

The President's Corner

"Hope is like a road in the country. There never was a road, but when many people walk together, a road comes into existence."

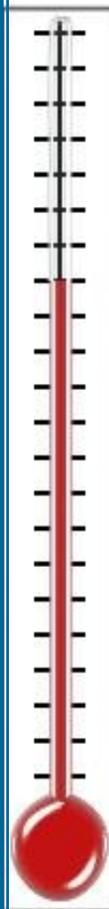
Ancient Chinese Proverb



This quote seems a perfect description of the Melorheostosis Association. Seven years ago most melorheostosis patients lived in isolation around the world. Now we have come together in search of the cause, treatments and cure for melorheostosis. Since our last newsletter alone, we have hosted our Fourth International Melorheostosis Conference in Madison, Wisconsin; become members of the Rare Bone Disease Patient Network which will host a Rare Bone Disease Conference in 2008; grown our posted personal histories to over 155 melorheostosis patients; welcomed Dr. Henry G. Bone and Dr. Vicki Rosen as esteemed members of our Medical Panel; established a website store; and produced a video featuring two of our beloved melorheostosis children, Monica and Mark, as well as a moving and informative statement by Medical Panel Chair, Dr. Fred Kaplan. In addition, three of our directors attended the highly successful UK Melorheostosis Conference in Oxford. We have been truly blessed by this extraordinary progress.

The Melorheostosis Association is now at a pivotal moment in its history. We have always known that there is a one word answer to the question of how we will find the cause, treatment and cure for melorheostosis and that word is **RESEARCH**. Research is essential but research takes serious funding and we are a small organization staffed entirely by volunteers. We are preparing to offer grant of \$30,000. to fund a melorheostosis research project. To raise funds for the grant, members of your board of directors, as well as generous patients, have held fundraising cocktail parties. To

Melorheostosis Research



\$30000 "Help Us Help You"

If you, or someone you love, has melorheostosis, please help us reach this critical goal.

\$21395 Please make your tax deductible donation online at: www.melorheostosis.org or by mail to:

Ms. Alice Martin, Treasurer
Melorheostosis Association
1754 Briggsville Road
Fowlerville, MI 48836

\$0

For information on hosting a fundraiser, see page 2.

date we have raised \$21,395. and we sincerely need your help in raising the remainder. Please consider making a personal donation. If you would like to host a 2-hour cocktail party fundraiser, let us know and we'll send you everything you need! It's easy and it's fun! (see page 2 for details)

Feel free to contact me — or any board member — if you have questions or would like information on how to become more involved.

Association Mission...

The Melorheostosis Association is a not-for-profit organization dedicated to finding the cause, treatments and cure of melorheostosis. Our focus will be on promoting greater awareness and understanding of this progressive disease and its manifestations through education, research, communication and advocacy efforts on behalf of those affected by it as well as those dedicated to alleviating it.

Fundraising

HOSTING A 2-HOUR COCKTAIL PARTY FUNDRAISER

The easiest – and most fun – way to raise money for melorheostosis is to host a 2-hour cocktail party. We'll send you everything you need – invitations, melorheostosis bracelets, a 5-minute video to show, and donation cards – all free of charge.

Here are the three easy steps to hosting the party:

- Send out the invitations to your friends and family after you have filled in the information about time, date, etc.
- At the party, after about 1 hour, tell people you are happy to have them there to tell them about melorheostosis and show them the DVD.
- At the end, give each person a bracelet and a donation envelope.

That's it! The key is to “keep it simple” and “keep it fun” because all you need is the chance to tell people about melorheostosis – in that sense it is a “friend raiser” as well as a fundraiser. The more people who know about melorheostosis, the better!

For information or questions, please contact Kathleen Harper, kathleen@harpervision.com.

