Neptune. The planetesimals soon acquire an eccentric orbit that injects most EKBOs into unstable regions of the belt, ultimately eroding the primordial belt mass to near the present presumed mass and exciting the eccentricities of the remaining bodies. Besides contributing to the elucidation of the EKB mass depletion, the theory can account for much of the known orbital configuration of the EKB. It does not, however, provide a good explanation for the resonant group, because it cannot explain the lack of plutinos in near circular orbits.

The two theories are not necessarily mutually exclusive, but one difficulty in reconciling the two is that close encounters of the large planetesimals with Neptune would cause a very noisy radial migration for this planet, hampering the trapping of planetesimals, which demands that Neptune's radial migration be smooth. A weighted combination of the two theories may explain the observations.

An increasing body of evidence suggests that the EKB is the source of a group of comets, known as Centaurs, whose first member, Chiron, was discovered in 1977 by Kowal (*11*). In total, 15 Centaur objects have been discovered. The spectral colors of Centaurs vary from neutral to nearly that of the reddest objects in the solar system (*12–14*). EKBOs and Centaurs seem to have the same spectroscopic characteristics. It remains controversial whether their colors lie in two well-separated populations (*13*) or in a continuous wide color range (*12*, *14*). A continuous wide range of colors could result if progressive global reddening, caused by the exposure of an object's surfaces to cosmic-ray bombardment, is counteracted by collisional uncovering of more primitive neutral color material (*12*). Alternatively, the different colors may result from different distances from the sun and temperatures at their time of formation. If this is the origin of the wide color spectrum and if planetary migration theory sculpted the EKB, then different EKBO colors should be correlated with different eccentricities for the resonant group, in particular for the plutinos. In contrast, no dependence of color on eccentricity is expected for the large scattered planetesimals theory. Right now, there is no evidence for a correlation of plutino colors with their eccentricities or their average distance from the sun, although there is some correlation with their inclinations. A better variable for identifying correlations between resonant EKBOs and color indices combines the different orbital parameters (*15*). However, given the small number of observations and large errors in the color indices, it is too early to draw firm conclusions from the available observational data. It is also doubtful whether the small temperature gradient prevailing in the primordial EKB would cause any surface diversity in the Kuiper objects.

Further observations may, on the other hand, confirm the alternative scenario of two distinct color groups. But primordial formation of EKBOs (and Centaurs) in two well-separated regions of the primordial solar system is also hard to explain. A confirmation of the discontinuous color feature would doubtlessly constitute a substantial challenge to solar system scientists.

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PERSPECTIVES: MOLECULAR MEDICINE

"Sickle Cell Anemia, a Molecular Disease"

Bruno J. Strasser

Fifty years ago this month, a report appeared that would lay the groundwork for establishing the field of molecular medicine. In November 1949, America's leading physical chemist, Linus Pauling (1901–1994) (see figure on next page), and his collaborators published their *Science* paper entitled "Sickle Cell Anemia, a Molecular Disease" (*1*). In this paper, they showed that hemoglobin from patients suffering from sickle cell anemia had a different electrical charge than that from healthy individuals. This report had a powerful impact on both the biomedical community and the general public (*2*).

Enhanced online at www.sciencemag.org/cgi/content/full/286/5444/1488

Pauling's paper was seminal in two ways. First, it showed that the cause of a disease could be traced to an alteration in the molecular structure of a protein, raising the possibility that all diseases might eventually be explained in this way. Second, as this disease was known to be inherited, the paper argued that genes precisely determine the structure of proteins. These two points are so obvious today, that it might seem surprising that they were once headline news.

As early as 1956 Pauling endorsed the view that "man is simply a collection of molecules" and "can be understood in terms of molecules" (*3*). Indeed, after his pioneering studies on the nature of the chemical bond in the 1920s and 1930s, which earned him a worldwide reputation, Pauling started to investigate molecules of biological interest, which at that time essentially meant proteins. As he put it in 1937, "the secret of life itself [is] how a protein molecule is able to form, from an amorphous substrate, new protein molecules that are made after its own image" (*3*).

