THE FA FAMILY NEWSLETTER

Newsletter Number 3

September 1987

c/o Frohnmayer
2875 Baker Blvd
Eugene, OR. 97403
(503) 686-0434

GREETINGS:

Forgive the delay in this third communication for Fanconi Anemia victims, their families, medical experts, and concerned friends. We have heard from nineteen new families since our last newsletter. Their names are listed inside. All have expressed the desire to share hopes, fears and information with others.

In this newsletter, we include the following:

- A description of fundraising successes. We can help make a difference!

- A long and extremely important communication from Dr. Auerbach. This report, of necessity, is highly technical in places. You should share it with your treating physicians. It contains some of the latest research information available anywhere.

- Fanconi's Anemia "Fact Sheet". Developed by the Aplastic Anemia Foundation of America, this fact sheet was published in July, 1987, and answers many commonly asked questions.

- Tips, personal items, new developments and shared thoughts. This is a major purpose of this newsletter.

- A helpful article by nutritionist, Carol Ceresa, on how foods we eat affect our immune system.

FUNDRAISER SUCCESSES FUEL RESEARCH EFFORTS ON FANCONI'S ANEMIA

Three major fundraisers conducted during the past year netted almost $70,000 for vital FA research:

Brad and LeaAnn Curry from Indiana organized a dinner and fashion show in October, 1986. This highly successful event brought in over $10,000 for Dr. Arleen Auerbach's research.

The Frohnmayers wrote 1000 potential contributors, and launched a public appeal in December, 1986. Interested friends were encouraged to make a charitable contribution while the tax climate was favorable.

Nearly $50,000 in donations came in response to this letter. Several families in our support group sent a similar letter to their friends, thus greatly contributing to the success of this effort.

Tony and Theresa Montella deserve tremendous credit for organizing a second fundraiser to generate research funds. (We reported on their first effort in the last newsletter). A fashion show in April, 1987 sponsored by the South Shore Rotary Club of Staten Island raised $10,000.

Special thanks and congratulations to all who assisted in these continuing efforts. Dr. Arleen Auerbach's research at Rockefeller University has benefitted greatly. She reports that the additional personnel who were retained by these funds have significantly speeded her work. We know time is of the essence for us all.

The success of these fundraising efforts shows that we can all help make a difference in the fight against this rare and lethal disease. Please continue on this front!

THE ROCKEFELLER UNIVERSITY
1230 YORK AVENUE • NEW YORK, NEW YORK 10021-6399

August 20, 1987

Dear Parents:

I would like to take this opportunity to communicate to you some recent developments in Fanconi anemia research from around the world. In October, 1986, a meeting devoted to clinical and laboratory research on Fanconi anemia (FA) was held in Berlin, West Germany, in conjunction with the International Congress of Human Genetics. The scientific papers presented at this meeting are to be published soon by Springer-Verlag, Heidelberg, as a book entitled "Clinical and Experimental Aspects of Fanconi Anemia", edited by Dr. T. Schroeder and Dr. G. Obe of West Germany, and myself. The following is a detailed summary of some of the reports related to the clinical aspects of FA to be presented in this book, followed by a brief summary of some of the more basic laboratory findings presented. I have decided to write a fairly technical report at this time, in order to make this information available to those of you who have been requesting it. For the many patients who find this report too technical, I will be happy to answer your questions at a future date.

