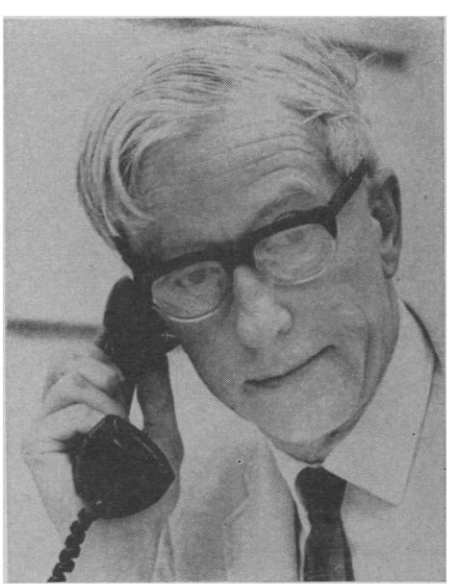
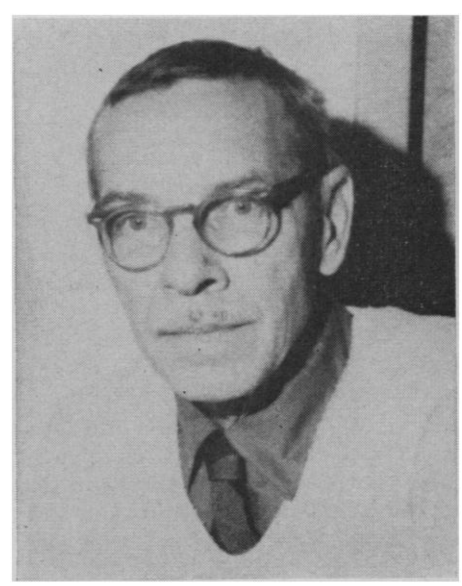
The 1969 Nobel Prize for Physiology or Medicine

With the award of the 1969 Nobel prize for physiology or medicine to Max Delbrück of the California Institute of Technology, Salvador Luria of the Massachusetts Institute of Technology, and Alfred Hershey of the Carnegie Institution of Washington, three men are honored at last who, 30 years ago, began to transform the landscape of classical Mendelian genetics into the latter-day "molecular" Crick-Watsonian scene. This long delay in bestowing the ultimate accolade upon the three prime movers of molecular genetics is only too comprehensible from the purview of the Nobel prizes. Indeed, to Nobelologists it must come as a surprise that this award was made at all, since neither Delbrück's nor Luria's name is associated with any of the kinds of spectacular breakthrough discoveries for which the prize is almost always given, and Hershey's best-known experiment represented merely an independent confirmation of an inference drawn by others 8 years before. That is not to say that these men have remained obscure and unappreciated until the present. On the contrary, all three are widely revered, but the basis of their fame is elusive and difficult to explain to strangers (and even to molecular geneticists under 30). In order to set forth the peculiar nature of Delbrück's contribution, his friends and colleagues (including Luria and Hershey) published a collection of autobiographical essays, *Phage and the Origins of Molecular Biology* (Cold Spring Harbor Laboratory of Quantitative Biology, Cold Spring Harbor, N.Y., 1966), on the occasion of his 60th birthday. These essays give a much better overall picture of the significance of this Nobel prize than can be provided in this brief appreciation.

Max Delbrück was born in Berlin in 1906, the scion of a well-known German family whose members included bankers, clerics, and savants, among them Delbrück's father Hans, the famous historian of war. Delbrück studied physics in Göttingen, in the wake of the revolution brought about by the development of quantum mechanics. Later he went as a postdoctoral fellow to Niels Bohr's Copenhagen laboratory at a time when Bohr was working out the philosophical implications of the fundamental changes which the new physics had brought to the conception of the nature of physical law. Bohr then believed that the general notion of complementarity, of which Heisenberg's "uncertainty principle" is but an example, ought to have important epistemological consequences also for other scientific domains, especially for biology. In particular, Bohr thought that, for the ultimate understanding of life itself, some fundamental complementarity relation holding for living aggregates of matter must first be found, and that this finding would devolve from the discovery of some deep paradox presented by life. Delbrück was profoundly influenced by Bohr's "Copenhagen spirit." He returned to Berlin to become an assistant to Otto Hahn and Lise Meitner, but in his spare time he joined a discussion group led by the Russian geneticist N. Timofeeff-Ressovsky. As a result of this contact, Delbrück published a paper in 1935 in which he pointed out that genetics is that domain of biology in which Bohr's anticipated complementarity relation is most likely to be found, because the long-term stability of the tiny gene bids fair to embody a deep paradox. In fact, Delbrück decided to do full-time work in genetics and went to the California Institute of Technology, where Thomas Hunt Morgan and his school then reigned over classical genetics. Delbrück thus left his employers Hahn and Meitner just before they discovered uranium fission. Contrary





