THE PROBLEM OF AIDS IN EASTERN LIBYA

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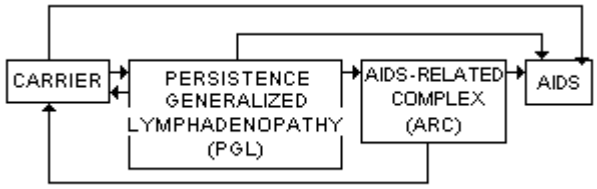
SUMMARY: Acquired immunodeficiency syndrome (AIDS) is a fatal disease, the victims of which were previously healthy and had no history of immunodeficiency. The victims of AIDS die of a variety of opportunistic infections which develop due to acquired inability of the patients to mount cellular as well as humoral immunity. The human immunodeficiency virus types I (HIV-1) has been implicated as the causal agent of AIDS. Regarding the mechanism of pathogenesis, HIV-1 enters susceptible cells through binding to HIV-1 -specific receptor which is closely related to CD4 antigen of T-helper/inducer lymphocytes; cells other than $CD4^+$ lymphocytes has now been shown to be infected by HIV-1. Infections through sexual contact, blood and body fluids, and from mother to child remain the main modes of transmission. The sero-epidemiological studies conducted so far in Benghazi have failed to find antibody to HIV-1 in eastern Libyans, and there has been no report of any case of AIDS from eastern Libya yet as of November 1990. Homosexuality, heterosexual promiscuity, prostitution and intravenous drug abuse are not expected to exist in Libyan society. Therefore, it seems at present that the traditional social life and social behavior pattern of eastern Libyans may be helpful in keeping the HIV-1 away from eastern Libya. Perhaps, a sero-epidemiological study of a second retrovirus HIV-2 should also be undertaken in eastern Libya and only then, can any definite conclusion be drawn about the problem of AIDS in eastern Libya.

Key Words : AIDS, HIV-1, HIV-2.

The purpose of this article is not the provide an exhaustive comprehensive review of all available information about acquired immunodeficiency syndrome (AIDS), but rather to high light and summarize those more important to known when we speak of the problem of AIDS.

What is acquired immunodeficiency syndrome (AIDS)?

In recent time it is almost impossible in the western world to find a newspaper without reference, once or twice at least, to AIDS. But for any of us in the developing world we may not be sure as to what is the disease 'AIDS'. In 1981, the first cases of a new disease syndrome were recognized by Center for Disease Control (CDC), Atlanta, USA. The victims of this new disease died of a variety of rare infections and malignancies, among them a pneumonia caused by the protozoan Pneumocystic carini and Kaposi's sarcoma, a cancer of the skin. They also suffered from other opportunistic infections caused by microorganisms that are ubiquitous but ordinarily not able to cause diseases. This new disease, as it appeared, killed the victims by destroying their immune system. All these patients were previously healthy and had no known underlying cause of immunodeficiency. Hence, this new disease syndrome was named as acquired immunodeficiency syndrome (AIDS) (2,6,7). Sub-sequently, cause of AIDS have been reported from Europe, Africa and many other parts of the world. Depending on the severity and patterns of the disease, AIDS is classified into various chronological stages as below (6):



What is the name of AIDS virus?

What is its pathogenesis?

The speed of research into the pathogenesis of AIDS has been breathtaking. Within no time in 1983 Robert Gallo's group at the National Institute of Health, Bethesda, USA isolated a retrovirus from patients with AIDS and PGL which has characterized as human T-cell lym-

