man cutaneous melanomas, for example, patent (noncollapsed) lymphatic vessels are common at the periphery but not in the center of the tumor (*9*).

The Padera *et al.* study reveals that the expression of VEGF-C in experimental mouse tumors correlates with the incidence of lymph node metastasis (but not pulmonary metastasis, which is dependent on dissemination through the blood). This suggests that VEGF-C may be a potential therapeutic target for treating lymphatic tumor metastases, but there is still much to learn. For instance, does VEGF-C contribute to lymph node metastasis by boosting the number of lymphatic vessels, by promoting hyperplasia or dilatation of peritumoral lymph vessels, or by stimulating angiogenesis (*10*)? Targeting VEGF-C to prevent lymphatic metastasis should be approached with caution because in many patients with visceral neoplasms, metastasis has already occurred by the time of diagnosis.

The homeostasis of body fluids requires an intact lymphatic system and hence fully active VEGF-C. Surgical excision of lymph nodes containing metastases can upset this dynamic equilibrium. The subsequent disruption of lymphatic drainage may result in the accumulation of fluid in the affected extremity, a complication known as lymphedema (see the figure). In a mouse model of congenital lymphedema—caused by an inactivating mutation in the VEGF C/D receptor–3 (VEGFR-3) (*11*)—the symptoms can be abrogated by treatment with VEGF-C gene therapy, which induces lymphangiogenesis. Similarly, inhibition of lymphangiogenesis in transgenic mice expressing soluble VEGFR-3 produces severe lymphedema (*12*). These studies suggest that systemic targeting of VEGF-C (and other lymphangiogenic molecules) could increase the risk of lymphedema in patients.

Any clinical trial involving VEGF-C–targeted therapy should include methods to identify the potential increased risk of undesirable side effects such as lymphedema. Similarly, any trial designed to assess the efficacy of VEGF-C treatment for reversing lymphedema in cancer patients must take into account the possibility that VEGF-C–induced lymphangiogenesis could enhance lymphatic metastasis. A better understanding of lymphangiogenesis is a prerequisite for developing effective targeted therapy for treating cancer patients.

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PERSPECTIVES: GEOLOGY

Flood Basalts—Bigger and Badder

Paul R. Renne

Flood volcanism is an episodic process whereby vast amounts of mass and energy are transferred from Earth's interior to its surface within a relatively short time. Such events have occurred about a dozen times during the last several hundred million years. There is increasing geochronological evidence that in each of these events, the magma was generated and erupted within 1 to 3 million years or so. The implied magma production rate, on the order of 10^6 km^3/year, is much higher than in Earth's main magma-producing environments at the boundaries between lithospheric plates.

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Increasingly, Earth scientists are trying to establish the causes and consequences of flood volcanism. The Siberian Traps have played a central role in shaping thought on the problem.

More than 20 years ago, Morgan (*1*) posited that this massive mantle belch might have been the first manifestation of a still-active magma source (hot spot) represented by a volcanic island, Jan Mayen, in the North Atlantic. A generalized theory soon linked flood basalts to hot spots created by buoyant, superheated mantle plumes, which were inferred to play a dynamic role in the rifting apart of continents (*2*). A leading alternative to these "plume impact" models holds that flood volcanism results when rifting of the lithosphere causes decompression of the mantle, allowing it to melt and rise buoyantly without requiring anomalous heating.

A volcanic province a million times the area of that shown here (in Kilauea's east rift) lies buried under Siberian sediments.

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The rifting that precedes decompression melting in the latter model cannot happen quickly for mechanical reasons: The lower lithosphere is ductile and does not break rapidly under extension. Pure decompression melting therefore seems less consistent with the observed rapidity of the eruptions than does the plume impact model. On the other hand, there is evidence that crustal extension predates volcanism in some cases, which suggests that at least some aspects of the decompression model are valid. But what initiates extension, if not the dynamic consequences of plume impact? One possibility is edge-driven convection (*3*), hypothesized to originate from discontinuities in lithospheric thickness and properties.

Besides establishing the brevity of flood volcanic events, geochronology has played a key role in defining the vast provinces wherein they occur. A recent example is the central Atlantic magmatic province (CAMP), whose 200-million-year-old remnants are now scattered across eastern North America, northeastern South America, western Africa, and western Europe. It had been hypothesized that CAMP's remnants formed a single contiguous province before the opening of the central Atlantic (*4*), but it was only through precise dating of the dispersed fragments that identification of an extensive flood basalt province was confirmed (*5*).

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Similarly, new dating results reported by Reichow *et al.* on page 1846 of this issue (*6*) document the subsurface extent of the Siberian Traps nearly 1000 km westward from the previously known limits of the province. The authors have analyzed drill-core samples from the West Siberian Basin (WSB). The new dating provides the first definitive evidence linking them to the same magmatic event.

