neutron stars. Lingenfelter is being coy. He says that in the middle of the night after the GRO announcement, he had a nocturnal flash that can explain the new findings in a way consistent with neutron star theory. But he's not telling just what it is yet: he plans to disclose his brainstorm at a GRO meeting in Huntsville, Alabama, in October.

Other astrophysicists, however, are ready to let the old model go and consider new possibilities. But as they do so, they face some tough theoretical problems. For one thing, the unexpectedly even distribution of the gamma-ray bursters (which would suggest that the bursts could come from anywhere, within or outside our galaxy) is difficult to reconcile with the other result: the lack of weak sources, which would seem to show the bursts are nearby, and hence bounded by something. But if they aren't bounded by our galaxy, what is the boundary? Astronomers cite two possibilities—both extreme. The sources could lie in a "shell" or "cloud" close to our solar system. But Fishman asks, "What could this cloud be? Why wouldn't we see other objects in such a cloud?"

On the other hand, the sources could come from very far outside the galaxy—perhaps being bounded only by the edge of the universe itself. But if that were true, it would mean that the bursts are more energetic than any other known astrophysical phenomenon—even a supernova.

That apparently radical notion doesn't faze Bohdan Paczynski of Princeton, who years ago rejected the idea that the gamma-ray bursts come from neutron stars in our galaxy. He argues that very rare events such as the collision of two neutron stars or an encounter between a neutron star and a black hole (very different and more infrequent events than those called for in the current model) could give rise to explosions with the requisite energy. "There's nothing that outrageous about gamma-ray bursts at those energies," he says. And, if the entire universe were involved, a rate of one a day corresponds to the relative rarity of one in 100,000 years in any given galaxy.

While the latest GRO results have set a new controversy in motion, Fishman hopes that a further dose of the same could restore consensus. Perhaps, he says, observation of a few hundred bursts will disclose a pattern that gives away the bursts' location. In addition, NASA scientists plan to do spectral analysis and classifications of different kinds of bursts to gather clues to the nature of the sources. Such new experiments are bound to turn up more clues. But whether they will resolve the longstanding puzzle and restore amity in the field—or merely deepen the perplexity and heighten the tension—is, for the moment, anybody's guess. ■ FAYE FLAM

Transgenic Animals May Be Down on the Pharm

Commercial production of human pharmaceutical proteins in the milk of dairy animals may soon be feasible

Pharmaceutical Proteins Limited

Protein producers. *The milk, not the fleece, of these transgenic sheep may be golden.*

IN AESOP'S FABLE, THE GOOSE that laid the golden egg endowed its owner with untold riches. Today, genetic engineers are creating their own versions of the fabled goose—new breeds of sheep, goats, and cows that secrete valuable human pharmaceutical proteins into their milk. Indeed, in the September issue of *Bio/Technology*, three independent research teams report new results that have brought the technology to the threshold of commercialization. "Two years ago, people were doubtful of this technology," says Robert Bremel, an animal biotechnologist at the University of Wisconsin, Madison. "But now the work shows that the mammary gland can be used as an impressive bioreactor."

What excites researchers like Bremel is the prospect of developing critters, otherwise ordinary dairy animals, that can produce large quantities of previously scarce—and therefore expensive—human proteins. Among the proteins are the clotting factors needed to treat hemophilia; erythropoietin, which is used to ameliorate the bone marrow suppression caused by drug therapies for AIDS and cancer; and alpha-1 antitrypsin (AAT), which is being investigated as treatment for emphysema and other degenerative lung diseases. Currently the proteins are either isolated from human sources or made in bacteria by recombinant DNA technology, and the costs range from about $110 per gram for AAT to $1.5 million per gram for erythropoietin.

But the recent successes don't mean that these and other pharmaceuticals will be commercially manufactured in mammary "bioreactors" tomorrow. Why? There's at least one major technical hurdle that has to be overcome: The yields in milk are, for the most part, still too low for commercial production. And on the regulatory front, the producers will have to prove that their proteins are not only safe but biologically equivalent to the natural human proteins.

Two of the three teams reporting their results in *Bio/Technology* have made major progress on the yield problem, however. The one closest to commercial production levels includes researchers from Pharmaceutical Proteins, Ltd., in Edinburgh, Scotland, and the Agricultural and Food Research Council's Institute of Animal Physiology and Genetics Research, also in Edinburgh. Using gene transfer technology, they have produced sheep that yield milk containing up to 35 grams per liter of human AAT. According to team leader Alan Colman, that's a good start, but they need to breed more high producers.

The second team, including researchers from Tufts University School of Veterinary Medicine in North Grafton, Massachusetts, and Genzyme Corp. in Cambridge, has also made strides recently, in their case developing transgenic goats carrying the gene for a longer acting form of tissue plasminogen activator. Their best goat produces the clot-buster at the rate of about 3 grams per liter of milk.

The Edinburgh and Genzyme groups didn't get their current high yields overnight, however. Both had to tinker with the gene constructs they use to create their transgenic animals, although they went at this differently. Based on mouse experiments, the Edinburgh group decided to switch from the cDNA construct (a DNA copy of the AAT messenger RNA that lacks the gene's intron sequences) they used at first to a copy of the genomic AAT gene for the current work. "We got a much better level of expression with genomic DNA than with cDNA," says Martyn Breeze of Pharmaceutical Proteins.

