FA Genetics Meeting Outlines Scientific Progress

Numerous promising reports of progress in understanding Fanconi anemia marked a recent meeting of internationally respected scientists. On October 5-6, 1991, the Fanconi Anemia Research Fund, Inc. sponsored a “satellite meeting” in Washington, D.C. on genetic research into FA. This is the third annual international scientific gathering supported by our Fund.

Dr. Manuel Buchwald of the Hospital for Sick Children, Toronto, Canada, and Dr. Arleen Auerbach of The Rockefeller University organized and co-hosted the meeting. It was held in conjunction with the 8th International Congress on Human Genetics.

Investigators from laboratories in numerous nations shared their latest FA research results. The pioneering studies of Dr. Buchwald and his colleagues in Toronto, Canada, show that at least four separate genes can cause the multiple symptoms of FA. Buchwald's work on identifying different “complementation groups” has greatly assisted other scientists in pursuing these genes separately.

Dr. Craig Strathdee of Dr. Buchwald’s laboratory reported finding a potential “excellent” FA candidate gene for one complementation group! Work to verify and refine these results is ongoing as this newsletter goes to press.

Laboratories in the United States and the United Kingdom showed progress in localizing one of the FA genes on chromosome 20. Alternative methods for locating one or more FA genes were reported by laboratories in The Netherlands, France, the United States and Canada.

Representatives of our Fund asked researchers to provide “lay summaries” of their reports. These reports are highly technical. We include them to share with your treating physicians. They demonstrate the advanced level of scientific expertise which is encouraged by the research funds we raise and distribute. See Appendix I.

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Luncheon Conversation – left to right:
Manuel Buchwald, Ph.D., Toronto; Arleen Auerbach, Ph.D., The Rockefeller University; William Bighue, Lawrence Livermore National Laboratory; Dave Frohmayer, Advisor to the Fund and Co-editor, F.A. Family Newsletter; Dr. Chris Matthew, Guy’s Hospital, London.

Scientific panelists evaluate reports on latest FA research.

Dr. Margaret Zdzienicka, Leiden University, The Netherlands (2), shares thoughts with Dr. Ethel Moustacchi, Institute Curie, Paris, France.

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Highlights

- Cell Repository Project ............. pg. 2
- Funded Research in Progress .... pg. 3
- Peer Review Scientists Sought ... pg. 3
- 1992 Family Meeting .............. pg. 4
- 1992 Scientific Conf. Plans ... pg. 4
- Helping Children Cope .......... pg. 7
- From Our Families ............... pg. 9
- Genetics Meeting Summaries .... pg. 12
New Fanconi Anemia Cell Repository at the Oregon Health Sciences University
submitted by Dr. Markus Grompe

There have been many exciting advances in Fanconi anemia research in the past year and the speed of progress is steadily increasing. In addition to the laboratories that have been active in the field for a number of years, new research groups are joining the efforts to find Fanconi anemia genes, to understand their function and thereby develop better diagnosis and treatment for the disease. This is excellent news for all patients and families with Fanconi anemia. Much of the research conducted is not carried out on patients themselves, but utilizes skin and blood cells that can be grown in the laboratory. These cells can be used to find FA genes, to test drugs that might help in FA and to understand better what goes wrong in Fanconi anemia.

It would greatly benefit FA research if such cell lines and samples were widely available to any researcher interested in studying FA. Unfortunately, this is not the current situation. Only a few FA cell lines and samples from their families are available. There therefore is a great need to establish a new FA cell repository. We plan to establish such a cell bank here at the Oregon Health Sciences University and we commit ourselves to making these cells available to any researcher who requests them.

We are basically interested in any patient and family with FA, but for genetic testing there are two groups of families that are particularly valuable for research. These are: (1) families in which there are 2 or more family members affected with FA and (2) families in which the parents are related to each other, even distantly. If you belong to one of the above categories, we urge you strongly to consider submitting samples to the repository. In addition, we also need samples from all other families.

What's in it for you?
Your family may benefit directly from this. There is a good chance that the mutation causing FA in your family will be found in the cells you submit. This translates into better, more accurate diagnosis at the least and possibly improved treatment. Fanconi anemia cells will be tested for the effects of different treatments and it is obviously to your advantage, if these tests are performed on your cells. In addition, you might also help other families with FA.

Who in the family?
In families where there are 2 or more patients with FA, samples are needed from the patients, all their brothers and sisters, the parents and grandparents on both sides. In other families the grandparents' samples are not needed, but we do request samples from parents, siblings and patients.

Which samples?
It would be best for research to be able to obtain both blood and a skin sample from all individuals within the family. A biopsy to donate a skin sample is a minor procedure, not more painful than a blood draw and very useful for research. The skin is numbed with local anesthesia (like at the dentist) and a tiny (1/10th inch) circle of skin is removed. The wound is covered with a band-aid and it's done. Blood cells from patients with FA grow very poorly in the test tube and it happens frequently that cell lines cannot be successfully isolated. This is not the case with skin cells, which grow quite well.

Only blood is needed from relatives, since their blood cells tend to grow well.

How to do it?
Make an appointment with your physician and show him/her this letter. It is easiest to bring the whole family for one session rather than drawing everybody on separate days. Two 10 cc tubes of blood drawn in a sodium heparin (not lithium heparin!) tube are required for all family members.

The samples need to be sent at room temperature (not refrigerated!!!) via overnight Federal Express to our address (see below).

Skin samples are also sent at room temperature in a special fibroblast tissue culture media (Dulbecco's Minimal Essential media with 10% fetal cell serum and antibiotics or equivalent). This media can be obtained from us if your physician or laboratory does not have it available.

Additional information:
We need the full name and birthdate on every person. It is also very important that you indicate who are the parents, siblings and patients are. If chromosome testing has been done, we need the reports of those tests also. Please include your phone number and that of your physician, so that we can contact you for additional questions.

When and Where?
Samples should be sent to arrive Tuesday, Wednesday or Thursday in Portland. Samples can therefore be drawn on Monday, Tuesday or Wednesday. It is critical that the samples take no longer than 24 hours to arrive here.

Address: Dr. M. Grompe
Department of Medical and Molecular Genetics
Oregon Health Science University
3181 SW Sam Jackson Pk Rd,
L 103
Portland, OR 97201
Ph: (503)494-6888
fax: (503)494-6882

Who pays for it?
Federal express charges and laboratory costs which are not covered by your insurance will be picked up by us. Please send the appropriate documentation.

We sincerely hope that many of you are willing to participate in this effort. Please make it a goal for you and your family to help establish the repository in 1992. Many thanks!

