Fanconi Anemia
RESEARCH FUND, INC.

The Fanconi Anemia Research Fund Story:

Building Something from Nothing

Extension of remarks at the 20th annual Fanconi Anemia Scientific Symposium

Eugene, Oregon

October 5, 2008[1]

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[1] Substantially revised and updated for distribution at presentation of the Medical Research Foundation Mentor Award for "outstanding contributions to biomedical research" to Lynn and Dave Frohnmayer, Oregon Health & Science University, Portland, Oregon, November 10, 2009. This paper also will be provided as background for the presentation of Dave and Lynn Frohnmayer to proceedings of the Institute of Medicine, Committee on Accelerating Rare Diseases Research and Orphan Product Development, National Academy of Sciences Building, Washington, DC, November 23, 2009.

A Special Two-Decade Anniversary

Tonight we acknowledge the 20th anniversary celebration of the first scientific conference of the Fanconi Anemia Research Fund. We welcome and thank you for being part of our continuing effort. When a small group of 19 scientists met in the U.S. Bank Tower building in Portland, Oregon twenty years ago, we had no idea that this exploratory effort would expand to the vibrant group of research laboratories, quite literally from around the world, that you represent here.

Our program invites you to hear remarks entitled "The Fanconi Anemia Research Fund Story—Building Something from Nothing." That puts me in the slightly awkward position of having to introduce myself. I caution at the outset that I will not be an Alan D'Andrea or a Hans Joenje each of whom has spoken on earlier banquet occasions with great prescience and enormous scientific knowledge. We already have seen some of their predictions come to fruition.

This brief retrospective is more than just a trip down memory lane. It reminds us of where we started, it tells us about the journey of our science, and perhaps may serve to recenter us on future priorities. It might also serve as a guide to those afflicted with other life-threatening genetic conditions. Dr. David Nathan, Medal of Science winner and the former director of the Dana Farber Cancer Research Center, and Nobel Laureate Dr. Lee Hartwell of the Fred Hutchinson Cancer Research Center, have remarked that the Fanconi Anemia Research Fund is the finest orphan disease research and support group in the world. That's not an honor or first prize that we sought. The larger question obviously is what are we trying to do? We simply are trying to solve a problem and alleviate some quantum of misery in the human condition. All of you attending currently are part of this effort. You deserve to know and recall our history and its larger lessons.

Early Outreach to Families and Experts

Our own family's journey began in 1983 when our ten year old daughter, Kirsten, was diagnosed with Fanconi anemia. We discovered almost immediately that her asymptomatic younger sister, Katie, was also afflicted. I needn't recount to you how lonely, scary, and devastating that verdict really was. We soon began to contact scientists whose names were in the published literature to seek their help, advice and guidance. Dr. Arleen Auerbach was kind enough in 1985 to urge us to form a family support group. She agreed to send out our solicitation letter to families in her registry, with copies and postage prepaid, so that confidentiality could be respected. Families could respond directly to us if they wished. After about six weeks, 17 families had responded and our informal organization was underway. We gathered significant momentum when a young man from Germany, Ralf Dietrich, wrote us and described his plight with two daughters afflicted with FA. We quickly became an international family effort.

For those of you who are too young to remember, and happily that is a great number of people in this audience, there was no Internet and no Worldwide Web. There were no search engines. Everything was communicated through airmail letters, rather primitive copying technologies and long distance telephone calls.

Expansion into Research Funding and "Accidental" Organization

In our desperate process we were gratified that almost every researcher authoring any publication, no matter how busy, would actually talk to us. We extended our outreach effort to find all of those who were knowledgeable. Lynn and I personally visited or called countless hematology units of major medical centers, and asked them to contact FA patients who might be interested in our group. By the mid to late 1980s it became important to raise funds to help research. Three researchers, two of whom are among the scientific veterans in this room, asked us for about $30,000 each to advance FA research.