The great diversity of physical findings in FA patients and the occurrence of other disorders, both genetic and non-genetic, which are characterized by many of the clinical features seen in FA, make clinical diagnosis of FA difficult. We have demonstrated that sensitivity to the chromosome breaking effect of the DNA crosslinking agent DEB can be used as a unique cellular marker for prenatal and postnatal diagnosis of FA. A total of 222 patients have had DEB studies in our laboratory. The DEB-induced chromosomal breakage frequency in blood cells from the 98 patients diagnosed as affected with FA ranged from 1.06-23.9 mean breaks per cell. The breakage frequency for the 124 patients with some clinical features resembling FA, but diagnosed as non-affected, ranged from 0-0.36 mean breaks per cell, while the frequency in normal control individuals ranged from 0-0.10 mean breaks per cell. There was thus no overlap in the range for the FA group compared with the non-FA and control groups. We have never observed even a single DEB-treated cell with multiple chromatid exchanges in studies of non-FA patients. Thus the induction of this type of breakage by DEB seems to be unique to FA cells, and its occurrence in even a few cells is sufficient to make the diagnosis. While most FA patients exhibited typical chromosomal breaks and exchanges in most or all cells analyzed after DEB exposure, some patients appeared to have two populations of cells. In these individuals the majority of DEB-treated cells appeared to have no chromosomal breakage, while the remainder of cells in each case exhibited the high number of breaks and exchanges typical of FA patients. The significance of this phenomenon is unknown, but the finding must be considered in interpreting results of tests for FA.

FA. The first five patients were treated with a high dose of cyclophosphamide before the sensitivity of FA patients to this DNA crosslinking agent were understood. Only one of these patients became a long-term survivor; she is alive and doing well eight years after receiving a bone marrow transplant. All 16 patients receiving a modified pre-transplant regimen had previously been treated with androgens and steroids for aplastic anemia, and all but one had been transfused. In three of the patients physical abnormalities were limited to a few hyperpigmented spots. The mean age at diagnosis was 6.6 years and the mean age at transplantation was 11.5 years. Fifteen patients had a prompt take of the donor marrow; only one patient failed to engraft and died of infection. Three others died of complications such as graft-vs-host disease. This latter problem was observed in 11 of the 16 cases, but generally resolved. All the long-term survivors are back at school or at work with no long-term ill effects of the treatment. Thus FA seems to be a potentially curable disease if a suitable bone marrow donor is available. Gluckman states that the literature reports a total of 21 patients with FA treated with high dose cyclophosphamide prior to bone marrow transplantation. 38% of these became long term survivors with 71% having acute graft-vs-host disease. It is thus important to diagnose the disease correctly before transplantation because the pre-transplant conditioning regimen has to be altered in FA cases, and it is also important to test the siblings who are potential marrow donors for crosslink sensitivity, as they may actually have FA without any obvious clinical findings. Dr. Ebell, from Ulm, West Germany, reports that 7 out of 8 FA patients transplanted from HLA-identical siblings were surviving 4 to 26 months post transplant. The pre-transplant conditioning regimen used was similar to that of Dr. Gluckman. The treatment of patients with conventional therapy for aplastic anemia, including transfusions, did not have a detrimental effect on subsequent bone marrow transplantation. Depletion of the bone marrow prior to transplantation, to remove cells related to graft-vs-host disease, increased the rate of graft failure. Ebell reported trying HLA-mismatched transplants in two patients. One, from a cousin, mismatched for one antigen, was successful. The other, mismatched for one haplotype, failed to engraft. A report of a similar attempt at using marrow donors other than HLA-identical siblings, from Dr. Gordon-Smith's group at Hammersmith Hospital in London, showed that 1 of 4 unrelated, HLA-identical and 2 of 5 related, HLA-mismatched bone marrow transplants were successful. Ebell also reviewed his experience with conventional therapy in FA patients. About half of the patients responded to androgens or to steroids, similar to the results of other groups reported in the literature. On the other hand, he reports that in 9 patients who did not respond to either steroids or androgens, 6 were still alive, the longest for 8 years after diagnosis.

I will now briefly highlight some of the experimental results presented at the meeting. This summarizes extensive reports of laboratory data, which were interesting, but indicated that we still have little understanding of the nature of the basic genetic defect that causes FA. Results of studies of gene complementation, based on correction of the DNA crosslinking sensitivity defect in FA cells, was presented by Dr. Buchwald of Toronto, Dr. Moustacchi of Paris, Dr. Sperling of Berlin, and myself. There appears to be at least two

We are grateful to the Aplastic Anemia Foundation of America for the following "Fact Sheet" on Fanconi's Anemia. Dr. Lyle Sensenbrenner, formerly of Johns Hopkins University, and now Associate Director for Hematology at Wayne State School of Medicine in Detroit was a principal author.

