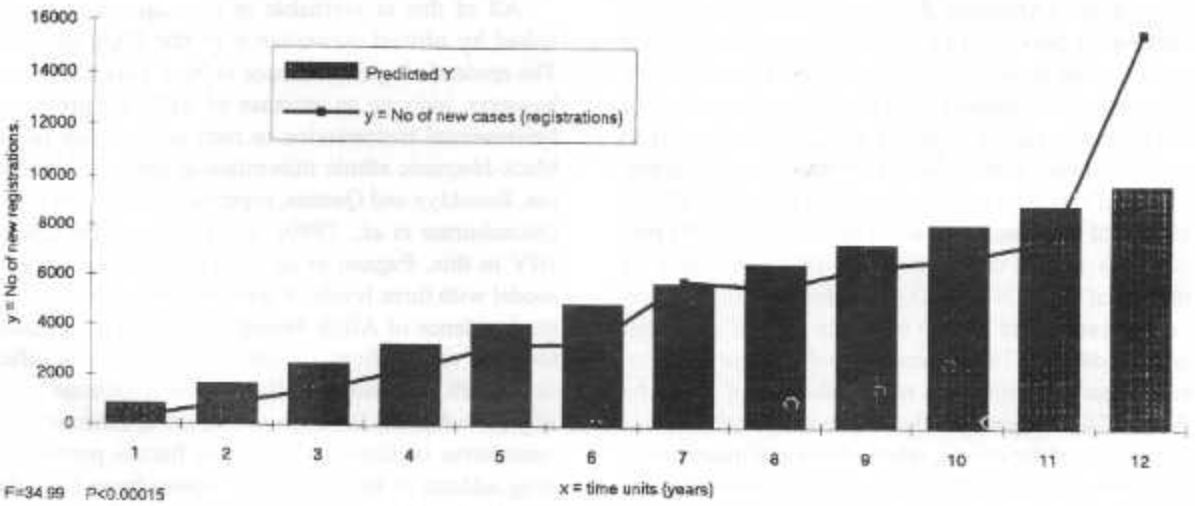

Fig. 1. New cases of AIDS in New York City, 1982-93.

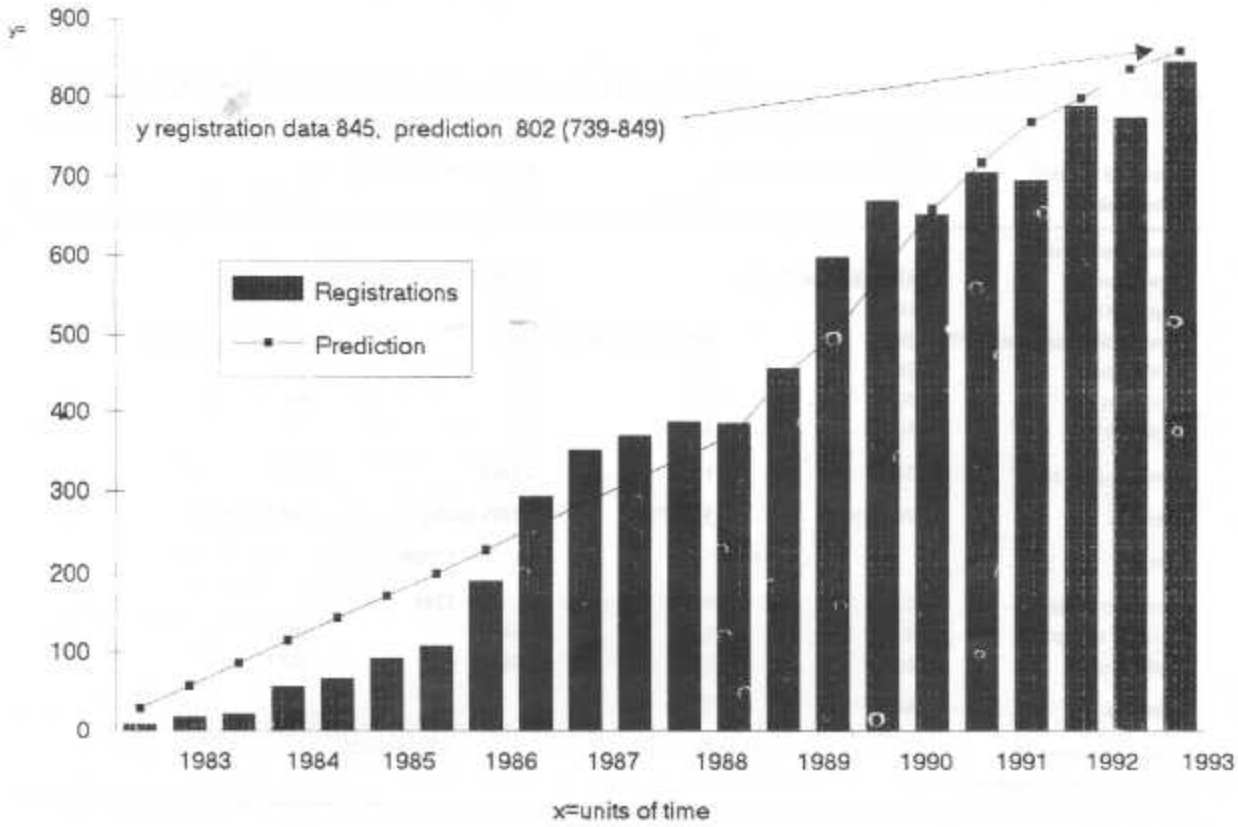

Fig. 2. AIDS in the UK: trend 1989-93 from regression y/x 1983-88.

outside the original risk groups of homosexual men and drug addicts. They were particularly wrong (Table 2) in the prediction that heterosexual transmission of AIDS in the general population would give rise to a general epidemic (Anderson & May, 1987; Public Health Laboratory Service, 1990). What the epidemiological evidence did show in the USA, in the UK, and most of Europe and Australasia, was a continuing increase of AIDS in the original high risk groups. This trend is so consistent that, even in New York City, an original epicentre of AIDS, a regression model (Stewart, 1992a, 1993a) of incidence over units of time since 1983 predicted in 1989 a cumulative total of 45,487 cases by the end of 1992 (N = 44,231). Predictions for the intervening years were correct to within 10% of registered cases though, in 1993, there was a departure from linearity caused entirely by reclassification of AIDS by the CDC in that year (see below) to include all cases of carcinoma of the cervix, tuberculosis and many bacterial pneumonias in HIV-seropositive patients (Fig. 1). In the UK, with a much lower incidence, regression models through 1993 and to date are equally accurate (Fig. 2). AIDS is a disease which began and spread in males. In females and their infants outside risk groups, the incidence of AIDS after ten years is negligible in the UK as in New York City (Table 2).

All of this is verifiable in the registrations published by official surveillance in the USA and UK. The epidemiological evidence in New York City does, however, indicate an increase of AIDS by presumed heterosexual transmission in men and women in the black-Hispanic ethnic minorities in parts of Manhattan, Brooklyn and Queens, especially if they use drugs (Stoneburner *et al.*, 1990). To investigate the role of HIV in this, Pagano *et al.* (1991) used an elaborate model with three levels of sero-prevalence to estimate the incidence of AIDS through 1995. Their estimates for 1991 ranged from 16,106 assuming no new infections to 29,962 assuming 10,000 new infections annually (N = 6,800). Fordyce *et al.* (1991) estimated the cumulative incidence of AIDS in female partners of drug addicts to be 3,900 (N = 4091) from formulae based on conditional probabilities of uninfected women acquiring HIV from infected male partners. But if

P/ivdu, the probability that a woman in New York will have a drug user as a sex partner, is replaced in the model by the alternative probability P/hiv that she is equally or more likely to be infected by any man who is HIV-positive, the estimate of AIDS again becomes exaggerated.

