Awakened Gene Aids Inherited Anemias

One could think of it as the "Sleeping Beauty" therapy for two inherited blood disorders.

Like a biochemical Prince Charming, a common food additive can awaken a sleeping gene that then ameliorates the symptoms of sickle cell anemia and beta-thalassemia, a new report suggests. Although tested on only a small number of patients so far, the substance may one day offer a lifelong treatment for the two devastating anemias.

The food additive, a flavor enhancer called butyrate, works by switching on the gene responsible for making the fetal form of hemoglobin – the protein inside red blood cells that ferries inhaled oxygen from the lungs to distant tissues. During embryonic development, organisms as diverse as humans, monkeys, and cows make lots of fetal hemoglobin – which has an enhanced affinity for oxygen – in order to draw sufficient quantities of the gas from their mothers' bloodstreams through the placenta.

The fetal hemoglobin gene usually slacks off within the first six months of life, and individuals switch over to making the adult form of hemoglobin. However, people with sickle cell anemia and beta-thalassemia have genetic defects in their adult hemoglobin gene. In sickle cell anemia, the faulty gene makes a sticky protein that causes red blood cells to warp and twist into the shape of sickle blades, causing them to lodge painfully in small blood vessels. In beta-thalassemia, the same gene may not function at all, leading to sparse, pale, short-lived red blood cells.

In the 1970s, physicians noticed that some adult Saudi Arabian and Indian patients with sickle cell anemia developed only mild symptoms because they had somehow continued to make high amounts of fetal hemoglobin, which prevented their red blood cells from sickling. In 1985, researchers led by pediatric hematologist Susan P. Perrine of Children's Hospital Oakland (Calif.) Research Institute discovered that the infants of diabetic mothers delayed their switch to adult hemoglobin because of their exposure to elevated concentrations of aminobutyric acid, a chemical compound related to butyrate, in their mothers' blood.

To capitalize on the link between the two findings, Perrine and her colleagues gave three sickle cell anemia patients and three beta-thalassemia patients daily infusions of a butyrate solution for either two or three weeks. In the Jan. 14 NEW ENGLAND JOURNAL OF MEDICINE, they report that the treatment boosted the patients' production of fetal hemoglobin by up to 45 percent, with few side effects.

Moreover, one of the beta-thalassemia patients experienced "complete reversal" of her disease, according to hematologist Douglas V. Faller of Boston University School of Medicine, one of the researchers who conducted the study. "Looking at her blood, you would not know that she had thalassemia," he says. He and his colleagues have just begun clinical tests of an oral form of their butyrate drug.

In a second report in the same journal, Griffin P. Rodgers of the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Md., and his colleagues report that a combination of the anticancer drug hydroxyurea and the red blood cell growth factor erythropoietin increased the fetal hemoglobin concentrations in four patients with either sickle cell anemia or beta-thalassemia.

Hydroxyurea blocks DNA replication, indirectly causing a buildup of fetal hemoglobin. However, the drug has serious side effects and may cause chromosome damage.

Nevertheless, hematologist H. Franklin Bunn of Brigham and Women's Hospital in Boston expresses guarded optimism about the prospects of butyrate and hydroxyurea. "It seems likely that such agents, either alone or in combination, will eventually lead to safe and effective treatment for two of our best-understood, yet most challenging genetic disorders," he writes in an editorial accompanying the new reports. However, he cautions that physicians must first test the efficacy of the potential therapies in many more patients. *– C. Ezzell*

Hazy summer days boost respiratory ailments

The number of people hospitalized for various respiratory ailments in New York State's largest urban centers increases significantly on days when summer's skyscraper-obscuring haze of air pollution hangs thickest, a new study finds.

Public health researchers have attempted to show links between air pollution and hospital admissions for various respiratory problems, especially asthma attacks (SN: 5/6/89, p.277; 4/6/91, p.212). A 1987 study conducted in Ontario, Canada, for example, indirectly linked concentrations of acid aerosols – fine, caustic droplets that form from gases emitted by coal-fired electric power plants and other industrial sources – with the incidence of respiratory illnesses.

In the new study, George D. Thurston of the New York University Medical Center's Department of Environmental Medicine in Tuxedo, N.Y., and his colleagues measured acid aerosols *directly* for the first time, then associated this form of air pollution with hospital admissions for a variety of respiratory illnesses.

Examining a population twice as large as the one covered in the Ontario study, Thurston explains, the researchers gathered statistics on people with acute respiratory complaints admitted to 139 hospitals in New York City, Albany, and the Buffalo-Rochester area during the summer months of 1988 and 1989. These patients suffered from asthma attacks, bronchitis, pneumonia, and other acute conditions. For the same period, the researchers tracked daily concentrations of acid aerosols and ground-level ozone, which originates chiefly from automobile emissions.

Thurston's team discovered a statistical correlation between acute respiratory problems and increased concentrations of pollutants in the summer haze that blankets New York's urban centers each year. On the worst ozone days, for example, admissions for asthma increased 23 percent in New York City and 29 percent in Buffalo, the researchers report in the just-released October-December JOURNAL OF EXPOSURE ANALYSIS AND ENVIRONMENTAL EPIDEMIOLOGY.

The study also suggests that acid aerosols worsen the effects of ozone on the sensitive tissues lining the airways. Although this relationship needs further investigation, "it makes sense that if you have acid around, it's going to irritate the lung lining and open it up to ozone's effects," Thurston explains.

The researchers also found that residents of urban centers suffer more often from air pollution's ill effects than people who live in suburbs, despite nearly identical exposures to ozone and acid aerosols. Since inner-city areas have the highest percentage of New York's disadvantaged population, poor nutrition or inadequate health care may play a role in these disparities, the report suggests.

Environmental epidemiologist Douglas W. Dockery of the Harvard School of Public Health in Boston cautions that the statistical links in Thurston's study are not strong enough to prove definitively that such pollutants trigger asthma attacks or cause other respiratory conditions. "But this study is important because it's one of the first to have direct measurement of acid aerosols, and there's been a lot of laboratory work suggesting that acid aerosols might be the most important air pollutant in the summer haze," he says. *– D. Pendick*