Scientific Supplement

FA Family Newsletter #16

Summaries of Presentations at the Family Meeting
May 30 - June 3, 1994 • Camp Sunshine, Point Sebago, Maine

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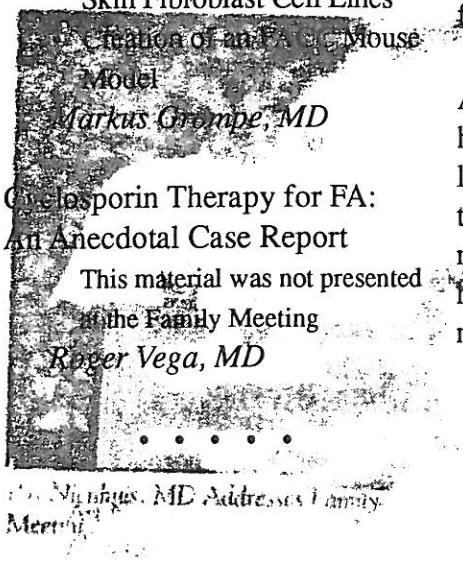

Dr. Nienhuis, MD Addresses Family Meeting

G-CSF (filgrastim) Trial Results to Date

Wayne Rackoff, MD, Indiana University School of Medicine, Indianapolis, Indiana

In the spring of 1993, Drs. David Williams and Wayne Rackoff at Indiana University School of Medicine organized a study of the effects of filgrastim (G-CSF) in patients with Fanconi anemia and other inherited bone marrow failure syndromes. Filgrastim had been used in patients with severe acquired aplastic anemia, with encouraging results. The primary goal of the study was to observe the effect of filgrastim on the neutrophil counts of patients with Fanconi anemia.

The first patient was enrolled in the summer of 1993 and has now completed the study. The enrollment of other patients began in December of 1993 after Amgen, Inc. agreed to support the study and the study was approved by the U.S. Food and Drug Administration. Drs. Blanche Alter (Galveston), Melvin Freedman (Toronto), and Richard Harris (Cincinnati) are now participating in the study. To date, eight patients have been enrolled.

The six patients who have completed at least eight weeks of filgrastim treatment were discussed with Fanconi anemia families at Camp Sunshine. This was the first report of results from the study, and was, therefore, very preliminary.

At least three patients appear to have had an increase in their platelet counts on filgrastim. One patient had a dramatic increase in hemoglobin, and two other patients had less dramatic increases in hemoglobin.

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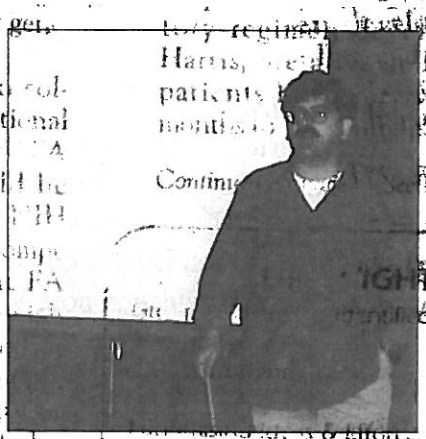

Dr. Wayne Rackoff

Long-Term Clinical Management of Patients with Fanconi Anemia

N.T. Shahidi, MD, University of Wisconsin Medical School, Madison, Wisconsin

It is well known that the genetic defect in Fanconi anemia involves all the cells in the body. This defect, which is characterized by increased sensitivity to DNA damaging agents in all complementation groups, is thought to be due to an abnormal DNA repair and/or inadequate detoxification of toxic oxygen species. The resulting cellular dysfunction is manifested in organs with the highest rate of DNA turnover such as bone marrow and male gonads at puberty. Bone marrow failure, abnormal response to environmental factors such as toxins and viruses, and propensity to malignancy demand long-term vigilant care not only to manage the complications but also to prevent them. One of the most prominent features of Fanconi anemia is bone marrow failure which results in decreased production of circulating blood cells which in turn results in anemia, bleeding manifestations, and decreased resistance to infections.

Dr. Nasrollah Shahidi

The aim of this article is to highlight some important aspects of the long-term management of patients with Fanconi anemia with the goal of improving both the survival and the quality of life. To achieve these goals, judicious use of both preventive and therapeutic measures is necessary.

