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Research Into Cardiovascular Effects of Rheumatoid Arthritis Focuses on Inflammatory Processes

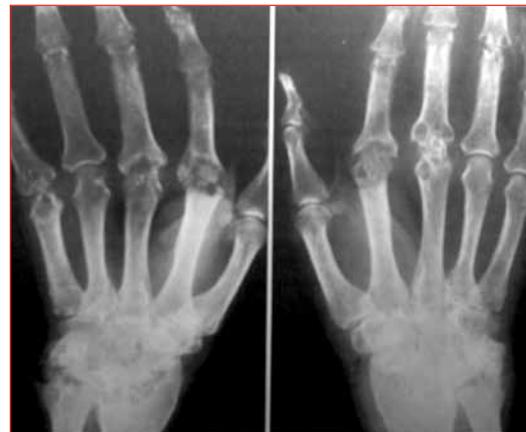
Rheumatoid arthritis (RA) carries with it a 1.5-fold increased risk for heart attack, heart failure, and stroke. Although the inflammatory effects of RA as they relate to joints—as well as many of the body's other organs—are well understood, their role in cardiovascular function among those who suffer from the disease remains a mystery. It has been suggested that obesity and diabetes—2 common comorbidities of RA—play a far more significant part in the heart health of these patients.

However, recent research led by Joan M. Bathon, MD, Director of the Division of Rheumatology at NewYork-Presbyterian/Columbia University Medical Center, has shed new light on the complex relationship between RA and cardiovascular disease, identifying possible connections between the mechanisms of the respective diseases. Her work has looked at possible causes for the increased prevalence of accelerated atherosclerosis and heart failure in the setting of RA, with an eye toward identifying possible prognostic markers for heart disease in general within this patient population and, perhaps, modifying existing treatment approaches. Dr. Bathon is also Professor of Medicine at Columbia University College of Physicians and Surgeons.

"In the case of accelerated atherosclerosis, it doesn't look like it's just due to more hypertension, obesity, or diabetes, although we know those are factors," noted Dr. Bathon, adding that in the past her team has reported that patients with RA have more hypertension and more body fat than non-RA patients. "We believe the chronic inflammatory process that typifies RA also plays a role in promoting the increased risk for heart disease, and that patients with RA have this unrelenting chronic inflammation that probably involves many organs, including the heart. Our thinking is that if we aggressively manage this inflammation, we can reduce the cardiovascular risk of patients with RA at least back to that of the general population."

NIH-Funded Research Continues

Dr. Bathon's research at NewYork-Presbyterian/Columbia continues and builds upon her ground-



breaking efforts at Johns Hopkins University, where she worked until she moved to New York City in 2010. Through a grant funded by the National Institutes of Health (NIH) while at Hopkins, she and her colleagues explored the prevalence of, and risk factors for, atherosclerosis in multiple vascular beds in RA patients compared with controls. They also reported in *Arthritis & Rheumatism* that RA patients—even if they have no known cardiac disease—have significantly less muscle mass in their hearts than those without RA (as much as 20% less, according to Dr. Bathon).¹ In a new NIH-funded study, which is already under way and recruiting patients at NewYork-Presbyterian/Columbia, Dr. Bathon and colleagues will attempt to identify the reasons behind this smaller heart size and determine whether or not they have a long-term effect on heart function.

"Our goal is to study these patients while they are still in the asymptomatic phase and figure out if there is a way to identify them before they suffer a heart attack or heart failure," Dr. Bathon said. "The difference in heart size is striking, and it isn't likely to be explained by reduced exercise, obesity, or diabetes, which are common comorbidities in RA, because we statistically adjusted for all of those risk factors in the original research."

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Genetics Research Across Medical Specialties Now Yielding Secrets and Improving the Practice of Medicine

The decoding of the human genome and subsequent concerted efforts by physician-scientists to decipher the relationships between specific genes and the diseases they influence have already yielded tremendous advancements in medicine. This work is fostering important strides in understanding and caring for people with diseases affecting all health systems, and much of the laboratory and translational studies, as well as clinical research, are being done at Columbia University College of Physicians and Surgeons, Weill Cornell Medical College, and NewYork-Presbyterian Hospital.