“Thank You” to those who have raised research funds

Cocktail Parties

Cocktail parties have been hosted by board members, patients and their families and friends (Gordy, Harper, Shapiro, Zepeda). They have been hugely successful, raising more than \$19,000. Jen Gordy said, “I just sent the invites out and had my friends and family over for cocktails. It was so easy and fun! I will definitely make this an annual event!” Lydia Zepeda said she even had fun addressing invitations with friends: “We drank a little wine while we filled in the invitations, had a bite to eat then had some more wine so we could lick the envelopes.” The “most dedicated patient” award goes to new bride Amanda Shapiro who contacted the Association *from her honeymoon* to say she wanted to host a party! She did and it was a huge success.

BBQ Bash at MSU

Alice Martin held a lunch-hour BBQ at work and netted about \$1000 for our cause.

Candle Sales

Donna DeLuca raised several hundred dollars by selling candles for melorheostosis.

Fundraiser for Melo at Work

One of Lyn Pickel's friends, Kay Allin, raised several hundred dollars by setting up a fundraising table at work and collecting donations for our charity.

Other Miscellaneous Donations

Linda Hembree, Amelio Collevchio, Lyn Pickel and Dan Papke have each gotten friends and family to donate to our cause. Some have even gotten their employers to match donations.

EVERY FUNDRAISING INITIATIVE HELPS!
It might surprise you to know that the average donation is around \$20-25!

Why should I?

Personally, my answer to this question is: I need to do this 'for the children'. I am inspired to make a difference—no matter how long it takes—for *the children*.

Fundraising is a challenge to all of us, your Board members included. As a non-profit organization, fundraising is the only way we can get the money needed to pursue our mission. Fundraising will be an on-going endeavor. There will never be a time when we don't need money to operate, to fund conferences, or more importantly, to fund research. How can we move forward as an organization without fundraising? The simple answer is *we cannot move forward without funding*.

As challenging as it may be, those of us who have had fundraisers have found them to be very rewarding endeavors AND a lot of FUN! People—your friends, your family, your work colleagues, members of civic groups that you are involved in—really do care, and they really do want to help. Asking for help is humbling, but I promise you will find it rewarding and fulfilling. Give it a try and you will see!

Alice Martin

Other *easy* things you can do to support the Melorheostosis Association

Searching the Web?

Please use www.goodsearch.com, and select the Melorheostosis Association as your favorite charity. Everytime you search .01 is added to our account! It adds up. Try it!!!

Visit the Melorheostosis Web Store

Wear your support for Melo! The Melorheostosis Association is thrilled to announce the launch of the new Web Store on our website. Here you, your friends and family can purchase items to support the Association. The items currently available on the site include silicon bracelets embossed with the words "ONWARD!" along with our website address "www.melorheostosis.org", and men and womens polo t-shirts with the Association logo on the front. 100% of the profits will help our continuing efforts to find the cause, treatment and cure of Melorheostosis!

States Where We Are Licensed to Fund Raise

California
Florida
Illinois
Kentucky
Massachusetts
Michigan
Missouri
New York
Oklahoma
Pennsylvania
Washington
Wisconsin

States Which Do NOT Require Special Licensing

Idaho
Indiana
Iowa
Montana
Nebraska
Nevada
South Dakota
Texas
Vermont
Wyoming



**Let's do it
"for the children..."**

Tax-Exempt Donations

Mail to: Ms. Alice Martin, Treasurer
Melorheostosis Association
1754 Briggsville Road
Fowlerville, MI 48836

Of Special Interest...

12 Year Old Melorheostosis Patient Gets Dream Visit to Rachael Ray Show



Twelve-year-old melorheostosis patient, Rachel Maeser, has a passion for cooking and her idol is Rachael Ray. Rachel got the thrill of a lifetime when she got to fly to New York and personally attend the taping of the Rachael Ray Show in New York City, along with her mom and Melorheostosis

Association President, Kathleen Harper.

The highlight of Rachel's visit was when she got to meet her idol Rachael Ray in person after the show. "It's something I'll remember for the rest of my life," Rachel said.

After watching the show from the VIP section, Rachel was given a tour of the studio and the prep kitchen. Then they stepped out into a hallway. The director said, "Come see Rachael." Rachel Maeser said, "I started crying." Overcome with the emotion of seeing Rachael Ray in person, Rachel hugged her and cried. The two then posed for a treasured photo.

