

# NIAMS *IRPartners*

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A newsletter for patients of the Intramural Research Program (IRP), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

## The Road to Results

By Susan Bettendorf

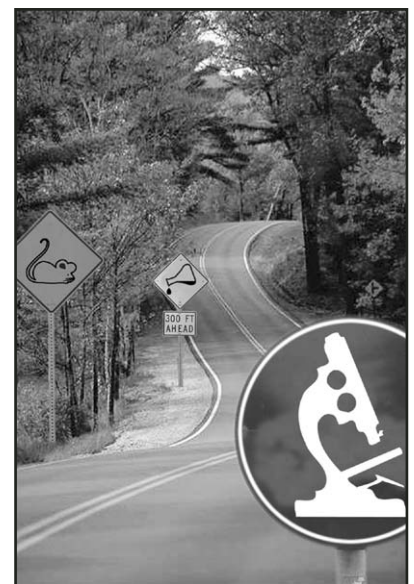
**D**id you ever wonder where medicine comes from? How researchers come up with a chemical compound that attacks a certain disease? Is it by trial and error? By chance? More often than not, it involves a little of both, *IRPartners* found out, but you can be sure that it also involves years of research and testing. Breakthroughs in human health don't happen overnight.

*IRPartners* talked with Paul Plotz, M.D., chief of the NIAMS Arthritis and Rheumatism Branch and a long-time employee of NIH, to get some insight into how much effort and time it really takes for the research in a lab to actually benefit people who are sick. Of course it varies, but Dr. Plotz shared with us some examples from his research to illustrate what the road to results looks like.

### An Interesting Mistake

In 1981, Dr. Plotz returned from a sabbatical in London, not sure what direction his research should take. Not long after he was back in the United States, he started hearing and reading about some exciting new findings in research in autoantibodies, a subject he'd been reading about for 20 years. (Antibodies, explains Dr. Plotz, are proteins that attach to harmful substances in the body so that the immune system can destroy them. In autoimmune diseases, the antibodies – called autoantibodies – attach to the body's own healthy tissues by mistake.) He was fascinated by these new findings. He wanted to explore how the antibodies developed and how they contributed to autoimmune diseases. Dr. Plotz says, "I was ready for a new idea." He set out to study the antibodies by researching myositis, a rare autoimmune disease that destroys muscles.

Ten years ago, while looking at patients who had myositis, a medical student working with Dr. Plotz on the project discovered that a patient had been misdiagnosed. It turned out the patient didn't have myositis



## From the Scientific Director . . .

Welcome to the winter issue of *IRPartners*. For our cover story, we talked with longtime NIAMS scientist Dr. Paul Plotz to gain insight into how the process of research promotes medical breakthroughs. As you read this article, it may occur to you that there is a lot of luck involved in a breakthrough. While that's true, it's equally true that in research you have to recognize luck and respond to it. I like a saying of Louis Pasteur, the nineteenth-



century French scientist, that Dr. Plotz keeps on his door: "Chance favors the prepared mind."

In this issue, you'll also meet Dr. Nikolay Nikolov, a doctoral fellow at NIAMS, as we follow him on his rounds at the Clinical Center. Finally, in the "Did You Know?" section, we give you tips on how to prevent osteoporosis, a disease that can affect men and children, as well as adult women.

Enjoy this issue!

*Peter E. Lipsky, M.D., Scientific Director  
National Institute of Arthritis and Musculoskeletal  
and Skin Diseases, National Institutes of Health*

### ROAD TO RESULTS, *continued from page 1*

but instead had Pompe (POM-pay) syndrome, a disease that mimics myositis very closely.

Pompe syndrome is a genetic disorder found in people who are missing the gene that triggers the body to make a necessary enzyme called acid maltase. Acid maltase helps keep muscles healthy, and without it, muscles atrophy and waste away. After much hard work, the same student who recognized the misdiagnosed patient also identified the mutations in the gene that causes the syndrome. Dr. Plotz says, "That patient and that medical student turned the direction of the research." After this, Dr. Plotz's lab added Pompe syndrome to its research portfolio.

