DENTAL CARE FOR THE PEDIATRIC HIV POSITIVE HEMOPHILIAC

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ABSTRACT

HIV positive hemophiliacs have specific dental needs. This patient population not only requires special consideration for invasive procedures, but is at considerable risk for development of serious intra oral pathology. The dental treatment, oral manifestations, infection control, as well as the epidemiology and biology of HIV will be discussed.

HISTORY

Historically, hemophilia has been recognized as an entity since Biblical times and was one of the first human genetic diseases to have been reported (Rosner, 1969). The report by John Otto in 1803 is generally accepted as the first in the medical literature to arouse general interest. He noted the pattern of transmission of the disorder to males through unaffected females, and described the bleeding symptoms and potential treatment regimens. Otto's paper attracted interest on both sides of the Atlantic, giving rise to several reviews and many individual case reports and family studies (Scriver 1989).

The first major review of this subject was compiled by Nasse in 1820 (Nasse 1820). He asserted that the bleeding tendency occurred only in males and was transmitted to them by normal females through their marriage with normal males. No mention was made of the possibility that a bleeder male could pass the disease to ostensibly normal daughters and thence to bleeder grandsons (Scriver 1989).

The first recorded usage and therefore presumably the invention of the term Haemophilie was by Hopff in 1828 (Hopff 1828). The cases referred to in this dissertation were four brothers who variously bled to death following trivial injury, or in the last case, a ruptured tumor of the thigh (Scriver 1989).

In 1893, Almroth Wright discovered the prolonged clotting time of hemophilic blood (Wright 1893). Whereas normal blood took 5 1/2 to 6 minutes to clot in a capillary tube, blood from a boy with severe hemophilia took over 10 minutes to clot. Thomas Addis (Addis 1910,1911), showed that the prolonged clotting time of hemophiliac blood could be corrected by a fraction from normal blood. This fraction was studied by Patele and Taylor in 1937 and termed antihemophilic globulin (AHG) (Petele 1937, Taylor 1937).

A further advance came when quantitative assays were devised for measuring the correcting fraction (Merskey 1951). Hemophilia came to be defined as the condition resulting from deficiency of AHG, inherited in an X-linked manner, although also occurring in sporadic cases due to new mutations (Scriver 1989). The decreased factor VIII in association with hemophilia A was first discovered in 1947 (Brinkhaus 1947) and the decrease in factor IX in Christmas disease, or hemophilia B, was discovered in 1952 simultaneously when three groups reported that classic X-linked hemophilia itself could be due to a deficiency of more than one factor (Aggeler 1952, Biggs 1952, Schulman 1952). This was based on finding cross-correction of the clotting defect in some hemophiliac's blood by that from other clinically identical cases. The vast majority of hemophilias are now known to be caused by a deficiency of one of two X-linked factors: Factor VIII deficiency (hemophilia A) is responsible for approximately 85% of all hereditary bleeding disorders, while Factor IX deficiency (hemophilia B) accounts for most of the remainder.

In 1953 Larrieu and Soulier (Larrieu, Soulier 1953) discovered that patients with the autosomal dominant bleeding disorder first described by E. von Willebrand in 1926 (von

Willebrand 1926) also had low factor VIII levels in their blood. It was subsequently shown that an antigen detected by antiserums against partially purified factor VIII was reduced in the blood of patients with von Willebrand (vWD) disease but present in that of hemophilia A patients (Zimmerman 1971). This antigen was termed factor VIII-related antigen (VIII:Ag) and gave rise to the idea that factor VIII and its related antigen are a single entity with multiple functions. This hypothesis, however, conflicted with the genetic evidence and also with a growing body of biochemical data showing that the factor VIII coagulant activity could be separated from the related antigen (Thelin 1961, Zimmerman 1973, Rick 1973, Bloom 1973).

A full understanding of the pathophysiology and genetics of these various disorders was long delayed by the difficulty of purifying factor VIII and IX to homogeneity. Eventually this problem was surmounted in conjunction with the cloning of the gene for factor VIII (Gitschier 1984, Wood 1984, Toole 1984, Truett 1985). It is now clear that Hemophilia A is due to any one of a series of possible defects in the factor VIII gene which is located in the X chromosome as is the gene for factor IX which is responsible for Hemophilia B (Chen 1985). Von Willebrand disease however is caused by defects in a gene coding for von Willebrand (vWF) factor located on the short arm of chromosome 12 (Verweig 1985). The low factor VIII levels in vWD are explained by the observation that vWF acts as a protective carrier for factor VIII so that depressed levels of vWF in some manner lead to lower levels of factor VIII (Scriver 1989).

Early therapy of hemophilia was supportive, but following the observation that plasma corrected the clotting time of hemophilic blood, treatment evolved to include

transfusion with whole blood and plasma to achieve improved clotting function in the 1930's (Patek 1937). The modern era of hemophilia treatment began in 1964 with the discovery of cryoprecipitate (Pool 1964) and shortly thereafter with the introduction of clotting factor concentrates (Tullis 1965, Abidbaard 1966).

Concentrated preparations of factor VIII became commercially available in 1965, and were soon widely used in the United States and throughout the world to treat Hemophilia. The development of these concentrates represented a tremendous therapeutic advance (Roberts 1989). This and the development and implementation of hemophilia centers and home care represent the two major advances in the therapy of hemophilia since the mid-1960's (Aronson 1988). The enthusiasm that greeted the development of concentrates was only mildly dampened by the early realization that all factor VIII products were contaminated with hepatitis viruses and by the resulting epidemic of hepatitis B and non-A, non-B hepatitis among people with hemophilia. Although 90% of the patients severely affected with hemophilia eventually became seropositive for hepatitis B antibody and although non-A, non-B hepatitis was thought to develop in virtually 100%, the consequences of chronic liver disease were considered to be acceptable, given the alternative risk of hemorrhagic complications. Nevertheless, attempts by the manufacturers of factor VIII products to inactivate hepatitis viruses and other viral contaminants were welcomed at about the same time (1979) the acquired immunodeficiency syndrome (AIDS) began to receive increasing attention, especially the possibility that it was due to a virus that could be transmitted by blood and blood products. From the retrospective analysis of stored serum samples we now know that human immunodeficiency virus (HIV) seroconversion occurred

in some patients with hemophilia as early as 1978 (Roberts 1989), with the first cases of AIDS being recognized in 1982 (C.D.C., 1982).

The next major improvements in replacement therapy were a result of attempts to limit transfusion-related viral infections during the 1980's (McCDougal 1985, Mannucci 1988). Although pasteurized factor VIII products were prepared as early as 1979, their initial supply was limited, clinical trials of their efficacy against hepatitis had not been completed, and HIV was not identified as the causative agent of AIDS until 1984 (Schimpf 1987). Factor VIII preparations that had been heated in the lyophilized state to inactivate hepatitis viruses became available in 1983. Some physicians favored their immediate use in the hope that the then putative AIDS agent would also be inactivated but unheated concentrates continued to be used until 1985. In 1985 the genes for both factor VIII and factor IX were cloned (Eaton 1984, Vettar 1984, Tool 1984, Yoshitake 1985), and in 1989 recombinant factor VIII was first used clinically (White 1989, Schwartz 1990).

EPIDEMIOLOGY OF PEDIATRIC HIV INFECTION

The first cases of the acquired immunodeficiency syndrome (AIDS) in children were reported to the Centers of Disease Control (CDC) in 1982. Since that time over 4,000 cases of AIDS in children under 13 years of age have been reported. Of those 4051 cases reported as of September 1992, 5 percent or 183 cases have been in patients with Hemophilia or coagulation disorder and 7 percent or 303 have been in recipients of blood transfusions of blood components or tissues. AIDS is now among the top ten leading causes of death in children over 1 year of age (Kilbourne 1990).

Children in the United States have acquired HIV infection primarily through two routes: perinatally (mother to infant) and transfusion of blood or blood products. In most developed countries, transmission of HIV through blood products virtually ended in 1985 when donor screening for HIV antibody began (Ward 1988). Both donor screening and heat treatment of blood clotting factor products have virtually stopped most new infections in persons with hemophilia (CDC 1988). In the United States, only two children with AIDS following HIV infection acquired from screened blood have been reported to CDC. In these cases, the donors were seronegative at the time of donation, but later seroconverted.Only 18 cases in persons with hemophilia receiving heat-treated factor products have been published. The demographic characteristics of children with transfusion-acquired AIDS reflect the characteristics of children receiving transfusions. In the United States, most children with transfusion-acquired AIDS were transfused in infancy as a result

of perinatal problems such as prematurity or congenital abnormalities. There is a slight male predominance (Table 1). In a study of blood transfusion practices, male infants were more likely to receive transfusions than were female infants (Freidman 1980). In contrast to children with perinatally acquired AIDS, most children with transfusion-acquired AIDS are white; however, compared with the U.S. population, blacks and Hispanics are also overrepresented among children with transfusion-acquired AIDS. Although little information exists on the race distribution of persons receiving transfusions, minority children are more likely to suffer from perinatal morbidity (NCHS 1989) and may be more likely to receive transfusion in infancy (Rogers 1992).

Children with clotting factor disorders have also been at increased risk for HIV infection and account for 5% of pediatric AIDS cases and 31% in adolescents in the United States. Since most cases occur in persons with sex-linked genetic disorders, 98% of these cases occur in males. Racially, they are more reflective of the U.S. population: 68% are white, 13% are black, 17% are Hispanic, and 2% are of other race/ethnicity (Rogers 1992).

TABLE 1 Demographic characteristics of children (less than 13 years of age) with AIDS reported to CDC as of December 31, 1990 by transmission category, Un

Demographic characteristic	Perinatal n=2,327 [No.(%)	Transfusion acquired n=252 [No.(%)	Hemophilia n=139[No.(%)	Unknown n=68 [No.(%)
Sex				
Female	1,158 (50)	90 (36)	3 (2)	34 (50)
Male	1,169 (50)	162 (64)	136 (98)	34 (50)
Race				
White	366 (16)	133 (53)	95 (68)	8 (12)
Black	1,326 (57)	56 (22)	18 (13)	39 (57)
Hispanic	617 (27)	58 (23)	23 (17)	21 (31)
Asian/Indian	10 (<1)	5 (2)	3 (2)	0
Unknown	8 (<1)	0	0	0
Age at diagnosis of AIDS				
Median	12 months	4.75 years	10 years	10 months
Range	1 mo-11 yrs	4 mos-12 yrs	13 mos-12 yrs	1 mo-12 yrs

The geographic distribution of transfusion-acquired and hemophilia-associated AIDS cases has been more diffuse compared with perinatally acquired cases. Whereas 57% of perinatally acquired cases come from New York, New Jersey and Florida, 40 states have reported transfusion acquired and/or hemophilia-associated cases and the top three states account for about 40% of the cases (Rogers 1992). The age at diagnosis of AIDS in these three groups of children (perinatal, transfusion-acquired, and hemophilia) reflects the age at the time of infection and the incubation or latency period of the disease. Transmission of HIV from mothers to their infants takes place during gestation, labor and delivery, or

(rarely) in the post partum period through breastfeeding (Rogers 1989). The median ageat diagnosis of perinatally acquired AIDS cases reported to CDC was 12 months, and 80% of these cases were in children under age 3 years at the time of diagnosis. Because most children with transfusion-acquired AIDS were infected from blood transfusions in infancy, this disease has also largely affected infants and toddlers; however, nearly all cases being reported today received their contaminated transfusion at least 6 years ago, and thus are largely school-aged children. The median age for all reported children with transfusion-acquired AIDS is 4.75 years; the median age for those children diagnosed in 1989 and 1990 is 7.4 years. AIDS cases in children with hemophilia have largely been in those who were school-aged: their median age is 10 year (Rogers 1992).

Transfusion-associated Transmission

Transfusion of blood or blood components from an HIV-infected donor is a highly efficient mode of transmission. Over 90% of persons receiving an HIV-seropositive unit acquire the infection (Ward 1987, Gonegan 1990). Both cellular and plasma components of whole blood have transmitted HIV infection (Curran 1984). Immunoglobulin preparations including Rh factor have not transmitted HIV because the fractionation process used to prepare these products effectively removes HIV by partitioning and inactivation (CDC 1987).

Persons receiving multiple transfusions between 1978 and 1985 were at greater risk HIV seroprevalence rates of 4-8% have been detected in leukemic (CDC 1987), hemodialysis (Peterman 1986), and other patients receiving multiple transfusions during this period (Jason 1985).CDC has estimated that approximately 12,000 transfusion recipients in

the United States who survived their underlying disease acquired transfusion-associated HIV infection between 1978 and 1984 (CDC 1987).

Since donor screening was implemented in March 1985,2 pediatric cases of AIDS following infection acquired from blood that was screened HIV negative have been reported to CDC as of January 1991 Ward et al. (Ward 1988) estimated the rate of HIV infection in screened blood to be 0.003% (26/1,000,000 transfusions). In a study of 4,163 cardiac surgery patients who were tested for HIV antibody before and after receiving blood transfusions, Cohen et al (Cohen 1989) also found that the risk of transmission of HIV by transfusion of screened blood was 0.003% (30/1,000,000 units). Based on estimates of the chance that blood will be donated during the "window period" (time period shortly after HIV infection when antibody is not yet detectable), Cumming et al (Cumming 1989) estimated that the transfused patient receiving the average transfusion (5.4 units) had odds of 1:28,000 of contracting HIV infection from the transfusions (Cumming 1989).

HIV has also been transmitted through transplantation of bone, kidney, liver, heart, pancreas and possibly skin (CDC 1988). HIV infection acquired through artificial insemination has also been reported, although the risk of acquiring infection following nonsexual exposure to infected semen is unclear. The U.S. Public Health Service (CDC 1988) recommends that all tissue and organ allograft donors as well as blood and semen donors be evaluated for risks associated with HIV infection and tested for HIV antibody (Rogers 1992).

Hemophilia-associated HIV Infection

Many persons with coagulation abnormalities, primarily hemophilia, require clotting

factor replacement derived from plasma pools donated by hundreds or even thousands of different individuals. Because clotting factor concentrate users were exposed to plasma of so many donors, the chance of having one or more exposures to HIV was enormous until 1985 when HIV antibody screening of donors and heat treatment of the lyophilized factor concentrate began. As a result, many of the estimated 15,500 persons with hemophilia A or B were infected with HIV. A study conducted by the National Hemophilia Foundation tested 7,214 patients between 1985 and 1989; 50% (3,633 of 7,214) were HIV seropositive (Drummond 1986). Because clotting factor concentrates are manufactured by a small number of suppliers for use throughout the country and internationally, HIV-infected persons with hemophilia are found in all geographic areas (Drummond 1986). The classic epidemiologic paradigm that applies to this aspect of the HIV epidemic is that of a point-source contamination with widespread distribution of a tragically tainted product. Although the HIV epidemic in persons with hemophilia essentially ended with the eradication of the contamination at is source, the AIDS epidemic that followed will be with us for years (Rogers 1992).

Both factor VIII and factor IX concentrates have transmitted HIV (Jason 1985). In the United States, up to 80% of persons with hemophilia receiving large-pool, non-heated factor products from plasma donated before HIV screening have developed antibody to HIV (Jason 1985). More severe hemophilia and greater factor usage have been associated with a greater risk of HIV infection. Persons with hemophilia treated exclusively with cryoprecipitate appear to have had a lower risk of exposure to HIV and subsequent infection (Kletzel 1987).

Some investigators have speculated that, in some cases, persons with hemophilia may have become "immunized" by receiving HIV inactivated during the preparation or storage of unscreened, non-heated factor products (Eyster 1985). However, in one study, 55 of 56 HIV seropositive persons with hemophilia were also culture positive, indicating active infection (Jackson 1988).

Sexual transmission from HIV-infected men with hemophilia to their female sex partners, with subsequent perinatal transmission to their infants, is also a problem for these men and their families. Approximately 10-20% of the long-term female sex partners of HIV-infected men with hemophilia have acquired HIV infection through heterosexual contact (Kreiss 1985). As of December 31, 1990, CDC had received reports of nine children with AIDS whose mothers acquired HIV infection from men with hemophilia (Rogers 1992).

ORAL PATHOLOGY AND ITS TREATMENT

Fungal Infections

Oral Candidiasis

Erythematous/Pseudomembranous

Topical -
1. Nystatin (100,000 unit troche 3x/day)
2. Mycostatin (200,000 unit pastille 4-5x/day)
3. Clotrimazole (Mycelex Troche 5x/day)
4. Gynelotrimin (Vaginal Troche 1x/day orally)

Systemic -
1. Ketoconazole (1-2 200mg tab 1x/day)
2. Fluconazole (1 100mg tab 1x/day)

Angular Chelitis

Topical - Creams
1. Nystatin
2. Clotrimazole
3. Ketoconazole

Viral

Hairy Leukoplakia (E.B. Virus)
1. Acyclovir (2.5-3.0g/day for 2-3 weeks)

Herpes Simplex
1. Acyclovir (1000-6000 mg/day x 7-10 days)
2. Phosphonoformate (Foscarnet)

Herpes Zoster
1. Acyclovir (800mg 5x/day x 7-10 days)

Human Papilloma Virus
1. Surgical Excision

Bacterial

Periodontal Disease
1. Thorough debridement with Betadine
2. Oral Hygiene with Betadine rinse
3. Peridex
4. Metronidazole (Flagyl)(250mg 4x/day)
5. Clindamycin (300mg 3x/day)
6. Augmentin (250mg 3x/day)

Idiopathic

Aphthous Ulcer

Topical Steroids
1. Fluocinonide (Lidex)(0.05% in orabase gel 6x/day)

2. Clobetasol (Temovate) 0.05% in orabase gel (3x/day)
3. Dexamethasone (Decadron) (0.5mg/ml rinse 3x/day)

Xerostomia

1. Stimulate salivary flow with sugarless gum, candy,
2. Artificial saliva
3. Topical fluoride

Malignancies

Kaposis Sarcoma

1. Chemotherapy with radiation therapy

Lymphoma

1. Chemotherapy with radiation therapy

THE BIOLOGY OF HIV

HIV is a retrovirus of the lentivirus family. The genes of a retrovirus are encoded in RNA and must be converted to DNA within a host cell before renewed viral expression occurs (Glick 1990). It became apparent that this virus was unique inasmuch as it proliferated within the cells of the immune system and markedly impaired their function. Other viral infections have been known to depress the immune system (Stiehm 1986), for example, cytomegalovirus, Epstein-Barr virus, and measles, but none with the relentlessness and irreversibility of HIV. This is primarily because the T helper cell has a viral receptor (the CD4 antigen) for this virus, and this cell is central to most immunologic reactions. Thus the virus infects and destroys the very cell that should be protecting the host from the viral infection. In addition, monocytes and macrophages, which also express the CD4 antigen, can also become infected and functionally compromised (Stiehm 1991).

It is clear that HIV can destroy the immune system without the aid of other organisms. However, other infections may precipitate and accelerate immunologic deterioration (Stiehm 1991).

While the Immunologic alterations in pediatric AIDS (e.g., AIDS in children younger than 13 years) are in general similar to those of young adults, there are significant differences. Indeed, most of the clinical abnormalities in HIV infection, particularly the great susceptibility to opportunistic infection, can be directly related to defective cellular immunity to one or more invading pathogens. Other manifestations, including bacterial infections associated with poor antibody production, propensity toward malignancy,

lymphoid interstial pneumonitis, and immunoregulatory abnormalities such athrombocytopenic purpura and glomerulonephritis, may result from diminished T cell accessory or surveillance function. In general, the course of the disease is determined by the degree of T-cell attrition (Stiehm 1991).

The first step of HIV entry into a target cell is the binding of a specific glycoprotein (gp 120), which protrudes from the viral membrane, to a specific receptor (CD4) situated on the membrane of the target cell (Landau 1988). After the initial binding to CD4, the viral membrane fuses with that of the target cell, and the virus enters the cell (Stein, 1987). Inside the target cell, a proviral DNA is formed when the viral enzyme reverse transcriptase catalyzes the formation of a double-stranded DNA copy from the original viral RNA (Wong-Stall 1987). This proviral DNA then becomes incorporated into the DNA of the target cell (Glick 1990).

Infected cells essentially become small factories for viral production and slowly cease to perform their original functions. Depletion and dysfunction of the target cells occur via various mechanisms (Yarchoan 1989), including formation of multinucleated giant cells (syncytium), balloon degeneration, and eventually cell death (Levy 1989).

A variety of cells have been shown to be infected with HIV, including hematopoietic cell lines such as T-helper lymphocytes, B-lymphocytes, monocytes/macrophages, promyelocytes, and stem cells; gastrointestinal cells; brain cells; cells of the skin and other cell types (Levy 1989). The T-helper lymphocyte, or T4 cell, appears to be the preferred target cell for HIV (Kletzmen 1989). The normal function of T-lymphocytes includes host protection against viral, fungal, and protozoal infections and B-lymphocyte regulation and

depression of neoplastic growth. Thus, with few or nonfunctioning T-lymphocytes, the body is highly susceptible to opportunistic infection and neoplasms. A healthy individual will have a T4 cell count of 600 to 800 cells/mm3 (Lui 1988). Signs and symptoms of HIV disease usually occur when the T4 cell count is below 400 cells/mm3 (Glick 1990).

All lentiviruses as their name implies cause a disease with a long incubation period. The mean incubation period from HIV infection to the development of AIDS currently is estimated to be 5 years (Longini 1989).

Most new infections with HIV are asymptomatic; however, a self-limiting acute mononucleosis-like HIV syndrome may occur. Both the acute HIV syndrome and asymptomatic infection are followed by the production of anti-HIV antibodies, which usually appear 8 to 12 weeks after infection. Rarely, seroconversion does not occur until several months or even years after infection. After seroconversion, an asymptomatic phase exists that, in adults, may span from several months to years, with a median incubation period estimated at approximately 10 years (Bacchetti 1989, Munoz 1989). Some perinatally infected infants may fail to produce significant levels of anti-HIV antibody following the loss of maternal antibodies and may be at higher risk for developing AIDS (Andiman 1989). Retrospective studies of children with AIDS who were infected perinatally with HIV suggest that the median time between exposure to HIV and the onset of clinical symptoms is between 8 and 10 months (Krasinski 1989, Rogers 1987).

Since HIV entered the pediatric population relatively recently, these retrospective studies are necessarily biased toward the identification of children with the shortest asymptomatic stages. The longest asymptomatic period reported in these studies was 7.3

years. As the time since HIV first appeared in the pediatric population lengthens, it is likely that the median asymptomatic phase will also lengthen. Long-term prospective of studies of HIV-infected infants are needed to delineate more accurately the natural history of HIV infection in children (Rosenberg 1991). Children infected after the newborn period (e.g. hemophiliacs) more closely resemble adults with HIV infection and have a slower, less severe course than do perinatally infected infants (Stein 1991).

The common denominator of infection with the human immunodeficiency virus (HIV) is a profound immunosuppression in children, rendering the host susceptible to the development of a variety of opportunistic infections and neoplasms. The virus also exerts other direct and indirect effects on the host that may be seen quite dramatically in infants and children during development stages of different organ systems such as the central nervous system (Rosenberg 1991).

It should be pointed out in discussing immunopathogenesis of HIV infection that infants and children often develop a wide spectrum of HIV-related disease prior to the appearance of serious immunologic impairment and resulting opportunistic diseases. To be sure, they ultimately develop profound immunosuppression together with its serious consequences. However, more so than in the fully developed adult,HIV seems to have an extremely deleterious effect on the developed fetus and infant in addition to and not directly related to immunosuppression (Rosenberg 1991).

The hallmark of immunodeficiency in AIDS is a selective depletion of CD4+ helper/inducer T lymphocytes (Fauci 1988). The CD4+ T lymphocyte is a central cell in the immune response and closely regulates other immune cells, which include

monocyte/macrophages, cytotoxic T cells, natural killer cells, and B cells (Gendelman 1992). HIV gains entry into the body via direct bloodstream inoculation (blood or blood products.) HIV attaches to the CD4 molecule, a high-affinity receptor, on helper-inducer T cells, monocytes, and other cells of the monocyte-macrophage lineage (Ho 1987, Fauci 1988, Weber 1988).

The ability of HIV to kill T helper cells has been assumed to be the central immunopathologic event in HIV infection (Levy 1988). The selective loss of helper/inducer T cells during HIV infection results in opportunistic infections, neoplasms, and inevitably death of the virus-infected host. There are numerous postulated mechanisms for CD4+ T-lymphocyte depletion. These include direct cytotoxicity resulting from productive viral infection, and killing (Schnittman 1989, Ho 1989, Brinchmann 1991) from indirect mechanisms. (Zagury 1986, Klatzmann 1986, Lynn 1988, Cloyd 1991, Hoxie 1986, McDougal 1985, Hildreth 1989, Valentin 1990, Pantelo 1991, Chang-Meyer 1988, Fenyo 1988, De Rossi 1986, Ziegler 1986, Stickler 1987). In support of the former is the demonstration of high numbers of CD4+ T Lymphocytes infected by HIV in blood. However, the number of productively infected cells in blood is low. HIV-specific RNA is detected in 1/10,000 to 1/1000,000 circulating leukocytes (Harper 1986, Schnittman 1989). Indeed, the paucity of viral RNA-expressing cells in blood makes other mechanisms for CD4+ T-lymphocyte depletion possible. The normal turnover of T lymphocytes in the body is rapid and one would expect that the T-cell pool would compensate for the numbers of productively infected and subsequently killed lymphocytes. Furthermore, the *in vivo* environment is not very conducive to supporting productive and efficient viral replication.

In hematopoietic tissues, immature CD4+ progenitor cells continually divide but are poorly differentiated, while their circulating progeny are quiescent and respond to only a few specific activation signals. In lieu of these observations, indirect mechanisms for CD4+ T-cell destruction during disease are proposed by numerous investigators and supported by experimental analyses (Gendelman 1992).

