this age group is invited to a screening programme or not—which is a matter of debate because the benefits of screening this group are still not clear⁸—has little effect on demands for resources for surgical care. The high prevalence of cancer in women over 70, on the other hand, shows that this group should be accorded great importance in the planning of mammography screening. The study also indicated that screening programmes should be scheduled to invite women of mixed ages, not specific age groups.

Many mammographically diagnosed cancers (around 40%) are detected at an occult stage and require preoperative radiographic localisation and perioperative mammographic examination of the specimen. The increase in the use of services will therefore be concentrated at hospitals where such resources are available.

The low incidence of operations for benign lesions of the breast and the insignificant effect of screening were unexpected, though they probably reflected the high specificity achieved in the trial (98.9%).¹³ During the first round of screening two out of three women referred to surgery had breast cancer; the corresponding figures for the second round were three out of four.¹³ Low specificity, entailing referral to surgery for many women with benign and often occult lesions, can obviously increase the workload. The management of women requiring surgery for a mammographic lesion that is not unequivocally malignant is also important. Inpatient care may be advisable to achieve accurate preoperative diagnosis and radical removal of the lesion and for a better psychological care of the patient. Differing policies with regard to such cases will influence the demands made on resources for surgical inpatient care.

It is too early to make confident predictions about the long term consequences of mammographic screening for surgical inpatient services. The reduced absolute numbers of stage II and more advanced cancers found during screening¹⁶ and the increased diagnosis of non-palpable lesions should influence policies for diagnosis and treatment. An increasing number of women will be

offered breast conserving treatment and fewer will undergo chemotherapy. Reduction in recurrence of and mortality from breast cancer should also have long term effects⁸ as the treatment of recurrent breast cancer is expensive and time consuming.

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Seroepidemiology of human immunodeficiency virus in Africa

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Abstract

Serum samples from 6015 African subjects without symptoms of the acquired immune deficiency syndrome (AIDS) or contact with the disease were examined for antibodies to the human immunodeficiency virus by a combination of an enzyme linked immunosorbent assay and radioimmunoprecipitation (2567 samples) or by immunofluorescence (3448 samples). Serum samples had been collected between 1976 and 1984 in Senegal

(n=789), Liberia (935), Ivory Coast (1195), Burkina Faso (299), Nigeria (536), Gabon (1649), Zaire (15), Uganda (164), and Kenya (433). Only four samples contained antibodies. Three of these were from attenders at the Lambarene clinic in Gabon and one from a villager in Senegal. By contrast, two out of six AIDS suspects from Guinea-Bissau, all 13 patients with AIDS from Kinshasa (Zaire), and two out of three of their contacts were seropositive, all these specimens having been collected in 1985.

These data show that fewer than one in a 1000 subjects were seropositive for AIDS at the time of sampling before 1985 and do not support the hypothesis of the disease originating in Africa.

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Introduction

The acquired immune deficiency syndrome (AIDS) was diagnosed in patients from equatorial Africa from about 1981 at roughly the same time as the epidemic was recognised in North America and Europe, and AIDS is now widespread throughout central and eastern Africa.¹⁻⁵ Transmission in tropical Africa differs from that in North America and Europe, being primarily by heterosexual contact; risk groups have been identified as urban dwelling, wealthy, mobile, and promiscuous heterosexual men, their wives and children, and women prostitutes.⁵⁻¹² Only in South Africa is transmission more common among homosexual men than in other groups.¹³

Various seroepidemiological studies on African populations have used purified virus from H9 cells infected with human T cell lymphotropic virus type III (HTLV-III) as antigen for the enzyme linked immunosorbent assay and the Western immunoblot as a confirmatory test. Serum samples from over 12% of symptom free subjects in eastern Zaire gave positive reactions.^{14,15} Frequency of positivity was highest in children under 5 and rose with age in adults; it was highest in the uneducated, agricultural workers, rural dwellers, and those of low weight. The age specific profile for antibodies against HTLV-III paralleled closely that for antibodies against *Plasmodium falciparum* and there were strong positive correlations between positive enzyme linked immunosorbent assay results against HTLV-I, HTLV-II, and HTLV-III on the one hand and antibodies against *P. falciparum* and levels of immune complexes on the other.¹⁵ Similarly, 21% of healthy subjects tested in Kenya were positive for antibody to human immunodeficiency virus.¹⁶ Serum samples stored since 1970-3 from a small group of Ugandan children with Burkitt's lymphoma and age matched controls gave positive reactions in over 60%.¹⁷

