Arthritis: Looking for Immunotherapy

Preliminary results released last week may offer a better alternative to current treatments for rheumatoid arthritis, many of which either treat specific symptoms or affect the entire immune system. Concentrating on specific elements of the abnormal immune response that characterizes the disease, scientists are reaching into biotechnology's bag of tricks to develop immunotherapy techniques.

Rheumatoid arthritis, which primarily strikes middle-aged women, is a crippling disease affecting 7 million people in the United States. This severe form of arthritis not only affects bone joints but can also spread to body organs. Although the exact cause of the disease remains unknown, individual cases of rheumatoid arthritis are apparently due to one or more factors thought to include genetic predisposition and viruses.

Whatever initiates the disease, it is the immune system's inappropriate response – by attacking the body's own cartilage and joint linings – that brings about the characteristic symptoms. This autoimmune response has caught the attention of scientists seeking replacements for the standard treatment, regimens of ingestible gold or anti-inflammatory drugs (SN: 10/19/85, p.244). Tinkering with the immune system was the focus of several preliminary research projects reported at last week's annual meeting in Washington, D.C., of the Federation of American Societies for Experimental Biology.

At Case Western Reserve University in Cleveland, Thomas F. Kresina and his coworkers are using a common animal model of arthritis to study the effect of so-called hybridomas on the disease. When collagen (the tough structural protein of cartilage) from another species is injected into certain strains of mice, the mice produce anticollagen antibodies, which eventually destroy the joints and cause collagen-induced arthritis. However, if mice are given collagen from their own species prior to immunization with foreign collagen, they become resistant to collagen-induced arthritis. Researchers can pass the resistance from animal to animal by cell transfer.

Taking advantage of this resistance, Kresina's group created hybridomas by fusing a strain of cancer cells with spleen cells from resistant animals, thereby making a cell line that multiplies indefinitely (thanks to the cancer cells) and suppresses collagen-induced arthritis. According to Kresina, injection of hybridoma cells into 13 mice with the disease resulted in reduced hind-paw redness and swelling in six of the mice. Nonhybridoma cells used as a control did not suppress arthritis in 10 of 11 mice tested.

One month after injection of nonhybridoma cells into the arthritic control mice, foot swelling remained at an average of 40 percent above that found in nonarthritic mice, and in some cases it even increased. Yet in the hybridoma-treated animals, swelling had decreased to an average of 8 percent above normal. Microscopic examination of joint tissue supported the findings that arthritic mice were helped by hybridoma treatment, says Kresina.

Because injection of cancer cells is ultimately an unacceptable treatment, the Case Western group is exploring ways to kill the cells prior to injection. Another probable drawback, explains Kresina, is that the human body, recognizing mouse cells as foreign, may reject them before any benefit occurs.

Using a variation of the same test system, scientists at the University of Tennessee in Memphis have treated nonarthritic mice with spleen and thymus cells from resistant mice in an attempt to prevent the onset of collagen-induced arthritis. Compared with mice that did not receive resistant cells, the cell-treated mice developed much less severe arthritis at a slower rate after both groups were later immunized with collagen, according to Linda K. Myers.

In a parallel study, Myers has separated a small subpopulation of spleen cells that may be responsible for the resistance. She told SCIENCE NEWS that these cells could be the same as those used by Kresina to make hybridomas. Myers and Kresina agree that much remains to be learned about the process leading to resistance, but that the significance of the resistance-inducing cell may be its production of a soluble factor that could be used in arthritis treatment. Both groups are searching for such a factor.

Taking a narrower approach to treatment of collagen-induced arthritis, scientists at the Mayo Clinic in Rochester, Minn., and the VA Medical Center in Memphis are targeting the T-cell lymphocyte in attempts to stop the production of anticollagen antibodies. Because a T cell, when activated by exposure to collagen, aids in the production of anticollagen antibody by B-cell lymphocytes, these researchers are using antibodies against receptors on the T-cell surface, according to Mayo's Subhashis Banerjee. He says the onset of arthritis took two weeks longer in the receptor-antibody-treated mice than in mice not given the blocking antibody.

When arthritis does appear, it is less severe than that seen in mice not treated with the antireceptor antibody. As in other studies of collagen-induced arthritis in mice, the progression of arthritis was measured on the basis of paw swelling, joint deformity and whether joints were immobile.

