Alpha

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HEMOPHILIA

A NEWSLETTER DEVOTED TO HEMOPHILIA

LETTER

In our winter 1982 issue, we brought you up to date on Alpha's attempts to protect the nation's hemophilic population against Acquired Immune Deficiency Syndrome (AIDS). We will continue our updates in an attempt to temper alarmist publicity until what the US Public Health Service now terms their number one priority has been solved.

Needless to say, Alpha has stepped up efforts to protect hemophilic patients, but new evidence suggests there is no proof that AIDS is necessarily associated with blood or blood products (see accompanying article).

There is also mounting evidence from the specialists to show that to avoid use of plasma products by cutting back on so-called elective surgery – most of it orthopedic – has had some unexpected and negative results. When surgery has not been performed, some urgent joint problems have been created, requiring the use of more concentrate than might have been used initially.

At the beginning of 1983, some authorities were urging hemophiliacs to switch from concentrates to cryoprecipitate to treat bleeding episodes. Most specialists, and the National Hemophilia Foundation (NHF), however, recommended that existing treatment methods continue. As we go to press, the only patients for whom cryoprecipitate rather than concentrate is still being recommended are patients with mild hemophilia who receive treatment for bleeding episodes only once or twice a year, newly diagnosed patients, newborns and children under the age of four. There is some question as to whether use of cryoprecipitate would actually be safer than concentrate in any case.

Although AIDS has passed to the general population (six percent of the 1500 documented cases in the US do not fit the high-risk categories for the disease), according to the Centers for Disease Control (CDC) in Atlanta, it is still mainly confined to homosexual or bisexual males who have many sex partners, intravenous drug abusers and recent Haitian immigrants.

In face of this fact, our medical director, Clyde McAuley, MD, states: "We feel we have a moral responsibility to exclude these donors from our donor pool." In the first six months of Alpha's screening program, in fact, 800 potential donors voluntarily disqualified themselves from the pool. None of Alpha's 27 plasmapheresis centers is located in the high-risk cities of Los Angeles, San Francisco and New York, in any case.

The American Red Cross was actually one of the last groups to institute donor screening, and many fear their screening programs may be less effective than Alpha's because of peer pressure to donate rather than to exclude oneself when business or church groups participate in a blood drive.

As part of Alpha's commitment to the problem of AIDS, we have sponsored a number of seminars on this subject. From one of these, held in March in Puerto Rico, we produced a cassette tape featuring experts such as Drs. Louis Aledort, Shelby Dietrich, Marvin Gilbert, Margaret Hilgartner, and Alice Forster, RN; you may order this tape for only $2.50 (to cover our costs and postage). You can also receive, free, a pamphlet designed to answer questions hemophilic patients and their families may have about AIDS.

We have recently updated our guide for hemophilic patients who travel; it is called *Passport* and it will be sent to you for only $1.50, to cover our costs and postage. You may order all these items on the attached reply form.

We have also included in this issue an evaluation form which we would appreciate having you fill out. It will take only a few minutes to answer the questions as you order the cassette tape and patient literature mentioned above. And it will help us make this newsletter more relevant to your needs. Thank you.

Sincerely,
Alpha Therapeutic Corporation

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Thomas P. Stagnaro
Director of Marketing, Therapeutic Products

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The Specialists Speak Out

New Clues Minimize AIDS' Risk to Hemophiliacs

"AIDS has not changed the need to treat hemophilia appropriately"

It has been two years since the first case of AIDS was reported and the syndrome's causes are still a mystery. The prevailing view at press time is that a novel virus – perhaps a mutant – may cause shutdown of the immune system, making patients susceptible to unusual opportunistic infections such as *Pneumocystis carinii*, Kaposi's sarcoma and cytomegalovirus.

AIDS Not Spread by Blood Products Alone

The outbreak of AIDS is making very slow inroads and current evidence suggests that the disease is of very low infectivity. It now counts 20 new cases a week in the US. Unexplained immunodeficiency and opportunistic infections have now been reported in children who had received no blood products, confirming earlier suggestions that exposure to blood products is not necessary for AIDS transmission. *The New York Times*, in fact, ran an article in early June stressing that the risk of AIDS was slight for people needing transfusions.

At a spring conference held by the American Blood Commission, it was pointed out that if AIDS were transmitted through blood, the incidence of the disease would increase among transfusion recipients in areas designated as "hot spots" by the CDC. No such increase has occurred.

Further, no common lot number or common manufacturer has been identified as the source of factor VIII concentrate received by those hemophiliacs who have developed AIDS. And many hemophiliacs who received essentially the same material have not developed the syndrome.

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Most sources agree, however, that AIDS cannot be spread through casual contact. AIDS has been transmitted to female sexual partners of AIDS patients and to children of Haitians and of drug abusers. There have been no suspected cases of transmission of AIDS to health-care providers, nor has there been any suspected transmission from laboratory specimens to lab workers.

