

LEAP

Johns Hopkins University
School of Medicine
Division of Rheumatology
Winter 2017



A DETECTIVE STORY

HOW RA BEGINS

**GOUT:
SHADOW ILLNESS**

**A DANGEROUS
COMBINATION IN
SJÖGREN'S**

PRECISION AND PEOPLE

For more than a decade we have worked hard, in collaboration with our patients, to establish a framework that allows us to make real strides toward understanding disease mechanism, and toward better therapy and prevention.

This framework involves collecting large amounts of detailed information about disease characteristics and how they evolve over time, coupled with collecting samples that offer snapshots of disease at successive times. This framework has grown enormously, and it is supporting new programs in Precision Medicine.

Precision Medicine means taking everything we know about the patient clinically – evidence we can see in physical symptoms, that we can glean from what the patient tells us, observe in scans, and measure in increasingly sophisticated lab tests. You may have heard the expression, “You can’t see the forest for the trees.” Well, Precision Medicine is *seeing groups of trees and seeing the forest, too*. It’s seeing that within a waiting room full of people with the same disease, these three have the same particular symptoms, and these five over here have their own set of symptoms. They’re similar but essentially different – and we now know that people in these distinct subgroups have diseases that are being driven by different mechanisms, and thus may need different treatment.

Sir William Osler, first chief of Medicine at Johns Hopkins, pointed out that the understanding of human disease would come from studying humans, and would require perfecting the art of observation, bringing to bear the science of experimentation, and sharpening the reasoning faculty so as to know true from false. Our current era brings enormous opportunities to accomplish this, using novel measurement and analytical tools. This is the moment for Precision Medicine.

You can read about our precision approach to an increasingly common illness, gout (Page 6), to a rare illness linked to Sjögren’s (Page 10), and to cancer patients who are developing some autoimmune-mediated complications (Page 12). And we are especially excited to share with you a tremendous breakthrough in understanding how rheumatoid arthritis begins (Page 2).

In *Leap*, we have always shared stories about ourselves because we want you to know why we do what we do. In our Story Project (Page 14), you’ll get to know three wonderful people whose smiling faces you may have seen in our clinics. They are incredibly dedicated to making your life better.

Antony Rosen, M.D.
Director, Division of Rheumatology
Vice Dean for Research

WINTER 2017

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HOW RA BEGINS

A DETECTIVE STORY

FEATURE STORY

WHAT CAUSES RHEUMATOID ARTHRITIS?

The search, by scientists around the world, has been exhaustive, and the prey surprisingly elusive – but in breakthrough Hopkins research, scientists Maximilian Konig, M.D., and Felipe Andrade, M.D., Ph.D., believe they have pinpointed one culprit: a kind of bacteria that lives in the mouth and is present in gum disease.

THIS FORM OF BACTERIA has an unpronounceable name, *Aggregatibacter actinomycetemcomitans*, so the scientists who have discovered the terrible and important role it might play in RA just call it by its initials: Aa. “We are very excited about it,” says Konig. If their hypothesis is verified by other scientists and in larger studies, the possibilities of preventing RA from developing, and of treating early RA and possibly reversing symptoms, are enormous. This work is in press in *Science Translational Medicine*.

The idea itself – that RA, like tuberculosis, anthrax, or pneumonia, is caused by a bacterial infection – is not new. “For a long time, people thought that the disease did not start in the joints,” says Andrade, who is a rheumatologist and immunologist. Back in the days of Louis Pasteur, in the early days of microbiology, scientists “strongly suspected that RA was like rheumatic fever (caused by streptococcal bacteria), in that it was at least triggered by an infectious agent,” says Konig, who did a postdoctoral fellowship in Andrade’s

lab and now is a resident physician at Massachusetts General Hospital.

But nobody could prove it. Unlike other diseases, in which the time between exposure to a certain pathogen and development of symptoms takes days or weeks – so it’s easier to make the link between cause and effect – the gap in RA between exposure to something bad and actual illness could be a matter of years. Also, scientists “didn’t know what they were looking for, because there was no understanding of what kind of disease RA is, and how it works immunologically.”

Within the last 20 years, scientists at Hopkins and elsewhere have made huge leaps in understanding what happens when the immune system attacks the body in RA. They found strange proteins in the joints of people with the disease. These proteins are modified – “as if they are wearing a costume or makeup,” says Andrade. The modifications are what scientists describe as *citrullinated*; they’re decorated at the molecular level. Imagine someone wearing a wig, a fake mustache and specta-

cles – in short, a suspicious-looking character. The immune system errs on the side of caution, decides these shady-looking proteins are up to no good, and attacks them.

“A lot of the field, including us, has focused on what it is that changes the structure of these proteins to let them be altered in this chemical way,” says Antony Rosen, M.D., Director of the Division of Rheumatology and Vice Dean of Research. “The alteration is catalyzed by PADs,” enzymes found in inflammatory cells, “and when they’re activated, they change the structure of the molecules into something that is seen as a threat by the immune system.” The antibodies the body makes in response to this protein mutation are very specific. From long-term studies of military personnel, scientists learned that these citrullinated proteins, and antibodies to them, can show up in the blood *as early as 14 years before someone develops the first symptom of RA*. “We always believed that if we understood what drove it, we would understand what turns on and drives RA.”

So here’s the chain of events so far: the enzymes change the proteins, and the immune system makes antibodies against the interlopers. The antibodies cause inflammation, “which causes the damage that leads to this disabling and destructive joint disease,” says Konig.

