the cancer connection

LOSE FEAR AND **FIND HOPE.** LYMPHOMA IS NOT A SURE THING IF YOU HAVE RHEUMATOID ARTHRITIS AND TREAT IT AGGRESSIVELY. BY NANCY ROSS-FLANIGAN

To learn more about the biologics and their side effects, go to **www.ArthritisToday.com**.

Maureen Lengel has enough on her mind.

There's her demanding job with a school district in suburban Pittsburgh. Add to that a few home-remodeling projects and a head-spinning family and social life, with season tickets to Steelers games, a subscription to Broadway shows, and frequent out-of-state visits to friends and relatives.

Oh yes, and then there's the rheumatoid arthritis (RA) the 52-year-old has been living with since her teens, as well as the hip replacements and other surgeries she's endured throughout the years as a result of the condition. The last thing this woman needs is having to worry about an even scarier health problem – cancer. But worry is there, lurking in the back of her mind.

"I know that people with RA have a higher risk of developing cancer," says Lengel, who keeps up on the latest news related to her disease by reading, sharing and discussing information with her doctor. The worry first set in for Lengel in the mid-1980s, when she realized that the methotrexate she was taking for her RA was the very same drug her friend's mother was receiving for breast cancer.

"Whether it's the disease itself or the drugs people take for it that increase the risk – I've seen articles on both sides of the story," she says. "Some say RA drugs may not raise cancer risk, but other articles link cancer – specifically, lymphoma – to one of the drugs that I'm

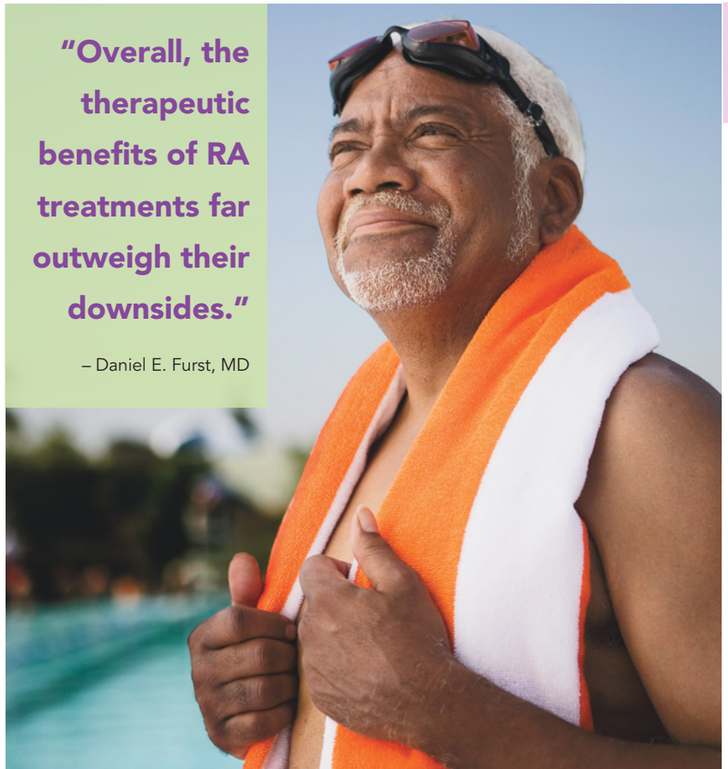
taking now. (See "A Look at Lymphoma," below.) Naturally, I'm concerned."

So are many of the patients who Lengel's rheumatologist, Mary Chester Wasko, MD, sees at the University of Pittsburgh Medical Center. Trying to help them sort out the facts isn't always easy.

"The RA and cancer connection is such a worry of so many patients," says Dr. Wasko. "They read about studies that are highlighted in the press, and then wonder why their doctors can't give them a straight answer. It's not that we're trying to be elusive; it's just that many of the studies have limitations that make interpreting the results difficult."

"Overall, the therapeutic benefits of RA treatments far outweigh their downsides."

– Daniel E. Furst, MD



CANCER AND RA: same system, opposite effects

"RA IS NOT CANCER – LET'S BE CLEAR ABOUT THAT – but RA has some features that resemble cancer, so treatment we normally would think of as oncolytics (cancer-killers) have application to RA," says Gary S. Firestein, MD, chief of the Division of Rheumatology, Allergy & Immunology at the University of California, San Diego. Kinship at the cellular level makes such treatment crossovers possible, says Dr. Firestein.