The high levels of accumulated unintegrated HIV DNA in infected cells may produce cytopathicity, based on the known association between unintegrated DNA and cell death in avian and spleen leukosis virus-infected cells (Weller 1980, Keshet 1979). HIV does not usually allow superinfection, and the high numbers of latent PBMCs demonstrate on average one to two copies of proviral DNA (Schnittman 1989). Alternatively, HIV may induce terminal differentiation of the infected T4 cell, leading to a shortened lymphocyte life span (Zagury 1986, Klatzman 1986). This may occur, for example, by induction of host cell membrane permeability changes (Lynn 1988, Cloyd 1991). Indeed, Lynn et al demonstrated that following productive HIV infection the cell membrane becomes more permeable to small cations and that phospholipid synthesis decreases. Furthermore, temporal studies have recently shown that acute HIV infection affects host-cell macromolecular synthesis and membrane function. However, there is no direct evidence for this mechanism *in vivo*. The observation that HIV infection of CD4+ HeLa cells results in cell lysis (Maddon 1986) opposes the notion that HIV cytopathicity is induced by terminal cell differentiation (Gendelman 1992). Mechanisms other than those mediated by viral replication may be operative, including:

1. The interactions between the CD4 molecule and the virus envelope protein (Lifson 1986, Sodioski 1986) may play a prominent role in CD4+ T-lymphocyte cell death. Infected or uninfected CD4+ cells may be coated with free gp120, which could be recognized as foreign and then cleared by the immune system (Klatzman 1986, McDougal 1985, Hildreth 1989). This could explain the pancytopenia commonly seen in patients with AIDS. Interactions between the HIV envelope glycoprotein present on the surface of infected antigen-presenting cells (e.g., monocyte/macrophages or CD4+ T lymphocytes) and uninfected CD4+ cells could lead to the elimination of the latter (Lifson 1986, Sodroski 1986). Indeed,productive in vitro HIV infection is typified by syncytia formation and often terminal cytopathicity. The process of syncytia formation involves the HIV-infected cell and other uninfected CD4+T lymphocytes. During productive viral infection uninfected cells are recruited into syncytia through fusion of gp 120 on the surface of infected cells. The high level of HIV *env* glycoprotein on the surface of infected CD4+ lymphocytes results in cell fusion with neighboring uninfected CD4+ cells,leading to multinucleated giant cell formation and cell death. Thus, uninfected CD4+ cells are recruited into growing multinucleated giant cells through the interactions between the gp 120 on the surface of infected cells and CD4 on the uninfected cells. In this regard, intracellular complexing of CD4 and *env* proteins may also play a role(s) in the cytopathogenicity induced by HIV infection (Hoxie 1986). Leukocyte surface molecules also play roles in syncytia formation (Valetin 1990, Pantelo 1991, Chang-Meyer 1988). The fact that productive HIV infection can occur in LFA-1-deficient cells, leading to viable productively infected cells, supports the notion that the recruitment of CD4+ T Lymphocytes into the syncytia precipitates their

demise. Indeed, CD4 is rapidly downregulated following viral infection and non-CD4-expressing HIV-infected cells persist for long time periods despite demonstrably high levels of viral gene products. Furthermore, viral species with defined biologic and molecular properties occur over time in infected individuals. HIV-1 isolates from asymptomatic carriers produce low levels of virus and syncytia (slow/low viruses) and those from patients with AIDS or AIDs-related complex (ARC) grow rapidly at high titers and induce syncytia (rapid/high) (Fenyo 1988, De Rossi 1986). These observations, in toto, would support a virus-induced mechanism for CD4+ T-lymphocyte depletion in AIDS. However, although multinucleated giant cells are commonly seen in HIV-infected cultures *in vitro* , it is important to point out that in only a minority of infected tissues, such as brain and spinal cord, can syncytia be demonstrated (Gendelman 1992).

Virus-induced syncytia in peripheral blood has never been demonstrated. Furthermore, syncytia formation occurs predominantly in specific cell lines, often at frequencies that do not involve the majority of the cell population. Most HIV-infected cells die without fusion. Moreover, monocytes and macrophages express CD4 on their surface and are not depleted but productively infected by virus. That HIV often does not induce significant cytopathic effects in monocytes strongly suggests that either the density of CD4 receptor expression is important in determining cytopathic effects or that gp 120-CD4 interactions are not the sole determinant for viral cell killing. In support of the former hypothesis are studies demonstrating HIV-1 superinfection of human T-cell leukemia virus type 1 (HTLV-1)-transformed T-cell clones. Cell clones of either the CD4 or CD8 phenotype infected with HIV result in a productive infection; however, cytopathicity occurs

only in the CD4+ clones (DeRossi 1986). This cell death may be mediated through extracellular CD4-gp 120 interactions or from the formation of intracellular toxic complexes of CD4 and the HIV envelope.

2. CD4+ lymphocyte depletion may involve the expression or alteration of cellular epitopes in virus-susceptible cells (Ziegler 1986). Alteration in the HLA class II phenotype may occur in HIV-infected CD4_ T cells, thereby making them more susceptible to immune clearance. Here the HIV envelope binds to the CD4 molecule and may mimic a configuration of a portion of the Class II major histocompatibility complex (MHC) antigen. Alternatively, viral epitopes expressed on the surface of immune-stimulated and virus-infected cells may precipitate their own demise. In this scenario, host antibody and cytotoxic lymphocyte responses against HIV-specific epitopes clear virus-infected CD4+ T lymphocytes (Stricker 1987).

3. HIV-infected lymphocytes may become more susceptible to superinfection on by other pathogens. Cytomegalovirus (CMV) can abortively infect T cells and through dual CMV/HIV infection lead to an accelerated depletion of the CD4+ T lymphocyte (Schrier 1985).

4. HIV may preferentially infect a small population of precursor or memory cells that is responsible for growth of other CD4+ cells (Fauci 1988). This possibility has recently fallen into disfavor due to the inability to find infected precursor cells *in vivo* (Gendelman 1992).

5. A selective depletion of a critical subset of CD4+T lymphocytes (Schnittman 1990) could result in the elimination of all cells carrying this phenotype. Subsets of CD4+

cells that recognize and respond to soluble antigen are selectively deficient in patients with AIDS. This deficiency occurs early in the course of disease and is quite common.

6. Substances released as a consequence of viral infection, such as soluble cell factors, viral proteins other than gp 120, or other toxic elements, might ultimately destroy other CD4+ T lymphocytes (Giulian 1990, Merrill 1989, Ratner 1987, Margolick 1987).

HIV Infection of Monocytes and Macrophages

As a member of the lentivirus subgroup of retroviruses, HIV maintains the ability to infect cells of monocytic lineage. Since monocytes and macrophages express CD4 on their surface (Talle 1983), HIV infection may proceed via CD4 binding and direct fusion of the HIV envelope with the cell membrane. Phagocytosis of HIV particles may enhance the uptake of HIV by macrophages. However, most studies agree that the CD4 molecule is critical to the process (Nicholson 1986). In vitro, HIV has been shown to infect monocytic and promyelocytic cell lines, peripheral blood monocytes, and alveolar macrophages. In HIV-infected individuals, HIV has been found in peripheral blood monocytes and in macrophages from both the lung and brain (Rosenberg 1989). Unlike HIV infection of lymphocytes, infection of these cells does not lead to cell death and the number of monocytes and macrophages does not appear to the affected.

Infected monocytes and macrophages serve as a viral reservoir, evade host immune surveillance, initiate fulminant disease in specific target tissues, and serve as efficient host cells for the isolation and propagation of HIV (Narayan 1987). In the infected human host, HIV has been demonstrated in, or recovered from, CD4+ T lymphoncytes (Schnittman 1989, Ho 1989), monocytes in blood (Schuitemaker 1991, McElreth 1991), and macrophages

in brain (Koeing 1986, Stoler 1986, Wiley 1986, Vazeux 1987, Michaels 1988, Gabuzda 1986), spinal cord (Elibott 1989), lung (Salahuddin 1986, Chayt 1986), skin (Le Tourneau 1986) and lymph nodes (Tschacler 1987). Infected alveolar macrophages may play an important role in the high incidence of *Pneumocyctis carinii* pneumonia in AIDS patients (Chayt 1986). Lymphocytic interstitial pneumonitis, spinal cord myelopathy, and AIDS-associated encephalopathy are all strongly associated with HIV-infected tissue macrophages (Gendelman 1992).

During steady state, macrophages have critically important functions in providing antimicrobial defense for the host. Paradoxically, these scavenger cells perpetuate viral persistence. Indeed, they represent the major tissue reservoir for HIV. The mechanisms of viral persistence in macrophages involve the presence of virus in intracytoplasmic vacuoles, which may provide an important means for escape from immune surveillance (Orenstein 1988, Ringler 1988). HIV accumulates within Golgi-derived cytoplasmic vauoles of macrophages. Fusion with one another of small golgi complex-derived vacuoles containing small number of virons, along with the continued budding of progeny virus into enlarging vacuoles, probably accounts for the increasing size of the vacuoles and the enlarging number of viral particles. This mechanism of viral assembly and viron accumulation contrasts with infection of CD4+ T lymphocytes. Here the plasma membrane is the site of viral assembly; intravacuolar virus is only rarely identified in multinucleated cells (Gendelman 1992).

The viral life cycle in monocytes and macrophages is regulated by physiological factors involved in maturation and differentiation of the cells from their precursors in bone

marrow or blood (Gendelman 1986, 1984). Bone marrow infection by HIV has not been conclusively identified. Furthermore, the number of monocytes expressing viral RNA in blood is very low. After these infected cells migrate from blood and mature into tissue macrophages, viral gene expression increases several thousand-fold and the virus life cycle goes to completion (e.g., mature virion particles are produced) (Gendelman 1986). A similar phenomenon occurs *in vitro* as infected monocytes differentiate into macrophage-like cells. Not all mature macrophages in tissue are equally permissive for HIV infections. The specific susceptibility of tissues to the pathological process can be traced to permissiveness of local macrophage populations that support virus replication. In visna virus infections, for example, brain and alveolar macrophages are highly permissive, but the mature kupffer cells in liver, the histiocytes of connective tissue, or the Langerhans cells in skin all fail to support viral replication. Moreover, the lung and brain are primary sites for virus-induced lesions, while skin and liver tissues are not targets for pathological changes. These observation are consistent with the concept that genetically predetermined, cellular transcriptional factors (factors that vary with macrophage phenotype, maturation, and cell differentiation) may regulate viral gene expression and/or virus cell surface receptors. Indeed, cell activation is a necessary event for integration and provirally directed gene expression. Specific "cell activation" factors are probably only found in the subpopulations of macrophages that support viral replication and ultimately provide the molecular basis for the unique tissue tropism that underlies aspects of HIV pathogenesis (Bender 1988, Roy 1988, Pauza 1988, Fauci 1988).

Impairment of B-Cell Function

Individuals infected with HIV have significant abnormalities of B-cell function, and impairment of B-cell responses has been observed in HIV-infected individuals of all ages (Hamburg 1990). B cells from HIV-infected individuals have been consistently shown to be polyclonally activated, as evidenced by hypergammaglobulinemia, spontaneous B-cell proliferation, and increased in vitro spontaneous production of immunoglobulin. Although the quantity of immunoglobulins is elevated in HIV infection, numerous investigators have reported diminished in vivo vaccine responses to both T-cell dependent and independent antigens as well as decreased responses to B-cell mitogens (Rosenberg 1991).

B-cell abnormalities are of particular relevance to HIV-infected infants and children since they lack memory responses to common microbial antigens, particularly bacteria, and rely heavily on a primary IgM response for protection. Their decreased ability to mount an adequate IgM and subsequent IgG antimicrobial response results in a high incidence of infection with a variety of common bacterial pathogens. This is true to a lesser extent in adults, but in the pediatric population this defect in humoral immunity is responsible for substantial morbidity and mortality (McNamara 1989).

The pathogenesis of the B-cell defect is presently unknown. Polyclonal activation of B cells in children may be due in part to coinfection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV), both of which are known to cause polyclonal B-cell activation. However, children without evidence of EBV or CMV infection still exhibit B-cell abnormalities (McNamara 1989).

NATURAL KILLER AND ANTIBODY-DEPENDENT CYTOTOXICITY

Natural killer (NK) cells are non-T large granular lymphocytes with an Fc receptor that lyse virus-infected and tumor cells without presensitization. They make up about 5% of the lymphocytes. These NK cells and other cells that have an Fc receptor for IgG (killer cells) can lyse antibody-coated cells through a phenomenon termed antibody-dependent cellular cytotoxicity (ADCC) (Rosenberg 1991).

Several investigators (Pahwa 1985, Schnittman 1986) have demonstrated diminished NK function in AIDS patients, particularly in patients with advancing disease. The NK lytic defect may precede depletion of NK phenotypic cells. By contrast, ADCC activity is quite well preserved in HIV disease, even though mediated by the same or an overlapping population of lymphoid cells (Schnittman 1986). Serum containing antibody to gp 120 is best able to facilitate ADCC activity (Amedori 1989).

Polymorphonuclear Granulocytes

Quantitative defects (i.e., neutropenia) of polymorphonuclear (PMN) neutrophils are not uncommon in patients with HIV infection, particularly in late illness, and are often associated with AZT or other antiviral therapy. Severe bacterial infections are common in HIV disease, but consistent defects in PMN function have not been noted. ADCC of polymorphonuclear granulocytes is intact in HIV infection (Righi 1989, Rabbini 1987).

Table 2. Usual Sequence of Immunologic Changes in HIV Infection in Older Infants and Children

Stage of Illness	Immunologic Finding
Early asymptomatic	HIV antibody positive Normal total lymphocyte count (>1500/mm3) Normal CD4 cells (>1200)a Normal CD4:CD8 ratio (>2.0) Normal immunoglobulin levels (IgG+IgM+IgA = 600 to 1500 mg/dl) Normal antibody responses to neo and recall antigens
Late asymptomatic	Normal total lymphocyte count (>1500/mm3 lymphopenia CD4 cells slightly decreased (800-1200/mm3) Slightly reversed CD4:CD8 ratio (1-0.75) Hypergammaglobulinemia (IgG+IgM=IgA>1800 mg/dl) Selective antibody defects to neoantigens Increased B cells (>15%)
Early symptomatic (ARC)	Moderate lymphopenia, (1000-1500/mm3) CD4 cells decreased (400-800mm3) Moderately reversed CD4:CD8 ratio (0.75-0.50) Decreased antibody response to neoantigens Decreased proliferative responses to antigens Decreased natural killer (NK) cytotoxic activity
Late symptomatic (AIDS)	Marked lympopenia (<1000/cells/mm3) CD4 cells markedly decreased (<400/mm3) CD8 cells decreased (<200/mm3) Markedly reversed CD4:CD8 ratio (<0.5) No antibody response to neoantigens Decreased proliferative response to antigens and mitogens Very low Nk cytotoxic activity

a CD4 numbers and CD4:CD8 ratios are higher under age 1 year

ACTIVITATION OF LATENT HIV INFECTION

Infection with HIV in vivo is characterized by an asymptomatic state that can last for

many years. The average interval between human immunodeficiency virus (HIV) infection through blood transfusion and development of clinical acquired immunodeficiency syndrome (AIDS) is 5 years (Lui 1988, Castagliola 1989). The basis for such a prolonged period of clinical latency, and for the great variability in incubation periods among ostensibly similar hosts, is unclear. Several factors to accommodate such differences have been proposed, such as genetic susceptibility, viral strain diversity, age, development of HIV env variations after initial infection, and amount and route of the initial viral inoculum (Levrence 1992).

Intermittent activation of HIV expression in latently infected cells, by direct or indirect involvement of other viruses, plays a role in determining the rate of development of HIV-related disease. It is proposed that the slow but relentless progression of immunologic dysfunction and clinical symptomatology characteristic of HIV infection is not because HIV is an intrinsically slow-growing retrovirus, but is rather dependent upon the complex nature of viral gene regulation and interactions among the virus, the target cell, the infected cell, and the host, networks susceptible to modulation by infectious cofactors (Lavrence 1992).

Viruses with more restricted distributions have been more clearly defined clinically as cofactors in HIV expression. Human T-cell lymphotropic virus type I (HTLV-I) was implicated in enhancement of progression to AIDS in a small pilot study in Trinidad (Bartholomew 1987). Recently, two other independent reports have confirmed that HTLV-I or -II can hasten the clinical progression of HIV (Hattori 1989, Weiss 1989). Other viral infections are being pursued in large clinical surveys of HIV seropostive individuals. Hepatitis B virus (HBV) infection, although it can stimulate enhancer regions of HIV in

vitro is related to acquisition of HIV-I infection or more rapid progression of immune deficiency or clinical symptoms (Soloman 1990). It may, however, be a cofactor for malignancy in these individuals, similar to links between cervical and anal carcinoma and papillomaviruses (Caussy 1990), and Epstein-Barr Virus (EBV) and malignant lymphomas in AIDS (Laurence 1992).

Although HIV can be cultured from peripheral blood cells from individuals during the asymptomatic state, virus replication, as measured by the presence of HIV core antigen in the peripheral blood, occurs at significantly lower levels than during the symptomatic stage of disease. In both children and adults, persistence of HIV is highly prognostic of disease progression (Goudsmit 1987, Epstein 1988). These data suggest that, for variable periods of time following infection with HIV, viral replication is restricted to chronic, low-level expression. A shift from restricted to active replication presumably occurs following an indeterminate length of time. Although very little is known about the events that occur in vivo to initiate changes in the level of viral expression, a substantial body of in vitro data suggest that activation of T4 cells by a variety of factors may be a key step in the induction of HIV-expression (Rosenberg 1991).

PROGRESSION OF HIV INFECTION

After the initial diagnosis is established and baseline immunologic studies are completed, it should be possible to classify an HIV-infected youngster into a CDC Pediatric Classification.

Table 3. CDC Classification System for HIV in Children

CLASS P-O. INDETERMINATE INFECTION

Infants <15 months born to infected mothers but without definitive evidence of HIV infection or AIDS

CLASS P-1, ASYMPTOMATIC INFECTION

Subclass A. Normal immune function

Subclass B. Abnormal immune function; hypergammaglobulinemia, T4 Lymphopenia, decreased T4;T8 ratio, absolute lmphopenia

CLASS P-2 SYMPTOMATIC INFECTION

Subclass A. Nonspecific findings ($\geq$2 for $\geq$2 months): fever, failure to thrive, generalized lymphadenopathy,hepatomegaly, splenomegaly, enlarged parotid glands, persistent or recurrent diarrhea

Subclass B. Progressive neurologic disease: loss of developmental milestones or intellectual ability, impaired brain growth, or progressive symmetrical motor deficits.

Subclass C. Lymphoid interstitial pneumonitis

Subclass D. Secondary infectious diseases

Category D-1. Opportunistic infections in the CDC case definition

Bacterial: mycobacterial infection (noncutaneous, extrapulmonary, or disseminated): nocardiosis

Fungal: candidiasis (esophageal, bronchial, or pulmonary), coccidioidomycosis, disseminated histoplasmosis, extrapulmonary cryptococcosis

Parasitic: Pneumocystis carinii pneumonia, disseminated toxoplasmosis with onset $\geq$1 month of age, chronic cryptosporidiosis or isosporiasis, extraintestinal strongyloidiasis

Viral: cytomegalovirus disease (onset $\geq$1 month of age), chronic mucocutaneous/disseminated herpes (onset$\geq$1 month age), progressive multifocal leukoencephalopathy

Category D-2. Unexplained, recurrent, serious bacterial infections (2 or more in a 2-year period); sepsis, meningitis, pneumonia, abscess of an internal organ, bone/joint infections

Category D-3. Other infectious diseases; including persistent oral candidiasis, recurrent herpes stomatitis ($\geq$2 episodes in 1 year), multidermatomal or disseminated herpes zoster

Subclass E. Secondary Cancers

Category E-1. Cancers in the AIDS case definition; kaposi's sarcoma, B-cell non-Hodgkin's lymphoma, or primary lymphoma of brain

Category E-2. Other malignancies possibly associated with HIV

Subclass F. Other conditions possibly due to HIV infection: including hepatitis, cardiopathy,nephropathy, hematologic disorders, dermatologic diseases

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Within the P1 (asymptomatic) and P2 (symptomatic) classes a wide range of immunologic abnormalities exist (Stiehm 1991).

Infectious complications are related to the degree of immunologic impairment. Symptomatic antibody deficiency usually does not occur until there is either

hypogammaglobulinemia (IgG + IgM +IgA <400 mg/dl) or impaired antibody responses. Symptomatic cellular deficiency does not occur until CD4 cells are less than 200 cells/mm3 in children over 12 months of age or less than 1000 cells/mm3 in children under 1 year, or unless there are poor proliferative responses to specific antigens (Stiehm 1991).

MECHANISMS OF NEUROPATHOGENESIS

Neurologic dysfunction has been observed to varying degrees in the majority of individuals during the course of HIV infection (Snider 1983, Navia 1986). Whereas some of the neurologic abnormalities are caused by opportunistic infections, central nervous system (CNS) tumors, and vascular problems, a significant proportion of neurologic manifestation, including encephalopathy, myelopathy, and peripheral neuropathy, are detected in the absence of opportunistic disease. Although neuropsychiatric abnormalities are an important manifestation of HIV infection in the CNS in adults, this problem is of even greater magnitude in HIV-infected infants and children. HIV infection appears to have a profound effect on the developing brain. Indeed, HIV-related brain disease is one of the most common and devastating consequences of infection in the pediatric population. A progressive encephalopathy, as measured by the loss of developmental milestones, restricted brain growth, and progressive motor dysfunction, has been reported in 30 to 60% of children with HIV-induced disease. In addition, other HIV-infected children may experience a static encephalopathy with cognitive or motor deficits (Epstein 1988, Belman 1988).

Several lines of evidence support the theory that the HIV-associated encephalopathy is the result of HIV infection of the brain (Rosenberg 1989). Both HIV-specific nucleic acid

sequences and infectious virus have been detected in the brain and cerebrospinal fluid (CSF) of AIDS patients. Isolation of HIV from the CSF of individuals during the asymptomatic stage of infection implies that HIV can infect the brain well in advance of aneuropathogenic effect. Although HIV has been observed in a variety of different cell types in the brain, including capillary endothelial cells, oligodendroglial cells, and astrocytes, the macrophage is the cell that has been most consistently reported to be infected by HIV in the brain (Rosenberg 1991).

At present, there is little evidence for direct HIV infection of neuronal tissue as a mechanism for HIV-induced neurologic abnormalities. The presence of HIV-infected macrophages in the brain has led researchers to hypothesize that neurologic damage may be mediated through the release of factors that are neurotoxic or inflammatory (Favei 1988, Price 1988). Other potential mechanisms of HIV neuropathogensis include gp 120-mediated interference of the binding of neurotropic factors and neuropeptide transmitters to neurons (Lee 1987, Brenneman 1988).

HIV-2

Although all HIV positive Hemophiliacs in the United States are infected with HIV-1 a related virus has been discovered which is related closely enough to HIV-1 to deserve mention.

Both HIV-1 and HIV-2 are human lentiviruses with a number of similar virologicproperties. Both viruses have a target cell tropism for CD4+ T Lymphocytes and apropensity for establishing latent infections. Like other retroviruses, the HIVs are single positive-strand RNA viruses with particles approximately 100 nm in diameter. Virions have

a characteristic dense, cylindrical protein core that encases the genomic RNA molecules and viral enzymes (reverse transcriptase, integrate, and protease). This ultrastructural morphology is indistinguishable from other animal lentiviruses and distinct from type C retroviruses including HTLV (Gonda 1986).HIV-2 isolates have demonstrated tropism for cells bearing the CD4 marker, similar to HIV-1. It is of interest that HIV-2 has a lower binding affinity for the CD4 receptor as compared with HIV-1 (Moore 1990).

In vitro studies of HIV-2 isolates by a number of laboratories have described differences in cytopathicity of HIV-2 as compared with HIV-1 (Evans 1988, Kong 1988, Albert 1990). In comparison with HIV-1, HIV-2, isolates demonstrate decreased cell killing, less syncytial cell formation, reduced virus replication, and differences in interaction with CD4, in some cases related to the clinical state for the HIV-2-infected individual (Evans 1988, Kong 1988, Albert 1990).

In fact HIV-2 is more closely related to Simian Immunodeficiency Virus (SIV) than to HIV-1 (approximately 40% nucleotide homology) (Franchini 1987, 1987, Huyeder 1987). As more sequence data have become available from various HIV-2 and SIV strains, it has also become apparent that no branching order of divergence can be specified and that these virus types may in fact share a common ancestor (Kirchoff 1990). Sequence variability of structural genes such as env and gag has been similar between HIV-2 and HIV-1, with greater variability in the env genes. Interestingly, regulatory gene sequences are more variable among HIV-2 isolates compared with HIV-1 (Allan 1987).

HIV-2 infection appears to be rare outside of Africa at the present time. The HIV-2-infected individuals who have been detected in Europe and the United States usually had

connections to West Africa (Couroce 1987, DCD 1989, Horsburgh 1988). Limited studies conducted in the United States failed to identify HIV-2 in individuals from typical high-risk groups for HIV-1, such as homosexual/bisexual men, hemophiliacs, and intravenous drug user. Identified cases of HIV-2 have included both asymptomatic individuals and patients with AIDS. It is likely that increased international travel will enhance the spread of HIV-2 outside of West Africa (Ranki 1992).

TRANSMISSION

In previous studies, HIV-2 prevalence was higher in sexually active risk groups such as female prostitutes and sexually transmitted disease patients when compared with health control populations (Kanki 1987, 1990). In terms of clinical disease, most identified HIV-2-positive children have been healthy (Matheron 1988, Ovattara 1988). Two related cases have shown clinical abnormalities including generalized lymphadenopathy or generalized lymphadenopathy and diarrhea (DeCock 1989). The sparsity of case reports and the lack of any case-control or prospective studies make definitive conclusions difficult at this time. Despite many similarities in the clinical picture of HIV-1 and HIV-2 AIDS cases, a longer incubation period for the development of full-blown AIDS has been reported among HIV-2-infected individuals (Saimot 1988, Ancelle 1987, Gody 1988). Taken together, these reports seem to indicate possible differences between HIV-1 and HIV-2, in the length of the incubation period from initial infection to AIDS and a somewhat better outcome among HIV-2 AIDS patients. It therefore appears that the natural history and clinical course of HIV-2-infected individuals may differ significantly from that of HIV-1 (Kanki 1992). The data suggests that the pathogenic potential of these two immunodeficiency viruses differ.

Some have argued that the apparent low level of disease progression in this cohort may be due to the more recent introduction of HIV-2 infection in this population (Kanki 1992).

Despite numerous similarities in virologic structure and function, certain unique genes and differences in virus-cell interactions have been noted. It is widely believed that the modes of transmission of HIV-1 and HIV-2 are similar, but the comparative rates of viral transmission may be more important. Incidence data indicate that HIV-2 may spread through heterosexual transmission more slowly than HIV-I. Studies of perinatal transmission of HIV-2 also indicate that the transmissibility of HIV-2 may differ from that of HIV-1. In summary, despite a number of similarities between HIV-2 and HIV-1, important differences also exist. These include differences in risk determinants for sexually active populations, distinct incidence patterns of infection, and a prolonged induction period for the development of AIDS (Kanki 1992).

ORAL MANIFESTATIONS

Oral manifestations of the acquired immunodeficiency syndrome (AIDS) and AIDS related complex (ARC) were described in the very first reports of these syndromes. There is growing evidence that several otherwise relatively innocuous oral opportunistic infections, occurring in human immunodeficiency virus (HIV) - infected patients are indicators of marked immunosuppression and may predict the ultimate development of AIDS. The mouth has long been recognized as the site of residence of an extremely varied and complex microbial flora with marked potential to probe the host defenses and produce disease when those defenses are compromised. Examples include the frequent and troublesome expressions of fungal, bacterial and viral infection in patients with primary immunodeficiency, immunosuppressed graft recipients, and patients receiving immunosuppressive chemotherapy for malignancy (Greenspan 1983). The prevalence and incidence of oral lesions seen in associations with the AIDS epidemic has again drawn attention to the importance of this group of diseases (Greenspan 1987, Reichert 1985). During the course of the disease almost all AIDS patients present oral findings which vary from non-specific to pathognomonic lesions which may be the very first evidence of the underlying syndrome (Evans 1983).

Oral examination is an important part of any physical examination and nowhere is this more important than in suspected HIV infection. All mucosal surfaces should be

assessed using a mouth mirror, examination gloves, gauze squares for tongue extension and,of course, an adequate light source, which can be provided by a penlight if a better light source is not available. Any oral lesion should be subjected to further investigation with techniques such as smears, cultures and biopsy (Greenspan 1983). The oral findings associated with AIDS can be sub-divided into three groups: Those associated with opportunistic infections, those associated with malignant neoplasms and those of idiopathic origin (Evans 1987).