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phothropic virus (HTLV) (22, 23). Two retroviruses HTLV-1 and HTLV-2, have already been linked with acute and chronic T-cell leukemia of adults and termed as human T-cell leukemia viruses. The causal agent of AIDS isolated and characterized by Gallo *et al.* is morphologically and genetically dissimilar to HTLV-1 and HTLV-2 and so they named it as HTLV-3 which is however not entirely appropriate (22, 23). At about the same time Luc Montagnier's group at the Institute of Pasteur, Paris, France had isolated a new retrovirus from a patient with PGL and named this agent as lymphadenopathy associated virus (LAV) (3, 18). Both Gallo *et al.* and Montagnier *et al.* were reluctant to have the name of this virus changed from HTLV-3 and LAV. Therefore, the subcommittee empowered by the International Committee on the Taxonomy of Viruses proposed in 1986 that the AIDS retrovirus be officially called as the human immunodeficiency virus type 1 (HIV-1) (9). The mechanism of HIV-1 is still the subject for debate. It causes 'slow infections' in which the virus is persistent, and clinical syndrome follow initial infections after and interval of many years (4). The virus has been shown to enter susceptible cells through binding to HIV-1-specific receptor which is closely related to CD4 antigen (10). The $CD4^+$ cells characteristically include a subset of T-lymphocytes known as T-helper/includer cells. Following binding to the receptor, the virus enters through active endocytosis, fusion of viral envelop to cell membrane and hence entry to the cell. After uncoating, the viral RNA uses the retroviral enzyme RNA-dependent DNA-polymerase (reserve transcriptase) to produce a RNA:DNA hybrid. This is converted into double-stranded proviral DNA which circularizes and may subsequently integrate into the host cell genome at a random site. Viral expression and replication use bost's cellular enzymes, and the virus eventually buds off from the cell surface by an active process of exocytosis in the process $CD4^+$ cells are gradually knocked out and eventually leading to a very low ratio of $CD4^+$ cells to $CD8^+$ cells (i.e. low ratio of T-helper/inducer to T-suppressor/cytotoxic cell). Now, the question is how to the HIV-1 infected cells get killed? There are three principle hypotheses as to how HIV-1 infected cells are destroyed (15,16, 26). Common and central to all these theories is the acquired immunodeficiency which is produced due to qualitative and quantitative reduction of immunocompetent $CD4^+$ T-helper/inducer lymphocytes, following infection by HIV-1, leading to secondary infections which ultimately kill the patients. There is now direct evidence that cells other than $CD4^+$ lymphocytes may also be infected by HIV-1 in vitro as well as *in vivo* (17, 26).

What are the modes of transmission of HIV-1 infection?

Regarding the modes of transmission, HIV has been isolated from peripheral blood lymphocytes, bone marrow cells, spinal fluid and braid tissue, lymph nodes, cell free plasma, saliva, tears, semen and vaginal fluid (6, 20). In theory exposure to any of these body fluids, if contaminated with the virus, represents probable risk of infection. However, in practice the risk of transmission of the infection seems to depend heavily on the route of exposure. The most probable routes for transmission of AIDS are considered as: homosexual practice, heterosexual practice, intravenous drug abuse, prostitution, blood and blood products, vertical or perinatal transmission and occupational exposure. Transmission through sexual contact has remained the predominant mode of transmission, and laboratory and epidemiologic studies have so far failed to demonstrate possible transmission of HIV-1 through biting or blood-sucking insects (4). The implications of these various routes of transmissions in relation to apparently non-existence of HIV-1 infection (AIDS) in eastern Libya has been discussed later in item no 6.

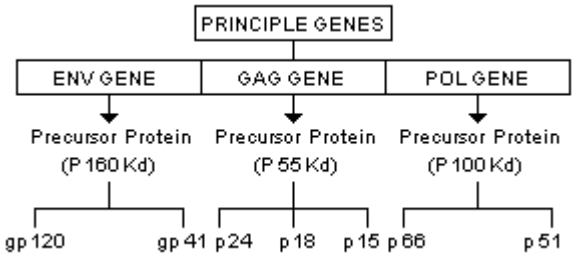
What are the criteria for diagnosis of AIDS?

The CDC, USA has formulated a definition for AIDS listing some diseases and laboratory tests (2,6,7). According to CDC definition, the patient: (a) must have done or more of the diseases indicative of cellular immunodeficiency; (b) has no known underlying cause of cellular immunodeficiency, nor any other cause of reduced resistance, which might predispose to the disease or diseases; (c) must be positive for two or more laboratory indicators of immunodeficiency including HIV-1 isolation or HIV-1 antibody (Table 1); the sera which are positive for HIV-1 antibody by enzyme-linked immunosorbent assay (ELISA)-screening test must be confirmed by western blot technique. The diagnosis of AIDS in a patients is excluded if all the laboratory indicators of immunodeficiency and HIV-1 infection are negative (3).

The isolation of the virus by culture is tedious, time consuming and expensive. On the contrary rapid, sensitive and specific laboratory tests for the detection of HIV-1 antibody are available and most widely used for diagnosing exposure to HIV-1. The specific antibodies detected coded by HIV-1 genome which consist of 3 principal genes unique to HIV-1 and 4 regulatory genes common to all retroviruses. Of the 3 principal genes: 'env gene' codes for 'envelope proteins', 'gag gene' codes for 'core proteins' and 'pol gene' codes for 'reverse transcriptase' (26).