Using the $^{40}Ar/^{39}Ar$ method, Reichow *et al.* (*6*) show that the WSB lavas are indistinguishable in age from those to the east, previously dated at 250 million years by similar methods (*7*). The new results suggest a total areal extent of 3.9×10^6 km^2 for the Siberian Traps. The total volume of magma represented by this enlarged province is difficult to estimate, but 2×10^6 to 3×10^6 km^3 is probable, clearly qualifying the Siberian Traps as the largest (by volume) known continental flood basalt province.

The WSB underwent rifting during the late Paleozoic or early Mesozoic (about 300 to 200 million years ago), bearing out the general relationship between extension and flood volcanism. Unfortunately, as in many other cases, existing data appear equivocal on the crucial question of whether extension began before or after the onset of volcanism. Establishing the relative ages of these events should now become a priority.

Upward revision of the dimensions of flood volcanic provinces will doubtless continue as research progresses. Recent work (*8*) shows that magmatism of essentially the same age as the Siberian Traps occurred as far south as central Kazakhstan, and a swath of contemporary magmatic activity may even extend semicontinuously from there to south of Lake Baikal. These complexes appear to represent the roots of silicic volcanic centers, whose explosive eruptions would have provided a mechanism for transporting volcanogenic gases into the upper atmosphere.

These increasing size estimates have important implications for the environmental consequences of flood volcanic events. The more voluminous a magma system is, the more likely it is to generate large quantities of climate-modifying gases such as CO_2 and SO_2. The amounts of such gases actually delivered to the atmosphere by flood volcanism remain difficult to quantify, but there is little doubt that the effects could be significant. The synchrony between flood volcanic events and mass extinctions in the geologic record has been noted for years. For the three biggest events (the Siberian, CAMP, and Deccan traps), a temporal correlation with the most severe extinctions at the end of the Permian, Triassic, and Cretaceous periods, respectively, is firmly established.

The empirical connection between major flood volcanism and severe mass extinctions is all the more intriguing in light of hints of evidence of large meteor impacts coincident with these events. The evidence is strongest at the end of the Cretaceous. The latest hint suggests that CAMP and the extinction at the end of the Triassic may have been coincident with an impact (*9*), although the impact evidence in this case is permissive rather than indicative.

To some Earth scientists, the need for a geophysically plausible unifying theory linking all three phenomena is already clear. Others still consider the evidence for impacts coincident with major extinctions too weak, except at the end of the Cretaceous. But few would dispute that proving the existence of an impact is far more challenging than documenting a flood basalt event: It is difficult to hide millions of cubic kilometers of lavas—even, as shown by Reichow *et al.* (*6*), when they are buried beneath 2 km or more of sediments in Siberia.

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PERSPECTIVES: STATISTICAL MECHANICS

Far from Equilibrium

David A. Egolf

For more than a hundred years, equilibrium statistical mechanics has elucidated the behavior of matter in all its phases. The theory tells us which phase we should expect for our experimental conditions, what characterizes the transitions between phases as conditions are varied, and how these transitions are "universal," such that almost all of the details of the specific experiment are irrelevant (*1*).

Much of the world around us, however, including life itself, is not in equilibrium. Scientists have successfully extended equilibrium statistical mechanics into "near"-equilibrium situations, such that the deviations from equilibrium can be described by linear equations. But theories of the behavior of systems far from equilibrium have been few and far between. On page 1832 of this issue, Liphardt *et al.* (*2*) provide the first experimental test of a remarkable connection (*3*, *4*) between an equilibrium property, the free energy, and a series of measurements performed far from equilibrium.

The free energy is of central importance in statistical mechanics and thermodynamics (*1*). The equilibrium phase of a system corresponds to the absolute minimum of the free energy, and the height of the free-energy barrier between two configurations determines the size of the fluctuation (and thus the amount of time) needed for the system to change from one configuration to the other. For large, complex molecules such as proteins, an understanding of the free-energy landscape (which describes the free energy of all possible configurations of the system) is crucial for determining folding pathways, the topology of the folded state, and the biological utility of the protein [see for example (*5*)].

Unfortunately, the free energy of a state (relative to an arbitrary reference state) is often difficult to determine. The free-energy difference between two thermal states is the work needed to move infinitely slowly (and hence reversibly) between the two states. In practice, the speed at which one can move quasi-reversibly along some reaction coordinate is determined by the relaxation time of the system, that is, the time it takes to reequilibrate as the experimental conditions are changed. If relaxation times are long, the determination of the free-energy differences of a large number of states becomes a daunting task.

In 1997, Jarzynski (*3*, *4*) developed a method for circumventing the difficulties of long relaxation times. He derived an exact relation between free-energy differences and appropriately weighted averages

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