attention. But the following year, evidence for a fourth quark was unearthed, a watershed event in quark history because from then on the particles were taken increasingly seriously. And in 1977, physicists reported on the possibility of a fifth quark. Since the unified theory has quarks coming in pairs, physicists suspect that a sixth variety is also waiting to be found, and Kobayashi and Maskawa's model has become a serious contender.

Another explanation for CP violation by way of gauge theories was made by Columbia's Lee, also in 1973. Although the particles are as yet unobserved, the unified theory as developed by Steven Weinberg of Harvard University and Abdus Salam of Imperial College, London, requires the existence of an altogether new type of particle called a Higgs boson. Lee suggested that if there were at least four such particles, another mechanism for CP violation would be opened up. Weinberg later worked out a more realistic model of this type.

Among the differences between the models stemming from gauge theories (which are often called milliweak theories of CP violation) and the superweak theory is that the former predict the observation of larger CP violating effects in more places than does the latter. Several extremely sensitive experiments are planned or under way to try to distinguish between the various models.

Interest in CP violation also revved up in the 1970's because of its implications for cosmology and the Big Bang model of the origin of the universe. The various conservation laws of physics had seemed to say that, in the Big Bang, equal amounts of matter and antimatter had to be created. Similarly, as the universe expanded and cooled, equal amounts of matter and antimatter would have to be annihilated, as in collisions between electrons and positrons where both are transformed into gamma rays. Yet, experimentally, the universe seems to be almost entirely matter, the only antimatter coming in cosmic rays and in accelerators. One consequence of CP violation is that particles and antiparticles do not have to decay by the same reaction at the same rates. Among the first published accounts of a way to incorporate CP violation into a model for a universe consisting of matter but not antimatter was that by Soviet dissident Andrei Sakharov in the mid-1960's.

In the mid-1970's, a number of grand unified gauge theories were proposed that attempted to encompass the strong nuclear, weak, and electromagnetic forces into one formalism. A fallout of some of these theories is that there is a new hyperweak force (even weaker than Wolfenstein's superweak force) that is responsible for the unequal decay of matter and antimatter. Several theorists have in the last 2 years constructed speculative models based on an assumed hyperweak force and CP violation that roughly account for the imbalance of matter over antimatter in the universe, provided that a period of thermodynamic nonequilibrium existed in the early hot universe when the imbalance was created.

Some physicists have speculated that the Royal Swedish Academy of Sciences placed considerable weight on the emergence of gauge theory models of CP nonconservation and on the cosmological connection in making the award to Cronin and Fitch. Physicists hope this is not true because the Cronin-Fitch experiment, they say, stands on its own. "It was such a beautiful and elegant experiment," said experimentalist Jack Sandweiss of Yale, "that it was the equivalent of listening to Rudolf Serkin play Beethoven."—ARTHUR L. ROBINSON

# 1980 Nobel Prize in Physiology or Medicine

## *Three immunologists win for their research on the identification and action of histocompatibility antigens*

A story that began more than 40 years ago with the identification of the first transplantation antigen in mice has culminated in the award of the 1980 Nobel Prize in Physiology or Medicine to three immunologists. The Nobel Assembly of the Karolinska Institutet has cited Baruj Benacerraf, Jean Dausset, and George Snell for their work on "genetically determined structures of the cell surface that regulate immunological reactions."

The structures in question, called histocompatibility antigens, are best known for their role in triggering the rejection of transplanted organs by the immune system. Their discovery has helped transplant surgeons select for grafting organs that are more likely to be accepted by the recipient. But, in addition, the histocompatibility antigens determine whether an individual can mount an immune response to a given antigen. In this way, they can influence the individual's susceptibility to disease.

The early history of the discovery of histocompatibility antigens is intertwined with that of the Jackson Laboratory in Bar Harbor, Maine. The laboratory was founded in 1929 by C. C. Little as a center for the study of mammalian genetics. Snell, who at age 77 is the oldest of the three new laureates, went to Bar Harbor in 1935 and has spent his professional life there. He had previously worked at the University of Texas with Herman Muller, who won a Nobel Prize in 1946 for studies of the x-ray induction of mutations in the fruit fly.

