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THE SKELETON IN THE CLOSET

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Abstract

The origins of fibrodysplasia ossificans progressiva (FOP) in human history are unknown but the condition has been well described since Freke's account in 1740. Important contributions by physicians and scientists in the past two and a half centuries have converged on the remarkable skeleton of Harry Eastlack at The Mutter Museum of The College of Physicians in Philadelphia.

The Biblical account of Lot's wife, the stark images of Michelangelo's captives, and the haunting story of Kafka's *Metamorphosis* subtend the story of fibrodysplasia ossificans progressiva (FOP), but the real origins of the condition in human history are shrouded in mystery (1, 2).

"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. 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 (2).

The childhood victims of this musculoskeletal sabotage seem ostensibly normal at birth except for telltale malformations of the great toe. Soon, the children succumb to progressive waves of ectopic osteogenesis that transform the body's soft tissue 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 (2,3).

The first case of FOP may have been described by Guy Patin in 1692 (4), but the first unequivocal description of FOP was recorded in the philosophical transactions of The Royal

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Society of London in 1740 by John Freke, a London surgeon and friend of Fielding who mentioned him in the novel ***Tom Jones***. Freke wrote:

> "April 14, 1736. There came a boy of healthy look and 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 (5)."

During the past 275 years, many physicians have contributed to the knowledge of FOP. Monophalangism of the great toe was first described as an isolated anomaly by Fränkel in 1871. The important association of brachydactyly of the great toe with FOP was first described by Helferich in 1879. The name *myositis ossificans progressiva* was likely assigned to this condition by von Dusch in 1868. The term *fibrositis* was substituted for *myositis* in the early 20th century to acknowledge the early inflammatory events that occur in the aponeuroses, fasciae, and tendons in addition to the skeletal muscles. McKusick noted that the muscles were only secondarily affected, and adopted the term *fibrodysplasia* in 1972, the term first suggested by Bauer and Bode in 1940. Many notable pathologists and physicians including Hutchinson, Volkmann, Kronecker, Virchow, Opie, Rosenstirn, Smith, McKusick, Connor, Evans, Rogers, Zasloff, and others have contributed important cases and summaries over the years (6).

Who Was Harry Raymond Eastlack?

Perhaps, the most famous of all patients with FOP was Harry Raymond Eastlack who was born in November 1933 in Philadelphia, and died there of pneumonia in November 1973, just six days before his 40th birthday (7).

The skeleton of Harry Eastlack, on display at The Mutter Museum of the College of Physicians in Philadelphia is the only fully articulated FOP skeleton in the world, and has become a valuable asset to physicians and scientists studying the disease.

Later in life, Harry Eastlack personally made the decision to bequeath his body and his medical records to the museum so that physicians and scientists in future generations could study and learn about FOP. Harry's skeleton has become a window into the medical mysteries and scientific challenges of FOP, and exemplifies the harsh reality of the condition more than any chart, slide, or clinical description could accomplish.

Normal skeletons collapse into piles of loose bones when the connective tissues that join bones together in life are removed. To be displayed in human form, skeletons have to be re-articulated or pieced back together with fine wires and glue. As a result of the bridges, plates and ribbons of heterotopic bone that form from FOP flare-ups, Harry's skeleton is almost completely fused into one contiguous piece. In essence, Harry had two skeletons: a normotopic skeleton formed during embryogenesis, and a heterotopic skeleton that formed as result of postnatal flare-ups of FOP.

Sheets of bone cover Harry's back. Ribbons, sheets, and plates of bone lock his spine to his skull, and his skull to his jaw. Additional ribbons of bone join the spine to the limbs, and immobilize the shoulders, elbows, hips, knees and jaw. Thin stalagmites of bone launch themselves from his pelvis and thighs. His upper arms are welded to his breastbone by slender white bridges of bone that cross his immobilized rib cage. The extra layers of bone on the outside of his skull are a permanent signature of numerous flare-ups at that site.

