Leptin linked to onset of monthly cycles

Nature seems loath to let women procreate if they are too lean. Some women who maintain harsh exercise regimens have seen their monthly cycles disrupted, and studies of African women with low-protein, low-calorie diets have shown menarche, the onset of the first menstrual cycle, delayed by several years.

Abundant nutrition yields the opposite effect. Industrialized countries have witnessed a trend toward earlier menarche in recent centuries, generally attributed to greater food consumption. Menstrual cycles, which usually started at age 18 in the 1600s, now start on average at age 12 in the United States.

In the early 1970s, Harvard University reproductive biologist Rose E. Frisch proposed that girls must attain adequate fat reserves to become reproductive members of society. She hypothesized that "a minimum level of stored, easily mobilized energy is necessary for ovulation and menstrual cycles."

Researchers have now found evidence that the hormone leptin acts as a biochemical trigger for the Frisch hypothesis.

Fat cells secrete leptin, which tells the brain how much fat the body has in storage and thus regulates appetite. The hormone has another role, however. By injecting leptin into young female mice, researchers have triggered early sexual maturation (SN: 1/25/97, p. 58).

Leptin may also be central to menarche in humans, a 4-year study now finds. In 1992, researchers at Ohio State University in Columbus started recording the biological history of 343 girls, age 8 to 13, who had not had their first menstrual cycle. The study confirmed the connection between fat and reproductive readiness. Each additional kilogram of body fat hastened menarche by an average of 13 days.

Once leptin was identified in 1994, the researchers were able to measure concentrations of the hormone in blood samples taken throughout the study. Girls with more body fat had more leptin, the group reports in the October JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM. On average, girls with low leptin concentrations reached puberty last—or not at all in the study's time span.

The evidence supports Frisch's idea that fertility "requires a certain degree of obesity," says Velimir Matkovic, a study coauthor and internist at the university's Davis Medical Research Center.

The Ohio team recorded the girls' height, weight, body fat, and leptin concentrations at 6-month intervals. The girls noted when their first period started. Leptin concentrations lower than 12.2 nanograms per milliliter of blood correlated with later menarche, but at higher concentrations no correlation emerged. This suggests that girls need to exceed a leptin threshold for menarche, Matkovic says.

Although Matkovic suspects that leptin plays a similar role in boys, the correlation might prove more difficult to establish because the onset of puberty in boys is less obvious, he says.

"I'm very pleased about these leptin findings," Frisch says. Low concentrations of leptin instruct the brain to withhold the release of hormones that bring on sexual maturation until the body is ready, or to halt fertility when a woman is unable to handle pregnancy, she says.

Leptin may prove to be more of a gatekeeper for this process than a cause, says Robert A. Steiner, a physiologist at the University of Washington in Seattle. His studies of rats show that females fed only 80 percent of a normal diet still reached sexual maturation at the normal time if given leptin. In females fed only 70 percent of a normal diet, the leptin didn't compensate fully; some matured late anyway. *—N. Seppa*

It came from Earth: Green-blooded fish

Green-blooded visitors from outer space have long been a staple of science fiction films, TV shows, and books. With the aid of genetic engineering and blue light, scientists have now bestowed that alien hue upon the blood of a more down-to-earth creature, the zebrafish.

The researchers took the gene for green fluorescent protein (GFP), a glowing molecule used by jellyfish, and inserted it into single-celled zebrafish embryos. Moreover, by adding to the gene a short stretch of regulatory DNA, they engineered the gene so that it turns on only in red blood cells.

"This is the first vertebrate animal that has tissue-specific expression of GFP," says Shuo Lin of the Medical College of Georgia in Augusta. In the Oct. 15 DEVELOPMENT, Lin and his colleagues describe the GFP-endowed zebrafish, whose blood cells glow green when exposed to blue light.

One payoff of this trick is that it lets the scientists see readily when and where red blood cells arise in the transparent zebrafish embryos. Confirming work by other researchers, they found that blood cell production occurs in the heart during early development but shifts to the zebrafish kidney towards adulthood.

"As early as 12 hours postfertilization, we're able to see where the blood progenitors come from," says Lin. "We can purify those cells as soon as they show up."

By studying the young cells, the investigators hope to identify the genes used in making a mature red blood cell.

The researchers' plans aren't limited to blood: "We've made fish that have green neurons," notes Lin.

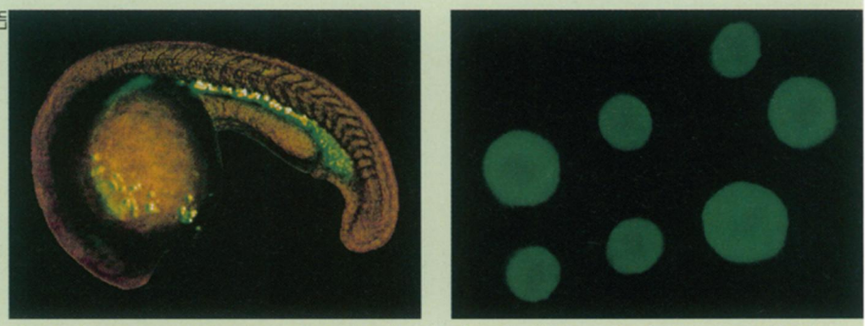
These glowing cells may help scientists understand how nerve cells form connections within the developing brain, he says.

Zebrafish have recently become the catch of the day for scientists studying the development of vertebrates. Last year, scientists published descriptions of hundreds of mutant zebrafish (SN: 12/7/96, p. 360); they are now searching for the genes responsible. By highlighting specific cell populations with GFP, investigators may spot even more subtle mutations, says Lin.

Beyond its effective use of GFP, Lin's work marks the first demonstration that scientists can permanently add functioning genes to the zebrafish, notes Mark C. Fishman of Massachusetts General Hospital in Boston.

While scientists had previously inserted working genes into zebrafish, the genes never remained active in future generations, he explains. In contrast, Lin's original green-blooded fish are already grandparents of fish whose blood also glows. *—J. Travis*

Lin



Green fluorescent protein makes blood cells glow inside a zebrafish embryo (left) and by themselves (right).