Incidence in the UK expressed as a rolling average or periodically since 1982 (Stewart, op. cit.) – and despite considerable fluctuations in reporting – follows the same close correlation with units of time ($r = 0.97$). Regression accurately predicted about 3,000 cases by December 1989 (N = 2,830), 1,254 in 1991 (N = 1,275), 1,365 in 1992 (N = 1,418) and in cumulative total, excluding visitors, of 6,540 (N = 6,929, including visitors) by the end of 1992 (Tables 1 and 2, Fig. 2). This is very much less than the range of 3,810 – 4,950 predicted by Anderson (2) for the year 1992 which gave a cumulative total, for planning, of 12,010 – 15,190 cases in the UK by December 1992 and much higher totals thereafter. In contrast, the regression model predicted only 1,554 new cases (excluding visitors) in 1993 when the actual total (including visitors) was 1,619, to give a cumulative total by 1994 of 8483 cases (N = 8529), over 3,000 less than the lowest official estimate for 1992.

The large errors in these predictions in Britain and in the USA are inherent. They derive from acceptance of the hypothesis that continuing sexual transmission of HIV is the main determinant of the incidence of AIDS. This led to further assumptions that heterosexual transmission will increase until females are equally at risk, that all who are infected with HIV will develop AIDS sooner or later and die, and that mathematical models based on this reasoning will predict the course of events correctly, within wide limits. The passage of time and the data since 1989 in the USA and in Britain falsify all this (Tables 1 and 2).

So also do back-projections for the UK, projections by Bregman and Langmuir (1990), based on Farr's Law of Epidemics, for the USA and estimates using socio-geographic data in New York City (Wallace, 1991). But predictions based on regression equations (Figs. 1 and 2) are more reliable because they leave less than 10% of residual variance in incidence since 1983 unexplained. Such accuracy in a deterministic model is highly unusual. The most obvious reason is that transmission and expression of AIDS is restricted to subsets of the population which engage in, or are exposed to, the effects of continuing risk-behaviour (Stewart, 1990a, 1991, 1992a). Even in those subsets, the incidence may now be decreasing in the USA and the UK. The accuracy of predictions from raw data by regression methods is consistent with the finding that, while HIV-1 has already spread widely in both sexes because of its presence in genital secretions and in needles shared by drug addicts, the occurrence of AIDS beyond risk groups, as predicted in all official surveys, is low or absent even in communities where HIV-1 is prevalent. The differences in levels of risk, calculated from best estimates of relevant denominators, are enormous (Table 3) and need much more attention.

The obvious conclusion is that, in such communities, AIDS cannot develop unless other interacting causes of immuno-suppression and cachexia are present. Registration data from the USA since 1985 show that prevalence of HIV and AIDS is strongly influenced by ethnic, urban, economic, social, occupational and mobility factors. In New York City, the situation is dominated by the fact that 60% of adults and 90% of infants with AIDS are in Black or Hispanic communities and by the 33-fold difference in rates of disease, from <50 to $>1,500$ per 10,000 adults, in different districts of the city (Table 2). In the UK, analytical data are much less precise but, to 30th June 1992, 1,354 cases of AIDS (38% of the cumulative total for Britain) were reported from NW London; 94% of these cases were male and 91% of them homosexual. Despite this prevalence of AIDS and also of HIV seropositivity, at least 20 times higher than the remainder of Britain, there were only 31 cases of AIDS in women transmitted by (presumed) heterosexual intercourse out of 401 who were seropositive. Infants born in London in 1992 were much more often seropositive than those born outside but, because surveillance is voluntary, unlinked, anonymous and confidential, it is impossible to know how this relates to the risks, status and treatment of the 50 mothers who have given birth from 1982–93 to babies who developed AIDS (about 1:120,000 births). In southeast England generally, it was estimated that 92% of neonatal seropositives and 7 out of 8 babies who developed AIDS in the first year of life came from mothers who were born in Africa (Ades, Parker & Cubitt, 1992). There is clearly a pressing need for a more informative data base and correlation matrix in the UK but, even in these limited data, it would appear that there is no appreciable spread of AIDS to infants from their mothers in the general population outside specified risk groups in or from well-defined locations.

Table 3. Cumulative prevalence per 1000 and distribution of AIDS in the UK by main risk groups.

Group	Population (estimates, in thousands)	AIDS in 1990 No	Prev	AIDS in 1994 No	Prev	Relative risk, Group/UK 1994 data*	do/LR
UK entire population	57,000	3845	0.06	9161	0.16	1.0	
UK 15–65 yrs Males	15,000	3234	0.2	7682	0.5	3.1	
UK do Females	15,000	207	0.007	597	0.04	0.25	
UK hom/bisex Males	840	3234	3.9	6879	8.2	51.3	2733
Central London, do**	50	2265	45.3	3577	71.5	469	24000
UK drug users	(200)	222	1.1	495	1.2	7.5	400
UK Heterosex M+F	33,000	268	0.008	1049	0.03	0.19	10
UK do . . . Low risk*	33,000	26	0.0008	98	0.003	0.019	0.12

*Ratio of prevalence in Group to that of entire population of UK, and to Low Risk Group (LR) ie = heterosexuals with no known contact with high risk groups.
**50–70% of this risk group are registered in two postal districts of central London

The current hypothesis

The hypothesis that HIV is the unique cause of AIDS is an inductive generalisation based on a few agreed facts and an acceptance in medical, sociological and political circles of corroborative reasoning, conjecture and consensus. The facts (Barre-Sinoussi, Chermann & Rey, 1983; Gallo, Salahuddin & Popvic, 1984; Dalgleish *et al.*, 1984; Levy & Chimabukuro 1985; Ho, Pomerantz & Kaplan, 1987; Hanafusa, Pinter & Pullman, 1987; Gallo, 1987) are that (i) HIVs can be isolated from, or identified by biochemical probes in cells, blood and secretion of an (unknown) proportion of patients with AIDS; (ii) in patients with AIDS who are tested serologically, antibodies specific for antigens prepared from envelopes of the original isolates of LAV1/HTLV III are usually detectable; (iii) in terms of this test, there is a correlation between the presence of HIV and AIDS in a community; (iv) HIVs appear to be transmitted from person-to-person by anal and vaginal intercourse, or parenterally via infected needles or blood transfusion, or congenitally; and (v) HIVs have high affinity for, and fuse with specific CD4 membrane receptors on helper T-lymphocytes and other mononuclear cells, transcribe their RNA into the DNA of the cells' nuclei and form virions which can infect other T-lymphocytes. The reasoning (Ho, Pomerantz & Kaplan, 1987; Blattner, Gallo & Tenin, 1988; Institute of Medicine, 1988; Baltimore & Feinberg, 1989; Fauci, 1988) is that HIVs can thereby weaken or destroy cell-mediated immunity, and that persons thus affected always or almost always succumb to a specific syndrome of generalised immune deficiency which then renders them susceptible to other, opportunistic infections and to various disorders of lymphoid cells and vital processes with fatal or near-fatal results. The conjecture of these authors and very many others is that infection with HIV is necessary and sufficient to explain this pathogenesis, irrespective of risk-behaviour. The consensus of the medical and scientific establishment, and practically all health authorities is that epidemiological evidence and predictions support this reasoning, and that any departure from it is heresy, a threat to public safety and efforts to control a dangerous epidemic, and to dedicated research.

Weakness in the HIV hypothesis

Despite this overwhelming consensus, or perhaps because of it, there are many uncertainties and flaws of reasoning in this hypothesis on epidemiological, clinical and microbiological grounds. Epidemiologically, the data presented above falsify the assumption that AIDS is spreading in general populations in the USA and UK by heterosexual transmission of HIV. The salient point that AIDS was described (Gottlieb, 1981; and see report from the CDC, Atlanta, Ga., from California State Health Department and from New York City, Dept. of Health) simultaneously in California and in New York City as focal incidents, with no evidence of anything comparable elsewhere at that time, is often overlooked. The first cases were registered in San Francisco on July 1st, 1981. By March 1985, 1,000 cases

had been registered, of which 992 (99%) were male and 98% homosexual or bisexual with multiple partners, with a very high prevalence of gonorrhoea, syphilis, hepatitis and other sexually-transmissible infections, with 13% using intravenous drugs and 98% resident in the Bay area. The position in 1992, in the UK, most of Europe, Australasia and North America at least, is that AIDS is still predominantly a disease of men (Table 2) and that the women who acquire it, at a much lower incidence, are those who expose themselves to high risks of infections from partners with AIDS or at risk of AIDS because of homosexual and bisexual behaviour, and from use of toxic drugs.

