genes and the daughter cells contain free factor molecules, the cooperative nature of the binding should help to ensure that complete complexes will again form around the two genes. If the entire complex stays with one of the genes, a stem cell lineage results.

One of the most difficult challenges faced by embryologists is how to account for asymmetric cell divisions during development. Often when an embryonic cell divides the daughters are not equivalent. They become committed to different fates, which can even include cell death.

The basis for the asymmetric divisions is apparently established in the egg cell. Embryologists have long observed that many egg components are asymmetrically distributed in the egg and may be unequally inherited by the daughter cells when the fertilized egg divides and during subsequent embryonic cell divisions. The unequally distributed components presumably contain the molecules that determine cell fates. Brown suggests that the determinants may be transcription factors. Asymmetric divisions, he notes, "must begin in early embryogenesis because the determinants, the transcription factors, are asymmetrically localized in cells and are thus unequally distributed to the daughter cells." In that event, when the transcription complex is disturbed during DNA replication, it may reform around the gene in one daughter cell, but not in the other. Without the complex the second gene is then prone to inactivation. If the genes activated by the transcription factors include those that themselves encode transcription factors, a cascade of changes can be produced.

A great deal more work will be required to test these models of development. As Brown puts it, "We can model all these states, but that is trivial. What is not trivial is how to prove it."

One of the first requirements is to show that pol I and II work the same way as pol III, that they, too, recognize stable transcription complexes containing multiple components. As already mentioned, there are indications that this may be the case. Such demonstrations are especially critical for pol II because this enzyme transcribes the protein-coding genes. One cell type is distinguished from another mainly by the proteins they produce. The ultimate proof that the various polymerases act on transcription complexes would be the duplication of the gene control systems in the test tube, but that will require the isolation and purification of the necessary factors.

Brown is optimistic that the models he is proposing will at least prove to be useful guides to further experimentation even if they are not borne out in detail. "In my view, developmental control of genes is going to boil down to some very mundane biophysical principles," he predicts. "It's going to involve the concentrations of activator versus repressor molecules. It's going to involve cooperative influences between molecules and binding constants of proteins to each other and to DNA. I think these things can be tested with modern methods."

—JEAN L. MARX

Additional Reading

1. D. D. Brown, *Cell* **37**, 359 (1984).
2. M. S. Schlissel and D. D. Brown, *ibid.* **37**, 903 (1984).

Acid Rain's Effects on People Assessed

Acids in the air may harm lungs, acids in water may mobilize toxic metals, but it is too soon to assess risks

The effects of acid rain on some lakes, rivers, and streams have been the subject of many studies, largely because of the sensitivity of fish and other aquatic organisms to acidification. The effects on crops, forests, wetlands, soils, and buildings have also been thoroughly studied. The potential for adverse effects on human health, however, has not received comparable attention. "The ecological toxicologists have simply not been human-oriented," says Robert Goyer of the National Institute of Environmental Health Sciences (NIEHS).

The available evidence about direct and indirect effects of acid rain on human health remains inconclusive. But, according to a 1983 report from the House Committee on Appropriations, "we have learned from other environmental problems that events in the plant and animal world can serve as sentinels for the human population. Prudence dictates that we heed these warnings in the case of acid rain." The committee thus requested that NIEHS and the Environmental Protection Agency assess present knowledge about such health effects. One outcome of this request was a recent "Conference on Health Effects of Acid Precipitation" at NIEHS.*

If the results presented at that conference were to be summarized in one word, that word would still be "inconclusive." There is suggestive evidence that breathing the trace quantities of sulfuric and nitric acids formed in the atmosphere from power plant and smelter emissions is injurious to human lungs. It is difficult to extrapolate results obtained with animal studies to effects on human lungs, however, and even more difficult to separate the effects of acids from those of other air pollutants in epidemiological studies. The acidification of water supplies leads to increases in the concentration of certain potentially toxic metals in that water, but those increases have not been linked to health effects. "About the only thing we can say with any confidence," says Goyer, "is that there appear to be no serious effects resulting from contact of acid rain with the skin."

"At this point in our studies," says Morton Lippmann of the New York University Medical Center, "I think it is clear that we cannot adequately describe the nature and the extent of the effects of the inhalation of acidic pollutants on human health. We just don't know enough about either population exposures or exposure-response relationships to make a satisfactory risk assessment. We do, however, know a great deal about some aspects of the problem. We know, for example, that acidic air pollutants have created health problems in the past."

