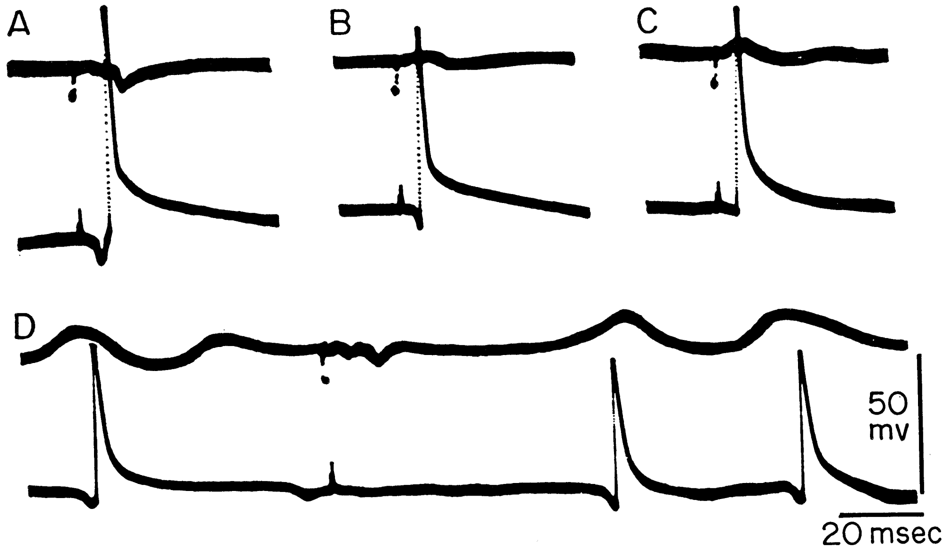
FREE RADICALS

Chemical clues to nerve transmission



With each successive discharge, a brain neuron produces an electrical spike.

The nervous system is like a happening. Electrical and biological changes take place simultaneously in and around the nerve all the time, presenting scientists with a puzzle of extraordinary complexity.

Some of these changes have been easier to isolate than others. The movement of sodium and potassium ions through the nerve cell membrane, for instance, is far easier to measure than molecular changes occurring in the biological material of the membrane itself.

As a result, nerve energy has long been described in electrical terms. For popular consumption, the impulse is sometimes compared to a telephone signal or radio transmission.

But such comparisons fall far short of explaining the driving force of energy in the nervous system—a major unknown in science.

Biochemists working with the protein material of the nerve membrane are just beginning to reveal how inadequate a strictly electrical model of that energy really is.

The nerve impulse moves in waves through membranes surrounding the cell body and its branching fibers. The membrane is, in effect, a chain of large protein molecules which theoretically change character and shape as the impulse wave passes. How they change and why all but defies scientific analysis; the living membrane is nearly impossible to work with.

But a clue is beginning to emerge from evidence that proteins in the molecular chain can exist in an excited, free radical form, meaning they have an unpaired electron and the capacity to control and induce chemical reactions.

The free radical work, conducted by Dr. B. David Polis, chief of biochemistry at the U.S. Naval Air Development Center in Johnsville, Pa., is not yet complete, but it suggests a possible alternative to long-established theory of nerve function.

The best explanation of nerve energy to date rests on ions—small electrically charged atoms of sodium and potassium. Because of the pattern in which these ions are dispersed inside and outside the cell membrane, they create an electrical potential. The nerve, in other words, is charged up and ready for action.

When an impulse comes along, it causes sodium ions to diffuse through the membrane, discharging the nerve. According to this view, it is the sequence of discharges that is the neural impulse. When the impulse wave passes, the nerve must then pump out sodium ions to reestablish a state of charged readiness.

The impulse can be seen on an oscilloscope. As nerves successively charge and discharge, they throw one electrical spike after another on the scope.

But a question has now arisen from molecular scientists, including Dr. Polis, over the importance of these ions. Rather than the source of energy in nerves, ionic shifts may only be reflections of more important events occurring in the protein molecules of the nerve itself.

