

above is the uncertainty in the amount of slip during great earthquakes. Yet, because the longer the time since the previous earthquake, the larger the potential slip will be to drive the next one, the more severe those less frequent great earthquakes will be. Even if only one segment has stored potential slip comparable to that of the 1950 Assam earthquake, the largest intracontinental earthquake in recorded history (19), a replication of that earthquake along the more populous segments of the Himalaya would be devastating.

The population of India has doubled since the last great Himalayan earthquake in 1950. The urban population in the Ganges Plain has increased by a factor of 10 since the 1905 earthquake, when collapsing buildings killed 19,500 people (10). Today, about 50 million people are at risk from great Himalayan earthquakes, many of them in towns and villages in the Ganges plain. The capital cities of Bangladesh, Bhutan, India, Nepal, and Pakistan and several other cities with more than a million inhabitants are vulnerable to damage from some of these future earthquakes.

The enforcement of building codes in India and Pakistan mitigates the hazards to this large population, but a comparison be-

tween fatalities in the 1819 Kachchh and 2001 Bhuj earthquakes is not encouraging. The population of Kachchh has increased by a factor of 10. Two thousand fatalities occurred in 1819 (23), compared with the 19,000 confirmed fatalities this year. The implemented seismic code apparently did not lessen the percentage of the population killed. Like the Himalayan earthquakes, the Bhuj event occurred in an identified zone of heightened seismic hazard. Projecting these figures to just one of the possibly several overdue Himalayan earthquakes (for example, a repeat of the Kangra 1905 event) yields 200,000 predictable fatalities. Similar conclusions have been reached by Arya (24). Such an estimate may be too low by an order of magnitude should a great earthquake occur near one of the megacities in the Ganges Plain.

References and Notes

1. See the supplementary material on Science Online at www.sciencemag.org/cgi/content/full/293/5534/1442/DC1 for a table of major historical earthquakes in India.
2. L. Seeber, J. Armbruster, in *Earthquake Prediction: An International Review*, Maurice Ewing Series, vol. 4, D. W. Simpson, P. G. Richards, Eds. (American Geophysical Union, Washington, DC, 1981), pp. 259–277.
3. P. Molnar, *J. Himalayan Geol.* **1**, 131 (1990).
4. K. Larson, R. Bürgmann, R. Bilham, J. Freymueller, *J. Geophys. Res.* **104**, 1177 (1999).

5. M. Jackson, R. Bilham, *J. Geophys. Res.* **99**, 13897 (1994).
6. M. Pandey et al., *Geophys. Res. Lett.* **22**, 751 (1995).
7. J. Paul et al., *Geophys. Res. Lett.* **28**, 647 (2001).
8. J. Lavé, J.-Ph. Avouac, *J. Geophys. Res.* **105**, 5735 (2000).
9. R. Bilham, *Curr. Sci.* **69**, 155 (1995).
10. N. Ambraseys, R. Bilham, *Curr. Sci.* **79**, 101 (2000).
11. R. Bilham, *Geophys. J. Int.* **144**, 713 (2001).
12. C. S. Middlemiss, The Kangra Earthquake of 4th April, 1905, *Mem. Geol. Surv. India*, vol. 37 (Geological Survey of India, Calcutta, India, 1910; reprinted 1981).
13. R. Bilham, P. England, *Nature* **410**, 806, (2001).
14. B. S. J. B. Rana, *Nepalko Maha Bhukampa* (The Great Earthquake of Nepal) (published by the author in Kathmandu, Nepal, ed. 2, 1935).
15. J. A. Dunn, J. B. Auden, A. M. N. Ghosh, D. N. Wadia, *The Bihar Earthquake of 1934*, *Geol. Surv. India Mem.* vol. 73 (Geological Survey of India, Calcutta, India, 1939).
16. R. Bilham, F. Blume, R. Bendick, V. K. Gaur, *Curr. Sci.* **74**, 213 (1998).
17. M. R. Pandey, P. Molnar, *J. Geol. Soc. Nepal* **5**, 22 (1988).
18. W.-P. Chen, P. Molnar, *J. Geophys. Res.* **82**, 2945 (1977).
19. P. Molnar, Q. Deng, *J. Geophys. Res.* **89**, 6203 (1984).
20. A. Bapat, R. C. Kulkarni, S. K. Guha, *Catalog of Earthquakes in India and Neighborhood from Historical Period up to 1979* (Indian Society of Earthquake Technology, Roorkee, India, 1983).
21. K. N. Khattri, *Tectonophysics* **138**, 79 (1987).
22. R. N. Iyengar, S. D. Sharma, *Earthquake History of India in Medieval Times* (Central Building Research Institute, Roorkee, India, 1998).
23. R. Bilham, in *Coastal Tectonics*, I. S. Stewart, C. Vita-Finzi, Eds. (Geological Society of London, London, 1999), pp. 295–318.
24. A. S. Arya, *Curr. Sci.* **62**, 251 (1992).