The Genzyme group, meanwhile, focused on the promoter sequences that regulate gene

expression, finding that tissue plasminogen activator yields increased 1000-fold when they switched from the promoter from the gene encoding mouse whey acid protein to the promoter from the goat beta-casein gene. Both groups expect that further tinkering will produce the yields they need. "We are now trying to identify the hottest promoter," says Karl Ebert of Tufts.

Gen Pharm International

Big daddy? *Young bull carries the human lactoferrin gene.*

The third group, a collaboration of researchers at GenPharm International, Inc., of Mountain View, California, Gene Pharming Europe BV in Leiden, the Netherlands, the Research Institute for Animal Production in Zeist, the Netherlands, and the University of Leiden, does not yet have secretion of human lactoferrin, the protein they are working on, in milk. Although the researchers have successfully introduced the human lactoferrin gene into dairy cattle, the only animal that acquired the intact gene turned out to be male. The young bull will be bred, however, in the hopes that his daughters will secrete the protein into their milk. Lactoferrin has both iron-transporting and bacteria-fighting capabilities, and might be marketed, says GenPharm president Jonathan MacQuitty, as a supplement to make store-bought infant formulas more like human milk and as an oral treatment for immunocompromised patients, such as people who have AIDS.

But getting high production of the human pharmaceutical proteins in milk may be the easiest of the challenges that the researchers have to surmount. There's also the safety issue. Although producing human proteins in domestic animals avoids the risk of contamination with human pathogens, the animals carry pathogens of their own, and some may have the potential to infect humans. For example, sheep and goats are susceptible to scrapie, a degenerative brain disease, and cows get the bovine equivalent, familiarly known as "mad cow disease." And it will also be necessary to ensure that the purification processes remove any animal proteins that might trigger allergic reactions or other toxic side effects.

In addition, producers of the pharmaceutical proteins will have to prove that their products have the same biological activity as the natural materials. Early indications are good, however. Preliminary work has shown that the proteins made in milk carry carbohydrate side chains, as the natural human proteins do. But for now it's unclear whether the molecules produced by the sheep and goat mammary glands are absolutely identical to the normal human proteins.

Nevertheless, the researchers are confident they can overcome the regulatory as well as the technical obstacles. Indeed, they are already beginning to develop dairy animals that will produce other pharmaceuticals in addition to those mentioned here, although for understandable reasons they are not always willing to say what the others are. For example, the Genzyme group has no plans to market tissue plasminogen activator, which is available from other sources, but simply used that gene to demonstrate the feasibility of their research approach. But when asked what they were really after, Genzyme executive vice president Allan Smith declined to answer.

The Edinburgh group is a bit more forthcoming. It has already made sheep that secrete blood clotting factor IX in their milk, and is also working on clotting factor VIII and erythropoietin. What's more, it might also be possible to create transgenic animals to produce specialized food products, such as low lactose milk for people who can't digest this sugar. With prospects this diverse, the payoff from the work on transgenic dairy animals may be far greater than mere golden eggs. ■ ANNE SIMON MOFFAT

A First Investment in a Kaon Factory

Buy a truckload of lottery tickets, and your chances of holding at least one winner get pretty high. That's the idea behind Canada's KAON project, a particle accelerator designed to create a vast number of subatomic particles in order to detect some of the most revealing but elusive particle decays. The project, to be built at the Tri-University Meson Facility (TRIUMF) near Vancouver, British Columbia, has spent years in bureaucratic limbo. But now Canadian physicists have gained new hope that their $700-million Canadian treasure hunt will take place as planned.

On 19 September, KAON's planners got word of a long-awaited offer of funding from the Canadian government. The offer of $236 million, made over heavy opposition from some Canadian scientists and officials (see box), would cover about a third of the accelerator's cost; funding promised earlier by the government of British Columbia would cover another third. That leaves the project's fate hanging on the outcome of negotiations between the federal and provincial governments to provide the $100 million a year in operating costs—and on the willingness of other countries, including the United States, to kick in the final third of the construction costs.

KAON maker. *Eric Vogt.*

"Now that the Canadian government has given us an offer I'm sure we'll be able to get together the funding to go ahead with the project," says KAON director Eric Vogt. If Vogt is right, KAON could be up and running in about 6 years. It won't set any records for collision energies: At 30 billion electron volts, KAON will pale next to the most powerful existing accelerators—not to mention the Superconducting Super Collider, which will achieve several trillion electron volts. But Vogt explains that KAON will make up for low energy with high intensity—an ability to accelerate and collide vast numbers of particles. The result will be the world's biggest supply of K-mesons, or kaons: particles consisting of a strange quark bound to an anti-up or anti-down quark (or an anti-strange and an up or down). Kaons decay in about 50 ways, and some of the rarest decays promise to shed new light on the very existence of matter.

The KAON design, which piggybacks a new accelerator ring on TRIUMF's existing cyclotron, should produce kaons about 100 times faster than existing machines, says project scientist Ian Thorson. The key will be to squeeze an unprecedented density of protons into the accelerator's beam—a feat that takes a lot of