Research abounds in every field. The field of geriatrics, for instance, was intrigued by a study led by Columbia University researcher Lawrence S. Honig, MD, PhD, Professor of Clinical Neurology in the Taub Institute, an Alzheimer's disease research center funded by the National Institute on Aging.¹ Dr. Honig's research found that telomere length relates both to the likelihood of the patient developing dementia and his or her overall remaining life span. This research could lead to the use of telomere length as an accurate biomarker of aging in people, as well as an early warning sign for future dementia.

The researchers examined telomere lengths from DNA samples of white blood cells obtained from 1,983 individuals aged 66 to 101 years. These patients were followed for an average of 8 years. After adjusting for age and education, among other factors, researchers found that those individuals with shorter telomeres had higher rates of both dementia and mortality. The researchers must now examine whether shorter telomeres directly increase the risk for dementia and death, or if the telomeres are being influenced by some other factor that is both shortening telomere length while at the same time increasing dementia and mortality risk.

Within psychiatry, schizophrenia has long been known to be genetic in origin, but the networks of genes involved in this disability have not been well characterized. A recent paper published in *Nature Neuroscience* found a link between schizophrenia and autism.² Columbia researchers examined a collection of mutations associated with schizophrenia and found occult interrelations among genes that had

previously been thought to be unrelated. The researchers found that most of the mutated schizophrenia genes were related to 2 main gene networks, which together affect key processes, including axon guidance, synapse function, neuron mobility, and chromosomal modification.

The research, which was led by Dennis Vitkup, PhD, Associate Professor in the Department of Biomedical Informatics at Columbia's Center for Computational Biology and Bioinformatics, also looked at genes mutated in patients with autism and found the similarities were surprisingly robust. Noting that the genetic networks for autism and schizophrenia are closely intertwined, the researchers postulated that many other psychiatric disorders also might share the same genetic networks and interrelated molecular processes.

Significant research on the genetics behind psychological illness is being undertaken at Weill Cornell Medical College. As just one example, Francis S.Y. Lee, MD, PhD, Professor and Vice Chair for Research in the Department of Psychiatry and Professor in the Department of Pharmacology, who is also an Attending Psychiatrist at the Hospital, directs efforts focused on using genetic models to define the role of growth factors, such as brain-derived neurotrophic factor, and their affect on the pathophysiology and treatment of affective disorders.³

Pulmonology has begun to explore the use of gene-based vaccines targeted against pulmonary infectious organisms. At Weill Cornell Medical College, a team led by Stefan Worgall, MD, PhD, Division Chief of the Pediatrics Pulmonology, Allergy and Immunology Division,



Telomere length relates to likelihood of developing dementia and overall life span.

has developed capsid-modified adenovirus vectors^{4,5} to heighten immune responses from genetic vaccines against both *Pseudomonas aeruginosa* and respiratory syncytial virus. In research on the pathogenesis of cystic fibrosis, Dr. Worgall is investigating the interaction of alveolar macrophages with *P. aeruginosa*.

Nephrologists and psychiatrists, meanwhile, were interested in the results of a large multinational study in which Columbia University played an important role.⁶ The study, led by Ali Gharavi, MD, Associate Director of the Division of Nephrology at NewYork-Presbyterian/Columbia, is the first to link congenital kidney disease, which together with urinary tract defects accounts for about one-fourth of all birth defects in the United States, with neurodevelopmental disorders. The study found that 10% of children born with kidney defects have genomic alterations that have been linked with neurodevelopmental delay and mental illness. The finding is important because it paves the way for identifying subgroups of patients with kidney defects whose treatment will be guided by specific genetic information. The finding also alerts physicians who care for children with congenital kidney disorders that there may be a genetic basis for a neurodevelopmental delay or a mental illness that will occur later in life.

