cursor on the basis of similar effects prior to other quakes, especially the 1971 San Fernando earthquake in the same region. He filters out the effects of small earthquakes and averages the otherwise noisy data over a large region to see the effect. The velocities returned to normal near the end of 1975. His hypothesis is based on the dilatancy model (see *Science*, 7 February 1975, p. 419) and is similar to that held by many seismologists. It is that the magnitude of an ensuing quake will be proportional to both the duration of the anomaly and the size of the area in which it is observed. Since his data do not adequately limit the size of the anomalous region to the north or the southeast, the magnitude of the quake he predicts could be still larger than the estimated 5.5 to 6.5.

More geodetic data will be obtained and Whitcomb's data closely scrutinized in coming months. The question is what other phenomena, if any, are present. As Press points out, not a single water well in California is being monitored for changes of level.—ALLEN L. HAMMOND

Diabetic Retinopathy: New Ways to Prevent Blindness

One of the more severe problems encountered by individuals who have had diabetes for a long time is degradation of vision resulting from diabetic retinopathy. This problem, which was rare 30 years ago, is becoming progressively more common as improved therapies for diabetes prolong the lives of diabetics. New results from several studies, however, suggest not only that it may be possible to retard the progression of visual impairment with currently available therapies, but also that it might be possible to prevent—or at least delay the onset of—the condition through rigorous control of diabetes.

Retinopathy is a widespread problem. It is observed in about half of those individuals who have had diabetes for 10 years, three-fourths of those who have had it for 15 years, and more than 95 percent of those who have had it for 25 years. Although not all those who have diabetic retinopathy suffer visual impairment, the disease is the leading cause of new cases of blindness in the United States among persons between the ages of 20 and 65. Some 48,000 individuals in this country are legally blind as the result of it.

Retinopathy results from the diabetes-induced deterioration of tiny blood vessels in the eye. Similar deterioration of blood vessels occurs throughout the body and causes disorders of the kidney and other organs. The cause of this deterioration is unknown. In the eye, small vessels become leaky and occluded and, occasionally, new vessels form on the retina. In the more severe form of the disease, known as proliferative retinopathy, new blood vessels grow on the surface of the retina and protrude into the vitreous, the normally clear, jellylike fluid in the center of the eye. Eventually, these vessels rupture and hemorrhage into the vitreous. And finally, fibrous scar tissue forms in association with the new vessels. This tissue may pull on the retina and detach it from the back of the eye. Proliferative retinopathy occurs in only about 3 to 4 percent of diabetics, but even so this comes to about 300,000 people in the United States who are susceptible to blindness from it.

Diabetic retinopathy is difficult to study in the laboratory because there are very few animal models for it, and these are not entirely satisfactory. One model of proliferative retinopathy similar to that caused by diabetes has been developed by Arnall Patz and Chung-Ho Chen of the Johns Hopkins School of Medicine. They observed that growth of blood vessels (vascularization) in the retina occurs naturally in puppies during their first 4 weeks after birth. If the puppies are exposed to an atmosphere of 85 percent oxygen for a 4-day period during this time, the peripheral vessels in the eye are destroyed, and new vessel formation begins at the border of the obliterated vessels after the dogs are removed to air.

Chen has found that the total amount of protein dissolved in the vitreous is closely related to the rate of vascularization in normal development, with the protein concentration declining to barely detectable amounts as vascularization nears completion. The new vascularization after exposure to oxygen is preceded by a sharp increase in the concentration of protein in the vitreous. Patz and Chen thus speculate that one or more of these proteins may be responsible for the new growth.

This speculation is supported by other experiments in which Patz, and his colleagues at Johns Hopkins, Daniel Finklestein and Steven Brem, implanted small malignant tumors in the vitreous. Such tumors have been shown by F. Judah Folkman and his associates at the Harvard Medical School to release a protein, named tumor angiogenesis factor or TAF, that stimulates the growth of new blood vessels toward the tumor. TAF may be similar to the protein observed in the vitreous of newborn and oxygen-treated puppies. When introduced into the eye, TAF produces retinal vessel proliferation.

The tumors thus provide another model for proliferative retinopathy. They also make it possible to study agents that may inhibit the process. Folkman has found, for example, that a substance extracted from cartilage inhibits TAF. Patz and his associates speculate that this or a similar inhibitor might block retinal vascularization. It might thus be possible, sometime in the future, to find ways to stimulate the activity of such a natural inhibitor or to develop synthetic agents that could block the growth of new vessels in the eye.

Another animal model has been developed by Albert E. Renold and his associates at the Institute of Clinical Biochemistry of the University of Geneva. They render a special strain of rats diabetic with streptozotocin, an antibiotic that destroys insulin-secreting cells in the pancreas. They then observe that most of the rats that survive for as long as 9 months without insulin therapy exhibit many characteristics of retinopathy. They further find that they can isolate the retina and, by studying it under a microscope, quantitate many of the physical changes and correlate them with biochemical changes.

One of their major findings is a marked decrease in the number of mural cells that line the exterior of blood vessels. They observe a strong correlation between the extent of loss of mural cells and the concentrations of insulin and glucose in the blood and the volume of urine. This loss of mural cells could produce structural weakening of small blood vessels and lead to their rupture. Such a loss of cells was observed in only about half of a group of rats that were diabetic only 5 months, indicating that the loss is time-related.

Renold has also conducted nutrition studies in which he observed that the loss of mural cells and of endothelial cells (which form the interior of the vessels) was greatest in diabetic rats fed diets high in either proteins or carbohydrates, but substantially lower in rats fed diets high in fats. Further studies of these effects are in progress.