After working for a time on the x-ray induction of mutations in mice, Snell decided in the mid-1940's to look for a new project, one consistent with his training as a geneticist and his location at Bar Harbor. And, he says, "I wanted in the long run for it to have a payoff."

He knew from the work of Little that a number of genes controlled the ability of mice to resist tumor transplants, but at that time the genes had not been isolated or identified. Snell decided to find a way to study the working of each transplant gene individually.

He proceeded, in the words of Elizabeth Russell, his longtime colleague at Bar Harbor, "to invent the idea of congenic mice." These are mice that are genetically identical except at the single locus or genetic region to be studied. They make it possible to follow the effects of a single gene in a constant genetic background, and today they are a mainstay of histocompatibility research. For this contribution, Frank Lilly, of Albert Einstein College of Medicine, describes Snell as "the father of modern immunogenetics."

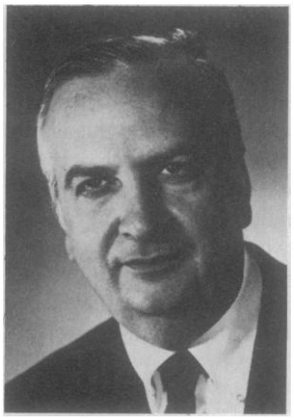
Breeding congenic mice is a tedious business, requiring some 14 to 15 generations. Snell met with an immediate setback when the Jackson Laboratory was burned out in 1947. But, he says, "The thing did work. Over the years we identi-


0036-8075/80/1107-0621$00.75/0  

fied a group of about ten loci that control graft resistance." They were not all equally effective, however. "One stood out like a sore thumb in determining whether a graft was accepted."

In work performed in the late 1930's, Peter Gorer, of Guy's Hospital in London, had prepared an antiserum that reacted with an antigen found on cells from one mouse strain but not on cells from a different strain. He showed that the antigen, which he designated antigen II, was also involved in tumor graft rejection.

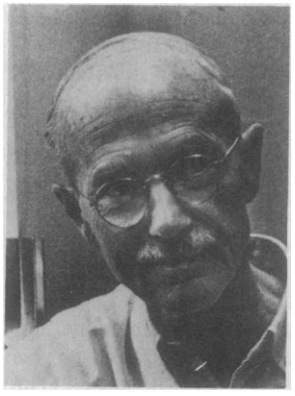
After World War II, Gorer, bringing his antiserum with him, went to Jackson Laboratory to work with Snell for a year. They found that the genetic locus coding for antigen II and the locus found by Snell to be so important for graft rejection were one and the same, and they gave it the designation H-2. The H stands for histocompatibility, a term coined by Snell in 1948 to denote the cell surface antigens that determine whether one tissue is compatible with another. Compatible tissues have the same histocompatibility antigens. Incompatible tissues carry different ones. If an attempt is made to transplant a tissue into an incompatible recipient, the tissue will be recognized as foreign by the recipient's immune system and will be rejected. The 2 refers to Gorer's antigen II.



*Baruj Benacerraf*

Wide World Photo

*Jean Dausset*



*George Snell*

Snell, in recognition of Gorer's contributions to the discovery of histocompatibility antigens, says, "I just wish Peter Gorer were still alive to share the prize." (Gorer died at age 55 in 1961, and Nobel Prizes are not awarded posthumously.)

Although H-2 was at first thought to designate a single gene, subsequent genetic analysis of transplant rejection showed that what was originally called the H-2 locus is in fact a complex of many closely linked genes. This gene complex is called the major histocompatibility complex (MHC) because of its dominant role in determining transplant rejection, and it is located on chromosome 17 of the mouse. Two loci, designated K and D, carry the genes specifying the tissue antigens involved in triggering graft rejection. Any of some 20 to 30 different alleles may occur at each locus. (Alleles are alternative gene forms that may occur at a single locus.) Among the many investigators who contributed to the development of this picture, in addition to Snell and Gorer, are D. Bernard Amos, of Duke University Medical Center; Edward Boyse, of Memorial Sloan-Kettering Cancer Center; Jan Klein, of the Max-Planck-Institut für Biologie in Tübingen; and Donald Shreffler, who is now at Washington University Medical Center.

