Research Update

Breakthrough in understanding bone breakdown

Researchers in Toronto and California have pinpointed a gene that regulates bone deterioration as well as the creation of lymphocytes and lymph nodes. The finding has stunning ramifications for treating osteoporosis and osteoarthritis as well as for understanding the immune system (*Nature* 1999;397:315-23).

"Heads are spinning — mine, for instance," says Dr. Josef Penninger of the Ontario Cancer Institute who, with colleagues Drs. Young-Yun Kong in Toronto and Bill Boyle of AMGEN Research Institute in California, showed the critical role played by osteoprotegerin ligand (OPGL).

"It is *the* central regulator," explains Penninger. Intriguing earlier research by Boyle had shown that OPGL regulated the differentiation and activation of osteoclasts — the cells that eat away at bones (*Cell* 1998;93:165-76). In normal bone development, the activity of osteoclasts is balanced by bone growth and by receptors that keep osteoclasts from running amok. However, if OPGL is mutated, osteoclasts eat at the bones aggressively "and you end up with osteoporosis or osteoarthritis," explains Penninger. Earlier research had also found that mice lacking osteoprotegerin had early-onset osteoporosis and arterial calcification (*Genes Dev* 1998;12:1260-8).

Penninger and colleagues took this research to the next level by creating genetically engineered mice completely lacking the gene needed to create OPGL. The mice appeared normal until 3 weeks of age, when they began to be severely stunted because of underdeveloped bones, bone deterioration and altered bone structure. They also lacked teeth. Surprisingly, they had no lymph nodes, and differentiation of T and B lymphocytes was defective. This was proof positive that OPGL is vital to regulating bone growth and developing the immune system.

"Until now, nobody knew what was the real trigger. There was a hint from Bill Boyle's work that it might be OPGL, but many other factors had also been implicated. Our paper showed that OPGL is the real thing."

The road from this discovery to a treatment for osteoporosis and osteoarthritis may be short. An exciting development is a "decoy receptor" for OPGL that keeps it from activating the osteoclasts that break down bone. "It makes sense to treat the central mechanism" rather than the symptoms, says Penninger. Scientists at AMGEN have tested the decoy receptor in mice that have a condition mimicking human postmenopausal osteoporosis. "When you give the mouse this decoy receptor, within a week it is completely healthy. We have a drug in our hands that completely abolishes the osteoporotic process. If it works in humans, the possibilities are endless."

He points out that the treatment would be effective in osteoporosis caused by aging, by a drop in estrogen or androgen levels, or by long-term use of steroids (as in many people with asthma). Phase I human trials of the decoy receptor have been completed, but Penninger cautions that its safety must be established before it is widely available.

In the meantime, it is still important for patients to take plenty of calcium. "Many factors, including estrogen and vitamins, are feeding into the system," Penninger says. "It's clear that calcium needs to be around for this system to work." — *C.J. Brown*

Cesarean section prevents HIV transmission

The risk of babies being infected by their HIV-positive mothers is cut in half by cesarean-section delivery, according to data from 15 prospective studies contained in an article to be published in the *New England Journal of Medicine*. It was released early on the Internet. If the mother has received zidovudine during pregnancy as well, the rate of infection in infants is only 2%. It is believed that infants are infected during vaginal delivery as a result of transfusion of blood during contractions, rupture of membranes or contact with secretions or blood in the mother's genital tract.

Certain antibiotics cut risk of heart attacks

Patients having a first heart attack are much less likely than matched controls to have taken tetracycline or quinolone antibiotics, providing evidence that a bacterial infection underlies many heart attacks (*JAMA* 1999;281:427-31). There was a 30% lower risk of heart attack in people who had taken tetracycline and a 55% lower risk in people who had taken quinolones such as ciprofloxacin, norfloxacin, ofloxacin or nalidixic acid. Other antibiotics had no effect. Given the size of the study — more than 3000 patients who had had a heart attack and more than 13 000 controls — there is a significant association between heart attack and lack of antibiotic treatment. There is a growing body of research showing that atherosclerosis is caused by bacterial infection, particularly with *Chlamydia pneumoniae*. The authors and an editorialist caution that, at this point, the data are too preliminary to justify prescribing antibiotics to prevent heart attack.