Research Update

Gene defect driving diabetes epidemic on Ontario reserve

Canadian researchers have discovered a gene mutation in aboriginal people living on a reserve in Northern Ontario that has catapulted the community's rate of non-insulin-dependent diabetes to the third highest in the world (*J Clin Endocrinol Metab* 1999;84:1077-82).

Using DNA sequence analysis, a team of scientists led by geneticist Dr. Robert Hegele identified a genetic mutation in residents of the Sandy Lake reserve that causes carriers' bodies to horde calories — a sure recipe for diabetes given the population's fat-rich diet and sedentary lifestyle. Nearly half of all Sandy Lake's Oji-Cree people with diabetes have the defective gene.

The adaptation was beneficial in the past, enabling this nomadic people to survive lean times between successful hunts, says Hegele, of the University of Western Ontario's John P. Robarts Research Institute. "In earlier days, there was a definite survival benefit to this mechanism. But now you have a metabolism functioning at peak efficiency, storing excess calories as fat, and the resulting obesity is leading to complications like high blood pressure and diabetes." Eighty years ago, there was no diabetes among the Oji-Cree people, he adds.

The study found that individuals who inherited one copy of the "thrifty gene" from their parents are more than twice as likely to have diabetes as those who did not inherit the mutation. Oji-Cree people with 2 copies of the defective gene are up to 15 times more likely to have diabetes. Researchers also discovered that the mutation brings on diabetes at an earlier age. In Sandy Lake residents with 2 copies of the mutation, diabetes developed before age 30; in those with a single copy, the disease developed by age 40. Researchers did not find the gene in any other major ethnic group in Canada.

Researchers don't yet fully understand how the faulty gene functions at the cellular level, says Hegele, but these findings offer hope that preventive and even possibly corrective measures can be developed. For example, providing intensive diet and exercise counselling to children and young adults without diabetes could lower their risk of the disease later in life. "Now that we know the pathway that's involved, we may at some point be able to prescribe exercise, or develop new drugs effective in high-risk individuals." — © *Greg Basky*, Saskatoon

Longer warfarin treatment cuts risk of repeat clots

Patients who have a first episode of venous thromboembolism should be treated with warfarin for longer than 3 months, according to newly published Canadian research (*N Engl J Med* 1999;340:901-7).

In a double-blind, randomized study involving 162 patients, Dr. Clive Kearon, associate professor of medicine at McMaster University in Hamilton, Ont., and colleagues, found that extending anticoagulant therapy reduced the risk of recurring blood clots by 95%.

Only one of 79 patients (1.3% per patient-year) receiving warfarin had a second episode of idiopathic venous thromboembolism, whereas 17 of 83 (27.4% per patient-year) patients receiving a placebo had a recurrent event. Two of the patients receiving warfarin experienced gastrointestinal bleeding, while a third had genitourinary bleeding. The anticoagulant was delivered at an international normalized ratio of 2.0 to 3.0.

"We found warfarin was very effective in those patients who stayed on it for longer than 3 months," says Kearon. "It essentially eliminated recurrence. The benefits from extending therapy outweighed the risks of bleeds."

While the research team had originally planned to continue the study for 24 months, an interim review of the data at 10 months revealed such striking benefits of extended warfarin therapy that the scientists concluded it would be unethical not to offer lengthened treatment to subsequent patients with thrombosis. Kearon's work builds on several large studies published within the last 5 to 6 years looking at shorter durations of warfarin for patients with a first episode of venous thromboembolism.

The researchers have extended their study follow-up to look at outcomes after 24 months. "The question we need to answer now is: How much longer than 3 months is optimal?" says Kearon. "We showed that patients are better off receiving warfarin for longer than 3 months, but we're still not sure whether that's still the case at 6, 12, or even 24 months. Is 2 years long enough, or too long?" Kearon and his colleagues are also investigating whether warfarin dosages can be reduced after the initial 3 months.

In an accompanying editorial, Dr. Andrew Schafer of the Baylor College of Medicine in Houston, writes that the study "continues the shift in our approach to preventing recurrent venous thromboembolism by treating the condition as a chronic disease." — © *Greg Basky*, Saskatoon