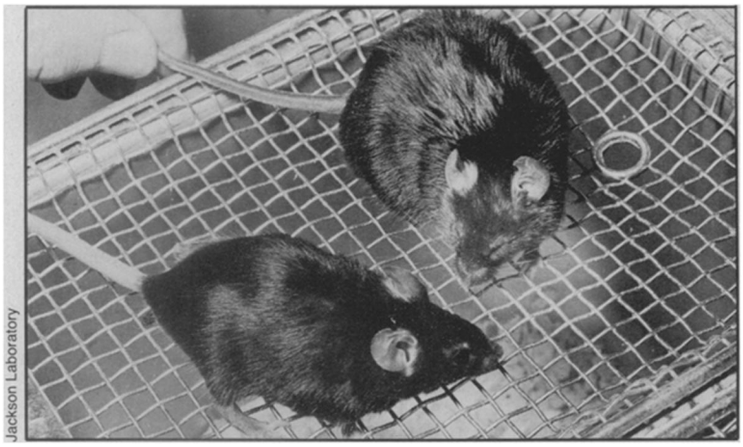
Diabetes theory: Frugal genes



Jackson Laboratory

Diabetes genes may help animals survive periods of food shortage. The mouse mutant named diabetes (top), shown with its normal littermate, can survive a 30-day fast.

Thrift in affluent conditions can lead to disaster, according to the "thrifty gene" model of diabetes. James V. Neel of the University of Michigan proposed in 1962 that people with particular genes, which allow them to more efficiently use a limited food supply, suffer from diabetes in a food-abundant society. He proposed that more efficient food use could lead to high levels of blood sugar, stressing the pancreas's capacity to make sufficient insulin. Primitive tribes all over the world have a low detectable incidence of diabetes, but when those people move into conditions of more and better food, 10 to 20 percent develop diabetes.

Interactions of numerous "thrifty" genes in human populations make a direct test of the hypothesis difficult. But Douglas L. Coleman of Jackson Laboratory in Bar Harbor, Maine, now reports supporting evidence from experiments on extremely obese mice. Several strains of mutant mice, whose deficiency seems to be that they don't know when to stop eating, show characteristics resembling maturity-onset diabetes. The mice have high sugar levels in their blood and urine and high blood insulin levels. Insulin producing cells in the pancreas deteriorate, and the mutant mice die by the age of eight months (normal mice live as long as three years).

Coleman finds that the mutant mice, one strain with a gene called "diabetes" and the other "obese," have a remarkable ability to withstand a fast. They can survive without food for up to 40 days (normal mice can survive only 7 to 10 days of fasting). But is that starvation resistance due to the diabetes and obesity genes or simply to the mutant mouse's excessive stores of fat? To explore that question, Coleman examined heterozygous mice, having one normal gene and one mutant gene for diabetes (or obese). These mice are identical in body weight and insulin and sugar levels to mice with both genes normal.

The heterozygous mice, with normal body composition, still survive a prolonged fast significantly longer than genetically normal mice, Coleman reports in the Feb. 16 SCIENCE. However, the survival increment is just 2 to 3 days. "This suggests that the heterozygotes exhibited increased metabolic efficiency, a feature normally associated with both homozygous mutants," he says. "The heterozygote is doing something a little better than normal."

Coleman has preliminary evidence that one thing the mutant does better is to use up its fat during a fast. The mutant mice seem to consume their large reserves of fat completely, while the normal mouse doesn't deplete all of its smaller fat deposit before it dies.

Coleman concludes, "Beneficial effects of normally deleterious genes may have played a role in the development of diabetes-susceptible human populations, as well as having provided the survival advantage that has allowed both the development and successful establishment of species in desert and other less affluent regions." The genes' persistence in human populations may be due partly to the heterozygotes' improved ability to survive scarcity without sacrificing their capacity to thrive on plenty. □

Clear advance in acne therapy

A spin-off of the war against cancer may be a cure for acne, and that's not trivial, say dermatologists. A small percentage of acne patients with severe and extensive disease show little response to current therapies, including antibiotics, hormones and X-rays. Now a group of eight National Cancer Institute and University of Iowa dermatologists report in the Feb. 15 NEW ENGLAND JOURNAL OF MEDICINE that a synthetic analog of vitamin A shows a remarkable therapeutic effect on such acne patients.

The experimental treatment uses 13-*cis*-retinoic acid, a chemical developed by Hoffmann-La Roche, Inc., and being tested as a cancer-preventing agent. Because other vitamin A derivatives have been used to treat acne the dermatologists, led by Gary L. Peck, examined its effect on 14 patients with scarring, antibiotic-resistant, cystic and conglobate acne. Thirteen patients were completely cleared of acne and the other showed a 75 percent improvement. Even 20 months after the end of the four-month treatment, the acne had not recurred. More recently the treatment cleared the skins of most of a larger and even more severely affected group of patients.

Long-term trials are now necessary before the compound will be routinely prescribed. The investigators estimate those will take about three years. However, in the preliminary studies the only widespread side effects were skin drying and redness, and those symptoms stopped when the treatment was discontinued. "We await with interest the necessary extension of these preliminary observations to larger-scale studies," says Peter E. Pochi of University Hospital in Boston in an editorial in the NEW ENGLAND JOURNAL OF MEDICINE.

The treatment seems to work by inhibiting the secretions of the sebaceous glands that are associated with hair follicles. With the sebum production decreased by as much as 90 percent, the composition of lipids on the patients' skin surfaces was similar to that of children. No other drug has inhibited sebum production enough to alter the skin-surface lipid composition.

A particularly attractive finding was that the therapeutic response in several patients continued after they had stopped taking the drug. Two months after the four-month treatment, the number of skin lesions was still decreasing. The investigators suggest that either the drug is stored in the sebaceous glands or that its effects are long lasting.

Areas of special concern for side effects are organs such as the eye where vitamin A is required for normal function and organs affected by an overdose of the vitamin. Since vitamin A causes fetal abnormalities in animal studies, the dermatologists advise that all women who receive the acne treatment should take contraceptive precautions.

The NCI study did not include patients receiving a placebo. However, both the researchers and Pochi agree that a placebo effect is unlikely because the patients had suffered from acne, on the average, for ten years, because they had not responded to any other treatment, and because the change measured in the skin-surface lipids is unlikely to be a placebo effect. Comparing 13-*cis*-retinoic acid to treatments such as estrogens and X-rays, the researchers suggest they have discovered a potentially safer agent that could fill a void in the therapy for severe forms of acne. □