In female prostitutes, who are a risk group for any sexually-transmitted disease (STD), HIV infection and AIDS are prevalent in African cities (see WHO: weekly epidemiological reports) but not in North America or Europe unless they use drugs habitually or have other STDs. Seale (1988) suggested that, for this reason, AIDS did not qualify clinically for classification as an STD, and also because it is essentially 'A blood-borne infection which is transmitted only with considerable difficulty during biological sexual intercourse' – from which he excluded penile-anal intercourse. This would be consistent with the findings, in multicenter prospective and many other studies (Marmor, Friedman-Kien & Laubenstein, 1982; Shilts, 1987; Gunzburg, Fleming & Millar, 1988; Detels, English & Visscher, 1989; Ma & Armstrong, 1989; Beral, Bull & Darby, 1990) of homosexual men, that rectal trauma and infections from bleeding, douching, fisting and other traumatic and ano-erotic acts are associated with progression to AIDS and ARCs.

In Africa, the Caribbean and Asia, notifications of seropositivity to HIV and of AIDS to the WHO are increasing sharply. The epidemiological and clinical patterns, at face value, are different from those of the western world. Cases are reported with equal frequency in males and females and homosexuality and use of drugs are uncommon as risk factors. In place of the opportunistic infections reported in developed countries, tuberculosis, diarrhoeal diseases, malnutrition, exhaustion and early death are the main clinical features. Occurring as they do on a considerable scale in young men and women, this is widely regarded as a new, uncontrollable epidemic in many sub-Saharan countries. Details of CD4 counts, isolation of HIV and other tests are seldom available.

There is considerable genetic divergence in the comparatively small number of strains of HIV isolated in third world countries (Louwagie, McCutchan & Van der Groen, 1992; Pfutzner, Dietrich & von Eichel, 1992). As in the USA and Europe, AIDS is very uneven in distribution. Originally, it was reported from Uganda (Serwadda, Sewankambo & Carswell, 1985) as a localised, wasting 'Slim' disease, but now it has become an acute infection strongly linked with tuberculosis (Konotey-Uhulu, 1989; Berkley, Widi-Wirski & Odware, 1989; de Cock *et al.*, 1992). Along with other STDs, AIDS is increasingly prevalent in certain cities on the international travel routes of persons who sample the local risks, and convey their own infections and risk-behaviour to local populations. Hence the ominous spread in Africa via truck-routes, and in the UK in certain immigrants, visitors, returning travellers and their domestic partners (Hawkes *et al.*, 1992).

AIDS was not described in Africa until 1984, some years after the first occurrences in white men in the USA and in black Haitian immigrants in New York City. This, together with the prevalence of seropositivity to HIV in unconfirmed ELISA tests in Zaire in 1985, led the consensus to the belief (Gallo, 1987; Mann, 1989) that AIDS had therefore originated in Africa. A wide search was therefore made to find support for a subsidiary hypothesis that AIDS had spread somehow from Africa to the USA, if not to the rest of the world. The reasoning is that HIVs evolved like Simian Immune Deficiency Viruses (SIVs) latterly identified in non-human primates in Africa, either by phylogenetic separation of a retrovirus from a common progenitor in the distant past, or by cross-species transfer to humans more recently (McClure & Schultz, 1989). If this is shown to be genetically plausible, or if immune deficiency occurs naturally in non-human primates infected with SIVs, or artifically with HIV in the absence of other infections, the argument might become credible. But a very extensive search has revealed no common progenitor, and no link between any SIV and HIV 1 in Africa (Seale, 1988). Irrespective of the simian or other origins of HIVs the view that AIDS in the clinical pattern now observed was already prevalent in Africa is entirely speculative. There is no comparable study of the alternative possibility that AIDS might have travelled from its observed origin in the USA in 1981 somehow to Africa.

Classification of AIDS

AIDS is registered internationally as if it were a single infectious disease, and is surveyed accordingly, that

is to say as if it were a self-defining dependent variable. But the original empirical classification by the US/CDC accepted internationally in 1983 was expanded in 1987 to schedule a range of neoplasms, infections, malnutrition and dementia in which seropositivity to HIV, with or without risk-group identification, or these symptoms without seropositivity in risk groups were made eligible for classification as AIDS. This increased the size of the epidemic in the USA by about 27%. To this list of 'indicator' diseases, a further revision in 1992, synchronous with identical changes in the International Classification of Diseases, added cancer of the cervix, tuberculosis and other diseases in persons who are seropositive. This has already added numerous females to the incidence of AIDS (Fig. 1) and manufactured an epidemic in women which is, otherwise, conspicuous by its absence (Stewart, 1992b). To add to the confusion, there are growing doubts (Couruce, Muller & Richard, 1986; Meyer & Panker, 1987; Midthum, Garrison & Clements, 1990; Mortimer, 1991; Davey, Dayton & Metcalf, 1992; Papadopulos-Eleopoulos, Turner & Papadimitriou, 1992) about the lack of an independent gold-standard validator, and therefore about the specificity of sero-tests for HIV, even with double testing by immune-absorption and blot, in the presence of other infections and immunological disorders, especially in tropical countries. The fall in CD4 lymphocytes, required for validation, but seldom performed outside specialised units, is also a non-specific event (Drew, Mills & Levy, 1985; Jason, Holman & Evatt, 1990; Root-Bernstein, 1993) which occurs in many other infections and after infusions of foreign protein, e.g. to haemophiliacs (Carr, Edmond & Prescott, 1984).

Clinical diagnosis

In centres with expertise and facilities, surveillance of AIDS is monitored, with appropriate checks and tests. In reports from such centres, the pattern of AIDS is consistent and predictable, as above. But HIVs can be isolated from persons with and without AIDS or related conditions (ARCs). The great majority of seropositives show no signs of disease. To accommodate the continuing absence of AIDS in such persons, the 'incubation' period between infection and the onset of disease has been extended to 15 years or more in the 1987 and subsequent classifications by the CDC and WHO. This had led to a muddled situation in which anyone with the wide spectrum of symptoms and signs in these various classifications who has antibodies to antigens in any one of the several antigen-kits, or a fall in CD4 counts, is liable to be diagnosed as AIDS: so are person in risk groups with some of the signs, whether or not they are seropositive, and seronegatives not in risk-groups with signs who then become seropositive. The Revised Classification now in use raises to 28 (in Section B20-24) the number of independent diagnoses that may now be registered as AIDS. Section B21.0-9 includes 6 specified and 3 unspecified malignancies, to which cancer of the cervix is now added. This alone has already added thousands of cases of AIDS to survey totals of AIDS internationally. Section B21.7-9 (any cancer) and B22 (any other specified or wasting disease) in anyone who happens to be seropositive and in many who are not, add many more. Details of collateral or co-incidental disease, and tests to exclude other diagnoses are not required for registration, not even the CD4 (T4) lymphocyte count, mandated by the consensus as the hallmark of AIDS. Against all logic, this extraordinary diagnostic gallimaufry is accepted by the medical profession and the consensus as input data, not only for surveillance, but also for prediction of the spread of AIDS internationally.

Microbiology

HIVs have several properties which may relate to the pathogenesis of AIDS (Gallo, 1987, Fauci, 1988; Evans, 1989a). In addition to the gag, pol and env genes common to all retroviruses, they have five or more non-structural genes including a **tat** master-switch (Carlin, Peterlin & Derse, 1992; Elangovan, Subramanian & Chinnadurai, 1992) which enable them to regulate their replication and to delete, insert and duplicate nucleotides so as to evade immune responses. They are naturally lymphotropic and enter T-helper lymphocytes, among other cells, because their envelope glycoproteins interact with specific CD4 surface receptors (Dalgleish, Beverley & Clapham, 1985). *In situ*, they transcribe their RNA into the cell's DNA and replicate to form virions which have been shown to infect monocytes and macrophages as direct transfer (Fauci, 1988; Li & Burrell, 1992; Innocenti, Ottoman & Morand, 1992). These migrate to other sites, including the brain and thymus, where HIV may infect other cells, remain latent or replicate in accordance with the interplay of positive and negative regulatory elements in its own genome, or in those of defensive cells.