"The whole issue of nerve function has opened up," says Dr. Carl F. Schmidt, research director at Johnsville. "The sodium pump business is now under considerable question everywhere."

The trouble facing most molecular biologists, however, is that they must work with a completely dead membrane, inducing chemical changes artificially.

Dr. Polis, on the other hand, has been able to isolate from pieces of the brain, nerves and the eye, protein molecules in an excited, free radical state. Unlike free radicals that appear elsewhere in the body when it burns energy, these excited-state molecules have a relatively long life.

They can be influenced by psychoactive drugs and chemicals known to be involved in nerve transmission. Tranquilizers, for instance, shorten their lifetime and reduce the number of free radical sites. Serotonin, a basic nerve chemical, also inhibits free radical activity, but LSD sets it loose again. The evidence happens to fit beautifully with the action of these chemicals in the brain; LSD is an anti-serotonin drug.

The Polis work could be the beginning of a free radical alternative to the ion theory, an alternative some brain scientists have been seeking.

Dr. Polis first found signs of free radicals in the melanin pigment behind a cow's eye. When he flashed light on the exposed pigment, melanin molecules converted into the excited free radical form. Repeating the experiment on motor nerves of a snail, he again found a free radical sign in the molecular system.

In isolated pieces of the nervous system, Dr. Polis has traced free radicals from eye to retina to nerve to brain. He believes the free radical could be a trigger of chemical reactions in the nerve membrane. It is, however, possible that the impulse itself is a wave of free radicals up the nerve chain.

Dr. Polis declines to speculate, but says he feels "we have something of some fundamental significance and perhaps a new approach to function in the nervous system."

The primary difficulty is in linking up free radical molecules with the nerve impulse. They have yet to be measured together—a difficult task. "Even if we found the two together, it would merely be an association," says Dr. Polis.

Although free radicals have in fact been pulled out of the nervous system, they could be a by-product of the electrical-chemical nerve impulse rather than its driving force.

The Johnsville work, however, has gone further than isolating free radicals. Dr. Polis made these excited-state molecules out of body proteins—the first time it has been done—and injected them into a rabbit's ear vein. The animal became highly excited, pulling electrodes from its head and kicking its box apart.

In essence, the free radical discovery represents a new kind of chemical energy in nerves. These chemically active molecules can be changed by drugs in ways consistent with drug action, and when injected back into the living animals, they markedly influence their behavior and brain wave patterns. But whether or not free radicals actually participate in basic nerve function is a matter of inference at the moment.

The free radicals are there; they must be explained, comments Dr. Samuel Bogoch, director of the Foundation for Research on the Nervous System in Boston. "You couldn't make as good a theory now with free radicals as with the ion shifts," he says, but he feels that the Polis work is a very important finding. If free radical changes are not the basis of energy in nerves, they might well be the energizing trigger.

HEART TRANSPLANTS

Seven of 25 survive

Dr. Philip Blaiberg continued to be the longest-lived of the seven survivors of heart transplants last week in spite of a bad setback with liver and lung complications that raised the question of a possible second heart donor. Dr. Christiaan Barnard raised the possibility of another transplant. But this, even for surgeons comfortable with the notion of transplanting human hearts, is a radical notion.

Although second kidneys and even third ones have been transplanted with good success, a second heart transplant has never been done and it is hard to predict the outcome, says Dr. Richard R. Lower of the Medical College of Virginia.

The idea of transplanting a lung or both lungs with the heart—a possibility also raised by Dr. Barnard—is technically feasible, he believes. But the rejection problem remains.

Dr. Theodore Cooper, director of the National Heart Institute at Bethesda, Md., points out that second or third heart operations have been performed on valve patients but that the entire heart transplant is a much larger and more difficult operative procedure.

"As for transplanting lungs along with a heart, there would be fewer suture lines on the heart itself," he explains, "but the connection of aorta and vena cava must be made as well as that of the trachea. Experimental evidence does not indicate that such surgery would be any less formidable than the heart transplant alone."

Dr. Denton Cooley of Houston, Texas, who has done six transplants into humans, of whom three still live, agrees that transplanting lungs with the heart is simpler from a suture standpoint.