The disparity between seropositivity being most frequent among the rural non-elite and children while the disease is most common in urban dwelling, elite adults has been explained by the hypothesis that the AIDS virus has evolved from a closely related virus infecting non-human primates in Africa. Having crossed the species barrier there is a high level of transmission, especially among young children in the most economically deprived rural communities of equatorial Africa, with so far unrecognised morbidity and loss of life. Those who survive to adulthood are immune, have no impairment of immune functions, and show none of the features of AIDS. The current epidemic is the result of urban drift and symptom free carriers from rural areas infecting non-immune urban adults.^{5,11,14,18-20}

An alternative explanation for these discrepancies between the African populations reported to be seropositive and the populations at greatest risk of developing AIDS is that the assay system yielded a high proportion of false positive results among the rural non-elite Africans.^{5,15} We have reported finding a high incidence of false positive results when we tested for antibodies to the human immunodeficiency virus in various parts of Africa; not one of 1794 serum samples could be confirmed as positive by immunoprecipitation, despite 18% reacting in the enzyme linked immunosorbent assay.²¹

This paper reports the frequencies of human immunodeficiency virus specific antibodies in 6015 serum samples collected between 1976 and 1984 from subjects without symptoms associated with AIDS in nine countries of Africa—namely, Senegal, Liberia, Ivory Coast, Burkina Faso (Upper Volta), Nigeria, Gabon, Zaire, Uganda, and Kenya. In addition, we examined samples from 13 patients with AIDS in Zaire and three of their contacts and from six AIDS suspects in Guinea-Bissau. These samples were all collected during 1985.

Materials and methods

CELLS AND SERUM SAMPLES

H9 cells infected with HTLV-III were provided by the National Institutes of Health, Bethesda, Md, and kept in Roswell Park Memorial Institute 1640 medium supplemented with 10% fetal bovine serum.

Tables I and II show the origins of the serum samples. Those from Gabon were provided by the Bernhard Nocht Institut; those from Senegal by the University of Tours, France; those from Nigeria by the Ahmadu Bello University, Zaria, and the University of Calabar; and those from Kenya by the Deutsches Krebsforschungszentrum, Heidelberg. The six samples from AIDS suspects in Guinea-Bissau were donated by the Universidade Nova of Lisbon.

SEROLOGICAL ASSAYS

The enzyme linked immunosorbent assay was performed as described with purified HTLV-III virus from the culture supernatant of H9 HTLV-

III cells.²³ Typically, 0.5 µg was absorbed per well of the microtitre plate and serum samples assayed in duplicate at dilutions of 1/50 and 1/250. The second antibody was a goat antihuman IgG coupled to horseradish peroxidase. Bis-diazobenzidine was used as substrate for the peroxidase reaction. All samples attaining optical densities twice or more than background obtained with a negative reference serum were re-examined by immunoprecipitation using cell extract and supernatant.

For the immunofluorescence assay H9 cells infected with HTLV-III and uninfected H9 cells (negative controls) were dried on slides, fixed with acetone at -20°C, dried, and incubated with a 20-fold dilution of the serum to be tested. Human antibodies bound to the cells were detected by staining with fluorescein isothiocyanate labelled goat antihuman antibodies.

TABLE I—Examination of serum samples from Africans for antibodies to human immunodeficiency virus by enzyme linked immunosorbent assay (ELISA) and immunoprecipitation (IP)

Country of origin	Year of sampling	Subjects studied	No of samples	No (%) reacting to human immunodeficiency virus		
				ELISA		
				+	±	IP
Senegal	1981	General population	789	3 (0.4)	63 (8.0)	1
Nigeria	1982	Hospital attenders	236	0	9 (3.8)	0
	1984	Blood donors	300	0	0	0
Gabon	1983	Pregnant women	144	0	1 (0.7)	0
		Hospital attenders	552	23 (4.2)	107 (19.4)	1
		Villagers	98	3 (3.1)	5 (5.1)	0
Zaire	1983	Hospital attenders	15	1	0	0
Kenya	1981	Students	300	0	16 (5.3)	0
	1984	Hospital attenders	133	1 (0.8)	6 (4.5)	0
Guinea-Bissau	1985	AIDS suspects	6	1 (16.7)	1 (16.7)	2
Total			2573	32 (1.2)	208 (8.1)	4 (0.16)

TABLE II—Search for antibodies to HTLV-III in serum samples from Africans by indirect immunofluorescence assay

Country of origin	Year of sampling	Subjects studied	No of samples	No positive
Liberia	1976-84	Villagers	935	0
Ivory Coast	1978	Villagers	1195	0
Burkina Faso	1983	Villagers	299	0
Gabon	1981-4	Clinic attenders	855	2*
Uganda	1983	Villagers	164	0
Zaire†	1985	{ Patients with AIDS	13	13
		{ Contacts	3	2
Total			3464	17

*One sample was from a white subject.

