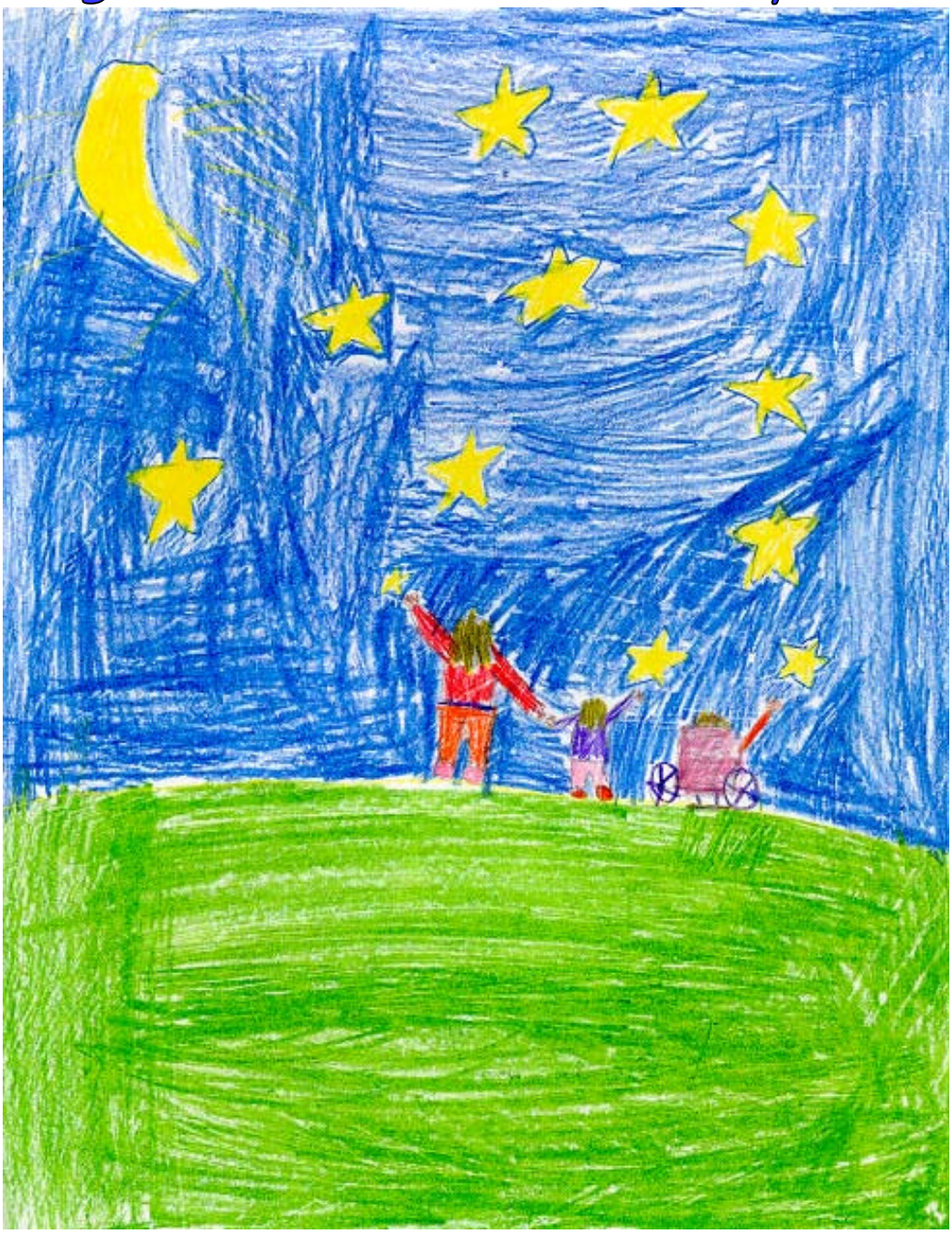
WHAT IS POH ?

Progressive Osseous Heteroplasia



A GUIDEBOOK FOR FAMILIES

SECOND EDITION

WHAT IS POH?

Progressive Osseous Heteroplasia

A GUIDEBOOK FOR FAMILIES

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Cover Picture: The cover picture of this second edition of The Guidebook, drawn by a 9-year-old child who has POH, depicts three POH patients (one in a wheelchair) looking skyward and reaching for the stars. This image captures the spirit of hope that propels all of us in the POH community.

DEDICATION

The authors and editors dedicate this book to the children and adults with POH worldwide. Your courage and spirit inspires us all.

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I. ACKNOWLEDGEMENTS AND CONTRIBUTIONS

This guidebook arose out of an imminent need to provide useful information for the families of children who have POH. The book reflects the thoughts and wisdom of many individuals whose constant and heartfelt guidance have made this work possible.

Remarkable progress has been made since POH was recognized as a distinct clinical condition in 1994. The first edition of this book was published in 1997, and the genetic mutation responsible for the condition was found in 2000. In a mere six years, the condition was described, the community organized, and the gene discovered. Much yet remains to be done, but the beginning has been strong and we are on the move to conquer this condition.

The editors wish to express their gratitude to each person who contributed to this project. This work will not reach a stage of completion until there is a treatment and cure for POH.

We noted in the first edition, just five years ago, that "we anticipate that this book will be first of many on the subject of POH, and will undergo extensive revisions and updates as progress occurs." So much progress has been made in understanding POH in the past five years that we are now ready for a second edition. We thank all of our friends and colleagues at The International FOP Association (IFOPA) for their extraordinary guidance and inspiration. The patient guidebook: "WHAT IS FOP? (Fibrodysplasia Ossificans Progressiva): A GUIDEBOOK FOR FAMILIES" serves as a model for this work, and can be found on the IFOPA website at www.ifopa.org.

The cover picture for "WHAT IS POH? (Progressive Osseous Heteroplasia): A GUIDEBOOK FOR FAMILIES" was drawn by Katelyn Jacobs, a 9 year old child who has POH.

II. PREFACE

This guidebook was written for the families of children who have POH, not because they are the only anticipated audience, but because too often, the families of children who have rare disorders have been the neglected audience who are unable to find anything to help them understand what was happening to their child.

The questions and answers presented in this book try to anticipate situations in which parents of POH children may find themselves. While common features of POH exist in almost everyone who is affected, POH affects each person in different ways. Certain generalizations have been made using the latest clinical and research data in an effort to help parents anticipate the needs of their child.

III. GENERAL QUESTIONS ABOUT POH

What is POH?

Progressive osseous heteroplasia (POH) is a rare genetic condition in which the body makes extra bone in locations where bone should not form. Extra bone develops inside skin, subcutaneous tissue (fat tissue beneath the skin), muscles, tendons, and ligaments. This "out-of-place extra bone formation" is commonly referred to as heterotopic ossification. In people with POH, nodules and lace-like webs of extra bone extend from the skin into the subcutaneous fat and deep connective tissues, and may cross joints. Extra bone formation near the joints leads to stiffness, locking, and permanent immobility.

The condition is often first noted in infancy with the appearance of small "rice-grain" particles of bone in the skin. A parent may describe this as a roughness in the skin. During childhood, bone formation may progress from the skin into subcutaneous tissue and extend into deeper structures including muscle, tendon and ligament. Affected areas may be small or large and involve scattered and variable regions of the body surface.

The condition does not involve any other organ system and does not affect the formation of any portions of the normal skeleton at birth.

POH is often congenital, meaning that it may be present at birth. In most children, symptoms of POH usually begin during the first few months of life. The majority of affected children are diagnosed with POH before the age of ten.

Bone formation begins typically in small patches of skin, and can occur in any region of the body. People who have POH experience different rates of new bone formation; in some, the progress is rapid, while in most it is more gradual. In each child, the exact rate of progression is unpredictable. In any affected area, there appears to be a progression from superficial to deeper tissues. For example, extra bone formation occurs first in the skin, then progresses down to subcutaneous tissue, and then to deeper tissues like muscle. In some individuals, the bone formation may involve a small area of the body, and in others, relatively large or multiple areas of the body. Very often, the extra bone formation may predominate more on one side of the body. Although the limbs are most commonly affected, bone formation may also involve the

head, chest, abdomen, pelvis and back.

