Nobel Prizes: Genetics and Symmetry

Chemistry

Gene research nearly swept the Nobel Prize board this year with the 1980 prizes in medicine and chemistry awarded for studies involving DNA components and the genetics of the immune system.

Paul Berg of Stanford University, Walter Gilbert of Harvard University and Frederick Sanger of Cambridge University in England share the 1980 chemistry prize for separate work in DNA research and genetic engineering.

Berg, cited for his biochemical studies of nucleic acids, was the first investigator to construct a recombinant DNA molecule using gene manipulation, according to Sweden's Royal Academy of Sciences. The Stanford biochemist chairs the Committee on Recombinant DNA Molecules, a group of concerned scientists who in 1974 initiated the historic "go-slow movement" that led to a six-month moratorium on certain recombinant DNA experiments to give scientists an opportunity to evaluate the theoretical dangers of such work (SN: 7/27/74, p. 52).

More recently, Berg and colleagues produced rabbit beta chain hemoglobin by infecting African green monkey cells with a virus carrying the hemoglobin gene, marking the first successful transplant of a functioning gene from one mammalian species to another using recombinant DNA techniques (SN: 10/28/79, p. 292).

Gilbert and Sanger split the chemistry prize with Berg for their independently developed techniques for determining the exact sequence of the nucleotide building blocks in DNA (SN: 11/24/79, p. 359). Gilbert's method uses chemical reagents to break the molecules, while Sanger's employs an enzymatic reaction.

Like Berg, Gilbert (a 1949 Westinghouse Science Talent Search winner) and Sanger have stepped into the scientific limelight prior to this year's Nobel Prize awards. Sanger, for example, received the 1958 Nobel Prize in chemistry for determining the structure of various proteins (SN: 11/8/58, p. 293). Gilbert's most recent claim to fame is his involvement with Biogen — a Geneva, Switzerland, based company that sponsored the gene-splicing research leading to the bacterial production of interferon (SN: 1/26/80, p. 52), a human protein thought to be involved in many of the body's immune reactions, possibly including cancer defense.

Gilbert photo: Harvard Univ., all others: Wide World

Chemistry winners, top row, left to right: Gilbert, Berg, Sanger.

Medicine winners, middle row: Benacerraf, Snell, Dausset.

Physics winners, bottom row: Fitch, Cronin.

Medicine

The genetics of the immune system is the basis of the 1980 Nobel prize in medicine. The award was shared by George D. Snell of the Jackson Laboratory in Bar Harbor, Maine, Jean Dausset of the University of Paris and Baruj Benacerraf of Harvard Medical School for work that has led to more successful tissue and organ transplants. In addition to extending understanding of the immune response, the work underlies the techniques for "typing" cells to provide a better match between transplant tissue and recipient.

Snell did the pioneering work in the 1940s. He set out to examine what genes in mice control whether a transplant is accepted or rejected. Snell developed strains of mice that are genetically identical except for a single gene and found that a set of genes, which he called histocompatibility genes or the H-2 locus, determine whether tissue grafts are accepted or rejected. Animals with the same genes in those positions accept grafts from each other; animals with different genes in those positions do not accept transplants from each other.

Dausset extended the histocompatibility work to human genes. He found that a comparable set of genes in one region of one human chromosome determines if a graft will be rejected. The human genes are called the HLA (Human Leukocyte Antigen) system. In both mice and humans, the histocompatibility genes code for specific proteins found on the surface of all cells in the body. These are the proteins recognized by the immune system.

Another set of genes important in transplant rejection was identified by Benacerraf. In experiments with guinea pigs he found genes that control the ability of an individual to respond to certain foreign substances. These genes, which he called Ir, for "immune response," are in the same region of the chromosome as the histocompatibility genes. While the details of how those genes work have not been established, the genes do appear to provide a protein on the surface of white blood cells. These proteins are thought to play a role in the interaction of two components of the immune system — lymphocytes and macrophages. The interaction between these two components is necessary for an immune response. More recent work has shown that some diseases — for instance, rheumatoid arthritis — are associated with particular genes at the immune response or other histocompatibility locations.

Physics

The science of physics may be described as an attempt to elucidate the symmetries by which the structure of material nature is designed and its behavior constrained—and once these symmetries are found, where and how they may be broken. The 1980 Nobel prize in physics is shared by James Cronin of the University of Chicago and Val Fitch of Princeton University for the discovery of one such symmetry break, the violation of what is called CP symmetry.

This is part of the total symmetry of matter and antimatter. Physicists used to believe that the universe is balanced between matter and antimatter, and that the various processes of particle physics maintain the balance. This is called CPT symmetry, because it can be divided into three parts: balance of negative and positive electric charge (C), parity or equality of left-handed things and right-handed ones (P) and time reversal, the proposition that matter going forward in time is equivalent to antimatter going backward in time (T).

In 1957 C.S. Wu and co-workers showed that certain interactions involving neutrinos violated parity. This seemed to indicate that total or partial violations of CPT might be found in processes governed by the weak nuclear force. In 1964 Cronin and Fitch found that such a process, the radioactive decay of the neutral K meson, violates C and P together. The combined violation implies a complementary violation of the time reversal principle. "The discovery emphasizes, once again, that even almost self-evident principles in science cannot be regarded [as] fully valid until they have been examined in precise experiments," says the citation.