Treatment, however, did not prevent the disease. "All we did was delay the onset and reduce the severity," says Banerjee, who adds that the next step will be to increase the dose of blocking antibody.

Whether data from an animal model of rheumatoid arthritis can be extrapolated to the human patient remains controversial. Nonetheless, although the results are preliminary and the numbers of animals tested are small, the current studies mark a possible advance in arthritis immunotherapy over previous studies using immunosuppressant drugs and radiation (SN: 4/20/85, p.246). As Kresina points out, these approaches are aimed at halting a specific component of the immune response, rather than general suppression with its possible adverse side effects. *– D.D. Edwards*

Marvelous mystery cosmic radiation

Over the decades, accelerator laboratories and cosmic radiation have tended to alternate as arenas in which new high-energy particle physics phenomena have been discovered. Right now, after a long stretch of time in which particle physics news usually came from accelerators, the cosmic rays are coming up with unusual effects. One of the most spectacular and controversial of these are what Gaurang Yodh of the University of Maryland in College Park calls "Marvin's marvelous muons." Now Yodh is adding a few unusual muons of his own.

Marvin is Marvin Marshak of the University of Minnesota in Minneapolis, and the muons are particles that he and colleagues have been finding in a detector called Soudan buried deep in a mine in northern Minnesota (SN: 1/3/87, p.8). Presumably these muons are produced in the detector by some highly energetic, extremely penetrating radiation that comes from certain sources in the sky – Cygnus X-3 and Hercules X-1 are among those implicated – and can penetrate the earth's atmosphere and several thousand feet of rock to reach the detector.

The existence of these strange, unidentified rays – which have been called cygnets because they were first seen coming from the direction of Cygnus X-3 – has been variously supported, denied and maybe-ed by other underground

detectors around the world that are more or less similar to Soudan, but few other physicists have found the evidence convincing. Now, an experiment on the surface – at a high altitude, in fact – operated by Yodh and graduate student Brenda L. Dingus has found a similarly unusual production of muons associated with cosmic-ray air showers. In this case the source seems also to be Hercules X-1.

When an ordinary cosmic ray, which can be a gamma ray, a proton or an atomic nucleus, strikes the top of the atmosphere, it initiates a shower of particles, some knocked out of the atoms of the air, some created in the collision. On the ground, physicists customarily detect these showers by spreading large areas of particle-detecting material. The experiment of Yodh and Dingus, which is located at Los Alamos (N.M.) National Laboratory at an altitude of 7,000 feet, differs from most in having in its center a flash chamber, which is actually part of an accelerator laboratory there, and which can identify muons. Yodh told the Heavenly Accelerators workshop, which met recently at Johns Hopkins University in Baltimore, that just a few months ago a series of air showers initiated by gamma rays that seem to come from Hercules X-1 had "too many muons" associated with them – that is, more than known and accepted physics would expect – and therefore something strange is going on.

To a chorus of murmurs from the audience, Yodh replied, "You are confused; we were surprised." Marshak had suggested that his cygnets were some previously unknown kind of particle. Yodh suggests that the source ot the anomalous muons may be known particles – neutrinos or perhaps those of the class called vector mesons – acting in previously unknown ways. A similar suggestion comes from Gabor Domokos and Susan Kovesi-Domokos of Johns Hopkins, who suggest that ordinary neutrinos could be doing it, provided they are not simple elementary particles but composites.

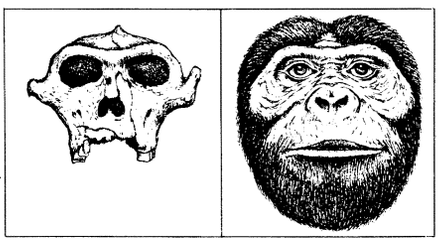
The most widely believed theory at this point holds that the elementary building blocks of matter consist of six quarks and six leptons. Neutrinos and muons are leptons and so are believed to be simple elementary particles. However, for reasons that seem good to them, some theorists have suggested that there may be a level of structure below that of quarks and leptons – that is, that the quarks and leptons are composites made of things called preons. If neutrinos are composites made of preons, Gabor Domokos told the workshop, then a neutrino striking the atmosphere might induce processes of preon exchange that could make numbers of muons that are impossible if preons don't exist.

