New Research and Clinical Strategies in OI
April 26-28, 2006

The fifth OI Foundation Scientific Meeting, *New Research and Clinical Strategies in OI*, was held April 26-28, 2006 in Chicago, IL. The meeting was co-chaired by Peter H. Byers, MD, Professor of Pathology and Medicine at the University of Washington; David Rowe, MD, Department of Genetics and Developmental Biology, University of Connecticut Health Center; and Michael Whyte, MD., Medical and Scientific Director of the Center for Metabolic Bone Disease and Molecular Research at Shriners Hospitals for Children in St. Louis.

This was the Foundation's most exciting Scientific Meeting because the level of collaboration has grown so much since the first meeting in 1999, and continues to grow. The level of communication is growing. The base of knowledge is growing. The scope of knowledge is growing. In 1999, the first scientific meeting lasted 9 hours and involved 9 speakers and 25 participants. This meeting lasted 17 hours and involved 26 speakers and more than 50 participants. Even during breaks and meals, the discussion continued. Doctors received advice about difficult cases and shared research strategies.

Of course there is still much to learn, but what we do know has expanded tremendously since 1999. For example, the purpose of this meeting was to better understand clinical and genetic variation between all types of OI, with a special focus on Type I (mild) OI. After the April 2004 scientific meeting, which focused solely on treatments and a cure for Type I OI, similarities and differences between Type I OI and Types II-VII continued to be discovered. It is now clear that we must look at all the Types together in order to best understand each Type individually, and to understand why people with the same mutation have different degrees of severity.

Everyone agreed that in order to learn more about OI, we need larger numbers – larger numbers of people in studies, more tissue samples, more genetic information, more surgical results, and more dollars. As the OI Registry and the Linked Clinical Research Centers (LCRC) move forward toward the goal of bringing together a large pool of patients for study, this Scientific meeting showed that OI doctors are already good at working together. According to Peter Byers, MD, "These meetings break down barriers and allow for shared information. This is the soul of progress. If each of us shares, we will all do better."

Sharing information is already increasing the pace of research, with frequent interchanges of data, tissue samples, and treatment results. Doctors who are expert in a specific scientific or surgical technique share that expertise with everyone. The participants, both clinicians (who see

patients and do research) and researchers (who work in the laboratory and may see a few patients), are enthusiastic and eager to learn more about OI. Applying research methods to clinical care is the only way to develop effective treatment and standards of care.

We were especially pleased to welcome representatives from OI Clinics that will become part of the LCRC, and Michael Geisman Research Fellows. The impact on these up and coming researchers was dramatic. In the words of Michael Geisman Research Fellow Michael Sohaskey, PhD, University of California, Berkeley, who is researching a cause of rare, recessive forms of OI, that may result in methods to improve bone:

> "Thank you for inviting me to participate in the meeting on "New Research and Clinical Strategies in OI" last week. The meeting was an invaluable opportunity to meet and interact with other basic and clinical researchers who are thinking about many of the same issues related to skeletal development, bone quality and bone integrity. The meeting was extremely helpful in focusing my own research strategies and objectives; in particular, I look forward to pursuing a promising new strategy suggested by David Rowe, MD's presentation and our subsequent conversation. At the same time, I appreciated the diverse perspectives offered by the clinical presentations, which significantly extended and broadened my depth of understanding of OI as well as those people affected (directly and indirectly) by the disorder.'
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> 'Again, thank you for the opportunity to join a top-notch community of bone biologists working together toward finding improved treatments and, ultimately, a cure for osteogenesis imperfecta. I look forward to my continued association with the OI Foundation and to presenting my own research findings at a future meeting."

Experts in bone biology who do not routinely study OI were invited to speak at the meeting and add their perspective to the discussion. Henry Kronenberg, MD, Chief of the Endocrine Unit at the Massachusetts General Hospital and Professor of Medicine at the Harvard Medicine School said afterward "I really enjoyed the meeting and was very impressed with the community of OI investigators and how they work together."

The participation of OI Clinic Directors in this meeting is helping to make the LCRCs a reality. These doctors are on the front line of clinical care. This meeting provided an opportunity for them to share their experience, and to learn cutting-edge information so they can continue to provide the best possible care for people with OI.

