monly described by individuals exposed to high concentrations of carbon dioxide. This phenomenon is termed an 'olfactory hallucination'."

An undetectable volcanic eruption could conceivably have triggered the gas release, says Kling, but the American team only specifically discusses several other possibilities. All that was needed, assuming the deep water was saturated or nearly saturated with carbon dioxide, was a disturbance that raised the water to the point that the resulting pressure reduction allowed the gas to come out of solution and form bubbles. That would have further reduced the weight of overlying water that had kept the gas in solution and begun a runaway release. In the case of Nyos, the team estimates, as much as 1.0 cubic kilometer escaped. An earthquake (none was reported), a landslide (a fresh scar on the lake's western cliffs was found but no subsurface disturbance was apparent), or a volcanic eruption could have triggered the release, but something as ephemeral as a wind that started the water sloshing within the lake basin would have sufficed.

Kling still finds quite suggestive the coincidence of both Cameroon lake disasters in the month of August (Lake Monoun on 16 August 1984 and Lake Nyos on 21 August 1986). August through September is the time of minimum stability of some Cameroon lakes, when they are closest to mixing their anoxic deep water with their surface water. The occurrence of two otherwise undetectable volcanic eruptions beneath lakes 95 kilometers apart at the time of minimum stability seems less likely to Kling than normally inconsequential disturbances striking lakes on the verge of turning over, as some Cameroon lakes do from time to time and temperate lakes do every fall.

Whatever the immediate trigger, the team recommends that the 40 crater lakes in Cameroon be better understood in order to predict and prevent future disasters. Nine of the lakes have not been sampled to determine if their bottom waters are highly charged with carbon dioxide. Repeated sampling would detect any buildup. Dangerous lakes, including Nyos, could be defused in a few years' time by starting fountains of water supplied by pipes from the bottom. Once started, the fountains would be driven solely by the lifting force of the gas release.

Understanding these lakes would come none too soon. The American team has been told that according to legends of the Lake Monoun area, there may have been at least three earlier cases of exploding lakes or mass deaths. And there is a new report of three small explosions on Lake Nyos within a 5-minute period on 30 December. ■

RICHARD A. KERR

Oxygen Free Radicals Linked to Many Diseases

The oxygen free radicals, although made as by-products of normal oxygen-using reactions, nevertheless have a wide potential for causing cell injury

BREATHING oxygen is, it seems, hazardous to your health. Although the element is indisputably necessary for life, many of the biochemical reactions in which it participates generate oxygen-containing free radicals as by-products. These highly reactive chemical entities can injure and even kill cells. "Oxidative damage is common, and DNA, proteins, and lipids are all at risk," says William Pryor of Louisiana State University. According to presentations at a recent symposium sponsored by the National Heart, Lung, and Blood Institute,* oxygen free radicals may contribute to the development or exacerbation of many of mankind's most common ills, including cancer, heart attacks, stroke, and emphysema.

The work may have immediate clinical application in the treatment of heart attacks. Approximately 700,000 heart attack victims are admitted to hospitals every year in the United States. Many of these individuals now receive therapy aimed at restoring the blood flow to the damaged heart muscle. Usually this involves treatment with the enzymes streptokinase or urokinase to dissolve the clots that block the coronary arteries. However, these enzymes may soon be replaced by another, tissue plasminogen activator, which may be more specific in its action. The arteries may also be opened mechanically by a technique called coronary angioplasty, in which a small balloon is inserted in a blocked artery and inflated.

Although these treatments are beneficial, there are indications that restoration of the blood flow to heart tissue that has been deprived of oxygen may contribute to the heart muscle damage, at least partly because of the production of oxygen free radicals. If that is the case, then treatment to destroy the free radicals may help to minimize the extent of the permanent damage to the heart muscle, and thereby improve the outlook for the patient. Evidence presented at the symposium suggests that such treatment can work, at least in experimental animals.

The superoxide radical is the usual free radical produced by cellular oxidation reactions, although its effects can be magnified because superoxide produces other kinds of cell-damaging free radicals and oxidizing agents. The therapies now being tested use two enzymes that normally help to protect cells against superoxide's effects. Superoxide dismutase converts it to hydrogen peroxide, which is then converted by catalase to water and molecular oxygen.