Beginning in the late 1950's, evidence for a human analog of the mouse H-2 system began to accumulate. At that time Jean Dausset, who is now at the University of Paris and St. Louis Hospital, was studying the antibodies produced by patients with serious blood diseases. He found that the patients who had received many blood tranfusions, and had thus been exposed to foreign tissue antigens, made antibodies that reacted with antigens found on white blood cells from other individuals but not with those on their own cells. Several of the patients produced antibodies against the same antigen, which Dausset called Mac. According to Fritz Bach, of the University of Minnesota Medical School, "This was the first serum to define an HLA antigen and led in part to the definition of the histocompatibility system in man." (HLA is the designation for the human MHC.)

In the years since Dausset identified the Mac antigen, the similarity between the mouse H-2 complex and the human HLA system has become clear. But for a time in the 1960's the situation was highly confused. Many antigen systems were being identified, and it was not clear how they were related to one another or whether they were. Amos says, "Different people were using different techniques and sera to identify antigens. It was hard to know what was going on."

Amid the confusion, however, there were some highlights. For example, Jon van Rood, of the University of Leiden, described two tissue antigens that were allelic products of the same genetic locus, which he called the 4 locus. And Rose Payne, of Stanford University, found another allelic system of antigens, which she designated LA.

In 1965 Dausset, with Pavol Ivanyi and Dagmar Ivanyi, who were then at the Czechoslovak National Academy, contributed a report that, in Amos's view, pointed the way to a better understanding of the antigen situation. The investigators described a system that included some ten antigens and implied that the genetic region coding for the system, which they called Hu-1, contained subloci that each specified a limited number of antigens. "That took us aback," Amos recollects, "we knew that a number of the antigens were related, but we did not think they all were."

Confirming this hypothesis and understanding the gene arrangement in the human major histocompatibility complex would require a few more years of work and the contributions of many immunologists. Meanwhile, efforts were under way to use the already identified tissue antigens for improved transplantation of organs, particularly skin and kidneys. Investigators, including van Rood, Ruggero Ceppellini, of the Turin Institute of Medical Genetics, and Paul Terasaki, of the University of California Medical School at Los Angeles, were finding that graft survival was greater when the donor and recipient (who were generally siblings) shared the same tissue antigens. This was a strong indication that the antigens being detected did in fact determine tissue compatibility, even though the investigators had not yet fully sorted them out.

Clarification of the tissues antigen solution was greatly facilitated by the his-

tocompatibility workshops begun by Amos in 1964. At these workshops, which are still held every 2 to 4 years, researchers share their resources, including the reagents and antiserums that they use to identify antigens, and tackle the currently outstanding problems in histocompatibility research.

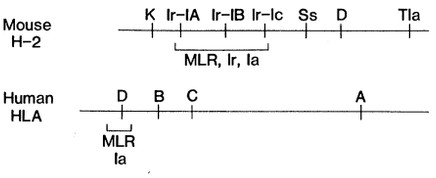
As it gradually developed, the picture of the human HLA system turned out to be just as complex as that of the mouse H-2 system. The LA and 4 loci—which are now designated HLA-A and HLA-B, respectively—are closely linked but separate loci within the HLA system. They are the human equivalents of the D and K loci of the mouse complex. The Hu-1 system described by Dausset and the Ivanyis included antigen products of both the HLA-A and HLA-B loci.

Identification of the HLA-A and HLA-B antigens has greatly improved the success of organ transplants, especially when the donor and recipient are related. The importance of matching for these antigens is less clear for transplants of kidneys from an unrelated donor. Recent results from a number of laboratories suggest that matching at another histocompatibility locus, designated HLA-DR (for D-related), may be more predictive of transplant success in these cases. The HLA-D locus (formerly the MLR locus) was brought under the human histocompatibility umbrella in the late 1960's by Bach and Amos.

But perhaps even more important is the role of blood transfusion to the recipient before kidney transplant surgery. A large body of data, principally accumulated by Terasaki and Gerhart Opelz at UCLA and recently extended by others, suggests that such transfusion improves the success of transplants from unrelated donors, possibly even overriding the effect of a tissue mismatch.