### Rare Diseases Make for Good Research

Pompe syndrome is even rarer than myositis, so it is easy to wonder why Dr. Plotz would pay attention to it when he could be researching something like, say, rheumatoid arthritis, which affects millions.

However, Dr. Plotz says that shifts in focus like this happen often in research. Many advances in treatment occur because researchers concentrate on a rare disease, which later yields insights into disease processes that are common in other illnesses.

"Sometimes the very obscure observations turn out to be the most important. You look at a disease where the problems are sharply defined, and then you try to solve them. What you find may have implications in similar diseases," he says.

For example, if Dr. Plotz's team (including Nina Raben, M.D., Ph.D., who is leading the effort) can find a treatment for the muscle wasting that



Deborah de Jong (left), a research fellow, and Dr. Plotz review findings from their work on Pompe syndrome.

characterizes Pompe syndrome, they may find new methods to treat more common diseases in which enzyme and metabolism problems lead to muscle deterioration.

### Of Mice and Maltase

After the mutation was identified, the group created a mouse model of the disease, which means they developed a strain of mice that is missing the gene necessary to make acid maltase. Once researchers produced this mouse model, they could begin testing different therapies in the sick mice to see how they responded.

## ***Plotz, Grammer, Blumenkron Honored***

**Paul H. Plotz, M.D.**, senior investigator and chief of the Arthritis and Rheumatism Branch at NIAMS, is doubly honored this year. Most recently, he received the Distinguished Rheumatologist Award from the American College of Rheumatology in October. The award is given each year to a rheumatologist who has made outstanding contributions in patient care, clinical scholarship or service to patients with rheumatic diseases. Earlier this year, Dr. Plotz was awarded the prestigious Carol Nachman Prize, which is given annually by the German Institute for Clinical Immunology for outstanding innovative research work in the field of rheumatology. Currently, Dr. Plotz's research interests include the immune system, inflammation and myositis and other muscle diseases. (See *IRPartner's* cover story, "The Road to Results," for more on Dr. Plotz's research.)

**Amrie C. Grammer, Ph.D.**, and **Fernando Blumenkron**, of the NIAMS Autoimmunity Branch, received minority scientist travel awards from the American Association of Immunologists this spring. They presented papers at the association's annual meeting, along with another awardee and former branch colleague, Y.K. Onno Teng. ▲

## ***Kastner's Research Noted by Arthritis Foundation***

Research conducted by Daniel Kastner, M.D., Ph.D., chief of the NIAMS Genetics and Genomics Branch, was recently cited by the Arthritis Foundation as one of the top ten research advances of 2003.

Dr. Kastner and his Research Fellow, Jae Jin Chae, Ph.D., established an important new finding about the protein pyrin: It helps to shut down the inflammatory process in the body's normal response to infection. When the gene that produces pyrin has a certain mutation, then the body does not get the proper signals it needs to shut down that inflammatory response. This finding has implications for the possible role of genetics in the development of arthritis, and it supports the theory that some rheumatic and inflammatory diseases begin when individuals with genetic susceptibility encounter certain types of infection.

The "Top Ten" list was developed by the Arthritis Foundation in consultation with clinicians, scientists, the American College of Rheumatology, the American Academy of Orthopaedic Surgeons, the Centers for Disease Control and Prevention and the National Institutes of Health. ▲



## ***Steinert Mourned***

Peter M. Steinert, Ph.D., chief of the NIAMS Laboratory of Skin Biology, passed away unexpectedly April 7. He was 57.

A native of Australia, Dr. Steinert came to the United States in 1972. He worked at Boston University Medical School and the Massachusetts Institute of Technology in Cambridge, Mass., before joining the National Cancer Institute's (NCI) Dermatology Branch in 1973. In 1990, he moved to NIAMS, where he became chief of the Laboratory of Skin Biology.