Retroviruses are characteristically latent (Duesberg, 1987; and see Hanafusa, Pinter & Pullman, 1989). HIV is no exception in the great majority of infected persons who remain, to date, asymptomatic. But this unusual combination of genetic heterogeneity and antigenic variability between strains of HIV, with mutability of nucleotide sequences within strains and tropism for migrant cells, would seem to offer plausible mechanisms for activation. In a search for amino acid sequences involved in cell tropism, Cheesebro *et al.* (1992) found homology in macrophage-tropic clones from different patients. T-cell-tropic clones were, in contrast, highly heterogeneous. Site-specific mutations in amino acid sequences in the V3 region of HIV isolates appeared to be responsible for these tropisms. This hypervariable domain within gp 120 is recognised (Shioda & Levy, 1992) as a major determinant of the ability of HIV-1 to infect T-cells and macrophages. These and other examples of genetic heterogeneity occur within as well as between strains, so much so that HIV has been described as a quasi-species in which no two genomes are identical (Wain-Hobson, 1989; Vartamian, Meyerhans & Wain-Hobson, 1992). Many are defective and, by the same token, non-infective. Proviral sequences vary accordingly, in the same or in successive isolates, and so do replication rates *in vivo*, as disease advances. The consensus accepts these properties of HIV as explanations of its ability to emerge from latency and of its pathogenicity. The impetus of over 60,000 supportive papers since 1983 is formidable even though much of it depends upon results obtained and elaborated *in vitro*. There is, as in other branches of biomedical research, a greater focus on the behaviour of the microbe than on that of the host.

The only prominent retrovirologist to question the consensus about HIV is P.H. Duesberg of the Department of Molecular Biology at Berkeley, CA, whose dissent is absolute. He considers that HIV is as inactive in patients with AIDS as it is in asymptomatic carriers. In fact, he goes further and rejects the wider claim by most virologists that latent viruses and mutated genes can be pathogenic (Duesberg & Schwartz, 1992). His arguments, dating from 1973 and extending far beyond the virology of AIDS, are set out in papers (1987, 1989a) and responses to criticisms (1989b, c). His main argument, as a retrovirologist, is directed against the central dogma that HIV infects, multiplies in and kills enough T-helper lymphocytes to destroy immunity. His observations that, in patients with AIDS, only 1 in 500 T-cells ever contain a provirus of HIV and that HIV cannot kill these cells have been confirmed independently by Lemaitre *et al.* (1990), the team which originally isolated HIV. His assertions that neutralising antibodies restrict multiplication of HIV, and that it does not have the biological energy or biochemical capacity to produce pathological changes *in vivo* have been disputed (Blattner, Gallo & Tenin, 1988; Baltimore & Feinberg, 1989; Evans, 1989a, b; Weiss & Jaffe, 1990) but not falsified. He offers evidence that, when latent viruses are reactivated after neutralisation by antibodies, this is due to independent factors (other infections, immunosuppressive conditions) and not to mutations in the coding region of the virus. He applies this view to other retroviruses and diseases no less than to HIV. If he is correct, or even partially correct, the implications will be revolutionary, for they will dismiss as circumstantial the current beliefs that latent viruses cause specific, progressive infections and that mutated oncogenes can ever cause cancer. HIV would then be merely a marker for AIDS while cancers would be more likely to arise from clonal chromosomal abnormalities.

In his original (invited) contribution to this field in 1987, Duesberg made a critical analysis of the facts and gaps in retrovirology in this regard. But in rejecting HIV as the cause, he also attacked the core of the biomedical research on AIDS. This led, after a considerable delay, to polarised reprisals with a minimum of reasoned debate (Blattner, Gallo & Tenin, 1988; AAAS Policy Forum, 1988) on his main question about the cytopathic effect of HIV. This is still unresolved. Even so, Duesberg would be wrong in rejecting a pathogenic role for HIV on this account alone because as Cheesboro *et al.* (1992), among others, have shown it can unquestionably infect monocytes and macrophages by cell-to-cell transmission, without killing them, and then travel in them to other tissues where the presence of infected cells would be enough to arouse inflammatory response and hence disease, e.g., a glial response in the brain. If there was already a latent infection with Toxoplasma, this could multiply to cause encephalopathy which is reported in about 30% of patients with cerebral AIDS (Root-Bernstein, 1993). When definitive signs of AIDS develop, HIV replicates and releases antigen (Ho, Pomerantz & Kaplan, 1987). It is insisted (Fauci, 1988; Baltimore & Feinberg, 1989; Weiss & Jaffe, 1990) that this is due to a regulated change from latency to accelerated replication, but it might equally be part of the general multiplication of organisms which occur in any immunosuppressive state, and is a main contributor to death in AIDS.

Duesberg's rejection of the claim that HIV kills lymphocytes *per se* is supported by the work of Lemaitre, Montagnier and their colleagues (1990) showing that the cytocidal effect of two archetypal strains of HIVs (LAV-Bru of HIV-1 and Rod of HIV-2) *in vitro* was lost in the presence of non-inhibitory concentrations of tetracycline analogues. Since these compounds do not interfere with the infectivity of HIVs, the likelihood is that a tetracycline-sensitive organism, now confirmed as a mycoplasma, plays the role of synergistic co-factor in HIV-induced cell lysis. It is now thought to be identical to *Mycoplasma fermentans (incognitus)* previously isolated by Lo (1986) from patients with AIDS. This mycoplasma has been visualised, isolated in culture and identified by DNA probes in thymus, lymph nodes, spleen, liver, brain and placenta of patients with AIDS and from HIV-negative patients with fulminant necrotising lesions or fatal disease in these organs. Most of the isolates were made from tissues without necrotic or inflammatory changes but ultra-structural examination showed, in some cases, intracellular mycoplasma and cytopathic changes in lesions from which no other pathogens were visualised or isolated. When injected into four monkeys, the mycoplasma caused systemic infection followed by wasting and death in 7–9 months with necrotic lesions without inflammatory reaction in which the mycoplasma (originally thought to be a virus-like agent VLIA) was identified by immunochemistry, *in situ* hybridisation and electron microscopy (Lo, Wang & Newton, 1989). DNA from *M. fermentans* has been detected in the blood of seropositive patients (Hawkins *et al.*, 1992) but, in a systematic study of patients attending an STD clinic, Katseni, Gilroy and Ryait (1993) found it also in peripheral blood mononuclears, throat swabs and urine from a majority of seronegative as well as seropositive homosexual men. This is unrelated to the stage of disease, CD4 count and cellular HIV load in the seropositive subjects.

Mycoplasmas are notorious as contaminants in tissue cultures, especially those requiring reinforcement. It is surprising that they have not been reported in the innumerable other laboratories which are working round the clock internationally with HIVs from many sources. Coming as they do from the scientists who discovered HIV, the results quoted above prove that HIV cannot kill T-lymphocytes without assistance from a mycoplasma. The work of Lo and his colleagues suggests, but does not prove, that this organism may have a synergistic or pathogenic role in AIDS.

The image of HIV as a universal pathogen is weakened further by the fact that the strains isolated in the USA and Britain were merely subcultures of the original strain (LAV-1) isolated in 1983 from a gland from a patient in Paris. Genuine independent isolates show continuous diversification (Shioda & Levy, 1992; Vartamian, Meyerhans & Wain-Hobson, 1992; Spencer, *et al.*, 1994). The strain type HIV-1 is uncommon or absent in some populations with AIDS in Europe and Africa, and is not cross-reactive with some prevailing strains (Quinn, Piot & MacCormick, 1987; Zwart, de Jong & Wolfs, 1990). Genetic heterogeneity and divergent sub-types of HIV on a wider scale, as reported above from Africa and India, might explain the variability in symptomatology and progression of AIDS. By the same token, this means that some strains are likely to be less, or much less pathogenic: a prospect already verified by the survival of the majority of infected persons in the USA and Europe. The consensus views that all who are infected will develop AIDS and probably die is falsified on this score alone.