Dr. Markus Grompe

Editors’ Note:
At our scientific workshop in Portland, Oregon in 1990, internationally acclaimed scientists concurred in both formal and informal recommendations that there is no universally accessible FA cell repository and that such a repository could greatly hasten scientific discovery. Speaking directly to the issue shortly thereafter, DR. MANUEL BUCHWALD wrote:

"...Finding the FA genes is the start of real FA research and it is at that point that many new researchers will enter the field. It would facilitate their entry if they can get FA cells easily."

After considerable additional investigations, we concur. Eds.
FA Research Supported: An Update

Since our incorporation as a 501(c)(3) tax-exempt entity in February, 1989, the Fanconi Anemia Research Fund, Inc., has raised rapidly to support promising scientific proposals.

A total of ten research projects have received financial assistance. Six projects involved genetic research and four were directed toward developing FA therapies.

Our Fund has granted a total of $62,638 (including $96,453 granted prior to our official incorporation) to ten research projects. Arleen Auerbach of The Rockefeller University has received $224,215 from our Fund, an amount which represents over one third of all the money we have awarded. Dr. Auerbach did not submit a proposal for the present funding cycle.

The following grants were awarded during the year ending December 31, 1991:

**Boston Children’s** - Eva Guinan
M.D. - $1,920

**The Rockefeller University** - Arleen Auerbach, Ph.D. - $41,140
U.C. Davis - James Boyd, Ph.D. - $53,333

**Mt. Sinai Hospital** - Blanche Alter
M.D. - $24,150

**Hospital for Sick Children** -
Janet Buchwald, Ph.D. - $76,000

**Leiden University** - Margaret Zdzienicka, Ph.D. - $50,000

1991 Total: $246,543

As of January 20, 1992, the Fund is actively supporting four research laboratories. These current projects are demonstrating exciting progress towards understanding Fanconi anemia.

Dr. Manuel Buchwald is receiving a grant to support his work in two crucial areas: to determine the number of genes involved in FA, and to isolate one or more of these genes. He states “We have found a new gene that has many characteristics consistent with being defective in FA, making it an excellent candidate gene.”

Margaret Zdzienicka, Ph.D. is attempting to isolate the Fanconi anemia (A) gene by using a Chinese hamster cell mutant which is homologous to the FA(A) gene and shows cellular characteristics of cells derived from Fanconi anemia patients.

Dr. Blanche Alter is examining the effect of various hematopoietic growth factors alone and in combination on Fanconi anemia bone marrow and blood cells, to see which factors stimulate blood production. She has demonstrated that stem cell factor increased marrow CFU-E and/or BFU-E in greater than 70% of FA studies. It is hoped that stem cell factor will be available for clinical trial in the not too distant future if early studies demonstrate that it is effective and not toxic.

James Boyd, Ph.D., University of California, Davis is attempting to clone an FA gene by first cloning a fruit fly gene which shares several characteristics with the FA genes. He states that his laboratory has made “substantial progress” in cloning the fruit fly gene.

The FA Research Fund, Inc. is presently evaluating two additional proposals for potential funding.

FA Research Fellowship Applicants Sought

After full review, the Board of Directors of our Fund approved a January, 1992 proposal to solicit applicants for a limited number of Fanconi Anemia Research Fellowships. Other foundations that support scientific research into hereditary diseases encouraged us to follow their successful experience in recruiting young investigators.

Beginning in spring, 1992, our Fund will advertise for applicants for a limited number of awards, preferably at the post-doctoral or junior faculty level, for intensive research efforts into FA genetic research, gene expression and therapy.

Dr. Bertil Glader, M.D., Ph.D., Professor of Medicine, Stanford University is an expert in blood diseases and anemia. In addition to his extensive involvement as a treating physician of FA patients, and other victims of genetic marrow failure diseases, Dr. Glader brings us access to the medical knowledge of one of the world’s most distinguished research universities.

Professor Charles Laird, Department of Zoology and Genetics, Child Development and Mental Retardation Center, University of Washington, Seattle, is a distinguished researcher and reviewer in the field of genetics and molecular biology. He has followed our FA efforts closely for some years. We welcome his expertise.

Dr. Frederick Appelbaum, Professor of Medical Oncology, University of Washington and Member, Fred Hutchinson Cancer Research Center, is expert in cancer research and marrow transplantation. He participated in our 1990 International Scientific Workshop on Fanconi anemia and has engaged in clinical consultation on the treatment of complex FA cases.

**PEER REVIEW SCIENTISTS AND RESEARCHERS REQUESTED**

This newsletter is addressed to research scientists and medical professionals - in addition to FA families - for obvious reasons. We need your help.

The Board of Directors invites FA physicians and researchers to nominate qualified experts for our Fund's scientific peer review panels.

Panelists review grant proposals, and make recommendations to our Board concerning funding priorities. Please include yourself, if you can commit some minimally reasonable time (of your choosing).

Contact Linda Solin at (503) 687-4658 with your suggestions or recommendations. Please volunteer, if you can. Many thanks! (eds.)
FA FAMILY MEETING: IMPORTANT NOTICE

Plans are confirmed for a Second Annual FA Family Symposium in Orlando, Florida (near Disney World) on June 27-28, 1992. Please mark your calendars now!

Every FA family is invited. The attendance of children, affected or unaffected, is specially encouraged. If you are grieving the loss of a child, or celebrating a successful transplant, you are equally welcome - and equally important to the strength of our association. Please make a special effort to attend.

Last year's family symposium was a great success, and this year promises to be even better. We will have scientists and physicians speak about the latest breakthroughs and therapies. A specialist in family counseling and grief therapy will present a session. We will spend some time in small group sessions so that families can talk about areas of special concern to them. This will give us a chance to make and build friendships with others who share similar experiences and feelings. We will also have counselors to meet with you privately or in prompt groups as needs are identified.

We have obtained greatly reduced room rates from the Hilton Gateway which is located one mile from the Walt Disney World Resort entrance. Single and double rooms are available at a very special rate of $50 per night. The Hilton will offer these special rates from June 23 through July 1 so you may extend your stay in the Orlando area. Financial support from the Meyer Memorial Trust has greatly assisted our planning. This grant will allow us to pay for up to two nights lodging per family. We will work with the Hilton Gateway and credit your room $50 per night with a maximum of 2 night ($100) credit. Dinner on June 27 and breakfast and lunch on June 28 will also be provided. Additional lodging or meals will not be provided by the fund.

Because of the "compassionate" character of our group, Walt Disney World Vacation Kingdom and Sea World will offer free admissions for our families. If you would like to visit these attractions, the facilities require that we request complimentary tickets by May 26. This newsletter's colored insert offers an application form which you must complete and return to this office by the deadline date of May 26.

The insert also contains information about discounts for airline tickets, rental cars and shuttle bus transportation. Please read this page carefully and make your requests and reservations early.

We have dealt with this disease in our family for many years. We recognize that it is not always possible to predict your family's health situation several months in advance. If you would like to come, but are uncertain of what your child's status will be in June, we urge you to complete the forms before the deadlines in order to secure your complimentary passes.