What does POH stand for? When was it first documented?

POH or progressive osseous heteroplasia (PRO-GRES-SIVE, AHS-SEE-US HETERO-PLAY-SEE-YAH) means "the progressive transformation of soft tissues into bone," and it always involves the skin. The earliest documented case dates back to 1948 to a paper in *The Journal of Pediatrics*, Vol. 33: p. 618-623. The article by Drs. Edmonds, Coe, and Tabrah was entitled, "Bone Formation in Skin and Muscle: A Localized Tissue Malformation or Heterotopia."

Over the years, several other cases appeared with different names including progressive osteoma cutis, hereditary osteoma cutis, familial ectopic ossification, dysplastic cutaneous osteomatosis, limited dermal ossification, limited intramembranous heterotopic ossification, and osteodermal dysplasia. The term progressive osseous heteroplasia was first used by Kaplan and colleagues in a paper entitled, "Progressive Osseous Heteroplasia: A Distinct Developmental Disorder of Heterotopic Ossification," which was published in *The Journal of Bone and Joint Surgery*, Vol 76-A, p. 425-436, 1994. The term "progressive osseous heteroplasia" was used to bring uniformity to the nomenclature of the disorder, and to distinguish the condition from Albright Hereditary Osteodystrophy and Fibrodysplasia Ossifications Progressiva, two other rare developmental disorders of heterotopic ossification in children. In their 1994 paper, the authors stated, "We believe that the unique constellation of clinical, pathological, and roentgenographic (x-ray) features that characterizes progressive osseous heteroplasia, justifies its consideration as a distinct developmental disorder of heterotopic ossification." Since the first use of the term (progressive osseous heteroplasia) in 1994, there have been approximately 40 new cases described using that name.

How many people have POH?

POH is an exceedingly rare condition, with approximately 40 patients identified in the world. It is likely, however, that there are many more patients who have POH who have been misdiagnosed as having other conditions. Our recent studies indicate that POH may be more closely related to several other genetic disorders than previously recognized, forming the far end of a spectrum of clinically distinct, but genetically related, conditions. As information is disseminated about POH through scientific

journals, meetings, the Progressive Osseous Heteroplasia Association, the National Organization for Rare Diseases, the National Institutes of Health, and the Internet, it is likely that many more patients who have POH will be diagnosed. The identification of individuals who have POH is important in order to learn as much as possible about the condition including the spectrum and severity of associated symptoms.

How is the extra bone in POH different than the bone of the normal skeleton?

In the normal skeleton, bone forms in one of two ways: indirectly from a cartilage scaffold (endochondral ossification; as in the formation of the long bones), or directly from a bone-forming membrane (intramembranous ossification; as in the formation of the skull). The extra bone in POH seems to form by intramembraneous ossification within the fat tissue underneath the skin (subcutaneous tissue), and in tissue within the skeletal muscle.

Once it is mature, the extra bone in POH is indistinguishable from normal bone, except by its very abnormal location. The POH bone can be strong, can support weight, and can respond to mechanical stress as normal bone will. In fact, if the extra bone is broken, it will respond to the break just as normal bone, and it will heal the fracture.

In POH, does muscle become bone or is it replaced by bone?

In POH, bone forms in the skin, fat, and muscle. Numerous types of cells comprise each of these tissues. At the present time, it is not known exactly which cells within these tissues give rise to bone.

Recent observations from diagnostic skin and muscle biopsies in patients with POH suggest that a transformation from fat to bone occurs in the deepest layers of the skin as well as in the fat tissue that is interspersed between the bundles of muscle cells that make up skeletal muscle. There is no evidence at all to suggest that fat cells become bone cells. Rather, it appears likely that adult stem cells (which are located in the deepest layers of the skin and within the muscle itself), have a dual potential to become

either fat cells or bone cells and are coaxed preferentially to become bone cells. Much work remains to be done to isolate and characterize these cells that have the potential to become bone.

Will POH get worse? Does POH ever stop or go away?

Unfortunately, POH does not improve over time. The "P" in POH stands for "progressive." That means that POH will likely progress, or get worse, as a person ages. As POH is part of a person's genetic make-up, people with POH are born with the condition, even though the extra bone may not be present at birth. People with POH will not outgrow the condition. The extra bone that has been produced by POH does not spontaneously disappear. Even within the same family, different individuals who have POH may have very different amounts of heterotopic bone and different rates of disease progression.

The body of a person with POH does not make extra bone all of the time; a person with POH may go for months or years without apparent progression of the condition. Nevertheless, there is always a chance that extra bone can form. Since bone in POH often involves the skin, a bump or fall can cause an irritation of the skin at the site of the bump. This can sometimes cause the bone in the skin to break through the surface of the skin. Unlike in FOP, there are no large flare-ups of POH with severe swelling and tissue inflammation. However, severe soft tissue injury can stimulate new bone formation at the site of an injury. POH seems to progress slowly most of the time. It is unclear why the disease is active some times and quiet or dormant at other times.

What is The Progressive Osseous Heteroplasia Association (POHA)?

The POHA was formed in March, 1995, as a not-for-profit 501(c)(3) tax-exempt corporation for the purpose of raising funds to:

1. Support research to identify the cause of POH.
2. Develop effective treatments for those with POH.
3. Ultimately find a cure for POH.

Additional goals include educating families, friends, physicians, and communities about this crippling disease. The POHA also provides moral support and encouragement to families who struggle with POH. There are no salaries, consulting, or fund-raising fees associated with the POHA. The web-site for the POHA is: www.pohdisease.org.

The POHA has welcoming information packets available for new patients and their families. Hopefully, this will help them in learning to live with this condition. If you would like to speak with a POH parent or family member or have any questions regarding POH, please feel free to call or write:

Cathy Jacobs
President of POHA
4247 Prairie Avenue
Brookfield, IL 60513
Email: cjacobs4247@comcast.net

Sandy Roth
Vice-President of POHA
384 Creek Road
Frenchtown, NJ 08825
Email: sroth@cscus.jnj.com

Sufficient funds were raised by June 1996 to establish the first two-year research grant for the study of POH. This research is being carried out at The University of Pennsylvania School of Medicine's Laboratory of Molecular Orthopaedics in Philadelphia under the direction of Dr. Eileen Shore and Dr. Frederick Kaplan. Additional research grants from POHA currently extend through June 30, 2004. In total, the POHA has committed in excess of $400,000 for POH research. This funding has played a significant role in the discovery of the GNAS1 gene mutations responsible for POH, and POHA desperately needs your help in raising funds for continued research.

Present research funding for the POH laboratory is provided by grants from the POHA, The Center for Research in FOP and Related Disorders, The National Institutes of Health (the People of the United States), and Johnson & Johnson, Inc.

Two POH families (Illinois and New Jersey) have established foundations in their children's names for the sole purpose of raising research funds for POHA. They have successfully sponsored bowl-a-thons, 5K races, yard sales, Shop & Share days at supermarkets, softball games, funeral donations, plus encouraging United Way and direct donations. In addition, the Ian Foundation/POHA was selected as the 1996/97 Charity of The New Jersey State Association of High School Student Councils.

If you can help in fundraising or need any information, please contact:
Fred Gardner, Secretary-Treasurer of the POHA, at the POHA Office
33 Stonehearth Square,
Indian Head Park, IL 60525.

Telephone: 708-246-9410, or
POHA@comcast.net

How did POHA get started?
(Katelyn's Story)

Katelyn Jacobs was born on August 7, 1992, and appeared to be a normal healthy baby girl. At the age of six months, strange rice-like particles were found under her skin on various parts of her body. Over the next one-and-a-half years, she underwent extensive examinations, tests, treatments, biopsies, MRIs, ultrasounds, EKGs, and x-rays. These tests were conducted at numerous hospitals. All of these tests failed to produce a satisfactory diagnosis of her illness while these particles continued to spread and grow in the skin and in the deeper tissues.