Rachel's condition first came to light when she became involved in gymnastics at age 5 and it was noticed that one leg seemed longer than the other. Numerous tests were done but the diagnosis was inconclusive. Finally, a radiologist recognized the characteristics of melorheostosis from a textbook. Rachel's melorheostosis involves her pelvis and the lower portion of her body on the right side. Her right foot is especially painful, because her toes are not in the proper position.

Rachel's trip was made possible by the charitable efforts of the Louisville-based Texas Roadhouse. Disease Scientific Conference in October, 2008.

SAMPLES OF TISSUE URGENTLY NEEDED FOR RESEARCH

PLEASE NOTIFY THE MELORHEOSTOSIS ASSOCIATION IF YOU ARE PLANNING SURGERY

Samples of tissue, such as bone, skin, blood or plasma, from your surgery are urgently needed for research purposes. It is important that arrangements be made as far in advance as possible. There is no cost to you. You can make a valuable contribution to the search for treatments and a cure. For questions or information: Kathleen Harper, kathleen@harpervision.com.

MELORHEOSTOSIS ASSOCIATION JOINS RARE BONE DISEASE PATIENT NETWORK

The Melorheostosis Association has joined the nationwide Rare Bone Disease Patient Network. The Network is a coalition of rare bone disease patient organizations. Ultimately, the intention is to bring awareness to rare bone diseases by the government, professionals, and research organizations. The Network will host a scientific conference in October, 2008. This will be a first in history—the focus will be on all rare bone diseases. The Network Co-Chairs are Hillary Weldon and Kathleen Harper.

Board News

Board Members & Role Changes

As with any new organization, it takes a number of years to get things running smoothly which includes assigning the appropriate roles for Board members. Many role assignments have changed over the course of the past year. Kathleen Harper became President, Lydia Zepeda became Secretary, Alice Martin became Treasurer, Lyn Pickel became a Director, and Jennifer Gordy was added to the Board as a Director. The only two Directors who did not change hats were Michelle Lundie and Donna DeLuca.

Current Board Initiatives

Research Grant Initiative. Two-thirds of the money has been secured to fund a \$30,000 research project on melorheostosis. It is hoped that the data collected from the research conducted with this seed grant will lead to a sizeable research grant on melorheostosis for the principle investigator from NIH. A timeline for funding has been established, and Lydia Zepeda and Kathleen Harper are in the process of preparing a Research Funding Proposal (RFP) under

the guidance of Dr. Fred Kaplan, Dr. Geert Mortier and Dr. Michael Whyte of our Medical Panel..

Patient Handbook. This handbook is meant to answer many patient questions about melorheostosis. The doctors have answered many of the common questions.

Melorheostosis Web Store Enhancements. Plans are underway to offer many things for sale through the website. Many people have volunteered items to list for sale on our website with part of the proceeds going to the Association. Currently shirts and bracelets are available on our webstore.

2008 Conference Funding. Lydia Zepeda is investigating opportunities to obtain funding for the 2008 Melorheostosis Association Conference.

State Solicitation License Renewals. Renewal applications to fundraise have been prepared and submitted. A list of states for which the Association are approved is on the Fundraising Page of the Newsletter. A big Thank You to Alice Martine for all her hard work in establishing and maintaining these licenses on behalf of the organization.

Scientific/Medical Advisory Panel News

Dr. Henry Bone and Dr. Vicki Rosen Added to the Scientific/Medical Advisory Panel

Dr. Henry Bone is Director of the Michigan Bone and Mineral Clinic and Head of the Endocrinology Division at St. John Hospital and Medical Center in Detroit, Michigan. He is Chair of the Medical Advisory Panel of the Paget Foundation and President of the Michigan Consortium for Osteoporosis. Dr. Bone has served as Program Co-Chair for the American Society for Bone and Mineral Research 2000 annual meeting and Chairman of the Endocrine and Metabolic Drugs Advisory Committee of the US Food and Drug Administration.