Harry was born in 1933 with telltale and characteristic malformations of the great toes. He experienced normal childhood until age five. At that time, he was playing with his sister Helene who was unaffected with FOP, when his leg was hit and fractured by a car. Shortly afterwards, heterotopic bone began to form in his lower limb and throughout his body in characteristic anatomic patterns (7).

Unfortunately, the diagnosis of FOP in Harry was delayed, as in most patients with FOP, and he was subjected to many unnecessary biopsies and surgical procedures that greatly exacerbated his condition. During his lifetime, Harry had 11 operations, most likely because well-meaning doctors never focused on the connection between the malformed toes and the heterotopic ossification. Had they done so, the diagnosis of FOP would have been assured and further harm might have been prevented (7,8).

Nevertheless, Harry had a relatively happy childhood. He listened to records and radio, loved reading, played cards, and went to the movies. In fact, Harry even had his own seat at the Hamilton Theater in Philadelphia, seventh row center, where he could recline and stretch out his leg, which did not bend. Everyone knew that was Harry's seat. In fact, if anyone else dared to sit in it, the ushers would chase them away (7).

Undoubtedly, the most important person in Harry's life was his mother Helen who was 41 years old when Harry was born. Harry's father worked on the railroad, but it was his mother who cared for him and doted on him, baked him cakes, and walked to him to and from school every day in every kind of weather. When Harry's mother could no longer care for him at home, he was moved to a Philadelphia nursing home called The Inglis House for The Incurables. There, Harry spent the last 20 years of his life, before he went to his final resting place at The Mutter Museum (7).

As FOP progressed, Harry had more difficulty with his activities of daily living and needed help for his daily toileting, feeding, dressing, and ambulation. At the end of his life, he was able to stand with assistance and shuffle with the use of a cane.

I met Harry's sister Helene, a music teacher from Philadelphia, years after Harry's death. Helene would visit The Mutter Museum annually and pay respects to her brother by visiting his skeleton which is on display there. Helene recounted for me Harry's last days in which he expressed to his sister his desire to have his body donated to medicine and to have his skeleton on display so that others might learn about FOP and possibly use the clues they obtained from his skeleton to solve this horrible mystery and misery.

During his lifetime, Harry never met another patient with FOP. FOP was (and still is) one of the rarest conditions known to mankind, and affects only one in two million individuals.

There are an estimated 3500 patients with FOP in the world. I personally have seen more than 700, and many of those patients gathered at the International FOP symposia in 1991, 1995, 2000, and 2007. In 1995 and 2000, Harry's skeleton was lent by The Mutter Museum to the International FOP Association for scientific and medical meetings at the second and third international FOP symposia. Physicians and scientists traveled to Philadelphia to learn about FOP and view this famous skeleton.

Nearly a century ago, in 1918, Jules Rosenstirn from Mount Zion Hospital in San Francisco wrote: "One does not wonder that a disease so baffling it is course from the first causes to its ultimate state, should invite the speculate as well as the patiently investigating observer to lift the obscuring veil and solve this embarrassing puzzle" (9).

An embarrassing puzzle it is. To physicians and scientists who study FOP, it has been one of medicine's most elusive mysteries. For patients who suffer from FOP, it is a painful metamorphosis into progressive immobility and a lifelong obstacle to physical freedom (3, 10).

We are now firmly entrenched in the era of molecular orthopedics. The ultimate goal of FOP research is to understand its precise genetic, molecular, cellular and tissue basis so that the crippling deformities it leaves in its wake can be prevented. In 2006, a monumental milestone was reached with the identification of the FOP gene and its recurrent mutation in a BMP type I receptor (11). The single nucleotide missense mutation – the substitution of an adenine for a guanine at nucleotide 617 in the coding sequence of ACVR1/ALK2 - leads to the substitution of a histidine for an arginine at codon 206. This mutation activates the ACVR1/ALK2 receptor and makes its mild constutive activity subject to hyper-activation by issue injury. Blueprints have been redrawn for the metamorphosis (12, 13). Animal models have been developed (14, 15). Progenitor cells have been identified (16, 17). New treatments are being explored (18–22). 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 and adults who struggle valiantly every day with this affliction.