After almost two years of much frustration and physical pain, Katelyn underwent extensive surgery of her buttocks and heel. Doctors removed several masses thought to be calcium. Upon detailed laboratory examination, the removed tissue was found to contain actual bone.

Katelyn was then referred to the doctors at the University of Pennsylvania Medical Center where she was diagnosed with progressive osseous heteroplasia (POH) and POH was first described.
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The formation of the POHA resulted from this two-and-a-half year period of utter frustration, which at times almost reached despair. If Katelyn had been diagnosed with cancer, muscular dystrophy, arthritis, or some other well-known disease, it would have been easy to sit back and rationalize that the millions of dollars being spent on treatment and research by the government, drug companies, etc. was all that could be done. However, it was apparent that this was not the case. It became obvious that if we did not become involved, nothing would be accomplished. With the help of Katelyn's family members and friends, the POHA was formed to raise funds for POH research and, of equal importance, to spread the knowledge about POH to doctors, hospitals and families around the world.

Fortunately Katelyn is by appearance healthy and is now attending elementary school. She wears a brace on her left foot to protect the extra bones in her heel and foot. Bones have also been found growing in her left leg and regrowing in the buttock area where falling is very painful due to the lack of protective fat. Katelyn's baby teeth were normal but many of the permanent teeth lack enamel and are decaying. It has now become a race between this progressive, disabling disease and research towards finding

a treatment or cure.

What is the POHA Resource Center?
How do I get more information?

The POHA Resource Center is a library of information about POH for POH families, physicians, and other interested parties. The Resource Center contains numerous medical research studies, medical journal articles and human interest stories about POH children. For information about the POH Resource Center and its contents, contact:

POHA
33 Stonehearth Square
Indian Head park, IL 60525
Telephone: 708-246-9410
Email: poha@worldnet.att.net

Information can also be found on the web-site of the POHA: www.pohdisease.org.

When did research begin on POH?
What are the physicians and scientists working on?

In 1995, physicians and scientists at The University of Pennsylvania School of Medicine established the POH Collaborative Research Project in an effort to share ideas with scientists and physicians worldwide. In 1996, their commitment helped to expand a laboratory that is exclusively devoted to the research of POH and related disorders. This unique laboratory is located in the Department of Orthopaedics of The University of Pennsylvania School of Medicine. The goal of the laboratory is to determine the genetic cause of POH, and to use that information to establish effective treatments and eventually a cure.

The POH Collaborative Research Project is an international group of physicians, scientists, technicians, and medical student-fellows who work together on all clinical and basic aspects of the POH project. The international working group is dedicated to finding the cause and establishing a cure for POH. The University of Pennsylvania Research Group has established collaborative basic and clinical research efforts with physicians and scientists throughout the world. In 1996, the group was awarded a research grant from the Progressive Osseous Heteroplasia Association (POHA) to study the molecular basis of POH. They also have been awarded a unique grant from The New Jersey Association of Student Councils. This was the first time in the history of medicine that the major funding for a genetic disease in children was provided by a group of high school students. The International Fibrodysplasia Ossificans Progressiva Association (IFOPA) and the Center for Research in FOP and Related Disorders also have supported research on POH. The National Institutes of Health (NIH) has awarded three years of funding, which began September 2000, through a grant to study the genetics of POH. Recently (2002), Johnson & Johnson, Inc. has joined in the support of the POH research effort by providing a three-year unrestricted research grant for POH.

In 1998, the POH Collaborative Research Group began the experimental analyses that led to the identification of the damaged gene responsible for POH. The gene that we have identified is called GNAS1 and is located on the long arm of human chromosome 20. This has been a watershed discovery. The report of this discovery was published in the January 10, 2002 edition of The New England Journal of Medicine. We will talk more about this fascinating topic under Genetics of POH (Section IV).

How can we predict a course of POH with so few cases?

The extreme rarity of POH makes it very difficult to understand with certainty the entire spectrum of disease activity. However, as more patients and families are identified with POH, a better survey will be obtained on the features of POH. This will allow the physicians and scientists to better determine both the features of the disease and its progression over time. Thus, the diagnosis of patients who have POH is important not only for advising and counseling those affected individuals and families, but also to help learn more about the condition so that the most productive research can be undertaken. The lack of large families with many affected members, the lack of a naturally occurring animal model, and the difficulty in obtaining tissue samples all hamper rapid progress in research on this condition. However, the recent discovery of the POH gene by the POH Collaborative Research Group will help enormously to focus the research on a productive path.

IV. GENETICS OF POH.

How does a person get POH?

The instructions to make a new human being result from genetic information (DNA) from both the mother and father. After birth, genetic information (contained in genes on the chromosomes) continues to provide the instructions that are necessary for growth and development during childhood and into adulthood. In the case of a child who has POH, the affected cells read the genetic information and encounter an abnormal instruction (which is called a mutation) that tells the body to make bone where it should not. This marks the beginning of POH.

What is GNAS1?

GNAS1 is the name of the gene that causes POH. GNAS1 is found on chromosome 20 and its name is an abbreviation for Guanine Nucleotide Binding Protein (G protein) Alpha Stimulating Activity Polypeptide 1. The gene and its activity are complex. GNAS1 encodes a protein, Gs-alpha (or "G stimulatory alpha") protein, that is located on the inside of the cell membrane in nearly every cell in the body. Generally, Gs-alpha functions as a relay switch in a multi-protein complex that monitors the environment of the cell and sends signals to the nucleus (the site of chromosomes), providing instructions to direct cell “behavior.”

We don’t yet know how mutations in the GNAS1 gene and corresponding abnormalities in the Gs alpha protein trigger ectopic bone formation. Early clues suggest that the Gs-alpha protein may normally act as an inhibitor of bone formation in soft connective tissue (skin, fat, and skeletal muscle) by suppressing the activity of other genes involved in bone formation. When the switch is broken, the inhibition ceases, and the cell becomes a bone cell by default. In children who have POH, bone formation occurs in the skin and in the fat tissue underneath the skin and then progresses into deeper tissue such as muscle, tendon, and ligament over time.

What is Albright Hereditary Osteodystrophy? What is its relationship to POH?

Albright Hereditary Osteodystrophy (AHO) is a rare genetic condition in which small amounts of bone form in the skin and subcutaneous tissues in conjunction with minor skeletal malformations and an altered response of glands to some body hormones. (When hormone resistance occurs, patients are also described as having pseudohypoparathyroidism type Ia or PHPIa.) The glands usually involved in AHO/PHPIa are the parathyroid glands in the neck, which control the body's calcium metabolism, and the thyroid gland. In some cases, bone formation in POH may look very similar to that in patients who have Albright Hereditary Osteodystrophy, but bone formation in POH generally is more extensive than in AHO. For example, bone formation in AHO does not generally involve the deep structures such as muscles, ligaments or tendons, although it might progress within the subcutaneous tissues. In addition, people who have POH do not show any AHO-like characteristic skeletal features or have any altered response to hormones.

How was it determined that GNAS1 was the gene mutation in POH?

The cause of AHO/PHPIa is a mutation in the gene, GNAS1. The similarities in skin ossification that can occur in POH and AHO led us to think that the two conditions may be related. The link between POH and AHO was strengthened by the identification of two patients with features of both AHO/PHPIa and POH, and evaluation of GNAS1 showed problems in the GNAS1 gene and/or the protein that it encodes in both patients. These findings could mean either that alteration of GNAS1 causes their AHO/PHPIa features but a second gene mutation causes POH, or that a mutation in GNAS1 can cause either AHO/PHPIa or POH. The answer - that GNAS1 mutations can cause extensive heterotopic bone formation in the absence of AHO/PHPIa - was provided by the identification of a GNAS1 gene mutation in a third patient who had atypical but extensive POH-like heterotopic ossification (also known as plate-like osteoma cutis or POC) but no evidence of AHO/PHPIa features.