The Link to Gum Disease

But what activates the enzymes? What starts the whole process?

This brings us to the mouth, and you may be wondering why. It’s because since the early 1900s, doctors have noticed that

As excited as the scientists are by this work, by the brilliant idea and the elegant science, they live day and night with the knowledge that RA is a devastating disease, and beyond anything, they want to help the people who suffer from it. They also hope to prevent further suffering, and this may be the first place to start if these results hold true.

people with bad RA tend to have severe periodontal disease (gum disease). “That was something that was quite puzzling,” says Konig, “but doctors didn’t focus on this observation. They thought maybe patients were not brushing their teeth properly because of their disabling joint pain.”

Over time, scientists began to suspect that there was something in the gums that might trigger both the periodontal disease and the RA – here’s the caveat – in *someone who has a genetic susceptibility, a faulty gene* that’s involved in how the immune system recognizes enemies.

Clearly, not everyone who has poor oral hygiene gets gum disease, and not everyone who develops periodontal disease gets RA. “I think you need to have both,” says Konig: “to have the right genetic background to be susceptible and to be infected with a bacterium that can initiate the production of these abnormal proteins. And probably a dose of bad luck, too. Only then will you develop the antibodies that are involved in the sustained immune response.”

Over the last decade or so, scientists have been looking for answers in the microenvironment of the gums in people who have periodontal disease. Scientists in England were convinced that they had found a likely candidate, a bacterium called

P. gingivalis. “People believed that this might contain a unique enzyme that could generate citrullination in the gums,” says Konig. In Andrade’s lab, he started investigating this. “Felipe and I didn’t have any preconceived ideas about it. But whatever we tried to do, whenever we tried to replicate the data that proposed to be the link between *P. gingivalis* and RA, all our experiments were negative. We could not replicate it. When we tried to understand more mechanistically whether this made sense, we came to the conclusion that even though this was a beautiful story, the biology tells us that this is likely not the way things work.”

“Max did elegant work,” says Rosen. “He purified the bug, made the enzyme, set up an assay to show whether it made RA antigens, and showed that it was not possible. The *P. gingivalis* PAD does not create RA antigens; it actually turns itself off and doesn’t work against self-proteins,” the proteins that are targeted by the antibodies. In fact, Konig and Andrade published a paper strongly suggesting that the *P. gingivalis* theory was incorrect.

Konig and Andrade were frustrated; in fact, Konig notes, “Felipe said, ‘That’s it, we’re dropping it. We are never going to work on gum disease and RA again.’” But Konig couldn’t let it go. “I was a little

obsessed with the idea that we were missing something.” At that time, Felipe had already published some work about how RA in the joint behaves. He realized that probably one of the most important points in the story is an immune system cell called the neutrophil.

Neutrophils are white blood cells. They rush to the site of an infection, eat microorganisms – think of Pac Man here – and release germ-killing enzymes. In the joints of people with RA, neutrophils turn on their PADs and generate a huge amount of the RA autoantigens (targets against which the immune system makes antibodies). In striking work, Andrade found the step that turns on the citrullination: in the joints of someone with RA, there are pathways that punch temporary holes in the membranes of the neutrophils, and this is what causes the many small changes in the molecules – which, in turn, stimulate the production of antibodies.

Think about crabs in the sand, scuttling around, making tiny holes that fill up again very quickly. These holes in the neutrophils are like little perforations that weaken paper – but unlike those in perforated paper, these holes may last only seconds. That tiny flash of time is enough for calcium to pour into the neutrophil. The calcium activates the enzymes that cause the citrullination. This overwhelms the immune cell processes, the neutrophil dies and spits out the “dressed up” proteins into the joint.

Konig believed that something in the mouth was punching the holes in the neutrophils, and must be the cause of the citrullination. “I was at the lab meeting when he came up with this proposal,” recalls Rosen. “I thought, that’s really clever, but what are the chances of finding it? But he went and searched for bugs in the mouth, for anything that would open a hole in a neutrophil membrane.”

In gum disease, Konig explains, “you have a very rich inflammation that is full of neutrophils and bacteria in the periodontal pocket,” the diseased area of gum around a

tooth. “It is very important for the immune system to be able to fight off these chronic pathogens in gum disease. Maybe a form of bacteria in gum disease fights back by poking holes in the neutrophil.”

After months of hard work, and with support from the Greene Foundation, Konig found Aa. “It makes a specific toxin, called leukotoxin A,” he says. “This toxin is a bacterial pore-forming toxin.” In other words, it pokes holes. Perhaps “someone with chronic gum inflammation has this specific bacterium, Aa, that makes this toxin that binds to neutrophils and creates short-acting holes, and that creates these autoantigens.” Add chronic infection with this particular form of bacteria with a ready entry into the body – through the gums – to having the genetic susceptibility, and it is likely that “this initiates the disease.”

Says Andrade, “we developed a diagnostic assay to identify people who have been infected by Aa, and found that as many as 47 percent of RA patients have evidence of this infection. The association is extremely strong.”

Where Do We Go From Here?

What does this mean? First, says Andrade, “it means that if our work is confirmed by others, this bacteria could be the closest thing to the cause of RA, something people have been seeking for many years.”

Now, what does it mean beyond that? As excited as the scientists are by this work, by the brilliant idea and the elegant science, they live day and night with the knowledge that RA is a devastating disease, and beyond anything, they want to help the people who suffer from it. They also hope to prevent further suffering, and this may be the first place to start if these results hold true.