Dr. Vicki Rosen is Professor and Chair of the Developmental Biology Department at Harvard. Dr. Rosen has a PhD in cell biology/physiology, and her research interest lies in the study of factors associated with bone formation, BMP signaling.

Bone & Tissue Registry

The bone and tissue registry has been established thanks to the diligent efforts of Dr. Pamela Robey, NIH. If you are scheduling surgery, please contact Kathleen Harper or Lyn Pickel for information on how to donate bone and tissue to the registry.

Recent Articles Published on Melorheostosis

[Couto AR](#), [Bruges-Armas J](#), [Peach CA](#), [Chapman K](#), [Brown MA](#), [Wordsworth BP](#), [Zhang Y](#). A Novel LEMD3 Mutation Common to Patients with Osteopoikilosis With and Without Melorheostosis. *Calcif Tissue Int.* 2007 Aug;81(2):81-4. Epub 2007 Jul 11. PMID: 17622481 [PubMed - in process]

[Mumm S](#), [Wenkert D](#), [Zhang X](#), [McAlister WH](#), [Mier RJ](#), [Whyte MP](#). Deactivating germline mutations in LEMD3 cause osteopoikilosis and Buschke-Ollendorf syndrome, but not sporadic melorheostosis. *J. Bone Miner. Res.* 2007 Feb; 22(2):243-50. PMID: 17087626 [PubMed—indexed for MEDLINE]

Conference Reports

2007 International U.K. Melorheostosis Conference was Held May 10-12, 2007 Green College, Oxford

The Melorheostosis Association—U.K. has kindly agreed to publish the results of the 1st International UK Melorheostosis Conference in this newsletter. Other information about the conference (and melorheostosis) can be viewed on their website: www.melo.eu.com. The U.S. Melorheostosis Association wants to take this opportunity to graciously thank everyone involved in organizing the UK conference; special thanks to Dr. Roger Smith for summarizing the conference; and thank everyone (scientists, practitioners and patients) who participated in the conference. We offer our sincere congratulations on your great success. Each conference provides new insight and leads us a few steps closer in our common quest to find answers to this puzzling disease.



2007 U.K. Conference Summary by Dr. Roger Smith, Oxford University

This meeting was held at the Nuffield Orthopaedic Centre in Oxford UK. It followed on the 4th International Melorheostosis Association Conference held in Madison Wisconsin on June 4-6 2006. There were presentations from the 12 members of the medical panel (three international), and 15 patients attended, some with their families. The main research aims of this conference were to learn about advances in the disorder, to discuss the relevance to melorheostosis of recent findings in related skeletal conditions, and to decide in which direction further research should go. Since this conference included patients as well as researchers it provided a novel opportunity to meet melorheostosis sufferers from the UK who had not been to the previous meetings abroad. We endeavoured to help them with their medical problems and we ourselves learnt a lot about melorheostosis.

The proceedings were opened by Andrew Carnell, Chairman of the Melorheostosis Association UK, who welcomed the participants and described the successful fund raising activities and the support for research. Paul Wordsworth (Oxford) introduced the first session of the sci-

entific meeting by a short description of the clinical and genetic aspects of melorheostosis and its management. Geert Mortier (Belgium), Michael Whyte (USA) and Yung Zhang (Oxford) then gave updates of the results of their research. Michael Whyte and Geert Mortier had examined the DNA obtained from patients at previous USA meetings: their results were largely in agreement and would soon be submitted for publication. The main conclusions remain unchanged, that is that mutations in the *LEMD3* gene can be found in osteopoikilosis (and the Bushke-Ollendorf syndrome) and also in melorheostosis when the two disorders are combined; but that when melorheostosis occurs on its own no such mutations can be found. The relationship between osteopoikilosis and melorheostosis remains obscure, and the possibility that in melorheostosis the distribution of the bone (and soft tissue) lesions is related to post-zygotic mutations has not been excluded. Geert Mortier re-emphasised the central importance of *LEMD3* since loss of function in this gene will (in theory) result in transcriptional activation of TGF β , activin or BMP-responsive promoters.