Myron Weisfeldt and his colleagues at Johns Hopkins University School of Medicine have found that treatment with these two enzymes limits the damage to dog hearts that are reperfused with blood after a period of deprivation. In these experiments, the investigators first clamp off one of the coronary arteries. Then, after 90 minutes, they restore the blood flow and at the same time administer superoxide dismutase and catalase into the coronary artery. This reduces the area of killed tissue by about one-third in the enzyme-treated animals compared with the nontreated control animals, Weisfeldt says. The Johns Hopkins workers find that the enzymes decrease the free radical concentrations in the treated dog hearts.

Weisfeldt plans to begin preliminary clinical trials of superoxide dismutase and catalase within the next 6 months in human heart attack patients who undergo reperfusion therapy. Other investigators, including Bennett Luchesi of the University of Michigan School of Medicine, expect to initiate similar trials.

Nevertheless, Eugene Braunwald of Harvard Medical School sounds a note of caution. He points out that the animal models in which the enzymes have been tested so far are significantly different from the situations of human heart attack patients. In the animals, the blood flow to a portion of the heart is stopped and restarted suddenly. For a brief period, the reflow of oxygenated blood is even greater than normal. This combination, oxygen deprivation followed by an excess, is ideal for free radical generation and may exaggerate the problem in the animal models.

*The NHLBI symposium, entitled "Oxygen Free Radicals" was held in Bethesda, Maryland, on 10 to 12 December 1986.

In contrast, when the blood supply to the damaged heart of a human patient is reestablished, the flow begins as a trickle. Moreover, Braunwald notes, arteries are still left with about a 70% obstruction at the end of reperfusion therapy. "It is important that we do some experiments that mimic the clinical reperfusion picture," Braunwald says, to determine whether a slow reestablishment of the oxygen supply has the same effects as the rapid restoration. He suggests, for example, that in the animals the arterial clamps could be released slowly and a 70% obstruction allowed to remain.

Despite his concern about the applicability of the animal models to the clinical situation, Braunwald notes that if he were not already deeply involved in a major clinical trial in which tissue plasminogen activator is being compared with streptokinase, he, too, would be interested in testing the effects of superoxide dismutase and catalase in patients undergoing reperfusion therapy.

The research on the oxygen free radicals may also have implications for the treatment of strokes, many of which are caused by the formation of clots that cut off the blood flow to a region of the brain. According to Hermes Kontos of the Medical College of Virginia, superoxide dismutase and catalase prevent the adverse changes in cat brains that are caused by superoxide and its products when the brains are reperfused after a period of complete oxygen deprivation. Strokes are not currently treated with clot-dissolving enzymes the way heart attacks are, but clinical trials to test the efficacy of tissue plasminogen activator in stroke patients are being planned.

Participants in the symposium also discussed the ways in which oxygen deprivation followed by restoration of blood flow may lead to superoxide production. According to Joe McCord of the University of South Alabama in Mobile, the enzyme xanthine dehydrogenase, which oxidizes xanthines to uric acid, may have an important role. McCord and his colleagues have found that when cells become oxygen deficient, xanthine dehydrogenase undergoes a biochemical change that causes it to switch from using nicotinamide adenine dinucleotide, the normal hydrogen acceptor for xanthine oxidation, to using oxygen instead—and consequently generating superoxide and hydrogen peroxide when the blood flow is restored. "The enzyme is capable of a kind of Dr. Jekyll–Mr. Hyde transition," McCord explains.

Inflammation, which commonly occurs in oxygen-deprived tissue, provides another source of oxygen free radicals. One of the hallmarks of inflammation is infiltration of the affected tissue with phagocytic cells, including neutrophils and macrophages. Several symposium participants presented evidence showing that when these cells are activated, they produce large amounts of superoxide radicals. This helps them to perform their normal functions of destroying foreign invaders and cleaning up cellular debris, but might also contribute to the damage suffered by heart attack victims during reperfusion.

In addition to exacerbating the damage of heart attacks, oxidative damage by free radicals may contribute to the early changes that lead to arterial blockage. According to a scenario described by Daniel Steinberg of the University of California at San Diego, oxygen free radicals may be involved in the initial development of atherosclerotic plaques, the abnormal arterial deposits of fat, calcium, and smooth muscle that may result in heart attacks or stroke.

"Oxidative damage is common, and DNA, proteins, and lipids are all at risk."

The low density lipoproteins (LDLs) are the most active of the blood lipids in promoting atherosclerosis. The accumulation of LDLs under the endothelial cells of the arterial wall lining to form "fatty streaks" is the earliest indication that atherosclerosis is developing. The LDLs in fatty streaks, Steinberg says, are exposed to oxygen free radicals that are released by the arterial endothelial and smooth muscle cells. Moreover, oxidatively modified LDLs both attract macrophages from the blood and prevent the migration of the cells from tissue. "You pull them in and then you don't let them out," as Steinberg puts it. The accumulation of free radical-releasing macrophages could further oxidize the LDLs.