The proximity of Harry's skeleton at the Center for Research In FOP and Related Disorders in Philadelphia has added enormously to its value in educating physicians, scientists, and patients across the generations. Although no member of the FOP research team ever knew Harry during his lifetime, they have come to know him well posthumously through his remarkable bequest. Physicians, scientists, and students are frequent visitors to The Mutter Museum where Harry's skeleton resides.

When an important FOP discovery is made, we return to visit Harry's skeleton in order to confirm the physical and the anthropological reality of the discovery. At other times, we may discover a clue from the skeleton that sends us back to the laboratory to test a new hypothesis about FOP. The gift that Harry has given to the FOP community is inestimable, and his bequest has given additional meaning and depth to the medical and scientific research well beyond the confines of his mortal existence. Harry has provided hope,

knowledge and inspiration well beyond the grave, and in fact bypassed that mortal resting place for a permanent residence in an institution of learning.

Harry's eternal gift and inspiration holds hope not only for those with FOP, but also for those with more common disorders of osteogenesis such 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. The 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" (23).

Harry Raymond Eastlack lived with FOP for his entire life. Our heartfelt thanks go to him across the generations, for his equanimity and nobility that provided 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 a soul, a spirit capable of compassion and sacrifice and endurance" (24).

Those are qualities that Harry had during his lifetime and they cannot be seen in the skeleton: But because of those qualities, we are able to see Harry's skeletons (both of them) and learn from them across the generations.

Summary

Most people have a skeleton in the closet. Harry Raymond Eastlack has two, and they both belonged to him in life. One of those skeletons, like ours, was endowed from conception and completed at birth; the other, unlike any most of us could ever imagine, was formed progressively during childhood and early adult life, caused him nothing but misery and suffering, and ultimately lead to his death.

Both skeletons stand entwined – rigid, silent, and austere - in a glass case in The Mutter Museum of the College of Physicians of Philadelphia. There, they reside for eternity - a silent tribute to the donor's vision and generosity, and a captive reminder of the depth of medicine's interminable quest for solutions to life's most enduring and intractable miseries. The key to the closet is the key to the kingdom (25).

Acknowledgements

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Abbreviations

FOP	Fibrodysplasia ossificans progressiva
BMP	Bone morphogenetic protein
ACVR1/ALK2	Activin A receptor, type I; Activin receptor-like kinase 2

