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The rheumatology program at NewYork-Presbyterian Hospital is comprised of faculty affiliated with Weill Cornell Medicine and Hospital for Special Surgery, and Columbia University College of Physicians and Surgeons. The program provides state-of-the-art care to patients with the broad range of inflammatory and autoimmune diseases, pursues groundbreaking research at both the laboratory level and through clinical studies, and offers comprehensive training to medical residents and fellows.

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Psoriasis and Psoriatic Arthritis: Kindred Spirits or Not?

How do psoriasis and psoriatic arthritis relate genetically, molecularly, and clinically? Do they relate? And, if so, to what extent? These and many other questions about genetic susceptibility to psoriatic arthritis have been the focus of extensive investigations by **Robert J. Winchester, MD**, a renowned immunologist in the Department of Medicine's Division of Rheumatology at NewYork-Presbyterian/Columbia University Medical Center, and a prolific researcher in autoimmune disease. Dr. Winchester is a member of the trio with Peter K. Gregersen, MD, and Lars Klareskog, MD, recognized in the 1980s for discovering how rheumatoid arthritis arises from the interplay of genes and the environment.

In his studies of psoriatic arthritis, Dr. Winchester collaborates with **Oliver FitzGerald, MB, BCh, MD**, a rheumatologist and clinical research professor at St. Vincent's University Hospital and the Conway Institute, University College Dublin in Ireland, and his colleagues.

"They are very serious experts in this area, and have the wherewithal to look at a large population of patients with psoriasis, which was key to the research," says Dr. Winchester. "Given the structure of the Irish healthcare system, they can essentially capture patients with the same diagnosis in a rather large geographic area because patients are referred to specific specialty hospitals. Not only do they cover a region that comprises almost half of Ireland, but they

Dr. Robert J. Winchester

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Utilization and Outcomes: Understanding Disparities in Total Knee Arthroplasty

While osteoarthritis does not discriminate in who it affects, getting surgical treatment for its debilitating symptoms and its outcomes apparently do according to research by **Susan M. Goodman, MD**, a rheumatologist and member of the multidisciplinary Combined Arthritis Program and Disparities Research Lab at Hospital for Special Surgery.

> "Blacks are clearly much more responsive to the effects of poverty. It doesn't turn out to be race in a direct sense that results in increased pain after these procedures, but rather a race effect mediated through the impact of socioeconomic status."
>
> — Dr. Susan M. Goodman

Non-white race and lack of education are known risk factors for pain and poorer function after knee replacement surgery. What isn't clear is how a community's poverty level affects the outcomes of having a joint replaced. Findings from the study conducted by Dr. Goodman and her colleagues suggest that lower socioeconomic status at the community level significantly increases the risk of pain and poor function following a knee replacement. These findings could allow clinicians to more effectively target patients at high risk for poor outcomes and provide support and counseling before their patients undergo the procedure.

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Psoriasis and Psoriatic Arthritis: Kindred Spirits or Not? *(continued from page 1)*

also have a relatively homogeneous population. For the study, we predominantly included individuals with Irish parents. In general, homogeneity of a study population decreases the variance of the study and gives you more power to discover what the genetic factors are. In fact, the genes that we're interested in – the HLA genes – are very variable among different races and different ethnic groups – even within different Caucasian subsets."

Drs. Winchester and FitzGerald designed an experiment to compare subjects with psoriatic arthritis presenting to a rheumatology unit to subjects with cutaneous psoriasis – excluding those with any musculoskeletal features – presenting to a dermatology unit. Once the diagnosis of psoriasis was ascertained by the dermatologist, the patients were then examined by a rheumatologist to rule out those who also had psoriatic arthritis. "This gave us a pure population of cutaneous psoriasis," notes Dr. Winchester. "Psoriatic arthritis was diagnosed when a patient had peripheral synovitis, enthesitis, or inflammatory spinal pain suggestive of axial disease, together with the presence of psoriasis."

Sorting Out Associated Genes and Traits

Both study groups were substantial in number, with nearly 360 in the psoriatic arthritis cohort and approximately 215 in the psoriasis cohort. The patients were followed, on average, for 20 years – long enough to determine which patients with cutaneous psoriasis would go on to develop psoriatic arthritis. "About 10 to 15 percent of individuals with psoriasis will develop psoriatic arthritis within 10 to 15 years of its onset," says Dr. Winchester. "Conceptually, this puts psoriatic arthritis under the aegis of psoriasis."