One thought, Konig says, is that “you might be able to specifically kill these bacteria in a patient who already has RA, and maybe if you take the bacterium away, you could either stop the disease or ameliorate the severity of it. We already have markers (the antibodies the body makes against the citrullinated proteins) that identify people

So here’s the chain of events so far: the enzymes change the proteins, and the immune system makes antibodies against the interlopers. The antibodies cause inflammation, “which causes the damage that leads to this disabling and destructive joint disease.” But what activates the enzymes? What starts the whole process?

at risk of developing the disease.” These antibodies may be circulating in the blood a decade or more before the onset of disease. “If we could reach people before they have the disease – but who already have a marker for it, because they’re starting to develop antibodies – we could specifically treat the inflammation in the gums by inhibiting the bacteria, or use specific drugs that inhibit the utility and function of the toxin, and maybe prevent people from getting RA in the first place,” continues Konig.

It may even be that one day, dentists will identify patients with periodontal disease, and a simple swab test might be able to determine the presence of the antibodies – and get these people to a rheumatologist for early treatment.

It may also be that treating the Aa bug may help prevent further damage and make life better for someone with established RA.

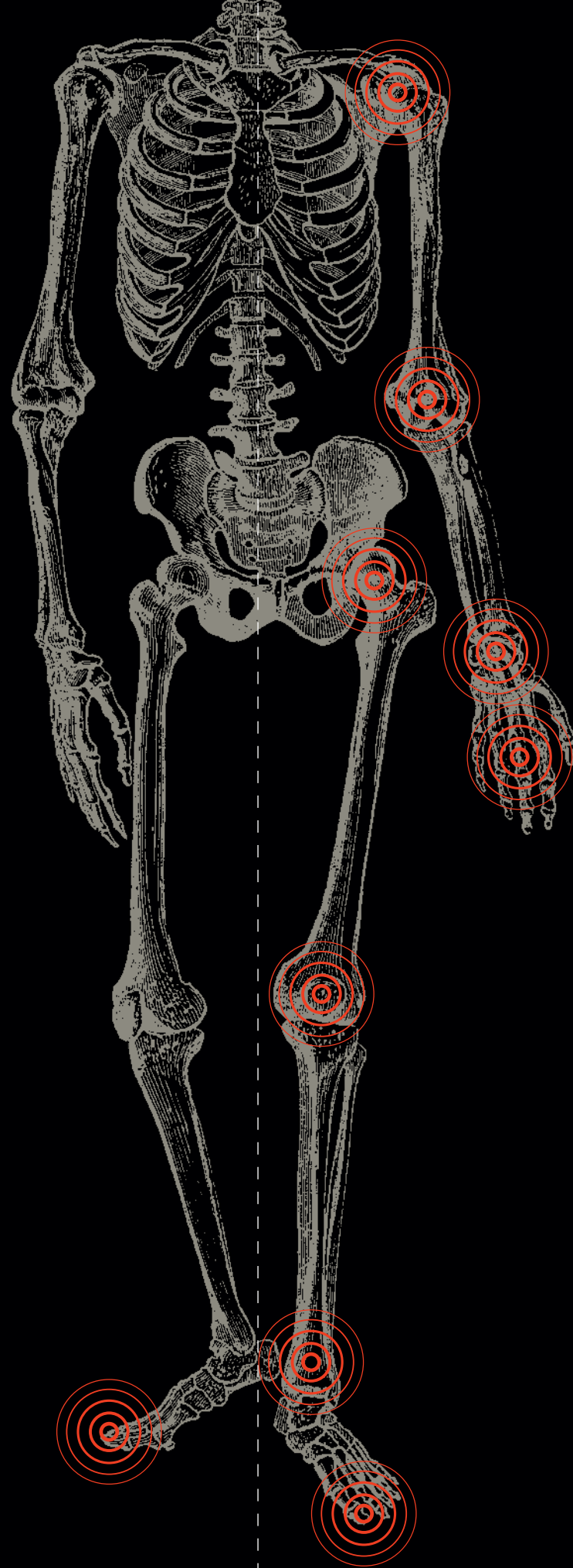
“We screen for heart disease, for some cancers,” says Konig. “Why not screen for RA?” ↓

RA AND MODERN LIFE

In Europe, before the 1800s, RA was virtually unknown. It was not written about in the medical literature, and it does not seem to have been the widespread problem that it is now (an estimated 1.5 million Americans have RA today). “Somewhere between 1800 and 1900, it became this large epidemic,” says Max Konig, “where you see RA cases and descriptions popping up everywhere.”

Why? Konig speculates that the rise in RA may have had something to do with the diet. “Sugar consumption increased by about 100-fold. Also, people started to smoke more.” Undoubtedly, as travel increased between continents, some new bacterial species were introduced, as well. Whatever happened, it resulted in a “shift in the microbiome of the gums.”

EARLY DISEASE



LATE DISEASE

FEATURE STORY

GOUT:

SHADOW
ILLNESS

If you are suffering from an acute attack of gout, you are most likely in too much pain to think about the risk factors of several million other Americans who have the same vulnerability to gout as you do. What do they have to do with you, and what do you have to do with them?

More than you might think. You are connected, and the result of understanding how will be better, more personalized care. That's precision medicine, and Antony Rosen, M.D., Director of Rheumatology and Vice Dean for Research, believes that "this is our calling, to bring science to the caring practice of individuals with disease, for prevention and monitoring and therapy and cure."