1. Viral and Bacterial Infections

Both viral and bacterial infections may exert a deleterious effect on hematopoietic cell production in Fanconi anemia patients. The bone marrow suppression is mediated through diverse mechanisms such as generation of superoxide anions by macrophages, production of inhibitory molecules such as interferon γ, Tumor Necrosis Factor α (TNFα), or direct invasion of bone marrow cells by the virus. Major viral agents likely to cause bone marrow suppression in Fanconi anemia patients are varicella virus, Parvovirus B19, hepatitis virus, Epstein-Barr virus, and cytomegalovirus. It is likely that other viruses not easily identifiable may exert a similar inhibitory effect on the bone marrow.

Varicella Virus

Varicella virus which causes chicken pox and herpes zoster (shingles) is known to cause a significant thrombocytopenia or total bone marrow suppression in patients with Fanconi anemia. Indeed, many patients with Fanconi anemia come to medical attention for the first time after the onset of chicken pox. Varicella virus is spread by direct contact or by airborne droplets. The infectious period is from 24 hours before until six or seven days after the appearance of vesicles. The scabs, after the vesicles have dried, are not infectious. Thus, the most important first step in prevention of chicken pox in patients with Fanconi anemia is to avoid contact with patients with active disease. The patients who have been exposed to varicella virus should receive, within 72 hours of exposure, varicella zoster immune globulin (VZIG). Patients who develop chicken pox or shingles, whether mild or severe, should receive antiviral agent acyclovir, as early as possible. Because of the poor absorption (about 15%) of the oral preparation, the parenteral administration is more desirable. The patients with milder disease could be switched to oral preparation three to four days after the initiation of the parenteral preparation if there is no further progression of the vesicles. It should be emphasized that the therapeutic decisions depend on individual patients and are made by the physician in charge.

A new derivative of acyclovir known as famciclovir, with an absorption rate of 77% is currently under consideration by the Food and Drug Administration.

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Fanconi Anemia: An Overview

Blanche P. Alter, MD, Children's Hospital, University of Texas Medical Branch, Galveston, Texas

This is Dr. Alter's summary, based on a comprehensive analysis of the literature:

In the United States, the carrier frequency rate for FA is estimated at one in two hundred individuals. The likelihood of one carrier marrying another is one in 40,000. Fanconi anemia occurs in one in 160,000 live births. As many as 500 families in the United States are estimated to have a child with FA.

Between 75% and 85% of FA patients have congenital abnormalities. Some of the more common described in the medical literature are as follows:

Short stature:	60%
Skin pigmented:	51%
Cafe au lait spots:	23%
Upper limb anomalies:	50%
Hypogonads (males):	40%
Hypogonads (female):	3%
Head abnormalities:	28%
Small eyes:	27%
Kidney abnormalities:	24%
Low birth weight:	13%
Retardation:	13%
Lower limb malformations:	9%
Ear abnormalities:	11%
Other skeletal problems:	7%
Cardiopulmonary anomalies:	7%
Gastrointestinal problems:	4%*
Other abnormalities:	6%
No abnormalities:	6%
Only short stature and/orskin anomalies:	8%

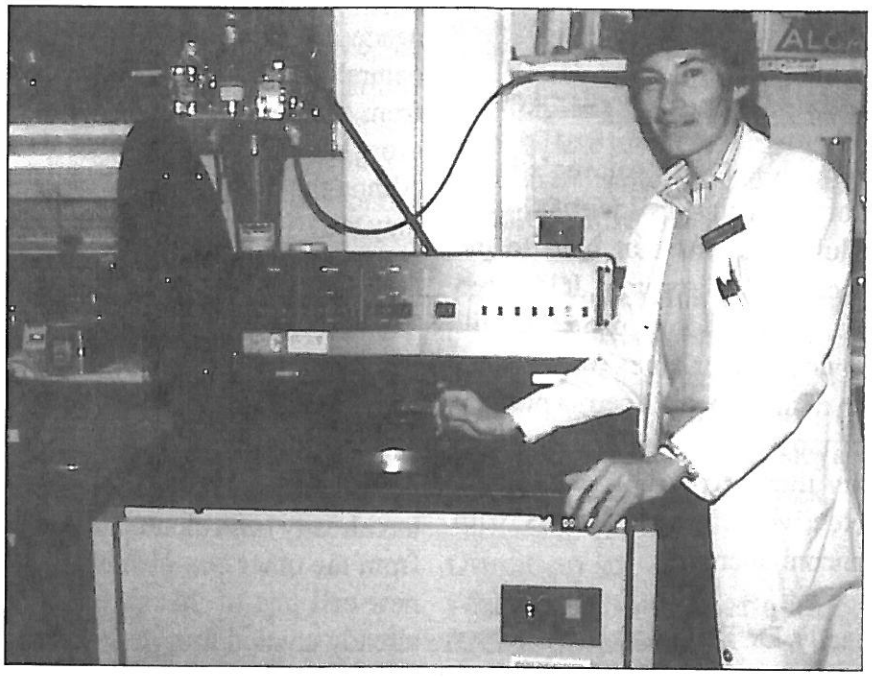
*This probably underestimates the actual incidence. The abnormalities can be subtle and are often underdiagnosed.