In melorheostosis ectopic mineralisation can occur in the soft tissues (and can be extensive). The reason for this is unknown. Clues may be obtained from the study of other disorders with ectopic mineralization. This is particularly relevant when the ectopic tissue is bone (i.e. ectopic calcification). Yun Zhang described the activating mutations in the *ANKH* gene, which leads to chondrocalcinosis, and current work on the structure of the ANKH protein. She also updated her work on the *LEMD3* gene and introduced the relevance of the described mutation in the *ACVR1* gene in FOP, where ectopic ossification is a major part of the phenotype.

Recent discoveries have re-emphasised the importance of the Bone Morphogenetic Proteins (BMPs), which belong to the TGF β superfamily, and their receptors in the control of normal and abnormal bone formation. The ways in which BMPs produce their cellular effects by signalling is complex but can be studied in the laboratory, and Philippa Hulley (Oxford) described how this could be done.

In the second session of the meeting Matthew Brown (Australia and Oxford) described the multinational work which led up to the discovery of the activating mutation in *ACRV1*, a BMP receptor, in fibrodysplasia ossificans progressiva and explained a project for generating *LEMD3* mutants in mice using a well-established method for random mutagenesis. Dealing more directly with melorheostosis Nick Athanasou (Oxford) described the changes in the skeletal and extrasketal tissues in melorheostosis and reviewed those rare conditions labelled as osteoscleroses which need to be distinguished from it. David Wilson (Oxford) emphasised the radiological changes which were characteristic of melorheostosis. These were wavy hyperostosis in a peripheral location, single limb or dermatome distribution crossing the joint, sometimes endosteal hyperostosis and/or soft tissue mineralization. Usefully he pointed out the role of isotope bone scanning to define which parts of the skeleton are affected and the indications for MRI scans in this disease.

Since melorheostosis is so rare there may be a

considerable delay in diagnosis. The disorder itself may present in a number of different ways which require different treatments (Paul Wordsworth, Oxford). Localised bone enlargement can cause pain and loss of movement in a nearby joint. Involvement of the soft tissues can lead to contractures. Where pain is a problem, appropriate analgesia is important and where disability is severe specialised rehabilitation is important. Close cooperation with an experienced surgeon is essential to control deformity and contractures (Martin McNally, Oxford). The Ilizarov method can be particularly useful where complex deformity is combined with asymmetry. Such operations should not be undertaken lightly.

One important aspect of this meeting was to give sufficient time to the patients and indeed this occupied much of the remaining space. Fourteen patients were seen individually by the medical panel (Martin McNally, Geert Mortier, Roger Smith, Michael Whyte and Paul Wordsworth). Radiographs were available (or had previously been seen) in most cases. There was a wide variety of phenotypes. With their consent blood was taken for diagnostic purposes and mutational analysis.

In the concluding (third) session Paul Wordsworth (Oxford) and Jim Triffitt (Oxford) briefly dealt with disorders related to melorheostosis. Roger Smith (Oxford) then summarised the day's meeting and thanked all those involved.

On the morning of 12 May members of the medical panel met briefly to discuss future meetings and research.

It was agreed that meetings should not be held more frequently than every two years, unless there was some spectacular advance, and since the present format seemed to work it should remain essentially unchanged.

So far as future research is concerned it will be most important to construct a melorheostosis registry, and Geert Mortier agreed to lead on this. Since Ghent and Oxford are close (by Eurostar) some informal meetings could take place.

2006 Conference Summary

4th International Melorheostosis Association Conference “BMPs on the shores of Lake Mendota”

By Lydia Zepeda

The 4th Conference of the Melorheostosis Association was held June 4-6, 2006 at the University of Wisconsin-Madison. It began with a reception at the University Club featuring jazz musicians Professor Richard Davis and David Stoler.