The two diseases have a faulty immune system in common, says rheumatologist Daniel E. Furst, MD, of the University of California, Los Angeles. "Cancer occurs when the body's normal immune response to cancer cells – which appear in us all the time – fails. The immune system doesn't catch something that's abnormal. In the autoimmune diseases – such as RA, lupus, Sjögren's syndrome, psoriatic arthritis, myositis, sarcoidosis and scleroderma – the immune system overreacts to the normal, turning against itself," says Dr. Furst.

It's true that those autoimmune diseases have been linked to an increased risk of cancer – lupus with lung or blood cancer; Sjögren's syndrome with lymphoma; psoriatic arthritis with skin cancer; myositis with all types of cancer; sarcoidosis with skin, liver, lung and lymphoma; and scleroderma with lung cancer. So why has RA's link to lymphoma been studied the most intensively? One reason is that many of the medications suspected of increasing the lymphoma risk are approved to treat RA, but not all of the other autoimmune diseases. Another is that RA involves a cellular process akin to tumor growth.

In RA, the delicate lining that surrounds and protects a joint, known as the synovium, becomes inflamed, making the joint swollen and painful. As the disease progresses, the cells that make up the synovium go through a process much like what happens in cancerous tumors: Normal cells multiply unchecked, and invade and destroy healthy tissue.

To complicate matters, says Dr. Furst, many drugs used to treat RA suppress the immune system, meaning the immune cells that search the body for cells gone bad aren't able to do their job. "If a drug suppresses not only the abnormality that's causing the disease, but also immune surveillance, one could get cancer from the therapy," he says.

That's the theory. But what about the evidence? It's been accumulating for some time. The first hints surfaced in 1978, when researchers in Finland matched hospital records of patients treated for RA with patients treated for cancer and saw an overlap. That study, as well as other studies of RA patients from around the world, showed a higher incidence of lymphoma – in particular, non-Hodgkin's lymphoma – in people with RA, compared with people without RA.

By current estimates, the lymphoma risk for people with RA is two to four times greater than for people without RA, when adjusted for age and gender. That may sound huge, but when you consider the rarity of non-Hodgkin's lymphoma – about 90 cases per 100,000 people in the age group affected by RA, compared with 213 cases for breast cancer and 150 cases for prostate cancer – even the elevated risk is still relatively low (less than 0.1 percent per year).

OVER THE YEARS: same worries, different drugs

THE RISK IS RELATIVELY LOW, BUT ELEVATED NONETHELESS. Patients who have RA want answers, and researchers who study the disease want to provide them. Whether it's the RA, its treatment or some combination of the two that raises patients' cancer risk is what medical scientists have been trying to determine ever since the 1978 Finland study.

Just as detectives first home in on suspects with criminal records, researchers turned their attention to a drug with a

A LOOK AT LYMPHOMA

WHAT IT IS: Lymphoma starts in the tissues of the lymphatic system, such as the lymph nodes, which is where your body's immune system fights off viruses, bacteria and other infectious agents. In non-Hodgkin's lymphoma, tumors evolve from the overgrowth of the immune system's white blood cells. Hodgkin's lymphoma (Hodgkin's disease) also involves the white blood cells, but has an extra distinguishing feature. It is more serious but less common than non-Hodgkin's lymphoma.

WHO GETS IT: Overall, lymphoma affects more men than women. Non-Hodgkin's disease affects people older than 60 more than younger people. Those with primary Sjögren's syndrome – Sjögren's disease that does not develop as part of rheumatoid arthritis or lupus – have high incidences of non-Hodgkin's lymphoma. Hodgkin's disease affects people between the ages of 15 and 40, as well as those older than 55. Those who have had an Epstein-Barr virus infection, such as mononucleosis, are more likely to develop Hodgkin's.

SYMPTOMS: See your doctor if you have persistently swollen lymph nodes under your armpits or chin, or in your groin. Those are the early signs. Later signs include persistent fever, regular night sweats, fatigue, extremely itchy skin, abdominal pain or swelling, weight loss, chest pain, coughing or trouble breathing.

TREATMENT: There are 30 or so types of non-Hodgkin's lymphoma. Most are treatable; some can be cured. Others are more challenging to treat, but have high five-year survival rates. Only a few types tend to be fatal.

SHARED CAUSES, SHARED TREATMENTS

THERE IS A HOPEFUL SPIN ON THE COMPLICATED CONNECTION BETWEEN CANCER AND RHEUMATOID ARTHRITIS (RA). Cancer researchers have begun to appreciate that inflammation may play as big a role in cancer as it does in autoimmune diseases, such as RA.

"It's clear now that there's cross talk between inflammation, immune activation and cancer. Many of the same pathways and molecules can go awry in parallel," says Gary S. Firestein, MD, chief of the Division of Rheumatology, Allergy & Immunology at the University of California, San Diego. "That's encouraging, because when you really start to understand the mechanism of one particular disease, a broad shadow is cast on others."

