Diabetic retinopathy, a dangerous complication of diabetes, is the leading cause of new cases of blindness among adults. An estimated 12,000 to 24,000 diabetics lose their sight each year in the United States to this insidious disorder—largely because they do not receive the regular eye exams that could catch the problem early. When caught in time the damaging changes in retinal blood vessels brought on by diabetes can be stopped—and in some cases even reversed—using the powerful, tightly focused beam of a laser. Timely laser intervention can prevent blindness in up to 90 percent of such cases.

Precision lasers also can repair small tears in the retina that might otherwise lead to retinal detachment, and they are used in surgery related to cataracts, although, contrary to popular belief, they are not used for the removal of cataracts themselves. Doctors recently have begun using lasers in a procedure called photorefractive keratectomy, or PRK, to “sculpt” the surface of the cornea—the eye’s clear protective covering—to correct nearsightedness. All of these procedures can be done in a matter of minutes, with relatively little pain or discomfort.

The following article describes how two streams of basic research—one in human anatomy and medicine, the other in physics—intersected in the early 1960s to produce a revolution in ophthalmology that has saved hundreds of thousands of people from severe vision impairment or blindness. As is so often the case in science, many of those who made the landmark discoveries were motivated primarily by the desire simply to understand nature—but their efforts paved the way for a host of unexpected practical results.

I Can See Clearly Now . . .

Diabetes ran in Bill’s family: both of his paternal great-grandparents and his paternal grandfather developed diabetes as adults. For Bill the onset of the disease occurred before he was 3 years old. At the age of 8, he took over administering his own insulin shots, beginning a lifetime of strict adherence to a routine vital to his health. This discipline probably delayed the onset of diabetic retinopathy, the insidious and vision-threatening complication that affects nearly all patients with younger-onset diabetes, by the age of 15 or 20. Bill didn’t have vision problems until he was 30, and because he had regular eye exams, doctors caught it early. Laser surgery could now be used to prevent blindness.

An ophthalmologist performs photorefractive keratectomy (PRK), a procedure that has become a practical alternative to glasses or contact lenses to correct nearsightedness. (Phillip Hayson/Photo Researchers, Inc.)
photocoagulation—making a number of small laser burns around the periphery of the retina—sealed off the abnormal blood vessel growth that can lead to blindness if left untreated. In 1992 Bill had the surgery on both eyes, a procedure that can be done in a doctor’s office simply by beaming laser light through the dilated pupil. “I go in four times a year now,” Bill reported a few years later, adding that his doctors are very pleased with the results.

In the fall of 1997, a 57-year-old entrepreneur named John woke up one morning seeing flashes of light and spots, or floaters, in front of his eyes. When they persisted the next day, he went to an ophthalmologist, who diagnosed the problem as posterior vitreous detachment and a small retinal tear. The vitreous, a clear, jelly-like fluid that fills the inside of the eye, tends to degenerate during middle age, shrinking and pulling away from the retina. This detachment is common in nearsighted people; John had worn glasses for nearsightedness since the age of 13. Occasionally, the retina is torn when the vitreous pulls away, causing a small amount of bleeding that appears as a sudden onset of floaters. To prevent the tear in John’s retina from developing into a retinal detachment, the doctor used a laser to seal it—in effect, spot welding the tear. The procedure took only minutes.

The ease and brevity of these two operations underscore the revolution that lasers have brought to the field of eye care. As recently as the 1950s, almost any eye surgery required a patient to be bedridden for weeks. Today, thousands of people each year have their vision restored or sharpened in procedures that are often virtually painless, owing to the laser’s precision and the fact that it operates not with a blade but with a beam of light. By sending a focused laser beam through a patient’s pupil, a surgeon can reach the interior of the eye without having to cut into the eye itself. The actual surgery causes little or no discomfort, there are no incisions to heal and no damage to other areas of the eye, and recovery time is minimal.

For all their high-tech wizardry, the application of lasers and other modern surgical techniques in ophthalmology would not have come about were it not for the researchers who first painstakingly figured out how the eye works and identified the causes of various defects in vision.

One long-held belief was that the lens, which lies just behind the pupil and helps to focus light on the retina, was the seat of vision and that removing it would result in blindness. The ancients had no notion of the retina and its crucial role.

