actually responsible for protecting against the disease. "It's all supposition," he maintains. What is more, Murphy says, there "is no data in humans that would suggest that [killer T cells] play an important role in protection and there's a tremendous amount of epidemiology that says otherwise." Though Merck's Liu takes issue with Murphy's arguments, she says the real point of the experiment is to prove that the concept—not this vaccine—is viable.

Merck's Maurice Hilleman, who has made several human vaccines, says a major value of naked DNA is that it can trigger immune responses against proteins without triggering one against the plasmid. Theoretically, this means the plasmid vector could repeatedly deliver DNA coding for different proteins and thus protect against a variety of diseases. "This is one of the most exciting things in modern vaccinology," says Hilleman.

Harriet Robinson at the University of Massachusetts wholeheartedly agrees. Robinson independently began making what she calls "gene vaccines" for influenza a few years ago with direct injections in chickens and mice of DNA coding for an influenza surface protein. Muscle, says Robinson, is but one cell type that can produce proteins this way. She has even had success with DNA nose drops, which may provide mucosal immunity, a powerful defense against respiratory viruses.

Robinson also has been collaborating with Joel Haynes from Agracetus, which has developed a way to coat DNA onto tiny gold beads. Haynes and Robinson shoot these coated beads into the skin with a "gene gun" to introduce the DNA into epidermal cells. With influenza, not only does this require three to four orders of magnitude less DNA, but, says Robinson, their technique gives "the best protection we've seen, with 100% survival" of the animals challenged. Haynes, Robinson, and colleagues now are beginning studies with an AIDS vaccine in monkeys. Merck and Vical are close-mouthed about their plans, but an AIDS vaccine is an obvious application.

Before a naked DNA vaccine is injected into humans, of course, it would have to clear safety hurdles. A chief question is what happens to the DNA and whether it can integrate with the host genome, potentially causing cancers. Though most researchers believe this risk is extremely low, NIAID's Murphy stresses that many safety tests would have to be completed first.

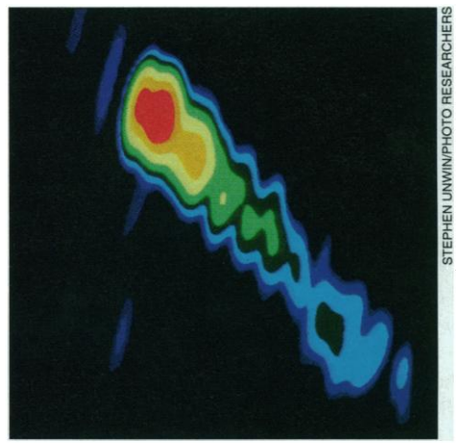
Researchers may be facing these safety questions sooner rather than later. As Vical's Felgner notes, naked DNA has progressed more quickly than anyone imagined. "Almost every experiment has worked the first time," says Felgner. "It's remarkable and you get suspicious, but it's clearly real and well beyond the stage of phenomenology." And well beyond analogies to cold fusion.

–Jon Cohen

ASTRONOMY

Could Quasars Get Their Shine From Stars?

Ever since they were discovered 30 years ago, quasars have been an enigma. Shining like beacons from the very edges of the universe, they emit such an astounding amount of energy—the equal, in some cases, of the combined brilliance of 100,000 ordinary galaxies—that scientists have turned to even more enigmatic constructs to explain them. The leading theory is that their extraordinary brightness is powered by black holes as massive as millions of suns, dragging material into the centers of newborn galaxies and heating it to incandescence. But if Roberto Terlevich of the Royal Greenwich Observatory and Brian Boyle of Cambridge University are right, the puzzle of quasars' power source may have a more prosaic solution: Synchronized bursts of starbirth and death in the cores of young galaxies, they argue in a forthcoming paper, could be enough to explain the brilliance of at least some quasars.