This meeting demonstrated an unprecedented partnership of the best minds working in OI and bone research today. Several other partnerships helped to make the meeting possible. The Children's Brittle Bone Foundation (CBBF) is the Foundation's valued partner in OI research, working with us to make these meetings possible and initiating OI research and the LCRC. The meeting was also sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the Office of Rare Diseases, and the Buchbinder Family.

We heard about collaborations between groups of clinicians who are sharing data to assess performance outcomes, nutrition and growth, rodding, and scoliosis. For example, the scoliosis group is comparing patients who receive corrective surgery with those who don't. The Nutrition

and Growth Protocol is looking at high and low levels of nutrients and intervention for patients who are 6 months to 16 years old.

The following is a brief summary of the key points presented during the meeting.

Session 1: Clinical Variation in OI

Peter Byers, MD, University of Washington, Seattle, reported that their lab sees variability in and between families. The same mutation can result in a different phenotype (symptoms) in each person who has it. An example is that a seemingly identical mutation in the alpha 1 collagen chain can cause either Type II (fatal) OI, or Type I (mild) OI. By looking at variations in a large number of people and families, we hope to be able to better understand this variability, allowing us to predict phenotype. Eventually we hope to be able to develop a common phenotype description so that we can compare phenotype across genotype. It is important to note that phenotype changes with age. If we can do this, then we will be able to tell a parent what his/her child's symptoms will be, based on the child's genetic data.

Frank Rauch, MD, Shriners Hospital for Children, Montreal, reported on Type V OI. It has been seen in 19 of 446 patients (4.2%) seen at the Shriners Hospital for Children, Montreal since 1999. Defining features are white sclerae, moderate to severe bone fragility, hyperplastic callus, and no dentinogenesis imperfecta (DI). There is no collagen mutation. The callus is not cancerous, but may be mistakenly diagnosed as osteosarcoma (bone cancer). People with Type V OI have the same response to pamidronate treatment as seen in other Types.

Deborah Wenkert, MD, Center for Metabolic Bone Disease and Molecular Research, St. Louis, reported on variation in families with Type I OI. She reviewed data from 23 years of type I OI patients. There were 35 families reviewed. Thirteen of the families had more than one child with OI. A parent and child were affected in 13 families (22 patients).

The average height of the women was 4'7" to 5'9", the average height of the men was 5'2" to 6'1". There was no change in height from one generation to the next. Height changes were more likely to be based on age or number of vertebral compressions. Height was similar to that of other family members. Siblings generally had about the same height. Arthritis occurred in some adults, but not in any of the children.

The age at first fracture for these Type I OI patients was in utero for 5, at birth for 11. The oldest age at first fracture was 19. Eighty-two percent of siblings experienced their first fracture within 1 year of each other. There was more variability in age of first fracture between parents and children. If one sibling had vertebral compression fractures, then all siblings had them.

If hearing loss was present in one family member with OI, it often was not present in any other family member with OI.

Session 2: Objectives of and Stratification of Response to Therapy in OI

Doctors were asked to re-analyze their data to try to determine if responses to treatments could be correlated with genetic or Type information. In most cases, these correlations could not be made, pointing to the need for the kind of larger studies that are only possible through LCRCs, where a large pool of patients will be available for studies. According to David Rowe, MD, Medical Advisory Council Chair: "If we don't build LCRCs that can conduct research and train new doctors, we are doing a disservice to people with OI. We are grateful for the promise of long term support from the OI Foundation and CBBF boards of directors, which will make these Centers a reality in the near future, to start answering the unsolved problems of OI."

Frank Rauch, MD, Shriners Hospital for Children, Montreal, reported on treatment with pamidronate (Aredia®) in Types I, III, and IV OI.

Children treated with pamidronate showed an increase in mobility when compared to untreated children. Forty percent of the children treated with pamidronate are community walkers (able to walk in their neighborhood) while less than 10% of the untreated children are community walkers.

Although genetic data could not be used to determine response, the level of mobility was influenced by things like muscle force, long bone deformity, presence of other medical condition, quality of orthopedic care, physical therapy, occupational therapy, and attitude of the medical staff. Children's mobility is also determined by their level of motivation, access to physical therapy, attitude toward risk, support of family members, and school situation (accessible or not).

