role in the climate system when large, Northern Hemisphere ice sheets are absent.

Although the mid-Holocene represents a period of change in the climate system under conditions not all that different from today, two temptations must be resisted. The first is to use the mid-Holocene as a direct analog for contemporary climate change. Although, like today, CO_2 concentrations increased during this time, it must be reiterated that the rate of CO_2 increase was more than two orders of magnitude smaller and was very likely a response to, rather than a forcing of, climate change. The second is to assume that we have sufficient data to confidently characterize mid-Holocene climate. Because the signal of Holocene climate change is small, the noise is correspondingly large, and in consequence Holocene climate is effectively more complex than glacial climate (*15*). The "complexity" in this case is spatial variability, which can be addressed only by obtaining high-quality, high-resolution paleoclimate data from many, widely distributed locations.

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PERSPECTIVES: PLANETARY SCIENCE

On the Edge of the Solar System

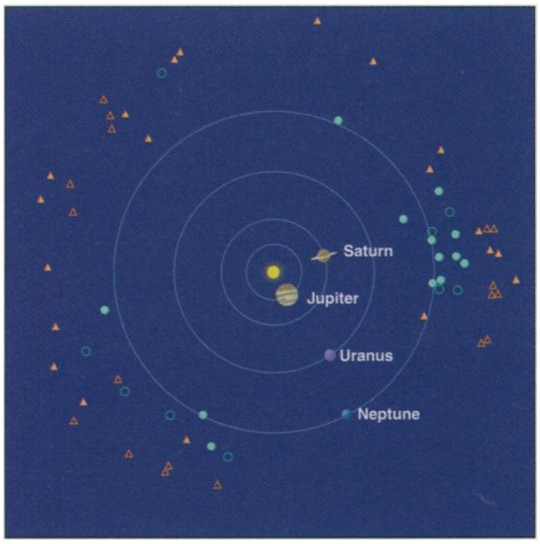
Rodney Gomes

Beyond the orbit of Neptune, the solar system does not contain any large objects. According to solar system models (*1*, *2*), a large number of smaller objects should orbit the sun in these distant regions, but with the exception of Pluto, these objects were long beyond the limits of detectability. New imaging has overcome this problem. Since the discovery of the first member of the Edgeworth-Kuiper Belt (EKB) in 1992 (*3*) confirmed the early predictions, nearly 200 objects have been observed at distances between 30 and 50 astronomical units (AU) from the sun (*4*). The wealth of new data has led to consensus on some and controversy on other central issues regarding the evolution and structure of the outer regions of the solar system.

According to Edgeworth (*1*) and Kuiper (*2*), the region now referred to as the Edgeworth-Kuiper Belt should be inhabited by a large number of small objects. The most probable scenario is that the primordial EKB was much more massive—a total mass of about 30 Earth masses is necessary to form its biggest members known today, including Pluto, two orders of magnitude larger than the mass indicated by observations. Subsequently, mass was lost, because the proximity to Neptune and Uranus created a dynamic orbital environment and led to collision of objects with these large planets, ejection from the solar system, or the breakup of larger objects (*5*, *6*). Beyond 50 AU, the planets are too distant to perturb orbits, and thus a larger amount of mass is theoretically expected to be found there. Unfortunately, there are no observations yet of any Edgeworth-Kuiper Belt objects (EKBOs) that remain outside the 50 AU boundary during their entire orbit, and this aspect of the theory cannot be confirmed or disproved without further data.

Three different groups of EKBOs are currently known. Most members of the resonant group are located in the 2:3 resonance with Neptune; that is, they complete two orbits around the sun in the time it takes Neptune to complete three orbits. The 2:3 resonance probably stabilizes these "plutinos" (see the figure) against disruptive gravitational perturbations by Neptune. A few resonant objects are in the 3:4, 5:7, and 3:5 resonances, and two are in the 1:2 resonance. Eccentricities and inclinations for plutinos can reach 0.34 and 40 symbol 176°, respectively. Members of the nonresonant group (see the figure) have been found mostly between the 2:3 and 1:2 resonances. They have average eccentricities and inclinations around 0.07 and 9.5 symbol 176 °, respectively. The scattered group consists of objects with very eccentric orbits. So far, only five members of this group have been identified, but their origin is the least controversial of all the objects. They are believed to be remnants of a collection of barely stable orbits with a perihelion (closest approach to the sun) a little beyond that of Neptune. These orbits were attained after close encounters with Neptune, either from a region of slow diffusion in the Kuiper Belt (*7*) at distances between 35 and 42 AU or from a more unstable region between the orbit of Uranus and just beyond that of Neptune in a primordial EKB (*8*). They are believed to be the source of the Jupiter family of comets (*8*).

There are two main theories regarding the origin of the first two groups: the planetary migration theory (*9*) and the large scattered planetesimals theory (*10*). Both theories assume a primordial configuration in which Neptune orbits in a planetesimal-rich environment. If the planetesimals are numerous and small, angular momentum and energy exchange of the swarm of objects with the precursors to the four major planets (or protoplanets) induce the planets to migrate radially. Neptune suffers an outward migration of about 7 to 8 AU and traps many planetesimals in resonance, whose eccentricities and inclinations are thus excited. This theory can explain the EKBOs at the 2:3 resonance with Neptune, including Pluto (*9*). However, the 1:2 resonance region seems far less populated than would be expected from numerical simulations. The theory also cannot explain the moderately high eccentricities and inclinations for the nonresonant group. The second theory assumes a few large (order of an Earth mass) planetesimals orbiting near



Position of Edgeworth-Kuiper Belt objects on 1 January 1998. The orbits of the giant planets (outward from the sun: Jupiter, Saturn, Uranus, and Neptune) are also shown. Blue circles, plutinos; red triangles, other Edgeworth Kuiper Belt objects; filled symbols, relatively reliable orbits, open symbols, less reliable orbits. Data from (*16*).

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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*).

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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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