

Proceedings Of The First International Symposium On Fibrodysplasia Ossificans Progressiva September 25-26, 1991

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For three days last September, The Children's Hospital of Philadelphia (CHOP) and the University of Pennsylvania School of Medicine became the focal point for the world of Fibrodysplasia Ossificans Progressiva (FOP).

The University of Pennsylvania collaborative research efforts in FOP were established in September of 1989, by Michael A. Zasloff, Chief of the Division of Human Genetics and Molecular Biology at CHOP and by Dr. Frederick S. Kaplan, Chief of the Division of Metabolic Bone Diseases at the Hospital of the University of Pennsylvania. These efforts arose out of a mutual desire to establish the cause and find a cure for this disabling disease.

In the broad spectrum of human afflictions, FOP is an extremely rare disease, and is estimated to afflict fewer than 2500 people worldwide. FOP is a developmental disorder of connective tissue characterized by congenital malformations of the feet, and progressive heterotopic ossification of the tendons, ligaments and muscles. Progressive bone formation usually begins during the first decade of life and is often heralded by painful swelling of the spine and limbs. The swellings can resolve but often mature into normal bone that bridges and rigidly immobilizes the joints. Bone formation can be triggered by slight trauma but often occurs spontaneously. Once extra bone has formed, it remains for life. Attempts to remove it are frustrated by more exuberant new bone formation. To date, there is neither effective therapy nor prevention. Patients with FOP often experience a normal life span, but may succumb to respiratory compromise as a result of abnormal bone formation involving the accessory muscles of respiration.

The First International Symposium on Fibrodysplasia Ossificans Progressiva was co-sponsored by Drs. Zasloff and Kaplan in collaboration with members of the national and international FOP community. The meeting was sponsored by the International Fibrodysplasia Ossificans Progressiva Association, The Jud Bogard Invitational Golf Tournament, the Division of Human Genetics and Molecular Biology of Children's Hospital of Philadelphia, and The Department of Orthopaedic Surgery at The University of Pennsylvania School of Medicine.

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Fig. 1: Cover of Abstract Booklet from the First International Symposium on Fibrodysplasia Ossificans Progressiva.

The major goal of the meeting was to bring together scientists, patients, and physicians to focus attention on the rare disorder of FOP, and seek a broad multidisciplinary perspective that would foster a better understanding of the condition. Accordingly, a distinguished group of experts from a broad spectrum of biological and medical sciences were assembled to discuss their work and to exchange ideas. Patients, family members, and caretakers participated in the historic proceedings that united all factions of the FOP community.

Many of the scientists attending the meeting had made seminal contributions to the understanding of FOP and related disorders of bone formation. Many others were introduced to the FOP community for the first time. The organizers hoped that the symposium would provide the opportunity for patients, families, physicians and scientists to obtain much needed first-hand information from each other. Such dialogue would serve to promote progress and understanding of FOP at all levels.

The importance and implications of FOP research for affected patients is unassailable. However, the importance of FOP research to the general medical community should be far greater than its rarity might indicate. FOP is, in fact, the paradigm of all disorders of renegade bone formation. By unravelling the complex pathogenesis of FOP, there is great hope that more common disorders

of bone formation will become understandable and treatable. During the past decade, there has been great progress in understanding the cellular and molecular mechanisms involved in bone formation. This work has prompted the formulation of new theories on the pathogenesis of FOP. However, the molecular basis of the disease remains a mystery.

The scientific portion of the meeting spanned two full days on September 25 and 26, 1991. Activities involved formal lectures, discussions, and a wide array of workshops for scientists, physicians, patients and families. On the final day of the meeting, there was a unique clinic for patients and families. There are approximately 100 known patients with FOP in the United States. Twenty-four patients attended the meeting. There were 10 children and 14 adults.

Introductory comments were presented by Drs. Kaplan, Zasloff and Kelley. Dean Kelley placed the problem of FOP in the broad spectrum of heritable diseases. He discussed the importance of interactive exchange between patients and scientists in this unique and historic forum.