The goal of the investigators was to determine the extent to which the contribution of the major histocompatibility complex (MHC) to psoriatic arthritis susceptibility resembles that in psoriasis, and whether MHC genes determine quantitative traits within the psoriatic arthritis phenotype. MHC genes were selected as the first candidates to be examined as they play an important role in regulating immune responsiveness and because psoriatic arthritis is considered an immune-mediated disease.

"There's no part of the human genome that has as many alternative gene forms at a given locus as the MHC," says Dr. Winchester, who led the HLA typing of the two patient groups. "Our group did the HLA typing at two HLA loci – HLA-B and HLA-C. HLA-C is very important in the development of psoriasis."

Dr. Winchester and his team, including Columbia rheumatologist **Jon T. Giles, MD, MPH**, used sequence-based typing to identify the nature of the alleles and make sense of a complicated array of numbers and disease traits. "HLA-C is important in psoriasis because one allele, C*06:02, is a molecule with a particular amino acid sequence that binds certain peptides," explains Dr. Winchester. "If you have that sequence you are at considerable risk for developing psoriasis. Basically, 70 percent of individuals with psoriasis have the C*06:02 allele."

This mirrors what Dr. Winchester expected to and did find in the study cohort of Irish patients with psoriasis. "If psoriatic arthritis is really a subset of psoriasis, you would expect that 70 percent of the patients in the psoriatic arthritis group should also have HLA- C*06:02. But they didn't; only 28 percent had it," notes Dr. Winchester. "That difference is very, very significant, refuting the hypothesis that psoriasis and psoriatic arthritis are genetically identical. Even so, the 28 percent still connotes an increased frequency in susceptibility, albeit a minor player in psoriatic arthritis. This is one subset of psoriatic arthritis patients – a little more than a quarter – that is truly related to the susceptibility gene driving psoriasis. The rest are not."

So then what are the major genetic players in psoriatic arthritis? According to Dr. Winchester, there are several other genes that play a role, including, HLA-B*27 – already linked with ankylosing spondylitis; HLA-B*38 and HLA-B*39, which are almost identical, distinct by relatively few amino acids; and a fourth gene, HLA-B*08, which is quite different.

"While these genes are not increased in frequency in the pure psoriasis population, they are seen in patients who have psoriatic arthritis," says Dr. Winchester. "So, then the question remains, if it's a different HLA, what can we extract from other features of the disease? The first, and particularly evident, feature of interest was that patients with the HLA-B*27 gene developed psoriasis about the same time as the onset of their arthritis – not 10 to 15 years later; whereas the HLA-C*06:02 patients, on average, developed psoriatic arthritis 14 years after the onset of psoriasis."

Drs. Winchester, FitzGerald, and their colleagues also found that different HLA susceptibility genes were associated with particular features that defined the psoriatic arthritis phenotype of a given patient and that additional interactions between different susceptibility HLA alleles defined the propensity for a more severe or milder musculoskeletal phenotype. "The psoriatic arthritis associated with C*06:02 was mild. These patients did not need to take TNF inhibitors or any major medicines and were able to manage with the medications used to treat their psoriasis," notes Dr. Winchester. "The individuals with B*27, B*38, or B*39 had a more severe arthritis; particularly those with B*27. These patients experienced a complication called enthesitis more frequently, suffered more from a form of psoriatic arthritis called 'arthritis mutilans,' an extremely destructive form of joint disease in the peripheral joints, and had a tendency for spine involvement in addition to the peripheral joints. Patients with B*08 and B*27 denoted a very severe phenotype with more arthritis, worse pain, and a greater need for major drugs such as TNF inhibitors."

These observations cast a new light on the psoriasis phenotype, revealing that it is not a homogeneous disease, but in fact, very heterogeneous. "It probably comes by way of a number of different pathways," suggests Dr. Winchester. "Someday we might think of psoriasis and psoriatic arthritis as different diseases, but we're not there just yet."