Pauling's attention was drawn to sickle cell anemia—a hereditary disease found mainly among people of African descent—in 1945 by William B. Castle, a clinician from Harvard. Both were serving on the Medical Advisory Committee that assisted Vannevar Bush in the elaboration of his famous report, *Science—The Endless Frontier*. Pauling had studied hemoglobin in research on blood substitutes during World War II, and had investigated how oxygen binds to hemoglobin as early as 1935. He was thus already familiar with hemoglobin when Castle told him that only venous (deoxygenated) blood of sickle cell anemia patients had sickle-shaped red cells under the microscope. The oxygen dependence of sickling suggested that hemoglobin was probably involved in the sickling process, causing the cells to acquire their distorted shape. Pauling then thought that for these patients "perhaps the Hb [hemoglobin] molecule changes shape" (*3*). He had been searching avidly for a medical problem to solve to demonstrate the power of his physicochemical approach to

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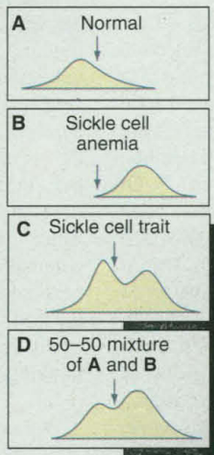
medicine. Like many other scientists, he was also eager to convert wartime research money into peace-time support for science along the lines of Bush's *Endless Frontier*, which called for a more obvious relevance of scientific research to American public needs. Thus, the sickle cell anemia project represented for Pauling a timely convergence of political, financial, and intellectual interests.

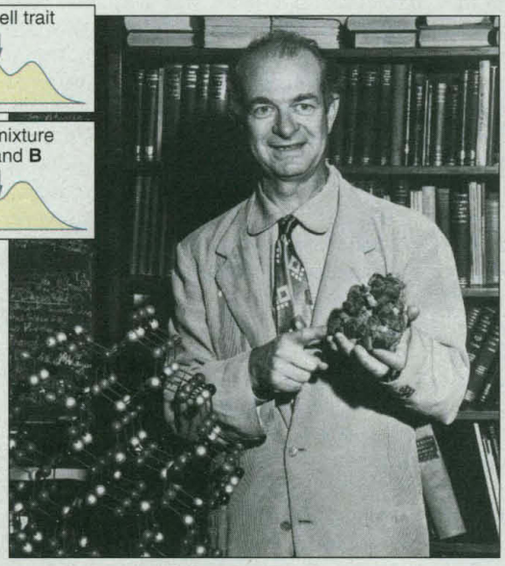
Pauling assigned the sickle cell anemia project to Harvey A. Itano in 1946 as a Ph.D. thesis topic. Itano tried several different physical and chemical methods to distinguish normal hemoglobin from sickle cell hemoglobin, but without success. He then turned to electrophoresis—at that time a new technique designed to separate molecules according to their electrical charge—which had already been used to analyze other blood proteins. Caltech (where Pauling spent more than 40 years) was one of the few institutes in the world to own an electrophoresis apparatus, an instrument not yet commercially available. Itano finally found a slight difference in electrophoretic mobility between normal and sickle cell hemoglobins, indicating that they carried a different electrical charge.



Not only was Pauling's group able to demonstrate that patients with sickle cell anemia have a different type of hemoglobin than healthy individuals, but they also showed that blood taken from patients suffering from sicklemia, a milder form of the disease, contained a mixture of normal and defective hemoglobin in about equal amounts (see figure, A to D). They concluded that sicklemia reflected a heterozygous condition and sickle cell anemia, a homozygous one. They reached this conclusion apparently independently of James Neel, who arrived at the same result by genetic analysis and published it several months earlier.