Perhaps no area of medicine has been as affected by research into the genetic

foundations of disease as much as oncology. Examples of genetic discoveries in oncology are plentiful. An important recent discovery is the revelation that certain cases of glioblastoma are caused by the fusion of 2 genes.⁷ Researchers, led by Antonio Iavarone, MD, Professor of Pathology and Neurology at Columbia's Institute for Cancer Genetics at the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia, conducted genetic analyses of patients with glioblastomas, searching for evidence of gene fusions. They found them, with the most common being fusions involving the fibroblast growth factor receptor (*FGFR1* or *FGFR3*) and transforming acidic coiled-coil (*TACC1* or *TACC3*) genes. The protein produced by the fusion of *FGFR-TACC* disrupts the mitotic spindle, causing aneuploidy, and from there

tumorigenesis. The finding is important because it provides researchers with a protein target for pharmaceutical research for a cancer that is especially difficult to treat.

The field of clinical genetics is rapidly changing and improving the practice of medicine. As the field of genetics continues to grow so too the physician-scientists at Columbia University College of Physicians and Surgeons, Weill Cornell Medical College, and NewYork-Presbyterian Hospital will continue to be at the forefront of integrating genetics into all specialties.

References

1. Honig LS, Kang MS, Schupf N, et al. Association of shorter leukocyte telomere repeat length with dementia and mortality. *Arch Neurol*. 2012;69(10):1332-1339.
2. Gilman SR, Chang J, Xu B, et al. Diverse types of genetic variation converge on functional gene networks involved in schizophrenia. *Nat Neurosci*. 2012;15(12):1723-1728.
3. Soliman F, Glatt CE, Bath KG, et al. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. *Science*. 2010;327(5967):863-866.
4. Halbreiner M, Pagovich O, Finnin E, et al. Disrupted adenovirus-based vaccines against small addictive molecules circumvent anti-adenovirus immunity. *Human Gene Ther*. 2012 Nov 9. [Epub ahead of print]
5. Krause A, Worgall S. Delivery of antigens by viral vectors for vaccination. *Ther Deliv*. 2011;2(1):51-70.
6. Sanna-Cherchi S, Kiryluk K, Burgess KE, et al. Copy-number disorders are a common cause of congenital kidney malformations. *Am J Hum Genetics*. 2012;91(6):987-997.
7. Singh D, Chan JM, Zoppoli P, et al. Transforming fusions of *FGFR* and *TACC* genes in human glioblastoma. *Science*. 2012;337(6099):1231-1235.

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Thanks to what Dr. Bathon refers to as the “collaborative culture” at NewYork-Presbyterian/Columbia, she is working with colleagues in the Cardiology Division at the Hospital—including Sabahat Bokhari, MD, and Cesare Russo, MD—using cardiac positron emission tomography-computed tomography (PET-CT) and 3-dimensional echocardiographic technologies to identify the presence of inflammation and microvascular disease in the heart muscle of patients with RA and assess for effect on heart function. The theory behind the study holds that the inflammatory components of RA damage the muscle fibers and/or cause dysfunction in small blood vessels in the heart, similar to what happens in diabetes. The study has already enrolled more than 50 patients, and the team plans to continue enrollment for at least another year, with the goal of including data from more than 150 patients.

“We’re finding a lot of inflammation and microvascular dysfunction; we’re actually really amazed,” she said. “Almost 30% of the patients enrolled in the study to date have inflammation in the heart or they have microvascular problems,

or both. This is much higher than we thought we’d see. We want to find out if this inflammation contributes to the small heart phenotype of RA and whether it is associated with any subclinical functional abnormalities.”

“This is the first-ever study looking at the direct effect of anti-tumor necrosis factor therapy on the RA heart.”