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Utilization and Outcomes: Understanding Disparities in Total Knee Arthroplasty *(continued from page 1)*

"Past research has shown that African-Americans, and particularly black men, are less likely to undergo joint replacement surgery compared with Caucasians, despite equal rates of osteoarthritis in both races," says Dr. Goodman. "When blacks do present for surgery, they tend to be in worse health, often have more severe arthritis, more pain, and less functionality. There have been a lot of questions raised as to why this might be, and it is not as clear as one would think."

Dr. Susan M. Goodman

Osteoarthritis reaches into all communities, and its symptoms are shared by an astounding 45 percent of blacks and whites combined in the United States. In 2000, however, 37 percent fewer black men than white men chose to have total knee replacement – a surgery with a 90 percent success rate. In 2006, this number grew to 39 percent, and the trend continues to indicate a growing divide.

"These disparities have been documented for the last two decades and haven't improved," says Dr. Goodman. "So whatever the reasons, it has been consistent over time. And the more you look at it, the more complicated it actually gets. If you ask blacks about their treatment preferences, there is a tendency toward nontraditional treatment. So part of the disparity in having surgery might be the role that factors like prayer, herbal medicine, or complementary therapy play in the black community. When those are studied, blacks are more likely to prefer a nonsurgical option – some nontraditional and some traditional, such as physical therapy."

Linking Poverty to Poorer Outcomes

To help delineate what might be driving the disparities, Dr. Goodman and her colleagues undertook two parallel studies: a systematic literature review and a second study at an individual level evaluating data from Hospital for Special Surgery's high-volume total knee arthroplasty (TKA) registry.

In their literature review, the research team included studies that used standard outcome measures, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Knee Society Score, or Knee Society Rating Scale, and had a minimum follow-up duration of six months.

"To our knowledge, this is the first systematic literature review to examine differences in pain, function, and satisfaction after total knee arthroplasty in whites and blacks in the United States," says Dr. Goodman. "We found that of 346 high quality studies addressing outcomes, only seven contained adequate information to allow assessment of racial disparities. Taken together, results from these seven studies included 5,570 patients of whom 482 were black. Postoperative pain, function, satisfaction, and quality of life appeared to be worse for black patients compared with white patients. This literature review also brought to light the frequent omission of race and socioeconomic status in studies of TKA outcomes despite these factors being important at the patient, provider, and healthcare system level."

With this in mind, Dr. Goodman turned to Hospital for Special Surgery's vast TKA Patient Registry to gain additional insight into the interaction between race and community poverty as it influences patient-reported outcomes. Their sample included 4,225 cases of which 3,841 (91 percent) were white and 194 (4.6 percent) were black. "We found differences in education levels and general health status," notes Dr. Goodman. "Blacks were more likely to have Medicaid insurance and more likely to live in high-poverty areas. In addition, they also appeared to wait longer to present for arthroplasty. Their pain and function when they did come in for surgery was worse than for white patients. Their outcomes were also not as good, but the differences were slight and did not reach the level of clinical significance.

"Since the answers we found in analyzing our data in the more traditional ways were not that revealing, we linked the addresses of individual patients in New York, New Jersey, and Connecticut to specific census tracks, analyzing the data in terms of census track variables, including community poverty levels," continues Dr. Goodman.

The researchers found that in neighborhoods in which only 10 percent of the population is below the poverty level – that is, the richer neighborhoods – there was virtually no difference in postsurgical pain and function between blacks and whites two years after surgery. However, in neighborhoods in which 50 percent or more of the population is below the poverty level, blacks had significantly more pain and poorer function than whites. The study also showed that patients without a college education had worse WOMAC pain and function scores two years after their surgeries than those with at least some degree of post-high school education, an effect that was also magnified by increased community poverty levels.

"What this demonstrates," explains Dr. Goodman, "is that blacks are clearly much more responsive to the effects of poverty. It doesn't turn out to be race in a direct sense that results in increased pain after these procedures, but rather a race effect mediated through the impact of socioeconomic status. As poverty is disproportionately experienced by blacks, this may contribute to the persistent racial disparities in knee replacement utilization and outcomes. Why blacks appear more vulnerable to the impact of community poverty is an important area for future research, and efforts to improve postsurgical outcomes among blacks will need to address the impact of disparities in socioeconomic status."

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