The Retina—The Seat of Vision

Recognizably modern concepts of the eye’s workings originated during the Renaissance, perhaps most notably with the efforts of the great German astronomer and physicist Johannes Kepler. On the basis of some fairly simple experiments and calculations, Kepler found that the lens was only a refracting body, working with the cornea to bend incoming light rays to focus on the retina. In Ad Vitellionem Paralipomena, published in 1604, Kepler produced new theories of light, of the physiology of vision, and of the mathematics of refraction. Among other things, he introduced the term “focus” and showed that the convergence of light rays in front of the retina is the

Astronomer and physicist Johannes Kepler in 1604 published the first explanation of how the optical structures of the eye work, including the first correct explanation of the critical importance of the retina. (Library of Congress)
cause of myopia, a condition in which distant objects are blurred and near objects are clear. People had been using spectacles for nearly 400 years by this time, but until Kepler—who himself was myopic, or nearsighted—no one understood why or how artificial lenses improved vision.

Over the next three centuries, physicians and anatomists continued to refine their understanding of the eye and its disorders, eventually coming to recognize why an injury to the retina is so devastating to vision. Simply put, this thin layer of cells lining the back of the eye is akin to the film in a camera. If the film is damaged, no images are possible even if the rest of the camera is working perfectly. This biological “film” is actually an extension of the neural tissue of the brain itself. Early in the development of the embryo, the neural tube, which gives rise to the brain and the spinal cord, forms two optic vesicles, each of which folds inward to form an optic cup. A layer of cells, the neural epithelium, on the inner wall of the optic cup eventually becomes the retina. In the course of development, cells of the inner wall differentiate into all the retinal cells needed for vision; cells on the outer wall differentiate into the pigment epithelium that lines the back of the eye. What makes the retina so vulnerable is that there is usually no adhesion between these two cell layers. Except for a few attachment points, such as around the optic nerve, the retina is held in place against the pigment epithelium and the back of the eye only by the fluid pressure of the vitreous.

For a long time no one understood why retinal detachments occurred spontaneously—that is, in the absence of a sudden blow, for instance. Then in 1918 Jules Gonin announced to the Swiss Ophthalmological Society that spontaneous retinal detachments typically are associated with a hole in the retina. As ophthalmologists eventually came to understand, fluid leaking from the vitreous through a retinal tear can seep between the retina and its outermost cell layer, the pigment epithelium, lifting the retina off the back wall of the eye. When this happens, vision is lost. Moreover, if the detached retina is separated too long from the pigment epithelium, which supplies essential nutrients, the neural cells in the retina die.

In 1920, two years after his initial discovery, Gonin reported that he had been able to cure a few people of retinal detachment, using a treatment he called “ignipuncture.” The technique involved cauterizing the sclera (the eye’s opaque outer layer) with a hot instrument and deliberately perforating it to allow the subretinal fluid to escape. The operation had only a 53 percent success rate and was highly controversial. Other techniques for treating retinal disorders were eventually devised, but progress was incremental. Diathermy, which involved applying a heat-generating electric probe to the retina, still required cutting into the wall of the eye. As the incision healed, the wall tended to shrink substantially. Not until the advent of cryotherapy, or freezing, in the 1960s did a technique become available that could treat retinal tears without damaging large areas of adjacent retina. All of these procedures, intended to seal breaks in the retina by inducing coagulation or scarring in retinal tissue, were risky and painful and required long recovery periods.

Meanwhile, in the World of Physics . . .

In 1917, just before Jules Gonin’s announcement on the cause of spontaneous retinal detachment, Albert Einstein published an article on a phenomenon he called “stimulated emission,” which would ultimately give rise to the laser. Einstein’s idea built on work by German physicist Max Planck in 1900 and Danish theoretician Niels Bohr in 1913. Planck had theorized that accelerated atoms radiate energy in discrete packets, which he called “quanta.” Five years later, in 1905, Einstein suggested that light itself was made up not of waves, as prevailing theory had it, but of discrete packets, or particles (later named photons),
each containing energy. He then demonstrated how matter could absorb and emit light energy, the energy of photons, and used this to explain the photoelectric effect, a phenomenon that had puzzled scientists for decades. This breakthrough would later earn him a Nobel Prize.

Physicists would debate for years whether light was a wave or particle phenomenon before accepting that it was somehow both. Today, electromagnetic radiation may be described in terms of its wavelength, the distance between the peaks of two consecutive waves, or its frequency, expressed in hertz, the number of wave cycles per second. The shorter the wavelength, the higher the frequency and the more energetic the photon.