If your family situation prevents you from attending, you may cancel your hotel reservations 48 hours in advance without penalty. Room cancellations made less than 48 hours prior to arrival date are subject to a penalty of your first night's room and tax. Please indicate on the registration form if you have child care needs. There will be a charge for these services. We are currently negotiating a rate with a reputable child care provider. We need to know your child care needs as soon as possible in order to secure an accurate contract with the Fairy God Mothers Day Care Service.

Please fill out and return the enclosed loose leaf form as soon as possible. Indicate your preference for small group sessions. If you have questions or ideas, feel free to call Linda Solin or Lynn Frohnmayer at (503) 687-4658.

Karen Dunn Lopez, R.N., who has been working closely with this trial, stated that five out of six Fanconi anemia patients have shown an increase in their white count and ANC count. Although GM-CSF has not affected the actual platelet count, four out of six patients experienced a decrease in bleeding, bruising and petechiae. The reader is referred to Appendix II (ASH Abstract) for additional information about this trial. It is anticipated that future trials will include combinations of different colony stimulating factors.

If you wish to explore GM-CSF therapy further, have your treating physician contact Dr. Eva Guinan's nurse, Karen Dunn Lopez, at (617) 732-3317.

Major Scientific Conference Planned

Plans are well underway for a major international scientific conference on Fanconi anemia. The National Institutes of Health will join with our Fanconi Anemia Research Fund, Inc. to co-sponsor a large international and interdisciplinary FA conference in the fall of 1992.

We thank Drs. Alan Levine, Neal Young and Helena Mishoe of the NIH, and Drs. Grover Bagby and N.T. Shahidi, among others, for their program planning collaboration.

This conference will be significant in at least three ways. It will be the largest modern FA conference yet - designed to attract between 100 - 180 highly competent investigators in molecular and cellular biology to FA research. Second, co-sponsorship by this prestigious federal government agency will give greatly increased visibility to our Fund's program efforts. Finally, the structure of the conference should demonstrate the importance of the study of FA, and should hasten further collaboration between laboratories and institutions.

Further details will be available at the FA family meeting and in the next regular FA Family Newsletter.

GM-CSF Trials Continue For FA Patients

Previous newsletters have publicized the potential of GM-CSF and other "colony stimulating factors" or "growth factors" to assist FA patients with low blood counts.

Medical experts at Boston Children's Hospital are eager to hear from fellow professionals whose FA patients might benefit from a GM-CSF clinical trial. At present, there is a limited number of slots available for this trial. This study will be closing in the near future.

Funds raised by FA families and friends in 1991 totaled $249,966. In 1990, our group raised $261,722 and in 1989, we raised $319,085. These amounts do not include special grants such as the Meyer Memorial Trust for Family Support or the Tiger Foundation grant for gene identification (see Newsletter 10), nor does this include money raised by families to offset their own extraordinary medical needs.

Linda Solin, our coordinator, provided the following breakdown concerning expenses related to the FA Research Fund: fundraising expenses, $6,830; and research grants, $246,543.

Funds spent to administer the FA Research Fund represent 8% of the amount raised by members of this support group. Compared to any other charitable organization, this is an astounding low figure.

Editors’ Update

Dave Frohmayer resigned after 11 years as Oregon Attorney General to accept appointment as Dean of the University of Oregon School of Law. The new assignment was effective January 1, 1992.

The Frohmayers retain their Eugene, Oregon residence and telephone number (503) 880-4133. Dave’s new office number is (503) 346-3531. Lynn Frohmayer can be reached at home or, on weekday mornings from 9:30 to 12:30 (Pacific time) at the FA Research Fund office in Eugene (503) 687-4658.

Nobel Prize Winner Joins FA Research Fund Board

In October, 1991, E. Donnall Thomas, M.D., 1990 winner of the Nobel Prize in medicine accepted our invitation to join the Board of Directors of the Fanconi Anemia Research Fund, Inc. Dr. Thomas has followed and assisted in our efforts for many years. He expressly conveys his sympathy with our goals and work.

Dr. Thomas, an internationally respected cancer researcher, was awarded his Nobel Prize for years of pioneering efforts in bone marrow transplantation, including unrelated transplants, to cure victims of cancer, aplastic anemia and a host of genetic diseases. Dr. Thomas and Dave Frohmayer of our Fund served together as founding Directors of the National Marrow Donor Program.

Thanks to Our Families For Continuing to Raise Research Dollars

We are so grateful to the many families who worked hard to raise money for scientific research. We are making progress because of your efforts! Please keep it up!

We are reporting on funds raised between July 1, 1991 and December 31, 1991. Many families previously raised substantial sums which have been reported in earlier newsletters and will not be repeated here.

Bill and Pat Danks generated $15,001 through creative efforts. Susan and Mark Trager raised $14,476. Leonard and Jan Riley raised $700, and donated an incredibly generous $12,500 to our Fund in memory of Katie Frohmayer. Their beautiful letter and stunning donation brought tears to our editors’ eyes.

Ed and Barb Brookover raised $5,135; Bill and Jackie Lucarelli another $2,331; Kevin and Lorraine O’Connor raised $1,501.80. Vicki and Andrew Athens raised $1,350 and Robert and Linda Scullin generated another $1,275. All of these efforts represented a great deal of effort; we are grateful to you!

Deane Marchbein and Stuart Cohen raised $800; Greg and Diane Hayes, $685; Dave and Lynn Frohmayer, $415; Joe and Lynn Linsenman, $375; Marlene Stone, $265; Joanne Bielewicz, $175; Lynn Lecuyer, $125; Leardon Keleher, $200; Nora Hersten, $170; the Ceresia Family, $150; Brian and Margaret Curtis, $100; Aaron and Jean Randolph, $100. Many families made individual contributions which are greatly appreciated as well.

Memorial contributions were received in memory of Haley Clendenning, Dee Dee Doutt, Donald Jordan, Brett Magill, Avi Weiner, Donna Williams, Dave Jansen and Katie Frohmayer.

Newsletter Production:
Special Thanks

Our “new look” continues again, thanks to the generous donation of time, materials, graphics and printing by American Greetings Corp. of Cleveland, Ohio. Martin Sankey, one of our FA parents, deserves our continuing gratitude. We extend our special appreciation to Martin’s colleagues and supervisors at American Greetings for this wonderful public service.

Our editorial “hats off” to Helen Wolff, Manager, and Don Hinkey, Computer Composition and Order Forms Supervisor and Supervisor of Office Services. We deeply appreciate this highly professional assistance.

January, 1992
BONE MARROW TRANSPLANTS:
NEW SUPPORT RESOURCE

Your editors have begun receiving the very helpful BMT Newsletter.

The newsletter is edited by Susan Stewart, a former BMT patient, and is published six times annually. For subscription information, call (708) 831-1913.