The body feels like it's on fire, because when those crystals come out of the bloodstream and deposit in the joint, gout incites an extreme inflammatory response: hot, swollen joints. Neutrophils and other inflammatory mediators swarm into the joint, turning it bright, beet red. Fire-engine red.

Doctors and scientists are able to do this on an unprecedented level today, he continues, because of advances in technology and knowledge that allow them to analyze vast amounts of data and look for patterns and connections. Understanding what's happening with many patients helps doctors do a better job of focusing on the individual patient at the bedside. "We have learned that diseases – even though you can aggregate them together under one label – are heterogeneous," Rosen continues. Imagine that you have 100 people in a room with the same disease. That's not one single disease, and it's probably not 100 different diseases, either. More likely, it's "a limited number of subgroups" – groups of patients with very similar symptoms and patterns of illness. "If you can identify these subgroups and understand what the disease mechanisms are, then you can treat them in precise, specific ways."

Sometimes this information comes from looking at small groups of patients at a single institution. Other times, it comes from looking at huge numbers of patients. Two Hopkins scientists have taken this latter approach, using national data sets to answer questions about gout. The results of their work are some precision conclusions about the mechanism of the disease, its diagnosis, risks, and treatment.

If ever an illness needed a closer look, it's gout – possibly the most airily stereotyped disease there is. Gout even has a poster boy, of sorts: a portly, wealthy gentleman who drinks too much red wine and eats too much rich food. It's portrayed in literature as an Epicurean affliction, the runoff of opulence and it even has a nickname: gout is the "disease of kings."

Actually, gout is not elitist at all; it attacks the poor as well as the rich, both women and men. It is rather sinister. Gout, the Hopkins scientists have shown, is a creepy shadow that follows other diseases, piggybacks off of their risk factors, and kicks sick people when they're down. It is also becoming more common.

Studies by Hopkins rheumatologist Allan Gelber, M.D., Ph.D., M.P.H., and general internal medicine fellow Stephen Juraschek, M.D., Ph.D., have shed new light on how gout is linked to kidney disease, obesity, cardiovascular disease and high blood pressure. In troubling findings, the scientists also have shown that half of all Americans who take medicine for gout are insufficiently treated.

Gout is caused by hyperuricemia, an excess of uric acid – which itself is a byproduct of the body's processing of purines (compounds that are among the building

blocks of DNA). Some foods – including alcoholic beverages and red meat, just as the stereotype suggests – are high in purines, and changing your diet can lower uric acid a little. But for many people, this is not enough. The problem is that uric acid makes crystals, which can build up in the joints. Sometimes this results in a "flare," an acute attack characterized by redness, tenderness, swelling, and terrible pain. But that's just the tip of the iceberg, and treatment for the flare is different from treatment for the chronic problem. Unfortunately, many people – including some doctors – think that treating the acute flare is sufficient.

It's not. When it's not screaming for attention, gout moves silently, still forming crystals, and – think of termites – wreaking unseen havoc. "Gout can cause severe damage over time if the uric acid crystals are not cleared," says Juraschek. "The crystals, and the inflammatory response they trigger, can cause degradation and erosion of the bone structure, can cause deformities and lead to irreversible damage affecting the joint. It is a progressive illness."

The gout flare itself is incredibly painful, says Gelber. "I've heard patients say it was the most incapacitating experience they've ever had, similar to and at times more excruciating than a kidney stone or childbirth. The body feels like it's on fire, because when those crystals come out of the bloodstream and deposit in the joint, gout incites an extreme inflammatory response: hot, swollen joints. Neutrophils and other inflammatory mediators swarm into the joint, turning it bright, beet red. Fire-engine red. During the worst pain, people might not be able to bear weight on the joint and get out of bed."

Because it attacks the joints, gout can mimic other immune-mediated diseases such as lupus and rheumatoid arthritis, and sometimes is misdiagnosed. This is where understanding the risk factors comes into play: gout keeps bad company, and is intricately linked to the risk factors of heart disease, including high levels of lipids, excess body

weight, high blood pressure, high glucose level, and to kidney disease and diabetes.

Why doesn't everyone with these other problems go on to develop gout? That's not clear; however, "some people have differences in genes in the epithelium, or lining, of the renal tubule," says Gelber. Renal tubules are long, thin, convoluted tubes in the kidney that carry urine from tangles of blood vessels known as glomeruli into a holding tank called the renal pelvis; they also absorb water and salts. Genetic alterations to these renal tubular transporters affect the release of uric acid from the body. "One of the newest FDA-approved drugs specifically targets a receptor in the renal tubule."

Gout attacks are fairly common on the medical and surgical services in the hospital, says Gelber, who is often called in to see these patients. Typically, someone has a heart attack, comes to the hospital, is treated, free of chest pain and starting to recover, and it's Day 3. "All of a sudden, that person is in pain, with a hot, red, swollen toe, knee, or wrist. It's like gout is kicking people when they're down." After the flare subsides, if the uric acid is not brought under control with long-term medication, gout can go on to cause a progressive, deforming arthritis. "Gout is the single most common form of inflammatory arthritis in the U.S." Although it is more common in men, the risk rises exponentially in women after menopause, he adds.

Gout is on the upswing in America. Juraschek, who has a Ph.D. in epidemiology from the Bloomberg School of Public Health, became interested in gout during his fourth year of medical school at Hopkins when he worked with Gelber, who also has a background in public health. Together, the two decided to explore what's happening with gout using data from tens of thousands of Americans in the National Health and Nutrition Examination Surveys. Their research resulted in four published papers co-written with Lara Kovell and Edgar Miller. Here's some of what they found:

• **Gout lurks in the risk factors of heart disease and stroke.** There is more gout in



Allan Gelber (left) and Stephen Juraschek: Making precision conclusions about the mechanism of gout, its diagnosis, risks, and treatment.