Ninety percent of FA patients described in the literature developed aplastic anemia. Ten percent developed leukemia, and another ten percent were afflicted by other malignancies. One hundred percent have chromosomal breaks.

Here is a brief overview of current therapies for FA patients. Androgen therapy is effective in 70% of the FA population and often increases blood production for approximately five years. One FA patient has survived for twenty years on androgen therapy. Matched sibling transplants offer good outcomes for a high percentage of FA patients. **Family members should not give blood products to an FA patient if a bone marrow transplant is being considered.**

A successful transplant will not affect complications of FA unrelated to the bone marrow. Patients receiving bone marrow transplants are still at risk of malignancies. That risk may even be increased due to the toxicity of the conditioning regimen.

FA women have become pregnant and produced healthy, normal children. At least two men with FA have fathered children. ••



Dr. Blanche Alter

Characterization of the FACC Protein

Alan D. D'Andrea, MD, Dana-Farber Cancer Institute, Boston, Massachusetts

Dr. D'Andrea's laboratory focuses on the protein encoded by the Fanconi anemia gene (FACC). His laboratory is trying to determine the actual functional role of the protein within a normal cell. One approach is to determine the cellular location of the Fanconi anemia protein. Its location, which is in the cytoplasm of the cell, suggests possible functions.

Dr. Alan D'Andrea

In addition, Dr. D'Andrea's laboratory is trying to identify other cellular proteins that bind to the Fanconi anemia protein. It is hoped that these binding proteins will provide further clues to the function of the Fanconi anemia protein. Perhaps these binding proteins may themselves be deficient or defective in some patients with Fanconi anemia.

Finally, Dr. D'Andrea's laboratory is studying the mechanisms of anemia and leukemia that result from loss of the Fanconi anemia protein.

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Two Research Projects at Oregon Health Sciences University

Markus Grompe, MD, Oregon Health Sciences University, Portland, Oregon

1. Creation of immortalized skin fibroblast cell lines from patients with Fanconi anemia

Researchers working on Fanconi anemia utilize mainly two different types of cells from patients for their studies of the disease. The two types are called lymphoblasts and fibroblasts. Lymphoblasts are derived from B-lymphocytes, specialized white blood cells, whereas fibroblasts are skin cells. Laboratories around the world have developed lymphoblast cell lines from Fanconi patients, and one such cell line was used by Manuel Buchwald's group to clone the Fanconi Anemia Group C gene. Although a lymphoblast cell line was used for this work, there are technical reasons why many scientists would prefer to work with fibroblasts rather than lymphoblasts in their attempts to clone Fanconi anemia genes. Unfortunately, it is very difficult to generate immortalized skin cell lines.

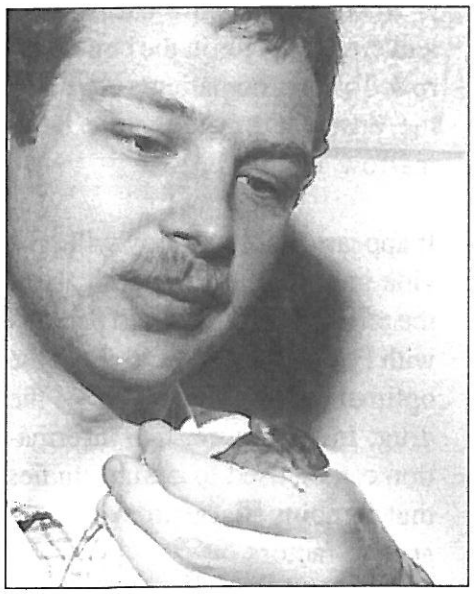
Let me back up here for a second and explain the term "immortalized". When skin cells are removed from a person's body with a skin biopsy and grown in culture, they normally have a limited life span. A fibroblast will divide up to 80 times and then become "senescent" or simply old. The aged cell just sits there and no longer divides. This phenomenon is undesirable when using cells for gene cloning. What is needed is a cell that keeps dividing indefinitely. Such cells are not naturally found in human skin and we therefore use genetic material from a cancer-causing virus (the SV40 virus) to make the fibroblasts grow better. These faster growing skin cells are called "transformed". Although they grow much more rapidly than regular skin fibroblasts, they too will stop growing after 80 cell divisions. It takes an additional event in the cell to overcome this aging block and to make the cell "immortalized", i.e. able to divide indefinitely.

