



# FA family newsletter

A Semi-Annual Newsletter On Fanconi Anemia For Affected Families, Caring Physicians & Research Scientists.

NEWSLETTER #12

SUMMER, 1992

## Fanconi Anemia Gene Discovered

Canadian scientists recently announced a major breakthrough in FA genetic research. Manuel Buchwald, Ph.D., Craig Strathdee, Ph.D. and other collaborators at the Hospital for Sick Children, Toronto, Canada published news of their discovery of a gene responsible for Fanconi anemia in the April 30, 1992 issue of the renowned scientific journal, *Nature*.\*

Dr. Buchwald and his colleagues used an FA feature characteristic — the sensitivity of FA cells to toxic agents — in a novel method to help recover the cDNA for one FA complementation group (FA[C]). This new method shows promise for recovering the other FA genes more quickly, as well as for speeding gene searches in a variety of disorders.

In a subsequent article (*Nature Genetics*, vol. 1, p. 194, June, 1992), Dr. Buchwald and fellow researchers reported the existence of mutations in at least four genes that can cause FA. They also identified chromosome 9q22.3 as the precise location for the FA (C) gene. This research may help explain prior observations about the wide variability ("heterogeneity") of Fanconi anemia in its physical and clinical severity.

In addition to speeding the process of isolating other FA genes, Buchwald's discovery is significant for at least five separate reasons:

First, discovery of the molecular basis for FA advances medical understanding by decades. Until now, scientists have been forced to study only the outward clinical, biochemical

and blood system manifestations of the disease. Now researchers can observe underlying causes, not merely physical effects.

Second, using copies of the defective gene, scientists may be able to reproduce the protein made by the gene in order to compare the abnormal FA gene product to the product of the normal gene. These studies are already underway in Dr. Buchwald's laboratory and in several others. Scientists now can investigate how the protein works — or fails properly to work — in the bone marrow and in other body organs. In addition, these protein studies are likely to produce new insights into possible drug therapies for Fanconi anemia.

Third, the gene discovery for FA (C) will allow diagnosis with certainty of affected FA patients and carriers for those victimized by this particular FA gene. Other FA families soon also may have this assistance.

A fourth major benefit of this discovery lies in bringing medical science closer to the goal of effective gene therapy. In this approach, a healthy gene might be introduced into cells to replace the defective FA gene. Potential obstacles include inserting the healthy gene into a sufficient number of bone marrow stem cells, achieving adequate and long-term production of the essential protein, and correcting deficient cells in other organs of the body. But some researchers believe this approach is feasible within the lifetime of children who now have FA.

Finally, this gene discovery vastly enlarges the scientific community interested in FA research. Consistent with observations by other distinguished scientists, Buchwald told reporters that the far-reaching result of this Fanconi anemia discovery may be insights into new drugs to treat or to prevent cancer in humans. FA patients are extremely susceptible to leukemia and other cancers. Understanding how the FA genes function will illuminate medical understanding of how cancers develop in normal cells, Buchwald said.

\* See correction of CDNA Sequence in the July 30, 1992 edition of *Nature* (pg. 434).

### Highlights

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# Second Family Meeting Unifies Group

Sixty-five FA families numbering more than two hundred thirty people gathered in Orlando, Florida on June 27-28, 1992 for our second annual FA family meeting. This represents a doubling of attendance in just one year! Four nations, two continents and twenty-eight states were represented.



Richard Harris, MD, describes Cincinnati FA Transplant experience.

Parents, relatives and friends heard scientific presentations ranging from medical overviews, genetic research and marrow transplantation to fundraising ideas, family counsellor presentations and reports of ex-

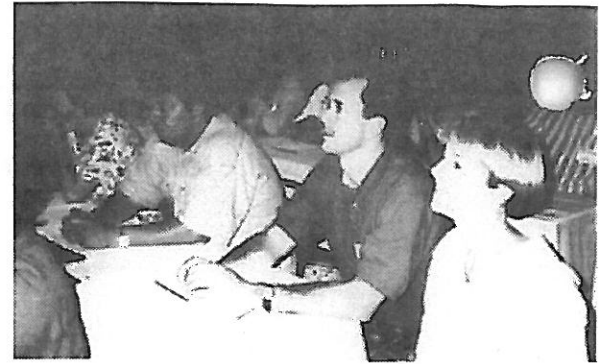
perimental drug treatment results. (See enclosed Family Meeting Supplement, Lay Summaries of Presentations.) Large numbers of FA children and their siblings quickly bonded and shared a wide range of activities. Following this meeting, several parents wrote or called to say how much this contact had helped their children.

A new addition to this conference resulted directly from last year's suggestions. Parents had opportunities to share thoughts and emotions in one of several small groups dealing with coping, grief and loss, and adolescent issues. These smaller meetings received extremely positive evaluations and will be continued next year. Those who attended began or renewed friendships with others who share the burden of this affliction. We were grateful for those who joined us, and share fond memories of others who could not attend this year.

Our special thanks, once again, to the Oregon-based Meyer Memorial Trust. The three-year family support grant from this charity defrayed substantial costs and directly helped many families to attend.

Before and after the symposium, families explored the wonders of Disney World and Sea World. With our deepest appreciation

we salute the compassionate help policies of our special hosts for family entertainment. They gave "in kind" contributions through free passes for family symposium attendees, approximating \$32,000 from Disney World and \$8,000 from Sea World. In your own way, please be an ambassador of gratitude for the generosity of these kind hosts.



Pat & Bill Danks (l.) and Ed & Janice Duffy (r.) listen to medical presenter.



Blanche Alter, MD, explains medical data to attentive group.



## Buchwald Receives Award of Merit

In June, 1992, the Board of Directors of the Fanconi Anemia Research Fund, Inc. voted unanimously to honor the work of Manuel Buchwald, Ph.D. with its first Award of Merit.

At the family meeting dinner in Orlando, Dr. Buchwald received an inscribed medallion and award plaque amidst the strains of "Oh Canada!". Dozens of FA children and their siblings waved red and white balloons and Canadian flags.

Dr. Buchwald recently wrote to express his appreciation. We quote his letter in part:

*"Receiving such an award is a humbling experience. I feel that I have been amply rewarded for the opportunity to work in my field and to make scientific contributions that are recognized by my peers. As well, the FA Research Fund has been an important contributor to my success; for you to give me the award is almost too much. Nonetheless, I take your award in the spirit with which it is given: we have been successful so far, but there is much that is still to be done.*

*Please give my thanks to all your members. I was privileged to share the weekend with many of them and to hear their stories. I really appreciated the opportunity to get to know them and to share with them my most recent work. I look forward to much more joint progress."*

Here's Some of What You Said - From the Family Meeting Evaluations

(We read them all!)

More psychological support topics for parents. We need it!"

"Thanks for a very enlightening and cathartic conference. I can only imagine the work that it entailed."

"It's just nice to know that there are other people in this world who are going through the same problems, having the same fears and wanting answers to the same questions as I am."

"The journey together and sharing is very supportive. I would recommend a second small group discussion."

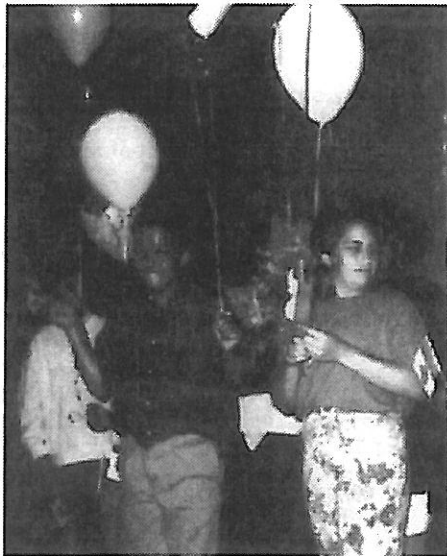
"I would like to see a handout with terms and definitions before the presentations."

"Thank you for stressing the importance of continuing to raise funds for necessary research."

"I would like to have a small group discussion for teenage girls only."

"Thanks for being there. We'd be lost without you."

"It's great being able to meet families and their FA children. You realize you're not alone - There's a camaraderie even tho they're strangers at first."



"This is a wonderful organization that has given hope to families and a great support that helps families get through some rough times."

"The benefits of the group are growing for me continuously."

"You have done a wonderful job."

"I would like longer breaks, more time in small group discussion on a personal level. I want to be touched and to care for others - not merely to be thrown a ton of facts."

"Our annual attendance is becoming larger. We must be careful not to lose touch with individual needs. As difficult as it may sound, we may need to consider more grouping by regions, medical status or some other common denominator. I am afraid that some will become lost in the masses."

"A second discussion group would have allowed more people and a variety of people to express themselves."

"Great information and good fellowship."

"The support of the researchers and their interest is amazing."

"I like knowing that another FA family is only a phone call away! Our FA support group is probably the best in the world because it is a very personal, one-on-one group. So many groups (cancer society, MDA) have become so large that information about a certain medical problem is available, but the personal touch is gone. Thanks to all of you."

"What is most helpful to me is witnessing the courage, strength and conviction of others who are enduring FA."

"FA research has given my family hope."

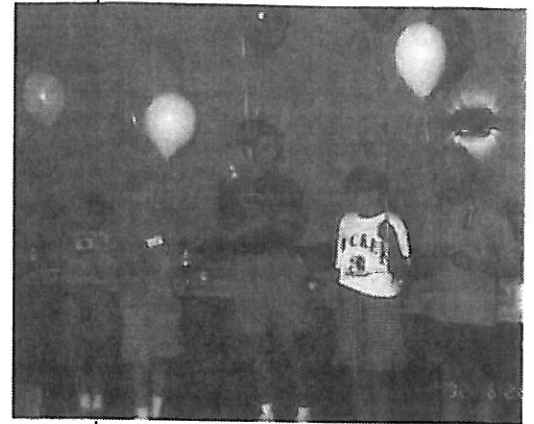
"Perhaps names and ages of children could be listed in the newsletters to help families in contacting one another for sharing information."