Financial Aid, Fund Raising, Special Services


National Children's Cancer Society (800-882-6227): Grants averaging $10,000 to children needing a BMT.

Organ Transplant Fund (901-684-1697): helps BMT patients organize fundraisers.

Children's Transplant Association (214-287-8484): counseling and financial aid to BMT patients.

Cancer Fund of America (615-971-3444): up to $50/month in aid to cancer patients.

Leukemia Research Foundation (708-480-1177): up to $1500 in aid to leukemia patients.

Leukemia Society of America (212-573-8484): pays up to $750 in aid to leukemia patients.

Children's Leukemia Foundation of Michigan (313-353-8222): provides financial aid to prospective BMT patients in Michigan.

Nielsen Transplant Foundation (904-798-8999): aids some Florida residents in need of an organ transplant.

Dexter Johnson Trust (405-232-3340): aids Oklahoma children needing a BMT.

Life Core (503-385-9125): organizes fundraisers for Oregon residents needing a BMT.


Information and Support Groups

Candlelighters (800-366-2223): local support groups for parents of children with cancer, a quarterly newsletter, a youth newsletter and research updates.

American Cancer Society (800-227-2345): information and support groups.

BMT Family Support Network (203-677-4546): links prospective families with others who’ve been through the experience.

Children's Leukemia Foundation of Michigan (313-353-8222): links prospective BMT patients in Michigan with others who’ve been through the experience, and offers a booklet about BMTs to Michigan residents and non-residents.

Aplastic Anemia Foundation (301-955-2803): informational brochures and support groups in some areas.

Leukemia Society of America (212-573-8484): informational brochures, including some specifically for children, and support groups in some areas.

Leukemia Research Foundation (708-480-1177): periodic newsletter and counseling.

Immune Deficiency Foundation (410-461-3127): newsletter, informational brochures, and support groups in some areas.

Assn for Brain Tumor Research (312-286-5571): newsletter and patient education materials.

Shands Hospital
A coloring book about BMTs for $5.
Write Coloring Book, Shands Hospital BMT Unit, Box 333, JHMHC, University of Florida, Gainesville, FL 32610.

KIDS' CORNER

Wendy Sauder, age 11, wrote a lovely letter to Phyllis Cafaro. She writes “I would very much like to help you with your fund raising. I am going to knit mittens and scarves. Could you please send me 6 beanie[s]?” Wendy, please know that we are all so grateful for your efforts to raise money for research. Thanks from all of the FA families.

HEALTH INSURANCE QUESTIONS:
IDEAS AND INFORMATION REQUESTED!

One FA parent recently wrote about a concern that potentially could affect many of us.

As FA children grow older – a prospect for which we all hope – parents’ health insurance may cease to cover them after age 18, 21, 23, completion of college or some other event. Where does the child then obtain health insurance?

Our concerned parent noted that even where the FA child’s employer provides health insurance, many insurance companies exclude coverage for “pre-existing conditions.” Sometimes that exclusion may be permanent for one year; for other carriers the exclusion may be permanent.

Your editors would like to know how other FA families have faced this problem. Please send us ideas or information so that we can respond more completely to our parent’s inquiry.
Q & A

Diana Fitch, child therapist and mother of an PA son, offers valuable advice to all of us who have to endure difficult procedures with our children.

Q. My child cries and cries when medical procedures are done to him. What can I do to help him?

A. Children cry not only because the procedures are painful, but also because they are scary. Anxiety tightens their bodies and increases their physical pain. There are four important ways you can support your child during medical procedures to reduce fear and marginal pain.

1) Help your child gain control through information and predictability.

Children must know what is going to happen to their bodies. Explanations of procedures must be given in words they can understand. Before each appointment, ask exactly what procedures will take place. Make sure you understand the procedures well enough to explain them to your child. Find out who will do the procedure (can it be someone with whom your child has developed a relationship?) Ask if someone at the hospital will answer questions your child might have. Encourage your child to ask questions. Answer them honestly or help him seek answers. (The source of a child’s fear might surprise you. A child might fear that all of his blood must be removed for a complete blood count).

Seek assistance from your hospital’s child life department. Specialists can help your child gain a sense of control and mastery by, for example, facilitating play with dolls where children practice the procedure that will be done to them. Breathing exercises and other techniques similar to prepared childbirth classes can be taught to children to help them manage pain.

2) Help your child process the experience after the procedure is completed.

Assure your child that being brave is doing something difficult even when he is scared. Let your child know it is okay to cry. State clearly when the procedure is done for that time. Allow some quiet time right after the procedure. When your child talks about the experience, you just need to listen with acceptance. Remember not to promise what you cannot deliver. Unfortunately procedures that cause pain or anxiety are often repeated.

3) Define a role for yourself during your child’s procedure.

Knowing how you are going to help will reduce your anxiety. Your feelings of confidence and purpose will ease your child’s fears. When appropriate, be your child’s advocate when talking to medical personnel about what your child wants them to know. (My son always wants the alcohol wiped off before the needle is inserted). Some children, however, greatly prefer explaining their preferences directly to medical personnel. If this is the case, respect your child’s desire to be “in control” and let him speak for himself.

Your presence or your spouse’s can be very reassuring to your child. If possible, give your child some say in terms of which parent he wants to accompany him. Consider, too, which spouse is better able to control his own fears and be helpful to the child. If neither of you can handle the situation, ask a last resort consider having some other adult whom your child trusts accompany him in your place. In most cases, children greatly prefer the presence of their own parents.

Remember that just as your child needs to process what happened, so do you. Seek support from another adult to vent your emotional response to your child’s pain.

In closing, we must remember that crying when hurt is normal. Although it is painful for us, we must accept our child’s tears and allow this natural outlet. There are times when children must bear sustained painful medical intervention. Sometimes children no longer cry as they resign themselves to these procedures. The shutting down may be their only means of coping. However, such a shut down of emotional response must be watched closely and may call for evaluation and support through your hospital’s psychological services.

EDITORS’ NOTE AND DISCLAIMER

Statements and opinions expressed in this Newsletter are those of the authors and not necessarily those 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.
Sisters continue living in the face of rare genetic disease

By LISA MARIE CISNEROS
Tribune Staff Writer

Living with a disease that affects everybody differently, but most often ends in early death, makes every birthday a milestone.

Such is the case with two local sisters, Robin Moroney, 28, of South Lake Tahoe, and Wendy Epps, 24, of Gardnerville. Both married with children, they are considered lucky to be alive.

"This will encourage others that their children can grow up to be our age," Moroney said of their decision to seek publicity.

While in the prime of their youth, Moroney and Epps were diagnosed to have Fanconi Anemia, a rare genetic disorder that usually kills its victims by early adulthood – as it did their brother, David Eichman, two years ago.

"We’re called senior citizens in this disease," Moroney said.