Oral lesions in HIV infected persons

Fungal

Candidiasis
- Pseudomembranous
- Erythematous
- Angular cheilitis

Histoplasmosis
Cryptococcosis

Bacterial

HIV gingivitis
HIV periodontitis
Necrotizing gingivitis and stomatitis
Mycobacterium avium-intracellulare complex

Viral

Herpes simplex
Hairy leukoplakia
Herpes zoster
Warts

Neoplastic

Kaposi's sarcoma
Lymphoma

Idiopathic

Recurrent aphthous ulcers
Immune thrombocytopenic purpura
HIV salivary gland disease
Abnormalities of pigmentation

Oral Oppurtunistic Infections

Oral Candidiasis (ie: Thrush) is the most common oral fungal infection seen in HIV-infected children (Leggott 1989, Ketcham 1990, Cooper 1988). Oral candidiasis is not uncommon in healthy infants and is seen relatively frequently in children born to intravenous drug-abusing mothers who are uninfected with HIV. Esophageal candidiasis is one of the opportunistic infections seen in AIDS and indeed is diagnostic of AIDS according to the Centers for Disease Control surveillance definition. Oral candidiasis is seen in more than 75% of patients, and candidal esophagitis has been reported to develop in approximately 20% of infected children (Parks 1987). However, recent reports of pediatric patients indicate that early aggressive treatment with ketoconazole may reduce the progression to esophageal candidiasis. In adult patients oral candidiasis among high risk groups has been shown to be of predictive value for the subsequent development of full-blown AIDS (Klein 1984).

Candida Albicans is the strain most frequently isolated from the oral mucosa of HIV-infected patients (Franker 1990). It is a commensal, found in more than 90% of the population and may be present as clinically distinct forms including pseudomembranous, erythematous, hyperplastic variants, and angular cheilitis. Pseudomembranous candidiasis is characterized by the presence of creamy plaques on any part of the oral mucosa but most frequently affects the palatal, buccal, and labial mucosa and dorsum of the tongue. The mucosa may appear bright red where visible. The white plaques can be removed, revealing a bleeding surface. Erythematous or atrophic candidiasis appears clinically as a red lesion. The color intensity may vary from fiery red to a hardly discernable pink spot. It is usually without clinical symptoms. The most common locations are the palate and dorsum of the

tongue. When the tongue is affected, patchy depapillated areas appear. Erythematous candidiasis may also appear as spotty areas on the buccal mucosa. It is seen commonly in adults, and it is not clear whether it is less common in children or underreported. Hyperplastic candidiasis is only rarely seen in pediatric patients. Angular cheilitis may appear either alone or in conjunction with either of the other forms (Leggott 1992). It is not known why an HIV-infected individual may develop a single or several types of oral candidiasis. An HIV infected individual with oral candidiasis is considered to be in Group IVC-2 of the Centers for Disease Control classification of HIV infection (CDC 1986).

Oral candidiasis has been identified as the most common oral manifestation of HIV infection and AIDS in all patients at risk worldwide (Pindborg 1986). Pindborg described the varied clinical spectrum of oral candidiasis and emphasized the importance of distinguishing between the different types in the early identification of AIDS and ARC (Pindborg 1986). However, most reports describing candidiasis in association with HIV infection and AIDS do not differentiate between the various clinical types of oral candidiasis.

There have been some exceptions: Schiodt et al (Schiodt 1990) showed that oral candidiasis correlated with HIV infection in Tanzania and found erythematous candidiasis and pseudomembranous candidiasis in 21 and 23%, respectively, of patients with AIDS; Barone et al (Barone 1990) reporting on candidiasis in asymptomatic and symptomatic HIV-infected patients, and in AIDS patients, described a higher frequency of erythematous candidiasis than of pseudomembranous candidiasis (56 and 28% of cases, respectively). Moreover, data have suggested that erythematous candidiasis is underdiagnosed, especially

in cases where oral examinations are performed by examiners not specifically trained in the identification of oral manifestations of AIDS (Dodd 1991).

Oral candidiasis has been shown to be predictive of the subsequent development of AIDS (Rothenberg 1987, Kelly 1990, Moss 1984). Rothenberg showed that oral candidiasis occurring with other symptoms such as dyspnea, night sweats, weight loss, fever, fatigue, diarrhea, arthralgia, cough and herpes zoster was highly predictive for the development of AIDS within a 12-month period. Very low CD4; CD8 ratios in patients with oral candidiasis have also been shown to be highly predictive for the development of AIDS, with 59% of the patients developing AIDS at a median time of 3 months (range 1-23 months) (Klein 1984). Dodd did not find any difference in the time to progression to AIDS for the different types of oral candidiasis, and there appeared to be a wide range of times to progression for all types of oral candidiasis (Dodd 1991). Pneumocystis Carinii Pneumonia (PCP) appeared to be the most common initial manifestation of AIDS in her studies.

Survival trends and mortality have been estimated for patients with AIDS (Lemp 1990, Moss 1984, Schechter 1989), but not for HIV-infected patients with oral candidiasis. Dodd found no significant difference in the time to death from AIDS for the different types of oral candidiasis (Dodd 1991).

In summary, it is clear that both the pseudomembranous and erythematous forms of oral candidiasis are markers for HIV infection and are highly predictive of the development of AIDS. Erythematous candidiasis may be underdiagnosed, with consequent loss of important prognostic information. Since Dodd showed it to be as important as pseudomembranous candidiasis as a predictor of AIDS, greater effort should be given to

teaching clinicians who work with HIV-infected individuals to diagnose this lesion (Dodd 1991).

Treatment of oral candidiasis in children involves the use of antifungal drugs such as 1:500,000 nystatin suspension, used five times a day (Pahwa 1988, Cooper 1988). The suspension has no substantivity and is not well tolerated by infants, so that generally the solution is in contact with the oral mucosa for rather short periods of time. This may contribute in part to frequently reported unsuccessful treatment outcomes. The other disadvantage of the suspension is the high sucrose content. Clotrimazole oral troches may be prescribed for older children; the tablets are sucked five times a day. Gynelotrimin vaginal troches 1 time/day in the mouth have also been used. Candida can be resistant to all forms of therapy and even when responsive may reappear soon after therapy is discontinued. Resistant forms are treated with ketoconazole and fluconazole (Leggott 1992). Ketoconazole, 200-400 mg/day, should be taken with food. Adverse effects include abnormalities in liver function, occasionally nausea or skin rash and others. Unfortunately, ketoconazole may not be adequately absorbed in people with HIV infection because of hypochlorhydria, or other gastrointestinal problems of HIV infection. Fluconazole does not require gastric acidity for absorption, but it is much more expensive than ketoconazole. The recommended dose of fluconazole is one 100-mg tablet/day. A recent study suggested that fluconazole inhibits candidal adherence to oral epithelial cells (Darwazel 1991).

Candidal esophagitis usually requires hospitalization and intravenous therapy with amphotericin B (Leggott 1992). Angular chelitis may be treated with topical creams containing nystatin, clotrimazole or ketaconazole. To date there are few data to suggest

that Candida resistance appears in vivo with any of these antifungal agents, although in vitro resistance has been demonstrated. Rather, lack of efficacy is probably due to poor compliance or poor absorption of the drug. Relapses are common and, once an individual has had two episodes of oral candidiasis, maintenance therapy is advised (Greenspan 1992).

Other Fungal Infections

A few cases of oral histoplasmosis (Weber 1988, Fowler 1989, Cohen 1987), geotrichosis (Greenspan 1991), cryptococcosis (Lynch 1987, Glick 1987) and aspergillis (Shannon 1990) have been reported in HIV-infected patients. Further examples of unusual oral fungal lesions are to be anticipated as the HIV epidemic progresses (Greenspan 1991).

VIRAL LESIONS

Herpes Simplex

Orofacial herpes simplex (HSV) is a fairly common feature of HIV infection (Silverman 1986, Reichert 1986). The lesions may manifest as recurrent intraoral ulcers (Reichert 1986) or recurrent herpes labialis. They may be larger and last much longer than in the immunocompetent individual and may be due to either HSV-1 or HSV-2. However in a retrospective study (Safrin 1991) found neither frequency nor severity of HSV were substantially increased despite severe immuno-suppression caused by HIV. Topical acyclovir may be useful in herpes labialis but systemic (oral) administration is needed for treatment of the troublesome intraoral lesions. Acyclovir resistant oral and perioral herpes due to HSV-2 has been reported in patients with HIV infection (MacPhail 1989). The lesions responded to foscarnet (trisodium phosphonoformate hexahydrate) (Greenspan 1992).

Varicella-Herpes Zoster:

The varicella-zoster virus (VZV) is another human herpes virus that is frequently the cause of oral lesions in association with HIV infection. Rare cases of chickenpox occur (Schiodt 1987) which may respond to high doses of systemic acyclovir, 800 mg 5 times/day for 7-10 days.

Herpes zoster, due to reactivation of VZV, may occur early in the clinical course of HIV disease. The development of AIDS has been reported in 23% of such cases in 2 years and 46% in 4 years (Melbye 1987, Colebunders 1988).

Painful vesicles and ulcers occur in the distribution of one or more branches of the trigeminal nerve. The lesions usually heal, but high-dose acyclovir (4 g/day as tablets, or even intravenous acyclovir, 10mg/kg every 8 hr) is indicated to prevent or treat eye lesions. Postherpetic neuralgia is common (Greenspan 1992).

Warts

In association with HIV infection, oral and labial lesions due to human papillomavirus (HPV) take the form of papilliferous and flat warts. Many of the former appear to be due to HPV-7, otherwise found only in skin warts in butchers, while oral flat warts in HIV infection (focal epithelial hyperplasia) are associated with HPV-13 and -32 (Greenspan 1988, de Villiers 1989). Oral warts may be excised surgically or by laser, but recurrence is common.

Hairy Leukoplakia

Oral hairy leukoplakia (HL) was initially seen only in homosexual men but has more recently been seen in other risk groups, including children, although not frequently. Leggott reported the first HL lesion in a child in 1987 (Leggott 1987). The patient had a white lesion on the lateral border of the tongue, that was clinically identified as HL and confirmed by cytospin in situ hybridization. Studies in adults indicate that the lesion is often an early sign of HIV infection that is followed by the subsequent development of AIDS (Greenspan 1987). However, it does not appear that HL is associated with early infection in children (Leggott 1992). The white lesion of (HL) is found on the lateral margin of the tongue and occasionally elsewhere on the oropharyngeal mucosa of a proportion of HIV-seropositive patients of all risk groups (Reichert 1989, Rindum 1987, Ficarra 1988, Barone 1990). It occurs in about 19% of persons who are asymptomatic, and in higher proportions of patients in CDC group IV, notably those with full AIDS (Schiadt 1988). HL in the presence of HIV infection is of itself a criterion for CDC group IV category C2. Many patients with HL, who do not have AIDS, subsequently develop AIDS, often within a relatively short time. Those with small HL lesions are as likely as those with large lesions to develop AIDS (Schiodt 1987).

The presence of EBV serves to distinguish HL from other lesions with similar clinical or histological appearances (Green 1989). EBV appears to be the cause of HL, for its elimination (Resnick 1988, Greenspan 1990) results in regression of the lesions, while clinical recurrence is accompanied by renewed EBV activity. The source of EBV infection of the differentiating cells in HL is not known. Three possibilities have been considered:

latent EBV infection of the basal cells as a continuing source of infection; salivary EBV continually reinfecting from the oral cavity; or circulating EBV-infected B cells entering from the connective tissue (Young 1992). No EBV DNA has been found in the basal cells, suggesting that latent EBV is not the source (Young 1992). It has been suggested that some HL lesions contain defective EBV (Patton 1990). However, no oncogenic influences of EBV appear to occur, in contrast to the suspected role of the virus in nasopharyngeal carcinoma. No cases of carcinoma arising in HL lesions have been reported and the pattern of keratin differentiation in HL is not suggestive of premalignant potential (Williams 1991).

Therapy for HL is rarely indicated. Indeed, the lesion may spontaneously change in appearance, waxing and waning in extent. A few patients complain of discomfort or dislike the appearance of the lesions. Antifungal therapy should be used to reduce or eliminate superinfection with Candida, while systemic acyclovir is occasionally indicated, 2.5-3.0 g/day for 2-3 weeks. Although acyclovir is effective, the lesions recur (Resnick 1988). An experimental antiviral agent, desciclovir, has been reported to be effective in eliminating the clinical lesion and all virologic evidence of EBV infection in a controlled study (Greenspan 1990). There are case reports of HL disappearing in association with ganciclovir or zidovudine (Newman 1987, Brockmeyer 19889, Kessler 1988, Phelan 1988).

HL must be distinguished from a number of other white lesions of the tongue and oral mucosa, including idiopathic leukoplakia, lichen planus, hyperplastic candidiasis, white sponge nevus, geographic tongue, and lesions due to friction or biting habits (Greenspan 1990).

BACTERIAL DISEASES

Unusual oral bacterial infections are seen occasionally in HIV-infected patients, including ones due to Enterobacteriaceae (Greenspan, Schmidt-Westhausen 1990), mycobacteria (Fowler 1989), and the organism causing bacillary epithelioid angiomatosis (Cockrell 1987). However, the most common and dramatic example of bacterial infection is the severe gingivitis and periodontal disease seen in this group of patients.

HIV-associated gingivitis and periodontitis have been reported in adult patients as a characteristic oral manifestation of HIV-infection (Winkler 1988). Leggott has seen HIV-associated gingivitis associated with both the primary and permanent dentition (Leggott 1992). The lesion is characterized by a linear erythema of the facial and interproximal gingival margins, and is unresponsive to improved oral hygiene. Free gingival erythema is observed in essentially all sites of HIV-G. In most cases this erythema can be described as an intensely red linear band that extends 2 to 3 mm apically from the free gingival margin into the attached gingiva. There is also punctate or diffuse gingival erythema involving the entire attached gingiva from the free gingival margin to the alveolar mucosa. In some regions, the punctate lesions give the appearance of coalescing, making the entire gingiva bright red, suggesting that punctate gingival erythema may be a precursor to the diffuse gingival erythema. Diffuse and punctate erythema of the mucosa are seen in nearly 75% of the patients. Both the bandlike and diffuse erythema are usually associated with spontaneous bleeding or bleeding on probing and does not typically respond to the removal of plaque by intensive scaling and root planing and improved plaque control measures (Winkler 1988).

In children, particularly in the primary dentition, HIV-G may be generalized or localized. In adolescents the more generalized form seems to occur, comparable to the lesion seen in adult patients. In adults characteristic microflora have been associated with the lesion. In HIV-infected adults gingivitis can rapidly progress to a destructive periodontal disease in a few months (Winkler 1988). To date, the non-progressive gingivitis lesion has been reported in prepubertal children (Leggott 1992).

HIV-P, which has all the features of HIV-G, is distinguished by severe soft tissue necrosis and rapid destruction of the periodontal attachment and bone. The loss of more than 90% attachment can occur in as little as 3 to 6 months. Before effective treatment regimens were established, extraction was common. Areas affected by HIV-P frequently do not show deep pocket formation because loss of crestal alveolar bone usually coincides with necrosis of the gingival margin. This necrosis sometimes leads to exposure of alveolar bone and subsequent interseptal bone sequestration. Sequestration of bone in conjunction with soft tissue necrosis can extend into the vestibular mucosa or palate and is suggestive of necrotizing stomatitis (Winkler 1988).

Rapid destruction of periodontal and alveolar bone contrasts with the typical situation in acute necrotizing ulcerative gingivitis (ANUG) (Grassi 1988, Winkler 1989). The lesions of ANUG are normally self-limiting to the soft tissue of the periodontium. Although bone loss can be seen in some cases of recurrent severe ANUG, it is usually the result of multiple attacks over many years. On the other hand, people with HIV-P typically report no previous long-term history of ANUG.

In developed countries, acute necrotizing ulcerative gingivitis (ANUG) has seldom, if ever, been reported in children under 10 years of age. Clinically, the gingival margins and the interdental papillae demonstrate necrosis with grayish ulcers and red, edematous surrounding gingiva. ANUG in adults with HIV infection appears to be a relatively common lesion (Winkler 1986).

Severe pain is a distinguishing feature of HIV-P and the chief reason many patients seek dental treatment. Unlike the pain associated with ANUG, in which pain is localized to the free gingival margin or "gums," the pain associated with HIV-P is usually described as localized in the "jaw bones" or as being a "deep aching pain." Frequently, patients say it feels as if their teeth are hitting "the jaw bone" when they chew. Often this deep pain precedes the development of the clinically obvious HIV-P lesion. The cause of this pain is unclear, but it is probably caused by the rapid bone destruction seen in HIV-P.

HIV-G most frequently involves the entire mouth and is usually distributed equally to all quadrants. In some mouths, however, it is found in limited regions involving one or two teeth. Although severe cases of HIV-P can affect all of the teeth and surrounding periodontium, more frequently HIV-P affects several localized areas independently, resulting in islands of severely involved periodontium surrounded by relatively normal tissue. Frequently, only one surface of a tooth is severely involved with HIV-P while the remaining surfaces are only slightly involved. The reason for such discrete localization is unclear. A distinguishing feature of HIV-G and HIV-P is a lack of response to the removal of plaque and maintenance of good oral hygiene. Conventional gingivitis is reversible and responds to treatment by the return of the gingival health. Even after extensive scaling and root-

planing in conjunction with improved oral hygiene, HIV-G lesions frequently show little response to therapy and can rapidly progress to HIV-P (Grass 1988, Murray 1988).

The causes of this group of lesions are poorly understood. The microorganisms appear to be similar to those seen in conventional periodontal disease and include Bacteroides intermedius, Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, and Fusobacterium nucleatum. Wolinella recta, Eikenella corrodens, and even Candida are also found (Zamben 1990, Vaccuro 1988). Polymorphonuclear leukocyte defects related to HIV infection may be involved (Ryder 1988).

Therapy

Treatment for these conditions involves removing necrotic tissue including bony sequestra, root planing and curettage, irrigation of the affected areas with 10% povidone-iodine, and administration of antibiotics such as metronidazole 250 mg 4 times/day, clindamycin 300 mg 3 times/day, or augmentin (amoxicillin-clavulamic acid) 250 mg 3 times/day, followed by chlorhexidine mouth rinses (Table 4) (Greenspan, Greenspan, 1992).

Table 4. Therapy for HIV-related periodontal diseases

Condition	Management
HIV gingivitis	Plaque removal, Povidone iodine (for acute tx.) Chlorhexidine mouth rinse (after initial lesions heal)
HIV periodontitis	Plaque removal Root planing and curettage Irrigation with povidone-iodine Antibiotics (Metronidazole, clindamycin, amoxicillin), chlorhexidine mouth rinse
Necrotizing gingivitis	Debridement Povidone-iodine irrigation Antibiotics (metronidazole, clindamycin, amoxicillin)
Necrotizing stomatitis	Debridement, including bone sequestra Povidone-iodine irrigation, antibiotics (metronidazole, clindamycin, amoxicillin) Chlorhexadine mouth rinse

(Greenspan & Greenspan 1992)

The routine premedication or prophylaxis of HIV-positive patients with systemic antibiotics during the treatment of HIV-G and HIV-P appears to be unnecessary. Obviously, some patients require antibiotic premedication for other reasons such as a history of rheumatic fever or presence of artificial joints and should be treated accordingly, using the recommendations of the American Heart Association and the patient's physician (Schulman 1984, AMA 1985).

Follow-Up Care

Immediate follow-up care for HIV-P is required to ensure success in treatment. Patients should not be placed on protracted unsupervised care. Ideally, the patient should return within 24 hours, but not to exceed 5-7 days, for an oral hygiene evaluation and for any necessary additional debridement of necrotic tissues. However, in many cases the follow-up visit depends on a variety of factors, such as the patient's ability to achieve adequate oral hygiene, the patient's compliance in the use of adjunctive agents, the effectiveness of the acute care debridement, and the presence of concomitant oral and systemic lesions (Winkler 1989).

Within a week to 10 days, definitive follow-up therapy may be started in most cases. This typically consists of quadrant-by-quadrant scaling and root planing to remove calculus left during the acute care treatment and removal of accumulated plaque, necrotic tissue, and materia alba during the healing phase. A significant amount of material may accumulate and require removal even when the patient faithfully follows the oral hygiene regimen. Continued severe destruction of the periodontal tissues often results in many residual areas that are difficult to maintain. Therefore, refinement in techniques by the patient are required to achieve adequate long-term plaque control (Winkler 1989).

A third appointment a week to 10 days after the second appointment is suggested for the evaluation and reinforcement of oral hygiene and the completion of required scaling and root planing. Considerable healing and epithelialization should be expected. Necrotic bone, if loose, should be gently removed from areas where bone is being sequestered.

Special attention should be given to the areas where fragments have not sequestered or cannot be removed to avoid the accumulation of food and bacteria which act as a nidus for additional intraoral infections (Winkler, 1989).

Neoplasia

Although various malignant neoplasms have been reported in patients infected with the human immuodeficiency virus (Robert 1984, Kaplan 1987, Overly 1987), and some cancers may become more aggressive as a result of HIV infection (Tirelli 1989, Serrano 1990), only non-Hodgkins lymphoma and Kaposis Sarcoma have been shown statistically to be in excess.

Kaposi's Sarcoma

Kaposi's sarcoma (KS) has been reported as the initial manifestation of AIDS in 10% of patients with AIDS (Valderding 1988). The sarcoma accounts for about 90% of all malignancies diagnosed in patients with AIDS (Gropman 1987).

KS has been reported in all groups of people who have AIDS including children and those with hemophilia. However, for unknown reasons, it is most common in young homosexual and bisexual men who have AIDS (Safai 1985).

As the predominant malignancy associated with AIDS, KS is nonmetastic, but often appears as a multifocal, vascular neoplasm that can occur on any site. It is aggressive, extensively disseminated, frequently involves the lymph nodes and viscera, and is often fatal. The presence of KS in an HIV-infected patient is considered a diagnosis of AIDS.

Oral lesions of (KS) were among the first oral features of the epidemic noted (Lozada 1982, 1983). The palate is the most common oral site while the gingiva and tongue

may also be involved. Salivary gland and cervical lymph node involvement are seen (Petow 1983, Yeh 1989). Oral KS may present as flat or raised patches of blue, purple, or red color. Yellow stain of the mucosa adjacent to the lesion may also be seen as a result of the lysis of red blood cells and the release of hemosiderin. They may occur bilaterally and symmetrically or as single lesions with ill-defined borders. Unlike hemangiomas, these lesions do not blanch under pressure. Because the clinical distinction may be difficult, a biopsy is needed to confirm a diagnosis of KS in these early lesions.

As the disease progresses, the lesions become larger, elevated, and nodular. In time, the lesions appear rounded or dome-shaped, pebbled, or plaquelike and have poorly demarcated borders. Large nodular lesions may ulcerate and become secondarily infected. Occasionally, oral KS may be covered by normal colored mucosa. The histopathology is the same as that of KS lesions elsewhere (Green 1984, Lummerman 1988).

Oral KS lesions may be painful and interfere with mastication and swallowing. Visible lesions may be embarrassing to the patient. Small lesions respond well to local therapy, including surgical or laser excision and intralesional chemotherapy, such as vinblastine (Epstein 1989, Ficarra 1988). Larger lesions may respond well to external radiation therapy (Lozada 1982). Early lesions should be treated to slow down progress and reduce the morbidity associated, in particular, with secondary infection, which may mimic HIV periodontitis.

HIV-associated Kaposi's sarcoma displays an uneven incidence among the groups at risk, occurring in 43% of homosexual or bisexual men, 4% of intravenous drug users, 12% of Haitians, and in only three reported cases in children infected with HIV, suggesting the

interplay of additional factors in the generation of this tumor (Steis 1988).

Interestingly, Kaposi's sarcoma also appears more likely to develop in patients in whom T-cell immunity is relatively well preserved (Afrasiabi 1986). Factors that have been implicated in the pathogenesis of Kaposi's sarcoma include cytomegalovirus infection and the use of amyl or butyl nitrate vapors (Mirvish 1987). Neither of these suggestions, however, has been substantiated.

Recently, the demonstration that the transplantation of cells grown in vitro from human Kaposi's sarcoma into mice results in the development of murine Kaposi's sarcoma lesions, as well as the demonstration that mice transgenic for the HIV *tat* gene develop lesions consistent with Kaposi's sarcoma, strongly support the view that Kaposi's sarcoma is a vascular proliferation resultant on the production of one or more growth factors induced by an HIV gene product. Basic fibroblast growth factor, which is strongly angiogenic, and interleukin-1 messenger RNA's have been shown to be secreted by human Kaposi's sarcoma cells (Ensoli 1989). Thus, Kaposi's sarcoma may not, at least in the setting of HIV infection, be a true neoplasm. Why it is so uncommon in children with HIV infection remains unknown.

Treatment

Treatment for KS is required because of functional impairment, to reduce or eliminate pain or bleeding, or for cosmetic reasons (Wescott 1989). Small oral lesions may be excised surgically, removed by laser or electrocautery, or frozen using liquid nitrogen on a cotton swab. The larger nodular lesions may be excised, removed by cryosurgery or laser, or injected with chemotherapeutic agents such as dilute vinblastine. Extensive lesions may

respond to radiation therapy. Treatment with anticancer drugs is limited as they tend to suppress bone marrow and thus further depress the immune system. Certain immunomodulators have shown some promise in treating KS in patients with AIDS. Two new drugs based on alpha interferon recombinant technology are now available for patients with AIDS-related KS (Mousselli 1989). The US Food and Drug Administration (FDA) approval or Intron-A (Schering-Plough) and Roferon-A (Roche) was based on clinical studies showing that alpha interferon can reduce the severity of lesions and significantly prolong the lives of patients. Alpha interferon has antiretroviral, antitumor, and immunoregulatory effects in patients with AIDS and KS and is beneficial in patients with CD4 cell counts over 200 who have not had AIDS-related opportunistic infection (Wescott 1989).

Dentists can treat these lesions when they are amenable to excision, cryosurgery, laser, or electrocautery. Dentists should also have referral sources available for management of the more extensive lesions or for those that do not respond to treatment (Wescott 1989).

The treatment of the child with HIV-associated Kaposi's sarcoma remains virtually uncharted territory. Physicians faced with determining the best therapeutic option for such patients are advised to avail themselves of the much greater experience with this problem in the adult oncology community (Horowitz 1991).

Lymphoma

The increased incidence of malignant lymphomas seen in patients at risk for HIV infection was first noted in 1984 (Ziegler 1984, Levine 1984). Current estimates are that

3% of HIV-infected adults will be diagnosed with non-Hodgkin's lymphoma (NHL) (HIV/AIDS Surveillance 1990, Levine 1987). Children with chronic immunodeficiency from any etiology are at significant risk for the development of cancer, particularly non-Hodgkin's lymphoma. Unlike the clinical profile of NHL occurring in the general population, HIV-associated NHL is predominantly high grade, has a higher frequency of extranodal sites, and is clinically aggressive with short survival following diagnosis (Horowitz 1991).