—Joan M. Bathon, MD

Dr. Bathon’s team also has received funding from the American College of Rheumatology—she serves as the Editor of the professional society’s journal, *Arthritis & Rheumatism*—to research possible biomarkers for asymptomatic coronary artery disease in the setting of RA. For the general population, metrics such as the Framingham Risk Score or the Reynolds Risk Score are used to assess risk for heart attack. However, as effective as these scales are, particularly in men, they are not as effective at measuring risk in women (RA is more common in women), particularly younger and middle-aged women—hence Dr. Bathon’s research focus. Using blood samples from the cohort that she assembled while still at Johns Hopkins

University, together with samples from cohorts gathered by collaborators at the University of Pittsburgh Medical Center and Vanderbilt University Medical Center, Dr. Bathon will be working with Michael Centola, PhD, and Jenny Van Eyk, PhD,

specialists in proteomics at the University of Oklahoma and at Johns Hopkins University, respectively, to assess 30 to 50 candidate serum proteins for their ability to identify RA patients at highest risk for heart disease.

“The ultimate goal would be to develop a blood test that could be added to the Framingham or Reynolds Score, for example, that would better identify these patients,” Dr. Bathon noted. “Once identified, the patients’ physicians can take a 2-pronged approach. One is to aggressively manage traditional cardiovascular risk factors such as blood pressure, cholesterol, sugar levels, and obesity. However, younger RA patients may not have

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any of these risk factors, so treatment with a statin drug to lower cholesterol may still be a justifiable strategy in the high-risk group. The second approach, which would be done in conjunction with the first, is for the rheumatologist to look at the patient's underlying RA and ask, 'Am I controlling it as well as I could be?' In my view, these are patients in whom we should be managing their rheumatoid disease aggressively, with the goal of reducing inflammation and hopefully bringing it down to remission. We think an aggressive approach, both in treating their RA and in managing their cardiovascular risk factors, will hopefully reduce the increased risk for heart disease that these patients face."

As a proponent of "aggressive" treatment of the inflammation associated with RA, much of Dr. Bathon's work has already been translated into clinical practice, and this trend is likely to continue. Before leaving Johns Hopkins University, she and her team acquired some preliminary data suggesting that anti-tumor necrosis factor (TNF) therapy, which has been thought to possibly cause or worsen heart failure, may actually have the opposite effect—that is, improve heart function. In her current NIH study at NewYork-Presbyterian/Columbia, she and her collaborators are

conducting "a small clinical trial" in which some patients receive a TNF inhibitor and others receive a more traditional therapy (ie, sulfasalazine); the patients are monitored via cardiac PET-CT to assess whether either or both treatments have any effect on heart structure and function.

"This is the first-ever study looking at the direct effect of anti-TNF therapy on the RA heart," she said. "We'll be looking at how well the patients' hearts contract while on these therapies and determine if these drugs suppress contractility or, in fact, improve it."

Dr. Bathon also has received, along with Daniel Solomon, MD, MPH, of Brigham and Women's Hospital in Boston, an NIH planning grant to design a clinical trial that will determine whether aggressive management of RA is associated with a reduction in cardiovascular risk. Dr. Solomon was among the speakers at a continuing medical education event entitled "Enhanced Risk of Cardiovascular Disease in Patients with Autoimmune Disorders," which Dr. Bathon organized recently at NewYork-Presbyterian/Columbia.

Among Dr. Bathon's long-term goals is the formation of an Autoimmune Cardiovascular Risk Management Clinic with colleagues from the departments of

Cardiology and Endocrinology at NewYork-Presbyterian/Columbia. The goal is to have a state-of-the-art clinical treatment program that also has a research focus designed to inform management of RA patients from around the world.

"As a researcher at an academic center, I always hesitate to add anything purely clinical because our mission is to contribute new knowledge to science and medicine," Dr. Bathon noted. "However, the treatment of RA has become very complicated with the development of many new therapies in the past decade. It becomes challenging for rheumatologists to manage all of the cardiovascular risk factors, plus RA and its effects on the joints, skin, the eyes, and any number of organs. It just makes some sense to have cardiologists and/or endocrinologists who specialize in lipids to see these people alongside the rheumatologists in a formalized way, and the environment at Columbia allows for that level of collaboration."

Reference

1. Giles JT, Malayeri AA, Fernandes V, et al. Left ventricular structure and function in patients with rheumatoid arthritis, as assessed by cardiac magnetic resonance imaging. *Arthritis Rheum.* 2010;62[4]:940-951.