STEPHEN UNWIN/PHOTO RESEARCHERS

A monster's tongue. The radio-emitting jet of this quasar *(upper left)* implies a massive black hole, say most astronomers.

Terlevich and Boyle are reviving an idea that was first proposed soon after the discovery of quasars themselves. This "starburst" model fell out of favor after 1969, when Donald Lynden-Bell of Cambridge proposed that quasars and their dimmer cousins, active galaxies, could be powered by black holes—far more efficient and compact powerhouses. Most quasar experts still doubt that starbursts are potent enough to explain the very brightest quasars. But, by showing that the number of quasars at different brightnesses matches what would be expected from starburst galaxies, Terlevich and Boyle have given the model a boost, notes one supporter, Jorge Melnick of the European Southern Observatory.

Where the black hole model explains a quasar's brilliance with a single display of brute force, the starburst model does it with many precisely timed smaller events. As dust and gas collapse to form a new galaxy, say Terlevich and Boyle, the dense core of the newborn galaxy would give birth to a large litter of hot, massive stars, all at roughly the same time. The biggest of them, stars 25 to 60 times as massive as the sun, would burn up all their hydrogen fuel within 3 million or 4 million years. As these aging, supermassive stars bloated in their old age and expelled their outer layers in strong stellar "winds," the stage would be set for the first phase of quasar activity.

The starburst galaxy would become a quasar as the massive stars entered their death throes, exploding as supernovae and creating a burst of brilliance. What's more, the explosions together with the winds from surviving stars would carve out a hot cavity in the interstellar gas. Ionized gas within the cavity could generate radio waves, accounting for the radio emissions broadcast by some active galaxies.

Following this first wave of spectacular deaths, less massive stars, eight to 25 times the mass of the sun, would start to expire as supernovae. The explosion of these stars—more numerous than their supermassive brethren—would drive the galaxy to maximum brilliance about 10 million years after its birth, reckon Terlevich and collaborators. Afterward, the young galaxy would dim and continue a quieter evolution.

One of the strongest objections to that model has been that starbursts simply cannot produce enough energy to account for a quasar's brilliance; after all, present-day starburst galaxies are much fainter. But Terlevich and Boyle now say they have indirect evidence showing that starbursts could do the job. Recent quasar surveys by Boyle and others have given investigators a sharper picture of the distribution of quasar brightness. To see whether starburst galaxies could match it, Terlevich and Boyle looked at the brightness of present-day elliptical galaxies—usually considered to be the oldest galaxies—and extrapolated backward to the early universe, calculating how bright the galaxies' cores would have been if they had undergone a spasm of starbursts early in their formation. The result: a predicted distribution of brightness that closely matches that of quasars, even the most brilliant of them.

The finding hasn't won over skeptics of

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)*.

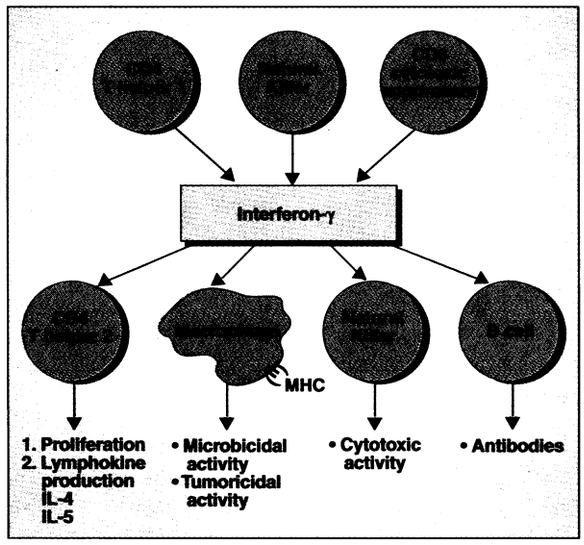
R. Terlevich and B. Boyle, "Young Ellipticals at High Red-Shift," to appear in *MNRAS*.

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