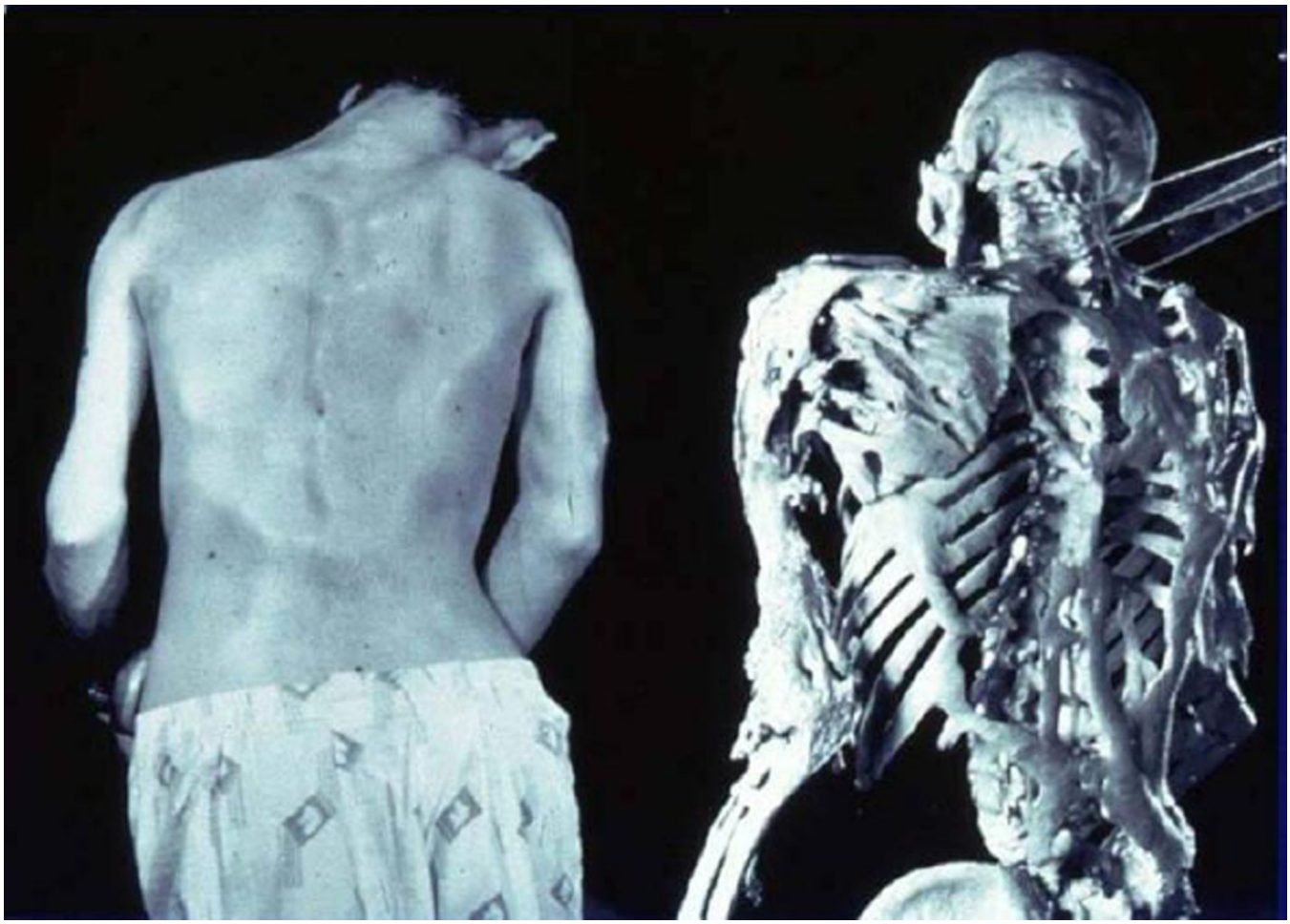
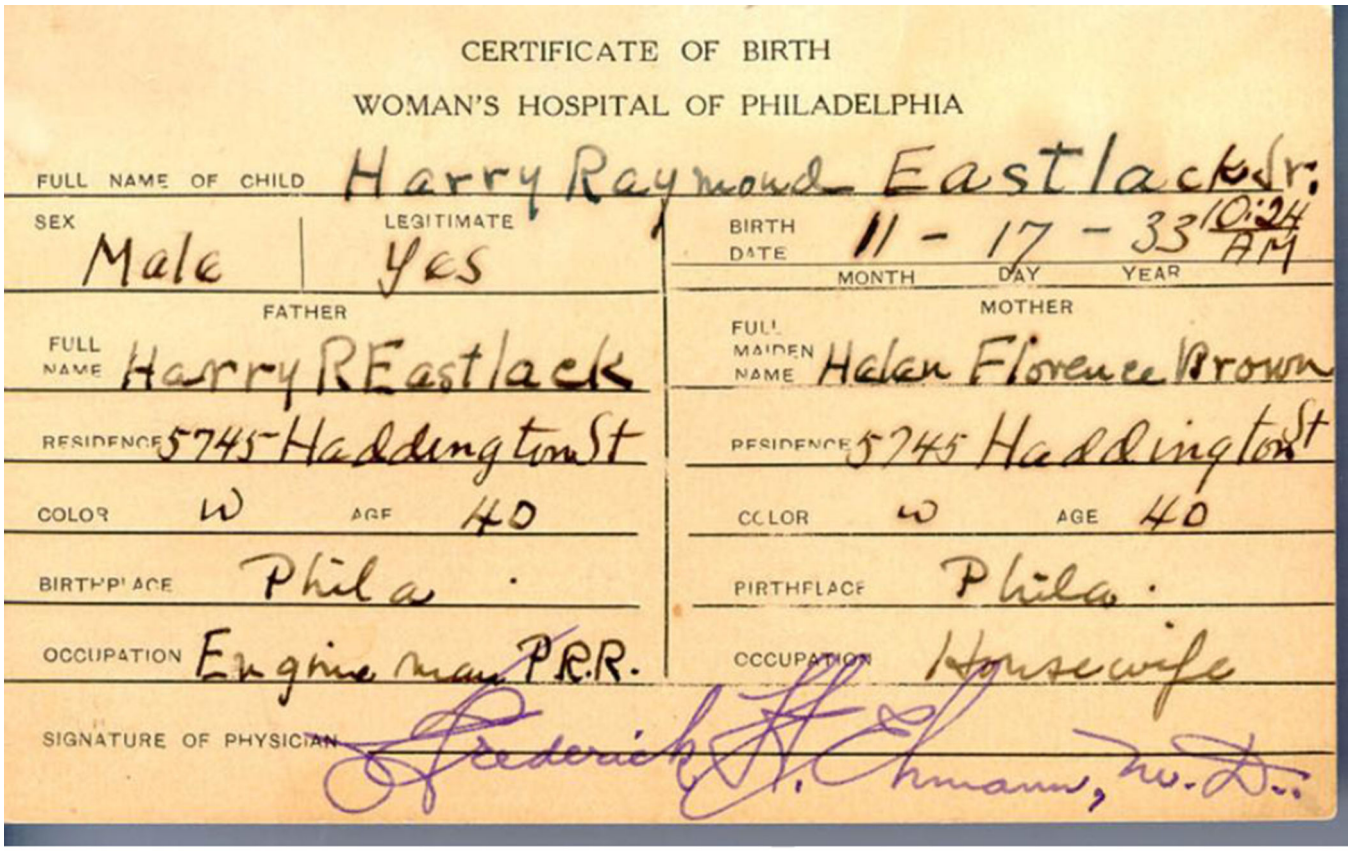


