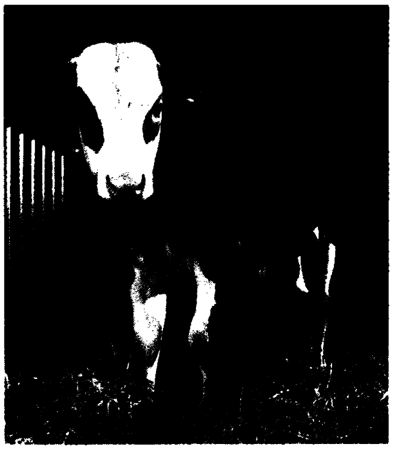
expression, finding that tissue plasminogen activator yields increased 1000-fold when they switched from the promoter from the gene encoding mouse whey acid protein to the promoter from the goat beta-casein gene. Both groups expect that further tinkering will produce the yields they need. "We are now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

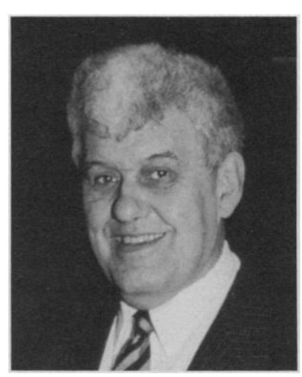
The Edinburgh group is a bit more forthcoming. It has already made sheep that secrete blood clotting factor IX in their milk, and is also working on clotting factor VIII and erythropoietin. What's more, it might also be possible to create transgenic animals to produce specialized food products, such 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 careful engineering, he says, since the charged particles repel each other. When the dense proton beam, accelerated to nearly the speed of light, collides with a fixed target, it will produce a huge yield of kaons—enough to make the rarest types of decays likely.

These rare decays promise insight into a fundamental physical loophole: a violation in what is known as charge-parity (CP) symmetry. According to CP symmetry, changing every particle in the universe to its antiparticle and reversing each one's parity—a process physicists often compare to reflecting everything in a mirror—results in an indistinguishable universe. Though it all sounds pretty, CP symmetry would have tragic results if it were inviolate. With each type of particle matched by an equal quantity of the oppositely charged anti-particle, matter and antimatter would annihilate each other as fast as they came into existence. So some sort of fortuitous violation in the symmetry must have tilted the balance toward an excess of matter.

Such a violation was actually detected in 1964—well before physicists had focused on the cosmological importance of CP violation. In the products of one particular kaon decay, Princeton physicists Val Fitch and James Cronin found evidence that something was amiss. The parent particle and its decay products differed in their total CP—a quantity that takes into account both parity and the proportions of matter and antimatter. To the physicists, the implication was clear: a tiny violation of CP symmetry had occurred.

Current theory predicts some other CP violations, but it also says they should occur only extremely rarely. As University of Chicago theorist Yau Wah explains: "We've already seen the basic CP violating event—that's old. To learn more we want to look at rarer CP violating decays." The problem? "These happen a million times less frequently," he says.

Which is why many physicists are rooting for KAON. An investigation of these rare decays, besides helping clarify the nature of CP asymmetry and hence the existence of matter, might also open a wider window on fundamental physics, they say. For example, new forms of CP violation might point out a way to improve the particle physicists' "standard model"—the contemporary picture of particles and the forces that govern them. The CP violation observed by Fitch and Cronin can be explained within the standard model, but theorists have predicted possible CP violating decays that, if seen, would contradict it.

But why fund KAON, ask skeptics, when other accelerators, existing or planned, could do the same type of research? CP violation would also be the target of the "B factories"—special-purpose accelerators analogous to KAON but specializing in a related particle called the B-meson—that Stanford and Cornell are now eager to build (see *Science*, 22 March, p. 1416). And some U.S. physicists think existing accelerators, like Fermilab's Tevatron, could, with a little work, serve as productive kaon factories. "We could do better kaon physics here at Fermilab," says physicist Edward Kolb. Such sentiments make it clear that KAON will face tough scrutiny as the Canadians come south in search of the funds they still need.

Others disagree. Donald Lazarus of Brookhaven National Laboratory (BNL) argues that while existing machines can be retrofitted to make kaons, the Canadian project will do it better. "You can do that kind of thing here at BNL, but you will probably get more kaons from KAON." As for B-factories, most physicists interested in CP violation want both kinds of machines. "For the last 25 years we've been looking left and right and haven't found any new information," says Wah. "Any new evidence will be a great help." ■ FAYE FLAM

Some Would KO KAON

Canadian physicists hail it for the unique science it promises. World class physicists outside Canada—including U.S. presidential science adviser D. Allan Bromley (who is a Canadian by birth)—give it ringing endorsements. But KAON, the project to expand the Tri-University Meson Facility in Vancouver, British Columbia, into a high-intensity factory of the subatomic particles called kaons (see main story) is deeply upsetting to many Canadian scientists from other disciplines and some members of the federal government. Aghast at the $709-million price tag and annual operating costs of $100 million, which make it Canada's most expensive science project ever, they fear KAON will starve the rest of Canadian science. All reacted with dismay to the government's announcement last week that it would underwrite a third of the accelerator's costs.

"This is not a wise use of limited science and technology resources at this time," said Janet Halliwell, chairman of the Science Council of Canada, an arm's-length advisory body. Her reaction echoes statements made before the announcement by several scientific organizations, including the big science subcommittee of the prime minister's own National Advisory Board on Science and Technology, which had rejected KAON in favor of other science priorities.

Federal minister of science William Winegard denies that funding for KAON is bad news for the rest of Canadian science. "This is a fixed and capped offer," he insists, with no provisions for inflation or cost overruns. He also stresses that the federal offer represents new money; it will not drain existing science and technology budgets. "We didn't want people to get the impression, in making an offer on KAON, that suddenly subatomic physics becomes the number one priority for Canada," he told *Science*. "The cabinet recognizes that there are other science and technology priorities on the table, and that those will be looked at."

KAON opponents don't buy this, viewing the decision as a victory of politics over science. Much of the pressure for funding came from the government of British Columbia, which has been touting KAON as a tool for economic development and has even offered to pay part of its costs. Indeed, some critics have construed the timing of the announcement—hours before a provincial election was called in British Columbia—as political opportunism, a move on the part of federal Conservatives to boost the fortunes of the ideologically related British Columbia Social Credit party, which has been trailing in the polls. Winegard dismisses such charges, saying the announcement was made because "there was just too much speculation going around."

All this has emitted an odor of pork-barrel politics. And that, in turn, has led to questions about how future big science projects should be decided in Canada. Halliwell notes that while decisions about large projects such as KAON will always be political, the process "could be opened up more, as in the United States. If [the approval of KAON] represents a turning point for science and technology in this country, we should applaud, but it begs serious questions about the role of the national advisory board on science and technology." ■ DOUGLAS POWELL

Douglas Powell works at the Information Technology Research Centre at the University of Waterloo, in Canada.