Many will remember Dr. Steinert as a superb scientist and a dedicated mentor. He made many important findings concerning the biochemistry of skin proteins and their disturbances in various genetic diseases of the skin. Moreover, he was an embracing friend to many. Colleagues say that he made them part of his family. He was well-known by his friends for planning ski trips and other outings and for welcoming colleagues into his home for holiday gatherings. Dr. Steinert is survived by his companion, NCI's Mario Anzano, Ph.D., and two brothers.



## Did You Know...Osteoporosis Can Be Prevented?

**O**steoporosis means thin bones, and it is caused by the loss of bone material, which leads to fragile bones and fractures. Many men, as well as women, suffer from osteoporosis, but it is a disease that can be prevented before it occurs or treated after it happens.

### What is Bone?

Bone is living, growing tissue made mostly of two components: a protein called collagen, which provides a soft framework for bone, and a mineral, calcium phosphate, which strengthens and hardens the framework. This combination makes bone strong, yet flexible.

Throughout a person's lifetime, old bone is removed (called resorption) and new bone is added to the skeleton (called formation). During childhood and the teenage years, new bone is added faster than old bone is removed, making bones grow larger and denser. Bone formation outpaces resorption until bone reaches its greatest density and strength sometime before age 30. With natural aging, bone resorption may slowly outpace formation. Osteoporosis develops when bone resorption occurs too quickly and/or when bone replacement occurs too slowly.

### Risk Factors

Certain risk factors are linked to the development of osteoporosis or to an individual's likelihood of developing the disease. Some risk factors can be changed, but others cannot.

### What You Can't Change

**Gender** – Women have smaller bones and lose bone more rapidly than men because of hormone changes

associated with menopause, so women are at higher risk for osteoporosis.

**Age** – The older you are, the greater your risk of osteoporosis because bones become less dense with age.

**Ethnicity** – Caucasian and Asian women are at the highest risk for osteoporosis. African American and Latino women have a lower, but still significant, risk.

**History of fracture** – Having had a fracture is one of the most important risk factors for future fractures. Anyone who has fractured a bone after age 45 or who has had several fractures before that age should see a physician to be screened for osteoporosis.

**Family history** – Susceptibility to bone loss and fractures may be partly hereditary.

### What You Can Change

You can lower your risk of developing osteoporosis. To reach optimal bone mass and continue building new bone tissue, consider the following recommendations.

**Calcium** – Researchers think getting too little calcium over a lifetime may contribute to osteoporosis. The most concentrated dietary sources of calcium include dairy products, such as milk, yogurt, cheese and ice cream. A typical American diet supplies approximately 300 milligrams of calcium from nondairy foods, such as dark green, leafy vegetables (including broccoli, collard greens and bok choy), sardines and salmon with bones, tofu, almonds and foods fortified with calcium. Recent guidelines suggest that adults need between 1,000 and 1,200 milligrams daily. If you're not getting enough calcium each day in the food you eat, you also may need to take a supplement that contains calcium.

**Vitamin D** – Vitamin D helps the body absorb calcium. The body makes vitamin D in the skin when it is exposed to sunlight, and many people obtain enough of it. Studies show, however, that vitamin D production decreases in the elderly, in the housebound, and during the winter. Milk (in liquid form) is supplemented with vitamin D; fish such as salmon and tuna also are good sources of vitamin D. Some people, especially the elderly, may need to take a supplement containing vitamin D to ensure that each day they get 200 to 600 IU (international units, the standard of measurement used for many nutritional supplements).

### Facts and Figures

- In the United States, more than 10 million people have osteoporosis and 34 million more are at increased risk for the disease.
- One out of every two women and one in four men older than age 50 will have an osteoporosis-related fracture in his or her lifetime.
- Each year, 80,000 men suffer a hip fracture and one-third of these men die within a year.