One of the most promising treatments to prevent rejection of kidneys has been that of the antilymphocyte globulin (ALG), which Dr. Barnard has now used to improve the condition of Dr. Blaiberg. Dr. Barnard obtained his ALG from France, where there are several good research centers making it. ALG also is produced at a few centers in the United States.

The drug prevents the lymphocytes (white cells that play a key role in the body's rejection of foreign tissue) from effectively rejecting a transplant, but more needs to be known about its mechanism.

It is made by injecting human lymphocytes into a horse, which becomes a blood donor. The horse's natural defenses work to resist the foreign lymphocytes before the blood is extracted. The purified serum is then used on humans. Although ALG weakens the body's natural defenses against infection, the body seems to recover its defenses faster than with other drugs when the treatment is stopped.

Both Imuran and prednisone have been used with Dr. Blaiberg, but the large doses of Imuran, a drug which is toxic to the liver, are believed to have caused his liver complications, including hepatitis. When Imuran is lessened, prednisone must be increased, and it has its own side effects. Lung complications indicating pulmonary edema and possibly pneumonia followed the liver problems.

Dr. Blaiberg underwent his heart transplant on Jan. 2. Of the 25 patients with heart transplants, in addition to the Capetown dentist, who is now 59 years old, these were still alive the middle of last week:

In Houston, at St. Luke's Hospital, Everett Claire Thomas, age 47, of Phoenix, Ariz., who received his heart May 3; Louis John Fierro, 54, of Elmont, N.Y., who got his transplant May 21; George Henry DeBord, a San Antonio contractor, living in Helotes, Texas, who was given his transplant July 2. In Paris Dominican Father Jean-Marie Boulogne still survives with his May 12 transplant; in Valparaiso, Chile, Maria Elena Penacola, and in Montreal, Canada, Gaetan Paris, both of whom had been given heart transplants on June 28, were believed doing well.

Among the others who have died are 45-year-old Frederick West, Britain's only heart transplant patient, who lived 46 days; 66-year-old Clovis Roblain, France's and Europe's first person to receive a donor's heart, and Joseph G. Klett of Orange, Va., Dr. Lower's patient. Louis Washkansky was the first to receive a human heart transplant on Dec. 3, 1967. He was the patient of Dr. Barnard, but died in Capetown 18 days after the surgery. Mike Kasperak, patient of Dr. Norman E. Shumway at Stanford University Medical Center, died Jan. 21, 1968, two weeks after receiving his transplant. Dr. Adrian Kantrowitz of Maimonides Hospital, Brooklyn, performed the second transplant of a human heart, Dec. 6, 1967, but the two-and-a-half-week old infant boy died six and a half hours later.

Dr. P. K. Sen, director of King Edward Memorial Hospital in Bombay, India, transplanted a heart on Feb. 17, 1968, but the recipient died hours later.

SCIENCE FUNDING

Looking beyond the war

The United States does not have a tradition of government support for basic science. What it has is momentum born of World War II. And Presidential Science Adviser Dr. Donald F. Hornig notwithstanding, the momentum seems to have run down.

"The country need not be convinced any longer," Dr. Hornig told the American Physical Society last year "that we need strength in basic research. This is accepted by the executive, by the Congress and by the people of the country."

By this view, the current tightening of the budget strings for the support of science is temporary, caused by the tightness of the Government's Vietnam budgets.

There is another view.

"There are many Congressmen who regard scientific research as a leak in the budget barrel," says Prof. Thomas Gold of Cornell University, "and having plugged it, are not likely to drill new holes."

The proof of the pudding may have to await peace in Vietnam.

If and when that war ends money will become available for civilian uses. A large part of the cost of the war as carried on the books—$30 billion a year—will remain in defense and diplomatic budgets so long as there is no change in foreign policy. But a portion, estimated by various economists at between $15 billion and $22.5 billion, will come loose.

Economists differ on what will happen to this money. Charles L. Schultze, former budget director now senior fellow of the Brookings Institution, believes it will probably disappear in a tax cut. But Schultze's Brookings col-