There is variation in response to pamidronate. The greatest benefit is to the vertebrae/spine. Results from Bisphosphonates are influenced by the amount of growth and the quality of OT/PT care. This is why there is a smaller effect on adults, who do not grow as rapidly as children do.

Participants noted that severe types of OI have an overlay of immobility that increases the severity. In fact, immobilization can be seen as a "second disease" in OI.

It is too soon to tell if intermittent vs. continuous doses of bisphosphonates will be more effective.

Joan Marini, MD, PhD, National Institutes of Health, Bethesda, reported on growth hormone therapy. This therapy may increase stature, increase volume in the thorax and abdomen, and improve bone quality. Children with Type IV OI are the best responders to growth hormone. 50% had a strong, sustained response over 2 years. There was a greater than or equal to 50% response in the 1st year of treatment and greater than or equal to 30% response in the 2nd and subsequent years. We don't know if childhood treatment lasts long enough.

A correlation between increased growth rate and genetic information was not found. A positive response was predicted when PICP was greater than or equal to 86 ug/m/ at baseline

In adult trials with growth hormone, the greatest improvement occurred after several years of treatment.

David Deyle, MD, University of Washington, Seattle, reported on gene targeting as a therapy for OI. After looking at several options for gene therapy, the gene targeting technique appears to be the most likely to succeed. Mesenchymal stem cells (MSCs) were selected for targeting because they make bone and they are easily expandable in a test tube. Using a person's own MSCs, the targeting "knocks out" the mutant collagen early in the cell's collagen–making process, so the targeted cell functions normally, producing good collagen. Approximately .05-1% of all cells are targeted. When the targeting is done in both the type 1 and 2 collagen genes (COL1A1 and COL1A2), the cells produce normal collagen and normal bone. There is no bone disease.

After the gene targeting occurs, the new collagen is stable. For example, tests show that OI collagen degrades quickly, but the new collagen produced after gene targeting degrades at the same temperature as normal collagen. The targeted cells maintain multipotency – the ability to form both bone and adipocytes (fat globules).

Previous studies attempting intravenous infusion of MSCs resulted in low engraftment. In human clinical trials, the targeted MSCs will be transplanted by direct injection, starting with a single bone, such as the humerus, and comparing it to the untreated humerus. In the lab, targeted cells are still showing in bone cells that received an injection up to 4 years ago.

Michael Whyte, MD, Center for Metabolic Bone Disease and Molecular Research, St. Louis, reported on a patient with hypophosphatasia who was cured when bone chips filled with MSCs were placed in his bones. After 6-7 years, the MSCs migrated from the bone chips into the bone. In another patient, when bone grafts loaded with MSCs were placed into a bone lesion, they repaired the defect

David Rowe, MD, University of Connecticut, Farmington, reported that his lab stopped trying to do the anti-dominant transplantation technique when the gene targeting paper was published, because it is such an improvement over previous techniques.

His lab is concentrating on developing markers to identify the level of cell differentiation, where the cells came from, etc. He uses genes that express color at different levels of differentiation so it is easy to study cell lineage. The technique also shows cells that engraft on the bone surface.

Several methods were tried that resulted in systemic engraftment of bone MSCs, but the MSCs remain on the surface of the bone and do not attach. The cells that do attach to the bone do make bone. The gene targeting technique proved that when MSCs are injected, they do engraft and they do make bone. When mutant and normal cells are injected together, the normal cells will outperform the mutant cells and displace them. In other experiments, donor cortical bone replaced host cortical bone and improved the quality of the host bone.

When using adult stem cells, by the time you do the manipulation, they have less ability to continue developing because of senescence. In the future, we will develop banks of matching tissue stem cells to use for transplantation. These will work for OI transplants. We will use embryonic cells for adults, because they will outperform the adult cells.

Patrick Ross, Ph.D., Washington University School of Medicine, St. Louis, reviewed the many new drugs being studied that will impact osteoclast regulation. These include: C-Src inhibitors, αvβ3, Cathepsin K, H^+ATPase, RANK L (denosumab®). Many of the more obvious osteoclast targets have been identified. Novel targets are becoming available to replace bisphosphonates with more targeted molecules.