"This organization and what it does is actually saving lives and helping families to handle the maladies. Without it, not enough funding or support would be available to treat, research and make progress toward curing this dreadful, family-devastating disease."

"The support and knowledge we have received has enabled us to seek out the best care for our daughter. When our child was diagnosed she had no hematological problems. Now, four years later she is showing signs of low blood counts. We feel we are ready to deal with this. We have done everything we can for her, and are totally up to date on her illness. Without the FA Research Symposiums and Newsletter, we feel we would have been in the dark."

"More people now have a sense of involvement. The sharing of the burden of maintaining a support group can only continue with face-to-face group meetings."

"I think it's a great group of people."



"FUNDRAISERS!! (Need I say more?)"

"This is a wonderful organization, with people that have a human compassion beyond belief, and yet are also tough enough to do what needs to be done."

"This was my first time to an FA meeting of any kind. I found it to be extremely informative and helpful. Don't change the dress code. (Editors' note: There is no dress code, other than wearing whatever is comfortable to you! The code therefore will not be changed.)"

"The format of the conference helps to mitigate the isolation our family has felt."

"We love you all as a family, and please keep up the great work."

"I would very much like to have outlines distributed from each speaker which we can follow and add notes to."

**Editors' note:** Whenever possible, we will try to implement your good suggestions. We share the warm feelings so many of you expressed, and truly treasure your words of appreciation.

## National Institutes of Health Helps Plan Fanconi Anemia Scientific Conference

Fanconi anemia research will receive major visibility and stimulation through a workshop now scheduled for November 23-24, 1992 in Bethesda, Maryland. The National Heart, Lung and Blood Institute of the National Institutes of Health is co-sponsoring this workshop on "Molecular, Cellular and Clinical Aspects of FA" with the Fanconi Anemia Research Fund, Inc.

Many of the world's leading FA scientists are scheduled as organizers, presenters or attendees. Five sessions will cover major aspects of the following topics: (1) Cell/DNA Damage and Repair; (2) Molecular Genetics of Fanconi Anemia; (3) Hematopoietic Regulation; (4) Hematopoiesis/Oncogenesis; and (5) Treatment Today and Innovations for the Future.

Recent progress in gene discovery makes this prestigious workshop especially timely. Your editors will attend and report highlights in the next edition of the *FA Family Newsletter*.

## Tiger Foundation Support Continues

The New York-based Tiger Foundation has extended its magnificently generous support of our Gene Identification Project.

In early Spring, 1992, Tiger officials awarded a \$50,000 grant to our Project, and promised \$80,000 additionally in a matching "challenge grant". We have already raised the challenge amount as this Newsletter goes to press!

We deeply appreciate the continuing outreach of Tiger Foundation (see Newsletter #10, page 5). We extend special thanks to **Gerald, Ron and Fredi Norris** for helping secure these indispensable grants.

Tiger officials were specially impressed by the rapid progress of our funded research, and by the broad base of donors we have attracted. Your efforts have been noticed and have made a difference! Please redouble them.

## Fundraising for Research: Family Ideas

Seven FA parents, a grandmother, and an expert on bone marrow transplantation led a stimulating and provocative discussion on fundraising at the FA Family Symposium. Our profound thanks to **Dr. Vicki Athens, Linda Scullin, Jeanne Atkinson, Jackie and Bill Lucarell, Pat and Bill Danks, Marion Rosenblatt** and **Dr. Richard Harris** for their inspirational, enlightening and entertaining presentations.

Families presented very different methods for raising funds, from letter writing campaigns to special events, to soliciting from large charitable foundations. What "works" for one family may not be comfortable for another, but every family can make an important contribution in this crucial area.

Several presenters described their fund-raising letters, which should be personal and focussed on the plight faced by one's own family. Presenters stressed the need to develop a comprehensive list of potential contributors, including relatives, friends, neighbors, church or synagogue members, and members of any group of which your family is a part (business associates, social or service clubs, schools, recreational facility, etc.)

It is common practice to re-contact potential donors on an annual basis. Donors want to know what progress has come from past contributions. They expect to be asked to contribute again.

For those wanting to learn how to get an entire community to rally behind a cause and assume much of the responsibility for initiating fund-raising events, the Lucarells are the experts. Pat and Bill Danks entertained us thoroughly with their hilarious descriptions of their "Beef & Beer" parties. And Marion Rosenblatt, a highly successful fundraiser for a private college, stressed the need for developing close one-on-one contacts with individuals or foundations that have the capacity to give large amounts of money. (Our Fund has a directory listing every major foundation in each state; we would be very pleased to share the list of your state's or local area's foundations with you).

Jackie Lucarell's plea hit a responsive chord with many of us as she repeatedly wondered who would take responsibility for pushing research forward if not the members of our group: "If not us, then who?"

## Families Generate Badly Needed Funds

Between January 1, 1992 and June 16, 1992, FA families and their friends raised a total of **\$97,692.82**. The amounts reported below may not appear accurate to many of you. Several families had begun to raise funds before our cut-off date of June 16. All funds deposited in our account after that date will appear in the next six month reporting period. These figures understate the efforts of many families.

**Dave and Lynn Frohnmayer** got an earlier start than most of you, writing their fundraising appeal immediately after the announcement of Dr. Buchwald's gene discovery. By June 16, their efforts had raised \$62,590. **Phyllis Cafaro** raised an impressive \$7,130 during this reporting period. **Bill and Pat Danks** generated \$5,758, **Ron and Fredi Norris** \$4,150; **Leonard and Jan Riley** \$2,550; **Delores Ceresa, Paula Guidara and Carol Matsumoto** \$1,795; **Pamela Baxter** \$1,541; **Deane Marchbein and Stuart Cohen** \$1,478; **Dr. Sidney Farkas** and his wife, **Ethel** \$1,285; **Jennifer and Robert Kiesel** \$1225 and **Susan and Mark Trager** \$1330.

**Diane and Michael Bradley** generated \$1,000 for our cause; **Craig and Stephanie Melancon**, \$1,000; **Ed and Barb Brookover**, \$725; **Vicki and Andrew Athens**, \$680; **Greg and Diane Hayes**, \$600; **Bill and Jackie Lucarell**, \$500; **Janice and Ed Duffy**, \$400; **Bonnie and Dan Rosen**, \$250; **Linda and Robert Scullin**, \$240; **Gayle Licari**, \$320; **Irene and John Kalman**, \$200; **Joe and Lynn Linsenman**, \$200; **Lorraine and Kevin O'Connor**, \$125 and **Lynn Lecuyer** \$165. An additional ten families made individual contributions to our Fund.

We are grateful beyond belief to all of you who were willing to give up a measure of privacy and pride for this crucial cause. It is sometimes difficult to ask friends for help, yet many welcome the opportunity to be of help to us. Everyone in this group has a different capacity to raise funds. Please know that we deeply appreciate every single effort that is made by each and every one of you.

With appreciation yet infinite sadness we report that contributions were received in loving memory of **Avi Weiner, Scott Bradley, Haley Clendingen, Gail and Myra Ceresa, Katie Frohnmayer** and **Cindy Lawrence**. These tragic losses strengthen our resolve to conquer this ugly illness.

## New Videos

### Fundraising Video Available

Families at our Orlando meeting pre-viewed an early version of an FA fundraising video. Based on comments and suggestions, a final VHS version now is in preparation for use by FA families, friends and fundraising allies.

The video runs approximately 10 minutes. It helps explain FA in lay terms, features FA families, leading researchers, Nobel prize winner E. Donnall Thomas, M.D., and concludes with a strong appeal for research funds. The video is suitable for showing to civic groups, news media, charitable foundations, corporate donors and others whose interest in FA must be increased. It will simplify presentation of basic material, and it provides an ideal introduction for your personalized appeal.

Please call **Linda Solin** or **Lynn Frohnmayer** at the FA Research Fund office, (503-687-4658) if you need a copy of the film for your fundraising efforts.

### Marrow Transplant Video Available

**Terry** and **Tino Huertaz'** son, **Emilio**, underwent a successful bone marrow transplant at Cincinnati Children's Hospital on May 22, 1991. The family prepared a helpful VHS videotape of the transplant process, and is willing to make copies available to other FA families. Contact the Huertaz family at: 3011 Sol De Vida NW, Albuquerque, NM, 87120; telephone: (505) 831-2194.

#### Editors' Note and Disclaimer

Statements and opinions expressed in this Newsletter are those of the authors and not necessarily views of the editors or sponsoring Fund. Information provided in this Newsletter about medications, treatments or products should not be construed as medical instruction or scientific endorsement. Always consult your physician before taking any action based on this information.

## New Brochure Issued

We have just re-written and updated our fund-raising brochure. The brochure can be effective when accompanied by a personal letter from you, explaining the impact of this illness on your family. The brochure will not be effective if sent alone, or left on a super-market counter. People give because they want to help your child. They want to help you! The pamphlet contains valuable information about our organization and our effort, but it needs your personal appeal.

We cannot overstate the importance of expanding our fundraising now that real progress is at hand. Please contact the FA Research Fund office with the number of brochures you will need. We would also be happy to send you sample fundraising letters and assist your efforts in every possible way.

## Recent Publications

Readers who desire updated technical information may wish to consult the following articles (partial listing only):

- \* B. Alter, "Fanconi's Anemia: Current Concepts," American Journal of Pediatric Hematology/Oncology, Vol. 14, No. 2, pp 170-176 (1992)
- \* C. Strathdee & M. Buchwald, "Molecular and Cellular Biology of Fanconi Anemia," American Journal of Pediatric Hematology/Oncology, Vol. 14, No. 2, pp 177-185 (1992)
- \* C. Strathdee, A. Duncan & M. Buchwald, "Evidence for at least four Fanconi Anaemia genes including FACC on Chromosome 9," Nature Genetics, Vol. 1, pp 196-198 (June, 1992)
- \* B. Alter, "Leukemia and Preleukemia in Fanconi's Anemia," Cancer Genetics & Cytogenetics, 58:206-208 (1992)
- \* B. Alter, "Bone Marrow Failure Disorders," The Mount Sinai Journal of Medicine, Vol. 58, No. 6 pp 521-534 (Nov. 1991)

## Social Security Disability Programs

Several FA families have received medical coverage and a monthly stipend through a social security disability program. There are two different programs with different rules for eligibility: Social Security disability insurance and Supplemental Security Income (SSI).