A woman whose fair skin barely reveals a wrinkle and whose hair lacks the grays of age, Moroney realizes her own mortality, yet remains confident.

"I just take it one day at a time," she said. "I’m going to be kicking and screaming all the way. I don’t want to go yet."

An inherited disease, Fanconi Anemia depletes bone marrow of its ability to produce white and red blood cells and platelets. The disease is closely associated with leukemia and other malignant diseases of the blood and often leads to anemia, infection and bleeding. Patients with Fanconi Anemia also may have congenital heart disease, absent or fused kidneys, gastrointestinal abnormalities, growth retardation and learning disabilities.

Other than witnessing their brother’s demise and knowing they have the disease, Moroney and Epps don’t experience any pain or obvious symptoms of Fanconi Anemia.

“We have to go regularly to get our blood count checked,” Epps said.

“It’s real hard not knowing what will happen," Moroney added. "But we’re not really suffering from it, so it’s easy to deny it.”

Getting the support and love they need from their parents and husbands has made them more tolerant to the mysteries of their own survival. Their sheer determination to watch their daughters, Breanna and April, grow up empowers their energy to exist.

"You start wondering whether you’ll live to see your daughter graduate," Moroney said.

For Moroney, who gave birth three months early to 1-pound, 14-ounce Breanna, just getting past a difficult pregnancy and seeing her daughter through infancy was a challenge. Their parents are deemed carriers of the disease, as are their daughters, although they may not be affected by Fanconi Anemia.

Their fears and frustrations of the future are compounded by the fact that research on Fanconi Anemia depends on funding of attempts to find an ultimate cure.

"Doctors still don’t know very much about it," Moroney said. "My husband hates when we have to see a new doctor because they freak out." Epps said. "They say, 'This isn’t right, it’s not normal,' but it’s normal for me.”

What is normal for Epps now was a nightmare when the disease first surfaced in her family. David had gone to the hospital after a ski injury when the disease was first diagnosed. That was the first of a series of trips to doctors working to fight the disease.

Some five years after he was diagnosed with Fanconi Anemia, David died of a brain hemorrhage at age 27.

Should the condition of either or both of the two sisters worsen, their chances of survival depend largely on whether they receive a bone marrow transplant. But finding a compatible bone marrow donor is another obstacle in a maze of medical uncertainty.

“(David) wasn’t able to find a bone marrow donor and within one year his bone marrow failed,” Epps said. "When a person donates blood they can volunteer for the bone marrow registry. It could save our lives.”

The Fanconi Anemia Research Fund, Inc. was established as a non-profit corporation to assist with costs for research as well as to provide assistance and support services to families affected by the disease.

To contribute to the fight against the disease, contributions can be sent to the Fanconi Anemia Research Fund, 66 Club Road, Suite 300, Eugene, OR 97401.
From Our Families

From Our Canadian Friends

Mary and Larry Heath of Oshawa, Ontario, Canada shared a lovely letter with our support group. We quote in part:

"Our little boy Matthew was born September 1, 1987. We knew two months before he was born that he was going to have problems. When he was born he weighed in at 5 lbs. and was transferred to the Hospital For Sick Children in Toronto. His known disabilities at this time included hydrocephalus, small optic nerves, bilateral radial arms, absent bone in right shoulder, absence of thumbs, bilateral dislocated hips, single pelvic kidney, undescended testes, and one overriding toe on his right foot.

Since his birth he had a VP shunt to drain excess cerebral spinal fluid, two operations to correct his hips, an operation to remove a twisted testis and an operation to lower the remaining testis. Last year he was diagnosed as having moderate hearing loss and narrow ear canals as well as fluid behind the ear drums.

He was admitted for further tests which led his doctors to suspect Fanconi anemia. Three weeks ago the final genetic test confirmed the diagnosis. Around the same time HLA tissue typing on our daughters (Emily, 3 years and Charlotte, 20 months) and ourselves did not yield a match.

This has been a very difficult time for us and we feel that it is made even more difficult by the attitudes of some people. They seem to think that since Matthew has different disabilities, having this potentially fatal disease is for the best. If you wanted to include anything in your newsletter about our family let it be our belief that Matthew's disabilities do not in anyway lessen the tragedy of him having FA. He is our precious son - always has been and always will be.

Sincerely,

Mary and Larry Heath"

---

Editorial Thanks and Remembrance

Katie bounced back from 14 hospitalizations in 18 months with raw courage. Treating physicians and specialists uniformly described her as the most baffling and complex FA case they had ever confronted.

We thank each of you who remembered Katie with your thoughts, prayers and messages of concern. The collection of memorials we received is an archive of inspiration. We will treasure it forever. Our deepest gratitude for your outreach.

We renew our commitment, lasting as long as we live, to eradicate the genetic curse that takes such beloved children of promise from their lives and from their full contribution to this world. Please continue to work with us. Redouble your efforts. Too many families have suffered enormous pain as a result of this devastating illness; too many of our precious children have died. We must work tirelessly until no one in the future is victimized so cruelly. That will be our best memorial contribution to Katie and the many other wonderful children we have lost.

Mary, 1992
Michael Sykes Remembered

Cheryl Sykes of Warwick, R.I. lost her son Michael to FA at the age of 13. Early in his life, Michael was removed from his home because authorities believed that his bruising and bleeding problems were indicative of child abuse. Finally, at age 4, he was diagnosed with Fanconi anemia and returned home.

Michael received most of his treatment at home, including shots, blood draws and his I.V. medication, so that he could spend as much time as possible leading a normal life. Sadly, Michael developed leukemia in November, 1990. A subsequent yeast infection, respiratory problems and renal failure led to his death on January 22, 1991.

Cheryl shares a very poignant, eloquent letter with us. We quote in part:

"Art and music were his first loves in life, and although he was born without thumbs on either hand and was missing the radius in his right arm he compensated for this and learned to play the violin. In fact, the first song that he learned was to play, he played for me as it was my favorite, The Rose. He went on to play the electric guitar, the recorder, the keyboard, and the drums. He also learned to draw exceptionally well. Many of his drawings were placed in our local art museum. We are very proud of him. He really touched our lives in a way that no one else ever could. We learned many lessons from him but I believe the most important one is not to take life for granted as you never know when it will end."

Life without Michael will never be the same but we try to make the next day. His 14th birthday is soon approaching and we will have to deal with that. I know it will be hard but with God’s help we will make it. Michael’s two sisters, Andrea, age 9 and Kristina, age 5, still do not fully understand what has happened and where their brother has gone. We explain as best we can and hope that they will someday understand.

My heart goes out to each and every one of you who are battling FA. It is not an easy disease to fight and even harder when you know that right now there is no cure. Please take the time to enjoy your child now, today, whenever you have a minute for you never know when those minutes will end and you are left with only memories. Memories are wonderful things to have but I would gladly trade the memories for my child. Life for today for tomorrow isn’t promised to anyone.