Denosumab is in phase III clinical trials. There is a concern about the immunology impact. RANK L receptors are on osteoclasts, but also on breast tissue and T-cells. How should the OI Community be thinking of Denosumab®? We don't know the impact yet, but scientists may be able to make it more specific for a dominant disorder. Then it would be a great strategy for OI.

Forteo impacts the osteoblast. Bisphosphonates decrease response to PTH (Forteo). How will bisphosphonates change the body's response to other drugs?

Session 3: Clinical Pharmacology, Pharmacogenetics and Pharmacogenomics of Bisphosphonates

Graham Russell, MD, PhD, The Botnar Research Centre and Oxford University Institute of Musculoskeletal Sciences, UK, reported that bisphosphonates started as water softeners. The key ingredient, pyrophosphate serves as the body's natural water softener by regulating calcification. Bisphosphonates are effective in Paget's Disease of Bone, Osteoporosis, myeloma, and bone metastases. Problems with these drugs are the exception, not the norm. Types of bisphosphonates are not the same – they vary by speed of onset of effect, speed of reversal of effect, turnover suppression rate, types of anti-fracture effect, and age of user.

Zoledronic Acid (Zometa®) is likely to be the last improvement for a while. Potential problems with Zoledronic Acid (Zometa®) include: renal impairment (with IV delivery), the acute phase reaction (also found with Pamidronate), and high dosages causing micro damage in bone.

Bisphosphonate effects depend on which bisphosphonate is being used. The total dose is the main determinant of effect, and it is cumulative. Long intervals between doses decrease the effect.

Risedronate (Actonel®) is the weakest bisphosphonate. It may be better for children than alendronate because it is milder, and the effects disappear faster. The degree of mineralization is higher than with other bisphosphonates after 3 years of Risedronate (Actonel®).

There is no convincing evidence for a genetic response to bisphosphonates-but this has not been studied. The variable response to oral bisphosphonates is related to absorption or noncompliance (people forgetting to take their medicine). Some resistance to bisphosphonates was observed in Paget's patients, with no known cause.

Michael Whyte, MD, Center for Metabolic Bone Disease and Molecular Research, St. Louis, reported that he has seen several cases of bisphosphonate toxicity in children who do not have OI. He has not seen any problems in mild OI or adults with OI.

In adult cancer patients, bisphosphonate toxicity (mostly using IV delivery, some with oral delivery of bisphosphonate) causes Osteonecrosis of the Jaw (ONJ), sometimes with infection. Merck says 17,000 patients over 10 years were treated with Fosomax and did not have ONJ.

ONJ is most likely with cancer patients and patients who use steroids. ONJ may occur in up to 10% of cancer patients on long term bisphosphonates. Many more adults are receiving high dose bisphosphonates as part of cancer treatment than are OI patients. For people with OI, the number of hyper brittle bone cases may increase as more people take bisphosphonates.

Zoledronic Acid (Zometa®) is most strongly associated with ONJ. ONJ and osteopetrosis (hyper dense bones) can be treated effectively with hyperbaric oxygen, but not if they were caused by Zoledronic Acid (Zometa®). The problem may be occurring because the infusion is too fast.

Session 4: Genetic Heterogeneity in OI-New Genes and Their Functions

Christophe Poirier, Ph.D. University of Chicago, is searching for new genes that cause OI. This will improve diagnosis, gain better understanding, and develop new treatments. He is working with the Fro/fro mouse which has a severe form of OI, but no type I collagen defect. A possible new gene is the one that makes Smpd3, which regulates bone formation in the womb. Although Smpd3 is found in the brain and bone, there is no evidence of cognitive impairment.

Ceramide is important for bone strength. Does ceramide have therapeutic potential?

Brendan Lee, MD, Ph.D, Baylor College of Medicine, Houston, reported on research that may explain recessive Type II OI, which occurs in less than 10% of all OI births. His lab identified the first non-Collagen gene, CRTAP, whose mutations cause recessive OI, with symptoms that go from moderate, such as in Type VII OI, to lethal, as in Type II OI.