Well before the debate ended, Einstein discovered something else. According to Niels Bohr’s model of the atom, electrons occupy specific orbits around the nucleus that are determined by the atom’s energy level. An atom can absorb only the exact amount of energy needed to kick an electron from one orbit up to a specific higher one, and it emits a specific amount of energy when an electron drops from a higher orbit to a lower one. This explained why atoms of a given gas, such as neon, emit light with a distinctive pattern of wavelengths and have a characteristic color.

Atoms in an excited state—that is, atoms whose electrons are in higher-energy orbits—will eventually, and spontaneously, fall back to their lowest, or ground, state, giving off their stored energy in the process. This spontaneous emission occurs at random; the emitted photons of energy head off in random directions. According to Einstein, if atoms in an excited state are stimulated by an encounter with photons of light having the right amount of energy (equal to the difference between the lower-energy and higher-energy states), the encounter can trigger a kind of chain reaction of emission.

Not only does the chain reaction amplify the intensity of the light passing through, but the emitted photons all head in the same direction as the incoming photons. However, amplification of the light intensity by stimulated emission occurs only if more atoms in the population of atoms are in an excited state than in the ground state—the opposite of the normal situation. Stimulated emission thus requires what is known as a population inversion: the population of atoms must be artificially boosted into an excited state, and this is usually done by exposure to light.
The Power of Light

The story now jumps to the period after World War II. In the wake of the explosion of the first atomic bomb, many researchers began investigating the retinal burns suffered by people who had seen the atomic flash from as far as 50 miles away and later went blind. A similar phenomenon, eclipse blindness, had been known at least since Plato’s time. In the spring of 1946, German ophthalmologist Gerd Meyer-Schwickerath became interested in the problem after examining a number of patients who had sustained retinal damage in association with the solar eclipse of July 10, 1945. He noticed that the retinal scars caused by their exposure to intense sunlight “resembled the sort of scar resulting from surface diathermy,” that is, the kind of scar that doctors were trying to induce by applying heat to the eye to seal retinal holes or treat areas of diabetic retinopathy.

Over the next several years, Meyer-Schwickerath carried out extensive experiments in an effort to perfect a technique of therapeutic photocoagulation using light to coagulate retinal tissue. It was not a simple proposition. On the one hand, sealing a retinal hole could prevent the retina from detaching. On the other hand, the area of the retina subjected to coagulation would be ruined. The trick was to coagulate as small a spot as possible and preserve as much vision as possible.

Meyer-Schwickerath’s research showed that some wavelengths of light—namely, between 400 and 900 nanometers—could pass through to the retina without losing energy through absorption or scattering by proteins in the cornea and lens. He also learned that, as the heat produced by the absorption of light energy in adjacent layers of pigmented cells raised the temperature of the retina, the normally transparent retina would turn white. The area would begin reflecting rather than absorbing the light, and coagulation would stop.

He needed an instrument that could produce precise localized coagulation burns at retinal tears and do so in a short time so as to minimize thermal damage to other parts of the eye. In the mid-1950s the American Optical Corporation in Southbridge, Massachusetts, developed high-pressure xenon arc lamps for a movie producer. These gas lamps produced light so bright that people who looked at it directly ran the danger of unintentionally coagulating their retinas.

Here was the light source Meyer-Schwickerath was seeking. Soon Zeiss Laboratories in Oberlochen,
Germany, had incorporated the xenon lamp into a photocoagulator that Meyer-Schwickerath praised as being “of the greatest technical perfection” and easier for physicians to use. In 1959 Zeiss sent three of these machines to the United States.

Generating Light with Molecules

At about the same time that Meyer-Schwickerath was experimenting with therapeutic photocoagulation, Charles Townes, of Columbia University’s Radiation Laboratory, was continuing research begun during the war on microwave radar. Townes wanted to sharpen radar images by using very short wavelength microwaves, in the millimeter range. In 1951 he got the idea to use molecules to generate the shorter wavelengths, and in late 1953 Townes and collaborators James Gordon and Herbert Zeiger demonstrated such a generator. Their device sent a beam of ammonia through an electric field that deflected ammonia molecules that were in a low-energy state and sent high-energy molecules to another electric field. Exposure to the second field caused all the high-energy molecules to drop almost simultaneously to the ground state, emitting photons that were all at the same frequency and traveling in the same direction. Townes called the device a maser, for microwave amplification by stimulated emission of radiation.

