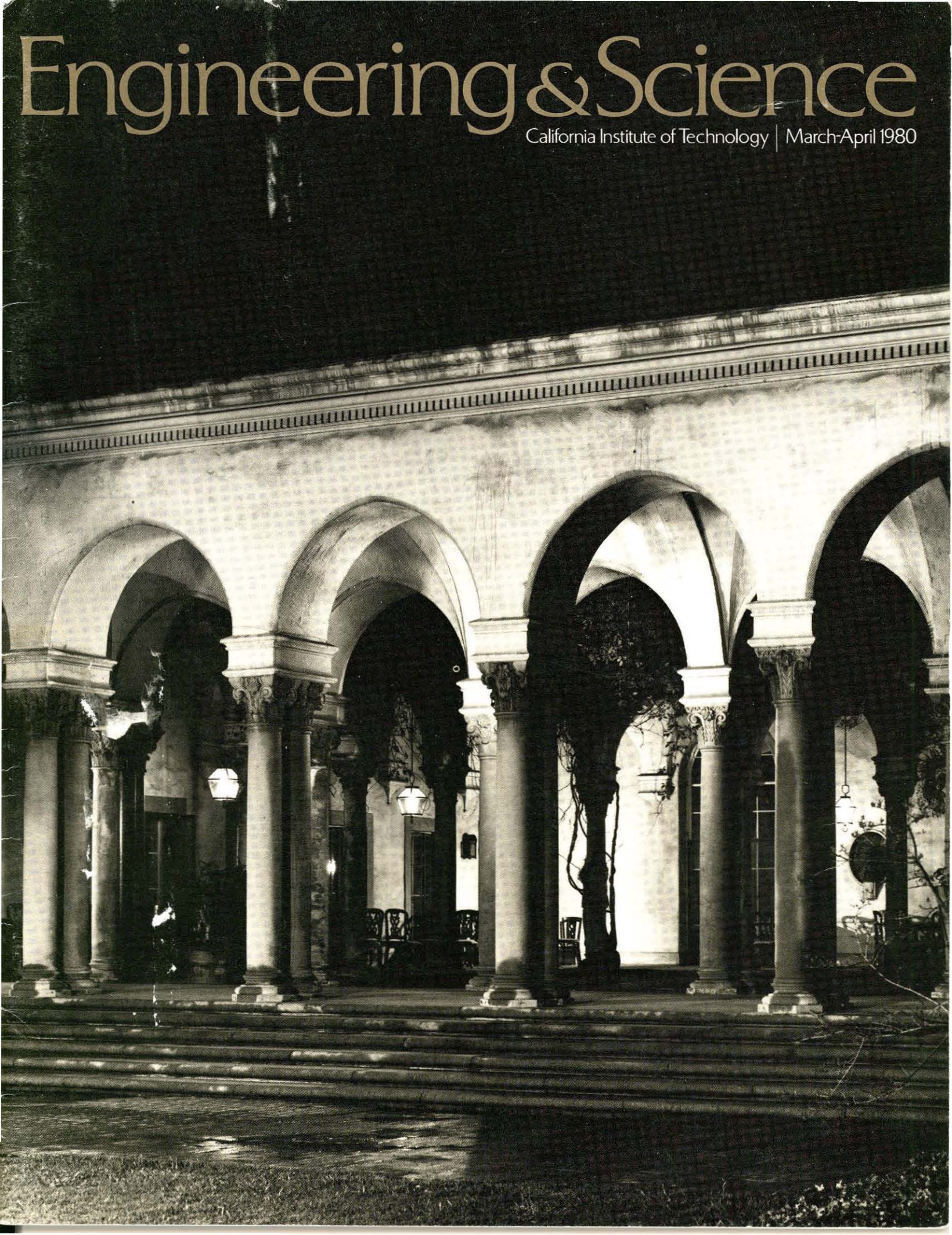
Engineering & Science

California Institute of Technology | March-April 1980



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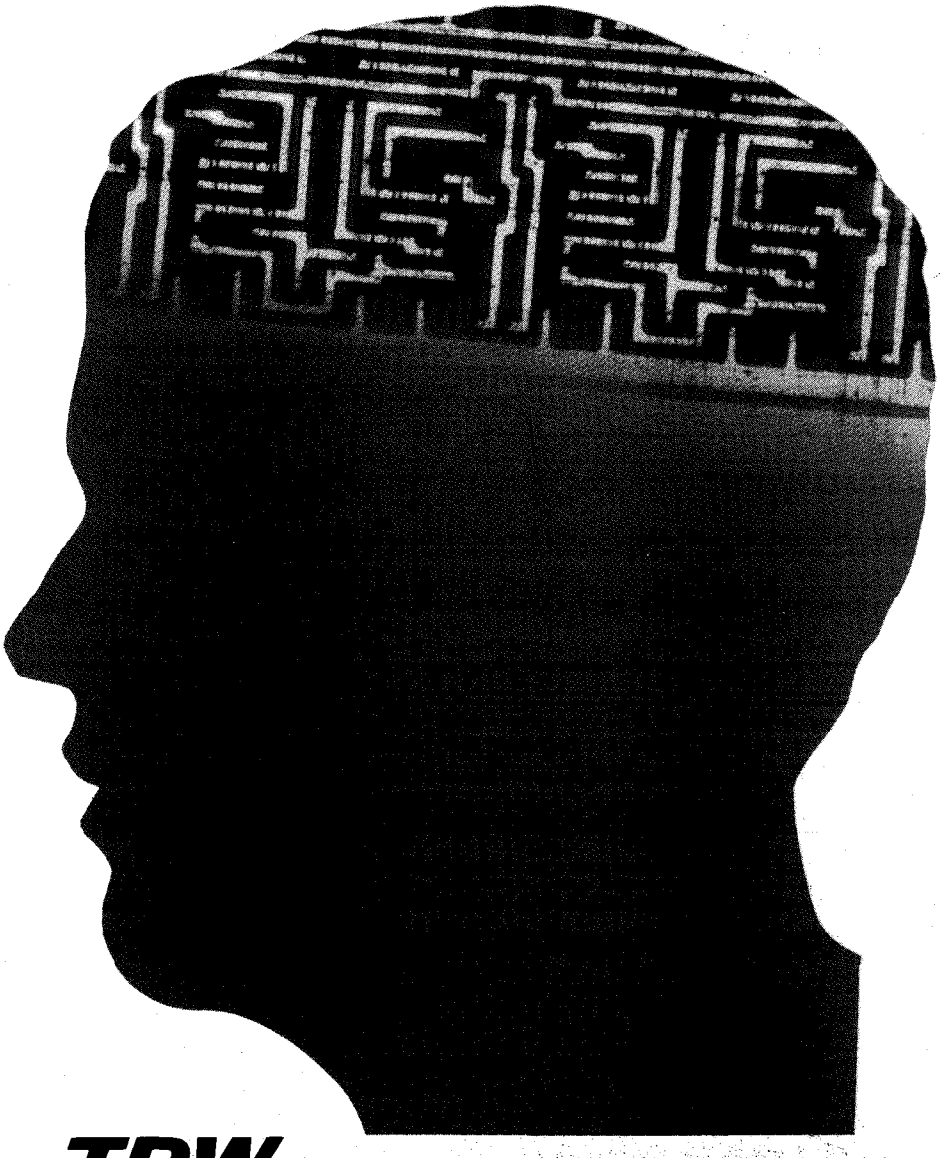