In their most recent work, Steinberg and his collleagues have found that oxidized LDLs can damage endothelial cells that are grown in culture. In the arteries, endothelial cell damage is a major step in the progression of atherosclerosis. Steinberg notes, however, that there is a question about whether oxidized LDLs have the same effect in the arterial wall as they do in culture. "Blood serum protects against the damage," he says. "This is the weak spot of the hypothesis." The hypothesis might still be correct, however, if the intact arterial lining can prevent the penetration of the protective serum components until the damage to the endothelial cells is done.

The effects of oxygen free radicals on the lungs also came in for a great deal of attention at the symposium. The agents may contribute both to the acute oxygen toxicity that occurs when individuals breathe higher than normal concentrations of oxygen, as may be required for some patients who are on respirators, and to the chronic damage that leads to such conditions as emphysema.

Physicians may be faced with a cruel dilemma when treating their critically ill, respirator patients, explains James Crapo of Duke University Medical Center. Although the lowest possible doses of oxygen are given, it is sometimes necessary to chose between allowing a patient to die immediately, and giving pure oxygen, which may kill in days.

High oxygen concentrations are toxic because of the free radicals they generate in lung tissue. For example, Crapo and his colleagues find increased production of the tissue-damaging radicals in the lungs of rats that are made to breathe high oxygen concentrations. The free radicals are produced by the lung cells themselves and by phagocytes that accumulate in the lungs, which become inflamed during oxygen toxicity.

The Duke workers have evidence indicating that treatments that remove oxygen free radicals can protect against the lethal effects of 100% oxygen. Although rats usually die within 3 days when breathing pure oxygen, the Crapo group has found that injecting the animals with superoxide dismutase and catalase that have been incorporated within the membranes of liposomes prevents the animals' deaths.

The development of emphysema is facilitated by chronic lung inflammation. The neutrophils and macrophages that infiltrate inflamed tissue have several weapons that they can use to damage cells. These include, in addition to superoxide radicals, secreted enzymes, such as elastase, which breaks down the connective tissue of the lung. The damage caused by elastase can lead to emphysema, unless the enzyme is held in check, as it normally is, by inhibitors, the most important of which is the protein called *alpha*$_1$-protease inhibitor.

The reactions of superoxide and hydrogen peroxide in neutrophils produce as secondary products certain potent oxidizing agents. According to Robert Clark of the University of Iowa School of Medicine, these oxidizing agents permanently inactivate *alpha*$_1$-protease inhibitor, thus allowing elastase to work unchecked. "It's clear that the neutrophil's weapons can be turned against the host itself," says Stephen Weiss of the University of Michigan Medical Center in Ann Arbor.

This situation can be further exacerbated by cigarette smoking, which has been linked to emphysema as well as to heart disease and lung cancer. Cigarette smoke contains free

radicals, although for the most part these are not oxygen free radicals, that can also inactivate the protease inhibitor.

Charles Cochran of the Scripps Clinic and Research Foundation described another way in which the superoxide radicals and other oxidants released in inflamed tissue can injure the lungs. The agents inhibit the production of adenosine triphosphate (ATP), which provides much of the energy for cellular activities. The oxidants block ATP synthesis both directly and indirectly by causing strand breaks in the DNA. One of the consequences of the DNA damage is activation of the enzyme poly-ADP ribose polymerase, which consumes a cofactor needed for ATP production.

Activation of this enzyme might also contribute to cancer development, according to Peter Cerutti of the Swiss Insitute for Experimental Cancer Research in Lausanne. Tumor promoters are chemicals that are not carcinogenic by themselves but enhance the formation of malignant tumors in cells that have been previously exposed to true carcinogens. A few years ago, Cerutti, among others, proposed that tumor promoters work by generating oxygen free radicals that produce DNA strand breaks.

This may alter gene expression, he notes, possibly because of the ensuing stimulation of poly-ADP ribose, which can modify DNA-binding proteins that may be involved in gene control. Decreased expression of the superoxide dismutase and catalase genes, for example, might enhance the damage caused by oxygen free radicals.