In the weeks after infection with HIV, some persons develop a brief illness with fever and lymphadenopathy, similar to infectious mononucleosis. Seroconversion then occurs, producing antibodies to HIV envelope proteins gp120 and p24. The majority of infected persons remain asymptomatic but a minority, identifiable in terms of risk-behaviour and exposure to further infections, show the hallmark fall in CD4 lymphocytes with reversal of the T4/T8 ratio, lymphadenopathy, anergy, loss of immunity, multiplication of infection organisms including HIV, and other signs of ARCs or AIDS. From then on, AIDS seems to be irreversible, despite specific anti-viral and symptomatic treatment. The main pathological findings are pneumonias (*Pneumocystis carinii* or acute bacterial), gastro-intestinal infections (Candida, salmonellae, shigellae, entamoebae), co-incident or secondary infections of the skin, viscera and brain with other pathogenic and opportunistic bacteria, fungi and protozoa (Table 4); and, mainly in homosexual men, Kaposi's sarcoma. Some or all of these, along with failing nutrition and exhaustion, lead usually to early death, though mortality since 1983 has decreased considerably in developed countries (D'Arminio, Vago & Lazzarin, 1992).

Haemophilia

The occurrence of serpositivity to HIV and of AIDS following transfusions of infected blood and blood

Table 4. Infections associated with deficiency of immunity, including indicator diagnosis of AIDS according to the criteria (1)–(4) of the Centers for Disease Control, Atlanta, Ga.

Infecting organism	Diagnosis*		Localising signs
Viruses:	1 and 4	+	
Cytomegalo-		2	hepatic, neurological.
Epstein-Barr		3	lymphadenomas
hepatitis		3	hepatic
herpes		3	cutaneous, genital, ocular
Molluscum contagiousum		3	cutaneous
Papova		3	genital, cutaneous
Varicella-zoster		3	muco-cutaneous, ocular
Mycoplasma		2,3	systemic
Bacteria	4	+	
Mimea-herrelea		3	pulmonary or systemic
Mycobacterium avia spp		2,3	granulomata
do kansasii		2	pulm, dermal, lymphatic
do tuberculosis		1,2,3	pulm., extra-pulm.
Steptococcus moniliformis		2	pharyngeal, pulmonary
non-typhoid salmonella		1,3	enteritis, septicemia
hemophilus		3	in children only
pyogenic		1,3	abscesses
Fungi	4	+	
Aspergillus spp		3	pulmonary
Candida albicans		1,3	esophagitis
coccidiomycoses		3	pulmonary, systemic
Cryptococcus neoformans		3	neurological
Histoplasma capsulatum		2,3	pulmonary
Nocardia spp.		1	pulmonary
Protozoa:	2	+	
Cryptosporidia			enteritis, malabsorption
Entamoeba histolytica		1,4	colitis
Giardia lamblia		1	enteritis
Isospora spp.		1	enteritis
Leishmania donovani		1,3,4	cutaneous, visceral
Pneumocystis carinii		1	pulmonary
Strongyloides spp.		2	intestinal
Toxoplasma gondii		1	encephalitis

*(1) Gross inspection/microscopy. (2) Microscopy. (3) Microscopy, culture, serology, detection of antigen or DNA in body fluid or tissue. (4) Culture.

products in some haemophiliacs and other patients, and the apparent cessation of this after donors were screened and blood sterilised by heat, have been advanced as self-evident and conclusive proof of the causation of AIDS by HIV (Tsoulkas *et al.*, 1984; Ludlam, Tucker & Steel, 1985; Hiltgartner, 1987; Ward, Bush & Perkins, 1989; Darby, Rizza & Doll, 1989).

The existence of seroconversion and signs compatible with AIDS in recipients of transfusions, especially in haemophiliacs, is not in doubt. But this has to be considered against background facts. Blood transfusions are, by themselves, well-known to be temporarily immuno-suppressive. Patients receiving frequent transfusions are, by definition, in a risk category. Mortality, even in the short term, is often high, inde-

pendently of the HIV status of donors and recipients (Ward, Bush & Perkins, 1989). Repeated transfusions were shown by Carr, Edmond and Prescott (1984) to cause lymphocytopenia, abnormalities in subsets of lymphocytes including decreased or inverted T-helper/suppressor ratios, low NK cells, and abnormalities in B-cells and immunoglobulins. These changes are much more marked in haemophiliacs receiving frequent injections of Factors VIII or IX concentrated commercially from large pools of whole blood from thousands of donors. Prior to concentration and antiviral treatment of blood, many patients had received, not only HIV, but other blood-borne organisms, some of which (CMV, HSV, EBV, HBV, VZV) multiply readily in any state of immuno-suppression and aggravate progression to AIDS in persons at risk (Webster, Lee & Cook, 1989; Makris, Preston & Triger, 1990; Root-Bernstein, 1993).

Sources of infection in pooled blood are not easily identified. Ludlam and his colleagues (1985) followed a cohort of 32 haemophiliac men in Edinburgh who received HIV, identified subsequently by RNA/PCR assay in a single batch of Factor VIII of intermediate purity. Of these 32, 18 became seropositive to HIV and 12 developed immunological abnormalities and signs 2–6 years later 'attributable to HIV infection', including six deaths. Cell-free circulating virus was found in both asymptomatic and symptomatic patients, but signs of illness (CDC-IV) were confined to those with a prevalent haplotype A1 B8 DR3 already associated with immunological hyper-reactivity (Steel, Beatson & Cuthbert, 1988; Medical Research Council, 1990). The 14/32 who remained seronegative in 1993 showed no signs of ARCs or AIDS. There were no secondary cases of HIV or AIDS in female sex partners (Ludlam, 1993).

In a randomised three-year study, Seremetics, Aledort and Sacks (1990) found that the CD4 count remained high in 20 asymptomatic seropostiive patients who received a monoclonally-purified Factor VIII, but fell significantly ($P < 0.001$) in 15 who received a standard product of intermediate purity. One patient in each group developed signs of AIDS. Likewise, de Biasi, Rocino and Miraglia (1991) reported a fall in CD4 cells in 10 seropositive haemophiliacs who received standard Factor VIII of intermediate purity after 96 weeks, but not in 10 similar seropositive patients in whom treatment was switched to a product purified by binding with monoclonal antibody. Only 2/10 in this group became anergic and none developed ARC signs, whereas in the other group 9/10 became anergic and two developed signs (CDC-III). Since high-purity Factor VIII and Factor IX are now replacing all others, a follow up of these cohorts is essential for therapeutic as well as for aetiological implications.

Female partners of seropositive haemophiliac men may sero-convert within a year of presumed exposure, but this is variable and has been shown by Ragni and her colleagues (1987, 1989) and by Jin, Cleveland and Kauffman (1989) to be not significantly related to frequency of intercourse, condom use or immunological abnormalities. The rate of secondary transmission appears to be below 25% overall, and of subsequent AIDS 0–20%. It is surprising that, in the many surveys of HIV infection and AIDS in haemophilia, and in an official, collaborative, prospective study in Britain, there is little or no reference to this vital aspect of transmission and control of infection. However, the virtual absence of ARCs and AIDS in other surveys (Marcus, 1988) of tens of thousands of health professionals exposed to needle-stick injuries, lesions and body fluids in the routine care for patients with AIDS and HIV seropositives show that, with one questionable exception (Lancet, 1992) the pathogenicity of HIV, even when transmitted, is minimal or absent in persons who are immuno-competent, in contrast with that of hepatitis B which is so readily transmitted that immunisation is now a routine for clinical personnel.

