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FULFORD ORATION

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)
(Present Status and Future Challanges)

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Definition

Acquired Immune Deficiency Syndrome (AIDS) is defined as a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease.[1] Kaposi's sarcoma, and other serious opportunistic infections namely *Pneumocystis carinii* pneumonitis, pneumonia, meningitis or encephalitis due to aspergillosis, candidiasis, cryptococcosis, ecythomegalovirus, nocardiosis, strongyloidosis, toxoplasmosis, zygomycosis or atypical mycobacteriosis; esophagitis due to candidiasis, cytomegalovirus or herpes simplex virus; progressive multiple leukoencephalopathies; chronic enterocolitis due to cryptosporidiosis; or unusually extensive mucocutaneous herpes simplex of more than five week's duration, are included in its spectrum.[1] It may, however, manifest in one or more combinations.

Now that the facilities for demonstrating antibodies to the causative HTLV-III/LAV virus have become available at many centres in US, CDC has revised the criteria for case definition of AIDS. In the revised definition, AIDS is indicated if, in the absence of the opportunistic diseases, either disseminated histoplasmosis, isosporiosis, non-Hodgkin's lymphoma, or histopathologically confirmed Kaposi's sarcoma in patients over 60 years is associated with the positive serologic or virologic test for HTLV-III/LAV. In addition, histopathologically confirmed chronic lymphoid interstitial pneumonitis in a child under 13 years will be indicative of AIDS unless the tests for HTLV-III/LAV are negative. Also, to increase the specificity of the diagnosis, AIDS should never be diagnosed in the absence of positive virologic/serologic tests for HTLV-III/LAV virus.

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History

Friedman-Kien *et al*,[2] Gottlieb *et al*,[3] Masur *et al*,[4] and Siegel *et al*,[5] in mid-1981, observed a novel form of acquired immune deficit in young patients, in whom no previous history of recurrent infections or histopathologic evidence of lymphoproliferative or other neoplastic diseases could be elucidated. They were formed either by male homosexuals,[2-5] intravenous drug abusers[4] or both.[4]

Immune deficiency state was manifested in the form of Kaposi's sarcoma,[2-4] *Pneumocystis carinii* pneumonia,[2-5] peri-anal ulcerations due to herpes simplex virus,[5] candidiasis[3,5] and other opportunistic infections.[2-5] Centres for Disease Control alarmed the medical professionals across the country of this novel syndrome. Many more reports appeared in the literature and upto mid-September 1982, 593 AIDS cases had been reported, with more than 75 percent occurring in New York city or California.[1]

In 1983, Pitchenick *et al*[6] reported 20 Haitian patients from Miami (Florida) and Atlanta

(Georgia) with evidence of acquired immunodeficiency. Subsequently, haemophilics,[7-9] those receiving blood transfusions,[9,10] infants born to mothers with AIDS,[11] and female sexual partners of hetero-sexual male, intravenous drug abusers with AIDS,[12] were found to be having varying degrees of immunodeficiency. By December 1983, over 3,000 cases had accumulated, including 36 in the United Kingdom.[13,14]

Although a transmissible biologic agent had been incriminated as the cause of this novel syndrome ever since its first report, yet it was only last year that investigators at the Pasteur Institute, Paris and the National Cancer Institute, Bethesda (Maryland), identified a lymphocytotropic retro-virus in the tissues of the AIDS victims.[15,16]

EPIDEMIOLOGY

Groups at risk

Homosexuals : Initial reports of AIDS were described in the homosexual men. Since then, cumulative data has suggested that homosexual males, especially those who change their sexual cohorts too often, form the single most frequent reservoir. In fact, over 70 percent of the cases have been reported in homosexually active males.[13,17] They account for 97 percent of the Kaposi's sarcoma cases in this epidemic.[18] Further, 12 percent of these individuals were also intravenous drug abusers.[1]

Drug Abusers : Intravenous drug abusers without a history of male homosexual activity account for 13 percent of all the cases.[1]

Haitians : having no apparent history of either male homosexual activity or intravenous drug abuse, constitute 6 percent of all cases.[16]