Up until now only two immortalized Fanconi anemia cell lines have existed in the world. A major focus of the new Oregon Health Sciences University Fanconi Anemia Cell Repository is to produce additional cell lines for the research community. Since the group C gene has already been cloned, we are primarily interested in generating cells from the other complementation groups. The process of generating a new cell line of this sort is very labor-intensive. However, we have already created four new immortalized FA cell lines since we started this work. One of these, PD20i, is especially useful, since it does not belong to complementation group A or C, and can therefore help in the cloning of this other gene. Additional skin fibroblasts are currently being grown and immortalized. The current goal is to create at least two good cell lines for each complementation group. →

2. Creation of a mouse model of Fanconi anemia complementation group C

This year's family meeting contained a lot of hopeful information on new therapeutic approaches to Fanconi anemia: gene therapy, growth factors, antioxidant vitamins, etc. Because of the small numbers of patients in each trial it is sometimes difficult to determine whether a given therapy is effective in the disease or what its side effects might be. An FA animal model would provide a major advantage in therapeutic research and for our attempts to understand the biology of Fanconi anemia.

There is no naturally existing animal model for FA, but genetic engineering techniques now permit the creation of mouse models of a human genetic disease, if the gene for the disorder has been isolated. Manuel Buchwald's discovery of the FACC gene has laid the groundwork for such an approach. We have recently succeeded in destroying the normal FACC gene in mouse embryonic stem cells. Embryonic stem (ES) cells are a special kind of cell that can be grown and manipulated in tissue culture, but retain the potential to form an entire mouse. After the FACC gene on one chromosome of ES cells has been "knocked out," the cells are injected into already developing mouse embryos and become part of the tissues of the new animal. If the genetically engineered ES cells become part of the germ cells (sperm or ova) of the developing mouse, the FACC gene knock-out can then be passed on to the next generation of mice via normal breeding. Our experiment is currently at the stage where breeding is taking place to see whether the knock-out is being passed on to the next generation. Once this is achieved, a new stock of mice will have been generated that is lacking the function of the FACC gene and should develop the mouse version of Fanconi anemia. It will take several more months before we will know whether we have been successful. ••



Dr. Markus Grompe

Cyclosporin Therapy for FA: An Anecdotal Case Report

Roger Vega, MD, Associate Professor of Pediatrics, Emory University School of Medicine, Atlanta, Georgia

We reprint the following communication in its entirety. We emphasize our editorial disclaimer: we are not medical experts; other scientists may have differing views on the use of cyclosporine; and all advice always should be reviewed with your own treating physicians and medical consultants.

Question #1: What is cyclosporine?

Answer: Cyclosporine is an immunosuppressive agent derived from a fungus, Tolypocladium inflatum Gams. Cyclosporine has become the cornerstone in prolonging the survival of allogeneic transplants (solid organs and bone marrow). It has been demonstrated to suppress some humoral immunity and to a greater extent the cell mediated immunity responsible for allograft rejection.

The exact mechanism of action of cyclosporine is unknown. Experimental evidence suggests specific and reversible inhibition of the immunocompetent lymphocytes, especially the T-lymphocytes.

Question #2: What are the side effects of cyclosporine?

Answer: The most common side effects of cyclosporine are renal dysfunction, tremor, hirsutism

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(hairiness), hypertension (high blood pressure) and gum hyperplasia. Increases in the BUN and creatinine, blood tests that measure kidney function, are common side-effects of cyclosporine treatment. The high blood pressure responds to adequate doses of antihypertension drugs. We have had great results using nifedipine to control cyclosporine-associated high blood pressure.