Non-Hodgkin's lymphoma may involve the oropharynx (Ziegler 1982, 1984, Kaugars 1989, Green 1989). The oral lesions may precede those at other sites, or be the only lesions and so be the presenting and diagnostic criterion for AIDS. The lesions can be found anywhere in the mouth as swellings, nodules, or ulcers. They may present a diagnostic challenge and repeated biopsies may be needed (Greenspan (1992). Treatment regimens used today include chemotherapy and radiotherapy.

There is no convincing evidence for an association between oral squamous cell carcinoma and HIV infection. However, as the life expectancy of HIV-infected individuals increases it is possible that oral cancer due to papillomavirus and tobacco may occur (Greenspan 1992).

IDIOPATHIC LESIONS

HIV Salivary Gland Disease

A large number of oral manifestations of unknown etiology have been reported in persons with HIV infection, and the most common of these is salivary gland enlargement (Leggott 1992). There may be a reduced salivary flow rate. Appropriate measures to

alleviate symptoms and prevent caries include saliva substitutes, control of sugar intake, fluoride rinses, and fluoride applications (Greenspan 1992).

Parotid swelling appears to be much more common in children than in adults (Schiodt 1987). Recently it has been reported to occur in about 5% of HIV-positive homosexual men, whereas approximately 14% to 30% of infected children are reported to have unilateral or bilateral involvement of the parotid glands (Oleske 1983, Rubenstein 1983). In children the initial and subsequent manifestations may be of an acute infectious nature that are associated with pain and fever and that require antibiotic therapy. The enlargement may be recurrent or persistent and diffuse. In some children the lesion resolves but in many the lesion is present for long periods of time. The lesions are generally much larger and more disfiguring in pediatric patients than in adults. In most children xerostomia is not usually associated with the parotid swelling, although in adult patients it is a fairly common complaint (Leggott 1992).

The swelling is diffuse and soft. There may be dry eyes and other features suggestive of Sjhogren's syndrome, but significant serological and immunohistochemical differences distinguish HIV SGD from Sjogren's syndrome. HIV SGD may include cases described as branchial cleft cysts or lymphoepithelial cysts of salivary glands (Finter 1988), and all of these may be the salivary gland expression of the diffuse infiltrative CD8 lymphocytosis syndrome in HIV infection described by Itescu et al. No viral or other microbial causes have been identified as causitive for HIV SGD (Itesw 1990).

In both adults and children the lesion often occurs in conjunction with generalized lymphadenopathy. Reasons for the differences between the adult and pediatric manifestations are not yet understood (Leggott 1992).

Recurrent Aphthous Ulcers

There is a slight increase in the prevalence of recurrent aphthous ulcers (RAU) in HIV infection (Feigal 1991) and a dramatic increase in their severity (Najjar 1989) with a shift towards the major variant (MacPhail 1991). Recurrent aphthous ulceration usually is limited to nonkeratinized mucous membranes. The lesions begin as small raised papules on the mucosa with central blanching that creates a white appearance. The papule expands and undergoes a central necrosis to form a shallow ulcer approximately 2-10 mm in diameter. The ulcers show a central, slightly depressed grayish fibrin border and surrounding halo (Leggott 1987).

The major form of RAU consists of large (1-2 cm) solitary, occasionally multiple, painful ulcers that may persist for weeks and hamper swallowing and mastication because of pain. The minor form consists of crops of ulcers about 5 mm in diameter, which usually heal more rapidly than the major form, but nevertheless persist much longer than in HIV-negative individuals. Finally, crops of tiny (1-2 mm) ulcers that may coalesce (Herpetiform RAU) are also seen. The etiology of RAU is unknown, but the nature and frequency of its association with HIV infection lend support to a role for defects in immune regulation or for the presence of as yet unknown microbiological agents.

These ulcers usually respond to topical steroids Fluocinonide (Lidex) 0.05% in orabase 6 times/day, Clobetasol (Temovate) 0.005% in orabase 3 times/day, Dexamethasone

(Decadron) 0.5mg/ml rinse 3 times/day. Systemic steroids are rarely indicated. In Europe, thalidomide has been used (Youle 1989). Very large necrotizing oral ulcers are seen in HIV infection. These may represent major aphthous ulcers further complicated by bacterial infection, or they may be a form of necrotizing stomatitis. They may be associated with similar lesions elsewhere in the gastrointestinal tract (Akula 1989). They respond to a combination of topical steroids plus antibiotics directed against gram-negative bacteria (Greenspan 1992).

RAU occurs far more frequently in immunodeficient children, particularly those with chronic granulomatous disease and severe combined immune deficiency disease. Treatment of RAU is symptomatic (Leggott 1987).

Idiopathic Thrombocytopenia Purpura

Thrombocytopenia is part of the clinical spectrum of AIDS related disorders. The exact pathogenesis of thrombocytopenia in AIDS patients is unclear although high levels of platelet-bound immunoglobulin G (Ig G) have been detected (Daugherty 1985). Thrombocytopenia results from the removal of altered platelets from the circulation by the reticulo-endothelial system, diminished megakaryocyte production is not involved. Defects in platelet function in these patients have not been reported (Hoffman 1989). Abrams (Abrams 1989) found that patients with platelet counts of 7,000-25,000/mm3 exhibited increased bruising with ecchymosis, petechiae and occasional epistaxes. Nearly half of these patients required no treatment and several patients experienced a spontaneous reversion to normal platelet counts over 5-27 months (Walsh 1985). Although idiopathic thrombocytopenia purpura (ITP) is seen in HIV infection, oral features are rare. When

present, they consist of small purpuric lesions, large ecchymoses, or spontaneous gingival bleeding (Greenspan 1986).

Treatment for thrombocytopenia include Corticosteriods, Splenectomy, Intravenous Immune Globulin, Danezol (an androgenic steroid). Rh o (D) Immune Globulin and vincristine therapy. In any case treatment should be reserved for symptomatic patients experiencing bleeding episodes or used in asymptomatic patients requiring invasive procedures (Hoffman 1989).

Hyperpigmentation

Unusual brown pigmentation of the oral mucosa in HIV-infected patients is most commonly associated with zidovudine or ketoconazole therapy. In some cases no obvious predisposing factors other than HIV infection are found (Langford 1989). A few of these cases may be due to adrenal cortical insufficiency (Porter 1990).

ORAL PROBLEMS IN PEDIATRIC HIV INFECTION

Oral candidiasis and HIV Salivary Gland Disease are common features of pediatric HIV infection (Leggott 1987, Pawha 1985, Rubinstein 1983). Hairy leukoplakia (DeSouza 1988), herpes simplex infections and gingivitis (Leggott 1988) are occasionally seen, while other oral lesions are rare. Caries may be a problem because of neglect and because of the high sugar content of many drug preparations. Oral hygiene instruction and maintenance is essential, while the use of topical fluorides as rinses or gels is recommended (Greenspan 1992).

HEMATOLOGIC CARE

NORMAL HEMOSTASIS

When a blood vessel is severed, hemostasis is achieved by a sequence of events. The vessel constricts, thus limiting the outflow of blood. Platelets adhere to the exposed subendothelial connective tissue and aggregate, forming a soft platelet plug which may suffice in smaller vessels. In the stagnant blood proximal to the platelet plug in the vessel, plasma clotting factors and phospholipid, released from the aggregated platelets, interact to convert fibrinogen to fibrin monomer. The monomers polymerize into fibrin strands, which enmesh the blood cells to form the familiar red clot (Kasper 1976).

There are two pathways, namely, the extrinsic and the intrinsic, by which clotting factors may interact to generate thrombin, and thereby cause the formation of fibrin (Kasper 1976).

In the extrinsic pathway, Factor VII acts as an enzyme catalyzing the interaction of tissue thromboplastin (a lipoprotein found in the tissues, especially in brain, lung, and placenta) and calcium with Factor X to form Factor X_a. Then, in a manner not yet clearly understood, Factor X_a, Factor V, phospholipid from platelets (platelet factor 3), and calcium form a complex which converts prothrombin to thrombin. Thrombin splits two pairs of peptides from fibrinogen, leaving fibrin monomer; monomers spontaneously polymerize by hydrogen bonding (Kasper 1976).

In the intrinsic pathway, coagulation may be initiated by the activation of Factor

XII. In vitro, surface contact activates Factor XII. The activation process in vivo is not clear, but small amounts of Factor XII_a can activate prekallikrein (Fletcher factor) to form kallikrein, which further activates Factor XII. Then, Factor XI may be activated by Factor XII_a or by some other mechanism as yet undiscovered. (Factor XII is needed for intrinsic clotting in vitro but not in vivo; persons with Factor XII deficiency have no bleeding disorder. Therefore, an alternate path of activation must exist in vivo.) Factor XI_a activates Factor IX. A complex of Factor IX_a, Factor VIII, phospholipid, and calcium forms which converts Factor X to Factor X_a. The reaction sequence then continues as described above (Kasper 1976).

The fibrin polymer then is stabilized by Factor $XIII_a$, activated from Factor XIII by thrombin and calcium. Factor $XIII_a$ catalyzes cross-linking peptide bond formation between adjacent fibrin monomers. Without Factor XIII, fibrin polymers may disassociate; they are soluble in 5 M urea or dilute acids. Patients lacking this factor have a serious bleeding disorder (Kasper 1976).

The following is a list of the International and the familiar names of the clotting factors:

International Name	*Familiar Name(s)*
Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue Thromboplastin
Factor IV	Calcium
Factor V	Proaccelerin, labile factor
Factor VII	Proconvertin, stable factor
Factor VIII	Antihemophilic factor (AHF) antihemophilic globulin (AHG)
Factor IX	Plasma thromboplastin component (PTC) Christmas factor

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Factor X	Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA)
Factor XII	Hegemon factor
Factor XIII	Fibrin stabilizing factor, Laki-Lorand factor

Tests of Clotting Factor Interaction

The bleeding time and the clotting time are not appropriate screening tests of plasma clotting factor interaction. The bleeding time measures the ability to form platelet plugs and is abnormal only if the quantity or function of the platelets is abnormal. Aspirin will prolong this test even in normal persons and should not be given for at least one week before the test (Montgomery 1991).

The whole blood clotting time is prolonged only in instances of a severe deficiency of a plasma clotting factor and is not long in moderate deficiencies which are clinically significant (Kasper 1976).

In the Quick prothrombin time test, tissue thromboplastin and calcium are added to citrated patient plasma and the time of appearance of fibrin strands is noted. The extrinsic pathway of clotting is being tested. The patient's plasma supplies Factors VII, X, and V and prothrombin and fibrinogen (Kasper 1976).

In the partial thromboplastin time test (PTT), a phospholipid reagent (supplying the equivalent of platelet factor 3) and calcium are added to citrated patient plasma and the time of appearance of fibrin strands is noted. In an activated partial thromboplastin time, a surface-active powder such as kaolin is added to the mixture to ensure maximal activation of Factor XII. These tests measure the intrinsic pathway of clotting. The patient's plasma supplies Factors XII, XI, IX, VIII, X, and V and prothrombin and fibrinogen.

If the Quick prothrombin time test or the partial thromboplastin time test, or both, are abnormal, assays which are specific for the clotting factors implicated by these abnormalities are performed (Kasper 1976).

The differential partial thromboplastin time may be useful if the patient's PTT is decidedly prolonged and specific factor assays are not available immediately. The patient's plasma is mixed with an equal volume of plasma from a person who has a severe deficiency of Factor VIII but adequate amounts of Factors IX, XI, and XII. If the clotting time of this mixture is normal or nearly normal, the patient probably has a deficiency of Factor IX, XI, or XII, but an adequate amount of Factor VIII. The combined plasmas provide all necessary plasma clotting factors for this test. If the clotting time of the mixture is still decidedly prolonged, the test patient is probably deficient in Factor VIII. Similar tests may be performed using plasmas known to be deficient in Factor IX, XI, or XII (Kasper 1976).

The use of serum or adsorbed plasma, as factor-deficient reagents, often leads to confusing results; naturally deficient plasma is preferable. The differential PTT technique is not appropriate if the patient has only slight prolongation of the PTT because results are likely to be confusing.

If the PTT is prolonged, a screening test for inhibitor should be performed. Most inhibitors can be detected by a modification of the PTT, as follows: An equal mixture of patient plasma and normal plasma is allowed to sit in a plastic tube at 37 C for an hour. Then, the PTT is measured and compared to the PTT of pure normal plasma which has been incubated similarly. If the patient has no inhibitor the PTT of the mixture will be a few seconds longer than that of normal plasma. If the patient has an inhibitor, his plasma will destroy some of the Factor VIII (or Factor IX or other clotting factor or clotting intermediary) in the normal plasma mixture and the PTT of the mixture will be prolonged markedly (Kasper 1976).

A test for an inhibitor to a specific clotting factor may be performed by mixing patient plasma and normal plasma and assaying the clotting factor level in the mixture after incubation. Unless an inhibitor is present, the Factor VIII level should be at least half that present in the mixture at the beginning of the test. If the Factor VIII is less than a quarter of that present at the beginning of the test, an inhibitor may be diagnosed.

In the thrombin time test, dilute thrombin is added to citrated patient plasma and the time of appearance of fibrin strands is noted. The clotting time is prolonged if there is severe hypofibrinogenemia or qualitatively abnormal fibrinogen. The test is also sensitive to the presence of small amounts of heparin in the plasma and to the presence of fibrin split

products (which interfere with the polymerization of fibrin monomer Kasper 1976).

A fibrinogen titer is a better way of estimating the fibrinogen level in plasma than the thrombin time, prothrombin time, or PTT. These screening tests may be normal when fibrinogen deficiency is moderately severe (Kasper 1976).

Tests of Platelet Function

A platelet count will determine whether there are enough platelets to carry out their functions in clotting. A bleeding time is a test of the ability of platelets to form a plug. The time may be prolonged if platelets are inherently defective or are too few in number, or if platelets have been affected by agents toxic to them, such as aspirin, or if the platelets lack a plasma substance necessary for their function, as in von Willebrand's disease.

In the platelet adhesiveness test, the platelet count of fresh venous blood is compared to that of blood which has been passed through a column of glass beads. Normally, the percentage of platelets adhering to the beads is high. In von Willebrand's disease, adherence is low. Platelets normally aggregate when exposed to such agents as adenosine diphosphate, collagen, epinephrine, ristocetin, and others. Aggregation with ristocetin usually is reduced in von Willebrand's disease whereas aggregation with other agents is normal. Patients with inherently defective platelets may have poor platelet adhesiveness, poor aggregation with one or several agents, abnormalities in tests for decreased storage of lipid, or inadequate release of lipid, or several of these defects (Kasper 1976).

DIAGNOSIS OF THE COMMON HEMOPHILIAS

Hemophilia A (Classic Hemophilia, Sex-Linked Factor VIII Deficiency)

In Hemophilia A, the patient's plasma is deficient in Factor VIII clotting activity but

contains normal amounts of an antigen which precipitates with a rabbit antihuman Factor VIII antibody. This finding suggests that the patient makes a Factor VIII molecule which is unable to function normally in the coagulation process (Kasper 1976).

The degree of Factor VIII deficiency is similar in all affected males in a given kindred. In some families, the deficiency is severe, and affected males have frequent joint and tissue hemorrhages which can lead to crippling deformities. Small cuts usually do not bleed excessively. In other families, the deficiency is moderate or mild, and affected males may bleed only after trauma or at surgical operations. Normal persons have Factor VIII levels ranging from about 50 to 200 percent. Patients with hemophilia have Factor VIII levels from a fraction of 1 percent to 30 percent of the average normal level (Kasper 1976).

Screening tests for hemostatic function in hemophilia reveal normal bleeding time, prothrombin time, and thrombin time but a prolonged partial thromboplastin time. An assay specific for Factor VIII should be performed to determine the level of deficiency. About 8 percent of patients with severe classic hemophilia develop antibodies to Factor VIII (inhibitors) which inactivate infused Factor VIII (Kasper 1976).

Most carriers have Factor VIII levels in the 30 to 70 percent range. Some have higher levels, and some have levels below 30 percent and bleed excessively with trauma or surgical operations. If a potential carrier, for example, the sister of a hemophiliac, is found to have a Factor VIII level below the normal range, she may be told she is definitely a carrier. If the level is in the normal range, she can be given a statistical estimate of the probability that she is a carrier (Kasper 1976).

Hemophilia B (Christmas Disease, Factor IX or PTC Deficiency)

In Hemophilia B, the patient's plasma is deficient in Factor IX clotting activity. In affected males in some families, an abnormal molecule can be detected by immunologic techniques. In other families, no abnormal molecules have been detected (Kasper 1976).

The clinical findings, genetic pattern and laboratory screening test findings in hemophilia B are parallel to those in hemophilia A, with few exceptions: (1) only 1 or 2 percent of patients with hemophilia B develop inhibitors to Factor IX and (2) carriers can be detected by immunologic techniques only in families in which an abnormal molecule can be detected in affected males (Kasper 1976).

Factor XI Deficiency (Hemophilia C, PTA Deficiency)

In hemophilia C, the patient's plasma is deficient in Factor XI clotting activity. No abnormal Factor XI molecules have been described as yet. Patients with Factor XI deficiency have prolonged bleeding after trauma or surgical operation. Unprovoked bleeding into deep tissues is uncommon even in severe deficiency of Factor XI (Kasper 1976).

Inheritance of Hemophilia C is of the autosomal recessive pattern, affecting both males and females. Parents and children of the patient will be heterozygous with low-normal levels of Factor XI (e.g., 50 percent) of no clinical significance (Kasper 1976).

Characteristic laboratory findings include a normal bleeding time, normal platelet function tests, and a normal prothrombin time but a prolonged PTT. If a differential PTT is performed with plasmas from patients with known deficiencies of Factor VIII and of Factor IX, correction may be obtained with both plasmas, though they may not correct equally well. A specific Factor XI assay should be obtained whenever this disorder is suspected (Kasper 1976).

Von Willebrand's Disease

This disorder is characterized by poor platelet plug formation and a variable degree of Factor VIII deficiency. A protein in our blood, termed von Willebrand factor (vWf), causes the platelets to bind to the damaged blood vessel wall (platelet adhesion). These adherent platelets activate other platelets to clump at that site (platelet aggregation), the surface of these activated platelets then promotes blood clotting (activation of factors that result in gelation of blood), and these events together cause the cessation of bleeding. Thus, if von Willebrand factor is absent, the ability to localize and concentrate the hemostatic process at the specific site of injury is impaired (Montgomery 1991).

The disorder of platelet plug formation leads to excessive bleeding from small cuts and mucosal abrasions and to heavy menstrual bleeding in females. In patients with very low Factor VIII levels, bleeding into joints and muscles may occur. All patients risk excessive bleeding from surgical procedures, including tooth extraction (Kasper 1976).

The platelet dysfunction is demonstrated by a prolonged bleeding time, by decreased retention of platelets by glass bead columns (platelet adhesiveness), and by decreased

platelet aggregation with ristocetin (although aggregation is normal with other reagents). The abnormal adhesiveness and ristocetin aggregation can be corrected by suspending the patient's platelets in normal plasma. Although infusion of normal plasma stops most hemorrhages, the bleeding time may remain long (Kasper 1976).

If the Factor VIII level is below 30 percent, the partial thromboplastin time is likely to be prolonged; the prothrombin time and the thrombin time are normal. In contrast to classic hemophilia, the lack of Factor VIII activity is associated with a comparable lack of antigen reacting with rabbit antibody. This finding suggests that patients with von Willebrand's disease produce less than normal amounts of Factor VIII molecule, whereas patients with classic hemophilia produce normal amounts of an abnormal Factor VIII molecule. In von Willebrand's disease, transfusion with normal plasma results in increased synthesis of Factor VIII by the patient for one or more days. The plasma factor missing in von Willebrand's disease, that factor which corrects the platelet dysfunction and stimulates Factor VIII production, is closely related in some way to the normal Factor VIII molecule (Kasper 1976).

Von Willebrand's disease is inherited as an autosomal disorder, usually dominant in mild or moderately affected families, and recessive in the most severely affected patients. Males and females can be equally affected. In contrast to sex linked hemophilia, Factor VIII levels vary from one affected person to another within the same family. Factor VIII levels and bleeding times also vary from time to time in the same person. An afflicted person might have an abnormal bleeding time and subnormal Factor VIII level on one

occasion, and, on another occasion, have test results within normal limits. Platelet adhesiveness usually remains abnormal on all occasions (Kasper 1976).

SYMPTOMS

Whereas patients with hemophilia often have severe bleeding that is detected and diagnosed in the first few years of life, von Willebrand disease is a milder disorder and may be discovered at any age. Usually a patient experiences recurrent nosebleeds, easy bruising, heavy menstrual periods, or has prolonged bleeding at the time of a surgical procedure such as a tonsillectomy or tooth extraction. Although normal young children may have bruises and do not recall the trauma, older children and adults who bruise frequently without known trauma may have von Willebrand disease. Since von Willebrand factor increases during pregnancy, bleeding at delivery is relatively uncommon except in patients with absent von Willebrand factor or in those who have an abnormally functioning molecule (type II variants) (Montgomery 1991).

Symptoms are highly variable, even in patients within the same family. Most people with this disorder have very mild symptoms, and many of these are undiagnosed unless a family member is identified or pre-operative hemostasis testing is performed. However, in other individuals life-threatening bleeding may occur after extensive injuries or operations. Thus, the recognition of this condition is very important, and often family studies identify affected persons who otherwise would go undiagnosed. Other than specific laboratory tests for von Willebrand factor, the clinical history may be the most important way to determine who has von Willebrand disease since the usual hemostasis screening tests may be normal in mild forms of von Willebrand disease (Montgomery 1991).

CLASSIFICATION

Classification helps determine the best and safest manner of treatment. This testing is most reliable if performed electively and as part of a family study. Von Willebrand factor antigen (VwF:Ag) is measured by an immunoassay. Commonly this is done by quantitative immunoelectrophoresis. Alternatively, von Willebrand factor can be measured using an assay termed ELISA (Enzyme-Linked Immunosorbant Assay) (Montgomery 1991).

Patients with mild von Willebrand disease usually have about 25-35 percent of the normal amount of von Willebrand factor. Severe patients have less than 5 percent to undetectable levels. A person's blood type may affect the level of vWf:Ag. Normal individuals who are blood group O have lower vWf:Ag levels (36-160 u/dl), and persons who are blood group A, B, and AB have higher levels (48-240 u/dl). Some laboratories have established normal ranges for each blood type (Montgomery 1991).

Von Willebrand factor activity (ristocetin co-factor activity, vWf:RCo) is a laboratory measure of the function of the von Willebrand factor. In some patients the amount of vWf:Ag is normal, but it does not function properly. In most patients with von Willebrand disease, the vWf:Ag and vWf:RCo are both reduced, often proportionately (Montgomery 1991).

Factor VIII clotting activity is measured by a clotting factor assay. Often this measurement is normal or only slightly reduced. In von Willebrand disease, the vWf:Ag is usually reduced more than the factor VIII level. In patients with severe von Willebrand disease, the factor VIII level may sometimes be less than 5-10 percent of normal with the

von Willebrand factor level being undetectable (Montgomery 1991).

Von Willebrand factor multimers are a qualitative measure of the structure of the von Willebrand factor molecule. Often, when the function of von Willebrand factor is abnormal, it is because the larger von Willebrand factor multimers are missing from the plasma. Sometimes additional studies of the vWf multimers (complex multimers or high-resolution multimers) must be performed to correctly classify the abnormality (Montgomery 1991).

Platelet vWf:Ag or vWf:RCo can now be determined by measuring the amounts of these proteins in platelets. Patients with low plasma vWf:Ag but normal platelet vWf:Ag may not be as symptomatic as persons with low platelet vWf:Ag (Montgomery 1991).

Although usual platelet aggregation studies (ADP, epinephrine, collagen, and arachidonic acid) are normal in von Willebrand disease, aggregation with ristocetin may be abnormal. This test is not as sensitive as the vWf:RCo assay and many patients will have normal ristocetin induced platelet aggregation (ristocetin 1.2-1.5 mg/ml). Aggregations with low doses of ristocetin (0.3-0.5 mg/ml) may detect patients with either Type IIB von Willebrand disease of platelet type von Willebrand disease (Montgomery 1991).

Genetic or DNA studies recently have detected von Willebrand factor abnormalities by evaluating the genomic DNA or cDNA derived from the mRNA of platelets. These studies are most commonly performed with unusual variants of von Willebrand disease such as Type IIA or IIB. The need for these tests must be determined by the hematologist and utilized accordingly (Montgomery 1991).

The diagnosis of von Willebrand disease may be difficult during pregnancy, in the

newborn period, during the post-operative period, or during stress, because all of these conditions will elevate von Willebrand factor and may cause a patient with von Willebrand disease to have normal laboratory testing. vWf:Ag also may be elevated into the normal range in a child who is extremely agitated and crying. It is often important for the technologist to comment on the ease of obtaining the blood specimen in young children. Repeat studies when the patient is not under stress or just performed at a different time may be necessary to rule out the diagnosis of von Willebrand disease (Montgomery 1991).

TREATMENT OF HEMORRHAGES

Hemophilia A (Factor VIII Deficiency)

Minor, superficial hemorrhages, such as small skin cuts, may respond to prolonged pressure and cool packs. More extensive or deep hemorrhages are treated by replacing the missing clotting factor. The sooner the bleeding is stopped, the less damage will be done to the tissues, so treatment should be given at the first indication of a hemorrhage. Factor VIII must be given intravenously in the form of normal human plasma or plasma concentrate. A mild superficial or very early hemorrhage sometimes will subside if a Factor VIII level of around 15 to 20 percent is achieved, but the episode will more surely subside if a level of 30 percent or more is attained. For any serious hemorrhage, a Factor VIII level of 35 to 50 percent should be obtained to permit the formation of an optimal clot. One adequate dose of Factor VIII is sufficient to treat most hemorrhages. However, Factor VIII is rapidly metabolized in the body with a half-disappearance time from the plasma of about eight hours. If the patient bleeds again several hours after the initial dose, he may require another dose of Factor VIII to achieve a satisfactory level (Kasper 1976).

Minor operations, such as tooth extraction, can be permitted with a single dose of Factor VIII given immediately before the procedure. Another dose of Factor VIII is given only if bleeding occurs. Rebleeding is most common on postoperative days five, six, and seven; the patients should avoid stress on the site for 10 days (Kasper 1976).

For more extensive operations, the factor VIII level is maintained at a daily minimum of at least 30 percent for a healing period of 10 to 14 days; Factor VIII levels are checked by specific factor assay. The first dose of Factor VIII, to achieve a level of 80 to 100 percent, is given an hour before the procedure; the plasma Factor VIII level is checked by assay. A second dose of Factor VIII, half the size of the priming dose, should be given about five hours after the priming dose. The patient may be in the recovery room by this time, or still in the operating room. If several units of blood were lost during the operation, a third dose of concentrate should be given when the patient reaches the recovery room. A dose of concentrate is also given in the late evening. Concentrate administration is continued for 10 days for relatively minor procedures, and for 14 days for more extensive procedures. Concentrate is usually administered every 12 hours in a sufficient dose to maintain a minimum plasma Factor VIII level of at least 30 percent. The patient's hematocrit may fall slowly for several days after the operation without obvious bleeding. The patient adjusts his total blood volume by adding to his plasma volume; this enlargement of the plasma volume must be considered in the calculation of post-operative concentrate dosage. Patients undergoing postoperative rehabilitation, namely physical therapy, receive daily concentrate throughout the period of rehabilitation (Kasper 1976).