These and many other studies define a risk population of haemophiliac and a very small minority of other patients who may sero-convert after transfusions of infected blood or blood products, and an even smaller subset who develop signs of AIDS and die. The transfusion and haemophiliac data do not prove that HIV causes AIDS because foreign proteins in repeated or concentrated transfusions cause immunosuppression and similar changes independently of HIV. In haemophiliacs and other patients with pre-existing defects in immunity (see Immune activation, below), this allowed HIV and other organisms – prior to safety measures introduced in 1985 – to multiply. The outcome was variable, but secondary transmission of AIDS and ARCs has been minimal.

Rejection of HIV as the unique cause of AIDS

HIV can be transmitted, though not readily, in sexual secretions and whole blood or blood products, and causes viraemia, lymphadenopathy and a prolonged, usually latent infection of lymphoid and other tissues.

This can be diagnosed, and is now classifiable as HIV-disease. But the collateral hypothesis that the array of complex disorders diagnosed as AIDS are uniquely caused by HIV is flawed *a priori* by the circular argument which mandates indirect evidence of infection with HIV (i.e. seropositivity) as the main criterion for diagnosis, and by a contrived classification which preferentially schedules as AIDS common conditions occurring independently in persons who are seropositive whether or not they belong to risk groups. Diagnosis is therefore wide open to subjective errors, confusing options and misinterpretations which are not corrected in international surveillance except in centres where expertise and standardisation are available. The dependent variable used for epidemiological input is therefore unreliably subjective. Analyses of data are impeded by failure to allow for confounding variables such as alternative diagnoses, false-positive serology, coincident infections, toxic drugs, sexual practices and other factors which emerge consistently in surveillance as determinants. The hypothesis has not offered an adequate defence against competent criticisms of some of its integral genetic and microbiological tenets. Its official projections and predictions are falsified, especially those postulating a pandemic of fatal disease spread by heterosexual transmission in the general populations of developed countries. It depends, for continuance as in its origin, on denial of the logic of a decade of surveillance data and on subordination of open thinking to a consensus of circular thinking about the mandated correlation between HIV and AIDS which refuses to tolerate interrogation.

An ALTERNATIVE HYPOTHESIS is proposed, suggesting that although HIV can cause lymphadenopathy and serconversion (HIV Disease), as stated above, the origin, pathogenesis and spread of AIDS can be better understood and explained as follows:

AIDS became an instant diagnostic entity in 1982 because the first cases died – as most of their successors still do – with two rare but conspicuous terminal disorders, Kaposi's sarcoma (KS) and pneumonia due to protozoan *Pneumocystis carinii* (PCP), together with buccal and oesophageal candidiasis, amoebiasis, toxoplasmosis and other well-recognised but unfamiliar infections with pathogenic or opportunistic organisms. These, with signs of immune deficiency, cachexia and fatality in young homosexual men and drug addicts, constituted a novel and dramatic clinical event, well described by Gottlieb, Friedman-Kien, Sonnabend and other early investigators (Root-Bernstein, 1993), and promptly recognised as an emergency by the U.S. CDC. But is was confined to these groups of men whose lifestyles had, in an explosion of high-risk sexual activity and use of toxic and euphoriant drugs, exposed then repeatedly to high risks of genital, rectal and blood-borne infections in places and practices which are best described by insiders (Shilts, 1987).

Genital, rectal, intestinal, pulmonary and systemic infections acquired in this way reflect the local human and environmental microflora of latent and active pathogens, facultative pathogens and commensals (Table 4), long associated with cell-mediated immunity and now accepted for classification as indicators of AIDS. The resulting diseases vary accordingly, in pattern and severity, in different localities and regions. They comprise infections, re-infections and multiple infections which soon undermine immunity and vitality. HIVs are prominent but not unique members of a group of viral invaders (CMV, EBV, HSV, HBV, HCV, VZ and possibly HTLVs), all of which may impair cell-mediated immunity (Root-Bernstein, 1993). Similar clinical states are seen in lympho-proliferative disorders, reticuloses, graft-versus-host rejections, autoimmune conditions, malignancies, irradiation, protein-calorie malnutrition, syphilis, and especially in interactions and intoxications due to drugs.

In AIDS, the original and most prominent routes of transmission are firmly linked to self-selected and self-propelled behaviour, namely penetrative anal intercourse and sometimes other forms of sexual contact, especially when traumatic or promiscuous, use of drugs, or both. These produce infections locally and in the blood stream, and are the primary and necessary, though not sufficient, cause of the majority of cases of AIDS registered in the USA, Europe and Australasia. Multiple local and systemic infections thus conveyed, including HIV, undermine immunity, interfere with healing and nutrition and depress vitality. These infections, especially with continuing risk behaviour, are sufficient to explain much of the pathogenesis in the two main risk groups of homosexual and bisexual men and needle-sharing drug users. AIDS in other persons – risk-sharing partners of cases, babies, recipients of transfusions – result from secondary transmission of infections and antecedent weakness or dysregulation of immunity as in infancy, genetic defects, haemophilia, use of drugs and malnutrition. But some of this was happening before AIDS appeared in its contemporary form, so additional explanation is required.

Homosexual and bisexual behaviour

Male homosexual relationships without anal intercourse or injections of drugs – arguably the majority (Ma & Armstrong, 1989; Stewart, 1990b) – are not associated with AIDS; neither is lesbianism. AIDS began and prevailed among those who are still at highest risk, namely the passive male, and sometimes female, recipients of anal intercourse. This is because the rectal mucosa and its supporting tissues are relatively fragile, designed for excretory, not intrusive activity. When the thin submucosa is eroded and blood vessels damaged, the tissues and blood stream are opened to invasion by all the organisms of the faecal microflora, by the pathogens of all the sexually transmitted diseases, and many others. The risk of trauma and infections increases greatly with the frequency, variety (oro-anal, lingua-vaginal) and violence of the sexual activity and preference, as with 'fisting' and other accessory, traumatic and contaminating procedures, and with multiplicity of partners (Witkins & Sonnabend, 1983; Mavligit, Talpag & Hsia, 1984; Moss, Osmond & Bacchetti, 1987; Winkelstein, Wiley & Padian, 1988; Sonnabend, 1989).

In such persons, the unregulated use of antimicrobial drugs for self-treatment of gonorrhoea and other infections inhibits the competitive flora of the intestine, opening it to bacterial and fungal super-infections which are indicator conditions for diagnosis of AIDS. Notable among these are *Pneumocystis carinii, Candida albicans*, cryptosporidia and organisms causing chronic diarrhoea, and hence dehydration, loss of electrolytes and exhaustion. The frequent presence of semen in the rectum and blood adds allogenic, 'non-self' reactions which dysregulate immune responses (Witkin & Sonnabend, 1983; Root-Bernstein, 1993). The faecal microflora interacts with semen to form N-nitroso compounds, some of which are immunosuppressive and carcinogenic (Schoental, 1988). Immunosuppression also occurs (Newell, Mansell & Spitz, 1985; Mirvish & Haverkos, 1987; Vandenbrone & Pardoel, 1989) from the use of volatile alkyl nitrites (poppers) as aphrodisiacs and relaxants – an effect which conveniently extends to the rectal sphincter. In experimental animals, these nitrosating agents are lymphotoxic, causing immuno-suppression followed by death from acute and chronic infections. Surviving animals sometimes develop lymphomas (Schoental, 1988). It is possible that the conjunction of N-nitroso compounds from semen with volatile nitrites contribute to Kaposi's sarcoma which occurs in this context independently of HIV (Beral, Bull & Darby, 1990). All this, combined with frequent, promiscuous anal and bisexual intercourse with dozens or hundreds of partners had become a way of life in the dedicated communities in which AIDS was first observed and in those (of remarkably similar persuasions and micro-flora) to which it quickly spread, internationally. Knowledge of the dangers sometimes led to a reduction in risk-behaviour but, by this time, genital and other infectious diseases were accepted as features of their way of life.