## *A Day in the Life of Dr. Nikolay Nikolov*

**W**e all have experience being patients, but do you ever wonder what it's like to be the doctor – the one doing the poking, prodding and prescribing? How do doctors get advice when they aren't sure of the answers? How do they spend their time when they are not in the exam room? *IRPartners* wondered about just these things, and Nikolay Nikolov, M.D., a doctoral fellow in the NIAMS arthritis clinic in the NIH's Warren G. Magnuson Clinical Center, was good enough to give us a window into a doctor's life recently when he let us shadow him for a day.

### 9:50 a.m.

Dr. Nikolov rushes to the ninth floor clinic for a 10 a.m. meeting with Gregory Dennis, M.D., director of the NIAMS Clinical Care and Training Program, to discuss the case of a 10-year-old boy with kidney problems, anemia, osteoporosis (a bone-wasting disorder) and possibly an autoimmune disease. Dr. Nikolov presents information about the child's symptoms and medications to Dr. Dennis, who mostly takes notes, breaking in once in a while to ask questions or give his opinion. Dr. Dennis tells Dr. Nikolov to consult other NIH clinics about the boy's anemia and kidney problems and suggests a DEXA scan – DEXA is a technology that uses small amounts of radiation to measure bone density – to determine the severity of the child's bone loss. He suggests that Dr. Nikolov consult the Food and Drug Administration about medicines to treat osteoporosis in children before prescribing any adult-strength medicines.

### 10:20 a.m.

Dr. Nikolov returns to his office to do paperwork: reviewing case histories and noting his patients' progress or setbacks. He also must prepare for two patients and for a lunchtime presentation he is giving to other NIAMS staff on the boy's case.

### 11:30 a.m.

Dr. Nikolov sees his first clinic patient of the day. She is in her mid-40s and has lupus (a rheumatic disease) and osteoporosis, as well as depression. Dr. Nikolov reviews her vital signs and asks if she has any concerns about her health since her last visit. She says she sometimes forgets to take her evening medication, and she may have a broken toe. She also mentions a recurring skin



Dr. Nikolov (right) examines a patient for joint pain and tenderness as part of her participation in a clinical study on Familial Mediterranean Fever.

rash. Dr. Nikolov gives her a complete physical examination and examines the foot injury, determining that the pain is due to aggravated soft tissue around the big toe. He tells the patient to take acetaminophen (a pain reliever) for the foot pain and recommends a few techniques for remembering her medicine, such as putting it by her toothbrush so she will not forget it.

### 12:05 p.m.

Dr. Nikolov consults with the attending physician, Gabor Illei, M.D., a NIAMS rheumatologist, to discuss the woman's exam results. Dr. Illei sees no changes in the woman's health that require immediate follow-up, so he tells Dr. Nikolov to schedule another exam for three months later.

### 12:30 p.m.

Dr. Nikolov joins the other NIAMS fellows and attending physicians for a brown bag lunch session on the most interesting cases of the week. Other doctors present their cases, and then it is Dr. Nikolov's turn.



DR. NIKOLOV, *continued on page 6*

**Exercise** – Like muscle, bone responds to exercise by becoming stronger. The best kind of exercise for your bones is weight-bearing exercise, which forces you to work against gravity. Such exercise includes walking, jogging, stair climbing, weight training and dancing.

**Smoking** – It is easier said than done, but quitting smoking can reduce your risk of developing osteoporosis, not to mention heart disease and a number of types of cancer. Smokers may absorb less calcium from their diets. Women who smoke have lower levels of estrogen than nonsmokers and frequently go through menopause earlier.

**Medications** – Long-term use of glucocorticoids (commonly called steroids, although these are not the same type of steroids abused by some athletes) can lead to a loss of bone density and fractures. Other medications that increase osteoporosis risk include certain antiseizure drugs, such as phenytoin and barbiturates; gonadotropin releasing hormone (GnRH) analogs used to treat endometriosis; and

excessive use of aluminum-containing antacids. It is important to discuss these medications with your physician and to consult him or her before you stop taking them or alter your dosage.