Infected patients can produce, *in vivo*, antibodies against all these gene products and all infected patient have antibodies against core proteins, particularly p24, are reduced and less frequently detected in patients with AIDS (24). Median titres of anti-envelop antibodies were shown to be much higher than anti-core antibodies in healthy anti-HIV-1 positive persons (drug addicts, hemophiliacs, and blood transfusion recipients) and in patients

with ARC or AIDS. It has been shown that as the clinical disease progresses anti-core antibodies decline and may of the ARC and AIDS patients do not have anti-core antibodies but do have anti-envelop antibodies (24). Serial monitoring of sera from healthy but sera positive infected people for a decline in anti-core antibodies may, therefore, be an early warning of development of the clinical disease. However, in sera positive hemophiliacs a lack of anti-core antibody may indicate contact with none-infectious HIV-1 envelop protein present in pooled clotting factor concentrates but not true infection. A negative anti-core antibody result may, therefore, give hope to hemophiliacs and blood recipients with recent sero-conversions. Thus special attention must be paid to anti-envelope and anti-core antibodies in ELISA-screening test and confirmatory western blot technique for the diagnosis and prognosis of HIV-1 infection. The diagnosis of



HIV-1 infection in infants with passively acquired antibody is difficult because loss of passively acquired antibody takes as long as 15 months; however, the diagnosis of HIV-1 infection in these infants can be made by following-up for at least 12 months (4).

Is there any treatment or vaccine available against AIDS?

Now that the pathogenesis of HIV-1 is well known, it is possible theoretically at least to imagine therapy for HIV-1 infection which may be based on the following principles: (a) blocking viral entry to the target cell by receptor blockers or neutralizing antibodies or vaccines; (b) blocking viral replication by reverse transcriptase inhibitors or cellular DNA polymerase inhibitors or blocking transcription of viral DNA or blocking viral protein synthesis and (c) enhancing immune cell function by lymphokines or thymic hormones or bone-marrow transplantation or immunomodulators. Of these many possibilities, the most promising therapeutic target is inhibition of reverse transcriptase as this is a uniquely retroviral enzyme with no mammalian counterpart. The first approved drug available to treat HIV-1 associated disease is Zidovidine (developed by Well-come Foundation, UK), formerly known as Azidothymidine (AZT) and it acts by inhibiting reverse transcriptase (12,19,26). This drug is associated with significant bone-marrow toxicity, severe myopathy and other side effects (12, 26). Another promising therapeutic agent for treatment of AIDS seems to be 'peptide T' which is an octapeptide (Alanine-Serine-Threonine-Threonine-Asparagine-Tyrosine Threonine) derived from the HIV-1 envelope glycoprotein, gp 120, and it acts by blocking the binding of the viral envelope to the CD4 receptor. Improvements in AIDS patients treated with peptide T have been recently reported which justifies further investigation (1). Whether it is zidovudin or peptide T or any other agents (interlenkin 2/Interferony), there is no drug as yet available which can cure the disease 'AIDS'; they can only prolong the life of the patient for a little longer (16). It is dear clear that progress is being made at a rapid pace, but not at a pace equal to the death and devastation inflicted by HIV-1.

In the vaccine front, many different approaches to the development of AIDS vaccine have been undertaken simultaneously by researchers throughout the world. Four of these approaches-purified natural products, synthetic peptides, recombinant DNA products and vaccinia vector recombinants-focus on the outer glycoproteins of the virus gp 120 and gp 160. Several vaccines are now belling tested in humans: a recombinant gp 160 expressed in baculovirus, a gp 160 vaccinia virus recombinant, autologus cells infected with a gp 160 vaccinia virus recombinant and a whole killed virus vaccine. Perhaps the most novel approach to the accomplishment of an AIDS vaccine is the development of an anti-idiotype which is still gleam in the immunologist's eye. However, the development of a safe and effective vaccine against HIV-1 infection is complicated by several unique scientific, logistic and ethical issues including a lack of understanding of protective immunity to HIV-1 superimposed by the absence of an adequate and convenient animal model for evaluation of candidate vaccines (11, 26).

Is there any case of AIDS in eastern Libya?

AIDS has been recognized in all the continents and as of January 1989, a total of 139.886 cases of AIDS had been reported from 112 of the 177 countries reporting to the Global Programme on AIDS of the World Health Organization (4). The largest number of cases have been reported from USA, western Europe, Latin America, western Pacific and the central and eastern regions of Africa. From Africa, 52 countries have been reported a total of 21, 213 cases of AIDS.

Sero-epidemiological studies have demonstrated that the prevalence of HIV-1 in several large cities of central Africa varies from 4% to 15%. In some rural areas of Uganda and Northwest Tanzania the prevalence of HIV-1 has been reported to be as high as 40% in general population (4). Considering this world situation, particularly the situation in Africa (5), the question arises as to why there is no report of any cases of AIDS from eastern Libya as of November 1990. Since our report on failure to find antibody to HIV-1 in Libya (13), nearly 10.000 specimens

Table 1: The disease and laboratory tests included in the CDC definition of AIDS / ARC / PGL / HIV-1 carrier.

