the starburst theory, who include most of the workers in the field. The problem isn't the ingredients, it's the recipe as a whole, says Martin Rees of Cambridge, a leading proponent of the supermassive black hole hypothesis: "To make [the starburst model] work, you have to synchronize everything to within 10 million years, which is a rather short time by cosmic standards." And much of the galaxy has to take part in those finely timed events: About 5% of its mass has to undergo a starburst at the same time to generate enough energy for the brightest quasars, Terlevich and Boyle calculate. The reason, as Roger Blandford of the California Institute of Technology points out, is that "the efficiency of converting matter into energy is [low] with a starburst."

Boyle himself admits that some quasars have special features that can't be explained with a starburst: the jets of radio-emitting material that squirt from the centers of some quasars, for example, and the flickering of some quasars' x-ray emissions, which vary over timescales of several minutes. An object that can change its brightness that quickly can't be more than a few light-minutes across, or about the size of the earth's orbit around the sun. A black hole and the "accretion disk" around it could fit handily in that space, but the core of a starburst galaxy would be much bigger. What's more, notes Timothy Heckman of Johns Hopkins University, quasars emit as much as 10% of their energy at short wavelengths like x-rays, compared to only about one-ten-thousandth of the energy from present-day starburst galaxies.

But Boyle and Terlevich's demonstration that starbursts produce the right pattern of brightnesses has reawakened interest in the scenario as a way of explaining some quasars and active galactic nuclei (AGNs). As Heckman puts it, "It is possible that the starburst model is relevant to some types of AGNs." He and his colleagues would leave out variable quasars and those with jets. And for the brightest quasars, there's no competing with black holes, says Caltech's Blandford: "While some types of activity in galactic nuclei may be genuinely stellar, most of us don't believe that the majority of the brightest quasars can be explained with starbursts."

But Boyle is unmoved. Starbursts, he says, should have the upper hand over black holes in at least one respect: "Supermassive black holes are still only conjecture," while massive stars and supernovae are known to exist.

–Ray Jayawardhana

Ray Jayawardhana is a free-lance science writer based in New Haven, Connecticut.

Additional Reading

M. Haenelt and M Rees. "Formation of Nuclei in Newly-Formed Galaxies and the Evolution of the Quasar Population," to appear in *Monthly Notices of the Royal Astronomical Society (MNRAS)*.

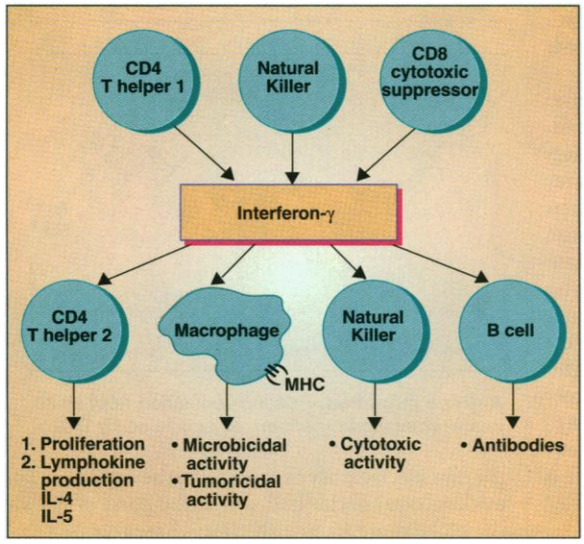
R. Terlevich and B. Boyle, "Young Ellipticals at High Red-Shift," to appear in *MNRAS*.

IMMUNOLOGY

Interfering With Interferon

Interferon-γ has been something of a mystery. Researchers have learned that the protein seems to play key roles in mounting normal immune responses to parasitic and viral infections, as well as in triggering abnormal immune attacks against an organism's own tissues. But exactly how it performs these functions has been hard to fathom, primarily because the immune system is so complex that it's hard to sort out the precise roles of the individual players in the diverse cast of characters that act together in an immune response. Now, two groups have taken advantage of the latest in genetic technology to create new strains of mice that ought to help resolve the outstanding mysteries about interferon-γ's role.

On page 1739, Dyana Dalton, Timothy Stewart, and their colleagues at Genentech Inc. in South San Francisco report that they've produced a strain of mice with an inactivated interferon-γ gene. And in a complementary report on page 1742, Michel Aguet, Rolf Zinkernagel, Sui Huang, and Wiljan Hendriks of the University of Zurich and their colleagues describe a strain of mice in which they knocked out the gene for the interferon-g receptor, which cells need to respond to the cytokine.