Transmission in heterosexuals

This is regarded by the WHO and the consensus as the usual mode of transmission of AIDS in many third world countries. In North America and Europe, surveillance shows some increase in AIDS occurring in both sexes from presumed heterosexual transmission but, in the UK and USA at least, the increase is fractional, even in persons with high risk partners (Tables 2 and 3) and in those attending STD clinics, and is confined to major urban areas. It is uncommon in prostitutes unless they are using drugs. AIDS in women outside the main risk groups is minimal or zero. Since seropositivity to HIV in random samples may be equal in the sexes, and since sexual intercourse with more than one partner by the age of 18 is now common, the key questions arising from the absence or infrequency of AIDS in females are if and why it occurs at all. Confidentiality of records and lack of contact-tracing deemed necessary in other STDs preclude answers. How much of what there is has been acquired from bisexual men, from anal intercourse, from undeclared use of drugs? But a thorough search of registration data in key areas of the USA and UK (Stewart, 1992a, 1993a) and of a vast international literature (Root-Bernstein, 1993) discloses no convincing reports of outbreaks of AIDS in females exempt from risk-behaviour or from circumstances which impose risks upon them.

Use of psychoactive and immuno-toxic drugs

An amalgam of debilitating infectious and wasting disease had been noted from the late 1960s onward in young adults and adolescents who injected themselves repeatedly with impure and unsterile, illegally-obtained psychoactive drugs (Gay, 1972; Moss, 1987; Selwyn, 1989). This practice causes bizarre, often intractable infections in the blood and various organs

from contaminants in the drugs. Needle-sharing, promiscuous sexual intercourse and general disregard of hygiene – a notorious feature of the drug scene everywhere – leads to sharing also of whatever infections are endemic in that community – PCP, HIV, hepatitis, herpes, EBV, VZ and CMV which may impair cell-mediated immunity and reverse T4/T8 ratios (Louria, Hensle & Rose, 1967, McDonough, Madden & Falek, 1980; Drew, Mills & Levy, 1985; Creglev & Mark, 1986; Moss, 1987). All the psychoactive drugs currently in use in this way, especially heroin and experimental mixtures, are profoundly depressing to appetite, general health and immunity. Cocaine and crack damage the respitory ephithelium which is a main barrier to all air-borne infections. Alternation of excitement and depression leads quickly to habituation, overdosage and reckless disregard of all the personal and societal consequences of this life style.

Drug use has been escalating in conurbations in the USA for 25 years, and is now the main reason for heterosexual spread of AIDS (Moss, 1987) there and in many other countries. If infection is minimised by using uncontaminated drugs and needles, or especially by opting for less toxic oral drugs such as methadone, many addicts can live equably with their habit for many years (Capel, Goldsmith & Stewart, 1972; Creglav & Mark, 1986). Otherwise, chronic infection, especially with therapy-resistant protozoa and fungi, leads to severe disease in target organs and often to death. A pregnant woman in this state transmits her infections and her drug-toxicity congenitally to her child. In some countries, drug addicts donate blood for payment and transmit their latent or active infections to plasma pools. Most or all of the extending range of infections listed as indicators for AIDS (Table 4) and other microflora from the local environment were perceived, together with defects in immunity, in persons in these categories before AIDS appeared. They now include multi-drug resistant forms of tuberculosis. The illegal use of drugs is also diversifying as a predictable but usually uncontrollable disaster in large and growing sectors of youth and young adults in the conurbations of the western world. HIV was well-established in this population internationally by 1985, and is continuing to spread within it.

Immune system activation

HIV differs from non-retroviral infections because of the affinity between glycoprotein 120 on the surface of the virus and CD4 receptors on T-cells. This facilitates entry of HIV into a minority of cells and initiates a generalised immune response: activation of T-cells, lymphadenopathy, antibodies to envelope proteins, antigen-specific tolerance, neutralisation of virus and latency of infection. The HIV hypothesis, postulating reactivation of virus by internal regulation and destruction of immunity by killing of T-helper lymphocytes is falsified by the fact that immunity is sufficient to arrest replication of virus and delay onset of further disease, in the absence of risk behaviour, by ten years or more. The usual signal of advance of disease is not viral replication, but a continuing fall in CD4 lymphocytes. In so far as it can occur in other infections, in graft-host disease and in disordered immunity, this is a largely non-specific event. But it is a significant event in AIDS because it is associated with the appearance of lympho-cytotoxic antibodies (LCTAs) acting against non-HLA antigens and peripheral blood B- and T-lymphocytes in some haemophiliac and homosexual patients (Pruzanski, Jacobs & Laing, 1983; Kiprov, Anderson & Morand, 1985; Ozturk, Koller & Horsburgh, 1987; Stricker, McHugh & Moody, 1987; Daniel, Schimpf & Opelz, 1989). These occur in seronegative and seropositive patients, but are much more prevalent in the latter and in homosexual and haemophiliac patients with AIDS. They are cross-reactive with major histocompatibility (MHC) class II proteins on B- and T-cells, with spermatozoal antigens (Ashida & Schofield, 1987; Root-Bernstein & Hobbs, 1991) and with antigens from *C.albicans*, the cause of the oro-oesophageal infection which was and is a main and early indicator for AIDS.

Male homosexuals have anti-spermatozoal antibodies in the blood, which cross-react with T-cells and have been linked to the occurrence of azoospermia and testicular atrophy in homosexual men (Adams, Donovan-Brand & Friedman-Kien, 1988; Ma & Armstrong, 1989). The same antibodies have been detected in female patients with AIDS (Sheppard & Ascher, 1990) and are cross-reactive with T-cells and HIV antibodies. The common factor is obviously anal intercourse, a main risk-factor for female as for male AIDS. These cross-reactions reflect a mixed state of allogenic and auto-immunity in which patients, with and without HIV, reject their own T-cells because they cannot distinguish them from antigens from spermato-

zoa, HIV, other infections, foreign proteins and cells in transfusions and in injection needles used for street drugs. This explains the selective incidence of AIDS in homosexual men, in women with bisexual partners or who engage in anal intercourse, and in haemophiliacs, some of whom would be additionally at risk because of innate disorders of immune regulation or of immunosuppression by drugs.

Sheppard and Ascher (1988, 1990, 1992) go further. They see the pathogenesis of AIDS as the outcome of two sets of signals acting on T-cells in a continuous process of immune activation. The first (specific) signal comes from the interaction of a T-cell receptor with an antigenic peptide presented as an MHC molecule following infection with HIV. The second signal is non-specific and is provided by self-molecules on cells which react with other T-cell receptors and regulate the activation produced by the first. Most of the progeny of the activated cells (lymphocytes and thymocytes) are eliminated by 'programmed death' (apoptosis) which restores the immune system to equilibrium (Zacharchuk, Mercep & Chakraborti, 1990), but a minority remain as 'memory' cells in a resting state in which they retain their capacity to respond to an appropriate stimulus (Beverly, 1991). This may come in various ways: in HIV infection, from activation of T-cells by interaction of gp120 with CD4, leading to lymphadenopathy and non-specific auto-immune responses. The shift toward programmed cell death then causes a fall in CD4 cells (McClure & Dalgleish, 1992). But there is evidence also of antigen tolerance by clonal deletion of reactive thymocytes and of B-cells of the spleen, by activity of superantigens (Quarantino, Murison & Knyba, 1991) which act on VB regions of T-cell receptors, and by what Sheppard and Ascher (1992) call a 'paradoxically-intense response' to peptides involved in allo-reactivity. It is likely that some of the many drugs used in the treatment of AIDS contribute to this. The outcome depends also on the frequency of exposure to antigens and on the ability of HIV quasi-species to induce the second signal.

One of the well-recognised immunological anomalies in AIDS (Duesberg, 1989) is that HIV can only replicate in the antigen-presenting T-cells which it suppresses. These cells multiply during the period of general immune activation in the onset of infection, and accept the gp120/CD4-TCR antigen complex (Dalgleish, Wilson & Gompels, 1992), after which they decrease. This is restricted to subsets with MHC Class II allo-determinants which mimic HIV-1, supporting the likelihood that the response is auto-immune, similar to that in graft-v-host disease, in persons in VB subfamilies with selective HLA-associated susceptibility to HIV-1 (Fabio, Scorza & Lazzarin, 1992). In a comprehensive investigation of the immunology, Root-Bernstein suggests (1992, 1993) that this response is a multiple antigen-mediated auto-immunity (MAMA) provoked by the various infections, drugs and allo-antigens. These theories offer an explanation of the mechanism of immune activation, but they do not explain the long periods of latency which may follow.