As more shared chemicals and pathways are uncovered, the number of possible targets for treating both increases. Here are two of the latest finds:

TARGET: B Cells. The biologic agent rituximab (*Rituxan*) was approved by the FDA in 1997 for treating aggressive lymphomas. In 2006, it received FDA approval for treating RA. Rituximab zeroes in on B cells, which are a type of white blood cell that proliferates out of control in certain types of lymphoma and also is important in promoting RA, says Mary Chester Wasko, MD, a rheumatologist at the University of Pittsburgh Medical Center. As part of the normal immune system, B cells kill foreign invaders indirectly by triggering production of chemicals that kill the foreign substances. In RA, B cells flock to the affected joints, secrete chemicals that encourage inflammation and produce autoantibodies.

TARGET: NF kappa B (NF-κB). At the University of California, San Diego, immunologist Michael Karin, PhD, is studying NF-κB, a protein that has been called the "master switch" of inflammation. Karin's research suggests that NF-κB may be the "smoking gun" connecting inflammation and cancer. "Inflammatory cells don't undergo any genetic changes in cancer and don't become cancerous themselves, but they are major players in tumor development," says Karin.

Karin's group has found that activation of NF-κB prompts production of growth factors, which, in turn, stimulates the multiplication of cells that will become cancerous. One of those growth factors, it turns out, is interleukin-6 (IL-6) – a real "bad guy," Karin says. Recently, his lab group showed that IL-6 is "absolutely critical" for the development of liver cancer, and – surprise – research in other labs indicates that the same villain, in cahoots with TNF, contributes to RA.

It stands to reason, then, that IL-6 blockers – as well as anti-NF-κB agents – are being studied actively in labs and clinics throughout the world. In June 2007, Austrian researchers reported promising results from a clinical trial of the anti-IL-6 agent tocilizumab (*Actemra*) in patients with moderate-to-severe RA. Also within the past year, one pharmaceutical company announced plans to test its NF-κB regulator on RA patients.

known cancer connection. The immunosuppressive drug azathioprine (*Imuran*) first had been linked to lymphoma in transplant patients who took it to prevent organ rejection. When investigators looked at RA patients who took *Imuran* to keep the immune system from overreacting against itself, they found the same association. And the longer a person had taken the drug, the higher the risk was.

Methotrexate (*Rheumatrex*) was the next scrutinized drug, after a 1991 report of a patient developing lymphoma while taking it. A phenomenon called "reversible lymphoma," which arises when people begin taking methotrexate and disappears when they stop, has been reported in some 50 RA patients. But large-scale studies have failed to finger methotrexate as the culprit.

Now, attention has turned to the newer biologic drugs that inhibit tumor necrosis factor (TNF), and for good – or at least logical – reason. TNF is a versatile protein that promotes the inflammation associated with painful, swollen joints and bone tissue destruction in RA, but it originally was pegged for eliminating cancerous tumors.

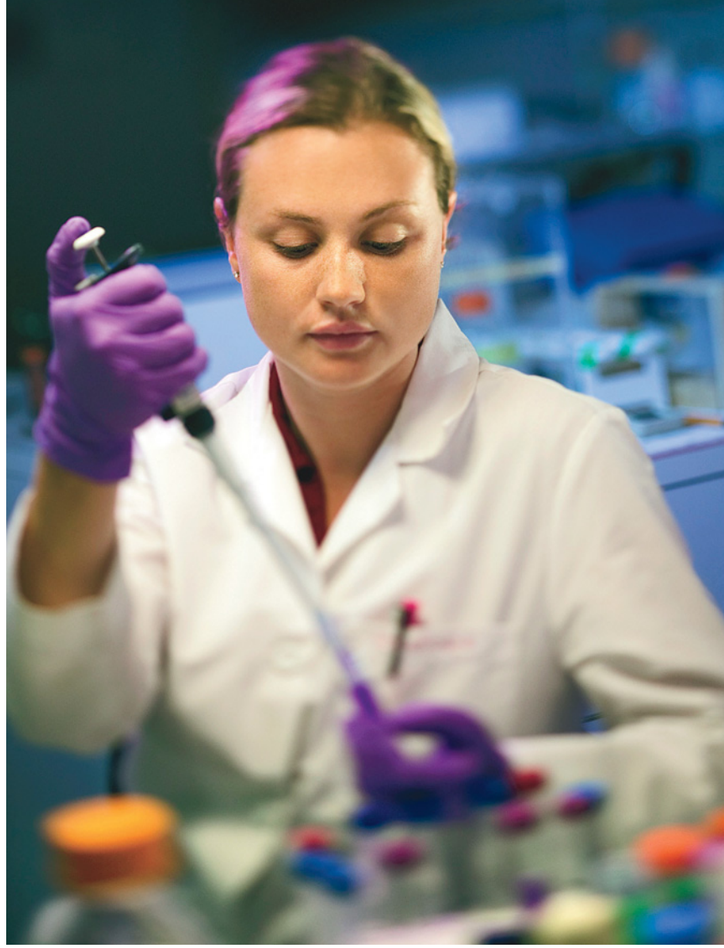
Might the drugs that block TNF's proinflammatory properties also hamper its tumor-fighting tendencies? That's been the concern ever since TNF inhibitors, such as adalimumab (*Humira*), etanercept (*Enbrel*) and infliximab (*Remicade*), came on the scene during the past decade. But because they've been around for a relatively short time, many studies looking at lymphoma risk haven't been done. So far, "the evidence is mixed," says Dr. Wasko. "Some studies point to a slight increase in risk of lymphoma in RA patients who receive TNF inhibitors, but it's not a consistent finding."