By the time the Pauling *et al.* paper appeared, it was well established that adult and fetal human hemoglobins differed in their electrophoretic mobility and that several diseases correlated with altered electrophoretic patterns of blood proteins. So what was new about the *Science* paper? Beadle and Tatum had elaborated the "one gene–one enzyme" hypothesis in the 1940s, but it was not yet clear whether genes controlled anything beyond the absence or presence of a particular enzyme. Pauling's sickle cell anemia work demonstrated that genes could qualitatively alter the structure of proteins—in this case, with dramatic consequences for human health. It also demonstrated a causal link—not a mere correlation—between the existence of "defective" hemoglobin molecules and the pathological consequences of sickle cell disease (*1*).

Under Pauling's energetic advertisement in numerous speeches and papers, the discovery became emblematic of how basic science could solve medical problems. In 1956, for example, he asserted "I believe that chemistry can be applied effectively to medical problems, and that through this application we may look forward to significant progress in the field of medicine, as it is transformed from its present empirical form into the science of molecular medicine" (*3*). Immediately after publication of the 1949 paper, Pauling tried to establish a medical research institute at Caltech devoted to "molecular medicine." However, public and private funding agencies remained skeptical of Pauling's approach, and he was unable to attract the necessary funds.



Hegemonic hemoglobins. Linus Pauling with a model and sample of beryl silicate. (**Inset**) Figure 3 from Pauling's seminal paper (*1*) showing that normal and sickle cell hemoglobin have different electrophoretic mobilities.

Based on their knowledge of the molecular nature of sickle cell anemia, Pauling and Itano proposed several treatments (carbon monoxide or sodium nitrite) to prevent sickling of red cells. After 2 years of clinical trials the results turned out to be disappointing and were never published. Unfortunately, this would not be the last of such failures. Even today, our extremely detailed understanding of the molecular etiology of sickle cell anemia has led to new diagnostic possibilities, but has contributed only modestly to improvements in therapy.

In the 1950s, Itano and others moved on to generalize their approach to other blood pathologies. But for Pauling the main challenge was to pinpoint the origin of the electrophoretic difference—presumably a difference in the amino acid composition of the normal and pathological hemoglobins. With Walter A. Schroeder, he performed chromatographic analysis of normal and sickle cell anemia hemoglobin but was unable, in 1950, to find a difference in amino acid content that could explain the electrophoresis result, a conclusion soon confirmed by others.

Then, in 1957, groundbreaking news arrived from England. Vernon Ingram had succeeded in identifying a single amino acid difference between normal and sickle cell hemoglobin that explained the different electrophoretic mobilities of the two proteins. His success was the result of a new method he had devised, combining paper chromatography with electrophoresis for the separation of peptides—he called it fingerprinting. The importance of this result went far beyond the etiology of a particular disease. Indeed, for the first time it was demonstrated that an alteration in a Mendelian gene caused an alteration in the amino acid sequence of the corresponding polypeptide chain (*4*). Ingram had brought the understanding of gene function one step further. Not since the proposal of a double helical structure for DNA in 1953 had the research interests of geneticists, biochemists, and structural biologists merged so closely. Just how it was that DNA sequences determined the amino acid sequences of proteins (the coding problem) became a pressing challenge that molecular biologists and biochemists sought to address. By 1966 the genetic code had been deciphered, and it was finally clear how the information in DNA was translated into protein.

The sickle cell anemia project represented a turning point in Pauling's career. After he received the Nobel Prize in chemistry in 1954, Pauling became increasingly involved in political activities and shifted his remaining research toward medical problems such as the molecular basis of mental illness and his controversial vitamin C crusade. His medical research resonated with his peace activism, for example, he proposed that nuclear bomb testing was the source of an increased mutation rate, causing innumerable "molecular diseases."

The legacy of early sickle cell anemia research cannot be underestimated. Pauling's grand vision of molecular biology and medicine has been realized to an extent he could never have foreseen, even if our therapeutic power does not yet match our understanding of the molecular basis of disease.