The best example of such effects was reported earlier this year by the late Tetsuzo Kitagawa. He studied some 600 cases of severe lung disease that occurred over a period of 8 years in a small part of the city of Yokkaichi in Central Japan. All of the victims lived relatively close to a titanium dioxide pigment plant that emitted 100 to 300 tons of sulfuric

*Held 15 to 16 November 1984 at the National Institute of Environmental Health Sciences, Research Triangle Park, N.C.

acid aerosols per month. In one area with the highest incidence of disease, Kitagawa's measurements indicate that acid concentrations averaged 160 micrograms per cubic meter ($\mu g/m^3$). Average concentrations of acids and the incidence of lung disease declined with increasing distance from the plant. The incidence of lung disease dropped sharply, furthermore, when the plant installed controls to remove sulfuric acid from its emissions. These results all indicate that the disease was a direct result of sulfuric acid in the air.

It is also likely, but not proved, Lippmann says, that high concentrations of acidic pollutants were responsible for much of the excess mortality associated with the episodes of high pollution in London during the 1950's, in the Meuse Valley of Belgium in 1930, and in Donora, Pennsylvania, in 1948.

Other evidence is more circumstantial. Richard Schlesinger of New York University reported that when healthy adults at rest were exposed to 100 $\mu g/m^3$ of sulfuric acid for 1 hour, transient changes in the rate of particle clearance from lung airways resulted. Similar transient responses were seen in donkeys after single 1-hour exposures to sulfuric acid at that concentration. Daily 1-hour exposures of the donkeys produced persistent changes in clearance rate and alterations in the distribution of cell types in the airway epithelium and its thickness.

Other human volunteer studies have been performed by Mark Utell of the University of Rochester and Jack Hackney of the University of Southern California. They reported that short exposures—generally 15 to 20 minutes—to sulfuric acid at concentrations of about 100 $\mu g/m^3$ induce bronchoconstriction in asthmatic children exposed to stress, such as exercise. Asthmatic adults appear to be one-half to one-tenth as sensitive as asthmatic children, and healthy adults, in turn, are an order of magnitude less sensitive than asthmatic adults. Actual concentrations of sulfuric acid in polluted air, in contrast, may reach only about 20 $\mu g/m^3$, but those exposures can last for hours or days. The effects of acids can also be potentiated by other pollutants, particularly ozone.

Some of the most suggestive epidemiological evidence, Lippmann said, has been obtained by David Bates of the University of British Columbia. Bates studied admissions at 79 hospitals in southern Ontario and compared them with pollutant concentrations at 15 monitoring stations in the area. He found that admissions for respiratory diseases in the summer correlated with sulfur dioxide and ozone concentrations and with temperature, but that the strongest correlation was between concentrations of sulfates and admissions for asthma, particularly among young people. There were no correlations with nitrogen dioxide or other pollutants.

During the interval of the study, furthermore, the number of admissions to the hospitals declined by about 14 percent, but the number of admissions for respiratory diseases remained constant (indicating a relative growth) and the number of asthma admissions increased. During this same period, concentrations of sulfur dioxide and ozone decreased, but concentrations of sulfates increased to an average of about 11 $\mu g/m^3$. At those concentrations, says Lippmann, it is "highly unlikely" that ammonium sulfate was the cause of the respiratory effects. Instead, he says, it probably served as a marker for sulfuric acid and bisulfate, which were not measured by the monitoring stations. Other epidemiological studies, Lippmann concludes, have not been as conclusive, but have shown similar trends.

"We have learned that events in the plant and animal world serve as sentinels for the human population."

The potential for hazard from acidification of water supplies seems more clear-cut. The source of the concern is the fact that the solubility of many toxic metals, such as lead, cadmium, mercury, and aluminum, increases sharply with decreasing *p*H. Acid water can thus leach metals from the soil, from lake sediments, from metal pipes used in water systems, and from the soldering materials used to join the pipes together. It can also free calcium ions and asbestos fibers from cement-asbestos pipes used in some water supplies.