PERSPECTIVES: BIOREMEDIATION

Anaerobes to the Rescue

Derek R. Lovley

Polluted groundwater systems are one of the most difficult environments to clean up. The most ancient of all life processes—microbial metabolism in the absence of oxygen (1)—is beginning to show significant potential for solving this very modern problem.

Removal of the contaminated water is often not viable because of the sheer volume of contaminated water that needs to be pumped and treated. Furthermore, contaminants continue to leach out from sediments and pollute more groundwater after the contaminated water has been extracted.

To treat contaminated groundwater in situ, reactive barriers may be placed in the subsurface to remove contaminants from groundwater. But this is only feasible and cost-effective for treating shallow, restricted areas of contamination. Microorganisms that naturally live in the subsurface may also degrade, detoxify, or immobilize

contaminants (2), a process called in situ bioremediation.

Until recently, practical applications of in situ bioremediation have focused mostly on aerobic microorganisms (3), which gain energy by oxidizing organic compounds to carbon dioxide with oxygen serving as the electron acceptor. When oxygen is available in the subsurface, aerobes can clean up contaminated groundwater by oxidizing organic contaminants to carbon dioxide.

However, this approach has had limited success, not least because oxygen—an absolute requirement for aerobes—is scarce in many contaminated subsurface environments. The amount of oxygen dissolved in groundwater is low, and the rate of oxygen supply through diffusion from overlying unsaturated soils is slow. In subsurface environments polluted with organic contaminants, such as petroleum or leached materials from landfills, aerobes dutifully oxidize the contaminants to carbon dioxide, consuming the available dissolved oxygen in the process. Usually, the most heavily contaminated portions of the aquifer

quickly become oxygen depleted; oxygen is only found at the fringes of the contaminant plume (see the figure).

The scarcity of oxygen in many contaminated subsurface environments has raised interest in the in situ bioremediation potential of anaerobes, which grow in the absence of oxygen. Anaerobes also oxidize organic compounds to carbon dioxide but use electron acceptors such as nitrate, sulfate, or Fe³⁺ oxides instead of oxygen.

The diverse metabolic capabilities of anaerobes represent a potentially potent force in the fight against groundwater contamination. The degree of natural degradation of hydrocarbon contaminants in the anoxic subsurface is much higher than previously thought. For example, benzene is often the contaminant of greatest concern in subsurface petroleum contamination because it is water soluble, toxic, and carcinogenic. Recent studies have shown that anaerobes recovered from the subsurface can degrade benzene. In some contaminated aquifers, substantial natural removal of benzene and other aromatic hydrocarbons in the anoxic zone was observed (4).

In some cases, natural degradation by anaerobes and aerobes may limit the spread of contamination; if no important water resources are threatened, no further remediation action may be necessary. If the natural rates of contaminant degrada-

The author is in the Department of Microbiology, University of Massachusetts, Amherst, MA 01337, USA. E-mail: dlovley@microbio.umass.edu

tion are too slow, increased sulfate or nitrate levels may accelerate the rate of anaerobic contaminant degradation (5, 6). This is analogous to the more common practice of adding oxygen to the subsurface to enhance the activity of aerobic microorganisms.

The addition of oxygen is technically difficult and expensive because its solubility is low and it reacts with reduced components in anoxic groundwater, such as ferrous iron. Adding enough oxygen to effectively stimulate aerobic microorganisms is thus often difficult. Electron acceptors such as sulfate and nitrate do not have these limitations because they are highly soluble and are not consumed by nonbiological processes. In a subsurface environment that was heavily contaminated with benzene and could not be cleaned up through addition of oxygen, benzene was readily removed when sulfate was added (5).

Another bioremediation problem is posed by subsurface environments contaminated with chlorinated solvents. Aerobic microorganisms do not degrade common chlorinated contaminants such as perchloroethene (PCE) and trichloroethene (TCE) under the conditions typically found in aquifers (7). In a shallow, aerobic aquifer, these solvents persist unless cocontaminants such as petroleum cause the development of anoxic conditions.

