would place sampling and remote-sensing instruments in close orbit around a cometary nucleus. The ultra-fast spacecraft flybys of comet Halley in 1986 provided a tremendous advance in cometary knowledge, but what is really needed is a mission that can remain at the comet, gather materials more carefully, and perform more thorough elemental, molecular, isotopic and physical analyses, as well as watching changes with time.

The European Space Agency is now planning just such a mission, called Rosetta, in many ways similar to NASA's Comet Rendezvous Asteroid Flyby mission, which was cancelled in 1991 for budgetary reasons. The astronomers hope that Rosetta will prove as valuable as its namesake, providing the key to all the mysteries that the comets pose at present. □

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EARTHQUAKES

Learning from the whispers

Larry J. Ruff

THE notion that the faint whispers of a remote earthquake can trigger other earthquakes has been considered a 'wild idea', one with no observational support. But once again the Earth has proved to be more dynamic and interactive than many of us had presumed.

Writing in *Science*[1], D. P. Hill and others present convincing evidence that the large (magnitude 7.3) Landers earthquake in southern California directly triggered earthquakes at 14 distinct sites scattered over the western United States (see figure); the furthest site was Yellowstone National Park in Wyoming, 1,250 km from Landers. Most of the triggered seismicity occurred in areas with recent volcanic activity and, in some cases, also with geothermal activity — notably Yellowstone and the Geysers area north of San Francisco. (Hill *et al.* note that the San Andreas system did not show any obvious examples of triggering, nor did the geothermal areas in the Salton Sea trough only 150 km to the south of Landers.) The largest triggered earthquake, magnitude 5.6, occurred 250 km away near the California–Nevada border, about 22 hours after Landers. However, most of the triggered events were small, with magnitudes of 2 and less. At some sites, the triggered seismicity began within seconds after the passage of the seismic waves from the Landers earthquake; at others it was delayed. The long duration of triggered activity indicates that the seismic waves must spark off some local process that continues to operate for many hours to days.

Map of the area over which the remote influence of the Landers earthquake was felt. Large red star, epicentre of the Landers event; small star, the Petrolia earthquake. Red dots show some of the sites with triggered seismicity from the Landers earthquakes, as documented by Hill *et al.*[1]. Yellowstone is 1,250 km from the Landers epicentre.

The observations of Hill *et al.* are certainly exciting. The idea of earthquake interaction has now fired the imagination of many people, a common reaction being to ask three questions. First, how new and unique are these observations? Second, what is the physical cause of the triggering? And third, how will this evidence of earthquake interaction change our view of earthquakes?

The answer to the first question depends on one's initial assumption about the nature of earthquake occurrence. Everyone agrees that there is a strong spatial clustering of earthquakes at tectonic boundaries, and that there is a strong space–time clustering of aftershocks after a large earthquake (for a case intermediate between aftershocks and triggered activity, see ref. 2). Beyond the example of aftershocks, attitudes about the temporal occurrence of earthquakes are quite varied and contentious. If your initial assumption is that all earthquakes occur randomly, then the Landers observations are exciting because they force you to change your thinking. If you already think that all earthquakes are triggered, then the Landers observations are still exciting because they offer some vindication for your belief in the face of considerable scepticism over the years.

There is a strong tradition in Russian seismology of earthquake-triggering research. For example recent papers[3–5] have discussed triggering of small earthquakes not only by remote strong earthquakes, but also by Earth tides, seismic noise levels and artificial sources of seismic waves. Indeed, when A. Nikolaev, director of the Institute of Physics of the Earth in Moscow, visited our laboratory earlier this year, he was not surprised by the Landers observations; rather, he was delighted to see that his seismological colleagues in the United States now had such convincing evidence in their own backyard.

Yet if remote earthquake triggering is a common process, then surely there must be some evidence from previous large earthquakes, even in the western United States. Hill and colleagues point out, however, that of the four earthquakes with magnitude 7 or larger in the area since 1980, only the Landers event caused triggering at multiple sites. With respect to the rest of the world, it is also difficult to find clear examples of multiple-site triggering — but then again there are few places on Earth with as many seismographic stations as the western United States.

It is easy to answer the second question: we don't know the cause of remote triggering. This follows from the fact that we do not yet understand the details of 'frictional failure' within the fault zone, and it is these details that ultimately determine exactly when the earthquake will occur. Nonetheless the combination of theoretical, experimental and rare observational evidence suggests that there might be a distinct precursory phase of accelerated failure that eventually leads to the dynamic rupture of the earthquake (see ref. 6 for discussion). So one good idea to explain triggered seismicity is that some regions are 'ready' to have an earthquake, and the final preparatory phase can be initiated by any small disturbance, including the passage of seismic waves. The time delay between the trigger and the eventual earthquake could vary from seconds to days. This basic idea is sufficient to explain the Landers observations, though the reliance on unspecified processes is bothersome.

Given that the Landers earthquake trig-

gered seismicity in volcanic or geothermal areas, Hill *et al.* suggest that the specific triggering mechanism and time delay is due to the properties of the fluid systems (see abstracts from the recent meeting of the American Geophysical Union[7–9]). But there are still some mysterious aspects of this case history. Hill *et al.* show that dynamic stress levels of the Landers seismic waves at the triggered sites are larger than tidal stress levels, generated by the Sun and Moon — but are they larger than dynamic stress levels of other nearby earthquakes? The Petrolia, California, earthquake of 25 April 1992 (magnitude 7.1) did not trigger seismicity at the Mount Lassen and Mount Shasta areas, only 200 km from the Petrolia epicentre (see figure). But, just 64 days later, the Landers earthquake occurred more than 800 km to the south and did trigger seismicity at these volcanoes. Perhaps there is more to triggering than just the peak dynamic stress. But what?