SOURCE: DYANA DALTON ILLUSTRATION: H. BISHOP

Major player. Interferon-γ is made by at least three types of immune system cells and has effects on at least four different cell types.

Up to now, researchers could only block interferon-γ activity by using antibodies to soak up the molecule in the bloodstream, a method that leaves open the question of whether all the activity has truly been removed. But the activity is completely prevented in the knockout mice, making it possible to see the full extent of the immune defects caused by its loss. "Giving an antibody is never as direct and clear a demonstration as a knockout mouse," says Stanford University immunologist Hugh McDevitt, who studies the role of interferon-γ in autoimmune disease. "I think these will be tremendously valuable mice." In addition to helping to answer basic questions about the role of interferon-γ, the mice also promise to be useful models for studying such important human diseases as tuberculosis.

The knockouts are already causing some rethinking of interferon-γ's roles. For example, although the interferons were first identified as antiviral agents, interferon-γ has developed more of a reputation as an immune-system modulator, while the interferons-α and -β have gotten credit as the front-line protectors against viruses. But Aguet's group found that in the case of vaccinia virus, interferon-γ is essential to back up those front-line defenses: Without it, the mice can't fight the virus. "There has been a controversy over whether interferon-γ is an efficient antiviral agent," says Robert Schreiber, who studies interferon-γ at Washington University in St. Louis. Aguet's results, he says, show that "there are viral infections in which interferon-γ plays an obligatory role."

The knockouts have also apparently settled a controversy over interferon-γ's role in stimulating the growth of killer T cells. Before the knockout mice, the importance of interferon-γ for growth of these cells, which kill virally infected cells, tumor cells, and foreign tissues, was unclear. Some studies found the cytokine necessary for killer T cell growth, and others didn't. But both Dalton and Aguet found that their knockout mice make normal killer T cells. "This [work] gives the clear answer that although interferon-γ may enhance [killer cell] differentiation, it is not required," says Robert Coffman, an immunologist at DNAX Research Institute in Palo Alto, California.

The most striking, but perhaps least surprising, defect seen in the new mice is their vulnerability to intracellular parasites, such as *Listeria* and *Mycobacteria*, the bacterial

group that includes the tuberculosis bacillus. Plenty of experiments had suggested that interferon-γ is critical for activating macrophages, the scavengers that scarf up parasites and parasite-infected cells. It's importance was also apparent in living animals, since mice treated with interferon-γ antibodies succumb to such infections. So it was a good bet that the knockouts would meet a similar fate—and they did.

What's more, experiments by both groups on cells from the knockout mice confirm that interferon-γ is needed for production by the macrophages of nitric oxide, which serves as their antiparasite poison. There are no surprises in this, says Schreiber. But he adds, "You'd like to be able to prove the same point in at least two if not three different ways," and the mice provide a "more definitive" confirmation of previous results.

But bigger things than such confirmations clearly lie ahead for these mice. It should be possible, Coffman says, to answer such major questions as which of the cells that produce and respond to interferon-γ are most crucial to different immune responses. One way to do this is to systematically add back an active interferon-γ gene or interferon-γ receptor gene to each of the different cell types that make or respond to the cytokine. Aguet says his group is already beginning such an approach with their receptor-knockout mice, adding back the functional interferon-γ receptor in such a way that it will be expressed in only one cell-type, such as macrophages. "This is a way to formally show that the macrophage is actually the crucial cell that needs to respond to interferon-γ," he says.

Besides helping to unravel such basic questions in immunology, the mice also seem likely to provide useful models for understanding diseases caused by intracellular parasites, such as tuberculosis. Mice have been less than ideal for studying tuberculosis, says TB researcher Ian Orme, of Colorado State University, because they don't develop the full-blown disease. But both Orme's group, and that of Barry Bloom at Einstein University, working in collaboration with the Genentech group, have found that the interferon-γ knockout mice develop severe tuberculosis. "I'm very optimistic, and very excited about this," Orme says. "It may prove a very promising model for experimental chemotherapy."