A. Diseases included in the definition of AIDS
a. Opportunistic infections with laboratory confirmation:
(i) Protozoal and Helminthic ⇒ Pneumocystic carinii pneumonia, toxoplasmosis (pneumonia or cerebral), cryptosporiodiosis (intestinal), strongyloidosis (systemic), (ii) Fungal ⇒ Candidosis (oesophageal, bronchial or pulmonary), Histoplasmosis (disseminated), Isosporiasis (Chronic diarrhea) (iii) Bacterial ⇒ Atypical mycobacteria (disseminated), (iv) Viral ⇒ Cytomegalovirus (Pulmonary, gastrointestinal or central nervous system), Herpes simplex virus (mucocutaneous with ulcers for more than one month), Progressive multifocal leucoencephalopathy.
b. Malignancies (Histologically confirmed):
Kaposi's sarcoma B-cell lymphoma, cerebral lymphoma, High-grade non-Hodgkin's lymphoma of unknown immunological phenotype.
B. Sings and symptoms included in the definition of AIDS-related complex (ARC)
Pyrexia of unknown origin for two months or more: Chronic diarrhea; Weight loss (10% of body weight); Malaise and lethargy; Persistent generalized lymphadenopathy; Hepatosplenomegaly; Hairy leukoplakia; Minor oral infections (e.g. Oral candidosis, herpes zoster).
C. Persistent generalized lymphadenopathy (PGL)
Unexplained lymphadenopathy in at least two extra-inguinal sites for more than three months. The lymphadenopathy may persist unchanged for years and the patient with PGL are generally well; Nearly all patients will have HIV-1 antibody; Occasionally seroconversion takes place within two years of the development of PGL.
D. Disease which may be more prevalent in HIV-1 carrier
Skin diseases (Seborrheic dermatitis, Folliculitis, Acute vulgaris Xeroderma, Fungal infections, Herpes simplex, impetigo; Malignancies (Hodgkin's lymphoma, Anorectal carcinomas); Pneumonia (Pneumococcal, Staphylococcal, Tuberculosis).
E. The laboratory tests included in the definition of AIDS / ARC / PGL / HIV-1 carrier
Isolation of HIV-1 by culture; Detection of HIV-1 antibody by ELISA-screening test and confirmed by western blot technique; Lymphopenia; Leukopenia; Anemia, Thrombocytopenia, Raised erythrocyte sedimentation rate; Raised serum cholesterol; Raised immunoglobulins; Low CD4: CD8 cell ratio.

have been screened and all of them have been observed to be negative for HIV-1 antibody (14). Does this mean that HIV-1 has not yet spread into eastern Libya or might Libyans conceivably be immune to HIV-1 infection? Despite the numerous epidemiological investigations conducted worldwide among many different cultures, no new important modes of HIV-1 transmission have been discovered. Infection through sexual contact, blood and body fluids, and from mother to child remain the main modes of transmission. Worldwide, the differences in epidemiology of HIV-1 infection and AIDS are primarily due to differences in the proportions of these modes of transmission. If no special geographical, environmental or cultural reasons for the emergence of AIDS are pre-requisite then there may be no reason why it should spread to other areas of Africa including eastern Libya.

In many developing countries surveillance for AIDS or other severe HIV-1 disease is hindered primarily due to lack of a public health infrastructure including good laboratory facilities. Secondly, AIDS is not a single clinical entity that can be easily recognized; the sophisticated tests or procedures often necessary to diagnose HIV-1 infection or the associated opportunistic infections are not uniformly available in developing countries; thirdly, some countries have been reluctant to report cases of AIDS for social, political or economic reasons. In Benghazi, Libya both ELISA-screening test and Western blot technique have been available since August 1986 together with experienced consultant immunologists and consultant physicians. In modern Libya, therefore, the chances are remote that AIDS may be present but undiagnosed. It is now becoming clear that AIDS is sexually transmitted disease and this transmission takes place equally readily from female to male, male to female and male to male. There does not seem to be anything special about intercourse between homosexuals as far as the virus is concerned. Homosexulas who have very many sexual partners are at the high risk of cantracting the disease, as of course are heterosexuals who are promiscuous. Homosexuality, heterosexual promiscuity, prostitution and intravenous drug abuse etc. are expected to exist in Libyan society. If they are present without documented evidence, then considering the long incubation period of HIV-1 perhaps we may have to wait for as long as 5-15 years from now to see any case of AIDS appearing in Libya. In fact in remote areas where people have a more traditional life-style, the prevalence of HIV-1 has been reported to remain low (21). Therefore, at present it seems that the traditional social pattern and social behavior of eastern Libyans are helpful in keeping the HIV-1 away from the eastern Libya.

A second retrovirus (HIV-2) has been shown to be the etiological agent of AIDS in West Africa (4, 8). The pathogenesis and sero-prevalence of HIV-2 is relatively unknown (25). A sero-epidemiological study of HIV-2 should also be undertaken in eastern Libya. Only then can any definite conclusion be drawn about the problem of AIDS in eastern Libya.

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