Aplastic Anemia Foundation of America

P.O. Box 22689
Baltimore, Maryland
21203

301 955-2803

FANCONI'S ANEMIA

1. What is it?

Fanconi's anemia is an inherited disorder which is usually manifested by progressive severe bone marrow failure. (Severe bone marrow failure - also known as aplastic anemia - is a disease which may be caused by events such as exposure to toxins or radiation in non-fanconi's patients). Bone marrow failure in Fanconi's anemia usually develops between the ages of 3 and 12. In addition, a Fanconi's anemia patient usually, but not always, has other body defects detectable at the time of birth. These may include any of the following:

a. bony defects, usually of the hands, wrists or arms, often manifested as missing bones (such as thumb or bone in arm), and occasionally the addition of fingers;

b. eye muscle imbalances, with resulting strabismus (cross-eyes);

c. short height for age of the patients;

d. microcephaly, or small head size;

e. light brown spots of varying size on the skin;

f. abnormal size or shaped kidneys.

2. What causes Fanconi's Anemia?

Fanconi's anemia is an inherited disorder of the recessive type. That is, a person can carry the tendency for Fanconi's anemia in his genes, and half of his children can inherit that tendency from that parent. Both parents must carry the tendency and both must transmit the tendency to their child (or her) to manifest the disorder.

3. What is this tendency that parents give to their children?

We are not sure of the exact nature of what is transmitted and how it can cause Fanconi's anemia, but we do know that the chromosomes (the thread-like structures in a cell's nucleus that carry the genetic information or genes) in cells of people with Fanconi's anemia break very easily when exposed to certain chemicals and cannot repair the break easily. Why the chromosomes are so fragile and easily broken is unknown.

11. If there is no match among the patient's brothers and sisters, is it feasible to look outside the family since the chances of finding a match are so low?

At the present time, a computerized listing of the bone marrow type of thousands of volunteer bone marrow donors is being developed, and should be ready in 1988. This registry will be used to search for matched donors. This will make the use of a non-related bone marrow donors readily feasible. Small local registries already exist around the country.

12. Will a bone marrow transplant cure the other manifestations of Fanconi's anemia?

At the present time we have no good evidence to believe that a successful bone marrow transplant will cure anything other than the bone marrow failure of the affected patients.

13. Where can I learn more about Fanconi's anemia?

The Aplastic Anemia Foundation of America publishes information on aplastic anemia, and has local affiliate chapters across the United States. Contact AAFA for more information:

P.O. Box 22689
Baltimore, MD 21203
301/955-2803

The Fanconi's Family Newsletter is a good way to contact other families:

FA Family Newsletter
c/o Frohnmayer
2875 Baker Blvd.
Eugene, OR 97403

Dr. Auerbach has forwarded a moving letter from a family in Germany. The Dietrichs would greatly appreciate hearing from other FA families.

We write this letter without knowing who will receive it. We will ask Dr. Schroeder-Kurth to send it to parents we do not know yet, but are closely connected by the heavy burden to have one child or more who suffer already from Fanconi anemia.

We have three children between two and seven years. Two and a half years ago began the suffering of our oldest daughter from aplastic anemia. Presently she needs every four weeks transfusions of red blood cells. Her hemoglobin, 2.5 before the transfusion, climbs to 7.5 afterwards. The thrombocytes (platelets) are mostly only about 10,000, even if sometimes a spontaneous increase to 130,000 occurs.

Since five weeks we know, that our youngest daughter has developed a thrombocytopenia of about 60,000. The other blood tests are still normal. This is now the second child in our family showing a severe blood disorder.

We have been advised to contact Dr. Schroeder-Kurth in Heidelberg for clarification of the diagnosis "Fanconi anemia" and undergo blood tests in her Institute. The result confirmed our suspicion: with highest probability both daughters suffer from FA, since both have also some characteristic anomalies for FA, e.g. on the thumbs.