The evidence from this active immunological front presents AIDS in many patients as an auto-immune disease precipitated by rejection of T-helper lymphocytes and thymocytes in complicated cross-reactions with any or all of several antigens, and in self-nonself discrimination (von Boehmer & Kisielow, 1990; Sprent, Gao & Webb, 1990) in persons in genetically susceptible sub-populations. This results in an upset of immunological tolerance and a suppression of cell-mediated immunity to the point where it can no longer cope with additional infections. With spermatozoa as allo-antigens and drugs as independent immuno-suppressants included, and with the immunoreactive haplotypes in Caucasian populations defined, this would seem to be sufficient to explain much, if not all, of the pathogenesis as well as the selective and continuing incidence of AIDS almost exclusively in subsets of populations in defined risk groups in North America, Europe and Australasia.

The need for an alternative hypothesis

This has been raised on several occasions especially by Duesberg (1987, 1989), Sonnabend (1989), Evans (1989a) and by the author (1989, 1992a). Sonnabend, working with patients in Manhattan, was the first to explain the vunerability of homosexual men, in particular the effect of spermatozoa in the rectum on immunity. He suggested that risk factors for seroconversion are different from those for AIDS in which auto-immunisation, release of interferon, massive inocula in tranfused blood and blood-products, and a trigger effect of coincident viral infections might account for the pathogenesis of ARCs and AIDS.

Conclusion

An alternative hypothesis must explain not only the pathogenesis of immune deficiency in AIDS, but also the pattern of transmission and epidemiology. In the hypothesis presented here, AIDS is presented as a disease acquired in the first place by self-preferred or imposed behaviours, which in themselves dysregulate immunity and homeostasis while also leading to exposure to various pathogenic and opportunistic infections. The complex syndrome which follows has infectious, immunological and metabolic features. The hypothesis rejects HIV as a unique and sufficient cause of all this but agrees that it is transmissible in sexual secretions and blood, causing HIV disease: lymphadenopathy and febrile illness followed by latency or minimal pathological change during which there is evidence of direct cell-to-cell transmission of virus to migrant mononuclears and neural cells, of direct encephalopathy and of immune activation.

AIDS and AIDS-related complexes (ARCs) develop, with and without HIV, because heterologous antigens in spermatozoa enter the rectum and bloodstream, or in whole blood and blood concentrates given as transfusions, provoke allogenic responses and elicit antibodies which are toxic to lymphocytes, and cause a fall in CD4 counts. HIV can do the same by joining with CD4 receptors on T-helper lymphocytes presented along with MHC Class II proteins because of molecular affinities. This complex is tolerated, because it is recognisable at first as self, so HIV survives in clones of activated lymphocytes and monocytes in the presence of neutralising antibodies. But repeated infections of the genital, alimentary and respiratory tracts conveyed with various heterologous antigens, as above, maintain the T-cell activation while anti-lymphocyte antibodies are being formed. This leads to auto-immunity with a fall in CD4 count, reversal of the T4/T8 ratio, anergy and programmed cell death of T- and B-lymphocytes, consistent with the collapse of immunity, and atrophy of thymic and splenic follicles found post-mortem in patients dying with AIDS. It explains the general absence of AIDS in immunocompetent persons, the special susceptibility of homosexual men and haemophiliacs, and the risk to the foetus of a mother with AIDS; and it is entirely consistent with the epidemiological pattern of AIDS in the USA and most of Europe to date.

The occurrence of AIDS in drug users is attributable, firstly, to the general immunosuppressive properties of most of the major psycho-active drugs at present in use and secondly, to contaminants and impurities which cause refractory infections and dysregulate immunity. Persons in this risk category often overlap with the male homosexual group. Girls and women place themselves at high risk by taking drugs or by having intercourse with men in high risk groups. If they are pregnant, their infants share these risks by intra-uterine or perinatal exposure. Otherwise, the spread of AIDS by heterosexual transmission in either direction is minimal or absent except in sub-Saharan Africa where registrations are increasing rapidly, but in a totally different clinical and epidemiological pattern which overlaps with other, prevalent infections and with malnutrition.

Predictions made on this basis are accurate to within 10% of registered totals of current and cumulative incidence in the USA and UK. The risk-behaviour hypothesis postulates that, for these reasons, AIDS will continue to occur in persons and communities in defined susceptibility groups although HIV disease will be much more widely prevalent. Along with other organisms (HSV, CMV, VZ, EBV, various protozoa, fungi and bacteria), HIV can be activated from latency by various forms of risk behaviour, as described above, because this leads to an overload of genital, alimentary, pulmonary and systemic infections compounded by dysregulation of natural immunity, either by spermatozoa in the rectum and blood in persons of either sex experiencing traumatic anal intercourse, or from organisms acquired in oral sex, or from the immuno-toxic effects of injected or ingested drugs or from self-medication by broad-spectrum antimicrobial agents or, frequently, from all of these in life-styles which disregard elementary rules of hygiene and nutrition. In persons choosing these life-styles, AIDS is essentially a self-inflicted disease which can only be prevented by awareness and self-control. For persons upon whom these risks are inflicted, one way or another, it is becoming increasingly and tragically obvious that protection is imperative.

Impact of this new hypothesis on research and control of AIDS

The monopolistic hypothesis that HIV-1 is the unique cause of AIDS has, since 1984, led not only to erroneous predictions, but also to widespread misinformation and grotesque errors in prognosis, treatment, allocation of resources and strategy for research (Rubin, 1988; Adams, 1988; Eigen, 1989; Stewart, 1989,

1992a; Craven, Stewart & Taghavi, 1994). Resources and funds for the longer term are allocated mainly for single-factor strategy based on the false assumptions (Montagnier, 1994) that a specific vaccine or drug will eliminate or cure AIDS. Even if this were possible, the ethical and logistic problems would be immense. To whom would the vaccine be given? Would recipients be encouraged to continue risk-behaviour? How else would exposure and efficacy be measured? Or will the vaccine or vaccines be used as shot-guns on the blind guess that everyone is already at risk? Since heterosexual spread is not occurring in developed countries on anything approaching the scale envisaged in official predictions, it is easy to see how a vaccine used widely at this stage could be given credit for control of a pandemic which is not occurring. On the drug front, the consensus jumped the gun by promoting the use of Azidothymidine (AZT, Zidovudine), a highly cytotoxic drug, for prophylaxis in seropositive pregnant women and infants on the assumption that without it, they would all develop AIDS and die. This policy continues, despite the evidence in the prolonged Anglo-French Trial (Aboulker & Swart, 1993; Concorde, 1994) which showed no significant prophylactic effect in symptom-free HIV-positive subjects in terms of survival or disease progression after five years.

If the HIV hypothesis is inadequate or wrong, the risks and misplacement of effort and research since 1984 will be enormous. The alternative hypothesis offered here differentiates HIV infection and disease from AIDS which, in developed countries at least, is a complex amalgam of diseases determined first and foremost by high risk behaviour in subsets of populations in restricted social, ethnic and geographic locations. It postulates that prevention depends essentially upon recognition and control of these existential determinants by education, notification, contact tracing and, if necessary, by legal constraints upon behaviour which places unaware or passive persons, including unborn infants, at equally high or higher risks. The situation in the developing world is even more serious but is different in ways which cannot be understood without a more informative data-base about the distribution and pattern of AIDS and other life-threatening and sexually-transmitted diseases, and about life styles in affected countries.

The data and predictions supporting the alternative risk-behaviour hypothesis are presented here in a manner which opens them in the short term to falsification and correction, for instance, by factual data excluding other diagnoses and confirming the occurrence of destruction of immunity with unremitting signs of AIDS and HI-viraemia by secondary transmissions to and between persons not engaging in risk-behaviour, or in infants of seropositive mothers not exposed to direct or indirect risks.

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