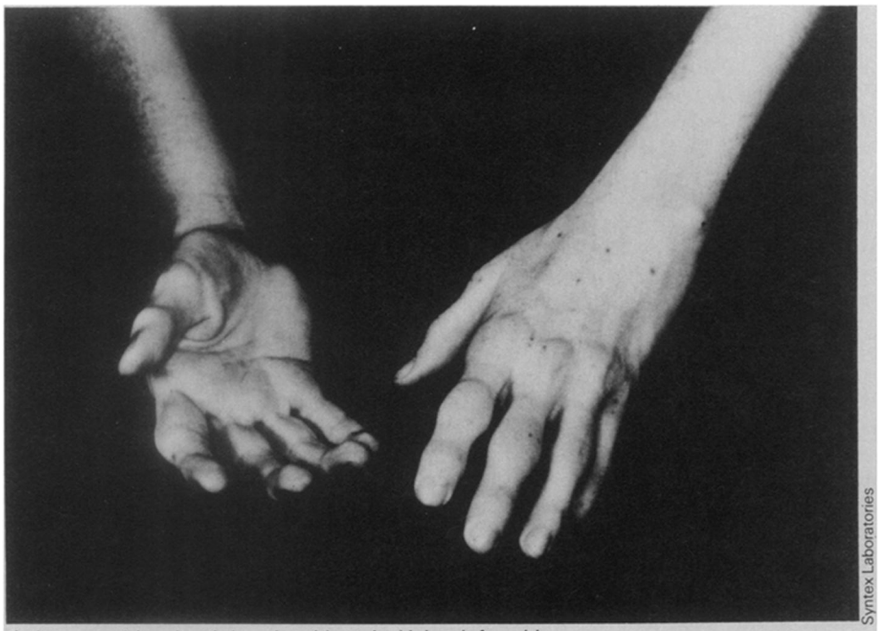
# The Joint Destroyers

**Many immune factors are proving to be involved in rheumatoid arthritis. This discovery may lead to a highly effective and safe drug for the disease — something that is not now available to patients.**



Syntex Laboratories

*A rheumatoid patient's hands with typical joint deformities.*

By JOAN AREHART-TREICHEL

Since ancient times millions of persons have suffered periodic, unpredictable, excruciatingly painful inflammation of the joints, often leading to irreversible joint destruction and ultimately crippling. Some have experienced inflammation in, and damage to, their lungs, skin, muscles or other body areas as well. A few have even died when their hearts were the targets of inflammation and injury. All have been victims of rheumatoid arthritis.

What causes this chronic, degenerative and generally vicious disease? The ancient Greeks thought it was bad humors in the blood. Scientists today still don't have the definitive answer. Genes seem to play some role. A virus may also be involved. But what investigators today are sure of that the ancient Greeks were not, and that even scientists of a decade ago didn't know, is that the disease process itself involves an astounding number of the body's immune factors.

The immune system normally comprises various kinds of white blood cells and molecules made by those cells. These cells and molecules usually reside in lymph tissue and the bloodstream, unless bacteria, viruses or other material that appears to threaten the body rally them into defense. Most of these cells and compounds have now been identified as well in human joints actively afflicted with rheumatoid arthritis. They include helper and suppressor T cells, B cells, monocytes, macrophages, neutrophils, antibodies and complement proteins.