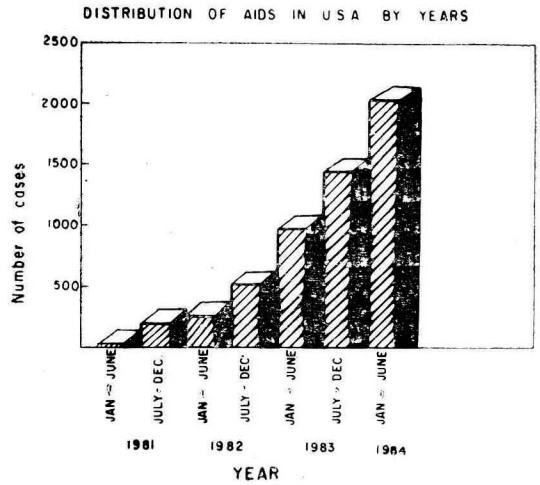
Haemophilics : 0.3 percent of all cases are made up by non-Haitian patients with haemophilia without homosexual activity or intravenous drug abuse.[1,7,8]

Blood Transfusion : No known risk factor could be found in 3 percent of 2157 patients analyzed by Currain *et al.*[9] They, however, could pinpoint that 28 percent of these patients had received blood transfusions in the preceding 5 years. Blood transfusions have also been incriminated by other authors as well.[10,19]

Sexual Partners of AIDS : Harris *et al*[12] investigated 7 asymptomatic female cohorts of male AIDS patients. They identified full-blown AIDS in one, another had prodrome of AIDS, and four others had generalised lymphadenopathy, or lymphopenia with or without a reversal of T-helper (OKT4), and T-suppressor (OKT8) cell ratio. AIDS may, thus, also be transmitted between heterosexual men and women.[12,20]

Offsprings of AIDS : Development of AIDS in infants born to the affected mothers has recently come to light. A possible transplacental, perinatal or postnatal transmission is implicated.[11,21]

Nosocomial transmission : Fortunately for the medical personnel, a report[22] suggests that when current hospital isolation procedures are employed, the risk of nosocomial transmission of AIDS agent is low/absent.



GLOBAL VIEW

The reports of occurrence of cases from different parts of globe is now well-recognized, condition being predominant in the United States of America from where over 6,000 cases have so far been reported (Fig. 1, Table I) not withstanding the fresh reports. Status of AIDS has been assessed from other parts of the

Table I. Reported cases and case fatality rates of AIDS in the US by half-year diagnosis, 1979 to June 1984.

Half year of diagnosis	Number of cases	Number of deaths	Percent fatality rate
1979			
1st half	1	1	100
2nd half	8	6	75
1980			
1st half	19	15	79
2nd half	27	27	100
1981			
1st half	82	71	87
2nd half	168	139	83
1982			
1st half	348	257	74
2nd half	629	424	67
1983			
1st half	1,145	685	60
2nd half	1,456	773	53
1984			
1st half	2,033	740	36

Table II. Reported AIDS cases in Americas excluding the United States, through June 1984.

Country	Number of cases
Argentina	8
Brazil	78
Canada	94
Colombia	4
Grenada	2
Guadeloupe	3
Haiti	287
Mexico	10
Suriname	2
Trinidad	16
Uruguay	3
Total	507

Table III. Reported AIDS cases in 12 european countries upto October, 1984.

Country	Number of cases
Denmark	28
Finland	4
France	224
Federal Republic of Germany	110
Greece	2
Italy	10
Netherland	26
Norway	4
Spain	18
Sweden	12
Switzerland	33
United Kingdom	88
Total	559

American continent, from where over 507 cases were deemed to have been reported upto June 1984 (Table II). Similarly reports from european countries indicate the occurrence of the disease, the details of which are shown in table III. In addition, 45 cases have been reported from Africa and 21 from Caribean countries.

Mode of Transmission

A transmissible biologic agent, now believed to be a lymphocytotropic virus, [15,16] is thought to be spread through:

1. Infected body secretions like semen, urine, saliva. [1]
2. Infected needles in intravenous drug abusers.[1]
3. Factor VIII concentrates, prepared from pooled plasma. [1]
4. Other blood transfusion products. [9]
5. Transplacental/perinatal/postnatal. [11]

Incubation Period

It is difficult to know for certain the incubation period of a sexually transmitted disease in a promiscuous homosexual man, as is the case in AIDS patients. However, Currain *et al*[9] investigated 18 patients who had received blood

transfusions within 5 years before the onset of the disease and found out a mean incubation period of 27.5 months (range 15-57 months). Another patient developed AIDS after 29 months of blood transfusion. [10] A child reported by Maloney *et al* [19] developed AIDS after 5.5 years of blood transfusion.