Figure 1.

Harry Eastlack and his skeleton.

Harry Eastlack was 25 years old when the photograph on the left was taken, 15 years before his death from pneumonia. His rigid posture is evident and secondary to the ankylosis of the neck, shoulders, elbows and spine. Harry's skeleton, pictured on the right, was a bequest from Harry to the medical community, and resides at The Mutter Museum of The College of Physicians of Philadelphia. Original pictures, courtesy of The Eastlack family, Gretchen Worden (former curator of The Mutter Museum), and Frederick Kaplan, were published in Shafritz, et al, 1996 (26).



CERTIFICATE OF BIRTH

WOMAN'S HOSPITAL OF PHILADELPHIA

FULL NAME OF CHILD: Harry Raymond Eastlack Jr.

SEX: Male | LEGITIMATE: Yes | BIRTH DATE: 11 - 17 - 33 10:24 AM (MONTH DAY YEAR)

FATHER	MOTHER
FULL NAME: Harry R Eastlack	FULL MAIDEN NAME: Helen Florence Brown
RESIDENCE: 5745 Haddington St	RESIDENCE: 5745 Haddington St
COLOR: W AGE: 40	COLOR: W AGE: 40
BIRTHPLACE: Phila.	BIRTHPLACE: Phila.
OCCUPATION: Engineman P.R.R.	OCCUPATION: Housewife

SIGNATURE OF PHYSICIAN: Frederick H. Ehmann, M.D.

a

b

Figure 2.
Harry Eastlack's birth certificate (a). Note the short, malformed great toe imprint (b).