There are less common side effects that are known by experienced doctors; these are reviewed in the PDR.

Question #3: Why do you think cyclosporine works in Fanconi aplastic anemia?

"Immunotherapy has no theoretical or factual basis", is the opinion of the experts. The fact of the matter is that we do not know why patients with Fanconi's develop aplastic anemia and we do not understand the pathophysiology of it; consequently I don't know what facts we are talking about. When you have a Fanconi's patient who has failed androgen therapy and doesn't have a donor for a bone marrow transplant, the fact is that he or she is going to die. In that case, I as a physician and the parents are willing to try anything that may help.

We (parents and I) used cyclosporine with Byron Joey Adamson because we did not have another alternative. I told them not to expect a response before 3 - 4 months, based on the experience with acquired Aplastic Anemia patients. At 4 1/2 months after starting cyclosporine/prednisone his platelets and hemoglobin started to rise and he has been doing fine without transfusions.

We don't know how long this response will last, how long to continue treatment, and whether we should taper the cyclosporine gradually or stop it altogether. We do know that patients who respond to androgens tolerate a decrease in the dose but do not tolerate total withdrawal. *[Ed. note: Dr. Nasrollah Shahidi has had success in removing some patients completely from androgen therapy, while maintaining adequate blood levels for prolonged periods of time.]* I suspect this may well be the case with cyclosporine/prednisone.

The answer to the question, how does it work? I do not know, but this may be a start to understand the pathophysiology of Fanconi aplastic anemia.

The questions I want to answer are:

1. Is there a T-cell immuno-mediated suppression?
2. How does cyclosporine affect (if at all) the characteristic chromosomal rearrangements in Fanconi anemia?
3. Is this indirect evidence that cyclosporine has another mechanism of action uknown to us

My recommendations in how to treat Fanconi aplastic anemia have not changed. First, treat with androgens and steroids while pursuing identification of a bone marrow donor. If the patient becomes refractory to androgens and there is no bone marrow donor, then try cyclosporine and prednisone. Give cyclosporine by mouth every 12 hours to obtain therapeutic trough levels. Give prednisone 2mg/kg/day x 28 days then taper to one mg/kg/dose, given every other day.

Throughout this treatment period, support the patient with blood and platelets as needed and wait patiently. ••

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The only toxic effect of filgrastim treatment has been mild fever in one patient. The fever resolved when the filgrastim dose was reduced. One of the important questions to be answered in this study is whether filgrastim causes preleukemic changes in the bone marrow. To date, no patients have had the onset of pre-leukemic bone marrow changes.

It appears that this study will provide important information about the effects of filgrastim in patients with Fanconi anemia and about the optimal dose and schedule of the drug. In the future, this information can be used to design studies that combine filgrastim with other growth factors. ••

Shahidi- continued from page 2

Famciclovir will be marketed by Smith-Kline-Beechum Pharmaceutical and will be sold under the trade name of Famvir. This drug, which is presumably equally efficacious because of its high absorption rate, may obviate the need for parenteral preparations. It should also be emphasized that the use of aspirin, and aspirin containing drugs should be avoided because of the strong association between their use in children with chicken pox and the subsequent development of Reye's syndrome. It may also be recalled that aspirin and aspirin-containing medications inhibit platelet aggregation. They should not be used in patients with a low platelet count and may cause bleeding. It is obvious that the best option would be vaccination against varicella virus. When approved by the FDA and commercially available, all Fanconi anemia patients with no immunity to varicella virus, as ascertained serologically, should be vaccinated.

NEXT ANNUAL
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Parvovirus B19

This viral agent is commonly associated with hematologic disorders and is the etiologic agent for the so-called fifth disease also known as "Slapped Cheek" syndrome, or erythema infectiosum, in children. Parvovirus can also be transmitted through transfusions. The parvovirus propagate in and kill actively dividing cells of red cell lineage. In patients with chronic red cell destruction who rely on increased production of red cells to maintain adequate hemoglobin concentration, such as patients with sickle cell anemia, thalassemia, hereditary spherocytosis, etc., parvovirus infection can result in severe anemia known as aplastic crisis. It can also cause prolonged anemia in immunosuppressed individuals. Consequently, because of limited erythroid pool, patients with Fanconi anemia may also experience a sudden drop in hemoglobin concentration following parvovirus infection. Parvovirus does not seem to significantly affect the number of platelets or white blood cells. Approximately 30-60% of the adult population in the United States is seropositive for parvovirus B19 which indicates prior infection and immunity to subsequent infections. Pregnant women who develop a parvovirus B19 infection may sometimes suffer fetal death, but the majority of fetuses are not adversely affected by the maternal infection. The diagnosis is usually confirmed serologically by detection of virus specific antibodies. Unfortunately, no specific treatment for the parvovirus B19 is available.