The point of the story is actually quite significant. The Fanconi Anemia Research Fund was formally established almost entirely by accident. We agreed to raise money; we wrote hundreds of letters to friends and supporters; and we asked people to give money to the "Fanconi Anemia Research Fund." Donors dutifully responded in $10, $20, $30, $100 bundles. We sent those bundles of checks, equally divided, to each of those three researchers. The researchers reported back that their institutions' treasurers would not cash the donation checks because there was no formal accounting entity in their books known as the Fanconi Anemia Research Fund. We promptly decided to form a 501(c)(3) charitable corporation, named it the Fanconi Anemia Research Fund, cashed all the checks and sent each of those respective researchers $30,000. We appointed a board, established articles of incorporation, secured non-profit status from the Internal Revenue Service, created a board of scientific advisors…and we were launched.

Learning from Other Efforts

So serendipity ruled and accidents sometimes can create great opportunities. Initially, we had no sense of the power of using a government-recognized nonprofit organization, but that's how we started. At that same time, we searched for examples of other hereditary disease organizations. The most advanced of them was the Huntington's Disease organization—Huntington's chorea is a dominant genetic disorder that causes horrific and progressive neurological deterioration in its patient population.

The HD group was led by a brilliant and dedicated researcher, Dr. Nancy Wexler. We had seen her work featured on a PBS "Nova" program around 1985 that explored the developing field of gene therapy science. Dr. Wexler generously advised us about how we might advance our own science. We frankly went to school on the HD organization. I was invited to observe several of their meetings. Those of you who were in the gene discovery business know that notwithstanding a cadre of highly collaborative researchers who were among the world's most advanced, that HD collaborative group was "stuck" on the long arm of chromosome#4 for ten years trying to find the elusive HD gene by "mapping and walking". The HD group had developed and conveyed to us four essential principles. We not only faithfully copied these principles, but tried always to improve upon them.

Essential Guiding Principles

The first was the critical importance of scientific collaboration. While competition is healthy and Nobel fever may be unavoidable, there is an irreductible need—especially in dealing with rare disorders—for combinations of brains, not division of intellects into competitive and warring or secretive camps.

The second was the power of interdisciplinary perspectives. It was crucial to have the insights of varieties of basic researchers, clinicians, treating physicians and even family physicians and patients. A family physician was on our board from the beginning, and helped us to understand more broadly the various clinical manifestations of this admittedly heterogeneous and puzzling disorder. But we needed molecular biologists, bone marrow transplantation experts, geneticists and hosts of medical treatment specialists. Holding the attention and cross-focus of these disparate groups still may be our strongest continuing challenge.

The third principle was the imperative to bring experts together face to face: invite them to a conference for maybe a day and a half, and ask them to bring their brains. The FA group could not pay salaries, but it could defer modest expenses. We needed these ad hoc intensive gatherings for the advancement and the excitement of science. We copied that fundamental HD strategy and perhaps even improved on it. And then, even though their HD gene discovery effort had become mired down,[2] their experts told us: "Get the gene." We needed to focus on the molecular understanding of this disorder even while never ignoring its clinical manifestations. Potential cures would be better informed by basic science understanding.

The fourth of those principles was the imperative always to seek out the best science; to assemble a credible science advisory board; to insist on peer review; and never to reward or sustain mediocrity. That was the background of our first conference. We invited most of the people whom we knew had been published or might know something about Fanconi anemia to that first Portland meeting.

Early FA Science: A Baseline Point of Departure

FA basic science at the time of our first scientific conference is well chronicled in the 1987 book: Fanconi Anemia: Clinical, Cytogenetic and Experimental Aspects, coauthored and edited by T. Schroeder-Kurth, Dr. Arleen Auerbach and G. Obay. I re-read that book this afternoon. In retrospect it is historically interesting, prophetic, and also highly reflective of the uncertain state of the science at the time. Was FA a DNA repair disorder or was it a phenomenon of reactive oxygen species? What is the extent of chromosome breakage in FA cells and what will break chromosomes to reveal the FA phenotype? Is caffeine a culprit or a diagnostic agent? Is the disorder due to an oxygen radical vulnerability? Why does the disorder seem genetically "heterogeneous?" That latter word runs through the various chapters written by the very distinguished researchers of that time.

The formal genetics largely was understood. For the most part, other than recent knowledge of the FANC B gene and its peculiarities, the explication by Dr. Traute Schroeder-Kurth of the autosomal recessive character of FA remains accurate to this day. DEB and mitomycin C and the properties of those clastogenic agents with respect to their capacity to break and disrupt FA patients' chromosomes were understood. But researchers did not understand why patient cells reacted differently, or whether ethnicity or the mildness or severity of the disease had anything to do with the gene.