Many hemorrhages can be prevented if the patient is "converted" from severe to

moderate or mild status by the administration of small doses of Factor VIII every day. For example, if a patient is transfused to a Factor VIII level of 10 percent in the morning, he may retain 5 percent by late afternoon and 2 percent by bedtime; some protection is provided during the most active part of the day. Prophylaxis is particularly appropriate for patients undergoing physical therapy and for patients with very frequent hemorrhages (Kasper 1976).

Choice of Materials and Dosage

Three types of plasma products are available for the treatment of hemophilia A: fresh-frozen plasma, cryoprecipitate, and lyophilized Factor VIII concentrate.

Fresh-frozen plasma was obtained from blood banks. Each bag contains about 175 to 250 ml of plasma from one blood donation. The plasma should be stored at -30 degree C. For administration to the patient, the bag of frozen plasma is placed in a pan of water at exactly 37 C. The bag, as it softens, may be manipulated to break up large chunks of frozen plasma in order to hasten thawing. Thawing should be complete since Factor VIII is among the last proteins to dissolve. The infusion of plasma should be prompt, because Factor VIII deteriorates at room temperature. The defrosted plasma may be expected to contain about 70 percent of the Factor VIII which was present in the fresh plasma. Different donors have different Factor VIII levels; the amount of Factor VIII in any given bag of frozen plasma is unpredictable (Kasper 1976).

Cryoprecipitate is prepared by blood banks. A bag of fresh plasma is quick frozen, then slowly thawed in a refrigerator until only a few milliliters of ice and sludge remain. This remaining material, or cryoprecipitate, contains about half the Factor VIII and

fibrinogen which had been present in the fresh plasma. The thawed plasma is drained off; the cryoprecipitate is retained and refrozen. For administration to the patient, the bag is placed in a pan of water at exactly 37 degree C and allowed to thaw thoroughly (about 15 minutes). Sterile normal saline may be added to wash out bags containing a small volume of cryoprecipitate. The Factor VIII content of cryoprecipitate varies depending upon the donor's Factor VIII level and the blood bank's method of processing. With care, a blood bank should be able to produce cryoprecipitate averaging 100 Antihemophilic Factor (AHF) units per bag; however, this standard is often not attained (Kasper 1976).

Factor VIII (with fibrinogen) is extracted and concentrated, distributed in 10 or 25 ml aliquots in glass vials, and lyophilized. The vials are stored at refrigerator or room temperature. The concentrate is reconstituted with water or saline and administered intravenously. A sample bottle from each lot is assayed in vitro by the manufacturer, and the number of Factor VIII units is stamped on the label. (A Factor VIII, or AHF, unit is the amount of Factor VIII found in 1 ml of fresh average normal plasma) (Kasper 1976).

Several factors affect the choice of plasma product used to treat hemophilia A. The cardiovascular system cannot accept an unlimited volume of osmotically active fluid, such as plasma, at one time. Patients with severe hemophilia are usually treated with cryoprecipitate and concentrate because a therapeutic level of Factor VIII can be achieved with a small volume of material. Patients with mild hemophilia, e.g., 20 percent Factor VIII, might be managed satisfactorily with plasma (Kasper 1976).

All blood products used in treating hemophilia can transmit the virus of serum hepatitis. Frozen plasma and cryoprecipitate are usually obtained from volunteer donors

and not pooled prior to use; one infected donor can infect only one recipient. Concentrates are made from plasma pooled from a great many donors who are usually paid donors; one infected donor can infect all the recipients of the pool. Patients with severe hemophilia who require frequent infusions of plasma products will inevitably encounter the virus; they may as well receive concentrates. Patients with mild hemophilia who require treatment on few occasions should receive the single donor products (Kasper 1976).

Most hemophiliacs who have received many infusions of plasma develop allergic reactions such as hives and chills during infusions of plasma; they should be given antihistamines before infusion. Allergic reactions are infrequent with cryoprecipitate and rare with concentrate. Patients with blood types A, AB, or B should receive type-specific plasma to avoid hemolysis. Crossmatching is not indicated for plasma or cryoprecipitate.

Factor VIII content is not equally predictable in concentrate and cryoprecipitate. Concentrates can be relied upon to contain the approximate number of Factor VIII units stated on the label. Cryoprecipitate varies. Clinicians should periodically assay the response of their patients to the cryoprecipitate available in their community to evaluate its potency.

Concentrate is more convenient for self-treatment because it can be transported at room temperature.

The price per Factor VIII unit varies among products and communities. The clinician faced with the high cost of treating severe hemophilia may want to seek the best bargain for their patient (Kasper 1976).

In general concentrates have been described by the terms crude, intermediate and high purity (Table 5). These generally refer to their important characteristic of specific activity i.e. the relationship between units of activity per unit of protein content usually expressed as u/mg (Bloom 1991).

Table 5. Contemporary designation of factor VIII concentrates.

Type	Names	Production method	Sterilization	Specific activity u/mg
Crude		Cryoprecipitate Cryo-ethanol precipitation	None or Solvent/Detergent (SD) etc.	0.1-0.9
Intermediate 8Y (BPL	Various		Dry heat (80 C-72 hr)	
	Profilate SD (Alpha)	PEG-amino acid ppt.	SD	
	Haemate P (Behring)	Chromatography	Wet pasteurization	-10
	Beriate P (Behring) (reduced vWF)	etc.	Wet pasteurization	
	Kryobulin (Immuno)	Vapor heat		
'High' Purity a) FVIII:CP high	Precipitation			
	purity (Behring) Glucose/Saccharose	and ion-exchange stabilization	Wet pasteurization	25
	b) Octa VI	Chromatography	SD	up to 250
	(Octapharma) FVIII VHP	Chromatography	SD	
	c) Monoclate P	Immunoaffinity on	Pasteurization	15
(Armour)		monoclonal	SD	
	Hemofil M (Baxter)	antibodies		(diluted from 3000 with human albumin

(Bloom 1991)

Crude concentrates such as single donor, freeze dried cryoprecipitate or cryo-alcohol precipitated factor VIII really represent other plasma proteins especially fibrinogen and fibronectin more or less contaminated with factor VIII. Specific activities range from 0.1 to 1 u/mg. This type of concentrate is no longer produced by commercial suppliers but is still produced by some voluntary or national organizations. Intermediate purity concentrates have specific activities of 1-10 u/mg. They are prepared by national and commercial fractionators. These concentrates are produced by various chromatographic and precipitation techniques. High purity concentrates have specific activity greater than 10u/mg. Broadly speaking, they are of two types. Those produced by more conventional chromatographic techniques have specific activities of up to 250 u/mg but still contain many plasma proteins albeit in very low concentration compared to intermediate concentrates.

The second type of high purity concentrate is produced by immunoaffinity purification on immobilized monoclonal antibodies either to factor VIII or to von Willebrand factor with subsequent elution or dissociation and further chromatographic purification. Theoretically these "monoclonally purified" concentrates have specific activity of 3000u/mg i.e. approaching the theoretical maximum but in practice for pharmaceutical reasons and stability they are diluted in human albumin so that the final specific activity is about 15u/mg. The high purity concentrates have less contaminating proteins than the previously described preparations but it should be noted that albumin may contain low concentrations of several other human proteins and murine proteins from the monoclonal antibodies may be present in minute amount. Similar principles apply to recombinant factor VIII. It should also be noted that monoclonally purified products contain virtually no (vWf) but significant and therapeutically useful amounts are present in crude and some intermediate factor VIII concentrates as well as at least one high purity concentrate (Bloom 1991).

Virucidal Processes

The realization that blood and blood products transmit infectious diseases has led to the development of virucidal procedures to sterilize factor concentrates. These were originally developed for hepatitis viruses but were found to be more effective against HIV (Bloom 1991).

Although albumin has been successfully sterilized by a form of pasteurization in aqueous solution and has been in clinical use for over forty years with a good safety record, extension of this technique to coagulation factor concentrates proved to be more difficult

because of their heat lability. Furthermore, addition of various stabilizers tend also to stabilize the unwanted viruses (Bloom 1991).

A pasteurized factor VIII concentrate was developed in 1981 (Heimburger 1981), but supplies were not generally available and were restricted to the German domestic market. In any case, yield of factor VIII at that time was unacceptably low. In retrospect also adequate clinical evidence of sterilization of hepatitis viruses and in due course HIV was not available although subsequent evidence suggests that the process was effective (Schimpf 1987). Also available at that time in Germany was a preparation of factor IX concentrate sterilized by B propiolactone and ultra violet light (Heinrich 1982). This preparation however has not achieved general acceptance and recent evidence has thrown doubt on the effectiveness of this process (Bloom 1991).

Apart from these preparations, other first generation concentrates included those dry-heated at 60-80 degrees C for periods of time varying between 24 and 72 hours. Second generation concentrates were heated in water vapor under pressure or in organic solvent to dissolve lipid viral envelopes. An extension of the latter principle but not involving heat is the use of organic solvent such as tri(n-butyl)phosphate (TNBP) and a detergent such as sodium chlorate or "Tween" 80. These cold methods have the advantage of high yield of factors VIII or IX. In the UK dry heat at high temperature (80 degrees C) for 72 hours has been remarkably successful and a high yield has been claimed for an intermediate grade concentrate sterilized in this way. An advantage of this method is that the individual vials are end-sterilized thus reducing the risk from in-process contamination or cross-contamination. Recently immunoaffinity purified and recombinant products have undergone

clinical trials (Bloom 1991).

All presently available products appear to be free of HIV contamination. No seroconversions have occurred in any viral safety trials in which HIV antibody status has been studied. Previously, from 1985-1987, 18 cases occurred with dry-heat treated factor VIII concentrate, some of which may have been due to unscreened plasma. These cases prompted withdrawal of the dry-heat treated concentrates altogether. The wet-heat treated and solvent-detergent treated products appear to be free of HIV contamination. Monoclonal products are also apparently free of risk of HIV transmission and are greatly purified. The added expense of these monoclonal products seems justifiable in view of much higher purity and decreased risk of immune function abnormalities (Mehta 1991).

Hepatitis B and C continue to be risks with any of the available products. Patients, therefore, should be vaccinated against hepatitis B infection prior to receiving products and monitored for hepatitis B or C on a regular basis (Mehta 1991).

The Medical Advisory Board recognizes that the risk of transmitting HIV infection with presently available products is so small that patients should not hesitate to treat themselves with factor preparations for bleeding which would otherwise cause deformities. The final decision on choice of factor should rest with the patient and his physician (Mehta 1991).

Treatment

The goals of treatment are to minimize disability and prolong life, to facilitate general social and physical well-being and to help each patient achieve their full potential, while causing no harm. Timely treatment of hemorrhages is facilitated by supervised self-

infusion programs in which patients and families, thoroughly instructed in the recognition and treatment of hemorrhages, infuse plasma products at home. Success in such programs requires that the patient keep careful records of infusions, cooperate with close supervision by a hemophilia center, and visit the center for periodic evaluations (Kasper 1989).

Products for Factor Replacement

In most developed countries, the mainstay of hemophilia treatment is clotting-factor concentrate, lyophized extracts from pooled normal plasma containing either FVIII (usually with some fibrinogen) or FIX (usually with factors II and X, and some VII). Concentrates are stable at cool room temperatures and require only small volumes of diluent for reconstitution. Their level of purification is associated with a very low incidence of immediate adverse reactions. Thus, concentrates are convenient for supervised self-infusion programs.

Frozen single-donor plasma products, including fresh frozen plasma and cryoprecipitate, are used successfully in some parts of the world. DDAVP (desmopressin) a synthetic vasopressin analogue that releases stored FVIII and vWF into the circulation, should be used whenever possible to treat mild hemophilia A and von Willebrand disease. However, patients who do not respond to DDAVP or who have severe factor VIII deficiency need factor replacement (Kasper 1989).

Prophylactic (maintenance) therapy using infusions of plasma product infusions is sometimes used to prevent hemorrhages. The standard of care in some centers is routine prophylaxis at a dose sufficient to prevent nearly all hemorrhages, especially during

DOSAGE AND CHOICE OF THERAPY

Hemophilia A without Inhibitor

The level of FVIII needed to secure hemostasis depends on several variables, with higher levels required for large hemorrhages and for those in joints with prior pathological changes. Generally, the higher the level attained (up to the normal range), the greater the likelihood of stopping a hemorrhage immediately. Most clinicians raise the FVIII level to about 50 U/dL for definite hemorrhages; incipient bleeding often halts with lower levels (Kasper 1991).

The initial T-1/2 of infused FVIII during equilibration is about four hours and the biologic T-1/2 is about 12 hours. If bleeding is in a dangerous area, FVIII may be given intermittently (for example, half the loading dose every 4-12 hours) or by continuous infusion to maintain a minimum plasma FVIII level of 30 to 50 U/dL. Continuous infusion provides stable levels of FVIII, facilitates monitoring of factor levels by assays of random blood samples, and uses less concentrate to maintain a given factor level than does intermittent infusion (Kasper 1991).

For surgical operations, the FVIII level should be maintained well over 50 U/dL during the procedure and at a minimum level of about 40-50 U/dL for the next 10-14 days. The level of FVIII needed for hemostasis after tooth extraction ranges from about 20 to 50 U/dL, depending upon the difficulty of the procedure. Prevention of bleeding during vigorous exercise, such as physical therapy, requires levels of 20-40 U/dL. The higher level is used if there is marked deformity and weakness. As strength is gained, lower levels may

suffice.

In mild hemophilia A, DDAVP is the treatment of choice if adequate FVIII levels can be attained, to avoid exposure to blood products. In severe hemophilia A, FVIII concentrate is used. The concentrates now sold have not been known to transmit HIV, and most have not been known to transmit hepatitis. Therefore, they usually are preferred over untreated random-donor cryoprecipitate. Patients not previously infected with hepatitis B should be vaccinated (Kasper 1991).

Hemophilia A with Inhibitor

Management of Inhibitors

Complicating therapy for hemorrhage is the presence of inhibitors to Factor VIII or IX. About 8% of Factor VIII-deficiency patients and 1% of patients with Factor IX deficiency have inhibitors. Inhibitors are thought to be gamma globulin antibodies formed as a response to factor replacement. In patients with strong inhibitors, replacement therapy may be restricted to life-threatening bleeds to prevent further inhibitor development. Factor replacement is also ineffective unless the patient is a low-inhibitor responder to transfused factor (Kasper 1976).

No one can predict who will develop an inhibitor, nor does anyone know how to prevent inhibitors. If a patient has the ability to develop a strong inhibitor, he probably will do so by the time he has been given plasma products on a hundred occasions or less. Since most patients with severe hemophilia in this country are treated vigorously for hemorrhages, this degree of exposure to plasma products usually will be achieved in early childhood. Severe inhibitors can appear in infants who have had only a few infusions; they can develop

also in adults who have survived youth without extensive exposure to blood products. If a patient has received plasma products on at least a hundred occasions, and does not have an inhibitor, he probably will never develop a strong one. Weak inhibitors, on the other hand, may develop in older patients who have had hundreds of plasma infusions. Patients with inhibitors do not bleed more often than patients without them. An inhibitor state should be suspected when a patient fails to stop bleeding after an adequate infusion of plasma concentrate (Kasper 1976).

Blood products and treatment of factor VIII inhibitors

In general the methods available include:

- Local measures
- Pharmacological elevation of factor VIII with DDAVP
- Factor VIII concentrates, human and porcine
- Plasmapheresis
- Extracorporeal immunodepletion
- Intravenous IgG which may act by various methods including its content of antiidiotypes which interact with anti-factor VIII or IX

Methods of by-passing factor VIII and its inhibitor include the use of activated prothrombin complex concentrate (PCC) and its possible components, factor Xa-phospholipid, tissue factor and factor VIIa. The role of PCC in inhibitor patients has been well described. In clinical trials non-activated PCC was effective in about 50% of patients. Activated PCC such as FEIBA was effective in about 65% of patients but not to the extent seen with factor VIII in ordinary haemophilia and as expected a placebo effect with albumin

was noted. Although these studies were performed with non-heated concentrates it appears that heat-treatment does not impair clinical efficacy (Hilgartner 1990).

In some patients with low inhibitor levels (under five Bethesda units, "BU"), FVIII infusion does not provoke increase in the inhibitor level (anamnesis). Hemorrhages in these "low-responders" can be treated with FVIII concentrate in a dose sufficient to neutralize the circulating inhibitor and reach the desired therapeutic plasma level of FVIII. A dose 2-3 times that used in a non-inhibitor patient usually is tried, and the post-infusion FVIII level assayed to be certain it is adequate. If the level is inadequate, more FVIII is infused.

In other inhibitor patients, "high-responders", infusions of FVIII stimulate increased production of inhibitor. Minor hemorrhages usually are treated with PCC (without heparin) in doses of 75-100 U/Kg, repeated once or twice at 8-12 hour intervals if needed. Prolonged treatment is avoided. PCC has only trace amounts of FVIII:Ag and rarely causes anamnestic responses; inhibitor levels in patients treated with PCC or AICC tend to drift downwards. AICC is more expensive than PCC, thus, PCC usually is the mainstay of therapy, and AICC is used in selected patients who appear to respond better to it than to PCC, or it is used in crises when PCC has been ineffective and another agent must be tried.

The management of serious hemorrhages in patients with inhibitors usually is difficult and best relegated to major hemophilia centers when possible. The probability of controlling a hemorrhage with the initial treatment is much better if a hemostatic level of FVIII can be attained with human or porcine FVIII concentrate than if PCC or AICC is used. A high-responder who currently has a fairly low inhibitor level can be given massive does of FVIII. Some clinicians use an initial bolus of 5000-10000 FVIII units in an adult,

followed by 300-1000 or more FVIII units/hour to maintain the FVIII level in the desired range. If direct infusion of FVIII concentrate is inadequate, as is likely with inhibitor levels over 10 BU, an exchange plasmapheresis can be performed for partial depletion of the patient's circulating antibody level for a short time, during which a massive infusion of FVIII can be given.

Most inhibitors have notably less affinity for porcine FVIII than for human FVIII, thus, an infusion of a given amount of porcine FVIII is more likely to be effective than is a similar amount of human FVIII. Porcine FVIII usually is the treatment of choice for serious hemorrhages in high-responders (Kasper 1991).

If levels of inhibitor to both porcine and human FVIII are too high (more than about 10 BU) for direct infusion, or if plasmapheresis is inadvisable (because the inhibitor level is very high, or delay would be life-threatening), then a serious hemorrhage may be treated with 75-125 units/Kg of AICC or PCC. Surgery is attempted in a "high-responder" only as a life-saving measure, using human or porcine FVIII as long as hemostatic FVIII levels are obtained, then using AICC or PCC (Kasper 1991).

Eradication of an inhibitor obviously would be highly desirable. Immunosuppressive drugs alone, such as predisone or cyclophosphamide, have little or no effect on inhibitors in hemophiliacs (in contrast to their efficacy in non-hemophilic patients with autoimmune inhibitors). Immune tolerance to FVIII can be induced in about 75 percent of hemophiliacs with inhibitors by daily infusion of 50 FVIII U/Kg for a few months. Inhibitor levels peak in the first month or two, then fall abruptly, and eventually become undetectable. In some

patients, the process is hastened by concomitant use of immunosuppressive drugs. Immune tolerance usually must be maintained by giving low doses of FVIII every few days. Some patients who have undergone immune tolerance induction retain low inhibitor levels, but behave as low-responders (Kasper 1991).

Treatment of haemophilia B and factor IX concentrates

For the main part the specific treatment of haemophilia B to date has consisted of administration of various types of prothrombin complex concentrates (PCC) which are produced by various chromatographic methods. These contain not only factor IX but also other vitamin-K dependent clotting factors, factor II (prothrombin) and factor X and some such as PPSP (prothrombin, proconvertin, Stuart factor, antihaemophilic factor B) also contain factor VII (proconvertin). Others such as BPL (UK)9A do not contain significant quantities of factor VII. A useful factor VII concentrate is a by-product of this technique.

One of the problems of these concentrates is that they may result in high circulating levels of prothrombin and contain activated forms of the K-dependent factors especially factor Xa, which may render them thrombogenic (Kasper 1975). In order to avoid this problem heparin has been incorporated into the purification process or added to the final product but an unpublished survey being conducted by the UK Haemophilia Centre Directors has demonstrated that thrombotic complication are still occasionally occurring. In order to avoid these complications factor IX concentrates devoid of other factors have been prepared. There are two main types. One is prepared by chromatographic methods (Menache 1984, Burnouf 1989). The other is by the use of immunoaffinfity chromatography using monoclonal antibody to factor IX (Kim 1990). Sterilization methods have been

similar to those described above for factor VIII. These concentrates have specific activity up to 200u per mg of protein and are much less thrombogenic in vitro tests and animal models than are the older three or four factor concentrates as well as in an in vivo study (Mannucci 1990). Plasma half lives have been comparable (Menache 1990) or in excess (Kim 1990) of those observed following administration of conventional PCC and preliminary clinical studies indicate that they are equally effective (Bardin 1990). There can be little doubt that these concentrates will rapidly replace PCC's for the treatment of haemophilia B.

Hemophilia B

The plasma levels of FIX needed to halt hemorrhages are similar to those sought in FVIII deficiency. When PCC is used, its non-specific thrombogenic effect may contribute to hemostasis. The initial T-1/2 of infused FIX is about 4 hours and the biologic T-1/2 is about 26 hours. If a hemorrhage is in a dangerous area, plasma FIX levels can be maintained at 20-30 U/dL for a few days, preferably with FIX concentrate. With PCC, the risk of thrombosis probably is related to dose and duration of use, so large overdoses or prolonged treatment should be avoided (Kasper 1991).

For surgical operations, FIX concentrate is used to keep the plasma FIX level over 50 U/dL during the procedure and then to maintain it at 40-50 U/dL for the necessary healing period. Levels of FIX needed for hemostasis after tooth extraction depend on the difficulty of the procedure and range from 20-50 U/dL. Prevention of hemorrhage during vigorous physical activity may require levels of 20-40 U/dL, depending upon the patient's physical condition. Because of the long biologic T-1/2, many patients with severe

hemophilia B take concentrate once or twice a week for general prophylaxis (Kasper 1991).

Table 6. Factor IX concentrates

	American Red Cross	Biotransfusion	Alpha	Armour
Preparation	Chromatography	Chromatography	Chromatography	Monoclonal antibody
Sterilization	Solvent detergent	Solvent detergent	n-heptane 20h 60 C	Na thiocynate Ultrafiltration
Specific activity u/mg		120 - 200	50 - 150	200
In vivo recovery %	48 - 56	40 - 45	61.8+14.4	25 -- 60 (mean c35)
Half-life (h)	18.6-18.8	20 - 25	21.03+4.08	34.6

Von Willebrand's disease

Most patients with von Willebrand's Disease (vWd) are heterozygous and much less severely affected than those with severe hemizygous haemophilia A. Until about ten years ago treatment was relatively straight forward. Factor VIII levels seemed to be most important for control of surgical bleeding and although epistaxis, mucous membrane bleeding and menorrhagia could be troublesome most of the crude concentrates and cryoprecipitate then available contained enough high molecular weight von Willebrand factor (vWF) to control this type of bleeding and stabilize factor VIII-the so called secondary rise. The advent of deaminoD-Argenine vasopressin, (DDAVP) also promised to be a useful adjunct to treatment. Since then several developments have complicated the issue.

a. the advent of AIDS and the realization of the importance of hepatitis viruses.

b. the differentiation of different types of vWd

c. the development of high purity factor VIII concentrates some of which are virtually devoid of vWF (Bloom 1991).

The advent of HIV infection was a considerable stimulus to fractionation technology in order to produce factor VIII products with high specific activity which could be adequately sterilized. Although donor screening for HIV has done much to render single donor cryoprecipitate relatively safe from HIV and hepatitis B, screening for NANBH is at a much less satisfactory stage and the value of such procedures as HCV antibody screening remains to be determined. Although sterilization processes have been developed for freeze-dried cryoprecipitate, in many Western countries the use of single donor frozen cryoprecipitate has been abandoned so that factor VIII concentrates effective in vWD are now limited in number. At the same time the demonstration of different types of vWD has clouded the issue regarding the effectiveness of DDAVP. In type I vWD with reduced production of normal vWF, DDAVP is likely to be most effective. In type II vWd other than Type IIB where there is production of abnormally polymerized vWF, DDAVP could be expected to be less effective because it may merely raise levels of abnormal vWF. However, DDAVP may correct haemostasis via other mechanisms and it may be effective even in Type II or Type III vWD (Cattaneo 1989). Type IIB and pseudo-vWd (platelet type vWD) are most controversial since in these diseases it may cause platelet agglutination and thrombocytopenia. However, the clinical significance of this apparent fall in platelet counts

is controversial and it is not an absolute contraindication to a trial of DDAVP in an appropriate clinical setting.

In spite of this discussion the role of DDAVP in vWD and mild haemophilia has tended to be overemphasized on account of the HIV crisis and hepatitis. DDAVP, has several drawbacks.

Table 7. Limitations of DDAVP in haemophilia and vWD

Only in value in mild patients for minor lesions

Unpredictable effect except by trial

Effect may be temporary (Tachyphylaxis)

Flushing, headaches

Osmolality changes after prolonged course

Thrombocytopenia in type IIB and pseudo vWD

Myocardial ischaemia (not advised over 40 or with relevant History)

The effect of DDAVP is unpredictable and for significant episodes or surgery a trial dose well in advance is needed to predict future response (Rodeghiero 1989). It's effect may be only temporary due to tachyphylaxis and a laboratory control may be needed. Side effects are experienced by some patients and with prolonged therapy there is a risk of fluid retention with osmolality changes. Finally, DDAVP administration has been associated with thrombotic episodes and ischemic heart disease and although these are rare, it is unwise to use DDAVP in persons over forty years old or in those with clinical atherosclerosis or a history of thrombosis (Mannucci 1989). It is also advisable not to combine DDAVP with antifibrinolytic therapy even though it enhances plasma plasminogen levels. On the positive

side a new aerosol preparation of DDAVP is rapidly absorbed and may be of value for domiciliary management symptoms such as menorrhagia.

Although it is possible to over-emphasize the importance of heterozygous vWD as a therapeutic challenge there is no doubt that a concentrate of vWF would be of considerable assistance as well as in the severe Type III disease. A commercial concentrate heat-treated in aqueous solution - Hemate P (Behring) contains a reasonable amount of HMWvWF and is effective (Schimpf 1987, Berntorp 1989, Fukui 1988, Rose 1990). Factor VIII8Y produced by BPL (UK) is also claimed to be effective (Cumming 1990, Posi 1990), but the evidence for this is not convincing. Biotransfusion, the fractionation arm of the French Blood Transfusion Service has produced a very high purity concentrate containing factor VIII and vWF (ristocetin co-factor) at concentrations of each of about 100u/mg of protein and sterilized by a solvent-detergent method (Mazurier 1989), and a similar concentrate but lacking factor VIII is under study by Behringwerke (Delvos 1990).

Hopefully, these types of concentrates will continue to be developed to counter balance the switch to high purity and recombinant factor VIII (Bloom 1991).