"The crystals, and the inflammatory response they trigger, can cause degradation and erosion of the bone structure, can cause deformities and lead to irreversible damage affecting the joint. It is a progressive illness."

people who have uncontrolled high blood pressure plus other cardiovascular disease risk factors including obesity, high cholesterol, diabetes, and kidney problems.

• **Gout goes up with a higher Body Mass Index (BMI) and obesity.** The likelihood of gout goes up incrementally with every bit of weight you gain. "The risk with morbid obesity is more than four times higher," says Gelber, "but it's one and a half times higher even in people who are just overweight."

• **Gout rises with impaired kidney function.** Close to one-third of people with the highest stages of kidney disease have been told they have gout. "We were surprised," says Juraschek, "at how high the prevalence is among U.S. adults with kid-

ney disease. That finding really highlighted this overlap in conditions."

• **Half of all Americans who have been diagnosed with gout and who take medicine are not lowering uric acid enough.** It's not clear why: it may be that people don't take their medicine as directed, or that they stop taking it. The bottom line: "Even though we have good drugs for gout and patients get to the doctor and are treated for it, the medical community achieves suboptimal care," says Juraschek, and long-term follow-up monitoring is needed to make sure that gout sufferers achieve relief and prevent further damage. "For doctors, gout may not be adequately on the radar – realizing who's at risk, and taking steps to prevent it." [L](#)

A DANGEROUS COMBINATION

An unsavory aspect of autoimmune diseases is that they seem to be quite hospitable – all too ready to extend a welcome to other autoimmune conditions to join them. This is the case in Sjögren’s, which sometimes overlaps with a particularly severe neurological syndrome known as NMOSD, for “neuromyelitis optica spectrum disorder.” Is this syndrome a direct manifestation of Sjögren’s itself? A new test developed by Hopkins scientists shows that it is not – but the presence of NMOSD has very serious implications for how Sjögren’s is treated.

NMOSD produces lesions in the brain that can be difficult to distinguish from those of another autoimmune disease: Multiple Sclerosis (MS). Like MS, it attacks myelin, the insulating layer of fat and protein that wraps around a nerve cell and helps conduct electrical signals efficiently. But there’s an overlap here, too: some people with MS develop particularly devastating problems

WHAT ARE AQUAPORINS?

Peter Agre, M.D., the Hopkins scientist who discovered them, has described aquaporins as “the plumbing system for cells.” Although scientists have known for a century that cells are mostly made up of water, they didn’t realize that the water actually circulates in an organized way through the cell; they thought it just kind of leaked in, sat there, and leaked out.

In some cells, this process is expedited; the water zips in and out quickly. These cells have water channels — aquaporins — that, like the Roman aqueducts, are waterways that deliver the extra water that some cells — in the cerebrospinal fluid, the eye, salivary glands, and other tissues — especially need. For this work, Agre shared the 2003 Nobel Prize in Chemistry.

such as blindness, incontinence, vertigo, numbness and weakness — complications so severe that back in the 1990s, scientists recognized this cluster of symptoms as its own entity, something outside the spectrum of most MS.

Antony Rosen, M.D., Director of the Division of Rheumatology and Vice Dean for Research in the School of Medicine, is leading Hopkins-wide initiatives in Precision Medicine — and he believes this is the key to helping patients with such complex and difficult clusters of symptoms. “Amazing advances in technology combined with our experience as clinicians in recognizing subtle differences in patients has made it clear that there are subgroups,” he says. Under the umbrella of a disease such as Sjögren’s, for example, are groups of people who have the same particular symptoms. Medicine is evolving to treat not so much the big disease, but the subgroup — because those people may respond differently, or require different treatment, from others. “Precise understanding of these small groups within the umbrella of a larger disease can dramatically improve diagnosis and treatment.”

In fact, when NMOSD is present, precision diagnosis can be life-saving. Julius Birnbaum, M.D., M.H.S., Associate Director of the Jerome L. Greene Sjögren’s Syndrome Center, explains: “What revolutionized our understanding of this syndrome was the recognition that these patients who had more severe attacks had a particular antibody.” The antibody targeted a protein called aquaporin 4 (AQP4), which “regulates the flux of water into and out of the central nervous system. If you have an antibody which targets AQP4, you could get abnormal water flux in the brain or spinal cord, and this could lead to significant edema.”

The antibody turned out to be a highly specific marker for NMOSD, and its discovery did two things: it “really established that NMOSD, this more severe phenotype, was clinically distinct from MS. It also proved to be prognostic: if you had the AQP4 antibody (called anti-AQP4), you were more likely

to develop severe spinal cord disease and to have more frequent relapses.”

Scientists speculated that just as NMOSD is different from MS, it is different from Sjögren’s, too, but they couldn’t prove it; previous studies looked at small numbers of Sjögren’s patients, some of whom had other inflammatory disorders, as well. “NMOSD is a very rare disorder,” says Birnbaum. “Very few centers have enough patients with this phenotype to study it.”

But Hopkins does — if only its scientists had a better way to test for these antibodies. Because standard assays for AQP4 antibodies are not always positive in patients with NMOSD, scientist Livia Casciola-Rosen, Ph.D., set out to develop a cell-based assay. Her assay was much more accurate and sensitive in finding these anti-AQP4 antibodies than previous tests, and Birnbaum and colleagues couldn’t wait to test it in patients — and maybe get some answers about the connection between NMOSD and Sjögren’s.