Eligibility for the former is based on work history (one must have worked 5 out of the last 10 years or 20 of the last 40 quarters) and a finding of disability. SSI, on the other hand, provides benefits to children or adults with low income, limited resources and who are disabled. The medical requirements for both programs are the same and disability is decided by the same process.

The Social Security Administration defines "disability" as "a physical or mental problem that is expected to last at least a year or result in death." Distressing as that is to state formally, stressing the life-threatening nature of Fanconi anemia has enabled some of our families to obtain SSI.

If a person is found eligible for SSI, eligibility usually extends to food stamps and Medicaid as well. Medicaid helps pay for prescription drugs, and doctor and hospital bills. A young child will not be eligible for SSI if his family's income and possessions exceed a certain amount. Once he or she reaches the age of 18, however, the determination is made independent of the parents' assets. If the young adult continues to live at home, what the parents contribute to room and board will influence the amount of the monthly stipend.

It takes 3 to 6 months for the Social Security Department to determine one's eligibility for SSI or Social Security disability insurance. Often, the initial application is denied. One should appeal this decision. Chances of being found eligible increase as one continues through the appellate process. For additional information, call 1-800-772-1213.

### Aplastic Anemia Foundation: Toll-Free Number

In our last Newsletter, we listed the Aplastic Anemia Foundation of America as a support resource. **Marilyn Baker** of the AA Foundation has now provided us with their toll-free number for future use: 1-800-747-2820. Many thanks for your help and referral of FA families, Marilyn.

## Sunlight Exposure:

### A Caution

N.T. Shahidi, M.D., Professor of Pediatrics at the University of Wisconsin, writes families urging FA patients to avoid excessive exposure to sunlight. Ultraviolet rays may result in the generation of toxic oxygen species known as superoxides and free radicals. FA patients are defective in their ability to detoxify these substances, which can lead to skin cancer.

Dr. Shahidi concludes:

*"It is highly desirable for all the FA patients to apply a generous amount of a sunblock cream or lotion to the exposed area of the skin. There are numerous brands and they are all protective. Remember to use #15 or greater.*

*The following is a partial list of the most commonly used preparations:*

*Bain du Soleil #20 to #30  
Coppertone Sunblock Lotion #15 to #45  
Presun 29  
Shade 15  
UVA-UVB  
Johnson Baby Sunblock #30  
Hawaiian Tropic Babyface #25*

*For those patients who exhibit skin allergy, it is wise to stay away from preparations containing para aminobenzoic acid (PABA). None of the above products is known to be carcinogenic. The story about carcinogenicity of Padimate O, another sun screen lotion, remains unsubstantiated."*

## Toxic Agents to Avoid

Many parents have asked for information about toxic exposures which FA children should avoid. N.T. Shahidi, M.D. prepared the following advice for our families:

**\*Tobacco smoke:** contains many cancer-causing chemicals, including benzene, formaldehyde, heavy metals, radioactive particles, and benzopyrenes. Second-hand smoke increases cancer risk significantly even in children not affected with FA. **Do not let anyone smoke in your home or around your child!**

**\*Organic solvents:** paint thinner, paint remover, gasoline, benzene, wood preservatives (like pentachlorophenol), cleaning solvents. These are absorbed through the skin as well as through the lungs! Many are highly carcinogenic (cancer-causing).

**\*Herbicides (weed killers), pesticides (bug killers) and other killers:** These are highly toxic; some are carcinogenic, and many are contaminated with small amounts of far more deadly and carcinogenic chemicals (like dioxins). Don't let your child play in an area that has recently been treated (home, field, lawn).

**\*Formaldehyde:** present in tobacco smoke, new foam insulation, new carpets, new particleboard. Present in any new construction. Especially dangerous in new mobile homes or tightly sealed buildings.

**\*Gasoline:** contains benzene, and is one of the major sources of exposure to benzene by the general public (tobacco smoke is the other major source). Elevated levels of benzene were found in the blood of children who were in the family car when it was being filled with gasoline! Try to fill your tank when your child is not present. If your child is in the car, be sure to close the windows while the tank is being filled! Never let your child handle gasoline!

**\*Fumes of all kinds:** from automobiles, lawnmowers, boats, snowmobiles, or any gas or oil burning engine. Burning of almost any organic material (gas, oil, leaves, wood, plastic) produces carcinogens which are easily absorbed by the body.

### Editors' note:

Lyle Sensenbrenner, M.D. also has prepared and published a similar extensive list of toxins, drugs and compounds which victims of aplastic anemia should avoid. See *Aplastic Anemia Foundation of America Newsletter*, Spring, 1992, page 2. Write or call the FA Research Fund office if you want a reprint.

## Q & A

Diana Fitch, child therapist and mother of an FA child, offers valuable insight into how a medical crisis can affect other children in the family, even at very young ages.

**Q.** At our time of greatest crisis with our FA child, our youngest child was under one year. I thought he wouldn't remember the trauma and thereby be unaffected by it. Now I'm not so sure. At two and a half, he is such a difficult child - whining, demanding and hating me to leave him. What's going on?

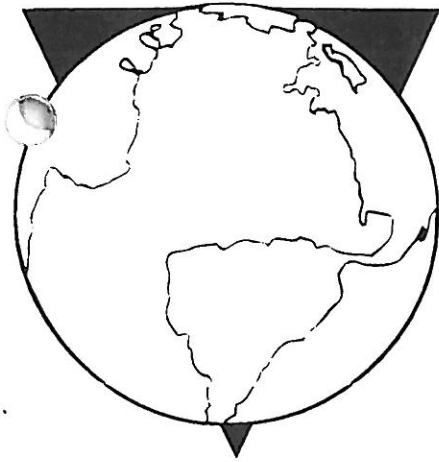
**A.** Probably lots is going on - and you are wise to consider your young child's past experiences as possibly affecting his current development. The year between the ages of two and three is a time when children struggle to learn to identify appropriately and express their feelings. (The struggle continues in

different forms throughout childhood). They also concentrate strongly on being able to allow their parents to leave while believing they will return to them, and that relationships continue even during absences. Your child may not "remember the trauma" of over a year and a half ago. However, all children, especially young ones, are affected by the emotional environment in which they live. So your child remembers the atmosphere of that time.

The circumstances of your family's crisis are unique. Yet all of us know that when one of our children's lives is threatened, we respond by focussing on that child. The threatened child's needs are pressing in a particular way. So the situation may have demanded your emotional and/or physical absence from your baby with possibly many comings and goings necessary to meet your FA child's crisis.

Now, your two and a half year old is resolving his sense of constancy in relationships and is separating himself more as an individual from you as part of his developmental stage. Normal two and a half year old behavior — whininess, demandingness, clinginess along with those infamous tantrums - may be intensified due to his early life experiences during trauma. This doesn't mean that his development won't proceed. It just means that he may use this time to re-experience and re-work those early feelings. Your attentiveness and reassurance now help him resolve his past and present issues.

Since these past experiences will always be a part of your child, you may again see more intense reactions during stressful developmental periods. You might also begin to look for strengths these same experiences may have helped create in your child. Remember that it is a combination of temperament, developmental level and life experiences that makes each unique self.



# FA family newsletter

## SUMMARIES OF PRESENTATION AT FAMILY MEETING

### SPECIAL SUPPLEMENT

SUMMER, 1992

#### FAMILY MEETING SUPPLEMENT Lay Summaries of Presentations

1. Fanconi Anemia Research Fund and the National Institutes of Health  
Alan Levine, Ph.D.
2. Overview of Fanconi Anemia  
Grover Bagby, M.D.
3. Fanconi Anemia Cell Repository  
Markus Grompe, M.D., Ph.D.
4. The Internal Challenge of Living with Fanconi Anemia  
Nancy Cincotta, MS, Social Worker
5. Genetic Research  
Manuel Buchwald, Ph.D.
6. Gene Therapy Developments  
David Williams, M.D.
7. Current Concepts from a Hematologist's Perspective  
Blanche Alter, M.D.
8. Therapeutic Potential of Cytokines in Fanconi Anemia  
Laura Reilly, RN, BSN, MBA
9. Heterogeneity in FA - Implications for Diagnosis and Treatment  
Arleen D. Auerbach, Ph.D.
10. Bone Marrow Transplantation for Fanconi Anemia  
Richard E. Harris, M.D.

Editors' Note: A VHS video recording of the Family Symposium, 1992 is now available. Cost for reproducing and shipping the tapes is \$45.00 (U.S. dollars). Please contact the FA Research Fund at 503-687-4658 or write to 66 Club Road, Suite 390, Eugene, OR 97401 to order a set of tapes.

#### FANCONI ANEMIA RESEARCH FUND AND THE NATIONAL INSTITUTES OF HEALTH

Alan S. Levine, Ph.D., Chief, Cellular Hematology Branch, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute, NIH  
The National Heart, Lung and Blood Institute supports basic and clinical research, and research on disease prevention and education both on site in Bethesda, Maryland and at universities and medical schools throughout the country and abroad. Dr. Levine writes "In both our Intramural and Extramural programs, a great deal of effort and dollars are directed towards research related to Fanconi anemia or research that will provide the necessary foundation for future advances in the treatment and possible cure of Fanconi anemia."

#### DIVISION OF INTRAMURAL RESEARCH

Dr. Neal Young's laboratory is involved in basic and clinical research on aplastic anemia; the immunologic basis for bone marrow failure; the effects of viruses on blood cell production; basic and clinical studies on the usefulness of superoxide dismutase in preventing chromosomal damage in Fanconi anemia cells; and gene therapy for selected Fanconi anemia patients is currently being planned.