Further circumstantial evidence that oxygen free radicals might contribute to carcinogenesis comes from Bruce Ames of the University of California at Berkeley. He and his colleagues have found that the concentrations of the oxidation products of DNA constituents increase with age in the urines of men and rats. The incidence of cancer also increases with age. Moreover, cell lipids are targets for oxidation by oxygen free radicals. The Ames group finds that rat tissues contain high concentrations of lipid peroxides, many of which are carcinogens. "Clearly, there is an enormous amount of oxidation going on all the time," Ames says.

Finally, oxygen free radicals may convert exogenous chemicals to active carcinogens, in addition to acting on normal cell constituents, notes Sigmund Weitzman of Northwestern University Medical School.

Not all the effects of the oxygen free radicals are deleterious. Phagocytes are, after all, an important part of the body's defenses against foreign invaders. Nevertheless, the oxygen free radicals produced by phagocytes and other types of cells can cause damage in many ways. ■ JEAN L. MARX

Record High-Temperature Superconductors Claimed

Several groups have reported evidence for superconductivity at temperatures up to 70 K in samples containing lanthanum, copper, oxygen, and either barium or another group IIA metal

LAST April, the European physics journal *Zeitschrift für Physik* received a manuscript from the IBM Zürich Research Laboratory titled "Possible high T_c superconductivity in the Ba-La-Cu-O system," which it duly published several months later. Although the paper reported evidence for the onset of superconductivity at temperatures as high as 35 K, well above the previous record of 23 K that had been set 13 years earlier, what little attention it initially attracted was mainly skeptical. That has now changed.

John Bardeen of the University of Illinois, who shared a Nobel Prize for his work on and is the "B" in the BCS theory of how superconductors work, says the new materials open a new era in superconductivity. "It's likely to be the biggest advance in superconducting materials since World War II," concurs experimentalist Theodore Geballe of Stanford University. Geballe adds that one of the most important features of the new materials for possible technological applications is that they are simple and inexpensive to make, once one learns how. Adds Douglas Finnemore of the Ames Laboratory at Iowa State University, "a hundred laboratories around the world are trying to make the material, including ours."

The source of this new enthusiasm is confirming evidence submitted in October by the Zürich researchers J. Georg Bednorz and K. Alexander Müller, and independently shortly thereafter by groups at the University of Tokyo and the University of Houston. A late news presentation in December at the annual fall meeting in Boston of the Materials Research Society by Koichi Kitazawa of Tokyo was particularly effective in turning the tide.

Still unknown is the maximum temperature at which these materials become fully superconducting. Researchers want to find the answer to the question for both fundamental scientific and technological reasons. Theorists had argued that the conventional explanation for superconductivity probably limited the phenomenon to temperatures less than about 35 K, and experimentalists have been unable to get above 23 K.

The highest temperature now reported is 36 K, achieved in a strontium-lanthanum-copper-oxygen compound by Robert Cava, R. Bruce van Dover, Bertram Batlogg, and Edward Rietman of AT&T Bell Laboratories. Kohji Kishio, Kitazawa, Kazuo Fueki, Shoji Tanaka, and five co-workers at Tokyo have nearly equaled this, reaching 35 K in a similar material.

A Chinese group at the Institute of Physics of the Academia Sinica in Beijing may have a claim to even higher temperatures. In a report accepted by the Chinese journal *Ke Xue Tongbao*, Zhongxian Zhao, Shanling Li and seven co-workers discuss materials containing either strontium or barium that seems to become fully superconducting at about 39 K. Unfortunately, the performance degrades markedly when the samples are exposed to air for a few days.

The highest temperature being mentioned anywhere is 70 K, which was also reported by the Chinese physicists. However, this temperature refers to the onset of the transition from normal metallic to superconducting behavior, rather than to the completion of the transition. Moreover, in their report to be published, the researchers say this performance is not repeatable and suggest only that "possible superconductivity might exist around 70 K."

In this issue of *Science* (p. 567), Ching-Wu (Paul) Chu, Pei-Heng Hor, Ru-Ling Meng, Li Gao, and Zhi-Jung Huang of Houston discuss the attainment of an onset temperature of 52 K in a lanthanum-barium-copper-oxygen compound under hydrostatic pressure, but it became fully superconducting at 25 K.

In theory, the switch from metal to superconductor, which is a second-order phase transition, should occur at a well-defined temperature. But, in inhomogeneous material, the transition may occur gradually over a wide range of temperatures. The justification for quoting the onset temperature is the hope that it represents the transition temperature of good quality material.

Applications of superconductors range from large-scale systems, including high-field magnets, electric motors and genera-