So far we could not talk to anyone with a similar fate, since this illness is relatively rare. Despite all understanding and support from friends and other members of our family we feel our isolation and would like to contact others who know our fears and sorrows from own experience. We will ask Mrs. Schroeder-Kurth to pass this letter on to parents she knows, who have a similar fate like us.

May we send you our greetings - we would be pleased if you contact us.

Cornelia & Ralf DIETRICH
Boeckenweg 4
475 UNNA - SIDDINGHAUSEN
FR - GERMANY
Tel: Area: 02308 - 2324

Carol Ceresa is the Chief Clinical Nutritionist for Children's Hospital of San Francisco. Her two sisters, Gail and Paula, both in their 30ies, are affected with Fanconi Anemia (see last issue). Carol has generously taken the time to discuss nutritional issues of importance to children with immune system deficiencies. We are very grateful for her valuable contribution to our newsletter.

NUTRITION: ITS SPECIAL IMPORTANCE TO YOU

Individuals with Fanconi's Anemia show increased incidence of infection. Although nutritional deficiencies are neither the cause nor the cure for the increased susceptibility, daily healthful eating can help the body defend itself against disease-producing organisms. Good nutrition may be even more important after an infection has occurred.

A. WHAT NUTRITION FACTORS AFFECT IMMUNE RESPONSE?

1. Protein-Energy Malnutrition (PEM)

Evidence suggests that immunity is compromised in healthy individuals who are subjected to prolonged mild or moderate deficits of calories, protein and necessary nutrients. For individuals with FA who already have poor immune responses and increased susceptibility to infection, the same prolonged periods of PEM - however mild- are likely to have exaggerated effects on immunocompetence.

2. Protein and Amino Acids

Both the quantity and type of protein affect the body's cell-mediated immune response. Vegetable protein diets have coincided with an increased incidence of bronchitis and other infections of the upper respiratory tract. And although the association between single amino acids (the building blocks of protein) and immune response in humans in unknown, studies in experimental animals show that isolated deficiencies or excesses of a single amino acid or imbalances among several amino acids result in changes in immunity.

3. Lipids (blood fats)

While essential fatty acids are critical for immune response, excess polyunsaturated fatty acids will actually suppress immunity. Furthermore, high intakes of fat, and in particular polyunsaturated fatty acids, encourages tumor growth. Breast and colon cancer, for example, have been partly explained by polyunsaturated fatty acids' suppression of the body's immune defense which might otherwise protect against cancer. Also, high blood cholesterol levels in experimental animals have been associated with increased susceptibility to infections.

4. Vitamins

Some vitamins exert unique effects on the immune system. Of the fat-soluble vitamins, vitamins A and E have been shown to influence the immune response. The increased incidence of infection due to Vitamin A deficiency may be due to epithelial changes and/or decreased cell-mediated and humoral immunity. In experimental animals, a deficiency of Vitamin E decreased

3. Fats

Avoid excess fats, especially polyunsaturated fatty acids (vegetable oils, margarines). Eat less fried foods and visible fats (salad dressing, sandwich spread).

4. Vitamins and Minerals

The Recommended Daily Allowances for most vitamins and minerals can be met while eating adequate calories - if your diet contains a good variety of foods. If your appetite is poor (causing you to skip meals or entire food groups) or if you eat the same few foods day in and day out, you need either to improve your diet or take a one-a-day multiple vitamin-mineral supplement that ensures 100% of the RDA's. Be sure to check with your physician or dietitian so that you are not taking any excess amounts of vitamins - as they could be doing you more harm than good.

Eating well can be pleasurable - and give you that extra advantage of increased ability to defend against infection. Eating well is something you can do each and every day to feel your best.

Please note change of address:

Connolly, Mrs. Kathleen
1 Leonard Court
Dorchester, Mass 02122
617-825-5845

Halteh, Ousama & Souha
799 Banbury Lane
Millbrae, Calif.
94030
415-589-5275

Sikora, Cindy
1264 N. Kellogg
Howell, Mich. 48843
517-546-4472