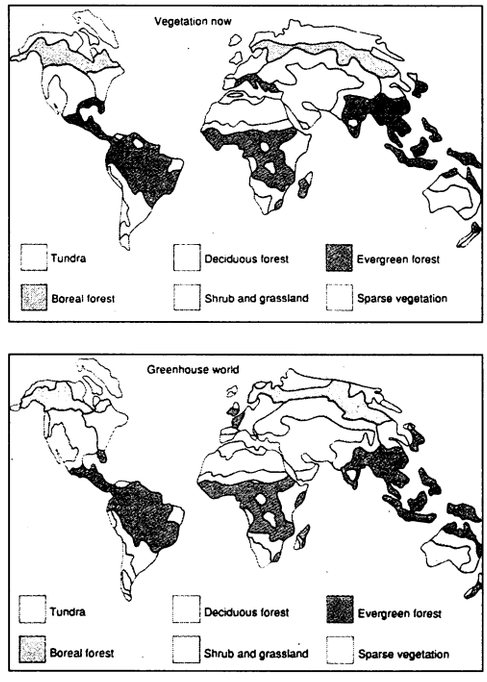
So even in a world becoming increasingly crowded with knockout mice, these two mouse strains promise to be in high demand. "For almost everything I study, interferon-γ is the key cytokine," says immunologist Alan Sher, who studies the immune response to parasitic infections at the National Institute of Allergy and Infectious Diseases. "These mice are the most interesting knockouts I can get my hands on."

–Marcia Barinaga

GLOBAL CHANGE

Ecologists Put Some Life Into Models of a Changing World

While 300 scientists gathered in a former casino in Ensenada, Mexico, in late January to talk about global change, bulldozers outside were clearing debris from roads and river channels after 2 weeks of disastrous flooding. The floods, the result of the heaviest rain in decades, provided a vivid reminder of why the International Geosphere-Biosphere Program (IGBP) had brought these researchers from 50 countries together: to talk about ways of reducing the uncertainties in predictions of global change. Nobody inside the hall was calling the rains a harbinger of climate change, but many scientists believe that, as human activity alters the atmosphere and the climate, weather extremes like the one so evident outside the hall will strike parts of the globe more frequently. Just where those changes might occur—and what their impact might be—is, however, beyond the ability of today's climate models to predict.



IAN WOODWARD

A green migration. Existing vegetation *(top)* shifts in a warmer world *(bottom)*, as simulated by DOLY.

That's one reason scientists at the conference* were talking so excitedly about a historic extension of the models that will take place starting this spring. For the first time, computer models of a green Earth banded with forests, grasslands, and swamps will meet simulations of the atmosphere and climate. At the end of each encounter, which will take place in computers at the UK Meteorological Office near London, the Laboratory for Modeling of Climate and Environment in Paris, and the Max Planck Institute for Meteorology in Hamburg, a new landscape and climate will emerge. Among them: a future Earth altered by a doubling of the atmosphere's carbon dioxide.

That world has been described often enough by one party to this spring's marriage: general circulation models (GCMs), computer models of atmosphere and climate that project a global warming of 1.5 to 4.5° C by the middle of the next century, when human activity may have doubled the amount of CO_2 in the atmosphere. But GCMs have been criticized for treating the earth as a dead planet, inert and unresponsive to climate. That's a major omission, because a shifting climate will have some of its sharpest impacts on ecosystems. What's more, ecosystem changes—the replacement of tundra by forest, grasslands by desert—may also feed back on climate change, influencing its overall severity and how it affects the world region by region. This spring's encounters will mark a first step toward filling that gap.

By coupling GCMs with computer models of the world's vegetation zones so that each climate change is allowed to affect the distribution of plants and each biological change is given a chance to affect climate, two international research teams led by botanist Ian Woodward of the University of Sheffield and plant ecologist Colin Prentice of the University of Lund hope to come up with a more complete picture of global change. Woodward, Prentice, and their climate modeling colleagues in London, Paris, and Hamburg aren't promising a lot of detail. Eventually, they hope to refine their predictions by cross-fertilizing their models with other vegetation models describing details of plant behavior and processes such as photosynthesis and decomposition.

But many of the IGBP scientists who gathered in Ensenada were dazzled by how far and how fast things have moved. "The maturity of this interface between the physical climate focus and biology has happened so much

*"Reducing Uncertainties in Global Change," Third Scientific Advisory Council meeting of the International Geosphere-Biosphere Program in Ensenada, Mexico, 25-29 January.