Professor Connor (University of Glasgow) discussed the natural history of FOP and provided extensive explanations of the diagnostic criteria which include malformations of the toes, and progressive heterotopic ossification in specific anatomic and temporal patterns. He discussed the poorly-recognized cervical spine anomalies seen in FOP and reviewed the classification of malformations seen in the feet.

Randolph Cohen, (University of Pennsylvania School of Medicine) presented the results of a study on the natural history of FOP in 44 patients. Cohen elaborated on the anatomic and temporal patterns of abnormal bone formation in FOP, and discussed them in the context of developmental gradients.

Drs. Kaplan (University of Pennsylvania School of Medicine) and Gannon (Jefferson University School of Medicine) presented the results of a large histopathology study in which they stringently documented the predominant ossification process as that of endochondral bone formation. Data included biopsy specimens from early as well as late lesions. These showed early perivascular infiltrates within muscles and tendons. An early fibroproliferative lesion was noted followed by transition to a cartilage template which was later replaced by bone and eventually normal marrow elements. Ultimately, mature bone in FOP is indistinguishable from bone of the normal skeleton. Kaplan and Gannon concluded that the developmental abnormalities, histopathology and occasional bony tumors seen in FOP suggest a predominant endochondral mechanism.

Subsequent discussion focused on putative growth factors and mediators of endochondral pattern formation. Dr. Sporn (NIH) discussed the potential role of transforming growth factor-beta (TGF-Beta) in bone formation. He reviewed the complex signaling processes involving TGF-Beta activity in both epithelial and mesodermal cells and

discussed the implications of TGF-Beta family members in the pathogenesis of FOP. Finally, he discussed theoretical mechanisms to inhibit bone formation experimentally, and elaborated on potential therapeutic implications.

Dr. Marshall Urist (University of California School of Medicine), discussed the historical perspectives of the bone morphogenetic proteins (BMPs) and reviewed definitions for morphogenesis. He discussed human pseudomalignant heterotopic ossification stimulated by BMP in athymic nude mice. Dr. Urist's pioneering work in the discovery of BMP was noted by the moderators and applauded by all.

Dr. John Wozney (Genetics Institute) discussed his group's pioneering work in cloning the bone morphogenetic protein genes and in describing the activities of these novel regulators of heterotopic ossification. Similarities to other molecules in the TGF-Beta family were noted, most strikingly between the BMP-2 and BMP-4 genes and the decapentaplegic gene in the fruitfly.

The afternoon session began with three concurrent workshops; on Disease Mechanisms, (chaired by Dr. Zasloff), on Clinical Research (chaired by Dr. Frederick Kaplan) and on Patient Needs (chaired by Sharon Palmateer). Sharon's dedicated work for the FOP community has focused on obtaining funding for motorized wheelchairs, and on identifying resources to help patients with progressive disability. She founded the I-Care Network, a non-profit organization to specifically pursue those goals.

Following the workshop sessions, the plenary session reconvened with a discussion by Dr. Gelbart (Harvard University) of decapentaplegic, the *Drosophila* homolog of BMP2 and BMP4. The Dpp gene controls proximal-distal development in the fruitfly. Mutations of the Dpp gene lead to abnormalities in pattern information in the fly similar to those pattern abnormalities seen with FOP in man. Dr. Gelbart discussed experiments in which the human BMP4 gene was used to rescue fatal mutations in the Dpp locus. Dr. Gelbart discussed the panoply of mutations in the Dpp gene and the possible relationship to FOP in man.

Dr. Garbern (University of Pennsylvania School of Medicine) discussed the homeobox genes as potential targets or controllers of BMPs. Dr. Lane (Cornell University School of Medicine) presented data on the use of BMP2 in orthotopic bone induction and further discussed how this exciting model might help elucidate heterotopic ossification in man.