The assay was much more accurate and sensitive than previous tests, and Birnbaum and colleagues couldn’t wait to test it in patients, and maybe get some answers about the connection between NMOSD and Sjögren’s. “The reason you could say that Sjögren’s might have a unique vulnerability to NMOSD is that anti-AQP4 is expressed in a lot of regions that Sjögren’s affects, including the kidney and the lungs — where immune-mediated damage could cause severe problems,” says Birnbaum, who is a neurologist and internist as well as a rheumatologist. “We speculated that NMOSD might be a direct complication of Sjögren’s, in which case you would expect to see these antibodies in patients who don’t have NMOSD. But we also thought, maybe it’s just coincidental; maybe NMOSD and Sjögren’s don’t have a direct causal relationship. Maybe they’re just two autoimmune disorders in an individual who has a highly active autoimmune process. In that case, you would not expect to see the anti-AQP4 antibodies in all Sjögren’s patients.”

Using the new assay, Birnbaum and colleagues including Nidhi Atri, M.D., Alan Baer, M.D., Raffaello Cimbri, Janelle Montagne, and Casciola-Rosen looked at the frequency of AQP4 antibodies in 11 Sjögren’s patients with NMOSD, in eight Sjögren’s patients with MS patterns, and in more than 100 Sjögren’s patients with no signs of NMOSD. “We found 100-percent syndrome specificity of anti-AQP4 antibodies in NMOSD. These antibodies were seen in 11 out of 11 patients with NMOSD, in zero of eight patients who had MS, and in zero of 100-plus patients who have Sjögren’s but not NMOSD. The antibodies are entirely syndrome-specific. They were not seen in one single patient who did not also have NMOSD. What that proves is that NMOSD is not directly caused by Sjögren’s.”

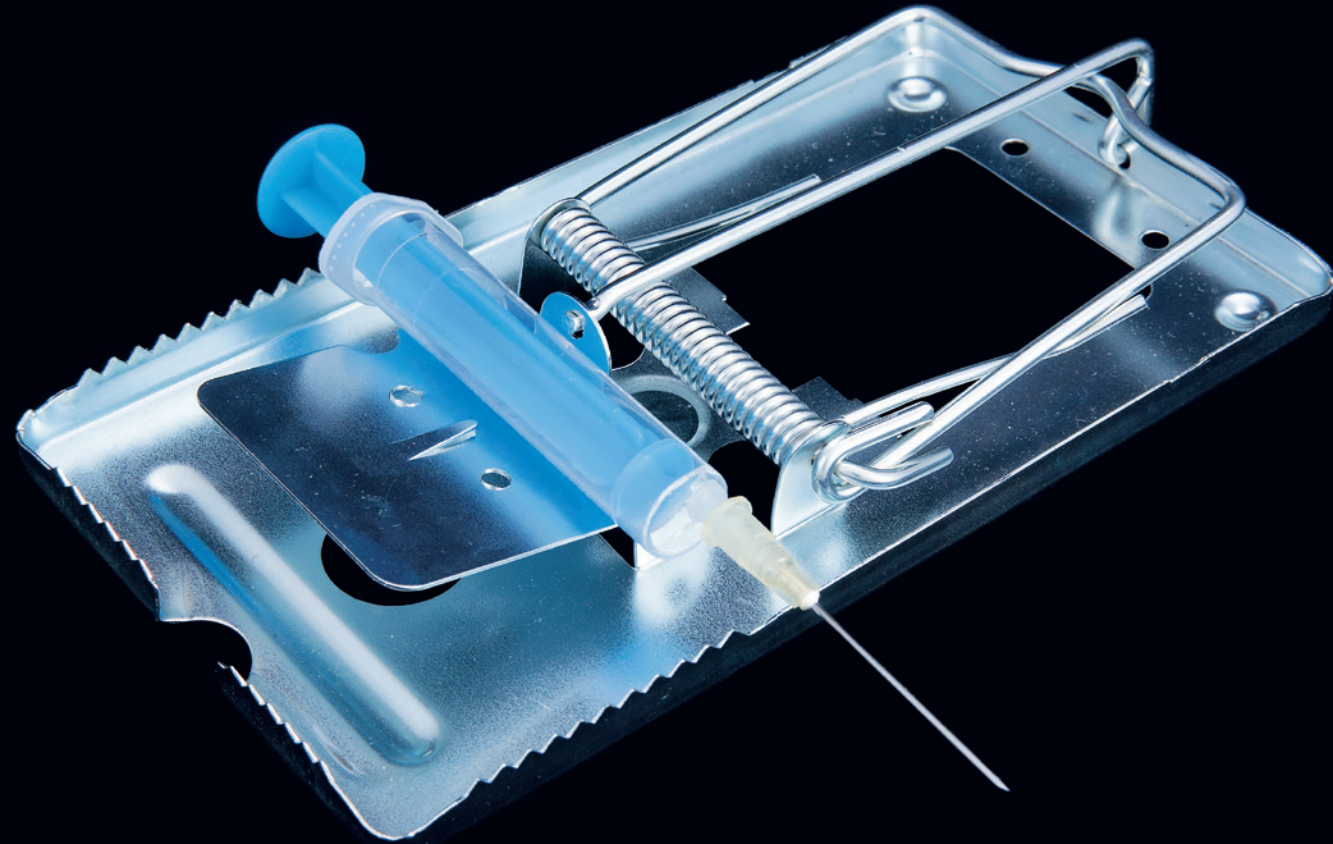
Casciola-Rosen’s assay found something else very important — which routine clinical assays had missed completely: “Anti-AQP4 antibodies were present in patients receiving prolonged immunosuppressive therapy,” says Birnbaum, and this has serious implications for treatment. “If you look at the clinical trials going on right now with Sjögren’s investigating different therapies, inclusion in these trials is based on activity measurements. If you have a Sjögren’s patient who has AQP4 antibodies and NMOSD, that patient should not be eligible for these studies. Even though commercial assays might say that the antibodies are no longer present, this assay can find them.