My love and prayers are with you all,

Cheryl Sykes and Family"

Cheryl shared a poem Michael wrote just prior to his death:

All For One

Take a look around
Won’t ya tell me what you see?
Is there love to be found in this
World’s pain and misery?

All for one and one for all
Isn’t that the way it should be?
Will we ever change this world?
United we stand up tall,
United we will never fall,
If it’s all for one and one for all.

Days are gain’t by,
It’s up to you to make a start
Before this earth of ours turns to
Dust and falls apart.
Right now, I know, we can make
A change.

In Loving Memory of Dee Dee DePeris-Doutt
— By her mother, Gayle Licari

Dee Dee bravely and courageously battled for her life from the day she was born on March 3, 1966. Many, many times she overcame difficult, life-threatening health crises. When Dee Dee was diagnosed with Fanconi anemia we learned she faced her biggest and toughest battle yet.

For 7 years she fought like a champ to overcome and win this battle, too, but it was not to be. Her battle ended on May 13, 1991 from complications from an unrelated bone marrow transplant. Dee Dee was so thankful and so grateful that a forty year old man from Wisconsin was willing to share his marrow in hopes that she might be cured.

Dee Dee’s family and friends will always love and remember her for her love, spunkiness, and zest for life. Her three favorites in life were swimming, skating and socializing. She amazed her friends with how well she could use her hands. They could not beat her at foosball or pool. This achievement delighted her. She amazed her doctors and nurses with how well she cross-stitched with her hands. My greatest treasure is the SERENITY PRAYER she cross-stitched.

Our family will continue the battle to find a cure for Fanconi anemia that has claimed Dee Dee and so many other young people in the prime of their lives.

But with the passing of the seasons
Life is still not done, not through
For there is yet another season,
When each spirit is renewed.

And it is in this calm fifth season,
In this hopeful second spring
A time of new awakening.

Each person’s life will come full circle,
Even as the seasons do
To start another different life,
Much better than the one we knew.
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Appendix I

The following is a compilation of lay summaries from the Fanconi Anemia Satellite Meeting held in conjunction with the 8th International Congress on Human Genetics in Washington, DC, October 1991.

CLONING OF THE FANCONI ANEMIA (A) GENE
Rodent Mitomycin C-Sensitive Mutants
Margaret Zdiernicka, Ph.D.
Leiden University, The Netherlands

This research project has been supported by Fanconi Anemia Research Fund, Inc.

In order to isolate the Fanconi anemia (A) gene, we have been using the Chinese hamster cell mutant (V-H4) which is homologous to FA(A) and shows cellular characteristics of cells derived from Fanconi anemia patients (i.e., hypersensitivity to crosslinking agents).

After transfection of V-H4 cells with human (HeLa) DNA, primary transfectants, which regained the resistance to crosslinking agents due to the presence of human DNA, were obtained. To confirm that secondary transfected cells were isolated from two independent primary transfected transfectants. The secondary transflectants showed a similar wild-type sensitivity to crosslinking agents indicating that DNA correcting the defect was transferred in the process of the secondary transfection.

When the presence of human DNA is determined it will support that it is due to specific human DNA, therefore, these transflectants will be used for the construction of a genomic library and hopefully the human FA(A) gene will be recovered.

FANCONI ANEMIA FIBROBLASTS ARE HYPERSENSITIVE TO THE DNA TOPOISOMERASE I INHIBITOR, CAMPTOTHECIN.
Inde Jeet Dokal, Ph.D.
Hammersmith Hospital, London, England

The primary defect responsible for Fanconi anemia (FA) remains unknown, but Mann, et al, have provisionally assigned the locus for FA complementation group A to 20q. The gene for DNA topoisomerase I, a candidate gene for FA, also maps to 20q(20q12-13.1).

Interestingly, it has been previously reported by Wunder, et al., that the sub-cellular distribution of topoisomerase I was abnormal in 3 FA placentae. In view of these observations we decided to study the effect of the specific DNA topoisomerase I inhibitor, camptothecin, on FA and normal cells.

The effect of camptothecin was assayed by counting the cells surviving a 24 hour exposure at various concentrations of camptothecin (0.01 -0.09ug/ml). At each concentration, the SV-40 immortalized FA fibroblast line (GM6914 obtained by Duckworth-Rysecki, et al., from a patient with FA belonging to complementation group A) was found to be more sensitive to camptothecin than the normal SV-40 immortalized fibroblast line (MRC5SV). In addition, 3 out of 6 primary fibroblast cultures established from patients with FA, also had increased sensitivity to camptothecin compared to normal primary fibroblasts. We are currently making nuclear extracts from FA and normal fibroblasts to see if there are any quantitative or qualitative differences in their topoisomerase I activity.

We are also studying the effect of camptothecin on peripheral blood lymphocytes from Fanconi patients, to see any qualitative or quantitative differences in their topoisomerase I activity.

We are also studying the effect of camptothecin on peripheral blood lymphocytes from Fanconi patients, to show any qualitative or quantitative differences in their topoisomerase I activity.

GENETIC COMPLEMENTATION OF FANCONI ANEMIA CELLS
Robb Moses, M.D.
Oregon Health Sciences University

This research project has received support from Fanconi Anemia Research Fund, Inc in 1990 and is currently in the application process for renewed funding.

Our goal is to identify the Fanconi anemia genes and the molecular basis for the defect in the disease as a prelude to appropriate therapy in the disease. Our approach is to use complementation at the cellular level to identify the genetic components responsible for Fanconi anemia. The system utilizes a permanent tissue culture cell line derived from a Fanconi anemia patient. These cells show increased sensitivity compared to normal cells in response to certain types of DNA damage. We have established conditions under which we are able to show that the transfer of normal genetic material will restore normal sensitivity (resistance) to such DNA damage.

In the future, we plan to rene the genetic components which complement the sensitivity to DNA damage in Fanconi anemia cells. Our approach will be to use techniques which transfer normal genetic material to the Fanconi anemia cell for complementation, until we have identified the smallest component which will restore resistance. At that point, we will begin a molecular analysis of that gene.

HYPMUTABILITY OF FA CELLS IN VITRO AT THE HPRT LOCUS
D. Papadopoulo, C. Guillouf, E. Mousacchi
Institut Curie, France

We have recently shown that FA lymphoblasts, belonging to complementation group A and B, are hypomutable after treatments with psoralen in combination with UV radiation of 365nm. This is true for the two genetic loci, HPRT and Na+/K ATPase analyzed. Southern blot hybridization analysis of the HPRT mutants allowed us to demonstrate that the hypomutability of FA cells is associated with an increased deletion frequency (K. Torpeulo, et al., 1990). In order to analyze the HPRT gene expression, Northern blot hybridization analysis of total RNA or analysis of cDNA after PCR amplification were performed on HPRT mutants without detectable rearrangements at the gene level. We found that the HPRT mutants arising from FA cells demonstrate much more frequently than normal cells an absence of mRNA as well as deletions in their cDNA.
potential for cloning the FA gene(s). Thus all our efforts have been directed toward the development of the human EBV-based genomic library of large inserts as a strategy to isolate the FA genes. The results of this novel cloning approach were presented at the "6th International Congress of Human Genetics" (Washington D.C., 10/91) and a paper on this topic was published in the new journal "International Journal on Genome Research".