Following a full day of scientific meetings, there was a gala reception for invited participants, patients, and guests in the Mosaic Room and Lower Egyptian Gallery of the University Museum. A certificate of commendation from The University of Pennsylvania was presented to Jeannie Peeper, the first President of the International Fibrodysplasia Ossificans Progressiva Association. Through Jeannie's courageous efforts, organizational skills and engaging enthusiasm, the IFOPA has estab-



Fig. 2: Drs. Kaplan and Zasloff with some members of the FOP community at the Banquet at University Museum.



(Left) Fig. 3: Dr. Michael Zasloff (left), Ms. Jeannie Peeper (President of the IFOPA), and Dr. Frederick S. Kaplan (right), at The First International Symposium on Fibrodysplasia Ossificans Progressiva; Children's Hospital of Philadelphia.

lished and developed interests in areas of clinical care, basic and clinical research, and patient and family education. Through these visionary efforts, the extraordinary dedication of the directors and members of the IFOPA, and the robust generosity of all of the sponsors, this historic gathering had become a reality. Jeannie noted that although FOP is not a new illness, the IFOPA is a relatively new organization, incorporated in June 1988. The IFOPA originated out of her desire to find and communicate with FOP patients. Although she was diagnosed with FOP at the age of 4 years, she had not met another individual with the disorder until three years ago. She and her family, like many others, struggled with the disease virtually alone. She noted that most of the doctors who treated her during her childhood and adolescence had never encountered another patient with FOP. Even more distressing, the medical literature contained little information on the disease. Through the help of many dedicated friends, Jeannie has made significant progress towards the goal of patient education, care, and research. She noted that one of the IFOPA's greatest achievements was a renewal of hope for all who suffer from FOP.

Jeannie emphasized the promise that research holds for the eventual cure of FOP, and indicated that efforts to find such a cure had inspired many patients with FOP.

She presented Dr. Jeffrey Tabas (now of the University of California, and a recent graduate of the University of Pennsylvania School of Medicine) with a plaque commemorating his receiving the first IFOPA Research Fellowship. Dr. Tabas was noted for his work in mapping three of the human bone morphogenetic protein genes, as well as seminal studies on the histopathology and genetics of FOP.

Mr. Nicholas Bogard (Board of Directors, IFOPA) presented Jeannie Peeper with a check from the proceeds of The Jud Bogard Invitational Golf Tournament. Through the foresight and generosity of the tournament sponsors and the Bogard family, FOP research has been revitalized.

Oliver Jordan (Executive Director of The Mayor's Commission On People With Disabilities Of The City of Philadelphia) extended his thanks to the IFOPA for their inspiring perspective on handicap and disability. In turn, Oliver was loudly applauded by the FOP community for his work in helping the I—CARE Network with patient needs and in helping locate vitally needed resources.

Drs. Zasloff and Kaplan thanked the invited guests for their participation in the symposium, and noted the appropriate locale of the meeting in the Egyptian Room at the foot of the Sphinx. Dr. Zasloff commented ironically that the riddles of FOP would be no less difficult to decipher than the riddles of the Sphinx. Mr. Harold Kaplan and Sharon Palmateer distributed stuffed animals to the children, which were kindly donated by the Gund Toy Company.

The second day of the meeting began with a sweeping historical perspective of FOP by Dr. Victor McKusick, Professor of Genetics at the Johns Hopkins University School of Medicine. Dr. McKusick placed FOP within the context of other heritable disorders of connective tissue, and discussed potential strategies for deciphering the complex molecular genetics of the condition. Dr. McKusick, who is internationally renowned for his studies in human genetics, acknowledged the value and importance of a combined clinical-basic science-patient meeting on this rare genetic condition.

Dr. Jeffrey Tabas presented detailed studies on a family with multifocal heterotopic ossification, and discussed the evidence for genetic transmission of FOP. Despite the noted sporadic and autosomal dominant nature of the condition, there has been scant evidence for the genetic transmission of the disease. Nevertheless, genetic transmission remains the most plausible etiology.