Hepatitis Virus

The occurrence of acquired aplastic anemia in association with hepatitis virus is well known. Although most cases have been associated with hepatitis non-A, non-B, other viruses such as hepatitis A and B have also been incriminated. The viral agents for non-A, non-B (including hepatitis C) resemble flaviviruses which are known to cause hematopoietic

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suppression. The exact mechanisms whereby hepatitis virus cause bone marrow damage are not known. The main route of transmission for hepatitis A is fecal-oral spread. Infection is commonly passed among household contact or contact within enclosed communities. Currently, there is no vaccination against hepatitis A but passive immunization (immunoglobulin) may be necessary to avoid a major outbreak. Hepatitis B, previously referred to as serum hepatitis, is one of the main causes of hepatitis, cirrhosis, and hepatocellular carcinoma. In children, it is primarily transmitted through blood transfusions. The latest CDC data indicate that the transfusion risk for hepatitis B is approximately one per 200,000 units of blood transfused. Prenatal transmission is of major importance in pediatrics. Transmission may occur from mothers who acquired their infection near the time of delivery or who are chronic carriers of hepatitis B virus. There is no effective therapy for hepatitis B virus infection. Therefore, prevention should be the main goal. Genetically engineered recombinant vaccine is available and should be considered for all patients with Fanconi anemia. Hepatitis C is also primarily transmitted through blood transfusions. It has been estimated that the risk for transmission through blood products is 1 per 3,300 units of transfused blood products, which is a marked improvement from one in ten transfusions some 10 years ago. Hepatitis C probably represents 95% or more of what was previously called transfusion associated non-A, non-B hepatitis. Unfortunately, to date there is no effective vaccination for hepatitis C.

Cytomegalovirus

Cytomegalovirus (CMV) is a member of the herpes virus family and is widely spread. An estimated 1-2% of all newborns in the United States are infected with CMV and about 90% of them are asymptomatic. Transmission of CMV occurs through contact with infected saliva and urine. The virus can also be transmitted by blood transfusions. Groups at risk for significant morbidity and mortality from transfusion related CMV infection are low birth weight infants, patients undergoing bone marrow or organ transplantation, and immuno-compromised patients. Older infants and children may develop a mild illness with pneumonitis, hepatosplenomegaly, and transient impaired liver function tests. In older children and adults, serious clinical features are uncommon. Fever, malaise, rash, hepatosplenomegaly, lymphadenopathy, myocarditis, low platelets, hemolytic anemia, and a condition similar to infectious mononucleosis have been described. Patients on immunosuppressive therapy are more likely to develop these clinical features. In patients undergoing bone marrow transplantation, the acquired CMV may result in significant thrombocytopenia, bone marrow graft failure, liver, lung, gastrointestinal, and retinal infection. Currently, the most effective treatment for symptomatic patients with acquired CMV is a derivative of acyclovir known as gancyclovir.

In the United States more than 50% of the adult population are CMV seropositive, which makes it more difficult to find CMV negative blood products. Because leukocytes are the chief, if not exclusive, agent for transmitting CMV in blood products, fresh frozen plasma and cryoprecipitate have not been implicated in CMV transmission. Screening blood products for CMV antibodies is the most common way to identify and supply blood products and will not transmit CMV disease. As will be discussed later, the current filters remove more than 99% of the white blood cells and therefore represent a potentially universally applicable method of effective white blood cell reduction. Current studies indicate that leukocyte depletion alone may prevent CMV infection.

Epstein-Barr Virus

Epstein-Barr Virus, which is of the herpes virus family, causes infectious mononucleosis. Numerous cases of aplastic anemia have been reported following infectious mononucleosis. The EBV target is primarily the B cells although the T cells may also be infected. The activation of the T cell may be responsible for hematopoietic depres-

sion. In addition to hematological involvement, EBV has been implicated in several other clinical disorders such as B cell lymphoma, head and neck cancer, and so called sex-linked lympho-proliferative syndrome which is an extreme example of abnormal immune response to EBV. Acyclovir may reduce the duration of the EBV excretion but its efficacy in improving the clinical illness is uncertain at the present time.