Research shows that a lack of prolyl 3-hydroxylation (P3H) causes low bone mass, osteoporotic bone, cartilage changes, decreased bone volume, decreased trabecular thickness, decreased trabecular number, increased trabecular spacing, normal collagen but poor fibril formation, no osteoclast defect, normal osteoclast resorption and formation, decreased osteoid, severe kyphosis, stretchy skin, and smaller size. CRTAP is required for P3H to work. Type II OI families and Type VII OI families with no collagen mutation were missing CRTAP.

Henry Kronenberg, MD, Harvard Medical School, Boston, discussed the growth plate and OI. Bone lengthening is the job of the growth plate chondrocytes. We know that height for all people with OI is low and head size is normal or large. Possible reasons for poor bone growth in OI could be systemic effects such as poor nutrition, stress, glucocorticoids, leg bowing, scoliosis or trauma to the growth plate. However, the most likely reason for poor bone growth in OI is that there is an ineffective transition from cartilage matrix to bone matrix. There may be defective signaling from the bone matrix or from Type I collagen producing cells. It is not clear why only some of the growth plates are affected.

Session 5: Phenotyping and Measurement and Outcome

Jay Shapiro, MD, Kennedy Krieger Institute, Johns Hopkins University, Baltimore, discussed the outcome measures that are being developed by a group of clinicians who met at the Kennedy Krieger Institute in December 2005. They are looking at measurements for growth, nutrition, pain, results after bisphosphonates, functional outcomes assessments, scoliosis, natural history and outcomes, and rodding techniques.

Reid Sutton, MD, Baylor College of Medicine, Houston, noted that it is difficult to classify someone's OI type if that person has been treated from birth. Because the genotype/phenotype correlation is imperfect, this makes controlled studies very difficult. The only way to overcome this variability is by studying large numbers of patients.

It is impossible to find clear outcome measures for a study. For example, does DEXA change enough over a year to be a good measure? Can you simply count fracture rate or should you somehow rate each fracture by severity? How do you measure mobility?

Like most rare disorders, OI lacks good historic data. It is important to do what we can to collect data for use as historic controls. Since we can't collect everything, we must decide what to collect. These measures should be standardized, quick, cheap, and low risk.

Scott Paul, MD, National Institutes of Health, Bethesda, emphasized the important of focusing on function. Investigators must prove that what's done in the therapy lab is going to have an impact at home on mobility and function. Function includes mobility, self care, communication, work and play. These are the things we do that allow us to interact with others. It is also important to focus on the social aspects of disability.

We know that exercise is an intervention for strength, mobility, balance and coordination. The Physical therapist can use pain relief, orthotics, bracing, adaptive equipment, or mobility aids to help improve mobility and function.

Research difficulties occur because:

- It is difficult to put the proper blinding technique in place (therapists know what each patient is doing)
- Using a control group may not be good medicine (can we justify NOT providing physical therapy?)
- There are multiple side effects impacting growth and development
- There are many variations in administration of treatment.

Attention to safety in OI means we can't use many standard strength or flexibility measurements safely, in some cases body proportions may rule out the use of a standard measurement tool. We can measure the effects of orthoses, exercise (aquatic therapy), trunk extension, heat, or electromagnetic therapy.

Some of the things that will improve our ability to study function are: categorizing the spectrum of the functional phenotype, correlating the phenotypic variation with genetic and proteomic variation, reaching consensus about capacity vs. ability, avoiding a floor/ceiling effect, learning

to account for confounders, developing observational measures, and deciding how frequently we should measure for longitudinal change.

Cathleen Raggio, MD, Hospital for Special Surgery, New York City, suggested a new method to measure bone mineral content, bone size, and geometry. She asked: "Should getting a bone biopsy be the standard of care?"

The Fourier Transform Infrared Imaging Spectroscopy (FTIR) provides more and better information than a DEXA scan. For example, it can measure the maturity of collagen and increases in crystallinity. There is a correlation between increased fracture risk and increased crystallinity. Current measures of bone mineral density (BMD) don't correlate with fracture risk, and only account for 60-70% of bone strength. Measuring bone strength is especially important with mild forms of OI. In the future, Raman Spectroscopy is being developed to look at bone through the skin.