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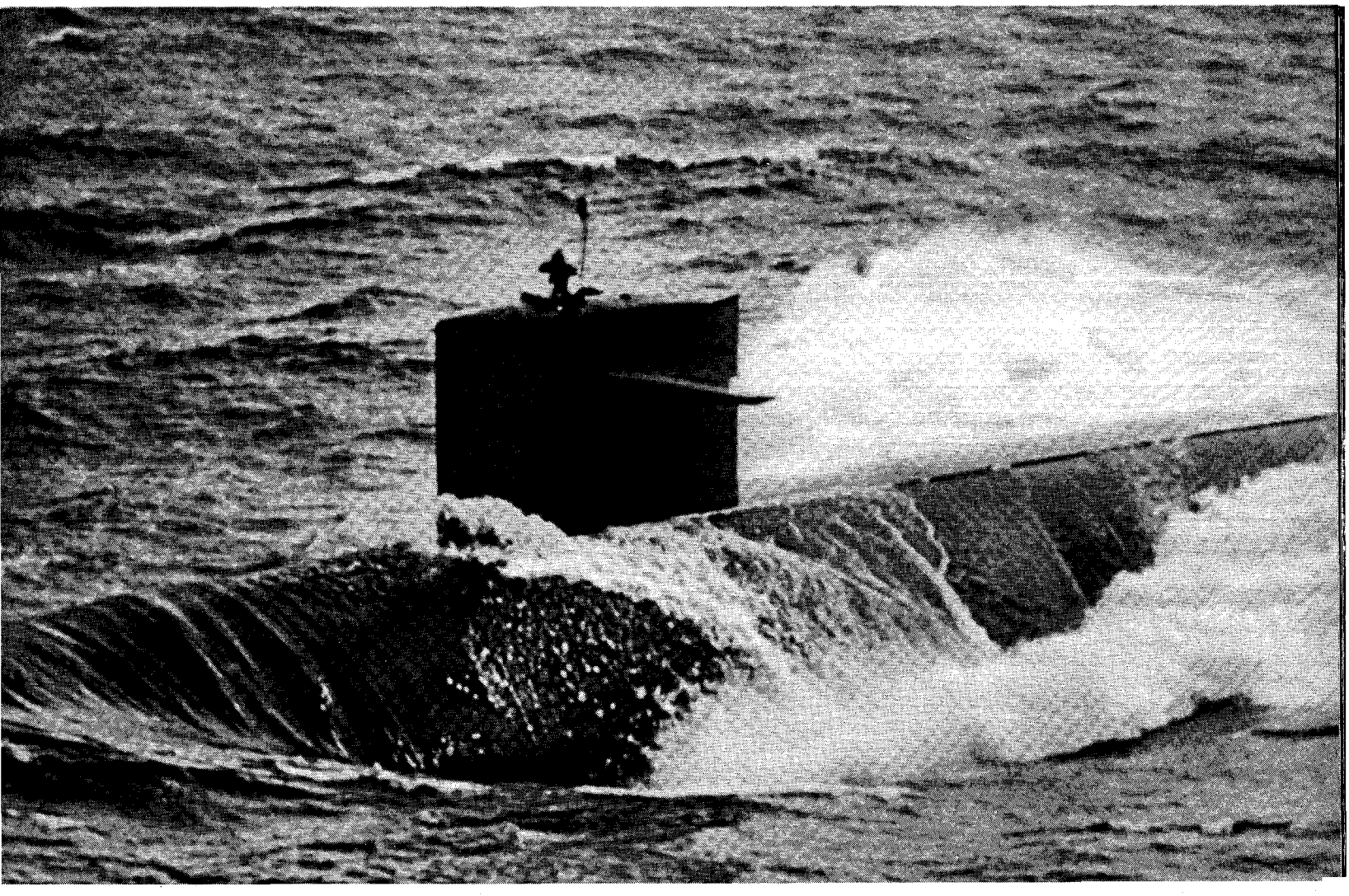