Based on these findings, we collected and analyzed DNA samples from as many people as possible who have POH. We discovered DNA sequence alterations in the GNAS1

gene in a very high percentage of POH patients. It should be noted that there are approximately 30% of patients with clinically evident POH in whom we have not yet found a mutation in the GNAS1 gene. One possibility is that the mutation in the GNAS1 gene in those affected individuals is in a regulatory portion of the GNAS1 gene that we have not yet examined. The regulatory regions of a gene are enormous in size and, therefore, more difficult to study and to pinpoint changes. An alternate possibility is that the mutation exists in a completely different gene involved in the same bone formation pathway as GNAS1. Continued studies are needed to examine this possibility.

What type of mutation causes POH?

Genetic damage (mutations) of the GNAS1 gene can affect people in a variety of ways, but the mutations are broadly characterized by whether they lead to increased or decreased protein function. POH and AHO/PHPIa are similar in that they both are the result of GNAS1 mutations that lead to reduced Gs-alpha protein activity (which is formally called an inactivating mutation). This has broad consequences for metabolic development and function.

Why do some people get POH and others get AHO/PHPIa with the same mutation?

Identical mutations can occur in both POH and AHO/PHPIa. The puzzle is why the same mutation could cause two different conditions.

Most of the human body's cells have two copies (or alleles) of any given gene – one inherited from the mother, and one from the father – and both gene copies are actively used by the cells. But, for some genes only one gene copy is used, and which allele remains active is determined by the parental origin of the gene. The contribution of gender in directing gene activation is called "genomic imprinting". The imprinted genes that have so far been identified have frequently been associated with activities affecting cell growth and development. The molecular basis of how imprinting occurs and is regulated is just starting to be understood.

Although our studies have revealed that the same GNAS1 mutation can occur in a

person with POH or AHO/PHPIa, which disorder results appears to be dependent on maternal or paternal inheritance of the GNAS1 mutation.

For the defective hormone response (a condition described as pseudohypoparathyroidism type Ia or PHPIa) that occurs in some people who have AHO, it has been recognized for some time that only the mother's GNAS1 gene is activated in hormonal cells. Therefore, a GNAS1 mutation in the allele inherited from a mother could cause this condition (since the hormonal cells are completely dependent on this gene copy), but a mutation in the allele inherited from a father would not (since the paternal copy of the gene is not used by these cells).

Although we have only had the opportunity to examine a few families with inheritance of POH and GNAS1 mutations, in each case we observe inheritance from fathers. It appears that expression of the GNAS1 gene copy that is paternally inherited is important in the cells that give rise to the extra bone in POH.

We hypothesize that while hormonal cells depend on the mother's GNAS1 allele, the father's allele may be responsible for determining which cells become bone and which cells do not. Furthermore, the evidence suggests that unless the father's copy of the GNAS1 gene functions properly, cells in skin, fat, and muscle, may lose the normal cellular controls that prevent them from becoming bone cells.

Nevertheless, even in individuals who have GNAS1 gene mutations that have been inherited from their fathers, not all of the skin, fat, or muscle turns to bone. This spotty (mosaic) anatomic distribution of POH bone formation in an individual who carries the mutant gene is difficult to understand. Perhaps, there are other genes that may modify the effect of GNAS1 in a particular individual. At the present time, very little is known about such potential modifying genes.

Is POH related to other diseases?

POH can be as disabling as its sister disease FOP, if POH bone formation is as extensive in its distribution. There is some preliminary evidence that part of the bone-inducing BMP pathway that is altered in FOP is also involved in POH, although the gene mutations that cause the two conditions are unquestionably different.

Much more research is necessary in order to determine similarities and differences between these genetic disorders at the molecular level. For FOP, we have a good understanding of the damaged signaling pathway by which the body forms extra bone but do not yet know the causative gene. For POH we know the damaged gene but still have much to learn about the signaling pathway that is changed in this condition. And, for neither condition, do we know the exact identity of the cells that receive the abnormal signal and begin the metamorphosis to produce bone where it is neither needed nor wanted.

POH is also related to a larger group of non-genetic disorders in which bone forms exclusively in the skin. Conditions such as trauma, burns, connective tissue disorders, and surgical scars have been associated with bone formation in the skin. In these disorders, bone may form in the deeper layers of the skin (dermis) but does not progress to involve the deeper tissues or muscle.

Recently, our laboratory (propelled by discoveries in FOP and POH) has identified bone formation in heart valves as a common finding in patients who have endstage valvular heart disease. Research in POH, therefore, has the possibility of elucidating mechanisms of phenotypic stability in disorders as fundamental as cancer, aging, and valvular heart disease.

What are the similarities and differences between Progressive Osseous Heteroplasia (POH), Albright Hereditary Osteodystrophy (AHO), Fibrodysplasia Ossificans Progressiva (FOP)?

(The following chart may help to differentiate among those conditions)

	POH	AHO	FOP
Formation of ectopic bone	+	+	+
Genetic transmission of the condition	+	+	+
Direct formation of ectopic bone	+	+	-
Indirect formation of ectopic bone thru cartilage	-	-	+
Involvement of skin	+	+	-
Involvement of subcutaneous tissue	+	+	-
Involvement of deeper skeletal muscle	+	-	+
Congenital malformation of big toe	-	-	+
Superficial to deep progression	+	-	-
Severe limitation of mobility	+	-	+
Severe spinal curvature	-	-	+
Generalized hormone imbalance	-	+	-
Ectopic bone formation following IM injections	-	-	+
Severe flare-ups of disease	-	-	+
Causative gene known	+	+	-
Causative pathway known	-	-	+
Causative cells known	-	-	-
Definitive treatment available	-	-	-

If one child in a family has POH, what is the chance that a second child will also have POH?

We have learned much from people with POH and their families by studying their DNA and, in particular, the GNAS1 gene in each individual.

For most children with POH, we do not have evidence that shows that a GNAS1 mutation has been inherited from either parent. In these cases, POH likely has occurred as a new mutation in the child, and it is highly unlikely that siblings of such a child would also develop POH. However, since the possibility that an undetected mutation has occurred in a parent's germ cells, there remains a low recurrence risk within the family.

It is very important for families to note that gene alterations are a very common occurrence in human biology – it is thought that all of us have a handful of genetic alterations. Some of these changes are readily detectable (like POH), some may be expressed in later life (such as heart disease), and some will never have any substantial effect on us at all. These changes are thought to occur randomly at a low rate of frequency in our DNA. Such new gene mutations are known as "spontaneous mutations" since they are not inherited from either parent but occur "spontaneously" in an individual. However, spontaneous mutations that occur in a person's germ cells (eggs or sperm) could be inherited by that person's children.

We have two copies of most of our genes. One gene copy (or allele) is inherited from our mother, one from our father. Some genetic disorders only occur when both copies of a gene are damaged; these are described as being recessive disorders. Other genetic conditions occur when only one copy of a gene is damaged; these are described as being dominant disorders.

POH is inherited as an autosomal dominant genetic condition. This means that a person who carries one mutated copy (out of two copies) of the GNAS1 gene can have POH (although some who have the disease-causing gene are silent carriers). Parents who have a mutated gene have a 50% chance of passing this copy of the gene to a child and a 50% chance of transmitting the non-mutated copy, like the flip of a coin. In some families, POH has been found to occur in more than one family member. In fact, it can be mild in some individuals and more severe in others within the same family. At the present time, we do not know why this variation occurs, but such patterns have been

seen with other genetic conditions as well. It is also possible that an unaffected person who carries the POH mutation could pass this mutation on to one or more of his children who may develop symptoms of POH.

As described in a previous section, inheritance of a GNAS1 mutation from a father has been associated with inheritance of POH while inheritance of a GNAS1 mutation from a mother is associated with hormone resistance and AHO. Our studies on the inheritance patterns of GNAS1 mutations are still in their early stages and much still remains to be understood about the specificity of the parental inheritance of GNAS1 mutations in POH.