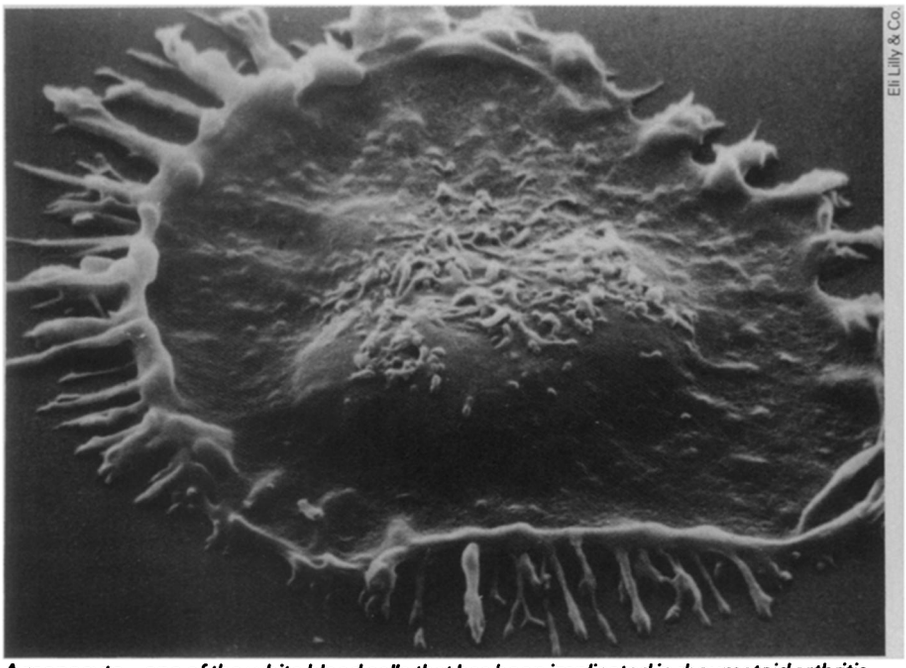
Why these immune cells and molecules congregate in the rheumatoid-diseased joint is baffling. Perhaps the initial disease trigger — a virus or an inherited defect in the body's immune system, for instance — prompts them to cluster there. How the cells and molecules inflict disease is even more perplexing; scientists are accumulating complex and sometimes conflicting data on the subject. As Steven Abramson, a rheumatologist with New York University Medical Center in New York City, confesses, "Everyone is finding out in their labs that this or that cell is doing more damage than we had anticipated."

Still, investigators are starting to get some idea of how the various cells and molecules contribute to the rheumatoid disease process. According to reports, including those presented at the recent Eighth Pan American Congress of Rheumatology in Washington, D.C., it looks as if all the suspects are responsible to a greater or lesser degree.

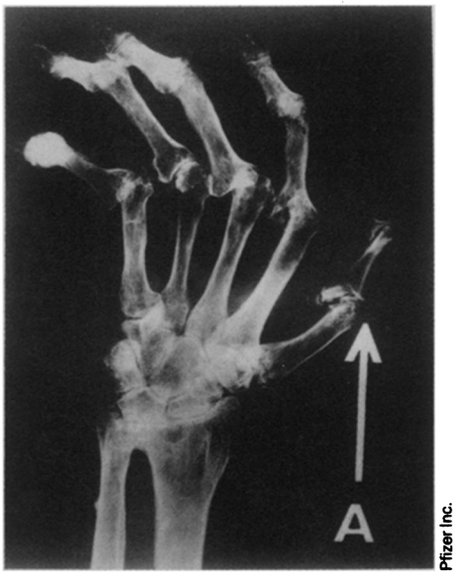
In the rheumatoid joint, antibodies that react against other antibodies — so-called "rheumatoid factors" — appear to spark both inflammation and destruction. So do monocytes, macrophages and T cells, which release inflammation-causing chemicals called prostaglandins. And so do neutrophils, which produce cartilage-destroying enzymes as well as prostaglandins. However, helper T cells (which kill foreign organisms) rather than suppressor T cells (which provide a check to the action of helper T cells) may be the major T cell culprits. One reason is that there are more helper T cells than suppressor T cells present, and the helper T's have been found to interact with the joint lining. Also, antibodies directed against suppressor T cells have been noted in patients with juvenile rheumatoid arthritis (SN: 11/18/78, p. 342). On the other hand, as Lars Klareskog and colleagues at the University of Uppsala, Sweden, cautioned in the June PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, "... the large number of helper T cells present in the rheumatoid synovial tissue might not represent necessarily a distorted balance between helper and suppressor T cells...."

These new insights into rheumatoid pathology have also provided a better means of determining how drugs currently available to treat rheumatoid arthritis exert their effects. Researchers have found that the nonsteroidal anti-inflammatory drugs inhibit not only prostaglandin but rheumatoid factor production; the nonsteroidal drugs also seem to be capable of increasing the number of suppressor T cells; when rheumatoid patients are treated with either gold or D-penicillamine, their production of rheumatoid factors slackens drastically; and both gold and cortisone inhibit macrophages.

