Biology

John Travis reports from San Francisco at the American Society of Human Genetics meeting

Trading mouse blood for human blood

In a research effort that one admiring scientist calls a "tour de force," a California team has genetically engineered mice to have sickle-cell anemia. This debilitating, often deadly human blood disorder results from a mutation in beta-globin, a protein subunit of hemoglobin, the oxygen-carrying molecule of red blood cells. Blood cells with the mutant protein have trouble holding oxygen and develop a sickle shape.

Scientists had previously added the human genes for mutant beta-globin and for normal alpha-globin, the other hemoglobin subunit, to mice. The animals' own globins, however, prevented the resulting blood cells from sickling.

In the new effort, Chris Pászty of the Lawrence Berkeley (Calif.) National Laboratory and his colleagues created mice that had the human beta-globin and alpha-globin genes and deactivated mouse globin genes. The mice also had the human gamma-globin gene, used to make hemoglobin during fetal development. "The goal was to create a mouse that generates only human hemoglobin," says Pászty.

The researchers found that mice thrive with normal human hemoglobin. More important, mice with the sickle-cell mutation in their added human beta-globin gene experienced anemia, liver and kidney damage, and enlarged spleens. "The mice are developing the classic multiorgan pathology of sickle-cell disease," says Pászty, who adds that the mice should be useful in testing potential new therapies.

Pitching in to find a musical gene

Among the musical elite are those with perfect pitch, the ability to identify, play, or sing a specific musical note without hearing a reference note. Hit a random piano key, and such people can instantly tell whether it was a C-sharp or a B-flat. They can even identify the pitch, or frequency, of nonmusical sounds. Musical training seems to be a key factor in whether or not a child develops perfect pitch. Not surprisingly, then, this rare talent is much more common among musicians than people in other professions.

Now, two research groups, working independently of each other, have observed that perfect pitch also runs in the family. The finding suggests that a specific gene, perhaps one involved in hearing, endows people with the ability to develop perfect pitch.

The first study was conducted by Peter K. Gregersen and Mariza de Andrade of the North Shore University Hospital in Manhasset, N.Y. "I've always been musical and wondered about what caused perfect pitch," notes Gregerson. The pair surveyed 126 people who said they have perfect pitch; 5.5 percent reported that their parents have perfect pitch, and 26 percent said they have siblings with the skill. In contrast, musicians without perfect pitch reported only 1.1 percent of parents and 1.3 percent of siblings with the talent.

A similar study was done by researchers from the University of California, San Francisco. Siamak Baharloo, who led the effort, and his coworkers surveyed more than 600 musicians and found that 40 percent of those with perfect pitch claimed to have a relative with the talent. Only 12 percent of those without perfect pitch said they had a family member with the ability.

Both groups stress that their surveys also confirm the importance of early musical training in developing perfect pitch. The researchers intend to collect DNA from families with perfect pitch and search for the musical gene hinted at by their work.

Cell suicide gets out of control

One of the hottest topics in biology is apoptosis, the phenomenon in which a cell kills itself through a series of carefully choreographed actions (SN: 11/21/92, p. 344; 1/15/94, p. 44). Often referred to as cellular suicide, apoptosis is a widely used natural mechanism that organisms employ to eliminate damaged, aged, or unneeded cells.

Several diseases may result from apoptosis gone awry. Autoimmune lymphoproliferative syndrome, a disorder marked by rashes, enlarged lymph nodes, and sometimes kidney damage, apparently stems from immune cells that persist too long after they have fought off an infection. Normally, "when the war is over, it's time for the troops to disarm and go away," says Jennifer M. Puck of the National Center for Human Genome Research in Bethesda, Md.

Puck and her colleagues have examined eight children with the autoimmune disorder and found that all possess mutations in the *Fas* gene. *Fas* codes for a cell surface protein that enables cells to receive specific commands to undergo apoptosis. The mutations in *Fas* apparently prevent unneeded immune cells from properly receiving this suicide signal, thereby triggering the autoimmune disease, says Puck.

Apoptosis may also play a role in amyotrophic lateral sclerosis (ALS), the neurodegenerative disorder better known as Lou Gehrig's disease. In 1993, researchers found that an inherited form of ALS results from mutations in an enzyme called superoxide dismutase (SN: 3/6/93, p. 148). The enzyme seems to protect cells from damage by reactive molecules called free radicals. Dale E. Bredesen of the Burnham Institute in La Jolla, Calif., and his colleagues now find that the mutant forms of superoxide dismutase trigger nerve cells to commit suicide. The normal enzyme protects cells from apoptosis, says Bredesen.

Apoptosis is a suspect in other neurodegenerative diseases as well, including Alzheimer's and Huntington's diseases. Scientists have just discovered, for example, that an enzyme involved in apoptosis interacts with huntingtin, the protein that causes Huntington's disease. That apoptosis enzyme, apopain, cleaves disease-causing forms of huntingtin much more efficiently than normal forms, reports a research group headed by Michael Hayden of the University of British Columbia in Vancouver. The change may cause the abnormal brain cell death seen in the disease, the investigators speculate.

A surprising eyeful of chromosomes

Sometimes a simple mistake can lead to a whole new line of scientific inquiry. "Somebody accidentally sent a bit of cornea to our laboratory and didn't tell us what it was," recalls Mark J. Pettenati, a medical geneticist at Wake Forest University's Bowman Gray School of Medicine in Winston-Salem, N.C. Physicians frequently ask Pettenati and his colleagues to analyze tissue samples, often from tumors, so they went ahead and examined the mystery specimen.

Its cells had extra copies of some chromosomes and were missing copies of others. This condition, known as aneuploidy, is rare in normal cells but relatively common among tumor cells. One small problem: The ophthalmologist who accidentally sent the sample to Pettenati's group told the researchers that it didn't come from a cancerous cornea.

Their curiosity piqued, Pettenati and his colleagues decided to analyze the chromosomes of other corneas. To their astonishment, they've found so far that all human fetal corneas are perfectly normal but that more than 75 percent of normal adult corneas suffer aneuploidy. "This is the first report that human corneas have acquired chromosomal abnormalities," says Pettenati.

Why are adult corneas afflicted? Pettenati speculates that corneal cells may duplicate or discard chromosomes to increase or decrease the activity of certain genes crucial to the cornea's function.

P. Nagesh Rao, who works with Pettenati, emphasizes that they're open to other hypotheses. "If you have an idea, let us know. We'll put you down as a collaborator," he laughs.