

Introduction

**Frederick S. Kaplan, MD,^{1,2,4} David L. Glaser, MD,^{1,4} Robert J. Pignolo, MD, PhD,^{2,4}
and Eileen M. Shore, PhD,^{1,3,4}**

Departments of ¹Orthopaedic Surgery, ²Medicine, and ³Genetics, and ⁴The Center for Research in FOP and Related Disorders, The University of Pennsylvania School of Medicine, Philadelphia, PA

“The more the marble wastes, the more the statue grows,” wrote Michaelangelo, thus framing the debate over “The Captives,” his unfinished marble sculptures of human beings struggling to extricate themselves from eternal captivity (1). Anyone familiar with both the arresting images of “The Captives” and the nightmarish reality of fibrodysplasia ossificans progressiva (FOP) will immediately see a haunting similarity. However, FOP is neither art nor imagery. Rather, it is a reality so stark, sobering, and inescapable that it transcends the imagination.

The childhood victims of this musculoskeletal sabotage seem ostensibly normal at birth except for telltale malformations of the great toes. Soon, the children succumb to progressive waves of ectopic osteogenesis that transform the body’s soft connective tissues into an armament-like encasement of bone. Ribbons, sheets, and plates of heterotopic bone seize the body’s joints, and relegate its victims to a state of permanent and lifelong immobility. Any attempt to remove this heterotopic bone leads to episodes of explosive new bone growth. At the present time, there is no effective prevention or treatment.

FOP, known by many names throughout history, was first placed on the medical agenda more than a quarter of a millennium ago by a London physician and ophthalmologist. In a letter to The Royal Society

Address correspondence to Frederick S. Kaplan, MD, Department of Orthopaedic Surgery, University of Pennsylvania School of Medicine, Silverstein Two, 3400 Spruce St., Philadelphia, PA 19104. E-mail: frederick.kaplan@uphs.upenn.edu.

of Medicine, dated April 14, 1736 (published in 1740), John Freke wrote the following:

There came a boy of healthy look, and about 14 years of age, to ask of us at the hospital, what should be done to cure him of many large swellings on his back, which began about three years since, and have continued to grow as large on many parts as a penny loaf particularly on the left side: They arise from all the vertebrae of the neck and reach down to the os sacrum; they likewise arise from every rib of his body, and joining together in all parts of his back, as the ramifications of coral do, they make, as it were, a fixed bony pair of bodice. (2)

Nearly 200 yr later in 1918, Jules Rosenstirn wrote:

One does not wonder that a disease, so baffling in its course from the causes to its ultimate state, should invite the speculative as well as the patiently investigating observer to lift the obscuring veil and solve this embarrassing puzzle. (3)

An embarrassing puzzle it is. To physicians and scientists who study FOP, it is one of medicine’s most elusive mysteries. To patients who suffer from FOP, it is a painful metamorphosis into progressive immobility and a lifelong obstacle to physical freedom.

Although definitive treatments and cures are not yet available, the goals of FOP research are clear: to establish the genetic and molecular cause of FOP, and to use that knowledge to establish effective preventions, treatments, and a cure.

In the nearly 8 yr since the last published symposium on FOP (4), tremendous progress has been made in understanding the pathophysiology of this mysterious affliction; however, much work remains to be done. Some day, a child with FOP will be born and everything about this embarrassing puzzle of FOP will be known—its genetic basis, its molecular origin, the nature of its pathways, the identity of its receptive cells and their downstream targets, the drugs to prevent it, and therapies to cure it. That day is not yet at hand, but the journey and the climb toward that summit continues unimpeded and uninterrupted.

Despite daunting obstacles, scientific and medical progress is being made, and the current state-of-the-art practices, however primitive, are documented and summarized in this issue. The articles in this issue subtend a wide range of scientific and medical disciplines, including medical history, molecular biology, developmental biology, cell biology, pathology and laboratory medicine, epidemiology, hematology, immunology, genetics, oncology, pediatrics, general medicine, cardiology, pulmonary medicine, rheumatology, orthopedics, dental medicine, anesthesiology, physical medicine and rehabilitation, endocrinology, statistics, and pharmacology. Rarely does a musculoskeletal condition require or attract such a diverse audience.

The word *orthopaedia*, coined by Nicholas Andre more than 300 yr ago as the title of his seminal book, means “straight child.” This book, subtitled “The Art of Correcting and Preventing Deformities in Children,” anticipated the future, but it did not specify how the art would be applied (5). We are now firmly involved in the era of molecular orthopedics (6–9). The ultimate goal of FOP research is to understand its precise molecular basis so that the crippling deformities it leaves in its wake can be prevented. As Michaelangelo said 500 yr ago, “I saw an angel in the marble and carved until I set him free” (1). Although surgical tools will not be the answer for FOP, molecular medicine holds hope for the future. The story of FOP has moved far beyond descriptive accounts that stir anguish and fear into the laboratory that provides hope. Eventually, the work must return to the clinic with genuinely useful answers for the children (9).

This work holds hope not only for those with FOP, but also for those with more common disorders

of osteogenesis, such as osteoporosis and osteoarthritis. FOP is an uncommon condition of uncommon brutality, but the challenge remains: to understand the molecular dimensions of the nightmare and to stop it.

As Thomas Maeder said in an article in *The Atlantic Monthly*:

FOP and its problems lie at the crossroads of several seemingly unrelated disciplines. Answers to questions that FOP poses will also address grander issues of how the body first creates its shape and then knows where to stop, how tissues decide to become what they are, and why they don't turn into something else.(10)

The mission to discover the cause and to establish a cure for FOP is not just a matter of scientific inquiry. It is nothing less than a declaration of physical independence and personal freedom.

The editors are honored to dedicate this issue on FOP to our patients with FOP worldwide who dignify the struggle for personal freedom. Our heartfelt thanks go to the children, adults, and families who live with FOP every moment of their lives. Their equanimity and nobility provide the perpetual inspiration that dignifies this work and all who are privileged to participate in it. As the author William Faulkner stated in his Nobel Prize speech in Stockholm on December 10, 1950:

I believe that man will not merely endure; he will prevail. He is immortal. Not because he alone among creatures has an inexhaustible voice, but because he has soul; a spirit, capable of compassion and sacrifice and endurance.(11)

FOP research is a collaborative venture and we are enormously grateful to our many fine collaborators and generous contributors who support this vital effort.

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