The most thoroughly studied metal in the environment is probably mercury, which has been shown to accumulate in fish. Although acid rain is not the sole cause of problems with mercury, those problems are being exacerbated by acid rain, says Arne Jernelov of the Swedish Water and Air Pollution Institute in Gothenburg.

The toxicity of lead has also been thoroughly studied. Above-normal concentrations of lead are often found in the blood of inner-city children, for example, and these increased concentrations are associated with learning impairments and central nervous system toxicity. The principal sources appear to be automobile exhaust and lead-based paint.

There is no evidence yet of increased lead concentrations in large public water supply systems in the United States, but there is some evidence in smaller systems. William Sharpe of Pennsylvania State University reported, for example, that about 1 percent of homes with private water supplies use cisterns associated with roof catchment systems. A substantial proportion of these have holding tanks lined with lead, and high concentrations of lead in the water have been observed.

Significant lead contamination has also occurred in water supplies elsewhere. Michael Moore of the University of Glasgow reported, for example, on problems with the water supplies of Glasgow and Ayr, both of which are in an area with the worst acid rain in the United Kingdom. The *p*H of water in the Glasgow reservoir is about 6.3, while that in the Ayr reservoir is between 4.5 and 5.0. In both cases, it was necessary to add lime to water in the system to reduce the acidity and the lead content.

In none of these cases have increased concentrations of lead in drinking water been clearly associated with health effects—possibly because the effort to find such a link has not been made. "Most investigators are so familiar with the toxic effects of lead," says John Wood of the Gray Freshwater Biological Institute in Navarre, Minnesota, "that they simply haven't felt a need to conduct such studies. Simply the presence of increased amounts of lead is enough to indicate a health problem."

A major new concern is the growing presence of aluminum in water. Aluminum, the most common metallic element, comprises about 5 percent of the earth's crust, but it is almost completely insoluble in neutral or alkaline water and thus has not been biologically available. As a result of acid rain, however, "the concentration increase of dissolved aluminum in lakes is absolutely massive," says Pamela Stokes of the University of Ontario. She has measured aluminum concentrations in Canadian lakes as high as 372 parts per billion. Aluminum is toxic to fish at concentrations of only 100 parts per billion. "It would appear," says Charles Driscoll of Syracuse University, "that much of the toxicity to fish previously attributed to acidic water is actually a consequence of the increased aluminum concentrations."

Aluminum may also affect other wild-

life. Investigators in Sweden, Wood says, have shown that birds living on insects from acidified lakes accumulate aluminum in their bodies. Eggs laid by these birds have shells with normal thickness but extreme fragility.

The link between calcium and aluminum is intriguing. Gwyneth Howells and Anthony Kellend of the Central Electric Research Laboratory in Leatherhead, Surrey, England, reported earlier this year that the toxicity of aluminum to fish is greatly increased in the absence of calcium and that added calcium exerts a protective effect against poisoning by aluminum. Wood speculates that calcium and magnesium compete effectively with aluminum in biological systems. If calcium is deficient, however, the aluminum can bind to enzymes and other proteins, be transported across cellular membranes, and disrupt biological processes.

As recently as 1974, aluminum was thought to be nontoxic to humans—except for industrial exposure to aluminum-contaminated dust particles, which produce lung disease. In the early 1970's, however, a new syndrome was recognized among patients with kidney failure who were undergoing long-term dialysis. The syndrome occurred after 3 to 7 years of dialysis and was characterized by a speech disorder, followed by the development of dementia, convulsions, and death. The syndrome was labeled dialysis encephalopathy or dialysis dementia. Investigators have more recently recognized a related aluminum-induced syndrome characterized by bone pain and excessive fragility of bones.

Studies by several investigators, particularly A. C. Alfrey of the Veterans' Administration Medical Center in Denver, subsequently showed that victims of the syndromes had high concentrations of aluminum in brain, muscle, and bone tissues, and that the syndromes occur primarily in patients at those dialysis centers where the water supply contained significant concentrations of aluminum. The only exceptions were patients receiving oral aluminum hydroxide as an antacid. (The dialysis patients also received oral aluminum hydroxide, but most investigators believe that aluminum in the dialysis water is more important). There is little doubt now that aluminum is the cause of dialysis encephalopathy, says Michael R. Wills of the University of Virginia Medical Center, but the mechanism is still open to question.