Treatment is usually planned after the type of von Willebrand disease is determined (table 8). Patients with von Willebrand disease need to take special precautions at the time of any surgical procedure, particularly when this surgery involves the mucous membranes (mouth, nose, throat, gastrointestinal tract, urinary tract), after suffering any sort of accident, or with the onset of any unexplained bleeding. They should seek medical attention by a physician familiar with this type of bleeding disorder. It is also wise for the patient to have a complete evaluation as soon as possible so that treatment can be properly planned.

Stress will modify the laboratory results, and laboratory results may take three to seven days to complete. Thus, treatment is best recommended when the person is evaluated in an elective manner Montgomery 1991).

Table 8.

Type of von Willebrand disease	Intravaenous treatment of choice	Back-up Treatment
Type I	DDAVP (Desmopressin)	Humate-P or cryoprecipitate
Type IIA	DDAVP if effective	Humate-P or cryoprecipitate
Type IIB	Humate-P or cryoprecipitate	DDAVP may cause thrombocytopenia
Severe vWd	Humate-P or cryoprecipitate	DDAVP is usually not effective
Platelet-type vWD	Platelet concentrate	DDAVP or cryoprecipitate may cause thrombocytopenia

Blood products may result in the transmission of "transfusion transmitted diseases" such as AIDS (HIV-1, HIV-2), hepatitis B, hepatitis C, or HTLV-I, and therefore should be used only when alternative treatments are either ineffective or contraindicated. Although cryoprecipitate is now always screened for antibodies to HIV-1, HTLV-I, hepatitis C, and hepatitis B, it is best prepared from carefully screened normal family members whose blood is drawn for a specific patient. At some centers the number of donations needed to treat patients is reduced by giving the family member donors DDAVP to increase the amount of von Willebrand factor in each donation and by the process of plasmapheresis, which obtains

more plasma or cryoprecipitate from each donation (Montgomery 1991).

Factor VIII concentrates (monoclonal antibody purified factor VIII concentrates such as Monoclate, Hemofil lM, or recombinant factor VIII) may not contain sufficient von Willebrand factor, or the von Willebrand factor may be modified so that it is structurally abnormal, and so are not effective in treating von Willebrand disease. Although Humate P has been shown to contain a nearly normal complement of vWf multimers, newer concentrates may become available that contain normal factor. VWf multimeters should be performed by the manufacturer on the concentrates to assess the amount and quality of the von Willebrand factor. These should be tested in non-bleeding patients to determine their ability to correct bleeding times (Montgomery 1991).

DDAVP (Stimate, desmopressin acetate, 1-deamino-8 arginine vasopressin) is a synthetic agent that releases von Willebrand factor from storage sites such as the endothelial cell lining of blood vessels. Once released, vWf has the same half-life as transfused von Willebrand factor in most patients. If a patient has no von Willebrand factor, DDAVP will not release any. As a rule of thumb, the patient who has less than 10 percent vWf:Ag does not usually respond adequately. However, a therapeutic trial is necessary to determine efficacy and normal half-life. The average rise in the factor VIII clotting activity is usually three times the base line value and the average rise of the von Willebrand factor is usually two to three times base line value. The maximum rise of the factor VIII:C comes within 30 minutes after infusion and has a half-life of six to eight hours. The von Willebrand factor rises at the same time but lasts somewhat longer (Montgomery 1991).

When repeated doses of DDAVP are given at 12-hour intervals, a diminished

response may occasionally occur. However, many patients have undergone surgical procedures with repetitive single daily doses of DDAVP. Patients with Type IIA von Willebrand disease may have only a transient correction of their von Willebrand factor. Such patients may require some form of transfusion therapy if bleeding is not controlled. DDAVP may cause or increase the thrombocytopenia in patients with Type IIB or "platelet type" von Willebrand disease, but its use may be beneficial in selected patients.

DDAVP can be used as a substitute for blood products when given intravenously in a dose of 0.3 micrograms/kg over 15-30 minutes in 30-50 ml normal saline. A concentrated intranasal preparation is not currently available in the United States, but may become available in the near future. When given too rapidly, the efficacy is reduced and side effects of headache, flushing, and rise in blood pressure are seen more frequently. The antidiuretic effect has not been seen in awake individuals with normal fluid balance. DDAVP may be less effective in infants under one year of age and occasionally has caused hyponatremia and seizures in infants. Additional treatment with Humate-P or cryoprecipitate may be required to control significant bleeding in some patients (Montgomery 1991).

Adjunctive therapy: The antifibrinolytic drugs aminocaproic acid (Amicar) or tranexamic acid (Cyclokapron) are often very useful to stabilize a clot and prevent lysis until healing has occurred. They are particularly useful for intestinal, oral, and nasal bleeding. The recommended dose of Amicar is 100 mg/kg every six hours in a child, with a maximum dose of 5gm every six hours in an adult. The intravenous dose is 10mg/kg every eight hours. The dose of tranexamic acid is 25 mg/kg. These agents should be avoided during urinary tract bleeding (Montgomery 1991)

PRECAUTIONS

Most individuals with mild von Willebrand disease are able to lead active lives without having serious bleeding, but they often require treatment before surgery or after major surgery (Montgomery 1991).

Individuals with more severe forms of von Willebrand disease should avoid activities that are likely to be associated with injuries. Since aspirin (and any other medicine that contains aspirin) causes a further defect in the function of blood platelets, individuals with von Willebrand disease should avoid taking aspirin or aspirin-containing medicines. Acetaminophen (Tylenol) should be used for fevers, headache, and aches or pains (Montgomery 1991).

It is recommended that patients with von Willebrand disease carry identification to alert medical personnel to their bleeding tendency in case of emergency. If DDAVP has been demonstrated to be effective and safe, this should be stated on the identification. A letter explaining diagnosis, type of von Willebrand disease, and recommended therapy is helpful for the patient who travels (Montgomery 1991).

MANAGEMENT OF HEMORRHAGE

Medical management of hemorrhage depends upon the following factors: (1) the diagnosis of the specific type and severity of the coagulation disorder, i.e., Factor VIII deficiency with an assayed FVIII level less than 1 percent; (2) the presence or absence of an inhibitor to Factor VIII or IX; (3) the age and general health status of the patient including the presence of diseases not related to hemophilia. A careful history is obtained including evidence of trauma. The particular bleeding problem is evaluated keeping in mind

such factors as: the site of hemorrhage, actual and potential blood volume loss, immediate problems, and long range sequelae.

The physical examination of the patient, including determination of pulse and respiratory rates and blood pressure, must include not only a general examination but, additionally, must focus on the area of suspected bleeding. It is helpful to remember that the patient's chief complaint or most obvious problem may not be the only site of hemorrhage (Dietrich 1976).

Concentrate dosages are calculated for minor and major bleeding episodes according to body weight and estimated plasma volume. Factor levels of 30 percent are usually adequate for minor bleeding problems such as external oropharyngeal bleeding. A dosage of concentrate to attain factor levels of 50 percent of normal is necessary for major hemorrhagic problems including cranial, submucosal oropharyngeal, and deep muscle areas; repeated infusions may be required depending upon the location, severity, and resolution of the hemorrhage (Dietrich 1976).

Oral Medications in Bleeding Disorders

Prednisone is given orally to reduce inflammation produced by a hemorrhage. An intravenous dose of corticosteroid may be used to rapidly reduce swelling around a hemorrhage if the hemorrhage is compressing a vital structure, such as the trachea (Kasper 1976).

Epsilon-amino-caproic acid (EACA) inhibits the activation of plasminogen to plasmin, the body's natural fibrinolytic agent. A clot will remain intact longer if EACA is present. EACA does not assist in the formation of a clot. EACA is useful for patients

having tooth extractions or in small children with a bleeding tongue or a lacerated frenulum. A dose of 40 mg/kg/day, up to a maximum of 10 gm/day given as an oral suspension, suffices for these purposes (Kasper 1976).

High-dosage estrogen-progesterone drugs may be useful in female patients to raise the level of Factor VIII or IX.

Some patients take aspirin or indomethacin to reduce the pain or stiffness of hemophilic arthritis. Both drugs prolong the bleeding time by interfering with platelet function. In severe hemophiliacs, the bleeding time may be extremely prolonged after a small dose of aspirin and remain long for two or three days. Acetaminophen, propoxyphene, and codeine do not affect the bleeding time and may be used for pain relief in hemophilia. Many patients feel that the relief from arthritic symptoms afforded by indomethacin outweighs the possible increase in bleeding tendency due to platelet dysfunction (Kasper 1976).

USE OF MEDICATIONS

Complaints of pain are evaluated and appropriate analgesia in adequate amounts is given. Aspirin or any compound containing salicylate is avoided because of its effect on platelet function. Patients are counseled to avoid common "over-the-counter" remedies, i.e., Anacin, Excedrin, "cold remedies," and Alka-Seltzer, since these contain aspirin.

Recommended medications for mild pain are acetaminophen or propoxyphene; for moderate to severe pain, codeine, pentazocine, meperidine, or morphine sulfate. Orally administered Dilaudid is also useful. Propoxyphene is not used in patients who are prone to drug abuse (Dietrich 1976).

To reduce drug abuse and/or dependence, one physician assumes responsibility for the individual patient's analgesic prescriptions. Complete medication records are maintained in the outpatient treatment area. Whenever possible, the mildest analgesic is used. Except at times when the patient is hospitalized and under close medical supervision, excessive use of tranquilizers and barbiturates is discouraged. The genuine pain of an acute hemarthrosis or postoperative pain is relieved promptly with effective dosages of analgesics; greater than normal amounts of analgesic drugs may be required for adequate pain relief.

A realistic attitude toward pain should be developed by the patient with a chronic, painful disease, i.e., not all his chronic discomfort can be alleviated (Dietrich 1976).

The physician must avoid assuming a punitive or judgmental attitude toward the patient who demands seemingly excessive amounts of analgesics. By setting firm limits and relieving acute severe pain promptly, both the physician and patient can develop attitudes of respect and confidence toward each other (Dietrich 1976).

GENERAL DENTAL MANAGEMENT

The HIV positive hemophiliac presents a challenge for the dentist to treat effectively and safely. Certain modifications in the dental techniques are made to assure safe treatment; however, quality dental care is not compromised. The patient must enjoy all the advantages of quality restorative and preventive dentistry to maintain good oral health. Dental neglect, resulting in the need to remove nonrestorable teeth, presents serious management problems. Comprehensive care including semiannual examinations, proper oral hygiene, and patient/parent education, will minimize greatly the need for extractions and extensive dental restorations.

Many HIV positive hemophiliacs have neglected dental care for a number of reasons. Many patients, because of their frequent needs for medical care and hospitalizations, are crisis oriented. Since dental problems are not life threatening, the importance of regular dental care is not acknowledged; additionally, many dentists are unwilling or unable to provide treatment (Powell 1976).

Hematologic advances have improved the clinical management of hemophilia. A dentist, with an understanding of these advances and a basic concept of the hematology of the disorder, can safely treat the patient. Contact between the dentist and the patient's hematologist and physician is imperative to ensure a safe course of treatment. Each patient's care and treatment plan must be evaluated on an individual basis after appropriate consultation as indicated (Powell 1976).

Dentists and other health care providers, knowingly or unknowingly, are in daily

contact with patients infected with HIV. Therefore, understanding the natural history of HIV infection is essential for primary health care providers, so that they can better evaluate and manage infected patients, and also be able to address concerns about HIV testing that are being increasingly raised by laypersons and patients.

Several considerations should be addressed in developing a treatment protocol for HIV infected patients:

(1) Contagion and infection control,

(2) Systemic ramifications of HIV disease on dental treatment

(3) Recognition and management of intraoral manifestations of HIV disease

(4) Patient prognosis]

(5) Rationale for dental procedures

(6) Modifications of existing therapeutic standards, and

(7) Psychosocial aspects that affect the dental team (Glick 1990)

As medical history, explanations, and laboratory findings cannot always reliably identify all patients infected with HIV or other bloodborne diseases, the same precautions should be used routinely for all patients. Body fluids capable of transmitting HIV include blood, semen, vaginal fluids, and breast milk (M.M.W.R. 1988). Universal precautions do not apply to saliva, except during dental procedures, when contamination of saliva with blood is predictable (Glick 1990).

HIV enters the body as free virus or within already infected cells. The amount of cell-free virus in the blood is related directly to disease progression, and HIV-plasma viremia is more common in the advanced stages of HIV disease (Coombs 1989). The level

of cell-free virus is even lower than the level of HIV infected cells (Levy 1989). In 1 ml of blood from an HIV-asymptomatic person, there are approximately 4 infected cells, while there are approximately 5,000 infected cells in the same amount of blood from an HIV-symptomatic person (Ho 1989). This indicates that persons who exhibit signs and symptoms of HIV disease are more infectious than asymptomatic HIV-infected individuals. It is important to remember that hepatitis B virus (HBV) infections are prevalent among individuals at risk of acquiring HIV infection (Griensven 1989). The modes of transmission for HBV are similar to those for HIV, and the potential for HBV transmission in occupational settings is far greater than for HIV (M.M.W.R. 1989).

Protecting the health care provider and minimizing cross-contamination are the two major concerns. Many reviews describe practical infection control procedures in the dental office (Council on Dental Materials, Instruments and Equipment 1989). Recommendations include immunization against HBV infection, obtaining from patients a thorough medical history with frequent updates, use of barrier techniques, cautious handling of sharps, use of disinfection and sterilization techniques, and following proper guidelines for infectious waste disposal (Glick 1990).

HIV has been found within the tooth structure, which emphasizes the need for careful disposal of all tissues from the oral cavity (Glick 1989). Elimination of all microbial transmissions during dental therapy is virtually impossible. Infection control procedures need to be implemented to minimize the extent of the transmission (Glick 1990).

Rationale for dental procedures

The first priority in treating HIV-seropositive patients is to eliminate potential

sources of infection. This follows the rationale used with other immunocompromised patients for whom nontreated oral infections may be fatal (Glick 1990). Restoring masticatory function, phonetic function, and aesthetic considerations have the same level of priority as they do in the treatment of HIV-negative patients (Glick 1990).

Modifications of existing therapeutic standards

Treatment planning and treatment for the Hemophiliac who is HIV seropositive and asymptomatic should be done according to unabridged standards of care. Modifications of dental therapy must be based on the patient's overall health. The severity of the disease and the prognosis of HIV-symptomatic patients, along with the management of the many systemic complications are among factors to consider in making such modifications (Glick 1990).

Shorter intervals between regularly scheduled periodontal prophylaxis decreases potentially severe and harmful periodontal infections. Daily use of an antibacterial mouthrinse, such as chlorhexidine, should be encouraged. Scaling should be performed by quadrant to evaluate tissue response and bleeding tendencies (Glick 1990).

Extensive KS lesions may cause the formation of periodontal pseudopockets that need meticulous care. Any trauma to a KS lesion during scaling will result in bleeding. Pressure on the area attenuates the oozing and establishes hemostasis, but an intralesional injection of a 1:20,000 concentration of epinephrine may be necessary to enhance local vasoconstriction (Glick 1990).

Local anesthetic should not be administered initially in inaccessible areas until a localized "test" injection is used to evaluate the potential for bleeding complications (Glick 1990).

Surgical interventions such as periodontal surgery or full-mouth extraction should be performed only after a laboratory evaluation has been done including bleeding time. The existence of transient AITP means a bleeding-time test must be scheduled shortly before planned surgical procedures. Hemostasis can be achieved after single extraction with adjunct local hemostatic agents (Glick 1990).

An occlusal radiograph is required before extractions in the maxillary arch are done if extensive KS is present on the hard palate. If the KS lesion has infiltrated the tooth socket, the tooth can be extracted in a "bloodless" fashion, in which a rubber band is placed around the crown of the tooth and is advanced slowly (over a period of a couple of weeks) along the root until spontaneous avulsion of the tooth occurs. If no bone resorption can be detected because of the KS lesion, teeth can be extracted in normal oral surgery fashion. Postsurgical flare-ups following extractions can be minimized if the teeth to be extracted are first carefully scaled and root planed to reduce the bacteremia introduced during surgery (Glick 1990).

While endodontic therapy also has a slightly higher than normal incidence of postoperative infections among HIV-symptomatic patients, antibiotic prophylaxis is not recommended prior to therapy, because the risk of super-imposed fungal infection is high in these patients. The usage of nonsteroidal anti-inflammatory prophylaxis needs to be evaluated. Postendodontic flare-ups, if they occur, are managed efficiently with a short

course of antibiotic therapy. Restorative treatment plans must include consideration of the patient's prognosis (Glick 1990).

Quality of life is an important aspect in health care. With this in mind, there are no contraindications for any dental procedure, if the patient has been properly evaluated and informed (Glick 1990).

Psychosocial aspects affecting the dental team

Treating HIV-infected patients requires more than technical skills and understanding of HIV disease. Psychological and social stigmas attached to this disease are likely to affect the dental team involved in the care of these patients. The fear of transmission goes beyond the dental office. Association with HIV-infected patients may result in isolation by peer groups and pressure from family members to stop treating infectious patients to avoid "bringing the infection home." An understanding of the pathogenesis and transmission of HIV may prevent or dissipate the irrational fear usually associated with this issue (Glick 1990).

The disease hemophilia does not directly involve teeth; dental problems are secondary and are related to a lack of adequate dental treatment. Because of long-standing fears of routine dental care, dental treatment has been neglected among the hemophilic population. As a result, significant dental complications frequently develop. Additionally, oral surgery for hemophiliacs requires careful preoperative evaluation and postoperative management. The cost of facilities, time, and blood products further complicates the management of dental problems for the hemophiliac (Evans 1977).

We now realize that there are few routine dental procedures which cause significant bleeding in hemophilic patients. The development of concentrate replacement therapy has greatly improved the management of hemophilia. With the current treatment available to

most hemophiliacs there should be no compromise in the quality of dental care (Evans 1977).

Any dental procedure in which bleeding is anticipated -- such as periodontal surgery or a tooth extraction -- should be handled by oral surgeons or dentists familiar with the management of patients who have coagulation disorders. If the hemophiliac cannot obtain quality dental care in his own community, he is obliged to seek dental care at a hospital-based comprehensive care hemophilia clinic which includes a dental facility (Evans 1977).

Mild hemophiliacs seldom have spontaneous hemorrhage but experience prolonged bleeding after surgery or major trauma. They also may have normal laboratory values for hematologic tests. Moderate hemophiliacs may not hemorrhage spontaneously but often bleed after moderate trauma. The severe hemophiliac has spontaneous hemorrhage or hemorrhage after minor trauma, which is often the first sign of the disease (Strauss 1972).

EVALUATION

A complete history and a physical examination are essential prior to performing any dental treatment. The type and severity of hemophilia should be known; the presence of inhibitors should be determined; the history should include information about affected relatives and siblings, about plasma products which the patient has received, pain medications the patient may have used and whether he is on a home transfusion program. A general medical history is obtained to determine the presence of concurrent medical conditions which could influence the treatment plan. The dental history encompasses the type and outcome of previous dental treatment including extractions, as well as any

complications with oral bleeding. The oral examination includes (1) extraoral findings: facial skin, salivary glands, temporomandibular joint, lips, etc.; (2) intraoral findings: tongue, throat, etc.; (3) periodontal findings; and (4) charting of the dental findings. Dental radiographs are necessary for complete diagnosis. The normal full mouth radiologic survey is taken. For the hemophiliac it is necessary to exercise caution in the placement of periapical films to avoid traumatizing tissues and producing sublingual hematomas. If dental impressions are required for evaluation, the dentist should exert care in the placement of impression trays. The borders of the trays should be edged with periphery wax to minimize trauma to the soft tissue. Care is exercised in the placement of the film to avoid producing a sublingual hematoma. A treatment plan is developed and discussed with the patient and/or parent; consultation with the patient's physician and hematologist is indicated since medical management of the patient will be a cooperative effort (Powell 1976, Evans 1977).

Laboratory tests for hemophilia can have variable that often depend on the severity of disease. Table 10-1 summarizes some characteristics of hemophilia, including expected laboratory results. Bleeding time, platelet count, and prothrombin time (PT) are normal in hemophilia, whereas partial thromboplastin time (PTT) and the thromboplastin generation test are abnormal. In cases in which a strong history of hemorrhage and normal screening laboratory test values conflict, platelet function tests (platelet adhesiveness, aggregation, prothrombin consumption, and platelet Factor III availability, Factor XIII determination, and VWD tests) should be performed to rule out other disorders (Strauss 1972).

Table 9. Hemorrhagic Disorders of plasma and platelets

	Etiology and transmission	Laboratory findings	Clinical findings	Treatment
Factor VIII deficiency (classic hemophilia, hemophilia A) 80% of hemophilias 8% with inhibitors	X-linked recessing inheritance Defects in antihemophilic factor (Factor VIII)	Normal bleeding time Normal prothrombin time. Normal thrombin time. Prolonged partial thromboplastin time. Normal platelet count. Factor VIII assay 0% to 40%.	Only males affected (clinical findings vary with severity of disease) Spontaneous hemorrhage. Easy bruising, Hemarthrosis, Prolonged bleeding after surgery.	Replacement with plasma product containing Factor VIII, Antifibrinolytic (EACA, Local and topical measures
Factor IX deficiency (Christmas disease, hemophilia B) 15% of hemophilias, 1% to 2% with inhibitors	X-linked recessive transmission. Defect in molecule identified in some cases.	Same as above Factor IX assay 0% to 40%	Same as above	Same as above but with plasma product high in Factor IX
Factor XI deficiency (hemophilia C)	Autosomal recessive inheritance	Normal bleeding time, Normal platelet function tests, Prolongs partial thromboplastin time, Abnormal thromboplastin generation test in severe cases, Factor IX assay 0% to 40%	Prolonged bleeding after surgery or trauma, Male and females affected	Replacement with fresh plasma or plasmapheresis, Local and topical measures
Von Willebrand Disease	Autosomal dominant inheritance	Prolonged bleeding time, Decreased platelet adhesiveness, Decreased platelet aggregation with ristocetin, Possible prolonged partial thromboplastin time if Factor VIII less than 30%	Hemorrhages from mucous membrane, East bruising, Menorrhagia, Becomes milder with age, Males and females affected	Cryoprecipitate in severe cases, Local and topical measures

(Strauss 1972)

PREVENTIVE MEASURES

Regular brushing, prophylaxis, and gingival massage will ultimately reduce decay and periodontal disease and decrease the tendency for gingival tissue to bleed secondary to abrasions from the toothbrush. Prevention is best initiated by the patient in his home environment. Maintaining oral hygiene is not the total solution to dental disease; but it may

prevent, or certainly aid in the control of dental decay and periodontal disease. The concept of good home care must be emphasized, (Powell 1976, Evans 1977).

The HIV positive hemophiliac should understand the principles of toothbrushing which will remove plaque and clean the teeth. He must learn to massage, but not abrade the gingiva. The dentist must dispel the fear of gingival bleeding; good oral hygiene will reduce and eventually eliminate this bleeding from the gingival tissues. The hemophilic patient should use a soft multitufted toothbrush of an appropriate size. Brushing techniques should be adapted to the patient's age, dexterity, and dentition and are the same as those for other patients. Disclosing agents are useful to demonstrate tooth cleanliness and to identify the dental plaque (Evans 1972).

Hemophiliacs should be instructed to carefully pass dental tape through the contact points between teeth to remove all debris and plaque. When flossing is correctly performed, interproximal hemorrhage does not occur. Slight gingival bleeding caused by flossing is not a reason for concern.

Parents of children under age eight perform the flossing. Slight gingival bleeding caused by the flossing is not a reason for concern.

Systemic administration of fluoride is encouraged for those children age 12 and younger when they live in areas without fluoride in the water supply. Bottled fluoridated water and fluoride tables, liquids, or vitamins are used systemically. A semiannual application of topical fluoride provides added resistance to tooth decay. In caries prone patients, topical fluoride administered on a daily basis is beneficial. Water irrigating devices

used in conjunction with toothbrushing and flossing can also be effective in oral hygiene at home (Evans 1977).

A preventive program is adopted for all hemophilic patients since the difficulties and financial costs associated with restorative or surgical procedures mandate prevention of dental disease. All patients receive preventive dental education. The role of various foods in causing decay is explained; a balanced, sensible diet is encouraged with limited consumption of refined carbohydrates. When patients do consume "sweets," it is important that these be eaten with a meal prior to toothbrushing. Between-meal-snacks are most conducive to caries. Dietary analysis is important for those patients with a high DMF (decay, missing, filled) index (Powell 1976).

Selection of an adequate and balanced diet is imperative. Some hemophiliac patients choose soft foods in an effort to avoid gingival bleeding. On the contrary, patients should be taught to avoid caries-producing foods which are soft, sweet, starchy, and gummy. They must be encouraged to select a diet beneficial to their oral and general health (Evans 1977).

Parents of a hemophilic child are made aware of the importance of regular examinations and prophylaxis so that restorative and surgical problems are prevented. Inadequate dental treatment only encourages eventual complications for all patients. Obviously it is in the best interest of the hemophiliac to limit his dental problems. The dentist who treats a hemophiliac must make a great effort to explain the principles of preventive dentistry to his patient (Powell 1976).

VISITS TO THE DENTIST -- CHECK-UP

HIV positive hemophiliac patients should have routine preventive dental treatment in the office on a regular basis. The best time for a child's first visit to the dentist is between 12-18 months of age; hemophiliac children are no exception. Most patients should be on a six-month recall program; patients with a high DMF (Decayed, Missing, Filled) index and poor hygiene should be more closely supervised and should be evaluated morefrequently. At each recall visit the teeth are scaled and polished, treated with fluoride, and X-rayed as indicated (Evans 1977).

Calculus present in the mouth of a hemophiliac should be removed without trauma to the gingival tissue. Superficial bleeding resulting from careful scaling ceases within a reasonable time, as will the slight hemorrhages which may occur with prophy-cup polishing. Patients who require deep scaling because of gross calculus should be initially scaled supragingivally. The tissue should be allowed to heal for 7-14 days during which time the gingiva recedes as edema and hyperemia diminish. Subsequent treatments to remove calculus and irritants will incur less risk of bleeding from the tissue (Evans 1977).

The determination to use replacement therapy is made on an individual basis with medical consultation. Factors to be considered are the severity of the hemophilia and the degree of anticipated trauma. When replacement therapy is used, the entire mouth is scaled at a single appointment so that the expense of blood products for subsequent appointments is avoided. Sufficient time is allowed at each appointment so that each procedure is performed with extra caution (Powell 1976).

If replacement therapy of Factor VIII or IX is utilized for scaling procedures, the entire mouth should be scaled in a single session if possible. This reduces the increased risks inherent in multiple transfusions and eliminates the additional expense of blood products for subsequent appointments. Sufficient time should be allowed so that procedures may be performed with extra caution. For subgingival scaling, hand instrumentation with proper finger rests is recommended for the removal of calculus with minimal trauma. Packing the sulcus with retraction cord can be helpful in obtaining access to remove gross calculi. If the cavitron is used for removal of gross supragingival calculus, it must be usedwith caution (Evans 1977).

