New Drug Thwarts a Chronic Leukemia

In 1960, two Philadelphia-based researchers, Peter C. Nowell and David A. Hungerford, found an odd chromosome lurking in the cancer cells of people with chronic myelogenous leukemia. It was the first genetic abnormality ever linked to a specific cancer (SN: 11/26/60, p. 341).

Scientists have continued to hammer away at the so-called Philadelphia chromosome, a shortened chromosome 22. They now know that it results when chromosomes 9 and 22 exchange genetic material. This translocation fuses two genes that shouldn't be together. The combination encodes a rogue enzyme that spurs lethal growth of white blood cells, usually beginning in adulthood.

Scientists now report that an oral drug known as STI-571 inhibits activity of this enzyme, rapidly killing the leukemia cells. The drug targets cancer cells because only they contain the rogue enzyme, called Bcr-Abl tyrosine kinase.

Researchers gave 61 leukemia patients various doses of STI-571, made by Novartis Pharmaceuticals of East Hanover, N.J. All 31 patients getting the highest doses improved dramatically within 4 weeks, says Brian J. Druker, an oncologist at Oregon Health Sciences University in Portland. These participants, who received at least 300 milligrams per day, showed reductions in the runaway growth of white blood cells. In three of these patients, the drug completely eliminated cells with the chromosome abnormality, Druker says.

The other 30 patients received smaller doses of STI-571 for the first 4 weeks of the study. Most made inconsistent gains or none at all—although a few getting at least 200 mg/day experienced steadily falling counts of white blood cells. After 4 weeks, all those not responding to the drug began receiving 300 mg/day. Up to 14 months later, patients are showing no serious side effects, Druker reported this week at the American Society of Hematology meeting in New Orleans.

"It's fantastic. These people had failed standard treatments" with injections of interferon, the best drug available, he says. "Their doctors said they didn't have long to live." Most are now feeling well, with good blood-cell counts, he says.

The genetic abnormality in chronic myelogenous leukemia isn't inherited. Rather, individuals somehow acquire the mutation during life. People exposed to radiation by the Hiroshima and Nagasaki nuclear blasts had a high incidence of the disease, but it also appears in others.

This leukemia strikes 4,300 people every year in the United States. Even with medication, they usually live only 5 to 7 years.

"It's one of the best-known types of cancer," says John Groffen, a molecular biologist at Children's Hospital and the University of Southern California, both in Los Angeles. Over the past few decades, Groffen and other researchers gradually deciphered the molecular basis of the cancer, including the site of the mutation and the role of Bcr-Abl tyrosine kinase.

Tyrosine kinases help choreograph cell growth. To work, they need to turn on and off appropriately. In people with chronic myelogenous leukemia, Bcr-Abl tyrosine kinase seems to be switched on all the time, Groffen says. "This accounts for the uncontrolled growth," he says. Proliferating white blood cells don't reach maturity and crowd out healthy blood cells in the bone marrow.

Knowing the role of Bcr-Abl tyrosine kinase, Druker and Novartis scientists were able to make an inhibitor for it. While STI-571 won't work against other forms of leukemia, the research unit boosts the concept of targeting abnormal enzymes, Druker says. Researchers have found such enzymes in other leukemias and lymphomas.

"This is a very promising approach," Groffen says. "On the other hand, one has to be a little careful." This leukemia has shown it can fluctuate from remission to recurrence unpredictably, he says.

Druker collaborated with scientists at Novartis, the M.D. Anderson Cancer Center in Houston, and the University of California, Los Angeles. He plans to enroll 800 patients in a more extensive study of STI-571 next year. —*N. Seppa*

Minds may track danger unconsciously

Feelings of anxiety typically flood consciousness with a vivid sense of foreboding. However, those anguished feelings may originate in an unconscious mental process that anticipates real or imagined threats, according to a new study.

The investigation, which combines classical conditioning with brain wave measurements, broadly supports a theory of anxiety formulated 70 years ago by Sigmund Freud, contends psychologist Philip S. Wong of the New School for Social Research in New York.

"Some kind of unconscious signal function in the brain for anticipating danger situations must be a central feature of any comprehensive model of mind," Wong says.

Freud theorized that individuals unconsciously perceive dangerous situations resembling past traumas and recreate weaker, sometimes distorted versions of the past event to achieve a sense of control. Under these circumstances, feelings of anxiety act as a signal for help and trigger psychological defense mechanisms such as denial and repression, in Freud's view.

To explore unconscious processes involved in signal anxiety, Wong relied on a research design that uses classical conditioning. For instance, other investigators have found that people conditioned to expect a finger shock after seeing certain images exhibit rises in skin electrical conductance—an indication of heightened stress—upon viewing the same images flashed too quickly for conscious evaluation.

Wong fitted 17 men, all physically and mentally healthy, with sensors to monitor the brain's electrical activity. Participants first viewed a series of frowning faces presented subliminally so the researchers could determine baseline neural activity. Participants then saw a new set of frowning faces shown long enough for conscious perusal. A mild finger shock occurred 2 1/2 seconds after the appearance of each consciously discernable face.

Finally, the men watched subliminal presentations of the faces that had been linked to a shock, but this time they received no shock.

Distinct slow-wave brain activity emerged about half a second before the time at which shocks had been delivered in the conditioning phase, Wong reports in the current JOURNAL OF THE AMERICAN PSYCHOANALYTIC ASSOCIATION.

Prior studies indicate that this so-called "expectancy wave" arises when volunteers consciously anticipate making a planned movement or receiving a conditioned reward or punishment.

In the new study, the expectancy wave was elicited unconsciously, Wong says. It represents part of an unconscious danger-evaluation process, common to many animals, that underlies human anxiety responses, he proposes.

"These findings make a lot of sense in trying to understand danger assessment and the experience of fear and anxiety," remarks psychologist John A. Bargh of New York University. Bargh studies unconscious influences on attitudes and goals (SN: 10/30/99, p. 280). —*B. Bower*