Can people with POH conceive and have children?

People with POH can conceive and have children. POH is an autosomal dominant genetic condition. This means that a person who carries one copy of the mutated gene for POH can have POH. However, the severity of the condition cannot be certain. A parent who has POH (and therefore has one gene copy with a mutation and one copy that is normal) could pass the gene with the mutation to a child. There is a 50% chance that each child (male or female) of the affected individual will develop disease.

Several families throughout the world have been identified in which a family member has severe POH, while other family members, following careful examination, have been found to have evidence of trivial bone formation underneath the skin in various locations throughout the body. In fact, it is likely that these other family members might not have been detected as having extra bone unless doctors were aware of what to look for. These individuals also have the same GNAS1 mutation found in the severely affected family member, but they do not have true POH as the heterotopic bone formation does not involve the deeper tissues. Instead, they may have osteoma cutis or mild AHO (without hormone resistance). Therefore, it is very important that all family members of patients who have POH be examined carefully for any extra bone formation. Such knowledge will help physicians and scientists to better understand the genetic behavior of the condition and to provide affected families with useful information on genetic transmission of the condition.

Can POH be prevented? Is prenatal testing possible?

In many cases, the genetic mutation that leads to POH occurs spontaneously (i.e., not inherited) either in the egg or sperm cell prior to fertilization, or just after fertilization in the very early embryo. In some families, the gene mutation may be inherited from a parent. At the present time, there is no known prevention for POH.

We are in the process of establishing clinical testing for the mutations that cause POH. At this time, only research testing of affected people is available.

V. HOW POH AFFECTS THE BODY

What parts of the body are involved in POH? Can POH appear anywhere at any time?

POH can affect any area of the body. The characteristic progression of POH from superficial tissues to deeper tissues, as well as the scattered regions of the body affected by POH, likely hold important clues to the cause and development of the disease. Unlike FOP, no characteristic pattern of regional involvement with POH has been found. Some individuals with POH have only very small areas of their body involved, while others have very large areas involved. In some individuals, POH affects one side of the body more than the other. The muscles of the diaphragm, tongue, and heart, are characteristically spared.

The progression of ectopic bone formation at any given body location follows a characteristic pattern: usually extra bone forms first in the skin and progresses later to involve the fat layer underneath the skin. Eventually, the condition may progress into deeper tissues such as tendon, ligament, and muscle. Therefore, the characteristic pattern of POH progression is from superficial to deep structures.

POH may affect mobility. In POH, extra bone replaces the body's connective tissues. Consequently, movement in areas affected by POH may become impaired.

As POH progressively impairs the movement of a joint, a person with POH may need help in performing their activities of daily living. Some people who have POH involving the lower limbs find it easier to get around in a motorized scooter. However,

involvement of different joints is so variable in POH, that it is not possible to make a general statement about mobility needs in all individuals. Usually by late childhood, areas that will become involved with POH have already become evident by the involvement of the skin covering those regions. Very little information currently exists about adults who have POH, so it is difficult to determine how the disease progresses later in life.

However, from the information available in the few known adults who have POH, it appears that the disease progresses much more slowly in adulthood.

Are all the symptoms the same for each child and does the disease follow the same course in each child?

The symptoms and progression of POH can be highly variable from child to child. Even within a single family with several affected members, POH often does not take the same course for each child. Variability in the severity and the progression of the disease is a common feature for genetic disorders that follow the genetic pattern of POH. Thus, it is possible that one child may have more severe symptoms of POH than another child, even within the same family.

Once POH involves the skin how long will it take until the deeper tissues are involved?

The progressive nature of POH is unfortunately part of the condition. However, it is impossible to determine how long it will take for deeper tissues to become involved, if at all. In some individuals, the progression is so slow, that it is hardly apparent over many months or even years. In other individuals, the progression may be rapid over several months or a year, and then slowly progress over many years. Every individual with POH is different in terms of the areas affected, the rate of progression of deeper tissues, and the number of associated areas that will become involved.

When the extra bone grows, is it painful? What can be done about the pain?

Extra bone formation in POH is not always painful. In fact, it is often so slow that it is not very noticeable at first. However, the extra bone formation can, at times, be painful. Some of the discomfort arises from the fact that POH involves the skin and can cause breakdown of the skin especially in areas where there is excessive pressure.

Sometimes, bone formation can form in the foot and make it painful to wear shoes or walk. Sometimes the discomfort may arise from an infection due to breakthrough of bone through the skin. At other times, pain may arise from over-using a muscle that is only partially involved with POH. The act of stretching a muscle which is abnormal or in which bone formation is occurring can cause pain.

In general, pain may arise from many causes in POH. It is important to identify the specific reason for the pain and attempt to treat the specific cause of the pain. Sometimes, the pain can be relieved by placing special padding over an irritated area. At times, treatment such as with anti-inflammatory medication may help to relieve some of the irritation or inflammation of the extra bone formation. Rarely, narcotic pain relievers may be needed briefly to treat the symptoms of POH.

On rare occasions, the pain can be relieved by a surgical operation that places the affected body part in a better position. If the bone formation is small and discreet, occasionally the bone can be removed. However, the bone may possibly reform. Sometimes, if the bone infiltrates a region, the bone cannot be removed. Pain rarely can be relieved by removing the extra bone. (Also see Section VI, Care.)

How do I know whether an ache or pain is associated with POH? Are all aches or pains cause for serious concern?

Even with POH, a person can still have aches and pains that are not due to POH, just like in anyone else. The best rule with POH is to do what feels comfortable. Sometimes a hurt or ache is the body's way of telling us that we are doing too much. In POH, it is a good idea to avoid those activities or positions that cause discomfort. When muscles are stretched, they often react by pulling back in the opposite direction, creating tension in the body. In some ways, it is like stretching a rubber band; the more you stretch the rubber band, the more it pulls back. This causes additional strain on the body. The key with POH is to avoid activities that cause pain.

Most of the time, it is easy to recognize the clinical features of POH without any special tests. However, if there is a doubt as to whether the pain is related to POH, it is best to ask a physician.

In general, flare-ups (areas of tissue swelling that appear over a short period of time) do not occur in the progression of POH. The progression of POH may be slow or rapid, but generally does not involve a flare-up with severe swelling.

Early in the development of a new piece of bone, an x-ray will show only soft tissue. An x-ray at a later stage may show the bone that has formed.

A bone scan is a test that can be performed at most hospitals, and can show new bone formation early in the course of the disease. However, most of the time it is not necessary to do a bone scan, and an x-ray or a CAT scan will show the disease progression in the deeper tissues.

Bone formation from POH usually does not form in deeper locations such as in muscle, tendon, or ligaments before it forms in the more superficial location such as the skin or subcutaneous tissue. However, occasionally bone can form in the subcutaneous tissues and not in the skin. When that happens, it is still possible to feel the bone because it is close to the surface. An x-ray is an excellent test to distinguish calcium deposits from true bone formation. Tissues with calcium deposits appear white on x-ray due to the deposition of calcium crystals. However, tissues that contain bone reveal a characteristic structure that is usually apparent on the x-rays. In POH, almost all of the mineralization that occurs is due to true bone formation rather than calcium deposits.

Does POH ever spread?

POH is not a contagious condition, and it does not spread to other people. However, since POH is a progressive condition, it does "spread" within the affected person, and new areas of bone formation can appear spontaneously in the skin. It is not clear what triggers this new bone formation. Therefore, certain areas of skin may appear normal at first, and then later become involved with the rice-like grains of bone formation. In some places, bone may form only in the skin or in the subcutaneous fat. The bone formation does not always extend to the deep muscle tissue at every involved site.

Can a little piece of bone sometimes pop through the skin? How big can it be and what will it look like? What should I do about it?