Some anaerobes can degrade PCE and TCE by using these compounds as electron acceptors for the anaerobic oxidation of organic compounds or hydrogen gas (7). Under ideal conditions, the reduction process removes the chlorine atoms from the contaminants, yielding ethylene as the final product; the chlorine is released as chloride. PCE and TCE contamination may thus be remediated by adding organic compounds to the subsurface (7). Aerobic degradation of the added organics results in anoxic conditions; dechlorinating anaerobes then use the added organics (or hydrogen produced by other anaerobes from the organics) to dechlorinate and thus detoxify the contaminants.

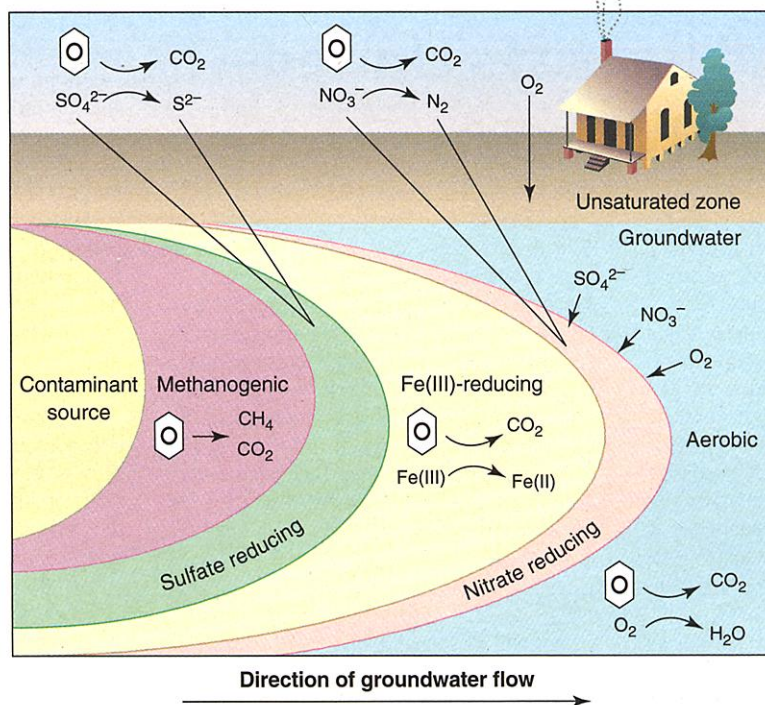
Nitrate contamination as a result of fertilizer use or the introduction of wastes in-

to the subsurface can be treated in an analogous manner (8). Denitrifying microorganisms in the subsurface can oxidize added organics or hydrogen, reducing nitrate to harmless dinitrogen.

Toxic metals and metalloids (9) are often soluble, and thus mobile, in aerobic groundwater. However, under anoxic conditions, microorganisms can reduce them to insoluble forms that precipitate from the groundwater (10). The metals and metal-

loids are thus immobilized, limiting their spread and threat to water resources. Elements that may be immobilized in this way include uranium, chromium, technetium, cobalt, and selenium. Their in situ bioremediation follows the same strategy as for chlorinated solvents: Added organics promote the development of anoxic conditions and the activity of the metal-reducing microorganisms.

To answer these questions, we need to know which microorganisms carry out the relevant bioremediation reactions in situ.



Microbial processes in a petroleum-contaminated aquifer. Oxygen inhibits the growth and activity of anaerobes but is typically only available at the fringe of the contaminant plume. Under anoxic conditions, anaerobes use electron acceptors such as nitrate, Fe(III), or sulfate to oxidize benzene and other contaminants. Once these electron acceptors are depleted, anaerobic metabolism proceeds by converting organic matter to methane and carbon dioxide. Methane production therefore dominates closest to the source of contamination where alternative electron acceptors have been depleted. Farther from the source, a succession of anaerobic processes is dictated by electron acceptor availability.

loids are thus immobilized, limiting their spread and threat to water resources. Elements that may be immobilized in this way include uranium, chromium, technetium, cobalt, and selenium. Their in situ bioremediation follows the same strategy as for chlorinated solvents: Added organics promote the development of anoxic conditions and the activity of the metal-reducing microorganisms.