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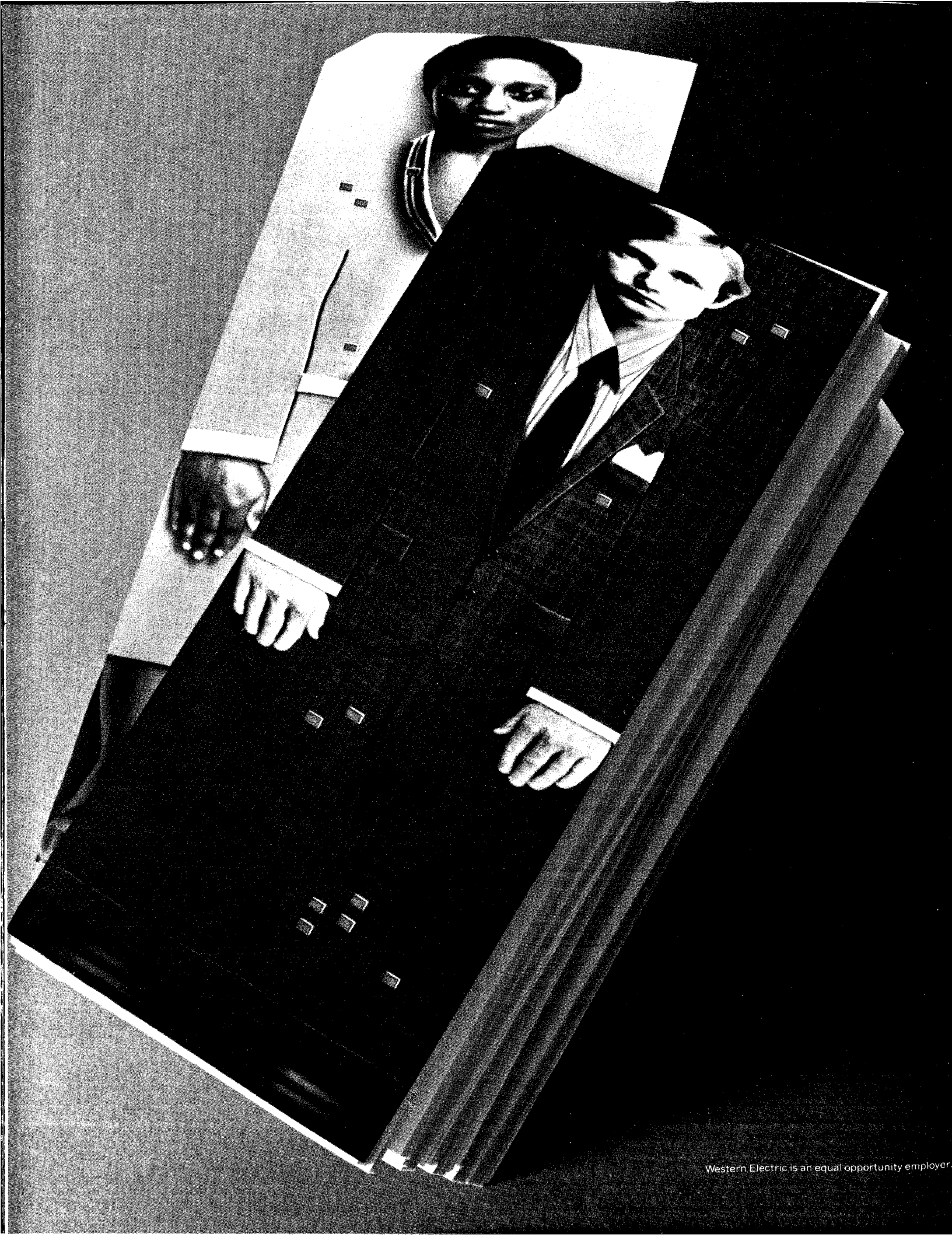