However, none of the arthritis drugs currently on the American market appears to be the wonder drug that the nation's seven million rheumatoid victims hope for. Injectable gold can retard or even pre-




*A monocyte – one of the white blood cells that has been implicated in rheumatoid arthritis.*




*A hand afflicted with advanced rheumatoid. There is almost total dislocation of the joints. There are also signs of a secondary degenerative disease, osteoarthritis, in the thumb (A).*

vent joint destruction in rheumatoid patients, a number of studies have suggested. But it does not work in all patients, and a number of patients cannot tolerate it because of toxic side effects such as itching, stomach discomfort, anemia or platelet disorders. There are also some data implying that the drug D-penicillamine can do the same, but it too does not help all patients and can cause serious side reactions such as bone marrow suppression or kidney disease in many others. Cortisone does not retard or prevent joint destruction in the amounts in which it can be given safely, although larger doses might theoretically be able to do so. While aspirin and other nonsteroidal drugs have been amply demonstrated to reduce joint inflammation and pain, there is no convincing evidence to date that any of them alters the course of the disease. And this includes the two new ones approved by the Food and Drug Administration last spring and hailed in a number of media reports as "exciting breakthroughs" — benoxaprofen and piroxicam.

For instance, as the July 9, 1982 MEDICAL LETTER ON DRUGS AND THERAPEUTICS (published by a group of physicians in New Rochelle, N.Y., to brief other physicians on the latest scientific status of drugs) pointed out, "the manufacturer of benoxaprofen [Eli Lilly] has issued press releases suggesting that this agent might arrest the underlying disease process in rheumatoid arthritis. The ability of benoxaprofen to inhibit the migration of monocytes and to suppress adjuvant-induced arthritis in rats appears to be the theoretical basis for this suggestion. Other nonsteroidal anti-inflammatory drugs, however, can also inhibit migration of monocytes, and all the nonsteroidal agents have similar effects on adjuvant-induced arthritis, which does not closely resemble rheumatoid arthritis."

What's more, during the first week in August, Lilly voluntarily withdrew benoxaprofen from the American market for an indefinite period of time because it had been linked with 61 deaths among elderly patients in Britain, where the drug had been sold for two years (SN: 8/14/82, p. 104). Lilly is now convening a panel of scientists from both within and outside of Lilly to determine if benoxaprofen was responsible for these deaths. Whether benoxaprofen ever returns to the American market will probably be heavily influenced by the panel's findings. In the meantime, Lilly is still proceeding with a three-year trial at various medical centers in hopes of finding that benoxaprofen can affect the course of rheumatoid arthritis.

Piroxicam suppresses neutrophils' generation of superoxides (suspected mediators of joint destruction) in rheumatoid victims, Abramson and colleagues have found. They will now attempt to see whether rheumatoid patients who experience disease remission are also those whose neutrophil manufacture of superoxides is suppressed. "If so," Abramson says, "it would be evidence that piroxicam affects the course of the disease."

An experimental gold compound, auranofin, "represents an important new medication," in the opinion of John Decker, chief of the Arthritis and Rheumatism Branch of the National Institute of Arthritis, Metabolism, Kidney and Digestive Diseases in Bethesda, Md. Taken orally, auranofin has been found to be much less toxic to patients than injectable gold is, he explains, and therefore can probably be tolerated by many more patients than can injectable gold. And because injectable gold appears to counter rheumatoid, oral gold probably does too, Decker suspects. The manufacturer of auranofin, Smith Kline and French Laboratories, has already conducted extensive double-blind trials where rheumatoid patients received their usual nonsteroidal drugs plus auranofin or their usual nonsteroidal drugs plus auranofin or their usual nonsteroidal drugs plus a placebo, a spokesman for the company told SCIENCE NEWS. The former showed significantly greater indications of disease remission, such as fewer joint erosions. The company has also conducted double-blind clinical trials comparing the effectiveness of auranofin and injectable gold; the drugs were comparable in arresting the rheumatoid disease process. SK&F has submitted the results of these trials plus others to the Food and Drug Administration in hopes of getting approval to market auranofin. There are reasons to believe that the FDA might give the drug the green light late this year or early next year.

But drugs that are really going to combat rheumatoid, authorities predict, are those that act on specific kinds of immune cells in the rheumatoid joint more potently, selectively and safely than drugs now available seem to do. Edward J. Goetzl of the University of California at San Francisco is pinning his hopes on drugs pitted particularly against T cells, B cells or macrophages, Thomas Zizic of the Johns Hopkins Medical Institutions on drugs countering T or B cells; Decker is placing his bet on drugs fighting the T's. Indeed, a heated search for such medications is already underway, attests Frederic C. McDuffie, medical director of the Arthritis Foundation, headquartered in Atlanta. □