These anaerobic strategies for in situ bioremediation are promising, but substantial research remains to be done before any of them can be adopted for routine application. A limited number of field studies have evaluated natural or stimulated in situ bioremediation under anoxic conditions. These studies have shown that

anaerobic processes are effective at some sites but fail at others (4, 7, 11). This disparity in effectiveness was even observed within different zones of the same aquifer. It is unclear whether this variability reflects heterogeneity in the distribution of the anaerobes or in environmental factors controlling their activity.

Environmentally important microorganisms are often difficult to recover in pure culture (12), but in the present case, microbiologists may be lucky. Studies of in situ bioremediation of hydrocarbons coupled to Fe³⁺ reduction (13), reductive dechlorination (11), and stimulated metal reduction (14) suggest that the anaerobic microorganisms involved in these processes in aquifers are closely related to those that carry out these bioremediation reactions in pure culture in the lab.

The genomes of these pure cultures are available (15). It should thus be possible to determine which genes are involved in the bioremediation reactions of interest and which genes enable the microorganisms to thrive in subsurface environments. It may even be possible to culture the anaerobes that are responsible for other in situ bioremediation processes. Once the functions of their genes have been deciphered, the study of anaerobic in situ bioremediation can begin in earnest. With the help of recently developed methods for cloning large fragments of environmental DNA (16), it will be possible to assign functions to genes of the closely related anaerobes living in the subsurface. Measurements of mRNA expression in subsurface samples (17) suggest that whole-genome expression analyses with environmental samples comparable to those now being conducted with pure cultures are within reach.

Coupled with the appropriate geochemical and hydrological studies, this information should help understand the activity of anaerobes involved in in situ bioremediation. This will provide better knowledge of the rate of natural attenua-

tion and promote the rational design of strategies for accelerating groundwater remediation.

References and Notes

1. E. Nisbet, N. Sleep, *Nature* **409**, 1083 (2001).
2. F. H. Chapelle, *Ground-Water Microbiology and Geochemistry* (Wiley, New York, 2001).
3. M. Alexander, *Biodegradation and Bioremediation* (Academic Press, New York, 1999).
4. D. R. Lovley, *Biodegradation* **11**, 107 (2000).

5. R. T. Anderson, D. R. Lovley, *Environ. Sci. Technol.* **34**, 2261 (2000).
6. J. A. Cunningham *et al.*, *Environ. Sci. Technol.* **35**, 1663 (2001).
7. M. D. Lee, J. M. Odom, R. J. Buchanan, *Annu. Rev. Microbiol.* **52**, 423 (1998).
8. R. L. Smith *et al.*, *Environ. Sci. Technol.* **35**, 196 (2001).
9. A metalloid is an element that is not truly a metal by definition but has some of the properties of metals. Environmentally important examples are selenium and arsenic.
10. J. R. Lloyd, D. R. Lovley, *Curr. Opin. Biotechnol.* **12**, 248 (2001).

11. D. E. Fennell, A. B. Carrol, J. M. Gossett, S. H. Zinder, *Environ. Sci. Technol.* **35**, 1830 (2001).
12. R. I. Amann, W. Ludwig, K.-H. Schleifer, *Microbiol. Rev.* **59**, 143 (1995).
13. J. N. Rooney-Varga *et al.*, *Appl. Environ. Microbiol.* **65**, 3056 (1999).
14. O. L. Snoeyenbos-West, K. P. Nevin, D. R. Lovley, *Microbial Ecol.* **39**, 153 (2000).
15. See www.tigr.org.
16. O. Beja *et al.*, *Environ. Microbiol.* **2**, 516 (2000).
17. M. S. Wilson, C. Bakermans, E. L. Madsen, *Appl. Environ. Microbiol.* **65**, 80 (1999).

PERSPECTIVES: BIOMEDICINE

Tauists and β aptists United—Well Almost!

Virginia M.-Y. Lee

The brains of Alzheimer's disease (AD) patients contain two hallmark pathological features: neurofibrillary tangles composed of tau protein and senile plaques composed of deposits of amyloid- β peptide. A controversy still rages over whether tau tangles or amyloid- β plaques are the primary cause of neurodegeneration in AD, and each has its vocal advocates—the

tauists and β aptists, respectively. Yet despite decades of intense research, the primacy of each pathology is still in dispute and the connection between them remains largely speculative. Work described by Lewis *et al.* (1) and Götz *et al.* (2) on pages 1487 and 1491 of this issue, respectively, provides convincing evidence that a causal connection exists between the two pathologies. Both groups independently demonstrate in transgenic mice that amyloid- β deposits influence the formation of tau tangles in brain areas that are known to be affected in AD.