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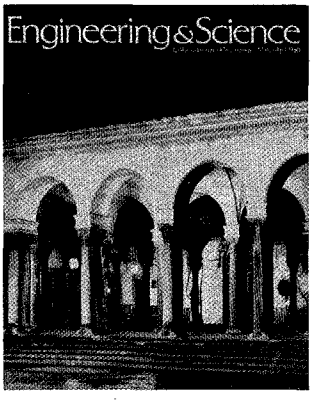
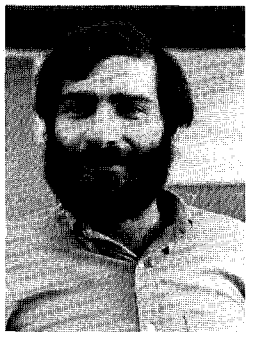
In This Issue



Happy Birthday
On the cover — an unusual and beautiful night view of the Athenaeum, the Institute's faculty club, which is celebrating its 50th year of service to the Caltech community. There is good cause for celebration because in the Athenaeum the members have had since 1930 a gracious and convenient place in which to lunch or dine, to hold a meeting or a banquet, to meet friends and colleagues, to house distinguished visitors, and "to hear discussions of topics of interest . . . by those best prepared to tell of the fascinating developments in science, art, literature, history, and government." At first, the membership was drawn from scholars and scientists at the Institute, the Mount Wilson Observatory, and the Huntington Library and Art Gallery, and from the newly organized Caltech Associates. Later other groups became eligible.

On March 21, the 50th anniversary of the Athenaeum's first dinner for its members was celebrated with another dinner that honored those of that first group who are still members today and their special guests. Lee A. DuBridge, president emeritus of Caltech, was the chief speaker, and on page 15 *E&S* presents "The Athenaeum — Fifty Years Young," an adaptation of his recollections of the early days of the club.



Henry Lester

Electrochemical Contact
The speaker for the Watson Lecture on December 5 was introduced by his colleague in neurobiology, Felix Strumwasser, who said in part: "Henry Lester is a biologist who specializes in synapses, the functional contact between one nerve cell and another cell. He came only gradually to biology, however, having received his undergraduate education at Harvard College, where he graduated with highest honors in chemistry and physics. He did his graduate studies in biophysics at The Rockefeller University in the laboratory of H. K. Hartline, F. Ratliff, and F. A. Dodge. Lester's postdoctoral research was done in Paris with Professor Jean-Pierre Changeux, a molecular biologist who converted to neurobiology.

"Lester came to Caltech in 1973 as assistant professor and advanced to associate professor in 1976. He is currently the recipient of a five-year National Institutes of Health award for research career development, and this is a highly competitive and prestigious grant. But his versatility and self-confidence can really be appreciated by the following two facts: First, this year he is one of two biology faculty members who are teaching sections of freshman physics; the other is no less than Nobel laureate Max Delbrück. Second, Lester's model research animal is the Amazonian electric eel. No doubt that will lead to an electrifying and educational lecture."

"Drugs and the Brain" on page 8 is adapted from that talk.

How It Is
For several years the Institute Archives under the direction of Judith Goodstein has been engaged in an Oral History project. To date more than 20 of Caltech's senior citizens have been interviewed about their recollections of childhood, anecdotes about others, and memories of the Caltech that once was.