CLINICAL FEATURES

The outstanding clinical feature of AIDS is the occurrence of opportunistic infections in individuals who have no known cause of immunodeficiency. Bizarre malignancies are also noted.

A patient of AIDS, thus, may present with one or more of the following complaints :

1. One or more asymptomatic faint pink or red macules or papules or blue purple plaques or nodules of varying sizes anywhere on the body. [2]
2. Fever of greater than 30°C of more than 3 weeks' duration without an identifiable underlying infection. [2,17]
3. Constitutional symptoms like malaise, weight loss, night sweats etc.[2,17]
4. Oral thrush. [1-5,17]
5. Diarrhoea. [17]
6. Peri-anal ulcerations, unresponsive to usual therapy. [5]
7. Cough and expectoration. [1,17]

Kaposi's Sarcoma : Kaposi's sarcoma is a rare disease in North America, accounting for 0.06 percent of all malignancies. [23,24] However, Kaposi's sarcoma has been observed with alarming frequency in patients having AIDS. The mean age of 26 patients described by Friedman *et al* [2] was 39 years.

Commonly, Kaposi's sarcoma presents with one or more asymptomatic, faint pink to red macules or papules or blue-purple plaques or nodules of varying size anywhere on the body.[2] Kaposi's sarcoma lesions associated with AIDS differ from classic Kaposi's sarcoma by their generally smaller size, frequently less than 1 cm in diameter, their tendency to be elongate and to follow the lines of cutaneous cleavage, and their lack of propensity to involve primarily the lower extremities.[25-27] Lymph node involvement by Kaposi's sarcoma in the absence of cutaneous disease was observed in 3 of 19 homosexual or bisexual male patients in the study by Friedman *et al.*[2] Some patients may have persistent generalised lymphadenopathy for several months prior to the development of cutaneous lesions.

Kaposi's sarcoma in association with AIDS resembles the generalised form of Kaposi's sarcoma occurring in equatorial Africa, not only by the frequent generalised lymphadenopathy, but also by the high incidence of the visceral involvement.[23]

The histopathologic appearance of the lesions of the AIDS associated Kaposi's sarcoma is indistinguishable from that occurring in elderly men or African children.[23]

Chemotherapeutic regimens, comprising doxorubicin, bleomycin and vinblastine, have produced a complete response in only about 15 percent of AIDS associated Kaposi's sarcoma in contrast to over 90 percent response rate in Africans with generalised Kaposi's sarcoma without AIDS.[18]

Pneumocystis-carinii Pneumonia : Lung infection with this protozoan is characteristic of conditions with defective cell-mediated immunity.[2-5] It is characterised by fever, malaise, weight loss, decreased appetite and cough and expectoration.

On roentgenography, unilateral or bilateral radio-opaque shadows are visible. Diagnosis may be confirmed by open-lung biopsy[2-5] or fibreoptic bronchoscopy.[28] *Pneumocystis carinii* pneumonia occurred in 50 percent of all cases of AIDS in USA[29] but Weber *et al*[17] could not

isolate the protozoan in any of the six cases, reported by them from United Kingdom.

This infection presents as a relatively insidious disease process in patients with AIDS[30] and drug therapy in these patients is complicated by frequent adverse reactions.[30,31]

Candidiasis : This ubiquitous endogenous fungus, *Candida albicans*, in immunodeficient states, causes serious infections.

Candida albicans, in AIDS, may cause severe oral thrush,[1-3,17] candidial oesophagitis[1-3,17] and/or pneumonia.[17]

The hallmark of the disease is the development of creamy-white patches on any portion of the mucous membrane. In extensive cases the patches may extend to involve the trachea, upper bronchi, and even the oesophagus.

In all varietes of mucosal candidiasis, the creamy white patch, which on microscopy is seen to be comprised predominantly of budding cells and filaments, is a condition *sine quo non* for diagnosis. Endoscopy or radiology may be used for diagnosis of oesophagitis.