The NHLBI continues to be at the forefront of gene therapy research and the internationally renowned laboratories of Drs. W. French Anderson and Arthur Nienhuis are heavily committed to developing genetic therapies for inherited blood diseases. Many of their approaches will be applicable to gene therapy for Fanconi anemia."

#### DIVISION OF BLOOD DISEASES AND RESOURCES (Extramural Division)

"The Division of Blood Diseases and Resources provides support for the following programs and research related to, or of importance to, Fanconi anemia: basic mechanisms of blood cell production and bone marrow failure; causes and treatment of aplastic anemia; molecular genetics

and prenatal diagnosis of FA; bone marrow transplantation using related and unrelated donors; the National Marrow Donor Program; improving the adequacy and safety of the nation's blood supply; stem cell biology research; alternate sources of hematopoietic stem cells for use in transplantation; in utero cures for genetic blood diseases, including stem cell transplantation without tissue matching and in utero gene therapy; increasing blood cell production using growth factors and cytokines; gene therapy for genetic blood diseases; and the support of scientific and medical workshops and conferences."

In addition, Dr. Levine has been working on two programs that are specifically targeted at Fanconi anemia. The first would solicit grant applications on the "Pathogenesis and Treatment of Fanconi Anemia." Implementation of this RFA (Request for Grant Applications) is uncertain at the present time.

The second program is a workshop entitled "Molecular, Cellular, and Clinical Aspects of Fanconi Anemia" to be held November 23-24, 1992 at NIH in Bethesda, Maryland. This workshop will be co-sponsored by the FA Research Fund and the NIH. "This workshop symposium will serve as a forum for assessing the state-of-the-art, providing recommendations for NHLBI initiatives, and helping to set priorities for supporting basic and clinical research in Fanconi anemia. The workshop will focus on cell and DNA damage and repair in FA; molecular genetics of FA; regulation of blood cell production; blood cell production and oncogenesis; and treatment today and innovations for the future, including gene therapy."

Dr. Levine concludes "The National Heart, Lung, and Blood Institute and the Fanconi Anemia Research Fund have certain common goals regarding Fanconi anemia. Although we have limitations in our resources, we are nevertheless committed to fostering and supporting meritorious research on Fanconi anemia."

## OVERVIEW OF FANCONI ANEMIA

Grover C. Bagby, Jr., M.D., Professor of Medicine and Medical Genetics, Oregon Health Sciences University

Fanconi anemia is an inherited disorder characterized by cellular hypersensitivity to DNA damaging agents, a high incidence of bone marrow failure (aplastic anemia), high incidence of skeletal abnormalities (particularly the thumb and radius) and a high risk of malignancy. The objective of this presentation will be to review the fundamentals of: 1) gene structure and function, 2) regulation of cell growth, 3) DNA damage and repair, 4) blood cell function, 5) blood cell production, 6) bone marrow transplantation, and 7) gene therapy.

### 1. Gene Structure and Function

The cell, the most fundamental unit of biological order, is a complicated structural component of each specific organ in the body. The nucleus of the cell contains all of the genetic material (DNA). DNA functions to produce proteins, the essential biochemical unit of cellular function. It is the failure of a single protein to function normally in the cells of children with Fanconi anemia that leads to the disease. The function of proteins is broad. Proteins constitute the structural skeleton of the cells, can function as growth factor receptors, catalysts for homeostatic metabolic pathways, to deliver oxygen, control movement of the cell - virtually all cellular activities.

DNA in nature exists as a double strand of purine or pyrimidine bases (A, T, G, or C) attached to phosphorylated sugar molecules. The order of the purine or pyrimidine bases in these long molecules specifies the structure and function of the protein. Each collection of three purine or pyrimidine bases corresponds exactly to the code for one amino acid, the fundamental unit of proteins. DNA in each cell, when unwound, could reach the length of six feet. Obviously, each DNA molecule must be wound and packaged tightly. This packaging unit of DNA is the chromosome. In certain parts of the chromosome, DNA unwinds so that RNA can be transcribed from specific genes. The RNA leaves the nucleus of the cell and is translated to protein.

The nucleus of normal cells contains duplicate copies of each chromosome; one maternal chromosome and one paternal chromosome. Some genes, including Fanconi anemia genes, are transcribed and translated to proteins from both chromosomes in a given cell. Therefore both the maternal and paternal gene can contribute to the production of protein. If one of the chromosomes is mutated and gives rise to abnormal protein, the other chromosome is capable of producing enough normal protein to keep the cell functioning normally. This is the nature of a "recessive mutation." However, if both the maternal and paternal genes are structurally or functionally abnormal, the nucleus of the cell will produce only the abnormal protein. Expression of this mutant protein by cells carrying two mutations characterizes Fanconi anemia.

### 2. Regulation of Cell Growth

In order to sustain the life of the organism, cells

which have a finite life span in the body must be replaced by new cells. New cells are produced by progenitor cells in that organ that can divide (so that each cell becomes two cells). In the bone marrow, for example, there are 50-60 billion cellular divisions per day. The production of cells is subject to tight regulation. For example, if a human develops pneumonia, the need for white blood cells increases. The environmental stimulus of infection induces the release of growth factor proteins by cells in the bone marrow and these growth factors stimulate cell growth in the white cell precursors. Similarly, lack of oxygen will serve as the environmental stimulus for cell growth in the red blood cell population. When the infection has abated, "stop mechanisms" or "braking mechanisms" occur whereby the growth of these cells is slowed. Therefore, the rate of cell growth can be increased when needed and decreased when needed. If mutations occur in bone marrow cells and the stimulatory mechanism for growth breaks down, the outcome would likely be aplastic anemia. Conversely, if the molecular components of the braking mechanism are abnormal, leukemia may develop because of an uncontrolled proliferation or production of white blood cells. This on/off switching phenomenon occurs at a basic genetic level.

### 3. DNA Damage and Repair

Certain chemicals and environmental factors (including radiation) can result in the chemical cross-linking of strands of DNA. Most cells have mechanisms by which these cross-linking events can be repaired and the DNA can be returned to its normal state. Fanconi anemia cells seem to lack this repair mechanism. DNA which is cross-linked very commonly results in permanent cross-linking, which can be visualized as one or more chromosomal breaks inside the nucleus of the exposed cell. This observation has resulted in the development of a diagnostic test for Fanconi anemia in which Fanconi anemia lymphocytes are stimulated to grow in the presence or absence of a chemical agent that cross-links DNA. Normal cells so treated will develop fewer than 5% abnormalities and there are fewer than 0.5 breaks per cell. In cells derived from children with Fanconi anemia, however, 85% of the cells will show chromosomal abnormalities and the average number of breaks per cell is 10. Not only are Fanconi anemia cells more susceptible to chromosomal breakage with DNA cross-linking agents, they are more susceptible to the killing effects of DNA damaging agents as well.

The linkage of DNA damage with bone marrow abnormalities is at the present time unknown, but mutations in the growth factor genes may fail to support the growth of bone marrow cells and result in aplastic anemia. The breakage of a gene that encodes a protein that "brakes" cellular growth may allow bone marrow cells to grow uncontrollably (i.e. leukemia). The DNA damage and repair that results from cross-linking agents has also led to evidence that there are mutations of more than one gene that cause Fanconi anemia. Normal cells fused with Fanconi anemia cells can correct the hypersensitivity to cross-linking agents (the normal cells donate the

normal gene to the abnormal cell). Fusion of Fanconi anemia cells from involved children of the same family will not correct the defect, but some FA patients' cells, when fused with cells from another child from a different family, can correct the DNA damage defect. Therefore mutations in more than one type of gene can cause Fanconi anemia.

### 4. Blood Cell Function

Red blood cells function to deliver oxygen to all parts of the body and lack of red blood cells is called anemia. Anemia is characterized by easy fatigue, shortness of breath, pale skin, and rapid pulse. White blood cells function to ingest bacteria, viruses, and fungi, and serve to protect humans from infections. Leukopenia (low white blood count) results in an increased susceptibility to infections and an increased severity of infections when they do develop. The platelet is a small circulating cell that contributes to the coagulation mechanism. Thrombocytopenia (low platelet count) results in easy bruising, purpura (pinpoint hemorrhages in skin), nose bleeds, gastrointestinal bleeding, central nervous system bleeding (rarely), and a prolonged bleeding time.

### 5. Blood Cell Production

The bone marrow is the site of production of all blood cells. The blood cells derive from parental cells which undergo a series of divisions. Most of these parental cells can be identified as belonging to a specific lineage of cells (for example, red blood cell parents are easy to distinguish from white blood cell parents under the microscope). However, there is a rare cell in the bone marrow that has not committed itself to being red cell, white cell, or a platelet precursor. It is this cell that is capable of replicating a number of times and re-establishing bone marrow production in transplanted animal. This is known as the stem cell. It is the stem cell that is the critical target of leukemogenic events (events that cause leukemia) and it is the stem cell that functions to establish the transplanted marrow in recipients of bone marrow transplants.

The production of blood cells therefore proceeds from the stem cell to committed progenitor cells, to precursor cells, and to well differentiated cells that ultimately leave the bone marrow to circulate in the blood. The rate of production of these cells is governed by a vast array of hormones (hematopoietic growth factors) most of which are produced by the stromal elements of the bone marrow that include endothelial cells, fibroblasts and macrophages.

### 6. Bone Marrow Transplantation

When mammals receive high doses of radiation, the bone marrow is permanently damaged and the radiated subject will die of irreversible bone marrow failure. However, it was discovered that bone marrow from unirradiated mice could be injected intravenously into lethally radiated mice and that the radiated mice would survive normally. This observation led not only to the establishment of the definitive test for stem cells, but also to an enormously successful and broadly utilized clinical treatment modality known as bone marrow transplantation.