“These antibodies are pathogenic; they cause harm,” setting off an autoimmune reaction that is self-sustaining. “NMOSD is one of the most aggressive autoimmune diseases there is. If these patients are not on immunosuppressive therapy, within less than five years, more than half are blind or in a wheelchair. People who have these antibodies need to remain on immunosuppressive therapy for life.” **⌄**

This work was published in the journal *Arthritis Care & Research*.

THE DOWNSIDE OF MIRACLE DRUGS

For an increasing number of people, new drugs called checkpoint inhibitors are achieving miracles, curing cancer that has never been curable. People are alive today who, even a few years ago, would have died from metastatic cancer. The drugs that have saved them have done something scientists have been trying to do for decades: unleash the mighty immune system to attack cancer.



But the mysteries of the immune system are still more unsolved than solved, and there is a problem: sometimes, when the immune system gets activated to kill cancer, it attacks normal tissue and causes harm.

Rheumatologists Laura Cappelli, M.D., M.H.S., Ami Shah, M.D., M.H.S., and Clifton Bingham, M.D., have been seeing many Hopkins cancer patients who have developed “immune-related adverse events,” including sicca syndrome involving dryness in the eyes and mouth – symptoms that can be seen in Sjögren’s syndrome – and inflammatory arthritis. They and colleagues have published their findings in two journals, the *Annals of Rheumatic Diseases*, and *RMD Open*, a journal on rheumatic and musculoskeletal diseases. “We noticed this was a pattern and wanted to get the information out there to the rheumatology community,” says Cappelli, “so these issues could be recognized.”

What’s happening? One of the most devious and effective things cancer does is to put blinders, or brakes, on the immune system – particularly, on T cells, powerful watchdogs that are supposed to recognize and attack enemy invaders such as viruses or cancer. Checkpoint inhibitors, by targeting molecules on the surface of T cells, take these blinders off. The results have been dramatic – stunning to scientists, physicians, and patients with widely metastatic cancer who had given up hope of being cured. Melanomas, lung and kidney tumors are melting away; metastases in places like the liver and brain are disappearing.

Drugs such as nivolumab and ipilimumab “have provided a lot of hope,” says Cappelli, and ideally, “we hope to understand and be able to manage these symptoms better,” without dimming the patient’s prospects of being cured of cancer. In one small study, nine of 13 patients being treated with ipilimumab, nivolumab, or with both drugs combined,

The mysteries of the immune system are still more unsolved than solved, and sometimes, when the immune system gets activated to kill cancer, it attacks normal tissue and causes harm.

developed inflammatory arthritis, and four developed sicca syndrome with a severe loss of saliva. All 13 patients were treated with corticosteroids, with varying response so far. “We’re following people over time to see how they do.”

The problem is that because the drugs themselves are so new, rheumatologists are just becoming aware of these side effects. “We don’t know how big a problem it is, and how many people develop these symptoms. Not everyone does. So we are very interested in figuring out who is most likely to have these complications, what features might make someone more susceptible. Even just knowing the percentage of people will be useful.

“We hope as we learn more about these side effects and how to manage them, that people will be able to continue on their therapies for cancer,” Cappelli continues. “We work closely with their oncologist; we’re always talking back and forth, determining what treatments for their side effects would be the safest, and would not compromise the cancer therapy.”

One challenge is that the standard way to treat inflammatory arthritis – with immunosuppressive medicines like methotrexate or Humira – would act in direct opposition to the checkpoint inhibitors, which turn the immune system up. “We want to treat the arthritis, but we don’t want to counteract the cancer drugs.

It’s a very tricky problem, which is why we always work closely with the patient and the oncologist.”

Treating sicca syndrome is a little different. “We don’t necessarily need to use drugs to decrease the immune system,” says Cappelli. Instead, there are good ways to treat the specific symptoms – medicines to increase saliva production, and drops to help with dry eyes.

Right now, because this is all so new, Cappelli and colleagues are doing recon: trying to define the perimeters and understand the scope of the problem. “We are working with oncology to study the whole group of people treated with immune checkpoint inhibitors – those who develop symptoms as well as those who don’t – and we’re working to understand the epidemiology.” Who’s affected? And, in these people, what is happening in the blood? Does the entire immune system need to be cranked up in order to kill the cancer, or could the treatment be more selective – could some fine-tuning limit the treatment to just the cancer, sparing normal tissue?

“This is an emerging issue,” Cappelli adds, “and if patients are taking these medicines and develop pain, swelling, or stiffness in their joints, or dry eyes and dry mouth, we hope they will let their oncologist know quickly, so we can evaluate them.” **L**

THE STORY PROJECT

In every issue of *Leap*, we have made it a point to shine the light on the people who work here in the Division of Rheumatology. Some of them are the first faces you see in the clinic, and others you may never see, because their work is behind the scenes in a lab or office. But it turns out that they all have one very important thing in common: you. They know how important their work is, because its purpose is to make life better for you, our patients. In this issue, we feature three people who do their own part to shine the light. Theirs are some of the faces you see in our clinic, and chances are, when you see them, they are smiling.