It soon became clear that stimulated emission could work with the much shorter wavelengths of infrared and even visible light, giving rise to the name laser, with the “l” standing for light. Townes approached his brother-in-law, Arthur Schawlow, a physicist at Bell Telephone Laboratories, to develop a more complete theory of laser action. In late 1958 the Townes-Schawlow paper “Infrared and Optical Masers” appeared in the journal Physical Review. Scientists were inspired to try to build a laser device, and in June 1960 physicist Theodore Maiman, of the research laboratory of Hughes Aircraft Company, was the first to succeed, using a synthetic ruby.

Lasers generated tremendous excitement in the scientific community, and a host of researchers began exploring ways to put the new phenomenon to practical use. Astoundingly, just a little over a year after Maiman’s success with the ruby laser, the device was used to repair a human retina. It was as though eye surgeons had been simply marking time until the laser came along.

Serendipity at Work

In a sense, perhaps, they had been, for the Zeiss photocoagulator had several disadvantages. It emitted light at a wide range of wavelengths, from 400 to 1,600 nanometers—a potential danger to the eye. Also, its light beam was wide, creating lesions about 500 to 1,000 micrometers in diameter, or about the size of the end of a paperclip wire. And because the wide beam required maximal dilation of the pupil, the treatment often caused pain when a patient’s iris contracted during the 250 to 1,000 milliseconds required to produce the necessary burn. The ruby laser, in contrast, produced light at precisely 694.3 nanometers, and its beam was tightly directional. It could coagulate a spot on the retina as small as 50 micrometers, about the diameter of a human hair, and do so in 0.2 to 1.0 millisecond—a striking reduction in time.

Over the next half decade, two groups, one on each coast of the United States, conducted critical
laser experiments in ophthalmology. On the East Coast were Charles Campbell, of the Institute of Ophthalmology at Columbia-Presbyterian Medical Center in Manhattan (which had received one of the first Zeiss photocoagulators in 1959), and Charles Koester, at the American Optical Corporation in Southbridge, Massachusetts. Before the end of 1960, Koester was involved in starting a research program on laser photocoagulation, and he soon brought Campbell into the project. In the fall of 1961 the two carried out the first therapeutic application of a laser on a human subject, using a prototype ruby laser photocoagulator to destroy a patient’s retinal tumor.

The West Coast group was based at Stanford University. In 1955 Milton Flocks, a researcher on the clinical faculty at Stanford, and Christian Zweng, a member of the Stanford faculty and a practicing ophthalmologist at the Palo Alto Medical Foundation, attended a conference at which Meyer-Schwickerath described the Zeiss photocoagulator. They were so impressed that they applied for a grant from the National Institutes of Health to obtain one of the instruments when they became available in the United States four years later. When Flocks and Zweng began looking into using lasers, they collaborated with physicist Narinder Kapany, who founded Optics Technology in 1960. The Stanford team performed its first laser surgery on a human subject in August 1963; less than a year later, at the annual meeting of the American Medical Association (AMA) in June 1964, they presented the results of the ruby laser treatments on 25 patients.

Also at that meeting was Milton Zaret, of the New York Medical Center, who was interested primarily in the effects of radiation on humans. In 1961 he had published one of the first scientific papers on the laser’s potential danger to the eye. Although he also recognized the laser’s therapeutic potential, Zaret expressed concern at the AMA meeting that researchers did not yet know the laser’s long-term effects on either human patients or the operators who were repeatedly exposed to its radiation. The medical community took these cautions to heart and devoted considerable effort over the next few years to devising safe laser devices specifically designed for medical use.

The Advent of Argon

One pioneer in that effort was Francis L’Esperance, of the Columbia-Presbyterian Medical Center. In 1963 he began working with the ruby laser photocoagulator, using it in an attempt to treat diabetic retinopathy. The abnormal blood vessels in this disorder have weak walls and may break, clouding the vitreous and interfering with vision. They can also grow scar tissue that can pull the retina away from the back of the eye, causing severe vision loss, even blindness.

In early 1965 L’Esperance presented a paper at a conference in New York on the results of his work. One of the key things he noted was that blood absorbs only 6 to 7 percent of the ruby laser’s red light, which meant that it took eight to 10 sessions to cauterize retinal blood vessels with the ruby photocoagulator. L’Esperance urged the development of a blue-green laser, whose light would be more highly absorbed by the blood vessels.

As it happened, such a laser, using ionized argon as the source, had been developed the year before. L’Esperance learned two weeks after the New York conference that Bell Laboratories had one of the devices. He persuaded Bell researchers Eugene Gordon and Edward Labuda to work with him in designing the optical and mechanical systems needed to deliver the argon laser’s energy to the eye. Eventually, L’Esperance acquired a 10-watt argon laser from the Raytheon Corporation, and after further refinements and careful experiments, he treated a human with an argon-ion laser in February 1968. By the end of the month he had begun using it to treat patients with diabetic retinopathy.