"I hope we will see the signal again," says Yodh. "If the data are good, it's up to the theorists." – *D. E. Thomsen*

Robust hominids: Tooth and consequences

It is a face that only a mother and a paleoanthropologist could love. The teeth are immense and hammer-like, particularly at the back of the mouth. Massive jaws and a broad face slope toward the back of the head, where a small brain is encased.

The face belongs to a member of the robust australopithecines, a group of hominids, or human-like creatures, that evolved at the same time as the lineage that led to modern humans, but became extinct around 1 million years ago. The size and shape of their fossil skulls, found in eastern and southern Africa, led to the view that they were large, heavily built creatures. That view appears to be wrong, according to Yoel Rak of Tel Aviv University in Israel.



Courtesy: Grine

Skull and artist's conception of robust australopithecine known as A. robustus.

Rak studied several skulls belonging to the east African species *Australopithecus boisei.* "Robust" facial features reached their peak in *A. boisei,* which has been dated at 1.2 million to 2.2 million years old.

"I was astonished at how delicate much of the *boisei* skull is," reported Rak at the annual meeting of the American Association of Physical Anthropologists in New York City last week. "It appears that a massive [chewing] system was imposed on a relatively small creature."

For example, says Rak, the walls of *A. boisei's* brain case were "amazingly thin." Cranial thickness reaches no more than 4 millimeters in the largest specimens, and no more than 2 millimeters in a smaller skull. Fragile bone also surrounds the eye openings.

A number of features typical of *A. boisei* skulls appear, he notes, to have been evolutionary modifications to cope with massive teeth and jaws. Among them are a flared, bony crest running over the top of the head, a visor-like crest over the eyes and the triangular shape of the brain case, all of which helped to anchor enormous facial muscles.

Rak's analysis feeds into the emerging view that east African australopithecines were not more "robust" in stature than their south African counterparts, who have been described as smaller or "gracile" (SN: 1/24/87, p.58). But the east African variety does appear to be characterized by larger teeth and thicker tooth enamel, said Frederick Grine of the State University of New York at Stony Brook, at a press conference held the day before the physical anthropology meeting began. His remark was generated by a five-day workshop in Stony Brook on the robust australopithecines attended by an international group of researchers.

It is difficult to make inferences about australopithecine biology, cautions Pat Shipman of Johns Hopkins University in Baltimore, because "it's hard to tell which heads go with which bodies." Nevertheless, in independent studies presented at the workshop, Henry M. McHenry of the University of California at Davis and William L. Jungers of the State University of New York at Stony Brook conclude that fossil remains provide no evidence of marked differences in body size between geographically separated australopithecines. Furthermore, they suggest that later australopithecines were about the same size as earlier australopithecines and early members of the human lineage.

Both scientists report that while south African robust hominids had thick tooth enamel, that of east African australopithecines was even thicker.

Most workshop participants agreed with McHenry and Jungers. "The terms 'robust' and 'gracile' should refer to australopithecine teeth only," comments Milford H. Wolpoff of the University of Michigan in Ann Arbor. Adds William H. Kimbel of the Institute of Human Origins in Berkeley, Calif., "The concepts of 'gracile' and 'robust' australopithecines should probably be dropped and we should just refer to species names."

One australopithecus species, however, may require revision, according to Ronald J. Clarke of the University of the Witwatersrand in Johannesburg, South Africa. At the workshop, he discussed a recently excavated skull of a creature known as *A. africanus* and proposed that it and other specimens previously found at the same site may in fact represent two species. *A. africanus* has been found only in southern Africa and is estimated to have arisen between 2.5 million and 3 million years ago.

Clarke says some of the specimens have larger teeth and flatter faces and brows, indicating that they were an ancestral stock for both southern and eastern robust australopithecines. Other skulls have smaller teeth and more prominent brows and nasal bones. This species may have been ancestral to the human lineage, he notes.

Kimbel and his colleagues also suggest that *A. africanus* specimens may represent more than one species, based on a study of fossil teeth. "If this proves to be the case," he says, "there may be interesting changes in how we reconstruct early hominid evolution." – *B. Bower*