The use of histocompatibility antigens as a guide in transplantation can be considered extraordinary—important, but not likely to be needed by the vast majority of people. What the antigens do in everyday life, so to speak, is another matter. This role of antigen has been clarified by the work of Baruj Benacerraf, who is now chairman of the Department of Pathology and Fabyan Professor of Comparative Pathology at Harvard Medical School and president of the Sidney Farber Cancer Institute. Benacerraf has shown that genes located within the MHC control the many interactions among immune cells that are necessary for an individual to have an immune response.

According to Benacerraf, he began investigating the genetic control of immune responses "accidentally" in the early 1960's, when he was at New York University. He was working with Gerald Edelman, of Rockefeller University, on the analysis of antibody structures and was having difficulty because the antibody preparations then available consisted of heterogeneous populations of molecules. Benacerraf thought he might be able to produce a pure preparation of a single molecular species by immunizing animals (guinea pigs in the first experiments) with simple antigens such as polylysine, a synthetic polypeptide containing only the amino acid lysine. "What I found," Benacerraf explains, "is that some animals responded by making antibodies [to the antigen] and others did not. I thought this was an important observation and decided to investigate further." Thus he was diverted from antibody structure determination, for which Edelman shared the 1972 Nobel Prize in Physiology or Medicine with Rodney Porter, of the University of Oxford, England.




***The MHC's of mice and men***

*Schematic comparison of the gene arrangement in the two MHC's. [Adapted from an illustration by Walter Bodmer of the Imperial Cancer Research Fund Laboratories in London; originally published by Academic Press]*

Benacerraf showed that guinea pigs possess genes—called Ir (for immune response) genes—that allow them to make antibodies in response to some antigens. Shortly thereafter, Hugh McDevitt, of Stanford University, and Michael Sela, of the Weizmann Institute of Science in Rehobot, Israel, observed similar genes in mice. McDevitt then determined that they are located within the mouse MHC, not in the K or D region but in a region designated I. Benacerraf soon showed that the guinea pig Ir genes are in that species' MHC. In the human HLA system, the HLA-D region may contain the Ir genes.

Exactly how the Ir genes (or their products) exert control is not clear, but there is strong evidence that they do so by mediating the myriad interactions between immune cells. Although the B lymphocytes of the immune system actually produce the antibodies, other cell types are involved in the regulation of B cell activity. The principal regulatory cells belong to the T cell class of lymphocytes. Some T cells kill their target cells, others are "helper cells" that cooperate with B cells to elicit antibody production, and still others are "suppressor cells" that inhibit the activity either of other T cells or of B cells.

The Ir genes control only those antibody responses in which the helper cells cooperate. Benacerraf, with David Katz, of the Scripps Clinic and Research Foundation, showed that the T and B cells of mice cannot cooperate unless they both carry identical genes, which they mapped to the I region of the MHC.

The T cells themselves must be activated before they can turn on B cells. This requires still another cellular interaction, this one between T cells and macrophages that have picked up the triggering antigen. This interaction also depends on the macrophages and T cells having the same Ir genes, according to Ethan Shevach, of the National Institute of Allergy and Infectious Diseases, and Alan Rosenthal, who is now at the Merck Institute of Therapeutic Research in Rahway, New Jersey.

The best candidates for the cell surface components that participate in these interactions are a group of molecules called Ia (for I region-associated) antigens that were discovered by Shreffler and Klein. The Ia antigens are probably the products of the Ir genes, although this has not been proved.

Finally, the suppressor and helper T cells also communicate with their targets by releasing factors that either inhibit or stimulate them. The genes for these factors also lie in the I region of the mouse MHC.

If all this sounds complicated, it is. Benacerraf points out, "A very complex system is needed for controlling immune responses; the only parallel is the interactions in the nervous system." Nevertheless, he says, "We are finally beginning to understand the workings of the immune system and the intricate mechanisms for distinguishing self from nonself."

In addition, study of the MHC may ultimately shed new light on the etiology of a number of diseases that are not fully understood. Over the past 10 years many investigators have noted an association between a disease and one or another histocompatibility antigen. Many of these diseases are thought to be of autoimmune origin; that is, an immune attack is mistakenly directed at the body's own tissues. What is still lacking is an explanation of how the presence of a particular histocompatibility antigen might lead to the development of some pathological condition.—JEAN L. MARX