†Serum sampled in Kinshasa.

Details of the immunoprecipitation technique and polyacrylamide gel electrophoresis have been described.^{24,25} Briefly, H9 HTLV-III cells were grown in sulphur-35 labelled cysteine for four hours. Cells were separated from virus and virus free supernatant by differential centrifugation. Cells were then lysed with detergent and the nuclei removed by centrifugation (17 000 g for 10 minutes at 4°C). The cleared lysate of 10⁵ cells or their supernatant was incubated with 3 µl of the serum to be tested in 30 µl buffer containing detergent. Immunoprecipitates were collected by adsorption on protein A Sepharose and washed as described. Precipitated polypeptides were separated by electrophoresis on 9-16% polyacrylamide gradient gels. Radioactive bands were visualised by autoradiography of the dried gels.

Results

POSITIVITY ON ENZYME LINKED IMMUNOSORBENT ASSAY

Of 2573 serum samples tested by enzyme linked immunosorbent assay, 2567 were collected between 1981 and 1984 from subjects not suspected of having AIDS or being in contact with the disease and six came from AIDS suspects in Guinea-Bissau during 1985. Altogether 238 samples (9.3%) from the non-AIDS subjects and two from the six AIDS suspects produced optical densities clearly above background in the enzyme linked immunosorbent assay (table I). Positive samples showed regional differences; the highest

frequency of increased reactions was found in attenders at the Lambarene clinic in Gabon, while the lowest frequency occurred in Nigerian blood donors. Variation of the frequencies with time, however, could not be determined from our data.

TEST FOR SPECIFICITY OF ENZYME LINKED IMMUNOSORBENT ASSAY BY IMMUNOPRECIPITATION

Serum samples reacting positively in the enzyme linked immunosorbent assay were re-examined by immunoprecipitation (figs 1 and 2). Samples from Kenyan students recognised a characteristic pattern of polypeptides in the cell lysate (fig 1 (a), lanes 3-12), some of which were also found in the immunoprecipitate of a negative control sample from a laboratory coworker (fig 1 (a), lane 2). The bands observed in the positions of 50 and 25 kd (fig 1 (b)) may have represented heavy and light chains of IgG labelled by 35 S-cysteine contained in the culture fluid. None of the samples, however, reacted with gp120 and p24 polypeptides of the human immunodeficiency virus. The failure of these serum samples to react with gp120 was seen more clearly when virus free culture fluid was used as the antigen source (fig 1 (b)).

When serum samples from the population of Senegal and Gabon with increased reactivity in the enzyme linked immunosorbent assay were tested by immunoprecipitation using cell extract (fig 2 (a)) the pattern of non-specific reactions was more variable compared with the pattern produced by negative samples from Kenya. One of the samples from Gabon, however, reacted strongly with gp120 from the culture fluid (fig 2 (b), lane 4). This unique positive reaction was also weakly detectable when the x ray film with the immunoprecipitation using cell extract was exposed for longer. One other serum sample collected in 1981 from a villager in Senegal precipitated gp120 from cell extract and culture fluid (autoradiograph not shown). Two samples from six Africans with symptoms of AIDS recognised gp120 in both immunoprecipitation assays (fig 2 (a), lanes 10 and 11). None of the African serum samples, however, recognised the viral core polypeptide.

FIG 1—Immunoprecipitation by serum samples from Kenyan students (lanes 3-12) giving positive reaction in enzyme linked immunosorbent assay. Samples incubated with either cytoplasmic extract ((a); CE) or cell free and virus free culture supernatant ((b); SUP) as antigen. Lane 1=Sample from German patient with AIDS. Lane 2=Negative control sample. Presence of gp120 (surface antigen of human immunodeficiency virus) indicates positive reactivity.

INDIRECT IMMUNOFLUORESCENCE

The second collection consisted of 3448 serum samples from non-AIDS subjects collected during 1976-84 and samples from 13 patients with AIDS in Zaire and three of their contacts collected in 1985 (table II). Antibodies to the human immunodeficiency virus sought by indirect immunofluorescence were detected in only two samples from non-AIDS subjects—namely, a black African and a white subject attending the Lambarene clinic in Gabon.

FIG 2—Immunoprecipitation of gp120 by serum samples from subjects in Senegal (lanes 2-5) and Gabon (lanes 6-9) giving positive reactions in enzyme linked immunosorbent assay. Lane 1=Reference serum positive for antibodies to HTLV-III. Lanes 10 and 11=Samples from patients with symptoms of AIDS in Guinea. Samples incubated as in figure 1.