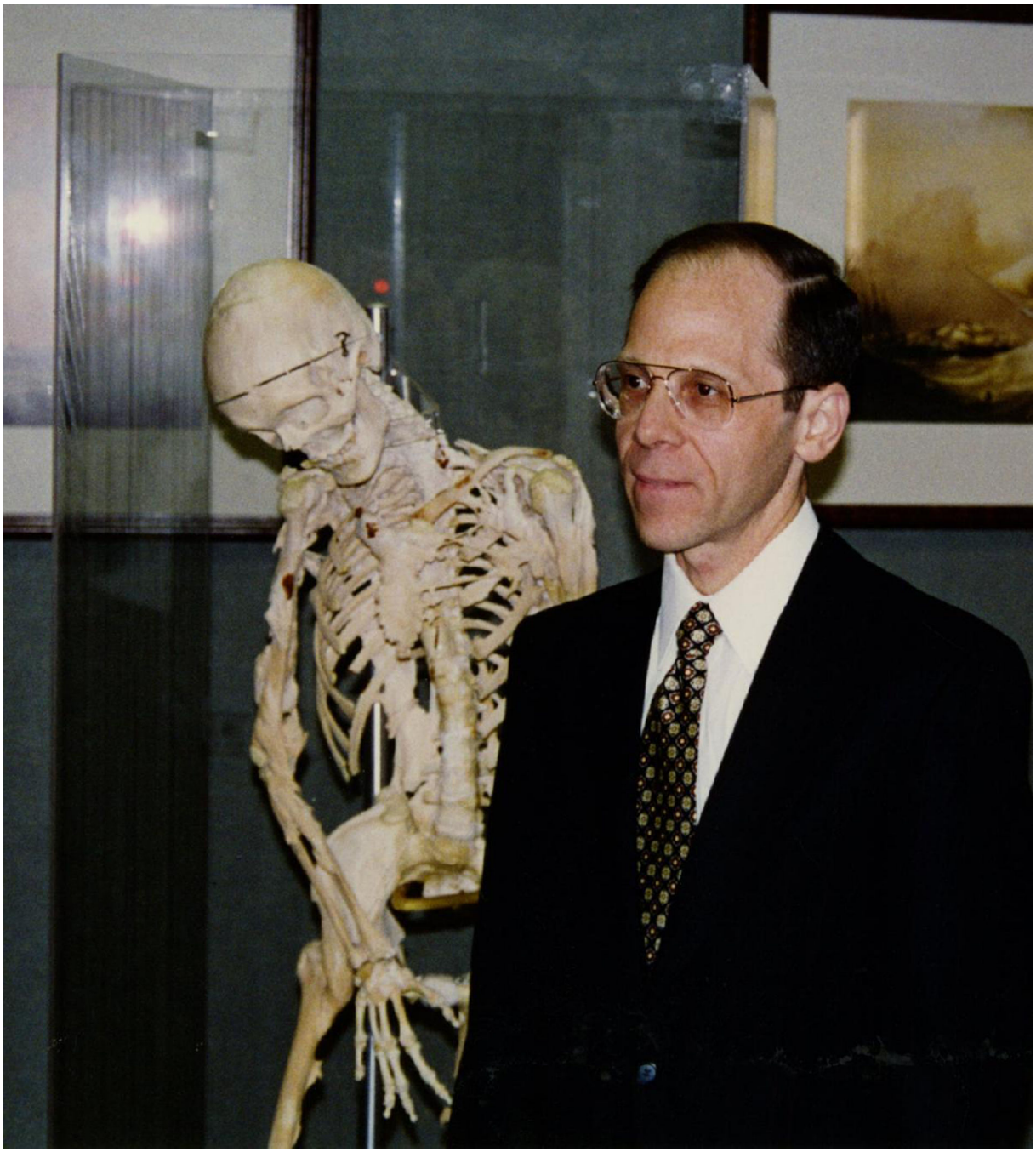


Figure 3.
Harry Eastlack's skeleton with Dr. Frederick Kaplan (the author) at The Second International FOP Symposium in Philadelphia, October 1995.