(Left to right) Max Delbrück, Salvador Luria, and Alfred Hershey [UPI Photos] to his expectation, Delbrück did not take up work with any of the standard experimental materials of classical genetics at Caltech, but instead joined Emory Ellis in a study of phage reproduction. In collaboration with Ellis, he designed the one-step growth experiment, whose publication in 1939 marks the beginning of modern phage research. This experiment showed very clearly that after the phage, or bacterial virus, particle infects its bacterial host cell, there elapses a half-hour latent period during which the parental phage multiplies to yield an issue of several hundred progeny. Delbrück realized that the phage-infected bacterium represents the ideal experimental system for studying self-replication, the evident capacity for self-replication being the most mysterious and, hopefully, paradoxical aspect of the gene. And since the small size of the phage particle is of about the same order of magnitude as what in the late 1930's had been estimated to be the size of the gene, Delbrück thought it should not be too difficult to work out just how, during that half-hour latent period, the parent phage manages to give rise to its progeny.

An American Phage Group

In 1940, at a meeting of the American Physical Society in Philadelphia, Delbrück happened to meet Salvador Luria, then recently arrived in America as a refugee from war-torn Europe. Luria, born in 1912 in Turin, had studied medicine in Italy. The outbreak of World War II found him working in Paris at the Pasteur Institute, where he (like the 1965 laureate André Lwoff) had learned the techniques of phage research from Eugene Wollman. Upon the fall of France, Luria fled to Marseilles, whence he managed to sail for the United States. He has described his meeting with Delbrück in these terms: "After a few hours of conversation and a dinner with W. Pauli and G. Placzek during which the talk was mostly in German, mostly about theoretical physics, mostly above my head, Delbrück and I adjourned to New York for a 48-hour bout of experimentation in my laboratory at the College of Physicians and Surgeons." Delbrück and Luria had found that they were both interested in the same fundamental problem (though Luria denies having had much use for such romantic ideas as paradoxes), and with their first meeting there had come into being the American Phage Group, whose members were united by the common goal of solving the enigma of self-replication. One of the first recruits was Thomas F. Anderson, in collaboration with whom Luria obtained an electron micrograph of phage particles in 1942. This picture confirmed H. Ruska's first report of the year before that phage particles consist of a round head and a thin tail. Just as the birth of genetics is considered to have taken place in 1865 upon the appearance of Gregor Mendel's paper reporting the conclusions he had drawn from his crosses of the garden pea, so the birth of bacterial genetics can be dated as of 1943, when Luria and Delbrück published a joint paper in which they showed that the appearance of phage-resistant variants in cultures of phage-sensitive bacteria represents the selection of spontaneous bacterial mutants. This conclusion was contrary to the then current teachings of bacteriology, which, according to Luria, was "the last stronghold of Lamarckism." Luria and Delbrück were not the first to study bacterial mutation, any more than Mendel was the first to cross plants for the study of heredity. But with their paper Luria and Delbrück did for bacterial genetics what Mendel had done for general genetics—namely, showed for the first time what kind of experimental arrangements, what kind of data analysis, and, above all, what kind of sophistication is needed for obtaining meaningful and unambiguous results. Whereas it did not announce any striking or unexpected result, their paper became the standard by which all later papers were to be measured.

While he was working on the manuscript of that paper, Delbrück (then an instructor of physics at Vanderbilt University) was paid a visit by Alfred Hershey. When returning the manuscript to Luria, Delbrück reported that Hershey "drinks whiskey but not tea. Simple, to the point, likes living in a sailboat for three months; likes independence." Born in 1908, in Lansing, Michigan, Hershey did his undergraduate work in chemistry at Michigan State College. He then went to Washington University, St. Louis, where he studied under J. Bronfenbrenner, one of the first bacteriologists to have taken up the study of phages in America, shortly after their discovery in Europe during World War I. Upon meeting Delbrück in 1943, Hershey became another charter member of the nascent Phage Group and began to address himself to the kind of genetic problems in which Delbrück and Luria were interested. In 1945 both Hershey and Luria demonstrated the occurrence of spontaneous phage mutants. And in the following year Delbrück and Hershey independently discovered the existence of genetic recombination in phage, a process which had been previously thought to be reserved for more evolved, sexually reproducing forms of life. (Delbrück actually believed at first that he had discovered specifically induced mutations rather than recombination, and it was Hershey and his student Raquel Rotman who later showed that phage recombination corresponds formally to meiotic crossing-over by chromosomes of higher organisms. These findings gave the start for phage genetics, whose ultimate refinement by Seymour Benzer a few years later led to reform of the classical concept of the gene.