Aluminum has also been associated with certain other types of dementia, including senile dementia, Alzheimer's disease, and Parkinson's disease. Alzheimer's disease in particular is associated with brain lesions called neurofibrillary tangles. In 1973, D. R. Crapper of the University of Toronto reported that samples of brain tissue from patients with Alzheimer's contain two to three times the normal amount of aluminum, with the highest concentrations being associated with the tangles. Other investigators have not been able to reproduce his results, however, and they have been highly controversial.

In the early 1980's, Daniel Perl of the University of Vermont studied brain cells with a more sensitive technique, called energy-dispersive x-ray analysis, which can be used to quantify the elements present in individual cells. He found high concentrations of aluminum in neurofibrillary tangles from patients with Alzheimer's and senile dementia and normal concentrations of aluminum in nearby unaffected cells. These results have been well accepted by other investigators, and there is now little doubt that aluminum accumulates in the tangles. It is not clear, however, whether this is cause or effect.

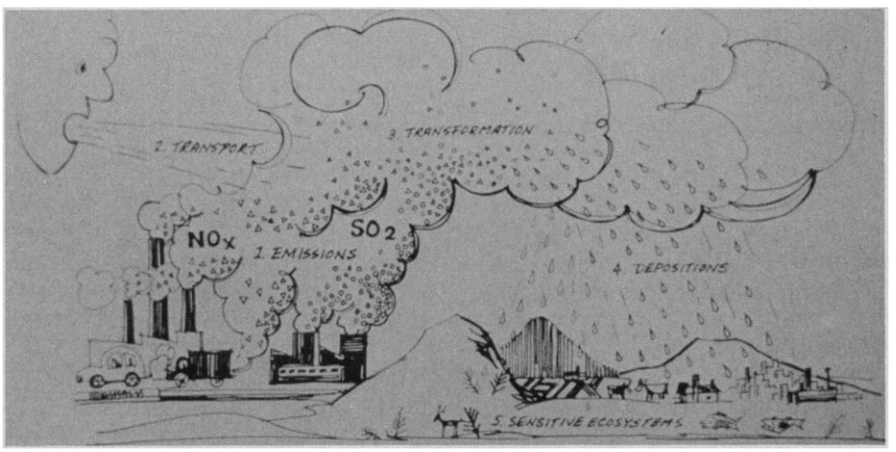
The possibility that the aluminum may be a causal factor is supported by more recent studies of Japanese living on the Kii Peninsula, Chamorros on the island of Guam, and residents of a small area of southern West New Guinea. These populations have a very high incidence of amyotrophic lateral sclerosis (also known as Lou Gehrig's disease) or a form of Parkinson's disease with very severe dementia. In Japan and Guam, the incidence of these diseases is 150 times the incidence in the United States, says Perl, and in New Guinea it is tenfold higher still. Autopsies of the victims show very large numbers of neurofibrillary tangles in the brains; lesser numbers of tangles are also present in many individuals with no disease symptoms.

Perl has performed elemental analyses on neurofibrillary tangles from disease victims from these areas and has observed "dramatic amounts of aluminum." Tangles from individuals without disease contained concentrations of aluminum intermediate between concentrations in the victims and concentrations in brain cells from controls who died from other causes.

There are no genetic links among these three populations, so the cause of the excess disease must be environmental. The primary common environmental factor at all three locations is the presence of soils rich in aluminum-containing bauxite. That, in itself, is not sufficient to cause the disease because soils rich in aluminum are common elsewhere in the world. But recent studies, says Perl, have shown that the three areas are very deficient in calcium and magnesium. Combined with the data presented earlier, he says, this makes a "persuasive" case that the dementias and related diseases are associated with an aluminum excess and a deficiency of calcium, although other factors may also be involved.

The relation of acid rain to other potentially toxic metals is much less clear. Preliminary results suggest that cadmium, arsenic, and zinc can be mobilized by acidic water, but that the concentration of available selenium might be reduced, leading to selenium deficiencies. The evidence, however, is quite limited. In fact, all of the evidence implicating acid rain as a human health hazard is much more limited than investigators at the conference would like. Concludes Goyer: "We are only beginning to scratch the surface."

—THOMAS H. MAUGH II



Acid rain

Acid rain results when sulfur dioxide and nitrogen oxides released into the atmosphere are converted into sulfuric acid and nitric acid.