Salmonellosis : Salmonella species are not currently listed as being associated with AIDS in the epidemiological protocol of the Centres for Disease Control.[1] However, Weber *et al*[17] brought attention to this epidemiologic difference in British patients. *Salmonella typhimurium* and other species were recognised to cause infections either restricted to the gut or disseminated. *Salmonella* species were also reported to be causative in the cases from Africa.[32]

Herpes Simplex Virus : Herpes simplex virus was seen to cause deep protracted ulcerations in AIDS patients.[5]

Cytomegalovirus : Cytomegaloviruria has been a common finding in homosexual men reported from USA[27,33] and was dubiously incriminated as the causative agent of the acquired immunodeficiency in the past.[2,7] Cytomegaloviruria, however, was rare in patients from United Kingdom.[17,34]

Others : A variety of other opportunistic infections namely aspergillosis, cryptococcosis, nocardiosis, strongyloidosis, toxoplasmosis, zygomycosis, atypical mycobacteriosis, tuberculosis, cryptosporidiosis have been seen in AIDS patients.[1,35]

Pre-AIDS or AIDS-related Syndrome : A milder version of the syndrome has been recognised amongst the risk groups and has been called pre-AIDS or AID-related syndrome.[36] It consists of persistent lymphadenopathy, night sweats, fever and weight loss. In a study of 90 homosexual males with lymphadenopathy, the lymph node biopsy showed 3 patterns : (i) explosive follicular hyperplasia; (ii) follicular involution with expansion of paracortical areas; and (iii) a mixed pattern. All had impaired cell-mediated immune response as measured by various laboratory investigations.[36]

Only a small proportion of patients, perhaps 10% with this prodrome, progress to the full-blown syndrome.[37] Yet the full-blown form of AIDS may occur without a prodromal stage.

Aetiopathogenesis

Ever since the reports of AIDS appeared in the literature, some blood-borne, sexually transmissible agent was thought to be causative. The evidence for its infective origin are enumerated below :

1. Clustering of cases among homosexual males, especially those who changed their sexual partners too frequently.[1-5]
2. The frequent occurrence among intravenous drug abusers who shared the needles for injection of drugs.[4,38]
3. The haemophilics receiving repeated transfusions of Factor VIII concentrate, prepared from pooled plasma.[7,8]

4. The Haitians who might represent a large reservior of AIDS, or at least its causative agent, in the Caribbean.[6,37]
5. Patients receiving blood transfusions.[9,10,19]
6. Infants born to AIDS patients.[11,21]
7. AIDS developing in female sexual cohorts of men with AIDS.[12,20]

The epidemiology of the disease resembled the spread of hepatitis B virus and suggested that blood and other body fluids were contaminated with the transmissible agent.[37]

As previously mentioned, two groups of investigators[15,16] have identified a lymphocytotropic retrovirus from the blood and node lymphocytes of patients with AIDS or with prodromal manifestations. The Pasteur group calls it lymphadenopathy virus (LAV),[15] whereas Bethesda workers have designated the agent as human T-cell leukemia virus III (HTLV-III).[16] It is similar to but distinct from HTLV-I and II. Seropositivity has been found in a very high proportion of all risk groups. It has been possible to propagate the virus in transformed human neoplastic T-cells.

Lymphocytotropic viruses have been known to cause immuno-deficiency in animal models. The incriminated virus appears to have a cytotropism for a helper sub-population of T-cells (OKT4).[39] It seems likely that the host defence mechanism in the form of cytotoxic/suppressor T-cells (OKT8) attempt to destroy the virus infected T4 cells.[37] The mounting number of T8 cells and the diminishing T4 cells cause an inversion of the normal T4 : T8 ratio (Normal 1.5 to 2.0).[37] The result is the diminished or absent cell-mediated immunity.

The lymph nodes, early in the disease, exhibit follicular hyperplasia, and the germinal centres are infiltrated by T8 lymphocytes; T8 cells become predominant in the T-cell area; and plasma cell infiltration, and disruption of the follicular dendritic reticulum cell structure precedes follicular involution.[40]

In functional terms, the patients lose cutaneous delayed hypersensitivity both to recall and to new antigens. *In vitro*, lymphocyte proliferative responses to mitogens, antigens and allo-antigens are lost. T-cell-mediated cytotoxicity is diminished. There is a failure of T-cells *in vitro* to synthesize and release T-cell growth factor or interleukin-2.[41]