### Treatment

Osteoporosis is a treatable disease. A person over age 65 or at high risk of developing osteoporosis for other reasons may wish to see a physician to have a bone mineral density test. Such a screening can lead to steps to reduce the risk of fracture. The Food and Drug Administration has approved several medications for the prevention and treatment of osteoporosis. A comprehensive treatment program often includes exercise, proper nutrition, safety precautions to prevent falls that may result in fractures, and sometimes medications. ▲

*Adapted from the NIH Osteoporosis and Related Bone Diseases~National Resource Center publication, Osteoporosis Overview.*

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### DR. NIKOLOV, *continued from page 5*

He has five minutes to describe the complex nature of the 10-year-old boy's case. Dr. Dennis asks the fellows for their opinions, and several other doctors suggest that the thyroid and kidney problems may indicate an autoimmune syndrome, together with hemolytic anemia, a blood disease. Dr. Dennis asks Dr. Nikolov to continue studying the boy's symptoms in order to establish a basis for signs of autoimmunity. Dr. Dennis then concludes the session – a good thing, because Dr. Nikolov has a patient waiting.

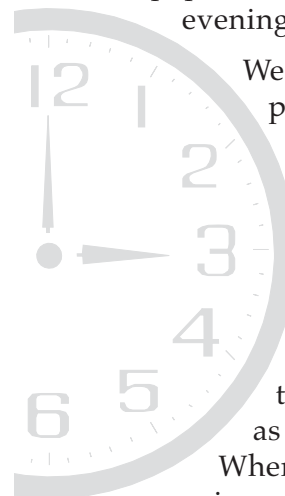
#### 1:30 p.m.

Dr. Nikolov's second and last patient of the day is a 72-year-old woman who might have Familial Mediterranean Fever, an inherited, rheumatic disease that affects the whole body. Dr. Nikolov takes her medical history, which includes osteoarthritis in her fingers and abdominal pain that required hospitalization, as well as the medical histories of her father, grandfather, sons and daughters. If rheumatic disease runs in the family, it might be the clue that leads him to a diagnosis. Dr. Nikolov notes that the woman's niece also had similar abdominal pain and that her father had psoriasis, an autoimmune skin disease.

Dr. Nikolov determines that Familial Mediterranean Fever or another rheumatic syndrome might be causing the abdominal pain, but he will have to consult with the patient's attending physician before proceeding with further investigations, including genetic testing.

#### 3:00 p.m.

IRPartners' day of shadowing is over, but Dr. Nikolov's is just beginning. He has more meetings and paperwork that will last late into the evening.



We caught up with Dr. Nikolov's last patient and asked her opinion of the staff and Dr. Nikolov. She said, "I have never been an inhibited person at all, which is why I didn't mind agreeing to being photographed or watched while I was being examined, but Dr. Nikolov is so deliberate and thorough with his exam, it seems as if no one else is in the room.

Whenever I come here, I know that I am in excellent hands." ▲



Of course, it would be great if every idea or experiment worked out the first time, but that's rarely the case. Setbacks are the rule, not the exception, in research. Dr. Plotz says, "There are lots of good scientists out there who fail all the time. Sometimes you go down blind alleys, but then you learn that you need to try something else. Successful science is built on unsuccessful science."

For example, in early studies, Dr. Plotz's group tried to introduce acid maltase into the mice with Pompe syndrome, but the mice developed an immune response, and their bodies rejected it. At this point, the researchers could have given up, determining that giving acid maltase to the mice was impossible, but instead they began working on getting the mice to make their own enzymes.

At present, the researchers' goal is to see if they can introduce the missing gene into the bodies of the mice so the mice can produce their own acid maltase. Studies are underway, so a cure should be just around the corner, right? Not so fast: Pompe syndrome is a complex disease, and living animals (especially humans) are complex organisms. Therapy for people with Pompe syndrome using such a method is still a long way off. First, Dr. Plotz's lab must see how the gene therapy works in the mice.