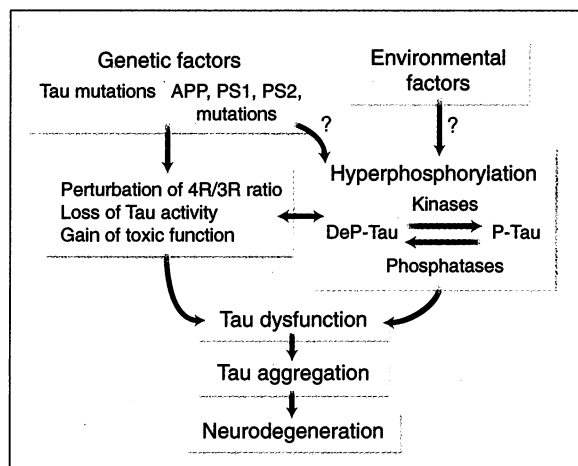
Patients with an early-onset familial form of AD carry mutations in genes encoding either amyloid- β precursor protein (APP) or one of the presenilin proteins (3–5). These mutations appear to cause AD by increasing the production of the stickier form of amyloid- β peptide ($A\beta_{1-42}$), thus implicating amyloid- β plaques in AD pathogenesis (6–9). Mutations in the gene encoding tau, a microtubule-binding protein, have been found in several neurodegenerative diseases linked to chromosome 17 (collectively called the tauopathies).

The discovery of tau neurofibrillary tangles in the absence of amyloid deposits in these diseases provides unequivocal evidence that tau abnormalities alone are sufficient to cause neurodegeneration in the brain (10–12). The puzzle is that mouse models of AD do not accurately recapitulate the dual pathology of the disease. For example, transgenic mice that overexpress APP carrying a familial AD mutation do not develop tau tangles (9, 13). Furthermore, bigenic mice—generated by cross-

ing APP transgenic mice (with amyloid deposits) and wild-type tau transgenic mice (with tau inclusions)—do not show classic AD pathology in which amyloid plaques are surrounded by a corona of dystrophic neurites containing intracytoplasmic tau tangles (14).

In the new work, Lewis *et al.* (1) and Götz *et al.* (2) independently demonstrate that amyloid- β influences the formation of tau tangles in transgenic mice. Lewis *et al.* detected many more tau tangles in the limbic system and the olfactory cortex of bigenic mice (Tau/APP) expressing both mutant tau (P301L) and mutant APP compared with transgenic animals expressing only mutant tau. This suggests that either APP or its product amyloid- β influences the formation of tau tangles. Taking a different approach, Götz *et al.* directly injected

the fibrillar form of amyloid- β peptide, $A\beta_{1-42}$, into the hippocampus of tau mutant mice and observed a dramatic increase in tau tangles in the amygdala, one of the regions affected in AD. It is intriguing that tau tangles did not develop in the hippocampus—the site where $A\beta_{1-42}$ was injected—but rather appeared in the amygdala, a site to which hippocampal neurons project. A remarkably similar separation of tau and amyloid- β pathology is described by Lewis *et al.* (1) in their Tau/APP mice. Amyloid plaques did not comele with tangle-bearing neurons, and the classic AD plaques with a corona of tau-positive dystrophic neurites were not found in these mice. Although neither of these two transgenic mouse models recapitulate all aspects of AD pathology, they both provide important insights into AD pathogenesis by showing that interactions between amyloid- β and tau lead to increased tau tangle formation



Tau in the middle. The importance of tau in the pathogenesis of neurodegenerative diseases, including AD and the tauopathies. Patients with the early-onset familial form of AD carry mutations in APP, or presenilin 1 or 2 (PS1, PS2), which result in increased deposition of amyloid- β peptide. In the tauopathies, mutation of the tau protein results in several changes including an upset in the 4R/3R ratio (tau isoforms with either four or three microtubule-binding repeats), an altered ability of tau to bind to microtubules, and increased aggregation of tau into filaments. These changes lead to accumulation of abnormally hyperphosphorylated tau filaments in intracytoplasmic clumps called neurofibrillary tangles. Amyloid- β deposits have now been found to exacerbate tau tangle formation in brain regions of transgenic mice that are known to be involved in AD. (DeP-Tau and P-Tau, dephosphorylated and phosphorylated tau, respectively).

The author is at the Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA 19104-4283, USA. E-mail: vmylee@mail.med.upenn.edu