It should be kept in mind that AIDS cases in hemophiliacs represent only a fraction of one percent of all the cases in the country. Only 14 hemophiliacs (out of a total of 12,000-15,000 hemophiliacs in the US) have been identified as having acquired AIDS. Based on this low incidence, Dr. Margaret Hilgartner stressed, at a meeting on the issue at the New York Blood Center, that "we are still talking about a very, very small proportion of the hemophilic population."

Elective Surgery Resumed

By late May, physicians such as Peter H. Levine, MD, of Worcester Memorial Hospital, in a letter to the *New England Journal of Medicine*, could state: "If AIDS is transmissible or inducible by exposure to whole blood, factor VIII concentrate, and platelet concentrate, it is hard to believe that cryoprecipitate will be much safer."

At a February meeting at the New York Blood Center, Drs. Louis Aledort and Margaret Hilgartner of Mt. Sinai Medical Center in New York City suggested that it might be even safer to receive lyophilized concentrates than cryoprecipitate because the plasma of a donor with AIDS will have been diluted by the addition of the blood of from 2500 to 22,500 other donors, whereas the blood of only a few donors goes into a bag of cryoprecipitate. Infectivity is known to be related to the concentration of virus. As Dr. Aledort summed it up at the March Puerto Rico seminar, "Any hemophiliac who is exposed to at least ten bags of cryoprecipitate might as well take concentrate. The risk for AIDS is about equal."

At a February meeting of the Southern California Hemophilia Foundation, Dr. Shelby Dietrich of Los Angeles' Orthopaedic Hospital had also reversed her previous recommendations of conservatism. "In December, we suspended elective surgery, but we're now resuming it on selected patients who really need and want it. These are patients who have already had considerable exposure to concentrates."

Specialists discussing AIDS at the Alpha seminar in Puerto Rico included (l. to r.) Alice Forster, RN, nurse clinician at Mount Sinai Hemophilia Center, NY; Dr. Marvin Gilbert, co-director, Regional Comprehensive Hemophilia Diagnostic and Treatment Center, Mt. Sinai Medical Center, NY, and NHF co-medical director; Dr. Clyde McAuley, medical director, Alpha Therapeutic Corporation, Los Angeles; Dr. Louis Aledort, vice chairman, Department of Medicine, Mt. Sinai Hospital, NY, and NHF medical director; and Dr. Margaret W. Hilgartner, professor of pediatric hematology at Cornell University Medical Center, New York Hospital.

Dr. Marvin Gilbert, co-medical director of the National Hemophilia Foundation and an orthopedic surgeon, also stated: "There's a certain amount of elective surgery we can

put off. But in a patient with synovitis of the knee that will progress to destruction, one surgical procedure may be preferable to six months of prophylactic replacement therapy."

Importance of Adequately Treating Bleeding Episodes

Other experts were speaking out at the same time against the rationale for the use of cryoprecipitate rather than concentrates for bleeding episodes. A member of the nursing staff at Orthopaedic Hospital in Los Angeles reported at the Southern California meeting that they feel that patients who were switched to cryo are getting less than adequate treatment. "They wait too long before coming in for treatment; they're not treating smaller bleeding episodes which eventually become major problems," she said.

Dr. Lois Boylen seconded this opinion at the same conference: "For patients with severe disease, we recommend immediate treatment of bleeding episodes. Patients who waited got into trouble. We recommended they use conservative measures most had forgotten about – like crutches, bed rest and ice packs.

"It doesn't do any good to switch patients to cryoprecipitate if you have to treat them longer because they didn't treat a bleeding episode early enough. Most patients who still use concentrate have treated bleeds right away and so have used less concentrate."

Alan Brownstein, director of the National Hemophilia Foundation, was quoted by *The Washington Post* as saying, "We strongly urge patients not to withhold treatment. The consequence of withholding is far worse than AIDS."

Potential AIDS Marker Found

A possible marker found in AIDS patients is an imbalance in the relative number of helper and suppressor T-lymphocytes. (Helper T-cells are white blood cells that interact with other cells to activate an immune response that combats infection, whereas suppressor T-cells interact to moderate or inhibit the immune response once infection has been eliminated). Normal individuals have twice as many helper as suppressor cells. In AIDS patients, the helper T-cell population is severely depleted, with patients showing five times as many suppressor cells as helper cells. Researchers have linked this phenomenon with a possible similarity between human T-cell leukemia virus and AIDS.

Since January, several published studies have documented a low helper/suppressor (H/S) ratio in healthy hemophiliacs as well, found more commonly among patients with hemophilia A who receive factor VIII concentrates. The H/S imbalance in hemophiliacs represents an increase in the number of suppressor T-cells rather than a decrease in the number of helper cells typical of AIDS patients. Physicians do not fully understand, however, the true significance of this finding.

Some of the specialists at a symposium sponsored by Alpha in March in Puerto Rico reported that between 40 and 60 percent of patients, regardless of whether they receive high- or low-dose concentrate, may have H/S imbalance. In an oral communication to the Orange County Medical Association and the

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Southern California Hemophilia Foundation in February, Dr. Dietrich estimated that a high percentage of hemophiliacs show abnormal T-cell ratios when tested.