The importance of diet and the control of metabolic symptoms in the development of diabetic retinopathy is particularly apparent in studies conducted by Ronald L. Engerman and James Bloodworth of the University of Wisconsin Medical School. They studied dogs made diabetic with another chemical, alloxan, and found that the dogs consistently developed, within 5 years, retinal lesions similar to those in humans. They then studied two groups of diabetic dogs. One group was given insulin in a conventional manner; nearly all of them died. The second group was meticulously treated with insulin and a restricted diet to control their symptoms. The urines of these animals were sugar-free from 25 to 50 percent of the time, whereas those of the first group were never sugar-free.

After 5 years, Engerman and Bloodworth found, the dogs on the controlled diet had a sharply reduced number of lesions of the eye, indicating that control of diabetes can retard the onset of retinopathy. The number of dogs involved in the study was rather small, though, and the effect needs to be studied in larger groups of animals and in humans. If the results are confirmed, Engerman says, it will then be necessary to find better ways to control the concentration of sugar in the blood. One approach might be the use of artificial pancreases or transplantation of either pancreases or islets (*Science*, 26 December 1975, page 1281).

There were no therapies available for proliferative diabetic retinopathy until about 1960. Around that time, Gerd Meyer-Schwickerath of the University of Essen in West Germany developed the concept of using intense light generated by a xenon arc lamp to fuse and destroy new capillaries in or on the retina, thereby preventing them from hemorrhaging. A few years later, Francis L'Esterance, Jr., of Columbia University, Christian Zweng and Hunter Little of the Retinal Group Eye Clinic in Palo Alto, and Patz began using an argon laser for the same purpose. By 1970, many individual scientists believed that photocoagulation was an effective therapy, but there was no conclusive evidence to prove it.

When the National Eye Institute was formed in 1970, one of its first goals was to determine the effectiveness of photocoagulation. A large-scale clinical trial was planned and, under the leadership of Matthew D. Davis of the University of Wisconsin Medical School and Genell Knatterud of the University of Maryland at Baltimore, 1727 patients with diabetic retinopathy were enrolled in the study at 16 medical centers. To be eligible for the study, a patient had to have either proliferative retinopathy in one eye or severe nonproliferative retinopathy in both eyes, but still have retained a visual acuity of at least 20/100 in both eyes.

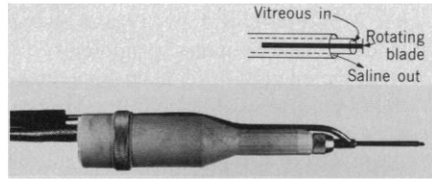

Fig. 1. The device used for vitrectomy. Entire apparatus is about the size of a fountain pen.

One eye from each patient was randomly chosen for treatment. This allowed each patient to serve as his own control and maximized the probability that useful vision would be retained in one eye. The patients were treated randomly with either the xenon arc or the argon laser. All new blood vessels that were not on the optic disk (the surface of the optic nerve) were destroyed; furthermore, areas of the eye away from the optic disk were treated in a checkerboard pattern on the theory that destruction of partially dead tissues might impede the release of substances that promote growth of new vessels.

The study is not scheduled to be completed until 1979, but the preliminary results have been so promising that they were released in April. Among some 470 patients who were studied for at least 2 years after photocoagulation, only 6.4 percent of the treated eyes were found to go blind, whereas 16.3 percent of the untreated eyes did. The therapy was most effective in patients with any two of the following three conditions: new vessels on the optic disk, hemorrhaging into the vitreous, and substantial growth of new vessels. Photocoagulation produced little improvement in patients who did not have at least two of these symptoms. Arc and laser treatments were equally effective in preventing blindness, but therapy with the xenon arc produced a somewhat greater loss of peripheral vision.

The initial results from the study have already been distributed to all ophthalmologists in the country. The second eyes of patients in the study are also now being considered for treatment in those cases where they meet the criteria suggesting therapy will be effective. Davis warns, however, that photocoagulation is not a panacea for diabetic retinopathy. It treats only the symptoms of the disease and not the disease itself. New vessels can thus grow in the eye after the therapy, although many of these can be destroyed by further treatments. It thus appears that photocoagulation is primarily a stopgap treatment that may only retard the onset of blindness, providing the diabetic with a few more years of useful vision.

Photocoagulation is of little value when vision is already severely impaired, and is not possible when the vitreous is severely clouded by hemorrhaging because light cannot pass through it. In some cases, it may be possible to restore vision by removing the opaque fluid—an operation known as vitrectomy. Robert Machemer of the University of Miami has developed a small instrument (Fig. 1) that cuts away blood vessels in the vitreous, removes the clouded fluid, and replaces it with a clear saline solution. This technique has shown great promise, and the National Eye Institute is now enrolling patients in a trial that will test vitrectomy in much the same fashion that photocoagulation was tested.

The optimum time for performing a vitrectomy has not yet been determined. It is possible, for example, that allowing a hemorrhage to persist for a long time might accelerate the growth of fibrous tissues on the retina and thus irreversibly damage the eye. It is equally possible, however, that the disease process in the eye might run its course within a year or so after the onset of severe visual impairment, so that the vessels and hemorrhage could be removed without fear of their return. Because it is not known which hypothesis is correct, patients in the study will be divided into two groups. One group will be treated as soon as possible after the development of severe visual impairment; treatment of the second group will be delayed for 12 months. Results from this study will probably not be available for at least 2 years.

Vitrectomy may also be a stopgap solution, since it too treats only symptoms. It is thus becoming increasingly clear that more work must be done to provide a better understanding of the mechanism by which diabetes impairs microvascular circulation throughout the body and of the basic cause of diabetes.

—THOMAS H. MAUGH II