There are numerous other viruses that may affect the hematopoietic cells such as rubella, measles, mumps, and influenza A. Fortunately, effective immunizations against most of these viruses are available.

Bacterial Infections

Bacterial infections may also result in exacerbation of pancytopenia (low blood counts) in Fanconi anemia patients by diverse mechanisms. The white blood cells primarily responsible for defense against bacterial infection are polymorphonuclear neutrophils (PMN) and mononuclear macrophages which kill bacteria by producing superoxide anions, some of which may escape to surrounding tissues. Since Fanconi anemia patients are presumably unable to readily detoxify superoxide anions and other toxic oxygen species, overwhelming bacterial infections can potentially cause significant cellular damage. It is obvious that patients with deep vein catheter and severe neutropenia are more prone to overwhelming bacterial infections and consequently require greater clinical vigilance.

2. Blood Product Transfusions in Patients with Fanconi Anemia

Most patients with Fanconi anemia in relapse require red cell and/or platelet transfusions. The aim of red cell transfusions in patients with Fanconi anemia is to maintain a red cell volume adequate to prevent excessive cardiac output and to minimize the danger of shock from sudden acute bleeding.

The decision concerning need for blood transfusions should be based on the patient's clinical condition and not on the hemoglobin concentration alone. Rapid pulse, lethargy, irritability, weakness, and apathy are the most common alarming symptoms. In most patients with Fanconi anemia, these symptoms occur often with a hemoglobin concentration of 5-6 gms/100 ml. **The choice of the most compatible donor and the careful cross-match are imperative. Therefore, complete typing of the patient's blood should be accomplished before even the first transfusion is given.** The development of antibodies to minor blood group factors such as c, Kidd, Duffy should be avoided.

It is also imperative that a transplant candidate NOT receive blood products from any relative!

In transfusing patients with bone marrow failure such as in Fanconi anemia, it should be remembered that each unit of blood increases the body iron by approximately 200 milligrams, and if there is no significant blood loss, repeated blood transfusions result in loading of the reticuloendothelial system with iron. This in turn may delay or prevent response to treatment. The depressive effect of blood transfusions on the bone marrow is well known. It has been found that it is directly related to the quantity of red cells infused. Consequently, small transfusions are preferred. **In our experience, levels of hemoglobin of 8-9 gms do not depress erythropoiesis to a great extent and are desirable levels to be reached after transfusions.** In multiply transfused patients with Fanconi anemia, the serum ferritin and liver function tests should be monitored periodically. Serum ferritin is a good indicator of total body iron. Excessive iron deposits in the body overwhelm the storage limit of the reticuloendothelial system and cause toxic overflow of iron into the liver, pancreas, heart, gonads, and other organs. Iron is a prooxidant and it can serve as a catalyst of free radical reactions capable of damaging normal cellular components. Since patients with Fanconi anemia are presumably more prone to damage by free radicals, the indication for iron chelation with deferoxamin (Desferal) in these patients may not be the same as compared to patients with acquired aplastic

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The requirements for platelet transfusions should also not be based on the number of platelets alone. Clinical manifestations are very important in determining the need for platelet transfusion. Since eventually antibodies are formed against foreign platelets (alloimmunization), and these antibodies result in increased platelet destruction in the patients' circulation, a conservative approach to platelet transfusion is highly desirable. The risk of alloimmunization is much higher when multiple donors are used. As a result, single donor platelets or partially HLA-matched platelets are preferred.

It is imperative that all blood products (red cells and platelets) be filtered to remove the white blood cells. The white blood cells can cause a severe febrile reaction, can result in graft-versus-host disease and can transmit certain viruses such as cytomegalovirus. Several filters on the market are able to remove over 99% of the white blood cells from the blood products. We, at the University of Wisconsin Center for Health Sciences are currently using Pall filters (Pall Corporation, Glen Cove, NY), which can filter the blood products at the bedside. In addition to filtration, all blood products should be irradiated to prevent the risk of graft-versus-host disease. The bone marrow transplant candidates who are serologically negative for CMV, should not receive blood products from donors who are CMV positive. Currently, studies underway will evaluate whether filter leukodepletion could be used as the sole method of CMV prevention in bone marrow transplantation. So far, 500 bone marrow transplants have been entered in this study and the data are currently under analysis. If this study demonstrates that such patients do as well as counterparts who receive CMV seronegative blood products, both with respect to CMV disease and overall outcome, filter leuko-depletion may obviate the need for the search for CMV negative donors.