This publication presented the excitement of speculation on scientific frontiers, but also contained a great puzzle. Dr. Manuel Buchwald wrote a provocative chapter which announced prophetically, "In this paper we have discussed two aspects of complementation in FA. The first is the unequivocal demonstration of the existence of two complementation groups in FA." But as of our

[2] The HD gene discovery effort ultimately was triumphantly successful, and resulted in a powerfully co-authored publication in the distinguished scientific journal, *Cell*.

first formal meeting in 1989, there had been no further discovery to advance Buchwald's path breaking insight that there almost certainly would be more than one FA gene.

So that was the state of FA science. I was caught by surprise today as I reviewed this important two-decade old treatise. I had forgotten the poignant fact that three children affected with Fanconi anemia are pictured in the very front of the book—those are photos of our three young daughters, not otherwise identified by name. Lynn and I co-authored the book's concluding chapter, trying to explain the catastrophic impact that a disorder of this kind creates for one's family and one's hopes.

Foundational Discoveries Still in Development

But at the time of our 1989 meeting, many techniques of the science that would advance us so rapidly had not yet been discovered, yet the tools were beginning to be within reach of most laboratories. PCR had basically just been perfected only three years before. The National Marrow Donor Program (NMDP) was formed in 1986—I served as a member of the founding Board of Directors. We had enrolled a mere 17,000 donors. But the best scientists in immunology told us that we probably would be able to transplant between 80 and 100 percent of the patients of the world with 100,000 donors. Such was the state of histocompatibility science. DNA tissue typing was still far in the future. There was no human genome project beyond the gleam in planners' eyes. Unrelated bone marrow transplantation was uniformly or nearly uniformly fatal with the FA population. Androgens and transfusion therapies were maintenance treatments. But FA patients usually became refractory to them. There were no antifungals that could safeguard immune-compromised patients during transplantation. The Gluckman transplant regimen, with its deliberate reduction of toxic preparative therapies was new in Paris and promising, but again only if the patient had a matched sibling donor.

Early Understandings Guide Organizational Development

But even then, thanks to the dedicated and continuing leadership of hematologist Dr. Grover Bagby and his colleagues on our Scientific Advisory Board, we established some nearly immutable early principles. Any departure from these principles has been an oversight, not our intention. First, our organization, including its lay members, needed to be scientifically credible from the outset. Even though our newsletters went largely to families, we could not boast of freak medicines or extend false hopes for cures. Our publications had to be scientifically grounded.

Second, we believed in setting goals and carefully writing them down. Every year with the assistance of the Scientific Advisory Board, our governing board revisits the goals of our organization. Although some nearly annual changes may seem like minor rearrangements of language, in fact, those goal revisions faithfully reflect scientific advances and new opportunities consistent with our major objectives.

Third, we needed to be interdisciplinary, as difficult as that cross-disciplinary dialogue can become. The recent addition of head and neck cancer specialists to our advisory processes has accompanied discovery of the startling incidence of these cancers in adult FA survivors.

Fourth, we needed to be based upon best science, so we have employed NIH standards and scoring systems for peer review. But we decided also to be deliberately provocative in making some types of grants; we would take risks; would be willing to make the pilot study investment in the

promising investigator or investigators if that might allow them to proceed later for more extended funding from government or foundation sources.

Strategies for Public Awareness

In addition to these principles, we knew we had to raise public consciousness of this rare orphan disorder. Our early publications emphasized a cancer connection, and we knew from FA patient data assembled by Dr. Blanche Alter and others of cancer susceptibility. But precise understanding of cancer-causing mechanisms wasn't clear. However, we also knew that if FA remained an "orphan disease" it would be a curiosity, a subject of pity, but very probably not a subject of robust scientific advance.

We needed always to keep attention on the larger human ramifications of our research effort and its connection to cancer. As Dr. David Nathan and others repeatedly have observed, FA is a "back door" to understanding cancer. This outreach has engaged scientific, fundraising and concerned publics. We have maintained a relentless focus on the broad human implications of discoveries and therapies that will draw interest, resources and scientific passion well beyond our orphan disease concerns.