### A Long and Winding Road

Dr. Plotz says, "Tracing the intellectual history [of a research project], trying to find a direct path from where we are now - back through all the knowledge and discoveries - to the point where research on a certain thing actually started, is often difficult. Science flows from one question to another. You are constantly exploring new pathways. You keep working until you get enough information or until you learn you can't solve the problem this way. Then you move on to something else." Dr. Plotz adds that people who do research "often don't have defined starting and ending points. You make a decision about what problem you want to solve, and you go from there."

A few lucky accidents can help. If the researchers had not discovered that one of their myositis patients truly had Pompe syndrome, they wouldn't

be where they are today, trying out a new therapy. But obstacles are important, too: The group's early attempts to introduce acid maltase into the mice, which failed, resulted in their trying new methods, which were successful. But while luck or the ability to push past obstacles are important, new therapies are the product of researchers who devote years to the relentless, hard work of research. ▲

### Mouse Models of Disease

Why worry about disease in mice when you want to cure people? That's a good question. Dr. Plotz says you can do informative studies in animals that lead to even better studies in humans. Researchers always hope that whatever insights they get from animal research will help with clinical research. The therapies tested in clinical trials today involving people would have been impossible without first trying those therapies in animals. And most animal studies would be impossible without earlier studies in smaller creatures, such as fruit flies, and even before that in single-celled organisms, such as bacteria.



All of this basic research is crucial to building a base of information from which researchers can then begin to ask questions about a certain disease. (Basic research means research that is not targeted to a particular disease but instead tries to understand how cells, organisms and body systems work.) "Research wouldn't be where it is today without decades of work in basic biology," Dr. Plotz says. "It's impossible to imagine reaching where we are now without building on the research that came before."



## NIAMS Has Free Health Information

**N**IAMS has free health information (some in Spanish) available to the public, health professionals and organizations. Information is available on arthritis, lupus and other rheumatic diseases, skin disorders, joint problems and musculoskeletal diseases.

Contact the NIAMS at 1-877-22-NIAMS (free call), TTY: 301-565-2966. Check our Web site at [www.niams.nih.gov/hi/](http://www.niams.nih.gov/hi/). Many of our publications can be printed directly from our site.

Free information on osteoporosis, Paget's disease of bone, osteogenesis imperfecta, primary hyperparathyroidism, and other metabolic bone diseases and disorders is also available from the NIH Osteoporosis and Related Bone Diseases~National Resource Center (NIH ORBD~NRC). Contact the NIH ORBD~NRC at 1-800-624-BONE, TTY: 202-466-4315, or at [www.osteoporosis.nih.gov](http://www.osteoporosis.nih.gov). ▲

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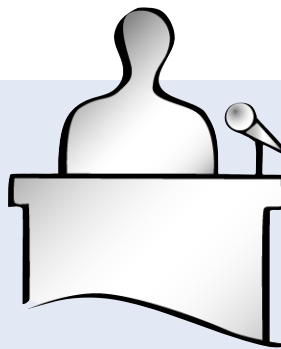
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### Need an NIH Speaker?

The NIH Speakers Bureau is a service that lists NIH researchers, clinicians and other professionals who are available to speak to

school groups and other local and national organizations. Speakers have expertise in such areas as arthritis, osteoporosis, autoimmunity and several dozen other topics covered by the NIH. To find out more about this service, sponsored by NIH's Office of Science Education, visit its Web site at:

<http://science-education.nih.gov/spkbureau.nsf>

### Questions To Consider Before Joining a Study

- What is the purpose of the study?
- What is required of me?
- Will the study benefit me or others?
- Are there risks? If so, what are they and what are the chances that they will occur?
- What discomforts are involved?
- How long will the study last?
- What will happen if I decide to leave the study?

### NIAMS Community Health Center

The NIAMS has set up the NIAMS Community Health Center to help doctors and scientists understand the causes of rheumatic diseases and why many of these diseases occur more often and more severely in certain minority communities. With this information, we can find better ways to treat and prevent these diseases. There are no experimental treatments or medications being used at the Community Health Center. Call 202-673-0000 for information.