AIDS patients were found to be hypergammaglobulinemic.[37] In fact, *in vitro* spontaneous hyperactivity of B-cells is yet another prominent feature.[42] However, *de novo* antibody responses to new antigens are lost,[47] although antibody titres to previously encountered antigens remain normal or elevated.[37] The aforementioned findings have been confirmed by yet another group of workers.[44]

Recent reports also appear to support that the causative agent is HTLV-III, by either isolation of the virus,[20] or demonstrating epidemiologic correlation by retrospective study,[45] or by demonstration of antibodies to HTLV-III by enzyme-linked immunosorbent assay (ELISA).[22,46]

Laboratory Investigations

Lymphopenia, with a total lymphocyte count in peripheral blood of less than 1.5×10^9 per litre, is the most common and characteristic laboratory abnormality.[10] It often precedes overt opportunistic infections.[17] The diagnostic test, however, is the inversion of the normal T4: T8 ratio (Normal 1.5 to 2.0).[37]

In addition, *in vivo* testing of cellular immune response with intradermal recall antigens (purified protein derivative, *Candida*, and streptokinase or streptokinase-streptodornase) shows absent or negligible response.[17] If facilities exist, antibodies to HTLV-III can be demonstrated.

Other secondary laboratory abnormalities include, elevated levels of circulating immune complexes, circulating antilymphocyte anti-

bodies, soluble suppressor factors, acid-labile interferon, B2 microglobulin and-1 thymosine.[37]

Diagnosis

The diagnosis of AIDS should be suspected in at-risk individuals, who present with fever of unknown origin, weight loss, malaise or evidence of severe opportunistic infections or bizarre malignancies. The unexplained finding of lymphopenia, oral candidiasis or both, is important and warrants further investigations.[17] Detailed physical examination should be performed to find evidence of occult/manifest opportunistic infections.

Estimation of differential T-cells number with reversal of normal T4:T8 ratio, and *in vivo* testing of cellular immune response with intradermal recall antigens will clinch the diagnosis. Demonstration of HTLV-III antibody will provide further evidence. However, the final diagnosis can only be made with the demonstration of HTLV-III in an appropriate culture.

Treatment

The choice of treatment depends upon the causative opportunistic infection, apart from the general supportive measures. However, even with adequate and specific treatment, the prognosis is very poor and over half the patients succumb to opportunistic infections or Gram negative septicemia.

Prevention

AIDS is the outcome of changing mores and attitudes. The wide acceptance, dissemination, and use of various birth control measures, especially the wide use of oral contraceptives and rejection of the physical barrier-contraceptives, freed many from the constraints and concerns of unwanted pregnancies, whereas the move towards self-fulfilment led many to self-indulgence and the overt challenge to established norms. This challenge led to an increased practice of homosexual activity. With the loosening of social codes, more frequent, casual and diverse relations among socially and sexually liberated people have occurred. The consequences of this potentially overwhelming scourge are of grave concern not only from the involved individual's standpoint, but also from that of the public, which may be involved either unwillingly or unknowingly.[48,49]

Reestablishment of social codes[48,49] and reacceptance of condoms[50] will go a long way in controlling the spread of all sexually transmitted diseases including AIDS.

Screening of those at risk of AIDS should form a special component of any programme for AIDS control. It has been recommended that asymptomatic homosexual men as well as others at risk should have a periodic complete physical examination with special attention to the buccal mucosae for oral candidiasis and lesions of Kaposi's sarcoma; the entire skin area should be screened. A complete blood count including differential and platelet count should be taken at every visit. A serum sample should also be stored at—80°C for future reference. In addition, a throat swab should be taken for candida in every case. If facilities exist, T-cell differential count and *in vivo* testing of cellular immune responses with recall antigens should be done.[17]

Epidemiological surveillance to determine the onset and spread of AIDS should be undertaken vigorously. This will help in early recognition of an outbreak, and possibly the source of spread.

In summary, primary prevention, early diagnosis and secondary prevention may help in controlling this dreaded disease.

Future Challenges[51]

Further studies are needed to understand the precise natural history of AIDS, natural reservoir of the virus in man, the degree of expression of the virus or viral antigens and the influencing factors more lucidly. In addition, evaluation of the blood test as a diagnostic and screening

tool, and the production of a vaccine may prove invaluable in achieving successful control of AIDS. The discovery or development of an animal model can be of tremendous utility for further research.

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