The positivity of these two samples was confirmed by immunoprecipitation. Anticellular immunofluorescence was observed in 35 samples, all of which turned out to be negative on immunoprecipitation. Samples from all 13 patients with AIDS and two of their three contacts were positive for antibodies (table II).

Five positive and five negative samples tested blindly by immunoprecipitation and immunofluorescence showed complete agreement of the two assays in all cases.

SUMMARY OF RESULTS

In summary, specific antibodies to the human immunodeficiency virus were detected in only four (0.07%) of 6015 serum samples collected during 1976-84 from Africans without other evidence of AIDS. Three of these (including one white subject) were from Gabon and one from Senegal. By contrast, two samples from six AIDS suspects from Guinea-Bissau and all samples from 13 patients with AIDS in Kinshasa (Zaire) and from two of their three contacts recognised human immunodeficiency virus specific antigens, all these samples having been collected during 1985.

Discussion

As in other studies using the enzyme linked immunosorbent assay,^{5 11 14-17} we found about 10% of serum samples from tropical Africa showing an increased reaction to the H9 HTLV-III antigen preparation (table I); in most of these samples, however, only non-specific immunoprecipitation of presumably cellular polypeptides was observed (figs 1 and 2). Only two out of 238 enzyme linked immunosorbent assay reactive samples from African subjects without AIDS collected between 1981 and 1984 showed immunoprecipitation of gp120, which is closely correlated with the human immunodeficiency virus and the clinical diagnosis of AIDS.^{23 26 27} None of the African serum samples reacted with p24, the viral core polypeptide. Such an exclusive reactivity with gp120 has been observed in samples from German subjects showing low titres in the enzyme linked immunosorbent assay.²⁶ This may be explained either by there being 17 cysteine residues in gp120 compared with only two in p24,²⁸ or by the antigenicity of the envelope being higher than that of core polypeptides, which is found generally in enveloped viruses.

Similar to our findings with the enzyme linked immunosorbent assay in combination with immunoprecipitation, specific antibodies to the human immunodeficiency virus were observed in only two of the 3448 samples tested by indirect immunofluorescence (table II). The brilliant immunofluorescent staining of human immunodeficiency virus proteins could be clearly differentiated from the homogeneous staining caused by anticellular reactions with 35 samples. The positivity of both immunofluorescence positive sera was confirmed by immunoprecipitation, and coded positive and negative sera gave identical results with the two methods.

In the two collections of serum samples specific antibodies to the human immunodeficiency virus were detected in four (0.07%) of 6015 samples collected between 1976 and 1984 from subjects without symptoms of AIDS or known contact with the disease in nine countries of tropical Africa. This frequency was lower than that found in German blood donors in November 1984.²⁹

The high prevalences of antibodies to the human immunodeficiency virus reported in tropical Africa by other workers^{5 14-17} were probably due to non-specific reactions and the result of high titres of antimalarial and other antibodies and immune complexes. The age specific profile for antibodies against the human immunodeficiency virus paralleled closely that for antibodies against *P falciparum*, especially below the age of 5, and there were strong positive correlations between positive enzyme linked immunosorbent assay results for all three HTLV types and antibodies against *P falciparum* and serum levels of immune complexes.^{5 15}

The hypothesis of the human immunodeficiency virus originating in Africa rests on the supposition that the enzyme linked immunosorbent assay used was specific for the AIDS virus and that the extremely high rates of positivity in African rural populations, such as in Ugandan children in 1970-3,¹⁷ included no or few false positives. Our data support the alternative explanation—that these positive reactions were largely non-specific. Our data do not support (nor do they totally disprove) an African origin for the human immunodeficiency virus. They do show that the virus has not been endemic in rural areas of sub-Saharan Africa until recently.

Specific antibodies were detected in all 13 patients from Zaïre with AIDS, in two out of three of their close personal contacts, and in two out of six AIDS suspects from Guinea-Bissau, all these samples having been collected during 1985 (tables I and II). AIDS has been reported previously in only three west Africans, a Malian,³⁰ a Ghanaian living in Zambia,³¹ and a Senegalese.³² We have confirmed the diagnosis of AIDS in two patients in Guinea-Bissau and seropositivity in one Senegalese (table I). We expect that AIDS will now be diagnosed in west Africa with rapidly increasing frequency.

Using the enzyme linked immunosorbent assay we found a high rate of positivity among the general population of Senegal, but specific reaction to gp120 was confirmed in only one case (table I). Some of the samples found to be positive by enzyme linked immunosorbent assay may have come from subjects infected with

the retrovirus HTLV-IV, recently described as prevalent in healthy Senegalese,^{33 34} or with lymphadenopathy associated virus type II,³⁵ but this possibility has not been investigated.

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