3. TREATMENT OF BONE MARROW FAILURE

Currently, there are several approaches to the treatment of bone marrow failure in patients with Fanconi anemia. Some treatments such as androgen therapy and bone marrow transplantation are well established. Other treatments such as hematopoietic growth factor and gene therapy are currently under investigation. Since the indications, methodology and the results of bone marrow transplantation have been amply described in previous newsletters and the Fanconi anemia handbook, in this article, I limit my discussion to the use of androgens in patients with Fanconi anemia.

Androgens were introduced in the treatment of patients with Fanconi anemia some 35 years ago. Originally, the parent compound, the male hormone testosterone, was used. Subsequently, testosterone was substituted by some of its derivatives known as anabolic hormones. This terminology is based on the fact that these hormones, while maintaining their tissue building properties (anabolic) are less virilizing as compared to testosterone itself. Unfortunately, none of the preparations is completely devoid of virilizing effects, particularly when given in large doses. Among various anabolic hormones, oxymethalone has been found to be most effective in patients with Fanconi anemia. In Europe, a similar compound known as primobolan has proven equally effective. In our experience, the injectable forms of anabolic hormones such as 19-nortestosterone derivatives (durabolin) are less efficacious and not desirable in patients who have significant thrombocytopenia. While the vast majority of patients with Fanconi anemia do respond to oxymethalone therapy, eventually (after several years) a large proportion become refractory. **As a result, the judicious use of androgens to obtain the maximum "mileage" is highly desirable.**

The primary effect of oxymethalone is the regeneration of erythropoiesis (red blood cells). As a result, non-anemic patients with Fanconi anemia who have a reduction in the white blood cells or platelets should not be treated with oxymethalone. Similarly, in patients who remain significantly thrombocytopenic despite normalization of the hemoglobin concentration after oxymethalone therapy should not receive higher doses of oxymethalone in the hope of achieving higher platelet counts.

The initial recommended dosage of oxymethalone is 2 mg/kg given once per day. Patients who do not respond to this dosage are not likely to respond to higher dosages. In successfully treated patients who achieve a hemoglobin concentration of 12-13 gms, the dosage of oxymethalone should be gradually reduced to obtain the minimum effective dose required to maintain a satisfactory hemoglobin concentration (such as 10-12 gms). A modification of the dosage of oxymethalone should be solely based on the hemoglobin concentration and not on the platelet or white blood cell count. While the vast majority of patients with Fanconi anemia depend on continuous oxymethalone therapy to maintain an adequate hematopoiesis, there are patients who have maintained satisfactory remission after discontinuation of oxymethalone. Factors determining the response to oxymethalone are not clear. Intercurrent infections and severe hemorrhagic manifestations requiring multiple transfusions hinder the effect of oxymethalone and thus are major impediments.

Sixth Annual FA Scientific Symposium
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Skamania Lodge, WA

It should be pointed out that oral androgens such as oxymethalone are toxic to the liver and may cause obstructive jaundice and, on rare occasions after many years of therapy, blood filled spaces in the liver (hepatis peliosis) and hepatic adenoma and hepatocellular carcinoma. These side effects are more likely to occur in patients who have been on large doses of androgens over many years. Consequently, periodic monitoring (i.e. every three months) of blood chemistry and parenchymal structure of the liver by ultrasound is very important. Most of these complications are reversible by temporary discontinuation or reduction in the dosage of the oxymethalone.

Another undesirable side effect of oxymethalone is some degree of virilization which varies from patient to patient. Usually smaller dosages such as 0.5 to 1 mg/kg are less likely to cause significant masculinization. In contrast to testosterone, oxymethalone and most other anabolic hormones do **not** cause premature closure of epiphysis (growth plates of the bone) which results in growth retardation. The bone age in patients with Fanconi anemia is often delayed. Oxymethalone may advance bone maturation in these patients. To delay excessive advancement of the bone age by oxymethalone, we usually advise the addition of small doses of corticosteroids such as 5 mg of prednisone every day to every other day. Prednisone, which is a catabolic hormone, delays the bone maturation and thus offsets the effect of oxymethalone.

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