The work has inspired continuing ferment over the CPT theorem. One of the great excitements of 1980, the possibility of neutrino mass and neutrino oscillations, has a connection. Much of the reason for the peculiar behavior of neutral K decay is that the neutral K has oscillations of identity between a long-lived and a short-lived form that are analagous to the identity oscillations proposed for neutrinos. If neutrino oscillations are confirmed then it seems, according to discussions at recent meetings on the subject, that there should be a CP violating aspect to their behavior too.

A native of Merriman, Neb., Fitch got his doctoral degree at Columbia University in 1948. He has been a member of the Princeton faculty since 1954 and is now Cyrus Fogg Brackett Professor of Physics and chairman of the department. Cronin was born in Chicago. He earned his Ph.D. at the University of Chicago in 1955, and then went to Brookhaven National Laboratory. In 1958 he joined the Princeton faculty, where he remained until 1971, when he went to Chicago to become professor of physics there. □

Genetic jump spawns inquiry

In what may be the first clinical use of human gene-splicing techniques, a University of California at Los Angeles researcher has attempted to place normal genes in the defective bone marrow cells of two patients suffering from a fatal blood disease. Martin J. Cline performed the experimental treatments on two women (one at the Hadassah Hospital in Jerusalem and the other at the University Poly Clinic in Naples) suffering from beta thalassemia major—a condition in which bone marrow produces red blood cells with abnormal hemoglobin, debilitating the blood's ability to carry the oxygen needed by all body tissues. Cline attempted to colonize the defective bone marrow with cells carrying genes for normal hemoglobin production and to beef up the cells' production of genetic material. The genes were produced in large quantities in bacteria by using gene-splicing techniques.

Cline and colleagues demonstrated the first successful use of genetic engineering in living animals this spring when they transplanted a gene from bone marrow cells of one set of mice into cells that subsequently populated the bone marrow of other mice (SN: 4/19/80, p. 244). While Cline then said he believed application of the technique to humans to be at least three years in the future, it now is evident that he was awaiting permission from a human subject protection committee at UCLA to do such human experiments; in fact, Cline proposed those experiments as early as the spring of 1979.

Eventually, after more than a year of deliberation, the UCLA committee refused to grant Cline permission to do the experiments he proposed without further animal research. But by the time the committee's decision was handed down in July, Cline already had performed the experiments on the two women overseas.

Enter the National Institutes of Health. Cline has four grants from NIH, and if these funds were used without the blessing of UCLA's human subject committee, he is in violation of federal and university rules. So officials at NIH and UCLA have begun an inquiry into the matter, despite Cline's claims that in addition to the fact that no NIH funds were used, at least in Israel, the experiment proposal was subjected to the same scrutiny required by U.S. guidelines. Still, as one NIH official explained, "Although on the basis of what we have now, I don't think we have a case against Cline, we asked for an inquiry, because it is unusual for someone turned down at their home institution to do the work overseas." Moreover, the UCLA committee may use the Cline case to identify the ambiguities in their own guidelines governing research with human subjects: Currently, there is confusion as to the precise jurisdiction of those rules.

Meanwhile, Cline continues to analyze blood and marrow samples from his two thalassemia patients for signs of normal hemoglobin production that will signal success in his experimental treatment. □

HHS fund misuse: The bucks stop here

Just two days after a University of California at Los Angeles researcher found himself in the center of a controversy regarding his use of genetic engineering on human subjects, the U.S. Department of Health and Human Services issued new rules to deny HHS funds to unethical researchers. The timing was coincidental, but the case of UCLA researcher Martin J. Cline — who used gene manipulation techniques on two women overseas shortly before his own institution's committee for protection of human subjects refused to grant Cline permission to conduct the experiments without further animal work — is an example of the kind of case the new HHS rules could cover (see previous story).

The rules, published in the Oct. 9 FEDERAL REGISTER, "are designed to weed out in advance individuals and organizations who, on the basis of past performance, would be likely to misuse HHS funds," says HHS spokesman John Blamphin. Fund misuse occurs, for example, when faculty members request kickbacks from graduate students they select for work funded by training grants. Other cases include violations of the conditions of a previous award and a record of unsatisfactory performance while using HHS funds.

Whereas existing provisions allow HHS only to suspend or terminate ongoing grants in cases of fund misuse or to refuse suspect individuals or institutions grants on a case-by-case basis, the new rules, effective Nov. 10, allow HHS to refuse even to consider past offenders for grants for a certain "debarment" period. In other words, individuals or institutions guilty of fund abuse are debarred for an amount of time depending on the seriousness of the offense and ineligible for HHS financial assistance during the debarment. □

NASA head resigns

Robert A. Frosch, administrator of the National Aeronautics and Space Administration, will resign as of Jan. 20, 1981, from the agency that he has headed since June 21, 1977. He will become the first president of the newly formed American Association of Engineering Societies, a federation representing 39 professional societies in the United States. He will thus be leaving NASA before the oft-delayed space shuttle ever leaves its launch pad. □