Bone marrow transplantation is preceded first by the ablation (destruction) of bone marrow of the recipient using radiation or chemotherapy, infusion of donor bone marrow intravenously into the recipient, and 20-50 days later by recovery of marrow function and establishment of normal blood cell production in the recipient. Complications of bone marrow transplantation are significant. Immune failure, leukopenia, anemia, and thrombocytopenia are severe during the recovery phase. Fanconi anemia patients have a unique sensitivity to both radiation and chemotherapy utilized to destroy their marrows, so lower doses must be used. Finally, graft vs. host disease is a serious problem in which the transplanted cells actually identify all the cells in the body of the patient as foreign and begin to attack them.

### 7. Gene Therapy

Gene therapy is a modification of the transplantation strategy whereby the patient's bone marrow is removed and the bone marrow stem cells are cultured using specific growth factors. A normal gene is introduced into these cells, and these corrected cells are then reinfused into the patient after their marrow has been subsequently ablated with chemotherapy. Recovery of blood cell production occurs after transfusion of the newly re-engineered stem cells without the complication of graft vs. host disease. If all of the stem cells now contain the new normal gene, all their progeny (the blood cells and their precursors) will express the normal protein rather than the mutant protein.

Current problems with gene therapy include bone marrow failure, immune suppression, and other technical issues that have to do with the methods by which the genes are introduced. Of greatest importance is that while the bone marrow stem cells may be completely repaired, other cells in the body of the Fanconi patient will not be, and it is conceivable that while the incidence of leukemia and aplastic anemia will be very low, later on in the life of the patient, cancer will develop in the recipient because of the mutations that occur in other cells and other organs of the body.

### 8. The Future

The future of Fanconi anemia research is promising. Of substantial importance is a research focus on: (1) identifying all of the Fanconi anemia genes, (2) determining the function of the Fanconi anemia protein, (3) developing safe methods for gene therapy (4) formulating methods for the introduction of normal genes or normal proteins into all cells of the body. Finally, it must be recognized by funding agencies, including the NIH, that Fanconi anemia must be viewed not as a rare "orphan disease" of little interest to the general population, but as a biological case study with a high degree of relevance to the problems of cancer, leukemia, environmental toxicology, gene therapy, DNA damage and repair, human development, and aplastic anemia.

## FANCONI ANEMIA CELL REPOSITORY

Markus Grompe, MD, PhD

The Oregon Health Sciences University

Scientists in the fields of genetics, blood diseases (hematology) cancer (oncology), DNA repair and pharmacology all contribute to the study and new knowledge in Fanconi anemia. Many of these researchers use blood and skin cells from patients and family members for their experiments. Unfortunately, a supply of these cells, which is easily accessible to any interested investigator is not available at the present time. Encouraged and supported by the FA Research Fund, we therefore decided in early 1992 to establish a repository or cell bank of Fanconi anemia cell lines here at the Oregon Health Sciences University.

The cells in the repository will be available to any Fanconi anemia researcher upon request. Cells in the repository can be used to perform family linkage studies, to clone yet unknown FA genes, to find mutations in already known FA genes, to test new drugs, to test gene therapy and to study the function of FA genes. The repository has the following functions: Creation of the immortal white blood cell lines from patients and family members, establishment of skin cell lines, isolation of DNA and RNA from patient cells and collection of clinical information on all families in the repository.

About 20 cc (4 tsp.) of blood from family members are collected and mailed to us by overnight Federal Express Mail. There are 3 major groups of blood cells: red blood cells, white blood cells and platelets. Among those only the white blood cells contain the DNA that is useful for genetic studies and can be made to grow and divide in the test-tube. In the lab these white blood cells are separated from the rest of the blood. Half of the cells are used to isolate DNA, the other half is put into tissue culture media and allowed to grow in an incubator. A special virus (Epstein-Barr Virus) is used to infect the cells and to enable them to divide permanently (make them immortal). When enough cells have been grown, they are frozen down in liquid nitrogen for storage and future use.

In order to obtain fibroblast cells, a small (1/8 inch) circle of skin is removed from the forearm by a doctor. It is then transferred into a tube with special growth media and sent to us for growth and expansion.

Many families have already participated in the repository collection. Prior to this year's family meeting, 12 families had sent in their blood to the cell bank. During the meeting 13 more families donated samples and we therefore already have collected 25 families since the repository opened in February 1992.

As part of our studies, we are analyzing all cell lines for mutations in the recently cloned FACC gene. We have initially analyzed 13 cell lines and found mutations in 4 of these. These numbers are in the same range as those found by Dr. Buchwald in his *Nature* publication. It appears that about 1/3 or less of Fanconi anemia can be accounted for by mutations in the FACC gene.

Much work needs to be done to clone the other FA genes, to understand their function and to improve therapy for the disease. The cells in the repository will be useful for all of these studies.

## THE INTERNAL CHALLENGE OF LIVING WITH FANCONI ANEMIA

Nancy Cincotta, MS, Social Worker, Mt. Sinai Hospital, NY

There is great excitement for me in having been here for year one and now returning for year two. There is a feeling here - that momentum is building. I thank you for inviting me to be part of it.

I have been a social worker for thirteen years and a child life specialist before that. Three years ago, Drs. Blanche Alter and Jeffrey Lipton asked me if I would help to get a support group for FA families in the Northeast off the ground. Barbara Adler, Dr. Arleen Auerbach, Dr. Blanche Alter and I now have been running a quarterly family group for about three years.

I began to explore what sorts of psychosocial services children with FA receive around the country. It is really somewhat of an orphan child. I worry sometimes that FA families may not be made aware of support resources: practical, emotional and financial. I use my various organizational roles to educate psychosocial staff who work with patients with hematologic and oncologic conditions. I tell them that FA is as real as cancer and other diseases which have a higher prevalence and visibility.

FA is a disease which is often misunderstood. One 23 year old woman whom I follow stated that she doesn't feel that people appreciate the situation at all. She said "If I said that I had leukemia, they would all think it was serious. But when they hear something that ends in anemia, they just think I'm anemic and that's it." FA is confusing to the lay community and rare enough to be unfamiliar to the average physician. As families, you become educators and advocates in many communities.

This organization has played a tremendous role in research support, community education, fund raising, and in supporting families both emotionally and with information. You will feel the power in your numbers in the next few days. Hold on to that feeling. Take it home with you. You are not alone with this disease and you are powerful as a group. The more money you raise, the louder you speak and the more influence you have.

In selecting a title for my talk, I came up with "internal" to highlight a concern about all the non-medical ways in which FA affects your life. If all of you could have chosen, you would not have chosen to have your child have FA. This is not a club which you would have joined voluntarily. And when someone else asks you how you can be so strong and how you can cope with it, you gently remind him that you really had no choice. You live by the concept in the Nike ads, "just do it..." You really don't enter the world of FA because you want to challenge your inner strength, you do it because you have to.

Some of you who have been gracious enough to

talk with me have provided some interesting words of wisdom and allowed me to share them with the group.

To begin with, nothing in life prepares you for the role you assume when your child is diagnosed with a life-threatening illness. You don't know the inner strength you have until you are forced to use it. I listen and am touched by your energy.

FA is a disease with many stages and transitions. Know that you will find ways to get through harder times to easier times.

FA is a part of your life and a part of your child's life, but only part. Each child is a child first. Kids want to be treated like kids. Spouses want to be treated like spouses. So, occasionally if you need to, you can let your frustrations out on the doctors.

You can not meet all the needs of other family members. Parents need time together. Children need expressive time away from parents, especially as they get older. Everyone protects everyone. Use all those people - friends and family - who ask how they can help. Use professional resources when you need to.

When a child is diagnosed with a life-threatening disease, the tenor of family life changes. Life's tenuous nature becomes an overt reality. Relationships change. The point of reference in the family group changes. Each member assumes a new role in relationship to the illness. A child with FA, a sibling of a child with FA, the parent of a child with FA. Among the relationships which change is that with your doctor. Suddenly you are reliant on physicians, and not just one doctor. You may come to know different specialists for different problems, frequently in different locations, and, on occasion, with different opinions.

Your lives become filled with blood counts, bone marrow transplant donor drives, drug therapy, genes, choices, decisions, prenatal testing, and perhaps a very unique bond with other people around the country with FA.

Parents must make difficult decisions both with and for their children. Those decisions must be made without the assurance of what the future will bring.

Living with FA can add a dimension to family life which is unequalled. Tasks change and emotional and financial resources can be depleted.

Enormous emotional energy goes into maintaining family life. You go from being (theoretically) normal families in normal situations to normal families in an abnormal situation. The question I have heard asked most frequently is what to tell our child(ren), both in style and context. The question is not bounded by considerations of honesty alone, but also developmental and emotional factors. The other part of the question is about the vulnerability which parents may feel in being unable to control or predict the future. Those adults in the room with FA are a testimony to that future. The dialogues with children are generally easier than the anticipation of the discussions. Simply because a child is not talking

about her illness doesn't always mean that she isn't thinking about it.

As much as parents want to take care of and protect their children, children want to take care of and protect their parents.

Adolescents want to begin to take charge of their lives. Sometimes children worry less than their parents. It is easier for them to roller-skate than it is for an adult to watch, even when they are wearing their helmets.

Sometimes a medical event will provoke a discussion for which an adult may feel prepared. However, children raise questions you can't answer, regardless of whether they have FA or not.

Sometimes children who don't want to talk will use play or other non-verbal means of expression to work out their feelings. Children are resourceful; they will most often ask what they want to know. Each of you reading this is resourceful; I know that because you got to Florida with a willingness to expose yourselves to information and feelings. You can share with each other the intricacies of what you tell your children about their illness at different ages and stages, what they want to know, and what the children themselves tell you in response.

Through the next year I will conduct voluntary telephone interviews with you precisely about the questions your children ask you and the answers you give them. I will send my compilation to anyone who desires it simply as a resource to stimulate your thinking for interacting with your children. As a reminder, children informed of their diagnosis at one cognitive level need new developmentally appropriate information when they reach another plateau.