About a year later, Dr. Arnall Patz of the Wilmer Ophthalmological Institute began using an argon laser to treat patients with diabetic and related retinopathies.
Unlike the other pioneers in laser ophthalmology, Patz had no private corporate support. He had mortgaged his home and borrowed money to pay the Applied Physics Laboratory at Johns Hopkins University to build an argon laser for him. But by 1970 he had treated 285 patients for various retinopathies, and by the early 1970s Patz, L’Esperance, and Christian Zweng were jointly teaching other ophthalmologists how to use the argon laser.

The most effective treatment for diabetic retinopathy has proven to be a method called pan-retinal ablation. Advocated by Lloyd Aiello of the Joslin Diabetes Center in Boston, the method involves using a laser to ablate, or vaporize, scattered areas of the peripheral retina rather than coagulate blood vessels directly. Today, the treatment of diabetic retinopathy to prevent blindness is the leading application of lasers in ophthalmology.

Tailoring Lasers to the Task

One of the most exciting developments in the application of lasers to ophthalmology was the use of an ultraviolet excimer laser to reshape the cornea in a procedure known as photorefractive keratectomy (PRK). The excimer laser itself, a device that uses a mixture of argon and fluorine gases, was developed in the mid-1970s. (The term “excimer,” a contraction of “excited” and “dimer,” is actually a misnomer; the argon and fluorine atoms used in the excited state are dissimilar, so they do not constitute a dimer.) A number of researchers were involved in early work with the excimer laser and its application to ophthalmology. In the late 1970s and early 1980s, John Taboada found that corneal epithelium is extremely sensitive to the excimer’s 193-nanometer wavelength light. Also in the early 1980s, R. Srinivasan, an IBM researcher, was using an excimer laser to etch microscopic circuits in computer chips and discovered that it could also be used to cut and remove biological tissue with extreme precision and—most important—without substantial thermal damage. Stephen Trokel, of Columbia University, worked with Srinivasan and in 1983 published his work on applying this laser to create linear “excisions” in the cornea.

Over the next four to five years, research and development work on the excimer laser blossomed all over the world. By the early 1990s, the U.S. Food and Drug Administration (FDA) had approved clinical trials with the instrument for the correction of myopia. Final FDA approval came in late 1995.

PRK and a slightly older form of refractive surgery called radial keratotomy (RK) are surgical alternatives to using spectacles or contact lenses to correct refractive error. Both procedures work by changing the shape of the cornea in a nearsighted person to move the point of focus from in front of the retina to the retina itself. In RK the reshaping is done by using a metal or diamond blade to make incisions in the corneal tissue. PRK requires no incisions. The laser is programmed to remove a tiny amount of corneal tissue calculated specifically for each patient. The surgery is performed with anesthetic eyedrops to numb the surface of the eye, and the patient remains awake and alert throughout the procedure. The session takes several minutes; the actual laser use requires about a minute. Within 20 to 30 minutes, the patient can go home, often with an immediate improvement in vision, although a small percentage of patients suffer persistent corneal haze that can permanently reduce fine vision. PRK has been performed on more than 500,000 people worldwide in the last decade, and it has dramatically reduced or eliminated the use of incisional surgery for nearsightedness in most countries.

Today, nearly 40 years after the advent of the laser, ophthalmologists continue to explore new possibilities for this sight-saving instrument, including the recent development of ultrashort laser pulses, lasting just quadrillionths of a second, that might be used for the treatment of glaucoma and cataracts. Just as Einstein could not have foreseen that the interesting phenomenon of stimulated emission would one day be used to correct myopia and prevent retinal detachment, today’s scientists doing basic research in physics, biology, and other fields are undoubtedly laying the groundwork for breakthroughs that will lead to practical human benefits that lie just over the horizon.

This article was written by science writer Roberta Conlan, with the assistance of Drs. Stephen J. Ryan, Alfred Sommer, and John Dowling for Beyond Discovery®: The Path from Research to Human Benefit, a project of the National Academy of Sciences.

The Academy, located in Washington, DC, is a society of distinguished scholars engaged in scientific and engineering research, dedicated to the use of science and technology for the public welfare. For more than a century, it has provided independent, objective scientific advice to the nation.

Funding was provided by the Markey Charitable Trust, Pfizer, Inc., and the National Academy of Sciences.