Scientific Summary:
Progress has been on the development of an infectious Epstein-Barr virus-based (EBV) human genomic library of 150-200 kb size inserts which is propagated exclusively in human cells. Using a mini-EBV as a genomic cloning vector and a resident EBV from human lymphoblastoid cells (HLC) as helper virus, we have shown by Pulse Field Gel Electrophoresis analysis that between 175 and 225 kb or engineered DNA can be packaged into infectious EBV virions. We are currently using Fluorescence Activated Cell Sorter analysis that EBV virions carrying the bacterial betagalactosidase gene can efficiently infect HLC. The mini-EBV DNA inserts which are established as extrachromosomal plasmid in HLC can be recovered as infectious EBV; as a test case we have been able to shuttle mini-EBV cloned DNA into HLC from several Fanconi anemia patients. We are currently using such EBV-based library in combination with a PUV-based selection scheme as a strategy to isolate the defective genes from these FA patients.

GENE IDENTIFICATION
Freie Universität Berlin
Martin Dugew, Ph.D., Karl Sperling Ph.D.

One strategy for identifying the FA gene is to transfer DNA fragments from normal cells to FA cells and then look for correction of FA-characteristic cellular behavior. The DNA fragment taken in "corrected" cells is expected to harbor the FA gene. Our approach uses not DNA but RNA from normal cells with the advantage that only protein-coding sequences are transferred; the 100,000 genes, which actually code for proteins, make up only about 5% of human DNA. The disadvantage of using RNA is that it is more difficult to get into the human cell than DNA. We use direct microinjection using very fine glass needles.

In our first experiments we were able to detect a correcting RNA in a group of about 2,500 RNAs all of a particular length. By recombinant DNA techniques we have now isolated the correct one, RNA, and its gene, responsible for the effect and are currently characterizing these. Already it has become clear that although the RNA has a corrective effect in a cellular assay, we are not dealing with the FA gene itself. The gene is not mutated in any of the FA patients so far examined, a prerequisite for any candidate gene. The organization of this gene and the function of its protein product are objects of current research. In addition we are attempting to extend our experiments on FA using the same strategy but a different assay for correction, an assay which is hopefully more specific for the FA defect.

FAVONI ANEMIA IN 11 SOUTH AFRICAN FAMILIES, A REPORT ON CLINICAL AND GENETIC RESULTS.
Stander Jansen, Ph.D.
The University of the Orange Free State Republic of South Africa

We report data on 11 FA families where at most one person is affected by FA. Clinical and hematological results are available on 14 FA patients whereas 6 affected were investigated cytogenetically using DEB to enhance chromosome aberrations.

Growth retardation (100%), microphthalmia (93%), increased knee reflexes (93%), macrocephaly (86%), cafe-au-lait spots (86%), learning problems (63%), and hypoplasia of the thenar and hypothenar muscles (36%) are major clinical features. Age at diagnosis of hematological features varies between four and nine. The oldest living patient is 17 years. Hemorrhage is a more serious problem than infections and the major cause of death amongst our patients. Treatment concentrates on blood transfusions, analobic steroids and glucocorticoids. With equivalent medical care and treatment, there seems to be a higher mortality rate among black patients than their white counterparts.

Cytogenetically, homoyogous show typical rearrangements. However, carriers cannot be distinguished from non-carriers with certainty. Research in co-operation with Mathew et al. concentrate on the application of chromosome 20q probes for linkage analysis.

GLYCOPHORIN A IN VIVO MUTATION ASSAY
William L. Bigbee, Ph.D.
Lawrence Livermore National Laboratory

In collaboration with Dr. Arleen Auerbach of The Rockefeller University my laboratory has been engaged in the last year in a study of Fanconi anemia families using its newly developed method called glycophorin A in vivo mutation assay. This assay measures the level of genetic damage occurring in bone marrow stem cells by stem cells produce all of the white cells, red cells, and platelets found in peripheral blood. The method studies circulating red cells present in a small sample of blood (less than a teaspoon) and provides an estimate of the amount of gene mutation occurring in the bone marrow cells of the person sampled.

When this assay was applied to blood samples from Fanconi anemia families it revealed that affected family members exhibit variable, but very significantly elevated levels of spontaneous gene mutation. Parents of the affected children and unaffected siblings showed levels characteristic of normal adults and children in the general population. In two interesting cases involving Fanconi anemia subjects sampled prior to the onset of anemia, the assay also revealed evidence for a significantly elevated level of mutation. Thus the glycophorin A assay, when used together with other assays of cytogenetic damage, may have clinical utility in predictive and corroborative diagnosis of Fanconi anemia.

SUMMARY OF FA WORKSHOP PRESENTATIONS FROM THE LABORATORY OF Aleen D. Auerbach, Ph.D.:
This research project and its predecessors have been substantially supported for many years by FA families and by the Fanconi Anemia Research Fund, Inc.

1. Fanconi Anemia: Linkage Analysis With New Chromosome 20q Microsatellite Markers.
William R. Mann et al.
We have previously presented evidence for linkage of a gene for Fanconi anemia with polymorphic DNA markers on the long arm of chromosome 20. This location appears to be excluded in some families. We presented new data based on studies of eight new PCR-based polymorphic DNA markers which again support a location on chromosome 20 for a Fanconi anemia gene. With the new markers, we have defined a region on the long arm of chromosome 20 more proximal than the region reported earlier, for which there is again evidence suggesting a location for an FA gene. Ongoing analysis of our data should help to better define the region where this FA gene(s) lie.

2. Molecular studies of Topoisomerase I as a Candidate Gene for Fanconi Anemia.
Arleen D. Auerbach et al.
We have done a variety of studies to see if we could detect any abnormalities in the gene for topoisomerase I, which is mapped to the long arm of chromosome 20, and may overlap the region to which the FA gene is mapped. Topoisomerase I is a candidate gene because of its role in DNA breakage and repair and because it is known to play a role in DNA synthesis, DNA repair and regulation of cell cycle, which may be defective in FA. Of the 12 patients we screened DNA from 69 FA patients and did not detect any large deletions or rearrangements in this gene. Preliminary studies in 12 FA patients did not detect any abnormalities in topoisomerase I mRNA. Preliminary studies of mutations in this gene were also negative. Studies of the effect of camptothecin, a specific inhibitor of topoisomerase I, on baseline and DEB-induced chromosomal breakage also did not provide any evidence that this is the defective gene in FA. On the basis of all the studies presented, there is no evidence that a lesion in the topoisomerase I gene is responsible for FA. Additional studies to search for point mutations in this gene are in progress.