The scientific portion of the conference began on June 5 with Dr. Vickie Rosen of Harvard University. She opened the conference with a presentation describing bone morphogenetic proteins (BMPs), signaling molecules that influence bone formation at the cellular level. Dr. Geert Mortier of Ghent University Hospital in Belgium presented work from his lab that linked mutations in a particular gene, LEMD3 to osteopoikilosis, Bushcke-Ollendorff syndrome (BOS), and melorheostosis. The mutation was not found in patients who only had melorheostosis, indicating another unknown gene(s) is responsible for melo. Dr. Howard Worman of Columbia University discussed the role of the LEMD3 gene in cell regulating proteins that known as smads. Mutations in the LEMD3 gene disrupt smad signaling, resulting in abnormal bone and tissue formation. Dr. Pam Robey of the National Institute of Health discussed stem cells and their theoretical use in potentially treating melorheostosis. In his presentation, Dr. Michael Whyte of Washington University ruled out mutations in the LEMD3 as the primary cause of melorheostosis. The researchers withdrew to discuss likely candidate genes. Meanwhile, Dr. June Dahl of the University of Wisconsin discussed chronic pain management with melo patients. Her presentation focused on the pros and cons of using non-steroidal anti-inflammatory drugs (nsaids) such as ibuprofen versus opiates to manage long term chronic pain.

That evening researchers, physicians, patients and their families reunited at dinner overlooking Lake Mendota. Dr. Eileen Shore of the University of Pennsylvania talked about the recent breakthrough

in finding the gene that causes Fibrodysplasia Ossificans Progressiva (FOP), a rare bone disorder characterized by bone formation in muscle tissue. Observations that BMPs signals were altered in FOP cells led her lab to identify the cause of FOP, a mutation in ACVR1, a gene that acts as a BMP receptor. Melorheostosis is similar to FOP in that BMP signaling also is abnormal. She concluded that better understanding of the BMP signaling pathways (there are many and they are complicated) will lead to identifying the gene causing melorheostosis.

The morning of June 6 included patient clinics with panel researchers and physicians. Twelve patients were seen and for many of the scientists this was the first time they had seen more than one patient. Feedback from the scientists and physicians was that the clinics were very useful because they were not aware of the many ways that the disease presents. While the patient clinics were taking place, two presentations were made targeted to melorheostosis patients. Mr. Steve Hill of the University of Wisconsin Hospital discussed the role of physical therapy to maintain motion and strength patients. Dr. Robert Fleming of St. Louis University provided a recap in layman's terms of the scientific talks which were presented on the first day.

That afternoon, Dr. Shunji Tomatsu of St. Louis University presented on the topic of enhancement of drug delivery to bone. Dr. Yun Zhang of Oxford University talked about genetic factors in melorheostosis. Dr. Rob Fleming discussed BMP pathways and their implications for melorheostosis. After these presentations, the scientific medical panel met separately from the patients and their families to discuss plans for the coming year. The two groups reconvened to close the conference and the participants retired to State Street for a jovial night of eating, drinking and conviviality.

2008 Conference Planning & News

5th International Melorheostosis Association Conference

Dates, location, and agenda are being determined. We expect the Conference will be held in the fall of 2008 immediately following a professional meeting where most of our scientific panel will already be in attendance. More information will follow.

**YOUR TALENTS CAN HELP
THE MELORHEOSTOSIS ASSOCIATION**

The Melorheostosis Assn. is a not-for-profit organization run entirely by volunteers. As you may guess that means we are always in need – of funding, resources, time, and talent. Your talent, expertise and/or experience could be very helpful to us in numerous ways. Among the areas we need assistance are:

**Fundraising expertise
Marketing and Publicity
Writers for the Newsletter**

**Website Development
Grant writing experience**

We welcome your inquiry and would be happy to be in touch with you.

*Thank you
for taking the time to read this newsletter.*

We hope we have convinced to you get involved. Please do not hesitate to contact any of the Board Members if you have questions or need information of any kind. We are all here to help you.

**2007
Melorheostosis Association
Officers & Directors**

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“Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the unusual law of nature, by the careful investigation of cases of rarer forms of disease.”
William Harvey, 1657