DNA, the Genetic Material

By 1950, Anderson had shown that the phage head is a proteinaceous bag stuffed with DNA and that the phage attaches itself to the surface of its bacterial host cell by the tip of its proteinaceous tail. According to Hershey, it was an appreciation of these facts that "literally forced" him and his assistant Martha Chase to perform their celebrated "blendor experiment" in 1952. This experiment showed that, upon infection, the phage DNA is the only, or at least the principal, phage component to enter the host cell, the bulk of the phage protein remaining outside, beyond the cell wall. This discovery showed that DNA, rather than protein, is the genetic material of the phage, in complete harmony with the demonstration by Oswald Avery, Colin MacLeod, and Maclyn McCarty in 1944 that DNA is the genetic material of bacteria. The Hershey-Chase experiment made a tremendous impact in its time and focused attention on DNA as a carrier of hereditary information. The fundamental problem of phage self-replication could now be restated in terms of two functions of the phage DNA: an autocatalytic function by means of which the DNA reproduces itself and a heterocatalytic function by means of which the DNA directs the synthesis of phage proteins. Upon learning the result of the Hershey-Chase experiment, James Watson, a student of Luria's, intensified his collaborative efforts with Francis Crick to find the structure of DNA, efforts which were to be crowned with success in the very next year. And with this development molecular genetics, which accounts for heredity in terms of nucleotide base sequences, had become established as a separate discipline whose frame of reference clearly transcends that of billiard-ball-gene classical genetics.

By 1953, the Phage Group counted dozens of members and Delbrück was beginning to lose interest. For, with the discovery of the DNA double helix, it seemed likely that the eventual solution of the problem of self-replication would not lead to any deep paradoxes and hence would fail to uncover any new complementarity relations (the self-complementary nature of the DNA double helix is not, of course, the kind of complementarity that Bohr had been talking about), and so Delbrück turned his attention to sensory perception, on which he has been working ever since. Luria and Hershey, however, continued to make important research contributions to the further growth of molecular genetics, which has meanwhile blossomed into an elephantine academic discipline.

No recitation of the research accomplishments of these three laureates can, however, give an adequate account of the real role they have played in the growth of molecular genetics. Although it would be difficult to imagine three personalities more unlike than those of Delbrück, Luria, and Hershey, they have one trait in common—total incorruptibility—and it is just this trait of their personalities that these three men managed to impose on an entire scientific discipline. Undoubtedly Luria and Hershey would agree that, in the personality department, it was Delbrück who actually wielded the greatest influence. For Delbrück managed to become a kind of Gandhi of biology who, without possessing any temporal power at all, was an ever-present and sometimes irksome spiritual force. "What will Max think of it?" had become the central question of the molecular biological psyche. Thus the award committee for the Nobel prize in physiology or medicine is to be congratulated for its wisdom in recognizing the contributions of three men who have made molecular biology not merely a nice place to visit but also a good place to work.

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NSF: McElroy Seeks to Impart Political Headway to Agency

No one can fault the new director of the National Science Foundation (NSF) for failing to "think big." William D. McElroy, who took charge of NSF on 1 July, is already talking of more than doubling the agency's budget and of making it the "lead" agency for supporting basic research and scientific education in this country. That's no small goal, considering that NSF's budget is currently on the decline and that NSF ranks fifth among federal agencies in dollar support of basic research. But McElroy professes optimism that he can boost NSF's budget to $1 billion—from the current level of less than $500 million—within 3 years. And, as a first step toward achieving this goal. McElroy has launched an ambitious drive to give NSF something it has sorely lacked in recent years—namely, a sure political touch and public-relations savvy that might help persuade Congress to provide larger appropriations. Traditionally, NSF's leadership has regarded politicking as a bit unseemly and has tried to stand aloof from the political arena, so McElroy's plans constitute a radical change in NSF's operating style.

For a variety of reasons, many of them beyond the agency's control, NSF has never been able to achieve the role in American science originally envisioned for it. Vannevar Bush and his colleagues, in their landmark 1945 report, *Science, the Endless Frontier*, proposed the creation of a "national research foundation" which they visualized as the major—indeed, the *only*—federal support of basic research. That report led to the founding of NSF in 1950, but even before NSF came into being, a number of other federal agencies began to actively support basic research. As the nation was confronted with seemingly urgent problems in defense, space and health, the role of the so-called "mission" agencies in supporting basic research related to their missions became increasingly important. The result, ironically, is that NSF, although it is the only agency with

William D. McElroy