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PERSPECTIVES: EVOLUTIONARY BIOLOGY

The Evolutionary Synthesis

Nils Chr. Stenseth

With his *Origin of Species* (*1*) Darwin enabled humans to be viewed as part of nature and provided a theoretical platform for rejecting the notion of a special creation. Today, no biologist questions the reality of evolution or that its mechanism is natural selection. Indeed, "nothing in biology makes sense except in the light of evolution" (*2*). Recently, the Royal Swedish Academy of Sciences awarded the 1999 Crafoord Prize to three giants in the field of evolutionary biology: Ernst Mayr (Harvard University, USA), John Maynard Smith (University of Sussex, UK), and George C. Williams (State University of New York at Stony Brook, USA). The Crafoord Prize (considered the Nobel Prize in fields for which no Nobel is awarded) was established in 1980 to promote basic scientific research in mathematics and astronomy, the geosciences, and the biological sciences (in particular ecology and rheumatoid arthritis). A conference on evolutionary biology that highlighted the contributions of the three prizewinners was held as part of the Crafoord ceremony.

The 1930s saw the emergence of the so-called "modern synthesis" (*3*) or "neo-Darwinism" theory of evolutionary biology. The "modern synthesis" integrated Mendelian genetics, systematics, paleontology, and ecology into a coherent theory of evolution that combined the theory of natural selection with the emerging understanding of how genes are transmitted from one generation to the next. With his *Systematics and the Origin of Species* (*4*), Mayr firmly established the modern synthesis. He promoted the idea of a "biological species," in which species are "groups of actually or potentially interbreeding natural populations that are reproductively isolated from other such groups" (*4*).

The next important embellishment of Darwin's theory—the notion of evolution for the good of the species (*5*)—began to crystallize in the 1960s but was soon rejected, and the original Darwinian emphasis on the importance of the individual in the selection process was substantiated. The other prizewinners—George C. Williams and John Maynard Smith—contributed significantly to this rejection, as did William D. Hamilton (an earlier Crafoord Prize winner) (*6*, *7*). Of particular importance was Williams' book *Adaptation and Natural Selection* (*7*), which proposed that the evolution of a trait must confer an immediate selective advantage on an individual (generally in a group with other related individuals) rather than yield an ultimate long-term benefit for the group or species as a whole. Williams' pioneering work on the evolution of sex, senescence, and individually harmful social adaptations was based on this premise.

Taking a mathematical approach, Maynard Smith introduced game theory to the study of evolution. (Game theory postulates that the net benefit to an individual in a group of two or more depends on the behavior or strategies of the other individuals in the group.) He also introduced the notion of "evolutionarily stable strategies," that is, strategies adopted by an entire population that cannot be perturbed by other competing strategies (*8*). Game theory has proved fruitful for solving a broad range of evolutionary paradoxes, such as why the life histories (reproduction and survival) of organisms are so different, why evolution has maintained sex, the variety of animal behaviors that exist, and in particular why there is cooperation between individuals in a population.

Collectively, the three prizewinners have participated in the two greatest advances in evolutionary biology this century: the establishment of the modern synthesis and the realization that individual selection is more important than group selection. Mayr was instrumental in incorporating evolutionary thinking into systematics and biogeography; Williams and Maynard Smith laid the foundation for what is called the adaptationist program. This program states that evolution can be primarily explained in terms of natural selection maximizing fitness under existing environmental conditions.

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Mayr continues to work on philosophical and historical issues within evolutionary biology (*9*). Maynard Smith has recently started to study the evolution of bacteria (*10*), and Williams continues his work on aging and has advocated the application of evolutionary thinking to medicine (*11*). An important development in the last 10 years has been the study by Maynard Smith, together with Eörs Szathmáry (*12*), of the "major transitions"—that is, the changes in complexity of organisms through evolution—and their attempt to develop a common theory to explain the evolution of eukaryotes, sex, multicellularity, colonial life, and culture. The three prizewinners have not only contributed enormously to the field of evolutionary biology, but have actively participated in bringing Darwinian thinking to a very broad audience (*13*).

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