Dr. Raggio also asked, do we need to treat Type I (mild) OI and if so, with what?

Session 6: Waiting for an Answer, Waiting for a Study: Unsolved Problems in OI

Several hours were devoted to identifying the unsolved problems in OI in order to stimulate research that will find answers to these timely questions.

Rick Wenstrup, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, suggested that the Foundation look at two models of organizations (The Children's Cancer Group, and the National Marfan Foundation) that have answered difficult questions. Both sought answers to a few simple questions. For example the National Marfan Foundation asked "Why do we die early?" and "What can we do about it?"

Dr. Wenstrup reviewed articles published about causes of death in OI. He found two.
1996 British Medical Journal, Life Expectancy in OI, Colin Paterson BMJ 312:351-353, 1996
and
J Clin Pathol 1996:49:627-630 Causes of Death in osteogenesis imperfecta. Susan J McAllion, Colin R Paterson, from which this chart is taken.

Table 5 Causes of death in osteogenesis imperfecta: comparison with the general population.[10] Deaths from each group of causes are expressed as percentages of all deaths

	Osteogenesis imperfecta type		
Cause of death	*III*	*I and IV*	*General population*
Respiratory	81.6	39.0	15.7
Cardiovascular	2.6	36.6	44.6
Neurological	0	12.2	1.6
Trauma	13.2	2.4	2.7
Other	2.6	9.8	35.4

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Dr. Wenstrup then looked for articles on respiratory function and found *Takken, J. Pediatrics 2004 145:813-818* which looked at 17 children with Type I OI and found that pulmonary function was normal when they were at rest, but not during exercise. This led him to ask: "Are pulmonary problems related to muscle function?" Dr. Wenstrup is studying pulmonary function in OI mice to try to learn more. He is looking at mortality data and the relationship of orthopedic pathology to pulmonary disease,

Laura Tosi, MD, Children's Hospital National Medical Center, Washington, DC, reported on a recent rodding surgery on an adult who had a plate on his femur. After a fracture, she had to replace the plate and insert a rod. The bone under the plate had deteriorated. She knows that for rodding to work, the bone has to surround the metal. She recommends that surgeons do not plate bones.

Dr. Tosi also discussed a case of Scoliosis in a teenager with Type I OI. Mild bracing corrected the scoliosis. Success directly correlates with the length of daily time in the brace. Does general scoliosis information relate to OI?

Marcia Willing, MD, Ph.D., University of Iowa, Iowa City, discussed the need for standard evaluation guidelines. When she sees a patient with OI, she wonders if and when she should do a full skeletal survey, hearing test, dental evaluation, cardiology function test, bone mass assessment, or biochemical vs. molecular testing? She also would like clear indications for treating with bisphosphonates or other drug therapies.

Linda DiMeglio, MD, MPH, Riley Hospital for Children, Indianapolis, is researching whether response to bisphosphonates varies with the severity of OI, type of OI, and dose. Even though people with Type I OI had a better response to alendronate (Fosomax®) than did people with Types III-IV OI, does that mean we should give it to patients who need it the least?

An interesting finding was that unaffected family members of children with severe OI had higher than normal bone mineral density (BMD), even higher than family members of children with Type I OI.

Joan Marini, MD, PhD, National Institutes of Health, Bethesda, reviewed findings on pulmonary function abnormalities in children with OI, correlated with OI type, and location of collagen mutation. She found there is a better correlation between arm span and trunk size than height.

In studies of children with OI up to age 24, lung volume and capacity declined. The decline is bigger for Type III than type IV. The decline occurs with or without scoliosis. Those with an Alpha 2 collagen mutation had more pulmonary decline. Does collagen affect lung development?

If we can prevent the decline in body height and/or scoliosis with bisphosphonates, will that reduce the decline in pulmonary function? Is the decline related to a change from a manual wheelchair to a power chair that often occurs in the teen years?

Robert Steiner, MD, Doernbecher Children's Hospital, Oregon Health & Science University, Portland, reported on a systematic literature review and concluded that there is a lack of well designed, adequately powered studies of OI, especially those that look at drugs other than bisphosphonates. This shows that studies have to involve more people.