Dr. Michael Whyte (Washington University School of Medicine) discussed disorders other than FOP associated with heterotopic bone formation.

Craig Levitz (University of Pennsylvania School of Medicine) and Michael Zasloff discussed some of their recent studies on prostanoid metabolites in the serum of patients with FOP. They discussed the possible role of these prostanoids in the pathogenesis of the disorder but

resisted further speculation until their new and putative molecules were chemically characterized.

Dr. Carl Brighton (University of Pennsylvania School of Medicine) discussed the role of perivascular cells in osteogenesis, as well as the role of mesenchymal stem cells in the generation and regeneration of the skeleton.

Dr. Hari Reddi (NIH) completed the morning session with a discussion of bone morphogenetic proteins and osteogenesis, and speculated on their implications for the pathophysiology of FOP.

The final session of the meeting began with a lecture by Dr. Fisher (NIH) on recent advances in the molecular biology of the noncollagenous bone proteins. This eclectic review was followed by a succinct discussion of the recent advances in the molecular biology of human collagens by Dr. Jeannie Meyers (University of Pennsylvania School of Medicine). Summaries of the workshops held on the previous day were discussed by the workshop chairmen. Two videotapes shown by Sharon Palmateer at The Patient Needs Workshop were replayed for the entire assembly. One videotape, sponsored by the Sun Oil Company, focused on mobility needs of patients with FOP. The other videotape featured a day in the life of a husband and wife with FOP.

Closing comments for the Symposium were offered by Drs. Zasloff and Kaplan, and were followed by an extensive question and answer session for patients and families.

Dr. John Parrish (The Children's Hospital of Philadelphia) conducted comprehensive psychologic evaluation of cognitive, behavioral and social development in children with FOP. Following the formal completion of the two-day Symposium, there was yet a third day devoted to the clinical evaluation of children and adults with FOP at the Children's Hospital Genetics Clinic. History and physical examinations were performed, and blood samples were obtained for immortalization of cells and isolation of DNA for molecular and genetic studies.

In addition, there was an extensive activity program for patients and families which included more detailed patient-need workshops, as well as art-therapy classes. An international art exhibit coordinated by Carol Orzel featured works of art produced by FOP patients.

Newspaper and television coverage of the Symposium added to the excitement of the meeting. Much of the film footage obtained will be used for an extended segment on local and perhaps national television.

The cover picture for the Symposium program was painted by Ashley Kurpiel, an eight year child afflicted with FOP. The picture captures the feelings of all of those involved in FOP research (see Figure 1).

Throughout the meeting, participants noted the extraordinary verve and intellectual excitement prompted by the interaction of patients, family members, caretakers, scientists, and physicians. One scientist leaving the meeting was heard saying to another, "I think we just declared full-scale war on FOP!"

**Parental Evaluation of the First International
Fibrodysplasia Ossificans Progressiva Symposium
Friday, September 27, 1991**

By Dr. Richard B. Steele, with the endorsement of 13 other parents of children with F.O.P.

Someone has said that hope is a good breakfast but a poor dinner. It is a valuable quality when you have a future to await or endure, but a bitter consolation prize when the lights seem about to go out on life. For us, the best gift of this Symposium has been the restoration of hope — a veritable smorgasbord of breakfast! For we can now see that our children are, like other children, living in the morning of life, and that there will be new and effective treatments ahead for them, and perhaps even a cure. Further, they will lead rich, productive lives, despite

their disabilities, if they follow the courageous path which so many FOPers of riper years have trod. For this glimmer of hope at daybreak, we are grateful to the doctors, the researchers, the organizers, and the older patients who have participated in this wonderful event. And we can, of course, congratulate ourselves, too, for having established the support network among ourselves and our children, which will see us through the years of waiting for our new hopes to come to fulfillment.