Sometimes a small spicule of bone that forms in the skin can pop through the skin especially if the skin is irritated. Sometimes a tiny splinter of bone may break off without any discomfort. Sometimes (in addition to bone), a thick chalk-like spicule of calcium gets extruded from the skin. If that happens, keep the area of the skin clean with soap and water. You can cover the area with a band-aid or gauze pad if it is irritated. If you can save the piece of bone and give it to the POH laboratory, it would help doctors and scientists to learn more about the condition.

In POH, what does the bone look like under the microscope?

Extra bone in POH looks like normal bone; it's just in the wrong place. The bone is formed by osteoblasts (or bone cells), and the bone arises directly from the tissues where it is found, often the fat tissue in the deepest layers of the skin and in the fat tissue that runs through skeletal muscle. Sometimes, bone can form on a scaffold of cartilage tissue, but in POH it most commonly forms directly without any intermediate steps. Under the microscope, the extra bone in POH usually looks very different from the extra bone that forms in FOP. A biopsy is **not** necessary to tell the difference between the two conditions.

Can POH affect or put pressure on the heart, lungs, kidneys, liver or other internal organs?

POH does not cause bone formation in any other organs except the connective tissues. No one who has ever had POH has had bone involvement of the heart, lungs, kidneys, liver or other internal organs. POH could theoretically put pressure on the internal organs, but no cases of that have been reported.

Do extra bones in POH only grow during growth spurts?

Due to the extremely limited number of individuals who have POH, there is a lack of

information on ectopic bone formation in POH, especially later in life. In general, the condition seems to slow somewhat as children get older. The most progressive stages of ectopic bone formation occur during childhood but could progress even after skeletal maturity. Unlike in FOP, there are generally no severe short-term flare-ups of the disease. Even when the disease is progressive, it generally progresses more slowly than the acute flare-ups that are seen in a matter of hours with FOP.

Will a person with POH be able to eat if the jaw becomes locked?

The jaw does not usually become locked in POH. However, it is possible that movement of jaw could become affected if POH involved that area. Also, there is no evidence that POH gets worse due to injections of local anesthetic or due to dental procedures. So far, only one patient with POH has been documented to have jaw involvement.

Does POH feel the same all the time?
Does the weather have any effect on the condition?

The weather can affect how anyone's body feels. Some people do not feel as comfortable when it is cold or damp. Others are more uncomfortable when it is hot. Some people do not notice any difference with change of weather or season. People who have POH do not seem to prefer a particular weather, season, or climate.

What is the life span of someone who has POH?

People who have POH can live a long life. There is no known effect on the life span of patients who have POH. Many individuals who have POH are otherwise in excellent health. Since POH does not directly affect internal organs, there is no known affect on life span.

VI. CARE

What type of treatment is available for POH? What can be done to lessen the pain?

The treatment of POH can ultimately be divided into two categories:

1. Disease-modifying therapies
2. Symptom-modifying therapies

At the present time, there are no known disease-modifying therapies that can prevent the formation of new bone. However, with the identification of the genetic cause of POH, we are in a much better position to focus research efforts on both the signaling pathways in which Gs-alpha acts and on the precise cells in skin, fat, and muscle on which it has its effects. From such knowledge, real therapeutic options are more likely to emerge. In the meanwhile, there are a few therapies that can provide some relief during painful exacerbations of the condition.

The source of pain should always be carefully evaluated in a patient with POH. Pain may arise from direct pressure over a bony prominence, irritation or inflammation of an underlying muscle, tendon, ligament or nerve, or due to muscle spasm from progression of the condition into deeper tissue. Various medications, splints, and pads may provide symptomatic relief. (Also see Section V. How POH Affects the Body.)

Can injections cause problems?

Injections into the muscle (intramuscular or IM injections) are not known to cause flare-ups of POH. In general though, it would be best to avoid intramuscular injections into any known areas of POH involvement.

Can the extra bone be removed in POH?

The technical answer is surprisingly "yes" but that does not tell the whole story. It is possible (under very rare circumstances) to remove heterotopic bone in POH to relieve pressure discomfort or to permit more joint movement. Unlike in FOP, surgical

intervention to correct limb position abnormalities (which have resulted from new bone formation in patients who have POH) may result in an improvement in the joint position for walking or other use. If the extra bone is a small discreet piece of bone, and if the piece of bone is causing pain by causing direct pressure in that area, it may be possible to remove the piece of bone. Some patients have had this done successfully, while in others the bone has returned. However, if the bone is web-like and infiltrating rather than discreet and nodular, it may be extremely difficult to remove the bone entirely, and more bone is therefore likely to form following the surgery.

Surgically removed bone may grow back and further impair mobility. Due to the few numbers of individuals affected with POH, it is not yet possible to predict who might benefit from a surgical procedure to remove the extra bone and who might not.

Although we now know the gene that is mutated or damaged in POH, we do not yet understand the reason that ectopic bone forms as a result of this mutation. However, as a more complete understanding of the genetic and molecular basis of POH evolves, we hope to be able to block renegade bone formation. At the present time, however, that is not possible. As a result, it is extremely important to understand that any surgical procedure to improve joint position or remove excess bone should be considered with great caution as it could potentially make the condition worse.

In general, if the bone formation is subcutaneous and discreet, then it could possibly be removed without returning. However, if the bone formation involves deeper tissues such as ligaments, tendon, or muscle, and is more web-like in its appearance, it is unlikely that surgical removal will be successful and may actually be harmful.

What is the risk of having surgery or stitches?

Although surgical operations to remove extra bone or to place an affected joint in a better position should be approached with great caution, emergency situations may exist where an operation may be necessary, as with appendicitis. Such operations should be performed if necessary. Just as in any one else, patients with POH can develop common problems that may require surgery.

Bone formation in the skin may impair surgical healing if surgery had to be performed through an affected area. The bone formation in the skin could potentially affect the

blood supply to the skin and impair healing. However, if stitches are needed in an affected area, they should be placed carefully with as little trauma as possible.

What happens if a POH bone breaks?

Patients who have POH heal fractures or bone breaks in their skeletal bones in the same way as anyone else who has a fracture. As the extra bone in POH is normal bone but in an abnormal location, it is not surprising that a fracture through the extra bone would heal normally. In fact, if the extra bone is broken, it has been found to respond just as normal bone would to a break and heal.

Should milk be provided in the diet if the body already generates too much bone? If someone with POH is allergic to milk, does this come from POH?

Milk is a good food that contains calcium which is an important element for every person's body, even if one has POH. While it is well-known that the calcium in milk helps build strong bones, it is not calcium that makes POH bones grow. POH bones grow because of a genetic signal in the body. Milk will not make the POH worse and it will keep the rest of the body healthy. While the body needs calcium for the bones to grow and stay healthy, it is vital for other body functions as well. Calcium allows the nerves to function properly, the heart to beat, and other important metabolic functions to occur. The body cannot live without calcium. An individual who has POH does not need to take more calcium than anyone else, but should drink one or two glasses of milk each day. In summary, POH is not a problem of too much calcium; it is a problem of too much bone.

Allergies to milk and intolerance of milk products is a common condition in the general population and is not related to POH.

Is there anything I can use to cover these bones to prevent skin irritation or constant chipping?

Skin irritation occurs commonly in POH due to the fact that bone formation occurs in

the skin, and such areas are easily bumped or bruised. There are two layers of the skin: the epidermis (or superficial layer), and the dermis (or deeper layer). The dermis contains the nerves and blood vessels. In POH, bone forms in the dermis. Bone does not form in the epidermis in POH, but can erode through the epidermis due to pressure or injury over an affected area. Occasionally, a small spicule of bone may work its way into the epidermis and out through the surface. Individuals who have POH have occasionally reported a little piece or spicule of bone eroding through the skin. When this occurs, there is often no bleeding or pain but some local irritation. If an area of the skin is affected with POH and seems to be easily irritated, the skin could be covered with a protective dressing. It is important not to dry out the skin in areas that are affected with POH. That can lead to cracking and infection in the skin which would make the POH worse. It is best to keep the affected areas clean with soap and water and avoid drying agents, such as alcohol, that can lead to cracking of the skin.