FELICIA AGEN-DAVIS,
MEDICAL ASSISTANT SINCE 2000

Felicia Agen-Davis may be one of the first people you see in the clinic. She's there at 7 a.m. to greet you, take your vital signs, and get you settled in. "Sometimes when patients come in, they're frustrated or sad and they have questions," she says. "If I'm able to, I answer them to the best of my knowledge. I talk to them and calm them down before they see the physicians."

Agen-Davis would like patients to know that "even though I don't know the disease they're struggling with, I have had my own health issues." She has had many surgical procedures over the course of her life. "Even though my issue is not the same as what they are going through, I understand how they are feeling, the frustration of not knowing what the outcome will be.

"Regardless of who we are, if you have enough strength, you can make it." The strength does not come from her alone, she adds. "My relationship with Christ is very important to me. Not everybody has a higher power, but knowing somebody is looking out for me gives me strength to know that no matter what I am going through, it's going to be okay."

Agen-Davis came to America from Ghana. She has family here, three brothers and an uncle who is a cardiologist. "When I was having the health issues, he thought it was best to bring me here. I came with my two kids and went to school, even though I had health issues. I was determined to raise my kids and to be a productive adult, and go on to have an education. I did all that by not giving up." She hopes to continue her education someday. "My family is my support system. It's very important to have that support around you."

Agen-Davis also wants patients to know this: "Even though most of the time I have a smile on my face, not every time you see me smiling means that nothing is going wrong or everything is perfect. It's just that I come in here to do a job, and I have to put my own issues on the side to make sure I attend to the patients with positivity. Putting other people in need ahead of yourself is a big thing for me."



**ESTELLE WILLIAMS, PATIENT
SERVICE COORDINATOR SINCE 1996**

At a recent meeting, we invited everyone in the Division to bring in an object that is meaningful and helps crystallize why they are here. Estelle Williams couldn't think of one to bring at the time, but now she knows what it would be: a plant. "I love plants," she says. "I feel a close connection with them, and always want to be around them." She is a nurturing person, and this shows in how she feels about the patients she sees every day.

"We try to maintain a level of service that can make our patients feel comfortable, from the time they enter the clinic to when they leave," she says. "I want them to know that I'm here for them, I will do whatever I can within my power to make the visit pleasant, and I know that a lot of them are very emotional when they come. Some are in terrible pain, and some are lonely. Everyone has a different situation, and we've got to be alert to identify it and work with it."

Of all the patients she has met and come to know in the Division, those who come to the Scleroderma Clinic may be closest to her heart, "because their disease is so critical. There are some nice people I build relationships with, ones I get very close to."

If you or a family member come to the clinic, Williams wants you to know that you're not just a face or a name; you're a person and you are cared about by everyone who works there. She feels the same way about the Division, from the top down: "Dr. Rosen is a very good boss to work for. You feel like he understands you as a human being, and that's great with me. The Division is great to work in." Recently, "when I got sick, I thought I wasn't going to come back. It was like being away from your family, and I thought, 'My goodness, I wonder how everybody's doing.' It's a family-oriented clinic, and we build close relationships. If and when I do retire, I will dread it, but my time has to come someday."

**ZAHIRA CLARK, MEDICAL
OFFICE COORDINATOR SINCE 2013**

When asked to choose an object to share with the Division that shows something meaningful to her and helps explain who she is, Zahira Clark brought in a picture: "It's of me and my coworkers. They're my best friends," she says, "they're my sisters at work." They are tight and that is a good thing, because what they do requires a certain extra strength. Clark works in the Scleroderma Clinic, and she wants patients to know this: "We care for them. Even though there's not a cure or a guaranteed treatment, we're here for them; we fall in love with them. I treat them as if they're my family. You never know if somebody in your family is going to be that sick ever, but you would want them to get the same care."

Clark came to Hopkins from New York, where she earned her bachelor's degree at the College of New Rochelle and then worked at the New York Blood Center for 14 years. Moving to Baltimore, she says, was a great decision, "especially in terms of my children: the life they have here is a different life; it was the best move I ever made."

At a recent meeting held in the aftermath of the death of Freddie Gray, when Baltimore was reeling from riots and the pain of those events, Director Antony Rosen wanted everyone to have an opportunity to talk about what had been unfolding in our city. "I'm not going to lie," says Clark, "when I got here, I felt there was a lot of racism – like some people are left out, just in general. But after we had that meeting, at first, everyone was so upset, everyone was looking at each other's color. That's how we all felt. But as everyone got to speak at that meeting, we realized how much alike we are, the same struggle we're all going through. Almost everyone cried at that meeting; it was awesome... I do feel like my voice is heard."

Realizing how much she and her colleagues have in common helps Clark, especially when one of their patients passes away. "We get really close to them, and that's one thing I still have to get used to," hearing about the death of a patient. "I never heard of scleroderma until I started working here. Even though some of it is a mystery, and not being sure of a cure, it is just an amazing place. Patients feel like they have a second chance. Usually by the time new patients get here, they kind of feel like it's the end of the world. But here they know that someone cares about them. We care about them so much that they feel better."





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“Life is a travelling to
the edge of knowledge,
then a leap taken.”

— D. H. Lawrence