It's possible that TNF-inhibiting drugs have contradictory effects – raising cancer risk in some situations and lowering it in others. That's a plausible scenario, given the mercurial nature of the protein they target. "The net effect of anti-TNF drugs on cancer risk could depend upon your ethnic background, your exposure to toxins in the environment or multiple other factors," says Dr. Wasko. "And it may depend upon the type of cancer you're talking about – the effect on lymphoma risk could be different from the effect on colon or lung cancer risk."

Frederick Wolfe, MD, director of the National Data Bank for Rheumatic Diseases, in Wichita, Kan., points out another factor. "If you have severe RA, you're more likely to be prescribed a biologic, but you're also more likely to get lymphoma – because of the severity of your disease – whether or not you get the biologic," he notes. "It's difficult to disentangle the effect."

To tangle matters even more, lymphomas are relatively rare, so researchers must study large numbers of RA patients in order to find enough lymphoma cases from which to draw meaningful conclusions. But RA itself, although the second most common arthritis diagnosis, is fairly rare, occurring in only 1 percent of the general population.

Keeping those caveats in mind, consider the results of recent studies, which shift the blame away from treatments and suggest that keeping RA in check should be your biggest concern.



NOW:

less worry, more aggression

IN RESEARCH PUBLISHED IN THE JOURNAL *ARTHRITIS & RHEUMATISM* IN 2006, INVESTIGATORS AT HARVARD MEDICAL SCHOOL AND THE UNIVERSITY OF BRITISH COLUMBIA, VANCOUVER, POOLED MEDICAL DATABASES from Pennsylvania, New Jersey and British Columbia to compare cancer rates between patients using the older disease-modifying antirheumatic drug (DMARD) methotrexate and those using a newer biologic drug, such as a TNF-inhibitor. The conclusion? Users of biologic agents probably are no more likely than users of methotrexate to develop cancer. Similarly, a study of 19,562 patients led by Dr. Wolfe and his colleague, Kaleb Michaud, showed no evidence for an increase in lymphoma incidence in those on TNF inhibitors.

In another investigation, Swedish researchers mined a national registry of nearly 75,000 RA patients, finding a dramatic association between lymphoma and disease activity, which is determined by currently swollen or tender joints, increased levels of inflammatory markers and X-ray evidence of erosion in at least one joint.

Compared with patients who had low RA activity, those with medium disease activity showed an eightfold increase in the likelihood of developing lymphoma. For the 1 percent who had high activity, the probability took a staggering 70-fold jump, leading the authors to conclude that suppressing RA disease activity with aggressive treatment actually may reduce, rather than raise, the odds of developing lymphoma.

As for other cancers, Dr. Wolfe and Michaud studied 13,000 patients in the National Data Bank for Rheumatic Diseases, looking specifically at links between treatment with a biologic agent and cancer risk. They found that biologic therapy doubled the odds of developing skin cancers, including melanoma, but did not put patients at greater risk for lymphoma, or breast, lung, colon or any other cancer.

"These increased risks are extremely small," Dr. Wolfe emphasizes. "Melanoma is serious but not common; most other skin cancers are not serious. I don't think anyone should be concerned."

Weighing all the evidence, Dr. Furst offers this advice: "Rheumatoid arthritis is a very serious disease, and, overall, the therapeutic benefits of the drugs used to treat it far outweigh their downsides. The risk from not doing anything to contain the disease is much greater."

Michigan-based Nancy Ross-Flanigan is a frequent contributor to Arthritis Today.