Another common cause of skin breakdown is residual moisture and perspiration in difficult-to-reach areas such as skin creases and skin folds near joints or where the arm or leg is fixed against the body wall. As perspiration occurs and moisture builds up, bacterial and fungal organisms can develop. Skin infection and breakdown can result. These problems are often difficult to prevent and even more difficult to treat.

Surprisingly, drying agents such as alcohol and powders make the problems worse. The irritated areas should be kept clean with soap and water. Sterile gauze moistened with saline solution and applied over the irritated area is better than drying solutions, powders, or antibiotic creams as it allows the regenerating skin cells to migrate into this area.

If an individual with POH has such difficult to reach areas, he or she needs to consult a physician about proper skin care. If skin irritation or breakdown begins to occur in a difficult to reach area, or an area affected with POH, consult a physician immediately.

Is there anything special we should or should not do when admitted to the Emergency Room?

Knowledge of your condition is important for any physician who sees you for any reason. You might like to give your doctor a copy of this book so that he/she can read about POH, and also have access to the scientific articles. If there are any questions,

please have your doctor contact one of the medical or scientific consultants to the POHA whose number is listed in Section IX.

VII. THINGS TO DO

Are any activities helpful in maintaining joint movement? Should a child with POH receive physical therapy or occupational therapy?

In general, physical therapy is not recommended for people who have POH since stretching the soft tissues around a joint affected with POH can be painful and possibly lead to a local worsening of the disease. Joints should never be passively stretched in people who have POH. Active range of motion should be encouraged, but an individual who has POH is the best judge of how much to do. It is best to avoid the rigorous routines of physical therapy and concentrate on movements that are comfortable.

Swimming or warm weather hydrotherapy is a good activity and enjoyable for many. The warm water may help an individual feel better. In some individuals with POH, however, chemicals in swimming pools may irritate the skin. Nevertheless, it is easier to move in the water than on land. One does not have to swim to obtain the benefits of warm water therapy. Simply being in the warm water may make one feel better, ease the discomfort, and facilitate movement.

What types of physical activity should be avoided?

Anyone who has POH should avoid activities in which there is a high likelihood of falling. People who have POH may have an increased tendency to fall due to impaired balance from stiff joints. If a person who has POH begins to fall, it is less likely that he or she will be able to break the fall. However, given POH's nature, let your child take advantage of things that he or she physically is able to do. It is important not to isolate your child from the joys of life or socialization with friends. In other words, don't be so afraid that you and your child forget to try new things and to have fun, important parts of life.

Can I play sports with POH? Do individuals with POH have any restriction in hobbies or activities?

Exercise is good for everyone, and people with POH should use their best judgment as to what activities they find most comfortable. Unlike with FOP, blunt trauma does not seem to severely worsen the course or progression of the disease. Nevertheless, individuals with POH should be careful not to overstretch involved muscles or have their joints stretched by someone else. Participation in modified physical activities should be based upon one's level of comfort and safety.

How can I help my child cope with things that he or she is not able to do?

Your child may need special help with many activities that those without POH can do by themselves. This will vary depending upon the areas that are involved with POH and the extent of involvement in these areas. However, your child may also be able to do certain things that others without POH cannot do. Focus on those things that make him or her special. You may be surprised - probably more so than your child - at what he or she is able to do with limited mobility. Children with POH often find a way of doing the things that they really want to do regardless of their limitations.

As there may be certain things that your child is unable to do, make sure that your child knows that it is okay to ask for help, if needed. Make sure that he or she understands that all people have both special talents and personal limitations.

Will POH affect how my child walks?

Areas of the body affected with POH may vary dramatically from one individual to the next. Whether or not someone with POH will have trouble walking depends primarily on the extent, severity, and location of joint involvement. Also, the eventual position of the joint may make a great deal of difference in the ease or difficulty that the patient has in walking. Some people with POH have no involvement of the lower limbs at all and, therefore, have no difficulty with walking. Others have extensive lower limb involvement, and they have great difficulty with walking. Still others may have more

mild or more slowly progressive POH and thus, have some (but minimal) impairment in mobility.

Is there any equipment that a person with POH can use to become more independent?

The type of auxiliary equipment that a child with POH may need depends entirely on the areas involved with POH. For those individuals who have upper limb involvement that limits joint movement, there is a tool called a "grabber" that will help picks things up, essentially extending the arm reach of a person with POH. Many people who have trouble bending also use it. Your doctor can also refer your child to an occupational therapist, a professional who can help custom-design or obtain tools to help make activities of daily living easier.

What types of work do people with POH do?

Most of our current knowledge about POH involves how the condition affects children. There are adults who have POH but we have little general information about them at the present time. In mildly affected cases, there may be few or no limitations. There is nothing about the condition that limits intellectual development in any way. Individuals who have POH should learn what interests them and adapt their careers to their lifestyles.

A HANDY LIST OF THINGS TO AVOID IN CHILDREN WHO HAVE POH:

1. Passive manipulation of joints

2. Aggressive physical therapy

3. Falls and injuries

4. Contact sports

5. Drying agents, such as alcohol or powders, that will irritate the POH-involved skin and may cause skin breakdown and infection

6. Tight clothing, hard buckles, buttons, tight elastic, straps, body braces (for example, to improve posture), tight shoes or shoe-laces, and any prolonged pressure on the body, especially over the skin in areas affected by POH

7. Surgery to remove extra bone, especially if the extra bone is web-like in its x-ray appearance and infiltrating into deep structures such as skeletal muscle

VIII. FEELINGS ABOUT POH

What should I tell my friends and family when they ask me about POH?

You should be truthful and educate them about POH. POH is a progressive condition where the body forms extra bones beginning in the skin and progressing down into deeper tissues including subcutaneous fat, muscle, tendon, and ligament. This extra bone may occasionally lock-up the joints, thus restricting mobility. Although the condition is not generally aggravated by minor injuries, the skin over affected areas may break-down and become infected when injured, due to the formation of bone in the skin. The amount of disability in anyone who has POH depends predominantly on the areas that are affected and the rate of progression of the disease into the deeper tissues.

Your friends and family probably have never heard about POH, and they may wish to learn about it. You will play an important role in their education about this condition, and you may want to share a copy of this book with them.

What does my child's teacher need to know about POH?

Your child's teacher needs to know about this condition. Since each child with POH has different areas affected and, therefore, different limitations, it is important that your child's teacher understands how the disease is specifically affecting your child. Be sure that the teacher also realizes that your child might be unable to raise his or her arms in order to gain attention, especially if the upper limbs are involved with POH. Some children may not have upper limb involvement and this may not be a problem. In other words, make sure that the teacher is aware of your child's physical limitations and special needs. Such an awareness will help alleviate much frustration. Apart from practical concerns, the teacher may have questions about POH, since it is unlikely that he or she will have seen another individual with the condition. It may be helpful to arrange a private meeting with the teacher to answer questions about POH.

Does POH affect girls only?

The original observations on POH were made in girls. However, more recently, numerous boys have been found to have the condition. Thus, POH occurs in boys and appears to be no different than POH in girls.

How will my child cope with having POH?
How will the family respond?

It may surprise you, but children who have POH generally cope better and more effectively than their unaffected parents. Although the physical manifestations of POH can be devastating for both children and parents, the children generally find ways to adapt and cope with the increasing immobility of affected areas. While it is difficult for parents to witness the progressive loss of mobility in a child, a positive and constructive approach appears to be most beneficial for all. At the present time, doctors are not aware of many adult patients who have POH, but as more information is disseminated throughout the medical community about POH, more adults with the condition are likely to be identified.

A constructive family attitude about POH may help to decrease feelings of hostility and frustration that naturally accompany the physical limitations caused by the progression of this (or any other) chronic condition.