Horacio Plotkin, MD, Children's Hospital and University of Nebraska Medical Center, Omaha, discussed the need to agree on a definition of OI and types of OI. He proposed that OI be defined as: A syndrome with congenital brittle bones secondary to mutations in the genes that codify for type I pro-collagen.

Deborah Wenkert, MD, Center for Metabolic Bone Disease and Molecular Research, St. Louis, asked numerous questions including: Do we treat early with bisphosphonates? How do we achieve maximum impact and prevent fractures? Is there a window of opportunity for bisphosphonates? How do we balance the possible benefits with the risk of side effects? Are we better off with a constant low dose to eliminate the transition zone in bone?
Is there a psychiatric impact of being on medication? Does overprotecting children interfere with development of a healthy self image?

Jay Shapiro, MD, Kennedy Krieger Institute, Johns Hopkins University, Baltimore, recommended that OI clinics add experts on mental health, drug addiction, and muscle weakness.

All of the participants agreed that the unsolved problems can't be solved with small numbers of patients. They also agreed on the need for Consensus Conferences to review the available information and develop consensus around guidelines for care and treatment.

Session 7: Identification Of Goals And Strategies For The Treatment Of OI In Linked Clinical Research Centers (LCRC)

At the end of the meeting, Peter Byers, MD, University of Washington, Seattle, discussed goals and strategies for the LCRC and summarized what the next phase of the LCRC will look like. It is being designed to answer many of the questions raised at this meeting.

In order to improve clinical care and find treatments and a cure, we need: imagination, patients and families willing to share their medical information, expert teaching programs, more and larger animal models, interactive clinician/researcher networks, the right cells, excellent and accessible data, and open and frequent discussion, and scientific meetings. When we have these things in place, we will be able to assess the current state of care, determine the genetic and environmental influences on response to treatment, greatly improve child and adult care, and understand the relationship between genotype (genetic information) and phenotype (symptoms). This will mean that when a child tests positive for OI, the genetic data will also provide clues to tell parents how severe the child's OI will be.

In order to have nationwide coordination of OI care, the LCRCs will create a network of centers for evaluation and care of OI, and application of up to date treatment with standard outcome measures.

The latest estimates of prevalence come from Finland where there are 6-7 people with OI per 100,000. This would mean there are 20,000 people with OI in the U.S., or about 350 births/year (50 cases per year would be lethal). It is important to identify a significant portion of these people to study. The University of Washington, Seattle, has 3,000 genetic samples, of which 600 are OI Type II. We estimate that perhaps 1/3 of the OI population is now being treated in existing centers. Intervention should start at birth. Are there windows of opportunity?

The LCRC will contain:

A registry to identify people with OI.

Central core language/description developed into widely usable format for intake, assessment, and standards. Checklists longer than 10 items are useless. How much information is needed and can be reasonably collected? A minimum data set will give us the most bang for the buck and allow for clear outcomes.

Central database with information from the intake form. This data will be available to all LCRC doctors.

Radiographic, clinical and genetic databases that are tied together. Then we can develop a medical history of OI. The natural history is probably lost.

The resources needed to make the LCRC a success are:

Expert teaching programs: There are probably 100 experts qualified to teach about OI. We need to decide how to disseminate information. For example, through Clinics or grand rounds trainings. We could identify high quality medical centers that do not have a program, and integrate one in through training.

Animal Models: We need more and larger models. We need to be able to share them with everyone. We'll have to determine what we want and how will they be used.

Frequent and open communication and meetings: This is the soul of progress. Meetings break down barriers and allow for shared information. We will need to improve our ability to work with multiple institutions, and improve communication and response time. These things can be resolved through annual meetings with center directors. If each of us shares, we will all do better.

Patients and Families: We will need them to work with us to develop a large enough pool of data to find new treatments and a cure and develop standards of care. How do we get access to more patients? We need to integrate as many people as we can into multiple centers, develop the LCRC structure, and develop opportunities to create programs and pilot projects at centers.

Three years from now, the LCRC should be eligible for NIH funding.

The 2007 scientific meeting will again involve the LCRC directors to build consensus on basic standards of care. Participants at this "Consensus Conference" will review research and clinical

experience and develop clear guidelines that will tell doctors how to treat OI and what data to collect.

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