Local Anesthesia

The management and elimination of pain is one of the most difficult problems in providing dental care to the hemophilic patient. With the advent of plasma concentrates and cryoprecipitates, anesthetic and analgesic techniques were added to the realm of restorative procedures. The technique used is the most conservative method of pain control which is effective for the individual patient and for the procedure. A patient is not asked nor expected to endure painful procedures without relief. When this occurs, poor dental care will result and patients will return with great reluctance. Certain children do better with local anesthesia than without it; others have become so fearful of needles that anesthetic injections are a source of psychological trauma. It may be possible to perform restorative dental procedures on primary teeth and on some permanent teeth without local anesthesia. Success for such procedures without anesthesia will depend on a gentle touch and very sharp burs under minimal pressure at high speeds (Evans 1977, Powell 1976).

1. No local anesthetic. Most procedures can be performed on the pediatric patients using this technique; however, the entire procedure is explained carefully to the child. He is reassured that anesthesia can be used if he feels discomfort. He is not allowed to "suffer through" the treatment.

   In the absence of an anesthetic agent, psychological preparation of the patient is important fortified with continuing verbal support.

   Analgesia or anesthesia are used almost routinely for restorative or operative procedures on permanent teeth except for "pit" fillings which may not require anesthetics.

2. Premedication analgesics are used to raise the pain threshold or to relax the patient; however, this technique is not sufficient for very painful procedures. Nitrous oxide is a useful adjunct to reduce mild pain sensations.

3. Peridental injections, although used in oral surgery, are not indicated for restorative dentistry because these injections do not produce the profound, long lasting anesthesia necessary for operative procedures. Additionally, these injections may produce a pressure ischemia resulting in a nonvital tooth.

4. Infiltration local anesthesia may be administered without prior replacement therapy in an area where the tissue is firm and confined without the development of hematoma or other bleeding complication.

5. Block anesthetics are used only when the patient has received prior replacement therapy to elevate the plasma factor level to 50 percent. By attaining this 50 percent level, the few hours' time lag between infusion and

the dental appointment are considered; thus, the dentist is assured that his patient has at least a 30 percent level during the dental procedures. The 50 percent levels are attained prior to the use of infiltration and block anesthetics since the injections often are deep into soft tissues and present greater potentials for problematic bleeding and its control. Twenty percent levels are sufficient for surgical procedures since bony areas are involved where better control of bleeding is possible; additionally, the injection is into more confined areas and not into deep soft tissues.

Mandibular blocks, posterosuperior blocks, and infiltration injections can be given safely. If the injection does not produce a bloody aspirateand no hematoma develops, further replacement therapy or other treatment is not indicated. However, with a bloody aspiration, careful surveillance is maintained for possible hematoma formation. If a hematoma develops, ice is applied to the area; the patient receives other infusions of plasma products with dosage and frequency at the discretion of the hematologist.

6. Intrapulpal injections are given safely for all pulpal procedures. Prior replacement therapy is unnecessary.

For all injections, a sharp 27 gauge or smaller needle is used. This size allows aspiration while minimizing tissue trauma. Slow injection of the solution, over a two minute period, further reduces tissue trauma.

Patients receiving local anesthetics must be warned of subsequent numbness of the soft tissues. The lack of sensation will last for an hour or more; and

children particularly should be observed so they will not purposely or inadvertently bite the lip, tongue, or cheeks. (Local anesthesia without a vasoconstrictor will shorten the duration of the anesthetic and may eliminate post-operative lip-chewing in children (Evans 1977, Powell 1976).

Preoperative Sedation

Premedication with hypnotic, analgesic, or tranquilizing agents may be an aid to management, and is especially useful for long surgical and operative procedures. Premedication may be indicated for problem children and for fearful, nervous and apprehensive adults. This technique can prove a worthwhile adjunct where raising the pain threshold or relaxing the patient is indicated. Medications may be administered orally, by suppository or by the intravenous route. Intramuscular injections are contraindicated forthe hemophiliac because of formation of hematomas (Evans 1977).

Inhalation Analgesics

Many patients claim they are fearful and apprehensive that a dental procedure will hurt, although they acknowledge that they are not actually having pain. Nitrous oxide inhalation analgesia can be used as an adjunct to allay mild pain sensation and apprehension without loss of consciousness (Evans 1977)

General Anesthesia

General anesthesia is the most effective technique to manage patients who are uncooperative or who must undergo extensive restorative treatment and/or complicated painful procedures. The intravenous route is safe for the hemophiliac; the intravenous technique itself does not cause bleeding problems and does not require infusion

replacement of the deficient Factor VIII or IX. The intravenous route may be used to sustain an ultralight level of general anesthesia utilizing a short acting barbiturate (Evans 1977).

When inhalation general anesthesia is administered, endotracheal intubation is sometimes indicated. Because of the possible trauma associated with intubation, prophylactic factor replacement is mandatory for any hemophiliac who requires an intubation. Oral intubations result in less trauma to tissues than do nasal intubations; therefore this technique is preferred for the hemophilic patient. However, we strongly advise against intubating hemophilic patients (Evans 1977).

Analgesics

The dentist must be cautious in prescribing analgesic medications for hemophilic patients because of problems caused by certain agents. Hemophiliacs experience pain whenthey bleed spontaneously into soft tissues and joints, and from the chronic persistent pain of arthritis and permanent joint changes. Additionally, hemophiliacs may have developed a low tolerance to pain. It is not unusual for a hemophiliac to require more potent analgesics than normal patients.

Analgesics containing aspirin, and classical anti-inflammatory agents (such as Butazolidine and Indocin) are contraindicated at all times because they potentiate the bleeding disorder by altering platelet function. For dental pain it is important to omit all analgesics (such as the compound drugs Percodan or Empirin) which contain aspirin.

Those analgesics which can safely control pain for the hemophiliac are:

Non-narcotics - Tylenol, Talwin, Darvon (plain)

Narcotics - Codeine, Demoral, Morphine, Dilaudid (All habit-forming, all have some side effects) (Evans 1977)

Restorative Procedures

Restorative dentistry is performed in the usual manner. A rubber dam is used to isolate the operating field. A lightweight rubber dam is used as there is less chance to torque the clamp which could abrade the gingiva. Additionally, the dam retracts the cheeks, lips, and tongue. Since these areas are highly vascular, their accidental laceration presents difficult management problems. Rubber dam clamps are selected and placed to minimize gingival trauma; wedges and matrices are used routinely, and, with careful placement, do not produce significant bleeding. Crown preparation and placement present no problems when the gingival portion of the tooth is carefully prepared and the crown is carefully fitted. Packing the tissues with gingival retraction cord is advantageous when extensive decay is evident. Crevice formation is avoided during the packing. Quality dental care is nevercompromised. Preparation of the tooth is not modified because the child has hemophilia. The usual principles of good restorative dentistry are observed. There are certain procedures unique to the child patient. The preparation for a stainless steel crown should be done in the routine manner for the hemophiliac as for the normal patient, with the crown adapted to fit about 1 mm. below the gingival tissue. No undue trauma should be created in cementing or finishing the crown. When taking impressions, periphery wax is used on the tray to prevent possible intraoral laceration during tray placement. High speed vacuum and saliva ejector are used with caution so that sublingual hematomas are not created. Those ejector with rubber padded tips are preferred since sublingual tissue

cannot be drawn into the opening (Evans 1977, Powell 1976).

Treatment of Deep Caries - Pulpal Therapy

Pulpal therapy or root canal therapy can enable a patient to retain and maintain badly needed teeth. Some patients come to the office for the first time with rampant deep caries. Pulp exposures in primary and permanent teeth may sometimes be avoided in such teeth if the carious dentin is not entirely removed in one procedure. Pulpotomy, pulpectomy, and root canal filling are all preferable to extraction. The replacement of a missing tooth is an expensive procedure; for a hemophiliac the extraction of a tooth and its subsequent replacement implies complicated treatment.

Anesthetics are usually unnecessary when the pulp is necrotic. If the nerve tissue of a vital tooth is exposed, the intrapulpal injection may provide sufficient anesthesia; or the patient may be medicated or receive general anesthesia. Usually any bleeding from endodontic procedures is insignificant and does not require factor infusion. Hemorrhage produced during pulp amputation or vital extirpation is controlled by pressure and/or ahemostatic agent such as epinephrine on a cotton pellet. Bleeding that is difficult to control usually indicates inadequate removal of tissue remnants in the canal. If necessary, to control hemorrhage, cotton is soaked in formocresol, dried, and then sealed into the pulp chamber for a week to mummify and fix the pulp tissue. The control of bleeding in pulpal therapy has not presented any problems in our experience with hemophiliacs.

When root canal therapy is performed for hemophiliacs, the dentist should be cautious to avoid instrumentation and filling beyond the apex of the root of the tooth. To prevent any periapical bleeding from occurring, Powell (Powell 1976) recommends filing and

filling 1 to 2 mm short of the radiographic apex.

Orthodontic Treatment

There is no contraindication to orthodontic therapy for improving the oral health and appearance of the hemophilic child. With care, minor and major tooth movement may be accomplished without fear of stimulating bleeding. The decision to perform orthodontia for the hemophiliac is made using the same criteria as for any child.

Early recognition of an orthodontic problem is important for the hemophiliac because selective guidance can diminish or eliminate complex orthodontic problems. Both interceptive (preventive) and full-banded orthodontics are routinely performed for hemophiliacs without bleeding complications. Serial extractions will require consultation between orthodontist, surgeon and hematologist. The choice of bicuspid or other extraction is determined individually. Indicated extractions are performed as elective surgery by the oral surgeon with the required preoperative evaluation and postoperative management.

Care must be taken in the adaptation and placement of bands to avoid the minor hazard of laceration of the oral mucosa, and to avoid protruding sharp edges and wires. Bleeding caused by an accidental scratch or minor laceration of the gingiva usually responds to pressure, with clotting taking place in 5 minutes. Preformed orthodontic bands and brackets which can be directly bonded to the teeth almost totally eliminate contact of orthodontic appliances with the gingiva during placement. Longer-acting wires and springs require less frequent adjustment of orthodontic appliances.

Oral hygiene is particularly important for the hemophilic patients undergoing orthodontic treatment, to avoid gingival tissues becoming inflamed, edematous, and

hemorrhagic from routine mastication. A water-irrigating device is an essential adjunct for good home care for the hemophilic child wearing orthodontic bands (Evans 1977).

Exfoliating Primary Teeth

Loose, deciduous teeth occasionally pose a bleeding problem for a child since the tooth continuously traumatizes the tissue causing prolonged oozing. When this occurs, the tooth is extracted following infusion of appropriate plasma products. At the discretion of the hematologist or pediatrician, replacement therapy may continue after extraction. Epsilon-amino-caproic acid (EACA) is a treatment adjunct since it prevents premature lysis of the formed clot. The usual dosage for a child is 5 grams/day given in divided doses four times daily; the EACA is continued for seven days. It is available in liquid and tablet form. Emphasis is made that primary teeth are not routinely extracted prior to exfoliation; extraction is performed only when the sharp edges of the roots traumatize the gingiva and cause prolonged bleeding (Powell 1976). Erupting, deciduous teeth rarely cause gingival bleeding. Vigorous chewing will aid the eruption.

Superficial lacerations of the face, mouth, tongue, or frenulum are annoying but generally minor problems of infancy and early childhood. These minor lacerations aretreated every 12 hours for two or three doses of appropriate concentrate to levels of 30 to 50 percent, or every 24 hours with a larger dose to attain a level of approximately 100 percent. Generally, two or three days of this treatment is sufficient for healing. Minor lacerations of the tongue or oral mucosa are not sutured or cauterized. Local pressure may be helpful using topical thrombin preparations or oxidized, regenerated cellulose gauze (Surgicel). Large, raspberry-like, friable clots are removed manually from the tongue or

mouth. Epsilon-amino-caproic acid is useful for management of these minor lacerations. A dosage of 38 mg/kg/day, up to a maximum of 10 gm/day, given as an oral suspension, suffices for these purposes. The child's hemoglobin and hematocrit are determined every 24 to 48 hours when bleeding persists from the mouth or lip. Since an infant's total blood volume is small, minor hemorrhages may lead to hemodilution and eventually hypovolemia. When whole blood transfusion is indicated, freshly packed red cells are preferred rather than whole blood in order to avoid transfusing unnecessary plasma elements and excess fluid volume. Restraints may be necessary to keep the child's hands from his mouth; chloral hydrate or promethazine suppositories are useful when sedation is required (Powell 1976).

Other life-threatening hemorrhages relate to bleeding in and around the vital structures of the neck producing tracheal compression. Patients with respiratory embarrassment or difficulty in swallowing are admitted to the hospital; maximum therapy is instituted. Intravenous administration of adrenocortical steroids (intravenous dexamethasone in an initial dose of 4 mg followed by 2 to 4 mg every 4 hours as indicated) may reduce pharyngeal or laryngeal edema. Antibiotics are administered if an infection is present. Plasma concentrates are infused every 12 hours until the dangers of respiratory complications are eliminated. A liquid diet is advised for 24 hours following the bleedingepisode; next, cool, pureed foods are consumed until the hematoma has resolved (Powell 1976).

Oral Surgery Management

Time must be spent with the patient and their family to answer questions and to explain the planned surgery as well as the expected postsurgical events including those normal occurrences such as blood on the pressure dressing or the discolored stain found on the pillow the morning after the extraction. Each of these events can alarm the unprepared patient and their family. Since much of the success of dental surgical management of hemophilic patients depends upon the cooperation of the patient and his family, they must be aware of what is expected of them (Mulkey 1976).

Medical Consultation

Consultation with the medical specialist-hematologist, pediatrician, or internist-in charge of the patient's medical care is essential. This specialist is responsible for determining the clotting deficiency and for establishing the type and dosage of plasma products needed to maintain hemostatic levels before and after surgery. Additionally, medical information can be supplied such as the presence of an inhibitor or other general medical problems which may alter the course of treatment. Background observations can also be furnished about the patient, i.e., how they react in stressful situations, how reliably they follow instructions. The oral surgeon informs the physician of the proposed treatment and exact techniques as well as the postoperative management; thus, possible postsurgical complications such as dehydration can be averted. The preoperative infusion therapy is planned; determination is made to treat the patient in or out of the hospital. Normally, surgeries are performed on an outpatient basis, however, if questions exist about thepatient's ability to cooperate, they are not treated on an outpatient basis (Mulkey 1976).

Where there is a question involving the patient's response to the administration of factor, it may be necessary to perform an infusion study prior to the actual surgical procedure. The coagulation laboratory should assess blood samples for factor levels prior to infusion, 15 minutes after infusion, and at appropriate intervals thereafter to determine the half-life of the administered product for a particular patient. The normal half-life for Factor VIII is anywhere from f6-12 hours and for Factor IX, 12-24 hours. With both substances there is an initial rapid disappearance, followed by a slower rate of disappearance. The patient with a Factor IX deficiency will have a longer effect from the pre-surgical infusion than the patient with a Factor XIII deficiency. The severely afflicted patient (less than 1%) usually has a greater potential for post-surgical bleeding than the patient who has a mild form of the disease. However, individual patients manifest different responses to treatment and each case must be carefully prepared and observed (Evans 1977).

At the present time between 5-20% of hemophilia patients have antibody inhibitors capable of destroying the administered factor (Evans 1977). It is essential that screening for this inhibitor be carried out prior to surgical intervention. If a hemophilic patient has an inhibitor, the administration of factor replacement therapy is contraindicated; extreme caution must be exercised in consideration of oral surgery. Close cooperation with the hematologist is imperative in management of such cases. Surgery for these patients, whether elective or emergency, must be limited and is not usually recommended. Should oral surgical treatment be necessary, local measures and adjunctive medications are utilized to control post-extraction hemorrhage (Evans 1977).

Operative Procedures

Tooth extraction in a hemophilic patient should be as simple and as atraumatic as possible since the patient will have less anxiety about uncomplicated treatment. On the day of surgery the patient receives their presurgical infusion of the deficient factor at the Hemophilia Center or at home if he is on a self-transfusion program. Sufficient replacement factor should be used to raise the patient's deficient factor level to 60 or 70%. Then they report to the dental office accompanied by someone, preferably a parent (Dietrich 1973).

Local anesthesia is used in all extraction procedures on hemophilic patients whether or not adjunct medication are used. The local anesthetic technique employs a 29 or 31 gauge needle, one half inch in length, and a carpule syringe. The needle is positioned in the periodontal membrane space with the bevel against the tooth and the solution is injected with considerable difficulty. If the plunger is easily compressed, the needle is in the wrong position; it should be removed and reinserted. This injection technique is repeated in all four quadrants of the tooth: mesial, distal, buccal, and lingual. This technique is appropriate for single and multiple rooted teeth. Unlike the usual local anesthetic techniques of infiltration or nerve block, this method is also effective when there is infection around the tooth (Mulkey 1976).

Extraction of Deciduous Teeth

Primary teeth are not routinely removed prior to natural exfoliation. By the time deciduous teeth are sufficiently mobile to cause bleeding, they are no longer completely supported by bone. Radiographs usually indicate that the underlying permanent tooth is in the process of erupting. In cases where a loose deciduous tooth is tissue-borne, it may

be possible to remove the tooth without administering any replacement therapy; often bleeding in such situations is minimal. A topical hemostatic agent such as thrombin or Microfibrillar Collagen Hemostat can be applied directly to the wound to encourage clotting. The extraction site may be protected for 12-36 hours by a cellulose bandage (Stomahesive) (Evans 1977).

For more complicated removal of deciduous teeth, appropriate plasma products should be administered prior to extraction. At the discretion of the hematologist, replacement therapy may continue after extraction, or Amicar may be utilized (Evans 1977).

Extraction of Permanent Teeth

The surgical technique used to extract teeth of adult patients with hemophilia is the same as that used with normally clotting patients. Where there is a fracture of the alveolus, the loose bone fragments must be removed and the margins smoothed. The major differences in care for the hemophiliac as opposed to normal patients are the preoperative infusion of the missing factor and the postextraction treatment (Evans 1977).

Following extraction of permanent teeth, local measures utilizing hemostatic agents (Microfibrillar Collagen Hemostat, Thrombin, Surgicel) are important in controlling hemorrhage. Such local measures enhance the formation of a stable clot. The technique of packing a socket is important; the hemostatic agent should be positioned in the apical third of the root socket. In case of multi-rooted teeth, each individual root socket is packed separately. If oxidized cellulose is employed it is cut to size and is then impregnated with a thrombin solution. Prior to placing the thrombin saturated agent, the root socket is cleaned of any small clot that may have formed. The hemostatic agent is placed directly

against the bleeding area. The thrombin acts immediately on the firginogen of the blood converting it into a fibrin clot which forms a plug in the socket (Evans 1977).

Adjunctive Therapy

Since surgical patients undergo preoperative replacement of clotting factor, a clot will form following extraction of the tooth just as with normal patients. It is the preservation of this initial clot which is vital (Evans 1977).

The clot may be protected by administering medication to inhibit the body's normal lysing process involving plasminogen which functions to break down the clot. Epsilon amino caproic acid (Amicar) has been very effective in the prevention of post-extraction bleeding without the necessity of repeated infusions of the missing clotting factor. Amicar must be used on a strict schedule and for a period of time sufficient to allow primary healing to occur (Evans 1977).

Following the preoperative build-up of Factor VIII or IX and the subsequent oral procedure an initial dose of 6 grams of EACA is administered to adults as soon as possible. We are currently utilizing a regimen of 6 grams EACA every six hours for a period of ten days. EACA is available for oral administration in tablet or liquid. The drug is effectively absorbed by this route and rapidly cleared by the kidney. Renal bleeding or abnormal kidney function contraindicate the use of EACA. Our usual dosage of EACA for children is 100 mg/kg body weight administered every 6 hours for a period of a week. Amicar liquid is recommended for children (Walsh 1971).

INFECTION CONTROL CONSIDERATIONS IN DENTAL TREATMENT AND HIV INFECTION

The primary modes of transmission of human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), are sexual contact, exposure to infected blood or blood components, and perinatal transmission from mother to neonate (Curran 1988). HIV has been isolated from blood and a number of other body fluids, including semen, vaginal secretions, saliva, tears, breast milk, cerebrospinal fluid, amniotic fluid, bronchoalveolar-lavage fluid, and urine (Oxtoby 1988, Barre-Sinoussi 1983, Ho 1989, Zagury 1984, Vogt 1986, Wotsy 1986, Ho 1985, Thiry 1985, Levy 1985, Fujikama 1985, Ho 1985, Levy 1985, Zizz 1985, Mundy 1987, Groupman 1984). However, epidemiologic evidence has implicated only blood, semen, vaginal secretions, and breast milk in transmission (Curran 1988, Oxtoby 1988). Although the National Institute of Dental Research has found cells infected with the human immunodeficiency virus to be present in the saliva of most, if not all, people who are seropositive for HIV the number of infected cells in saliva is low (Johnson 1992), and saliva is suspected to actually contain factors that may inhibit infectivity (Fox 1988). These facts together with the lack of any documented cases of HIV transmission via saliva support previous studies that suggest that the potential transmissibility of HIV infection by saliva is very unlikely (Barr 1992).

Among persons living in the same household with persons infected with HIV, transmission of HIV has occurred only to direct sexual contacts of infected persons and to

neonates of infected mothers; transmission of HIV through ordinary social or occupational contact with HIV-infected persons or through air, water, or food has not been demonstrated (Lifson 1988, Gershon 1990, Friedland 1980, Jason 1986, CDC 1987). The mode of transmission of HIV is similar to that of the hepatitis B virus, although the potential for hepatitis B virus transmission is greater (CDC 1989).

Given the low probability of HIV transmission via saliva, blood would appear to be the more likely virus transmitter in the dental operatory. Possible modes of transmission would include percutaneous injury with blood infected instruments, exposure of lesions on hands to infected blood or multiple and prolonged exposure of HIV infected blood to mucous membranes (Gruninger 1992).

Dentists routinely perform many invasive procedures such as extractions, root canal preparations, periodontal therapy and prophylaxis in an environment of blood infected saliva. Furthermore, hypodermic needles are used for administering local anesthetics, and sharp or abrasive instruments are used during dental procedures. There are many opportunities for accidental percutaneous injuries to the hands even with glove use (Gruninger 1992).

However abundant potential sources of infection may be, some appear to be more likely to cause infection than others. For instance, several reports (Gerberding 1985, Fox 1988) have indicated that the risk for HIV transmission from a needle stick injury in the dental environment is low. This is due to the fact that the average number of circulating HIV infectious units is relatively low and ranges from 10-100ml for asymptomatic patients (Ho 1989, Daar 1991) and 300-10,000ml for primary acute infection and symptomatic

individuals with AIDS (Ho 1989, Daar 1991, Levy 1985, Coombs 1989). Mean values have been estimated at 25 and 320 HIV tissue culture infective dose TCID/ml plasma in asymptomatic and individuals with AIDS respectively. On the other hand the blood of patients infected with HBV may contain up to 1014 HBV infectious units (U)/ml. Additionally, a needle stick from a used 22-gauge needle can be expected to deliver a mean of 1.4 microliter of potentially infected blood.

If the typical asymptomatic HIV-infected individual has a maximum of 100 HIV TCID per ml of blood, the entire 10 microliter contents of a 1 1/2 inch 21-gauge (0.3mm internal diameter I.D.) needle would have to be delivered through a single needle stick to transmit one HIV TCID. Conversely, the same needle stick episode could deliver 1,000,000 HBV I.U. In general dentists do not use large bore, 16-to-22 gauge needles for administering local anesthetics, and are therefore exposed to much smaller amounts of blood if a needle stick were to occur, thus decreasing the likelihood of infection with HIV. More likely HIV transmission routes in the dental operatory would probably include multiple and prolonged exposures of HIV-infected blood to mucous membranes to lesions on hands or through sharp instrument cuts/abrasions (Gruninger 1992).

Recommended Infection-Control Practices for Dentistry

Dental personnel may be exposed to a wide variety of microorganisms in the blood and saliva of patients they treat in the dental operatory. Most microorganisms known to be human pathogens have been isolated from oral secretions (Cottone 1991). These include *Mycobacterium tuberculosis,* hepatitis B virus, staphylococci, streptococci, cytomegalovirus, herpes simplex virus types I and II, human T-lymphotropic virus type III; lymphadenopathy-

associated virus (HTLV-III/LAV), and a number of viruses that infect the upper respiratory tract. Infections may be transmitted in dental practice by blood or saliva through direct contact, droplets, or aerosols. Patients and dental health-care workers (DHCW's) also have the potential of transmitting infections to each other (Ahtone 1983).

A common set of infection-control strategies should be effective for preventing hepatitis B, acquired immunodeficiency syndrome, and other infectious diseases caused by bloodborne viruses (Crawford 1985, Cottone 1985, CDC 1983). The ability of hepatitis B virus to survive in the environment (Bond 1981), and the high titers of virus in blood (Shikata 1977) make this virus a good model for infection-control practices to prevent transmission of a large number of other infectious agents by blood or saliva. Because all infected patients cannot be identified by history, physical examination, or readily available laboratory tests (Cottone 1985), the following recommendations should be used routinely in the care of all patients in dental practices.

UNIVERSAL PRECAUTIONS

In 1987, CDC developed the strategy of "universal blood and body fluid precautions" to address concerns regarding transmission of HIV in the health-care setting. This concept, now referred to simply as universal precautions, stresses that all patients should be assumed to be infectious for HIV and other bloodborne pathogens. Implementation of universal precautions for all patients eliminates the need for use of the isolation category "Blood and Body Fluid Precautions" previously recommended by CDC (CDC 1987). The basic components of universal precautions are (a) barrier precautions to prevent contact with blood and infectious fluids, (b) handwashing, and (c) prevention of percutaneous injuries

(e.g., needlesticks, cuts from sharp objects). Hepatitis B vaccination is also stressed as an important measure in prevention of bloodborne disease.

Universal precautions apply to (a) blood, which is the single most important source of HIV, hepatitis B, and other bloodborne pathogens in the occupational setting; (b) visibly bloody fluids; (c) semen and vaginal secretions, which have been implicated in the sexual (but not occupational) transmission of hepatitis B and HIV; (d) fluids for which the risk of transmission of hepatitis B and HIV is undetermined, including amniotic, pericardial, peritoneal, pleural, synovial, and cerebrospinal fluids; (e) laboratory specimens that contain hepatitis B or HIV (e.g., suspensions of concentrated virus); and (f) saliva in the dental setting, where contamination with blood is likely. Universal precautions do not apply to feces, nasal secretions, sputum, sweat, tears, urine, and vomitus, since these fluids have not been associated with transmission of hepatitis B or HIV (CDC 1987, 1988, 1989).

In addition to wearing gloves for contact with oral mucous membranes of all patients, dental workers should wear surgical masks and protective eyewear or chin-length plastic face-shields during procedures in which splashing or splattering of blood, saliva , or gingival fluids is likely. Rubber dams, high-speed evacuation, and proper patient positioning, when appropriate, should be used to minimize generation of droplets and spatter (CDC 1987).

Precautions during other procedures should be determined on an individual basis. Gowns or aprons should be worn during procedures that are likely to generate splashes of blood or other potentially infective sources (CDC 1987).

MEDICAL HISTORY

Always obtain a thorough medical history. Include specific questions about medications, current illnesses, hepatitis, recurrent illnesses, unintentional weight loss, lymphadenopathy, oral soft tissue lesions, or other infections. Medical consultation may be indicated when a history of active infection or systemic disease is elicited.