We knew that we had to gain financial capacity as well as financial credibility. Our Board and small staff formally set an objective in 1990 that we called our "Gene Identification Project." This was highly ambitious for a group of people based in Eugene, Oregon, albeit well advised by internationally respected scientists. We declared our objective to find the gene for Fanconi anemia in five years. "We" did! A distinguished investigator who took part in our first meeting described a gene in 1992. We celebrated the discovery by bestowing our first ever "Award of Merit" on Dr. Manuel Buchwald, Hospital for Sick Children, Toronto, Canada, at a wonderful family meeting in Disney World, Florida. The FA children walked in to the strains of "Oh Canada" carrying Canadian flags in a deeply moving ceremony of celebration. We just didn't realize there were more genes to follow until Buchwald and his colleagues published another discovery in *Nature* announcing that there were at least four FA genes, perhaps more. But this effort was an incredible start because, at least, broadly speaking, our new organizational community had made a commitment about scientific advancement to donors, scientists and the public that we could honor.

Family Engagement as a Central Strategy

This organization has been based on family involvement since the beginning. Our practice is faithfully reinforced by the kind comments that so many scientists make about our families. This is a greater partnership than many genetic disease organizations might otherwise tolerate—especially where scientific issues are difficult and at the cutting edge. But it is plausible, indeed essential, to observe that without family engagement, many of our scientific discoveries would not have occurred—the patients could not have been aggregated together in sufficiently meaningful numbers.

I well remember a summer at our FA family camp. Drs. Alan D'Andrea, Hans Joenje, and Marcus Grompe went around after the Emla cream was put on the veins of pretty unhappy little kids. Those researchers took blood samples of what was then the largest collection of FA patients ever assembled any place in the world at a given time. From that set of patient blood samples came the capacity to do the laborious and technically demanding complementation studies. The collection of patients was sufficient to discover the differences in gene group complementation. Without that tedious but crucial sample base, many subsequent gene discoveries could not have taken place—at

least at the speed that thereafter directly resulted. DNA mouth swabs and human genome knowledge that would come to be commonplace research techniques were still at least a decade in the future.

We learn from our stakeholders. One of our family members proposed to Lynn and to me early in our effort that we should assemble a family meeting. Lynn and I basically retorted: "Nobody will come. The kids are sick; the families don't have much money; we don't have a central place for them to gather. So if you want to do it go ahead and do it, we will help but go ahead and you do it." I trust that example illustrates how clearly one can be clearly wrong. It still helps us to recognize and learn from our human failings. In fact, one hundred people came to that first meeting. It was the first time most of them had ever met anyone else with FA. Families stayed up much of the night and so did we. That meeting was the basis of a family organization that although still small, is robust and engaged. We list 550 families in our international directory. We have at least 350 on line every single day, although many of them "lurk" rather than participate overtly. But the connection worldwide is made possible by the profound belief that families matter.

Our affected families speak significantly about future directions. They provide the funds that power our program. This year (2008) we will raise two million dollars. Eighty families are now actively engaged in that monumental task. Many more give what they can. Our money doesn't fall out of the sky; it comes from the cookie sales and the bikeathons and marathons and the jogathons, benefit dinners, golf tournaments and the letter writing campaigns of patients who are desperately afflicted and want to see a difference made in their world. They know in some fundamental way that they can advance scientific research which in turn can make a difference in an FA patient's chances at life.

Celebrating Success, Looking Back, and Taking Thoughtful Risks

We celebrate our successes. What are they? We've published three editions of a handbook for families and their physicians—one that has been translated into other languages. Thanks to the efforts of Ralf Dietrich and others in Germany the family handbook has been updated recently. After a major consensus conference, we just published the carefully researched and authoritative clinical care guidelines.[3]

In addition to our international scientific symposia, we have sponsored many other meetings on specialized FA topics, including stem cell transplantation, small molecule screening, gene therapy, clonal abnormalities and diagnosis and FA squamous cell carcinoma. We have published more than 46 editions of a semi-annual newsletter. The first newsletter was produced in our family living room on an Apple IIe computer and daisy wheel printer and went to several hundred people. Now we have a distribution list of many thousands from around the world. Any scientific error in the newsletter is by accident, not because the article hasn't been peer reviewed and carefully proofread by multiple pairs of eyes.