In early attempts to thwart further spread of AIDS in the hemophilic community, specialists recommended careful scrutiny of current modes of hemophilia treatment, going so far as to suggest that patients receiving lyophilized commercial concentrates of factor VIII might be at greater risk of having abnormalities of T-cell subpopulations than recipients of cryoprecipitate who would be exposed to fewer donors.

At a meeting in Washington, DC, in March, Dr. Aledort, medical director of the National Hemophilia Foundation, emphasized that the reversed T-cell ratio is close to the same percentage among patients who receive cryoprecipitate or concentrate. It has also been reported that in Australia, where all-volunteer blood donation system is in effect, the same H/S imbalance has been noted in hemophiliacs, minimizing the chance that non-volunteer blood products could cause the presence of this baffling marker.

Guidelines for Prevention Set

An editorial in the *Annals of Internal Medicine* (March 1983) states some simple guidelines to avoid contracting AIDS, seconded by the NHF: "As observed during the past two years, the syndrome will probably continue to be recognized in new risk groups. The highest incidence of new cases, however, will probably continue to be among sexually active homosexual men because the current prevalence of disease and risk factors are greatest in this group...Even in the absence of certainty about the cause of the acquired immune deficiency syndrome, there are opportunities for prevention. Because sexual transmission of a causal agent appears likely, sexual contact with known or suspected patients should be avoided...Prevention of the syndrome in recipients of blood and blood products may call for restricting use of blood from high-risk donors, improving preparation and processing of these products, and disseminating guidelines for their use."

This is exactly what Alpha Therapeutic Corporation has committed to do. According to Clyde McAuley, MD, Alpha's medical director: "All commercial producers of concentrate, following Alpha's lead, have taken steps to eliminate members of high-risk groups from their donor pools. Alpha now educates donors about the risk

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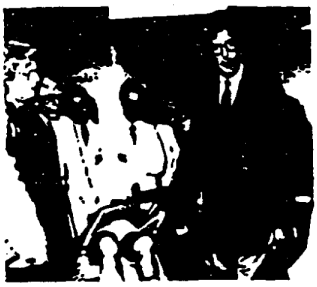
Alpha Seminar in Puerto Rico Includes Clinic

A delegation of U.S. hemophilia specialists attended an Alpha-sponsored seminar in Puerto Rico in March to meet with local treating personnel. During the seminar, the visiting physicians examined local patients (below, Alpha's Medical Director Dr. Clyde McAuley; at right, NHF Co-Medical Director Dr. Marvin Gilbert). These patients showed dramatic evidence of the lack of home care and prophylactic treatment, with many swollen joints, deformities and evidence of synovitis.



Frequent Factor Replacement Decreases Antibody Levels

(CR Rizza, JM Matthews: Effect of frequent factor VIII replacement on the level of factor VIII antibodies in haemophiliacs. Brit J Haematol. 52:13-24, 1982)

Results showing that hemophiliacs given frequent but relatively small doses of factor VIII may experience a decrease in antibody levels have led British investigators to speculate on what causes this phenomenon. It appears that sufficient factor VIII may neutralize antibody in the blood, or treatment may induce immune tolerance.

Of 24 patients with antibodies given factor VIII replacement for bleeding episodes, seven had low-level antibodies disappear over one to five years. (A fall in antibody level was generally accompanied by a decrease in secondary immune response.) High levels of antibodies fell in six patients. One patient showed a dramatic fall in antibody titer while receiving 1500 units of factor VIII weekly for eight months. Eleven patients showed little change.

Because amounts of factor VIII used by each patient varied with frequency of bleeding episodes, researchers could not determine whether frequency of dosage or amount of factor VIII replacement represented the cause for the improvement in antibody status.

Joint Laxity May Predispose to Bleeding

(JH Patrick, JL Bern, A Aronstam, SC Darby: An examination of joint laxity in haemophilia. Injury. 13:337-342. 1982)

Boys with severe hemophilia A have laxer thumbs and their fingers bend farther backward than those of normal boys. Attempting to define a possible cause of bleeding into joints, a team of British researchers postulated that increased laxity of joints in boys with hemophilia might allow an excessive range of motion, which in turn could cause the synovial membrane to rip and bleed.

The degree of joint destruction in 33 of the 47 adolescent boys (whose levels of factor VIII were less than one percent) prevented accurate measurement of knee, elbow and

> "Boys with severe hemophilia A have laxer thumbs and their fingers bend farther backward..."

wrist joints. Active and passive joint motion of thumb and ankle joints was assessed by goniometer.

Despite the fact that researchers found no convincing evidence of an association between bleeding frequency and joint laxity, they concluded some form of joint laxity might be a reason for variability in bleeding frequency in boys with severe hemophilia A. They suggested further work to determine whether joint laxity runs in families and whether hormonal environment can influence it.