New Linkage Consortium for Fanconi Anemia:
Dr. Chris Mathew of Guy's Hospital in London, and independent data supporting these findings. We have established a Consortium for linkage studies in Fanconi anemia with Dr. Mathews' group. We will coordinate studies in our sepa-
rate sets of families so that the same DNA marker dere are analyzed. Data will be pooled, and analyzed by Dr. Stephanie Sherman, our collaborator at Emory University in Atlanta, GA.

**GENE IDENTIFICATION: FUNCTIONAL COMPLEMENTATION**

Michael Bucheik, Ph.D.
Craig Straehle, Ph.D.
The Hospital for Sick Children
Toronto, Ontario CANADA

This very promising research project is receiving financial support from the Fanconis Anemia Research Fund, Inc.

Research has centered on two areas: To determine the number of genes involved in FA, and to isolate one or more of these FA genes. In the first area, we have extended previous work which demonstrated that FA cell lines can be categorized into at least two different groups, designated FA(A) and non-FA(A) (formerly FA(B)). To determine whether the non-FA(A) group itself consists of more than one class of cell lines, the appropriate hybrid cell lines were created from among the 3 non-FA(A) cell lines and then tested to determine if their FA defect was corrected. All of the hybrids exhibited full correction (genetic complementation) indicating that the initial 3 cell lines belong in different complementation groups, designated FA(B), FA(C), and FA(D). In conjunction with the previous work, this suggests that defects in at least four different genes could lead to FA, and thus parallels the situation seen in other DNA repair disorders.

In the second area of research, this group is attempting to isolate FA genes based on the prediction that introduction of the normal version of the gene defective in a given FA cell line will correct the defect. A gene library (actually a cDNA library) was prepared and introduced into FA(C) cells. These were then grown in the presence of a drug, mitomycin C, which kills FA cells but not normal cells or corrected FA cells. Cells that grew in the presence of mitomycin C were then grown in the presence of diepoxybutane, another drug that FA cells are sensitive to. The DNA from cells that survived in both drugs was extracted and analyzed. We have found a new gene that has many characteristics consistent with it being defective in FA, making it an excellent candidate gene. We are currently attempting to prove that it is an FA gene by looking for specific mutations in different FA cell lines.

**BONE MARROW TRANSPLANTATION IN FA-PATIENTS**

T. F. Schoenhuber-Keath
Cytogenetic Laboratory
University of Heidelberg

Aside from our involvement in the diagnosis of FA in Germany we have concentrated in the last four years our efforts on research related to bone marrow transplantation (BMT) in FA-patients.

The Centers for BMT asked us to test the lymphocytes of FA-patients before the transplantation for their sensitivity to cytosine arabinoside (ARA-C), because this substance is used for the conditioning procedure. In 1986 we had already observed that some of the FA-patients' lymphocytes are more sensitive than others to Ara-C. Now this finding has been confirmed with 5 out of 10 patients. However, among the Non-FA-patients with aplastic anemia there were also some with high sensitivity to Ara-C.

Whether this information is going to change pretesting and/or the conditioning procedure before BMT can take place will depend on the discussions with the BMT centers.

Furthermore, we investigate before and after BMT the donor cells sensitivity to Diepoxybutane (DEB) or Mitomycin C (MMC). We observed during months and years after BMT 10 patients, 7 of whom received donor cells of the opposite sex. In these cases the identification of the donor cells is simple and certain. Three patients received donor cells of equal sex; these cases can only be compared with the others. The results are surprising: donor cells acquire MMC-sensitivity in the body of the FA-patient; however, in general they do not become hypersensitive to DEB.

Today we do not yet know how to interpret these findings. We further have to observe the sensitivities of donor cells very carefully during years after BMT. It could very well be that a diffusible factor from the body cells damages the donor cells acting like a stress to the cells repair capacity and thus resulting in an increased chromosomal instability. It also could be that the hypersensitivity to MMC decreases after years. At least this finding has to be considered whenever medications become necessary to treat FA-patients after BMT.

Appendix II

**PHASE I II TRIAL OF RECOMBINANT HUMAN GRAHULOCYTE-MACROPHAGE CONFLONY STIMULATING FACTOR (GM-CSF) IN PATIENTS WITH FANCONIS ANEMIA (FA)**

E. Guinan*, D. Nathan*, R. Hahn*, K. Lopez*, F. Oldham*
Children's Hospital and the Dana Farber Cancer Inst.
Harvard Medical School, Boston, MA and Sandex Research Inst., E. Hanover, NJ

FA is a congenital disorder characterized in part by progressive marrow failure and increased risk of AML. To determine if the marrow failure of FA would respond to GM-CSF, we initiated a study of subcutaneous (SQ) treatment (RX). Thus far 5 patients (pts) (median age 8.9 yrs, range 3.9-28.3) have entered. Pts had been pancytopenic for median 21 mos (range 3-35); 3 had failed RX with androgens and 2 had refused androgen RX. Median WBC was 2.2 x 10⁹/L (range 1.1-3.9) and ANC was 79 x 10⁹/L (range 0.9-9). Four pts were RBC transfusion (tx) dependent and 1 had HCT of 25%. Three pts were platelet (plt) tx dependent. The other 2 had plt of 14 and 20 x 10⁹/L. Marrow cellularity ranged from 1-50%. RX for 4 pts at the first dose level consisted of a 21 day (d) cycle of 2.5 ug/kg/d SQ bolus followed by a second 21 d cycle at 5 ug/kg/d if response was inadequate (3/4 pts). The first pt at the 2nd dose level started at 5 ug/kg/d and escalated to 10 ug/kg/d and then returned to 5 ug/kg/d. At 21 d, median WBC for all 5 pts had risen too 3.9 x 10⁹/L (range 1-6.2) and ANC to 1.0 x 10⁹/L (range 2.2-2.1). Further increases were seen by 42d - WBC to 6.9 x 10⁹/L (range 1-14) and ANC to 2.2 x 10⁹/L (range 2-4.9). Responding pts received 6 more weeks of RX at the responding dose. All pts had some increase in reticulocytes and 1 pt became RBC tx free. 1 pt early in study has increased plt. At end of study, 3/4 evaluable pts had improved marrow cellularity, 1/4 had increased megakaryocytes, 0/4 had excess blasts. Toxicities were mild and short-lived: low-grade fever, injection site reaction, urticarial rash and fatigue. Thus pts with FA can respond to GM-CSF. Further trials are needed to define the precise role of GM-CSF in FA and other congenital marrow failure syndromes.

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