HANDWASHING

Handwashing is the single most important procedure for preventing nosocomial infections (Garner 1985). Universal precautions dictate that hands and other skin surfaces should be washed immediately and thoroughly if contaminated with blood or other body fluids to which universal precautions apply (CDC 1987).

For general infection control purposes, hands should be washed (a) after taking care of a patient(s), even if gloves are used; (b) after touching excretions (i.e., feces and urine) or secretions (e.g., from wounds or skin infections) and before touching any patient again; (c) after touching materials soiled with excretions or secretions; (d) before performing invasive procedures, touching wounds, or touching immunocompromised patients; and (e) immediately after gloves are removed, even if the gloves appear to be intact (Garner 1985). The rationale for handwashing after gloves have been worn is that gloves become perforated, knowingly or unknowingly, during use and allow bacteria to enter beneath the glove material and multiply rapidly. For many routine dental procedures, such as examinations and nonsurgical techniques,handwashing with plain soap appears to be adequate, since soap and water will remove transient microorganisms acquired directly or

indirectly from patient contact (Garner 1985). For surgical procedures, an antimicrobial surgical handscrub should be used (Garner 1985). Extraordinary care must be used to avoid hand injuries during procedures. However, when gloves are torn, cut, or punctured, they must be removed immediately, hands thoroughly washed, and regloving accomplished before completion of the dental procedure. DHCW's who have exudative lesions or weeping dermatitis should refrain from all direct patient care and from handling dental patient-care equipment until the condition resoslves (CDC 1985).

USE OF PROTECTIVE ATTIRE AND BARRIER TECHNIQUES

1. Surgical masks and protective eyewear or chin-length plastic face shields must be worn when splashing or spattering of blood or other body fluids is likely, as is common in dentistry (Peterson 1979, Bond 1982).

2. Reusable or disposable gowns, laboratory coats, or uniforms must be worn when clothing is likely to be soiled with blood or other body fluids. If reusable gowns are worn, they may be washed, using a normal laundry cycle. Gowns should be changed at least daily or when visibly soiled with blood (Garner 1985).

3. Impervious-backed paper, aluminum foil, or clear plastic wrap may be used to cover surfaces (e.g., light handles or x-ray unit heads) that may be contaminated by blood or saliva and that are difficult or impossible to disinfect. The coverings should be removed (while DHCW's are gloved), discarded, and then replaced (after ungloving) with clean material between patients.

4. All procedures and manipulations of potentially infective materials should be performed carefully to minimize the formation of droplets, spatters, and aerosols, where

possible. Use of high-speed evacuation, and proper patient positioning should facilitate this process (CDC 1989).

Routine use of the rubber dam, combined with the other accepted barrier techniques, can contribute significantly to the overall dental office infection control program. Three factors determine if an infectious disease will develop: the disease-producing potential of the microbe involved; the dose of the microbe that contaminates the person; and the resistance of the person to the microbe involved. The practitioner cannot lessen the disease -producing potential of microbes nor make his or her body resistant to microbes in thepatients' mouth; without vaccination (unless a vaccine such as that for hepatitis B is available). Thus, major efforts in office infection control must be directed toward reducing the dose of microbes that contaminate the body and operatory surfaces.

In the dental operatory, the primary source of potentially dangerous microbes is the patient's mouth. Reducing the amount of microbes spread from a patient's mouth during dental procedures attacks the problem of cross-infection and environmental contamination at the source. The rubber dam offers an adjunctive method of reducing the spread of infectious disease agents in the dental office and, more importantly, provides barrier protection at the source of microbial contamination (Cochran 1989).

PREVENTION OF PERCUTANEOUS INJURY

Among occupational exposures, percutaneous injuries, such as needlesticks and cuts from sharp instruments and objects, have been most frequently implicated in occupational transmission of bloodborne pathogens (CDC 1989, Marcus 1988, Henderson 1990). Precautions to prevent such injuries must therefore be implemented by all health-care

workers during procedures, when cleaning used instruments, during disposal of used needles, and when handling sharp instruments after procedures. To prevent needlestick injuries, needles should not be recapped, purposely bent or broken by hand, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable syringes and needles, scalpel blades, and other sharp items should be placed in puncture-resistant containers for disposal; the puncture-resistant containers should be located as close as practical to the dental operatory.

A study at a university hospital revealed that one-third of all needlesticks were related to recapping and that devices requiring disassembly had the highest rates of injury,suggesting the need for continued education of health-care workers as well as for development of devices providing for safer covering of contaminated sharps (e.g., self-sheathing needles) and disassembling of devices (Jagger 1988, 1990, 1990).

CRITICAL, SEMICRITICAL, AND NONCRITICAL ITEMS

The rationale for cleaning, disinfection and sterilization can be more readily understood if dental instruments, equipment, and surgical materials are divided into three general categories: critical items (e.g., forceps, scalpel, scalers, equipment for root canal therapy, etc.) which are introduced directly into the bloodstream or into normally sterile areas of the body; semicritical items (e.g., amalgam condensers, plastic instruments, mirrors, etc.) which come in contact with intact mucous membranes but do not ordinarily penetrate body surfaces; and noncritical items (papoose boards, neck rolls, pulse oximeter circuits and blood pressure cuffs), which do not ordinarily touch the patient or touch only intact skin (Garner 1985).

INDICATIONS FOR HIGH-LEVEL DISINFECTION OR STERILIZATION OF INSTRUMENTS

Surgical and other instruments that normally penetrate soft tissue and/or bone (e.g., forceps, scalpel, bone chisels, scalers, and surgical burs) should be sterilized after each use. Instruments that are not intended to penetrate oral soft tissues or bone (e.g., amalgam condensers, plastic instruments, and burs) but that may come into contact with oral tissues should also be sterilized after each use, if possible; however, if sterilization is not feasible, the latter instruments should receive high-level disinfection(Refer to Table 1) (Cottone 1985, Garner 1985, Ravero 1985).

METHODS FOR HIGH-LEVEL DISINFECTION OR STERILIZATION

Before high-level disinfection or sterilization, instruments should be cleaned to remove debris. Cleaning may be accomplished by a thorough scrubbing with soap and water or a detergent, or by using a mechanical device (e.g., an ultrasonic cleaner). Persons involved in cleaning and decontaminating instruments should wear heavy-duty rubber gloves to prevent hand injuries. Metal and heat-stable dental instruments should be routinely sterilized between use by steam under pressure (autoclaving), dry heat, or chemical vapor. The adequacy of sterilization cycles should be verified by the periodic use of spore-testing devices (e.g., weekly for most dental practices) (Garner 1985). Heat-and steam-sensitive chemical indicators may be used on the outside of each pack to assure it has been exposed to a sterilizing cycle. Heat-sensitive instruments may require up to 10 hours' exposure in a liquid chemical agent registered by the U.S. Environmental Protection Agency (EPA) as a disinfectant/sterilant; this should be followed by rinsing with sterile water. High-level

disinfection may be accomplished by immersion in either boiling water for at least 10 minutes or an EPA-registered disinfectant/sterilant chemical for the exposure time recommended by the chemical's manufacturer (CDC 1989).

DECONTAMINATION OF ENVIRONMENTAL SURFACES

At the completion of work activities, countertops and surfaces that may have become contaminated with blood or saliva should be wiped with absorbent toweling to remove extraneous organic material, then disinfected with a suitable chemical germicide (CDC 1989).

Chemical germicides classified as sterilants or disinfectants are regulated and registered by the E.P.A. (Favero 1985). The EPA requires testing under specific andstandardized protocols of chemical germicides formulated as general disinfectants, hospital disinfectants, and disinfectants applied to other environments (Favero 1985). EPA-registered tuberculocidal "hospital grade" disinfectants will inactivate HIV. The EPA has also approved a standard testing protocol that allows manufacturers to claim that a product inactivates HIV specifically. When using chemical germicides, the manufacturer's instructions for use, length of treatment, and specifications for compatibility of the medical device with chemical germicides should be followed (Tokars 1992).

A solution of sodium hypochlorite (household bleach) prepared fresh daily is an inexpensive and very effective germicide. Concentrations ranging from 5,000 ppm (a. 1:10 dilution of household bleach) to 500 ppm (a 1:100 dilution) sodium hypochlorite are effective, depending on the amount of organic material (e.g., blood, mucus, etc.) present on the surface to be cleaned and disinfected. Caution should be exercised, since sodium

hypochlorite is corrosive to metals, especially aluminum (CDC 1989).

Environmental surfaces such as walls, and floors are not associated with transmission of infections to patients or health-care workers. Therefore extraordinary efforts to disinfect or sterilize these environmental surfaces are not necessary. However, cleaning and removal of soil should be done routinely. Disinfectant-detergent formulations registered by the EPA can be used for cleaning environmental surfaces, but the actual physical removal of microorganisms by scrubbing is probably at least as important as any antimicrobial effect of the cleaning agent used. Therefore cost, safety, and acceptability by housekeepers can be the main criteria for selecting any such registered agent. The manufacturers' instructions for appropriate use should be followed (CDC 1987, Garner 1985).

TABLE 10. Disinfection and sterilization procedures

Sterilization	
Destroys:	All forms of microbial life, including high numbers of bacterial spores.
Methods:	Steam under pressure (autoclave), gas (ethylene oxide), dry heat or immersion in EPA-approved chemical "sterilant" for prolonged period of time (e.g., 6-10 hr) according to manufacturers' instructions. Note: Liquid chemical "sterilants" should be used only on those instruments that are impossible to sterilize or disinfect with heat. After use and before sterilization, surgical instruments should be decontaminated with a chemical germicide rather than just rinsed with water.
Use:	Critical items. Disposable invasive equipment eliminates the need to reprocess critical items.
High-level disinfection	
Destroys:	All forms of microbial life except high numbers of bacterial spores.
Methods:	Hot-water pasteurization (80-100 C, 30 min) or exposure to an EPA-registered "sterilant" chemical as above, except for a short exposure time (10-45 min or as directed by the manufacturer).
Use:	Semicritical items.
Intermediate-level disinfection	
Destroys:	*Mycobacterium tuberculosis,* vegetative bacteria, most viruses (including hepatitis B and HIV), and most fungi; does not kill bacterial spores.
Methods:	EPA-registered "hospital disinfectant" chemical germicides that have a label claim for tuberculocidal activity; commercially available hard-surface germicides or solutions containing at least 500 ppm free available chlorine (a 1:100 dilution of common household bleach-approximately 1/4 cup bleach per gallon of tap water).
Use:	Noncritical items that have been visibly contaminated with blood.
Low-level disinfection	
Destroys:	Most bacteria, some viruses, some fungi, but not *Mycobacterium tuberculosis* or bacterial spores.
Methods:	EPA-registered "hospital disinfectants" without a label claim for tuberculocidal activity.
Use:	Noncritical items or surfaces without visible blood contamination.
Environmental disinfection	
Methods:	Any cleaner or disinfectant agent that is intended for environmental use.
Use:	Environmental surfaces such as floors, woodwork, and countertops that have become soiled but not contaminated with visible blood.

Important: To ensure the effectiveness of any sterilization or disinfection process, items and surfaces must first be cleaned of all visible soil.

The manufacturer's instructions for use, length of treatment, and specifications for compatibility of the medical device with chemical germicides should be followed (Tokars 1992).

CLEANING AND DECONTAMINATING OF SPILLS OF BLOOD AND BODY FLUIDS

When spills of blood or body fluids occur in the patient-care setting, visible material should first be removed and then the area disinfected. With large spills of cultured or concentrated infectious agents in the laboratory, the contaminated area should be flooded with a liquid germicide before cleaning, then disinfected with fresh germicidal chemical. In both patient-care and laboratory settings, gloves should be worn during the cleaning and decontaminating procedures. Disinfection can be accomplished with chemical germicides that are approved for use as "hospital disinfectants" and are tuberculocidal when used at recommended dilutions, or with a 1:100 solution of household bleach (CDC 1989, Garner 1985).

DECONTAMINATION OF LABORATORY SUPPLIES AND MATERIALS

Blood and saliva should be thoroughly and carefully cleaned from laboratory supplies and materials that have been used in the mouth (e.g., impression materials, bite registration materials, etc.) and, especially before polishing and grinding intra-oral devices. Materials, impressions, and intra-oral appliances should be cleaned and disinfected before being handled, adjusted, or sent to a dental laboratory (ADA 1985). These items should also be cleaned and disinfected when returned from the dental laboratory and before placement in the patient's mouth. Because of the ever-increasing variety of dental materials used intro-orally, DHCW's are advised to consult with manufacturers as to the stability of specific materials relative to disinfection procedures. A chemical germicide that is registered with the EPA as a "hospital disinfectant" and that has a label claim for mycobactericidal (e.g.,

tuberculocidal) activity is preferred, because mycobacteria represent one of the most resistant groups of microorganisms; therefore, germicides that are effective against mycobacteria are also effective against other bacterial and viral pathogens (CDC 1985). Communication between a dental office and a dental laboratory with regard to handling and decontamination of supplies and materials is of the utmost importance.

USE AND CARE OF ULTRASONIC SCALERS, HANDPIECES, AND DENTAL UNITS

1. Routine sterilization of handpieces between patients is desirable; however, not all handpieces can be sterilized. The present physical configurations of most handpieces do not readily lend them to high-level disinfection of both external and internal surfaces (see 2 below); therefore, when using handpieces that cannot be sterilized, the following cleaning and disinfection procedures should be completed between each patient: After use, the handpiece should be flushed (see 2 below), then thoroughly scrubbed with a detergent and water to remove adherent material. It should then be thoroughly wiped with absorbent material saturated with a chemical germicide that is registered with the EPA as a "hospital disinfectant" and is mycobactericidal at use-dilution (CDC 1985). The disinfecting solution should remain in contact with the handpiece for a time specified by the disinfectant's manufacturer. Ultrasonic scalers and air/water syringes should be treated in a similar manner between patients. Following disinfection, any chemical residue should be removed by rinsing with sterile water.

2. Because water retraction valves within the dental units may aspirate infective materials back into the handpiece and water line, check valves should be installed to reduce the risk of transfer of infective material (Bagga 1984). While the magnitude of this risk is

not known, it is prudent for water-cooled handpieces to be run and to discharge water into a sink or container for 20-30 seconds after completing care on each patient. This is intended to physically flush out patient material that may have been aspirated into thehandpiece or water line. Additionally, there is some evidence that overnight bacterial accumulation can be significantly reduced by allowing water-cooled handpieces to run and to discharge water into a sink or container for several minutes at the beginning of the clinic day (Scheid 1982). Sterile saline or sterile water should be used as a coolant/irrigator when performing surgical procedures involving the cutting of soft tissue or bone.

STERILIZABLE HANDPIECES

Both the ADA recommendations and CDC guidelines in this area state that handpieces "must" be heat sterilized, if possible. Handpiece manufacturers provide detailed instructions for use and maintenance of their products. When these recommendations are followed, handpieces should continue to function at a maximal level and provide prolonged efficient use (Cotton 1991).

A second major concern regarding handpiece asepsis involves the role of anti-retraction valves for the dental unit. When a handpiece is turned off, expansion of attached tubing under pressure may occur, causing water retraction. The potential exists for drawing water or saliva, or both into the dental unit fluid line. Microorganisms entering the waterline may then be passed into the next patient's mouth when the handpiece is activated (Cottone 1991). Installation of anti-retraction valves on a dental unit can prevent this. Newer units (manufactured after 1984) come with these valves already in place. Older units can be fitted with anti-retraction valves that may be purchased separately (Cottone 1991).

ULTRASONIC CLEANING

The appropriate method for cleaning instruments before sterilization is another confusing matter for the dental profession. Ultrasonic cleaning before hand scrubbing instruments is highly recommended (USAF 1982) because ultrasonic cleaning: is 16 times more efficient than hand scrubbing (Sandord 1966), significantly reduces the aerosolization of potentially pathogenic organisms during instrument cleaning and greatly reduces the potential for puncture wounds with grossly contaminated instruments.

The OSHA statements emphasize work practice and engineering controls that isolate hazards from the workplace and reduce the likelihood of exposures by altering the manner in which a task is performed (OSHA 1989). Ultrasonic instrument cleaning is a prime example of using these modifications to provide a safer workplace.

After ultrasonic cleaning, instruments can be rinsed, rough dried and inspected. If instruments are still visibly dirty, it is necessary to hand scrub them. When clean, the instruments are ready to be placed into sterilization bags. These procedures should be performed while wearing nitrile utility gloves to reduce the likelihood of puncture wounds.

Ultrasonic cleaning works best if: a reliable ultrasonic cleaner is purchased; the ultrasonic cleaner is tested on a regular basis to ensure that it is delivering ultrasonic energy throughout the entire tank and is not losing power; an ultrasonic cleaning solution is used that is specifically formulated for use in an ultrasonic unit.

INSTRUMENT PACKAGING

Packaging instruments protects them from becoming contaminated after sterilization. It also prevents employee puncture wounds and is visible evidence of instrument sterilization

to subsequent patients. Heat sterilization bags with the best overall qualities are those that meet ADA acceptance criteria (Cottone 1991).

HEAT STERILIZER

Heat has been recognized as the most efficient, reliable method of achieving dental instrument sterilization (ADA 1988, CDC 1986). Accordingly, heat sterilization is required for all instruments and items that can withstand repeated exposure to high temperatures (Cottone 1991).

Steam under pressure, prolonged dry heat and unsaturated chemical vapor sterilization are the preferred methods for sterilization. The penetration capabilities of these methods are superior to those noted for any chemical sterilant/disinfectant. Routine use of any of these modalities is effective, although the inherent advantages and disadvantages may cause a practitioner to select a sterilizer type that is most compatible with the individual setting (Cottone 1991).

Ethylene oxide gas is classified as a chemical capable of sterilizing instruments and other contaminated objects. It is for this reason, as well as for its excellent penetration powers, that ethylene oxide is included with procedures that achieve sterilization (Cottone 1991).

MONITORING

Dental practitioners must monitor monthly the efficiency of office sterilization procedures. Many factors may diminish the effectiveness of an autoclave, dry heat sterilizer or unsaturated chemical vapor apparatus. Three of the more frequent problems encountered are operator error, improper wrapping of instruments and defective control

gauges that do not reflect actual conditions inside the sterilizer (Cottone 1991).

Chemically treated indicator tapes and biological monitors should be used to check for proper functioning of an office sterilizer. Indicators that change color generally inform the practitioner that sterilizing conditions have been reached, but do not necessarily indicate that sterilization of the chamber contents has been achieved (Cottone 1991).

Calibrated biological monitors remain the main guarantee of sterilization. The ampule or paper strip preparations contain bacterial spores that are more resistant to heat than viruses and vegetative bacteria. Proof of spore destruction by culturing after exposure to the sterilization cycle is used to infer that all microorganisms exposed to the same conditions have been destroyed. The demonstration of sporicidal activity by an office sterilizer represents the most sensitive check for efficacy (Cottone 1991).

SURFACE ASEPSIS

Just as it is important to clean an instrument before it is either heat or chemically sterilized, it is equally important to clean an environmental surface before it is disinfected. Some surface disinfectants are also good cleaners, such as the diluted iodophors, chlorines or the synthetic phenolics (Molinari 1988). Other products, formulated with a high alcohol content, are generally poorer cleaners. Alcohol will precipitate proteins in saliva and blood and make the proteins more difficult to remove from a surface (Cottone 1991).

The generally recommended procedure for surface cleaning and disinfection is use of a "spray-wipe-spray" technique. The first spray and wipe are actually the cleaning steps and the second spray is the disinfectant step. If the disinfectant is a good cleaner, then one product can be used for both steps; otherwise, separate products must be involved (Cottone

1991).

The use of surface disinfectants is another of the overly emphasized and confusing areas of infection control in dentistry. Experimentally, transmission of infectious agents from a surface has been indicated. Clinically documented cases, however, are rare (Ansari 1988, Brady 1990). Appropriate housekeeping, including surface cleaning and disinfection, is part of the ADA recommendations, CDC guidelines and OSHA statements (Cottone 1991).

Surfaces should be cleaned with a good cleaner and wetted with a disinfectant that meets ADA acceptance specifications. An ADA-accepted surface disinfectant has documented evidence of bactericidal, tuberculocidal and virucidal (lipophilic and hydrophilic viruses) activity. When a surface disinfectant is evaluated for dentistry, the area where most products fail relates to the hydrophilic (polio) virus kill claim (Cottone 1991).

Disposal barriers should be used to avoid the necessity of excessive cleaning and disinfection of both environmental surfaces and equipment. Aluminum foil, plastic wrap, plastic bags or plastic-lined paper can be used as a cover/barrier on equipment and surfaces (Cottone 1991).

GLUTARALDEHYDES

Use of glutaraldehydes to sterilize instruments has declined with the increasing use of heat sterilization. A glutaraldehyde should be used to sterilize an item only when the item can be immersed and is sensitive to heat. Chemicals should not be used as a short cut or as a substitute for heat sterilization when items can be heat sterilized (Cottone 1991).

The number of glutaraldehydes on the market can be confusing. They can be

compared by reviewing the tuberculocidal directions. Practitioners should disregard the general disinfection directions, as these are inappropriate for dentistry. The tuberculocidal recommendations are determined by using the Association of Official Analytical Chemists (AOAC) test or a more recently developed and preferred quantitative logarithmic reduction test method. The AOAC method does not guarantee 100 percent tuberculocidal action in the time frame used, while 100% tuberculocidal action can be more readily determined using the logarithmic reduction method (Ascenzi 1984). The 2 percent alkaline glutaraldehydes comprise the largest chemical category. Products with the same EPA registration number are the same chemical formation and should have the same directions on the label. Unfortunately, product labels do not provide the test used to arrive at the tuberculocidal directions (Cottone 1991).

In addition, glutaraldehydes have a re-use life that is measured in days. One day of re-use is equal to three cycle loads of precleaned respiratory therapy equipment. Thus re-use days mentioned on product labels do not relate well to dentistry. A report to Congress from the Government Accounting Office states that as many as 20 percent of the commercially available glutaraldehyde products are not effective (U.S.G.A.O. 1989). Most glutaraldehydes that appeared to be ineffective were those that are highly diluted or used to the end of their re-use time. Practitioners should avoid use of products in this manner (Cottone 1991).

HANDLING OF BIOPSY SPECIMENS

In general, each specimen should be put in a sturdy container with a secure lid to prevent leaking during transport. Care should be taken when collecting speciments to avoid

contamination of the outside of the container. If the outside of the container is visibly contaminated, it should be cleaned and disinfected, or placed in an impervious bag (Garner 1983).

DISPOSAL OF WASTE MATERIALS

All sharp items (especially needles), tissues, or blood should be considered potentially infective and should be handled and diposed of with special precautions. Disposable needles, scalpels, or other sharp items should be placed intact into puncture-resistant containers before disposal. Blood, suctioned fluids, or other liquid waste may be carefully poured into a drain connected to a sanitary sewer system. Other solid waste contaminated with blood or other body fluids should be placed in sealed, sturdy impervious bags to prevent leakage of the contained items. Such contained solid wastes can then be disposed of according to requirements established by local or state environmental regulatory agencies and published recommendations (Garner 1983, 1985).

No epidemiologic evidence suggests that most hospital waste is any more infective than residential waste or that improper disposal of hospital waste has caused disease in the community. However, it appears prudent to take special precautions in disposal of blood specimens or blood products and waste from microbiology and pathology laboratories. Such waste should either be incinerated or autoclaved before disposal in a sanitary landfill. Bulk blood, suctioned fluids, excretions, and secretions may be carefully poured down a drain connected to a sanitary sewer. Sanitary sewers may also be used to dispose of other infectious wastes capable of being, ground and flushed into the sewer (CDC 1987, Garner 1985). In all cases, appropriate local and state regulations should be followed.

LAUNDRY

Although soiled linen is a source of large numbers of certain pathogenic microorganisms, the risk of actual disease transmission is negligible. Rather than rigid procedures and specifications, hygienic and common-sense storage and processing of clean and soiled lined are recommended. Soiled linen should be handled as little as possible and with minimum agitation to prevent gross microbial contamination of the air and of persons handling the linen. All soiled linen should be bagged at the location where it was used. Linen soiled with blood or body fluids should be placed and transported in bags that prevent leakage (CDC 1987).

BLOOD OR TISSUE AEROSOLS

Aerosols are inspirable airborne particles less than approximately 100 μm in diameter and should be distinguished from larger, noninspirable droplets or spatter. Aerosols are not known to present a risk of transmission of HIV, hepatitis B virus, or other bloodborne pathogens in the health-care setting. In studies conducted in dental operatories and hemodialysis centers, hepatitis B virus could not be detected in the air during the treatment of infected patients, including during procedures known to generate aerosols (Peterson 1979, 1976, 1980). This suggests that detection of HIV in aerosols in clinical settings would also be uncommon, since the concentration of HIV in blood is generally lower than that of hepatitis B virus. Detection of HIV in an artificially produced aerosol in a laboratory experiment would not necessarily mean that HIV-containing aerosols are produced in clinical settings (Johnson 1990). CDC is sponsoring research to assess the potential for aerosolization of blood and tissue during various surgical procedures and the possible

resulting hazards to surgical personnel. At this time, however, the possibility that HIV may be transmitted via aerosolized blood remains theoretical (Tokars 1992).

DEPARTMENT OF LABOR AND DEPARTMENT OF HEALTH AND HUMAN SERVICES JOINT ADVISORY NOTICE

Detailed recommendations for employer responsibilities in protecting workers from acquisition of bloodborne disease in the workplace have been published in the Department of Labor and Department of Health and Human Services Joint Advisory Notice (U.S.D.L. 1987). General responsibilities can be summarized as a series of steps:

1. Work activities should be categorized as Class I (direct contact with blood or other fluids to which universal precautions apply); Class II (activity performed without blood exposure but exposure may occur in emergency); or Class III (task/activity does not entail predictable or unpredictable exposure to blood). Personal protective equipment should be available for Class I or II activities and should always be worn for Class I activities.
2. Standard operating procedures for all activities having the potential for exposure should be developed. These procedures should incorporate universal precautions, as well as recommended methods for disinfection, decontamination, and disposal of infective waste.
3. Initial and periodic worker education programs should be provided to potentially exposed workers.
4. Procedures to ensure and monitor compliance with standard operating procedures should be implemented.

5. The employer should, whenever possible, identify devices and other approaches to modify the work environment in ways that will reduce exposure risk (CDC 1989, USDL 1987).

In addition to these general responsibilities, the employer has the specific ressponsibility to make available to the worker a program of medical management, including hepatitis B vaccination, management of occupational exposures to blood and body fluids. Documentation of exposures and reporting in accordance with state and federal laws, and management of hepatitis B- or HIV-infected workers (CDC 1989, USDL 1987). The Public Health Service has provided guidelines on management of occupational HIV exposures, including considerations regarding zidovudine postexposure use (CDC 1990).

EFFICACY OF UNIVERSAL PRECAUTIONS

Use of universal precautions has been shown to reduce the number of blood contacts. After implementation of universal precautions, the mean number of contacts with blood or body fluids decreased from 5.07 to 2.66 exposures per month among physicians at two acute-care hospitals, and from 35.8 to 18.1 per year among workers at the Clinical Center, National Institutes of Health (Wong 1991, Fahey 1991). A study in emergency rooms revealed that use of gloves was associated with a reduction in the adjusted blood contact rate from 11.2 to 1.3 per 100 procedures (Marcus 1990).

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