In answer to the third question, I believe that the Landers observation will have a lasting influence on earthquake research. First of all, it changes our initial assumption about earthquake interaction, and allows for more serious scientific considerations of 'wild ideas' on the subject. Second, more documentation and acceptance of triggering may well provide valuable information on the detailed physics of frictional failure; further, the understanding of the final preparatory phase of frictional failure is of paramount importance for short-term earthquake prediction. Perhaps if we can listen in on earthquakes talking to each other, we may learn from the whispers that pass beneath our feet. □

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PHARMACOLOGY

Janus faces of nitric oxide

Solomon H. Snyder

NITRIC oxide (NO) has been implicated as a mediator of neuronal destruction in vascular stroke. In some studies, however, it seems to have neuroprotective effects. This paradox may be resolved by the observations of Lipton *et al.* reported on page 626 of this issue[1]. The authors find that NO might exert both of these effects, depending on its oxidation–reduction status.

Nitric oxide is rapidly emerging as one of the main neurotransmitters in the central and peripheral nervous systems[2]. For many transmitters, decades pass before their specific neural functions are elucidated. By contrast, NO, first reported in the brain only about four years ago, is already known to mediate intestinal relaxation in peristalsis, penile erection, and the actions of glutamate on cyclic GMP levels in the brain. It is also implicated in neuropathological conditions, in that it may mediate major neuronal damage in stroke and neurodegenerative diseases. Most neural destruction in stroke seems to result from a massive release of glutamate, which, acting through the *N*-methyl-D-aspartate (NMDA) subtype of receptor, somehow causes 'excess excitation' resulting in neuronal death[3]. This notion obtained strong support from demonstrations that drugs which are NMDA receptor antagonists provide marked protection against neural damage following vascular occlusion.

Recent evidence indicates that NO mediates these neurotoxic effects of glutamate. The NO-forming enzyme NO synthase (NOS) is activated by Ca^{2+} binding to the calmodulin associated with the enzyme. NMDA receptor activation triggers a massive influx of Ca^{2+} into neurons, and NO is formed and diffuses to adjacent cells to kill them. This model is supported by the ability of NOS inhibitors to block the neurotoxic actions of glutamate and NMDA in brain cultures[4]. The evidence from culture has been translated into clinically relevant models, as in several species low doses of NOS inhibitors, administered after ligating the middle cerebral artery, provide marked protection against stroke damage[5]. The clinical relevance of NO may extend to other forms of neurotoxicity. AIDS dementia, for example, may derive from neurotoxic effects of the coat protein gp120 of the HIV virus which kills neurons when acting in conjunction with glutamate at NMDA receptors. Inhibitors of NOS block this form of neurotoxicity and thus may have a role in the therapy of AIDS dementia[6].

Despite the strong evidence for NO-mediated neurotoxicity, in some studies it seems to be neuroprotective. The neuroprotective action may be explained by observations that NO can nitrosylate the NMDA receptor, thus blocking glutamate neurotransmission[7]. Insights into mechanisms for the neurotoxic and neuroprotective effects now come from Lipton *et al*[1]. who emphasize that NO can exist in distinct oxidation–reduction states which have very different biological actions. Indeed, the designation nitric oxide should be restricted to the reduced, $NO^{\bullet}$ form of the molecule, while the parent NO should be called 'nitrogen monoxide', and the oxidized form NO^{+}, the nitrosonium ion.

Lipton *et al.* present evidence that the neurotoxic actions of NO derive from the $NO^{\bullet}$ form of the molecule, which reacts with superoxide anion to form peroxynitrite, probably the final neurotoxic agent. On the other hand, NO in the form of the nitrosonium ion (NO^{+}) reacts with the thiol group of the NMDA receptor to block neurotransmission. Numerous other proteins can be S-nitrosylated, a modification which conceivably has physiological regulatory functions, akin to phosphorylation[8]. Lipton *et al.* use various NO donors in the presence or absence of reducing agents to form $NO^{\bullet}$ or NO^{+} respectively. In cerebral cortical cultures, conditions favouring $NO^{\bullet}$ give rise to neurotoxicity, whereas neuroprotective effects occur in the presence of NO^{+}. NO^{+} also blocks NMDA receptor-mediated currents.

These results may have substantial therapeutic implications. The observation that NOS inhibitors provide up to 70 per cent protection from neural stroke damage has triggered a great effort in the pharmaceutical industry to develop NOS inhibitors as antistroke drugs. Perhaps a more sophisticated approach is needed. The ideal therapeutic agent should be one that prevents the formation of $NO^{\bullet}$ while enhancing the formation of NO^{+}. Alternatively, one might seek to develop drugs that are converted to nitric oxide, but only to the NO^{+} form of the molecule. Similar considerations would apply to drugs aimed at AIDS dementia and neurodegenerative conditions, such as Huntington's and Parkinson's diseases, which may also involve excessive stimulation of NMDA receptors. □

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