One family preparing for transplant had spent a lot of time explaining to their four year old his role as a bone marrow donor for his ten year old sister. One night, shortly before transplant, the children's mother found the four year old crying in his room. When she sat with him to see why he was upset she learned that he was sad because he felt he could not help his sister. She was confused until he explained "I can't help her because I do not have a 'bow and arrow'". In his world "bow and arrow" were the closest words to bone marrow that made sense to him.

Open and honest communication plays an important role in emotional survival. You can't be "up" or "on" all the time. There is a place for sad, angry, or frustrated feelings. Learning to express and manage negative feelings actively aids in the ultimate expression of honest, positive, happy moments, or even perhaps the ability to enjoy the Magic Kingdom, EPCOT, or MGM.

Hearing medical information and emotional issues can set your head racing. Be kind to yourself in these few days. Take a moment here and there to process the information.

It is imperative for you to do what you can in fund raising, in supporting ongoing research however you can, and to work as an advocate in the interest of furthering your knowledge of FA. As

you travel your individual journey, remain hopeful. Recognize that where you are at a given moment is the only vantage point from which you can work at that time.

As a community, we must all hope for enhanced treatment and for a cure by tomorrow, while not neglecting all the non-medical needs of today in the process. I thank you for the opportunity to speak today, but more so I thank you for the privilege of allowing me to listen.

## GENETIC RESEARCH

**Manuel Buchwald, Ph.D., Professor, Medical and Molecular Genetics, Hospital for Sick Children, Toronto**

Dr. Buchwald described two areas of genetics research currently being carried out in his laboratory. The first is the effort to identify the number of genes that can lead to FA. Previous studies from his laboratory had used cells derived from FA patients to show that FA could be caused by at least two genes, called FA(A) and non-FA(A). It was known at that time that non-FA(A) could be a mixed group and the more recent work showed that there were at least three genes included in the non-FA(A) group. These genes have been called FA(B), FA(C) and FA(D). This result complicates the diagnostic aspects of FA but may help explain the tremendous clinical variability seen in FA patients.

The second part of the presentation concerned the recent studies that led to the identification of one of the genes defective in FA. In this work, a defective gene was identified by exploiting a singular property of FA cells: an increased sensitivity to certain drugs that damage DNA. Thus, for a given concentration of the drug (for example, diepoxybutane (or DEB), the drug normally used in the diagnostic test developed by Dr. Auerbach), FA cells die but normal cells survive. It was reasoned, therefore, that if an FA cell acquired the normal version of the defective gene it would survive under this drug treatment whereas all the other FA cells that did not acquire the normal gene would die.

To isolate the gene, a library of all human genes was constructed and introduced into FA(C) cells. These were then treated with DEB and mitomycin C, another drug to which FA cells have increased sensitivity. After a period of time, only cells that had the normal gene were growing. It was then possible to isolate this gene from the growing FA cells. To prove that this was the FA(C) gene, researchers showed that the gene corrected the defect only in FA(C) cells but not that in FA(A), FA(B) or FA(D) cells. Furthermore, a specific change (mutation) was found in the corresponding gene of the patient's cells. Presumably this change led to the defect in the patient.

The research currently being performed in Dr. Buchwald's laboratory concerns the identification of the other FA genes and the understanding of the function of the FA(C) gene. As well, in collaboration with other laboratories (D

Auerbach in New York, Dr. Joenje in Holland and Dr. Mathew in London), information about the FA(C) gene is being used to identify those FA families that have defects in this gene. The work

Dr. Buchwald's laboratory was carried out primarily by Dr. Craig Strathdee, a postdoctoral fellow. Other participants were Dr. Hanna Gavish, a postdoctoral fellow supported by the Fanconi Anemia Research Fund, and Mr. William Shannon, a medical student.

#### GENE THERAPY DEVELOPMENTS

David Williams, MD, Riley Children's Hospital, University of Indiana

Over the past decade, technology has developed which allows the introduction of new genetic material, called DNA, into a variety of living cells. Many severe genetic diseases which affect children and young adults, including Fanconi's anemia, are characterized by deficient or abnormal blood cell production. A large number of laboratories, including our own, have investigated the possibility of introducing normal DNA into the bone marrow cells of individuals who have a genetic deficiency in an attempt to correct disease, so called somatic gene therapy.

The work of many investigators over the past decade has now allowed successful introduction of gene (DNA) sequences into the bone marrow of mice. Subsequent introduction of this bone marrow into genetically identical mice by bone marrow transplantation methods effectively allows the introduced gene sequences to produce the desired protein in the blood of the recipient mice. A large amount of work has been focused on the disease Severe Combined Immunodeficiency Disease (SCID) which is due to the lack of the protein called adenosine deaminase (ADA). This disease has been studied as a model and information gained from the work on this disease will likely be useful in the treatment of a number of other diseases in the future. Although not yet possible in humans or other large animals, several laboratories have now shown that the ADA protein can be uniformly expressed in all mice receiving bone marrow transplants of genetically modified cells.

As the genetic defects (i.e. the DNA abnormalities) associated with Fanconi's anemia become known, one can anticipate that an alternative approach to bone marrow transplantation (especially in those individuals lacking an HLA-identical sibling) may be correction of the individual's bone marrow by gene transfer technology and treatment of the bone marrow failure associated with Fanconi's anemia with somatic gene therapy. At this point, significant progress in gene transfer technology as well as in the molecular understanding of Fanconi's anemia will be needed before serious thought is given to the use of gene therapy for the treatment of this disease.

#### CURRENT CONCEPTS FROM A HEMATOLOGIST'S PERSPECTIVE

Blanche Alter, MD, Chief, Division of Pediatric Hematology/Oncology, Children's Hospital, University of Texas Medical Branch, Galveston, Texas

FA remains a rare and underdiagnosed disease, with <1000 cases reported in the literature. We are attempting to heighten the awareness of physicians such as hand surgeons, etc. who see FA children before they develop hematologic problems.

Concerns about the significance of possible "preleukemia" led us to recommend annual bone marrow examinations for appearance, cytogenetics, and research cultures. In the past 1 1/2 years we have done 13 marrows, of which 3 had "myelodysplastic" appearance. Six had sufficient cells for cytogenetics, and 2 had clonal abnormalities. One year later one was now normal, and the other had entirely replaced the original abnormalities with a new unrelated abnormality. None of this group has developed leukemia. Prospective serial studies will be needed to determine whether clonal cytogenetic abnormalities have anything to do with leukemic evolution in this disorder.

The primary treatment currently remains androgens, to which >50% of patients respond. Transplant of stem cells can be accomplished by marrow transplant, or from placental blood; this requires a matched donor and has many potential complications. Some hematopoietic growth factors are just beginning clinical trials in FA, such as GM-CSF and IL-3. Newer molecules which we are testing individually and in combinations in the laboratory include stem cell factor (SCF), PIXY321, and several interleukins such as IL-6, IL-9, and IL-11. So far, SCF is the most promising, with an improvement in production of marrow-derived colonies of blood cells in 70% of patient studies. Although there is not necessarily a correlation between the laboratory and the patient trials, it is still encouraging to see these effects. We are also beginning to examine the role of antioxidant drugs on the marrow cultures, to determine whether there is a role for these drugs in the management of FA.

In the future, as patients are classified according to their molecular mutation, we will be able to correlate that information with the clinical classification and culture data, to determine whether there is any predictive value.

#### THERAPEUTIC POTENTIAL OF CYTOKINES IN FANCONI ANEMIA

Laura Reilly, RN, BSN, MBA

Memorial Sloan Kettering Cancer Center

This talk discussed cytokines (also called growth factors or interleukins) and up-coming human trials for several new growth factors. The hope for the future is that cytokines will prevent or reverse the pancytopenia associated with FA. The field of cytokine research is young since actual human clinical trials only began in 1985. Results are progressing quickly as evidenced by the approval of Epogen, Neupogen and Leukine in less than the usual 7 to 10 years needed for most other drug approvals.

The results of the Interleukin-3 (IL-3) study at Memorial Sloan Kettering Cancer Center were shown. Six children with FA were treated out of a total of 30. Three of the 6 had neutrophil responses, with one having a transient red cell response. No FA patient showed a change in platelets. The side effects were mild and included low grade fever, headache and joint and muscle aches.

Research has begun on Stem Cell Factor, IL-6 and IL-11. Memorial Sloan Kettering Cancer Center plans to do an adult clinical trial using Stem Cell Factor beginning in the summer of 1992. Based on the results of this trial, Sloan Kettering will initiate a pediatric trial including children with FA.

#### HETEROGENEITY IN FA — IMPLICATIONS FOR DIAGNOSIS AND TREATMENT

Arleen D. Auerbach, Ph.D., Associate Professor, The Rockefeller University  
Studies in our laboratory at The Rockefeller University in New York City have focused on several different aspects of Fanconi anemia (FA). From these studies it has become clear that FA patients exhibit great variability (heterogeneity) in all aspects of the disease. The clinical variability is so great that diagnosis must be based on a laboratory test, measuring the sensitivity of cells to chromosomal breakage induced by the DNA damaging agent diepoxybutane (DEB). We developed this test in 1977, and have been performing it in our laboratory since that time.

Since 1984, we have performed the DEB test on blood specimens from 1,670 patients, in order to determine whether or not they are affected with FA. Patients are referred because they have birth defects known to be associated with FA, with or without the presence of hematologic problems, or they have hematologic abnormalities, without the presence of birth defects.

Results of DEB testing in our laboratory indicate that there is great variability in the degree of the hypersensitivity in FA patients. Although all FA patients are much more sensitive to DEB than non-affected people, there is a wide range of sensitivity in affected individuals. Interestingly, there is no correlation of the degree of DEB hypersensitivity with the presence or absence of birth defects in patients. We also apply the DEB test to the study of fetal cells, obtained by chori-

onic villus sampling (CVS) in the 9-10th week of gestation, or by amniocentesis (AFC) in the 16th week. Our experience with prenatal diagnosis for FA from 1978-1992, in pregnancies at a known 1:4 recurrence risk (in couples who have had a previously affected child) are seen in the following table.