We've seen families empowered when they might otherwise feel hopeless. We have watched bone marrow transplantation science achieve an amazing rate of survival where earlier we would have thought such progress impossible to imagine. We have invested 12.6 million dollars in scientific research, supported 45 laboratories worldwide with 164 research grants, and have leveraged our seed money into literally tens of millions of dollars more from government and foundation sources

[3] *Fanconi Anemia: Guidelines for Diagnosis and Management,* Third Edition 2008, was published and distributed in early 2009.

in the Americas and Europe.[4] We have advanced science, sometimes even by brute force. We have supported experts who believed in taking chances, not just those who choose the safe paths.

The original publication by Buchwald and others announcing the existence of the "C" gene (discovered by functional complementation) had, at least I was told, two reviewers, one of whom said that the putative gene was just a polymorphism. Happily, the other review was sufficiently strong that *Nature* published the paper, and an avalanche of new discoveries changed the world of FA gene discovery.

Fludarabine had been known to be a powerful immunosuppressant that might permit unrelated donor FA marrow transplants to engraft in the face of a 30 percent graft failure rate. This possibility was suggested by a small and otherwise not very well noted paper from abroad. But this concept was advanced in a review grant that came to the FA Research Fund. Our scientific review committee agonized about it. Two of our reviewers were skeptical. One said it wouldn't work, because there never is just <u>one</u> drug that ever works to that degree. The second reviewer warned that the drug might be too toxic and dangerous for the patient. The Fund took a chance. The review committee very carefully and thoughtfully recommended that we fund it. And from that single drug change and the daring researcher, Dr. John Wagner who pursued it, we have witnessed the thrilling reality that young and not so young people can survive unrelated donor transplantation. Fludarabine now is used not merely in FA patients but throughout the world for many of the most difficult stem cell transplants. This innovation originated because an FA Research Fund grant wanted to stretch the world of the possible.

The first umbilical cord transplantation in the world occurred in Paris with an FA patient whose family was associated with the FA Research Fund. And the first child conceived intentionally as an HLA match was delivered to the Nash family. It resulted in the successful umbilical cord transplant that saved their FA daughter's life. The Fanconi pathway genetic mystery you all know about is a series of triumphs. Each new gene discovery has represented a major victory. The discovery of these FA genes, their protein products and how they operate in a complex, indeed a web of networks, could not have happened without the tireless energy of Hans Joenje in Amsterdam and his worldwide colleagues, and the wonderful discoveries that Markus Grompe made with the D2 gene function, and Alan D'Andrea made in isolating D1 and, with Grompe and others identifying BRCA2 as an FA gene. The huge influx of cancer scientists that entered our field with these discoveries—including many of you in this room—is a direct and proud piece of our history.

We have gone against the grain of some reviewers in order to take risks that might save lives. The role of FA families in finding the basis for the complementation group studies was a result of our efforts. Some of our old debates (and a good number in this room will remember them) now may seem quite arcane. Was the FA gene product active in the cytoplasm or was it in the nucleus? We saw shouting matches over that question and in related disputes. Is the defect of FA related to oxygen species or is it a problem of DNA repair—or could it be both? Is it "one gene, one protein, one function" or can some genes have more than one function? The discovery announced by Dr. Grover Bagby and others on this latter point now is accepted as an article of faith, but was controversial at the time—a "time" less than 10 years ago. As you may remember, we also were told "reliably" just a little more than a decade ago that there were at least one hundred forty thousand genes that determined our biological functions as proud homo sapiens. Now we understand we

[4] Statistics in this and preceding paragraph updated as of November 6, 2009.

don't have many more than 30,000 although we seem to function from time to time better than the earthworm does with 900.

A Translational Science Focus

The capacity of the NMDP to rescue patients in need of an unrelated stem cell transplant has been enhanced in a significant degree by bone marrow and stem cell donor drives by FA families, themselves who are raising money as well for FA. We still have a long way to go. Stem cell transplantation is dangerous; we wish our patients could avoid it. Dr. Frank Smith said earlier in this conference, and Grover Bagby added helpful perspective to hypothesize—we don't think this is jocular any more—that maybe some day there will be a "pill." Hopefully small molecule screening with cell assays and new animal models such as the mice, the zebrafish or others will speed progress in finding life-extending drug compounds. We profoundly hope so.