There are added stresses to families when one member has a disability. It is very important to allow siblings to talk about their feelings regarding the disabled family member and to allow them to express their feelings. Talking with a trained counselor can be helpful. It is hard for parents to be objective about a situation close to them, particularly when needs of different family members seem to be in conflict. Professional guidance, family counseling and consultation with other members of the POH community are all additional resources that may be useful.

What information should I leave for my babysitter?

All caretakers of children who have POH should be generally familiar with the condition. The list of handy things to avoid is probably the most important set of short-

term guiding principles for a babysitter who is taking care of a child with POH. As with any child, a list of appropriate telephone numbers to call when questions or emergencies arise should be available to the babysitter at all times.

Can people with POH live independently?

Despite the progressive nature of POH, it is likely that people who have POH will be able to take care of themselves with some degree of independence that is required to live alone. However, as with any condition, some will be more severely affected than others. Those who are severely affected with POH (those in whom numerous joints of the upper and lower limbs are involved or in whom progression continues robustly throughout life) are more likely to need long-term care and may have some difficulty with independent living. There are, however, no easy answers to this question, as the level of independence that can be achieved may vary dramatically from individual to individual depending on the extent and severity of POH involvement.

How can I help my child cope with things that he or she is not able to do? How can I prepare my child to deal with POH?

Your child may need special help with many activities that those without POH can do themselves. However, your child might be able to do certain things that others without POH cannot do. You may be surprised - probably more so than your child, at what he or she is able to do with limited mobility. Children with POH often find a way of doing the things that they really want to do regardless of their limitation, whether that involves basic skills that most people take for granted, such as dressing oneself, or something enjoyable, such as playing a musical instrument. Focus on those things that make him or her special.

As there may be certain things that your child is unable to do, make sure that your child knows that it is okay to ask for help, if needed. Make sure that he or she understands that all people have special talents and personal limitations.

What if people notice POH and laugh?

A direct matter-of-fact approach will be educational, disarming, and constructive. Hopefully, in time, your family and friends will see beyond your child's POH, and recognize that POH is just one part of who your child is. A child with the related condition FOP, was approached by a little boy who said, "Those bumps on your back are weird." She responded factually, and with a smile, "They're not weird, they're bone."

How involved with the POHA do I have to be?

Having a child diagnosed with POH may be overwhelming. Due to the fact that POH patients and their families do not have a large support network to rely on, it becomes necessary for each person to participate to the fullest extent that the family situation allows and needs. Any involvement, no matter how large or small, will be very significant in relation to the whole. At this point, the POHA is not an army but rather a basketball team, where each individual is a critically important member. As someone once said, “The fact that we are so few in number certainly makes the job harder, but the satisfaction of finding a treatment or cure will be that much greater.”

When will there be answers?

Just as POH results in physical limitations for people who have POH, the nature of this condition results in limitations for the researchers who are trying to understand its cause and develop effective treatments. The difficulty in obtaining tissue specimens and the current lack of animal models (which would be valuable for studying disease progression and for testing drug treatments and other therapies) have frustrated research on POH. The recent identification of the causative gene for POH may now make it possible to develop relevant animal models for POH. We are working constantly to design detours around these formidable obstacles in order to find better answers for people who have POH.

How can I keep in touch with research updates?

Eileen M. Shore, Ph.D and Frederick S. Kaplan, M.D. at The University of Pennsylvania School of Medicine are leading the POH Collaborative Research Project. Dr. Shore's and Dr. Kaplan's address and phone numbers are listed on the following pages of this Guidebook. Dr. Shore and Dr. Kaplan will be happy to answer questions on the progress of research. In addition, research progress on POH will be reported in *The FOP Connection*, a newsletter devoted to concerns of patients with FOP and POH, and on the Research page of the IFOPA web-site at www.ifopa.org and the POHA web-site at www.pohdisease.org.

IX. HELPFUL ADDRESSES AND PHONE NUMBERS

Cathy Jacobs (President)
Fred Gardner (Treasurer)
Progressive Osseous Heteroplasia Association (POHA)
14031 S. Tamarack Drive
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Email: poha@comcast.net

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Progressive Osseous Heteroplasia Association (POHA)
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Email: Sroth@cscus.jnj.com

Roberto Bufo (President)
Italian Progressive Osseous Heteroplasia Association (IPOHA)
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X. APPENDIX

Obtaining Tissue Specimens During Emergencies

Eileen Shore, Ph.D. & Frederick S. Kaplan, M.D.

Tissue specimens from biopsies and surgery have already made an enormous difference in our understanding of the molecular and cellular basis for POH. Tissue samples obtained during emergency procedures or operations would allow scientists to examine living cells from tissue that may otherwise not be possible. If a person with POH must undergo a surgical procedure, then tissue can be obtained without any extra risk to the patient. The cells from this tissue can be kept alive in the appropriate culture medium, and thus, can be available for long-term study.

On the following page are guidelines on how to collect tissue samples, how to preserve them, how to notify Dr. Eileen Shore or Dr. Fred Kaplan, and how to get them to the POH Laboratory in Philadelphia.

If any emergency surgery procedure is needed, please have your doctor call any one of the following people for instructions on obtaining tissue samples:

Frederick Kaplan, M.D.
215-349-8726 (Office)
215-545-0758 (Home)
Email: Frederick.Kaplan@uphs.upenn.edu

Eileen Shore, Ph.D.
215-898-2330 or 2331 (Office)
215-898-8653 or 5610 (Lab)
215-628-8211 (Home)
Email: shore@mail.med.upenn.edu

David Glaser, M.D.
215-349-8726/8727 (Office)
215-312-8953 (Pager)
Email: david.glaser@uphs.upenn.edu

Orthopaedic Offices

215-349-8726 (Kay Rai)
215-898-2330 (Susan Lippo)

If there is no time to make a phone call but tissue specimens are available:

- Tissue samples should be minced into small pieces, no bigger than a fingernail clipping, and placed directly in a labeled sterile tube with sterile saline solution.

- The tube should be well-sealed so it doesn't leak, and wrapped or packed so it won't break during shipment, and sent at room temperature by Federal Express to:

Drs. Shore and Kaplan
University of Pennsylvania
Department of Orthopaedics
424 Stemmler Hall
36th & Hamilton Walk
Philadelphia, PA 19104-6081
Phone: 215-898-2330

- Also include the following information with the tissue sample:

a. Name of patient
b. Date obtained
c. Time obtained
d. Site of body where tissue was taken
e. Type of tissue (skin, muscle, etc.)
f. Name of doctor
g. Telephone number of doctor
h. Email of doctor

- Please call one of the listed phone numbers to notify us that the tissue is being sent. (Answering machines are connected to Eileen Shore's office and home phones and to the Orthopaedics Offices).

Directions for Procuring Tissues:

1. For cells to be grown in culture:
   - tissue should be minced into small pieces (2-4 mm).
   - place tissue in tissue culture media or sterile saline in sterile tube or vial.
   - ship FedEx overnight at room temperature.

2. Fixed tissue for *in situ* hybridization.
   - tissue should be minced into small pieces (2-4 mm).
   - fix in 4% paraformaldehyde or glutaraldehyde
   - ship FedEx overnight at room temperature.

3. Fixed tissue for general histology and immunohistochemistry
   - tissue should be minced into pieces (2-4 mm; up to 2 cm).
   - fix in 10% buffered formalin
   - ship FedEx overnight at room temperature.

4. Frozen tissue for immunohistochemistry.
   - tissue should be minced into small pieces (2-4 mm).
   - place tissue in a freezing vial
   - quick freeze tissue
   - ship FedEx overnight with dry ice

5. Blood:
   - draw blood into green-top tubes (heparinized)
     - if possible, obtain 15-20 ml (two tubes) from adults and older children; 3-5 ml from infants, and 5-15 ml from other children is sufficient
   - package tubes to prevent breakage
     - keep blood at room temperature at all times; <u>do not refrigerate</u>
     - ship FedEx overnight at room temperature.

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