	FA	NORMAL	TOTAL
CVS	9	36	45
AFS	10	47	57
<b>Total</b>	<b>19</b>	<b>83</b>	<b>102</b>

In 1982, in order to understand better the varied clinical manifestations of FA, and to serve as a central clearing house for information for this rare disease, we established the International Fanconi Anemia Registry (IFAR) at The Rockefeller University. We provide physicians with general information about FA from our study of Registry patients by presenting data every year at hematology and genetics meetings, by publishing data periodically, and by answering physician questions by telephone. Information about FA patients is supplied by physicians caring for the patients.

We also see FA patients and their family at The Rockefeller University Hospital, at our clinical research center supported by NIH, for consultation with a panel of pediatric specialists. At this time we evaluate the varied clinical manifestations of FA in the child for entry into the Registry, and also try to help educate the family regarding the implications of a diagnosis of FA. Of the 24 FA patients evaluated on this protocol, several were found to have abnormalities in growth hormone production or thyroid function, as well as other problems associated with FA. Results of our evaluation are sent to the referring physician.

We have recently analyzed data from 370 FA patients in the American part of our Registry. These included siblings from 45 families with two or more affected siblings. We have found enormous clinical variability, from children with severe birth defects, to patients with only hematologic disease. In 15 sibships, all affected sibs were concordant (similar) for the absence of any birth defects, having only hematologic manifestations of FA. In 12 sibships, one sib had birth defects while another had only hematologic problems. In 18 sibships all affected sibs had birth defects, but in no cases were the birth defects exactly the same. Siblings are alike in the specific mutations in their DNA leading to FA; these differences in sibs must be due to other factors which affect how the FA gene manifests itself in the affected individual. Although we don't yet know anything about how the defective gene leads to the clinical problems in FA, information from this analysis helps us formulate ideas as to how the gene might work.

Results of gene mapping studies in FA families, reported previously from our laboratory, have led

to the provisional assignment of a gene for FA complementation group A to chromosome 20, near the end of the long arm of this chromosome. We have recently studied several DNA probes linked to the gene for FA complementation group C on chromosome 9, discovered by Dr. Buchwald. A combined statistical analysis of all of our linkage data indicates that approximately 10% of the families are linked to a chromosome 9 probe, about 10% to a chromosome 20 probe, and approximately 80% of the families have FA genes that are still unknown. We are optimistic that the application of methodology similar to that used by Dr. Buchwald to clone the group C gene can be applied to find the other genes. We are currently using this approach to try to clone the gene for group A.

The implications of the extreme clinical and genetic heterogeneity must be considered in the diagnosis and treatment of patients with FA. The gene defect is not the same in all patients, and the clinical manifestations are not even the same in affected siblings. A diagnosis of FA must be considered for all children with multiple birth defects of unknown origin, and the DEB test performed. Healthy-appearing siblings of FA patients should also be tested, especially prior to consideration as a donor for bone marrow transplantation. Hypersensitivity to DNA crosslinking agents makes it necessary to use milder conditioning regimens for transplantation. We don't know yet whether variability in hypersensitivity between patients affects the clinical response to the different conditioning regimens in use in different transplant centers.

There is at present a great deal of interest in gene therapy as a future method of treatment of FA. It will be necessary to identify the particular gene defective in an individual family in order to consider gene therapy for that family. Our research is currently focusing on attempts to correlate gene defects with clinical manifestations in FA. We are collaborating with Dr. Buchwald and many other researchers for these studies. Information regarding particular gene defects found in families in our registry may eventually benefit the individual patient, as well as lead to a broader understanding of this rare disease.

## BONE MARROW TRANSPLANTATION FOR FANCONI ANEMIA

Richard E. Harris, MD

Director, Bone Marrow Transplant Program  
Children's Hospital Medical Center, Cincinnati

For patients with Fanconi anemia who have available an HLA-matched sibling donor, bone marrow transplantation is considered by the physicians at Children's Hospital Medical Center in Cincinnati to be the treatment of choice. Data from several transplant centers reporting on 89 matched sibling donor transplants to the International Bone Marrow Transplant Registry (IBMTR) between 1978 to 1991 indicates that about 60% of the patients are alive and well with normal blood counts. Cincinnati Children's has now performed eleven matched sibling donor transplants in children with FA who did not have leukemia at the time of transplant. All eleven are alive and well a median of 14 months from transplant (range 2 to 57 months) with normal counts and no evidence of graft vs host disease (GVHD). Dr. Richard Harris, director of the Bone Marrow Transplant Unit at Cincinnati Children's, reported the data from the IBMTR and from his own institution at the Family Meeting of the Fanconi Anemia Research Fund on June 28, 1992.

Dr. Harris utilized the first half of his presentation to discuss bone marrow transplantation in general—how the procedure is done and the potential benefits and risks of marrow transplantation. Following this he presented his center's approach to aplastic anemia, then data from the IBMTR and his center specifically on transplantation for FA utilizing alternative donors such as partially matched family members and matched unrelated donors. Then he concluded with his recommendations for patients with and without a matched sibling donor. He then stayed around for a couple of hours answering questions from individual families about their children.

Dr. Harris obtained the following data from the Statistical Center of the International Bone Marrow Transplant Registry. The analysis has not been reviewed or approved by the Advisory Committee of the IBMTR. A total of 121 patients with FA have been reported to the IBMTR. Of these, 89 were transplanted from matched sibling donors. (MSD), 23 from partially matched relatives (Haplo), and 9 from matched unrelated donors (MUD). The preparative therapy used in over half of the patients as a regimen identical to or very similar to that used in Paris or at Cincinnati Children's — low dose cyclophosphamide combined with medium dose thoraco-abdominal irradiation. Many of the remaining patients received high dose cyclophosphamide. Prophylaxis for GVHD was varied, but almost all patients received cyclosporine with or without other agents. Overall survival among the 89 patients transplanted from matched sibling donors is about 60%. Patients receiving the Paris/Cincinnati regime have a considerably better survival than those receiving a regimen containing high-dose cyclophosphamide. Overall, acute and chronic GVHD was seen in half of patients, and graft failure in about 10%. About a

third to a half of the patients who were transplanted with partially matched relatives or with unrelated donors are surviving.

At Cincinnati Children's 15 patients have undergone marrow transplantation for FA. The mean age at transplant was 8 years. Eleven of the 15 had congenital anomalies. Twelve had received prior therapy: corticosteroids alone in 5, and corticosteroids with androgens in 7. All of the 11 patients with matched sibling donors and without leukemia at the time of transplant are alive with normal blood counts 2 to 57 months after transplant. None of these patients developed acute GVHD and one developed chronic GVHD which required about one year of immunosuppressive therapy with steroids and cyclosporine. Four patients were transplanted with alternative donors or after having developed leukemia. The one patient transplanted from a matched unrelated donor is alive and well 12 months after transplant. He developed moderate acute GVHD which has completely resolved with therapy. Of the two patients transplanted from parental donors, both were resistant to platelet transfusions and had numerous medical problems going into transplant. One patient died of multisystem organ failure a few days after transplant. The second had a rough transplant experience but engrafted and did well for several months. He then rejected his marrow graft and is currently in house after receiving a second transplant, this time from a matched unrelated donor.

Dr. Harris presented his recommendations to the group. He feels that patients with FA who have a matched sibling donor should undergo transplant with a regimen similar to that used in Paris Cincinnati (one dose cyclophosphamide and moderate dose thoraco-abdominal radiation) early in the disease course, even before being placed on androgens, if at all possible. He also feels that the GVHD prophylaxis regimen utilized at Cincinnati consisting of cyclosporine, anti-thymocyte globulin and steroids combined with isolation in laminar air flow, is important in leading to the very low incidence of GVHD seen in Cincinnati among the FA patients. If a matched unrelated donor is available, he feels a transplant should be considered only after the patient has failed to maintain adequate blood counts following a trial of androgen therapy. However, such patients should undergo such transplants before being heavily transfused with blood products. Patients with a long history of transfusions are at a higher risk of graft rejection and GVHD. Some patients who receive several platelet transfusions also develop a resistance to platelet transfusions, which will increase the risk of dangerous bleeding episodes. Also transfusions lead to a chance of developing hepatitis, which increases the risk after transplant of liver failure or a dangerous transplant-related complication known as veno-occlusive disease. Unrelated donor transplants should not be considered as a last ditch therapy. If done when the patient is in bad shape, the outcome is likely to be poor. Early referral for a MUD transplant is urged. Dr. Harris however was not very optimistic about utilizing partially matched family members as donors. He feels the

risks of graft rejection and GVHD are so high that other therapies should be tried first, such as growth factors. He feels that a matched unrelated donor transplant is preferable to a partially matched related donor transplant.

Dr. Harris stated he is willing to speak with any family or physician over the phone about his recommendations in individual situations. He can be reached at 513-559-4266 in Cincinnati.

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Nancy Williams writes in loving memory of her daughter, Donna:

**Donna Jean Williams**, age 34, passed on from complications of cancer and FA on August 15, 1991.

Donna graduated from Montevideo High School and went into L.P.N. training. She worked for 7 years at Sunnyside Presbyterian Nursing Home and loved her patients and those with whom she worked. As one nurse said "She was a very giving person".



She loved to give gifts on special occasions to her co-workers, many friends and family members.

Donna was a member of the Mill Creek Church of the Brethren, where she was a member of the Chancel choir and the Bethany S.S. Class. She had a great love for music and played piano, clarinet and the guitar.

She had several hobbies: collecting rocks and minerals, koala bears, Swarovski crystals and photography. She loved traveling, shopping, tennis, swimming and bicycle riding but most of all she loved just driving her Pontiac Sunbird.

Donna's first doctor, Alba Sanmarco, began treating Donna at age 5 and maintained contact with Donna and the family throughout the years. This helped the family greatly during trying times.

One doctor stated that Donna probably knew more about FA than he did. On many occasions I accompanied her to the closest University Hospital so that Donna could copy the latest about FA from medical journals.