The ominous incidence of squamous cell carcinoma is still horrendous. FA patients have died of this complication, and are developing it, and it is an awful death. We know that there is a fragile connection sometimes between the basic science and the clinicians. We urge you with every energy in our bodies to make sure that our translational imperative stays robust. This illness needs the widest range of insights and development into curative science.

Being guided by "good science" is never a guarantee of straightforward success, however. We are investigating new frontiers, and one cannot dictate "unpredictable" discoveries either as to outcome or timing. Gene therapy continues to be elusive, even though FA theoretically is an ideal candidate disease because correction of a few, even a *single* bone marrow stem cell would promise such hope for patients. New cytokine isolation and development has not proved to sustain cell lineages of blood in the face of an FA patient's failing bone marrow. Exciting as gene and "pathway" discoveries are to molecular understanding, they have yet to suggest a straightforward therapy. Gene identification has proved to be crucial, however, for family planning. And through prenatal genetic diagnosis and *in vitro* fertilization gene-specific detection has led to the birth of life saving umbilical cord blood sibling donors. Mutation screening can be used in some cases for prediction of the early onset of more serious conditions.

But some other recent discoveries, such as the role of impaired cytokine function can suggest help through more general new developments in other areas of the life sciences, for example, small molecule screening and genome-wide analysis of patient cells.

Some Generalized Leadership Lessons: What Dedicated People Can Do

There is much more that might be done. But look for larger lessons out of it. I often present our case example to eager youngsters in my long-standing University of Oregon freshman seminar on "Theories of Leadership." Ten principles emerge. You probably try to observe these principles in other contexts. They are founded in common sense, but they form the basis for our continuing focus. These are some of the reasons why even though we are only a small group of people, by determination, by persuasion and by raw intelligence of our dedicated experts we <u>can</u> advance science—and make life better, not just for a subset of FA patients, but for those who are afflicted by a much larger universe of diseases.

- We need to establish and <u>keep our organizational credibility</u> by doing, learning and developing good science.

- We need to find communities of interest larger than ourselves, engage with them and work with them.

- We need to develop strategic alliances with the powerful because, by ourselves, we are not powerful. Enlisting the aid of others brings not only power, but the resources of the National Institutes of Health and private foundations. Professional organizations bring connections, investigators with new insights, and can make a huge difference.

- We need to seize opportunities, not wait passively for things to happen.

- We need to study and observe unashamedly, the strategies of others and adopt and adapt them when they make sense.

- We need to learn from our stakeholders. Lynn and I were happy to tell fellow parent, Dr. Vicki Athens that we were wrong about whether we should expend the effort to gather for family meetings. We smile when we see the robustness and the payoffs of that family effort.

- We need continuously to ask questions—searching inquiry is central to our mission. As an association we—and you as scientists—faithfully should follow our "there are no dumb questions" rule. The maxim is important because knowledge is power, and ignorance is not bliss.

- We celebrate successes as we celebrate tonight. When you have a chance to recognize a triumph, take it!

- We recruit other leaders. The continuation and growth of an organization in this kind of effort needs a process that is renewing and self renewing. Nothing made me prouder today than when we asked those of you attending our symposium for the first time to stand. Nearly a third of this room of 200 researchers rose. That is a sign of health and growth of an organization of inquiry, and of the advancement of science.

- And, finally, we try always to personalize our cause.

You are not surprised, we trust, that by the end of the day our collective effort is about people, not cells under a microscope or PowerPoint graph presentations of kill curves of chromosome-breaking chemicals. These people—mostly youngsters—want and deserve a chance. They are bright, loving and caring. They have dreams, hopes, and incredible courageous insight. They came onto this earth innocent and blameless of fault of their own. Their DNA has tiny mishaps that beset them with enormous dangers and often pain—but they possess enormous potential and joy as well.

You saw, in our video earlier this evening, those "Faces of FA." We hope they continue to be your motivation to redouble your efforts into an enduring and dedicated future.