Donna spent her last birthday at Medical College of Virginia Hospital in Richmond, VA. Four of her favorite doctors sang "Happy Birthday", which meant a great deal to her.

Donna preplanned her music selections and Bible readings for her funeral. She wrote personal letters to each family member in which she told us not to worry or cry because she would be with Jesus in Heaven.

We miss her so very much and wish it could have been different but we feel fortunate to have had her for 34 years. Even though she had a lot of dark days, I now have great

### Dear FA Family and Friends:

At the FA Family Symposium I was so nervous giving my presentation on fundraising. I wanted to write in the newsletter to inform those of you who were not in Florida about our success in fundraising.

Our first fundraising letter, three years ago, explained the ordeal that led to the diagnosis of FA for our youngest son, Jonathan — age 7 at that time. We explained how our older son, Robert, then age 10, was a match for a bone marrow transplant, and the risks of a transplant. We briefly described the disease itself and how monies were urgently needed to fund numerous research projects because of a lack of government funding. We included a picture of the boys and a self-addressed envelope.

In a few short weeks we raised \$40,000. Some of our donors have continued to support the FA Fund on an annual basis.

Our second letter went out this June. In this letter we explained Jonathan's progress and explained in greater detail the devastation caused by FA and the dropping of blood counts. We included the new information on Dr. Buchwald's discovery of an FA gene and our hopes for the future. We thanked people for all their support in the past and asked for their continued support. We included a new picture of the boys and a self-addressed envelope.

The letter three years ago went out to 1750 people. This letter will go out to 2000 people. We sent a letter to our original list even if a response was not received from the first mailing. We felt we had great news to tell of tremendous progress. We believed that people would donate again and maybe would this time if they had not last time.

Only 1325 letters have been mailed thus far. We already have received \$10,000. Some contributions were from people who did not respond the last time.

We are in the oil business in Pennsylvania and used the Pennsylvania Petroleum Association membership list, our country club list, vendors, customers, church lists, family and friends. We tried not to overlook any possible contributor in building our list.

All checks are sent directly to us. We send a personal hand-written thank you before we forward contributions to the FA Research Fund in Oregon.

My home phone is 717-473-9915; work number is 717-286-4519. Our address: Robert & Linda Scullin, P.O. Box 223, Sunbury, PA 17801. I would be glad to discuss fundraising with you, or send you copies of our letters if you would like to try a fundraising effort.

Thank you,  
Linda Scullin

memories of her better days to hold on to. None of us ever expected Donna to pass away so young but her memories will always be a part of us.

While waiting in a doctor's office, I happened to read a magazine article about the Frohnmayer family and the support group. Through this, Donna met two great friends, Paula Ceresa Guidara and Dee Dee Doutt. Just knowing there are others who have similar situations was always a big help to us. I would like to thank the Frohnmayers for sharing the Newsletters with us.

Donna's parents, Nancy and Reese Williams.

### Those Who Love Me

*When I am gone, release me, let me go —  
I have so many things to see and do.  
You mustn't tie yourself to me with tears.  
Be happy that we had so many years.*

*I gave you my love. You can only guess  
How much you gave to me in happiness.  
I thank you for the love you each have shown.  
But now it's time I traveled on alone.*

*So grieve a while for me if grieve you must  
Then let your grief be comforted by trust.  
It's only for a while that we must part  
So bless the memories within your heart.*

*I won't be far away, for life goes on  
So if you need me, call and I will come.  
Though you can't see or touch me, I'll be near  
And if you listen with your heart, you'll hear  
All of my love around you soft and clear.*

*And then, when you must come this way alone,  
I'll greet you with a smile, and "Welcome Home."  
Author Unknown*

## Fredi Norris Volunteers to Write About our Children

Several families have suggested that our Newsletters should focus more on the accomplishments, activities and interests of our FA children. All too often, we read

tragic rather than positive news. Fredi Norris has generously volunteered to edit this section of our Newsletter. Please write to Fredi at: 1592 Rockwin Rd., Rockville Center,

NY, 11570 and tell her about your child or children. A photo would be most helpful as well. Many thanks to Fredi for this most valuable improvement to our Newsletter.

### Let's Meet our Kids!

Jimmy Lucarell is the energetic 7-1/2 year old son of Bill and Jackie Lucarell of Girard, Ohio. The Lucarell family which includes their son, Billy, participated at the Family Symposium in Orlando.



Jimmy has a strong enthusiasm for music. One night in Orlando at the hotel's small ensemble group was fine tuning for an entertainment session, there was Jimmy totally engrossed with the preparations. You

could see his mind working, trying to absorb every detail involving the setting up and tuning of each instrument.

Jimmy enthusiastically describes his love of musical instruments, his favorites being the bass guitar and drums. He has three guitars and is beginning to learn to play. He's never had a lesson, but taught himself everything he's learned. He'll begin drum lessons this August.

His favorite musical group is the Beatles. Jimmy recently met Ringo Starr at a concert at Blossom Studios. He received an autographed drumhead from the famous drummer. Jimmy's aunt had arranged for this special trip.

Jimmy's interests extend beyond music. He is very athletic. He is an excellent mushball player and plays on the local community team. He is a good swimmer and diver. He is very sociable and loves meeting people. And Jimmy maintains a straight "A" average in school.

But music is his main love. Keep your eyes and ears open because Jimmy would eventually like to be a musical entertainer with the stage name of JAMES LUCARELL.

### A Look At Alex Norris

Alex Norris is the 15 year old son of Ron and Fredi Norris of Rockville Centre, New York. Alex and his family attended the 2nd FA Family Symposium in Orlando, Florida, where I had the privilege to meet and interview him.

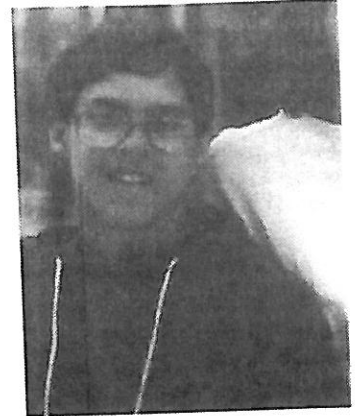
During his time at the conference, Alex performed a magic show for the other FA children and their siblings. Alex became interested in magic at an early age when it was introduced to him by a family friend who performed at his birthday parties. He directed Alex to some stores where he was able to buy the supplies he needed to perfect his act. Alex's magical abilities seem to grow out of his desire to work with kids and make them happy.

Alex and his friend Matt, who is a juggler, have joined together in a small business partnership putting on shows for local birthday parties within Rockville Centre and the surrounding area.

When asked what his hardest trick is, he responded "Things may look hard, but nothing's hard because there's a trick to everything." His favorite trick is the magic coloring book — it starts out blank and then you color it and uncolor it, but he said, "The kids like the one where at the end I give them Hershey kisses."

Alex's other interests are playing the piano and singing. He has just been chosen for a select choral group at school called the Chamber Singers. He also involves himself in track (running sprints) and playing tennis. He went on to say that basketball is his "game" and his father coaches a team he's on.

His leadership abilities will be put to the test this next year when he serves as Sophomore Class President. Alex had wanted to be President over the last two years, but ended up losing to a popular girl who didn't do anything. "I guess people realized it this year". Alex's presidential thrust will be working on money making ideas, which will hopefully allow a class gift to be bought for the school upon graduation.



When asked whom he admires or looks up to, Alex stated, "Besides my parents, which I guess is a pretty nice thing to say, I used to have a rabbi, who is no longer the rabbi in my congregation, who was a really good influence on me. He was a very warm, caring person who understood kids very well."

Alex's future goals are to work with kids and help them laugh and enjoy themselves, especially the younger ones. That's why he likes magic so much, because he knows they enjoy it. He's also thought about being a lawyer.

A highlight of the Family Symposium for Alex was meeting all the other kids. "It's a little different when you're dealing with kids like you in some way." His friends at home try to understand what he's going through having FA, but they can't always relate. "But I met Chris, I love Chris. He says, 'I bruise easily', and I can relate to that."

Alex impressed me as a special person who loves people, and has the self-confidence to face any challenge that may come his way.

By Leslie Roy

Fifth grader **Jessica Paulson** allows us to quote from the courageous essay she wrote for the Redding, California Literary Festival:

"Hi, my name is **Jessica Irene Paulson**. I'm writing about growing up with **Fanconi Anemia**. I was born on Feb. 18, 1981. I was 17" tall and weighed 6 lb. 7 oz. I am now 10 years 11 months old, 45 1/2" tall and weigh 41 lbs.



**Fanconi Anemia** is a rare disease. Besides being small, I have two thumbs on

my left hand. It's hard to have two thumbs because people go around calling me pincher bug. It makes me unique because most people only have 10 fingers to count with and I have 11.

It's sort of scary to have **Fanconi's Anemia** because you never know when it will become active. I could die if or when it becomes active.

When I was 4 years old I had to have surgery, a ureter reimplantation. Now I have 80% of one kidney and 2% of the other. Having these bad kidneys is one of the side effects of **FA**."

Jessica describes several hospitalizations for surgery and tests in 1985 and 1986. She writes "They were trying to make me eat because I didn't eat much. On February 13 they brought me a carrot cake because they thought it was my birthday and said I could only have it if I ate all my dinner. I thought that was very mean! I was never hungry so I didn't eat my dinner and they took the cake away.

When I left the hospital I was 20 lbs. After I got home from the hospital I was put on **N.G. tube** feedings for about 1 1/2 years. It helped me grow a lot. But I stopped eating solid foods so my mom and dad took me off it.

People are amazed about how small my head and body are. They have a hard time believing that I'm in the fifth grade.

The average age is 16 years for people with **Fanconi's Anemia** to live. I hope I live until I'm 50 years old.

With God's blessings I might."

[Thanks, Jessica, for your brave and honest statement of faith! eds.]

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Blanche Alter, M.D. Relocates to  
Galveston, Texas

Dr. Blanche Alter, who has treated many children with Fanconi anemia and has served as a consultant to physicians treating this rare disorder, has recently changed positions. Her new address:

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