A completed Oral History represents more than memories, however. It also involves several hours of interviews and the time and skills of a researcher, transcriber, editor, indexer, and binder — and finally the approval of the subject as to the future use of the material. At that point *E&S* has twice entered the situation — in the case of the oral histories of Henry Borsook and L. Winchester Jones. We have each time had the difficult job of choosing and printing small portions of much longer reminiscences. On page 21 we present the third in our series, which was equally difficult to excerpt, "Max Delbrück — How It Was." This is the first of two installments.

Lee DuBridge

STAFF: *Editor* — Jacquelyn Bonner
Staff Writer — Jane Dietrich
Photographer — Chris Tschoegl

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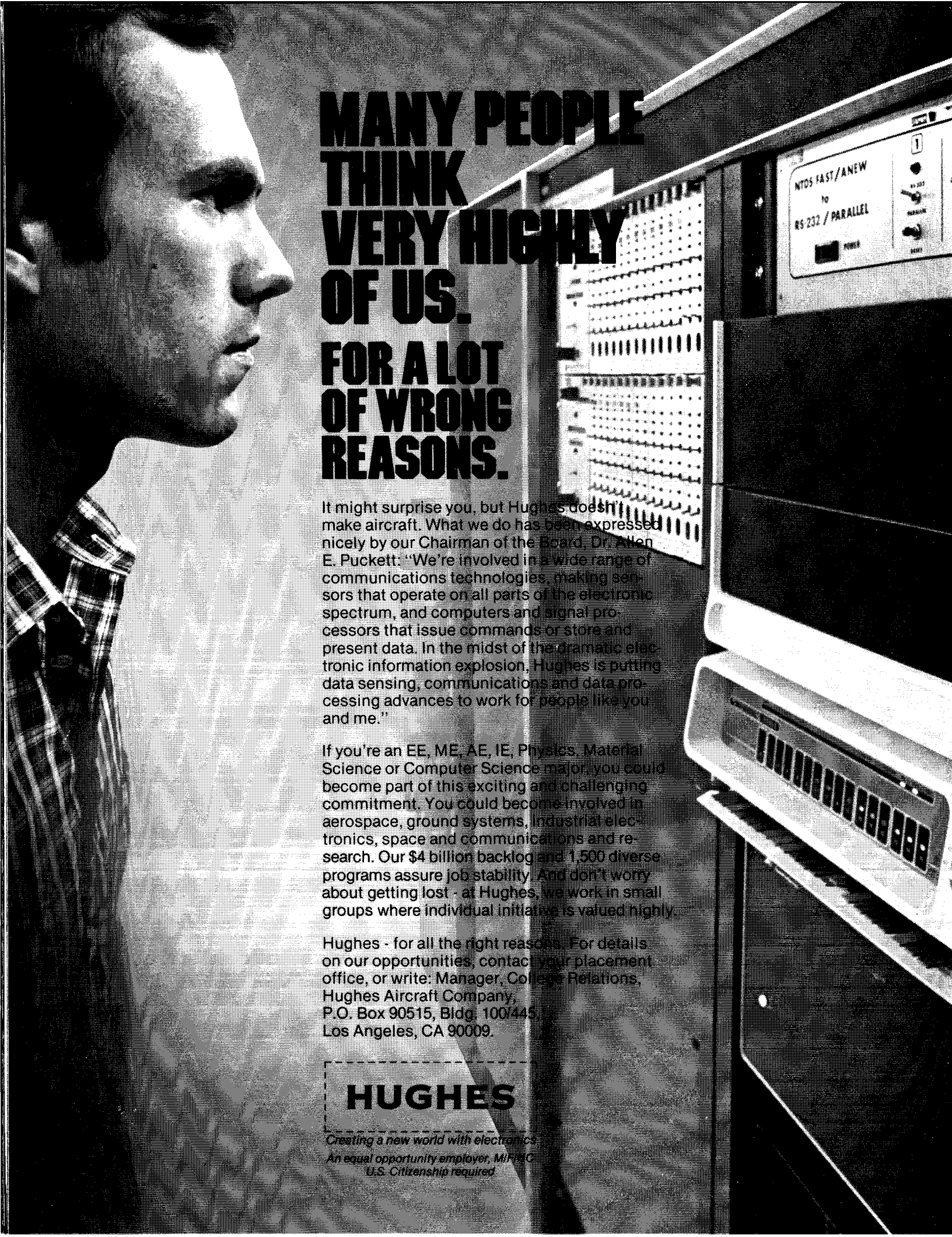
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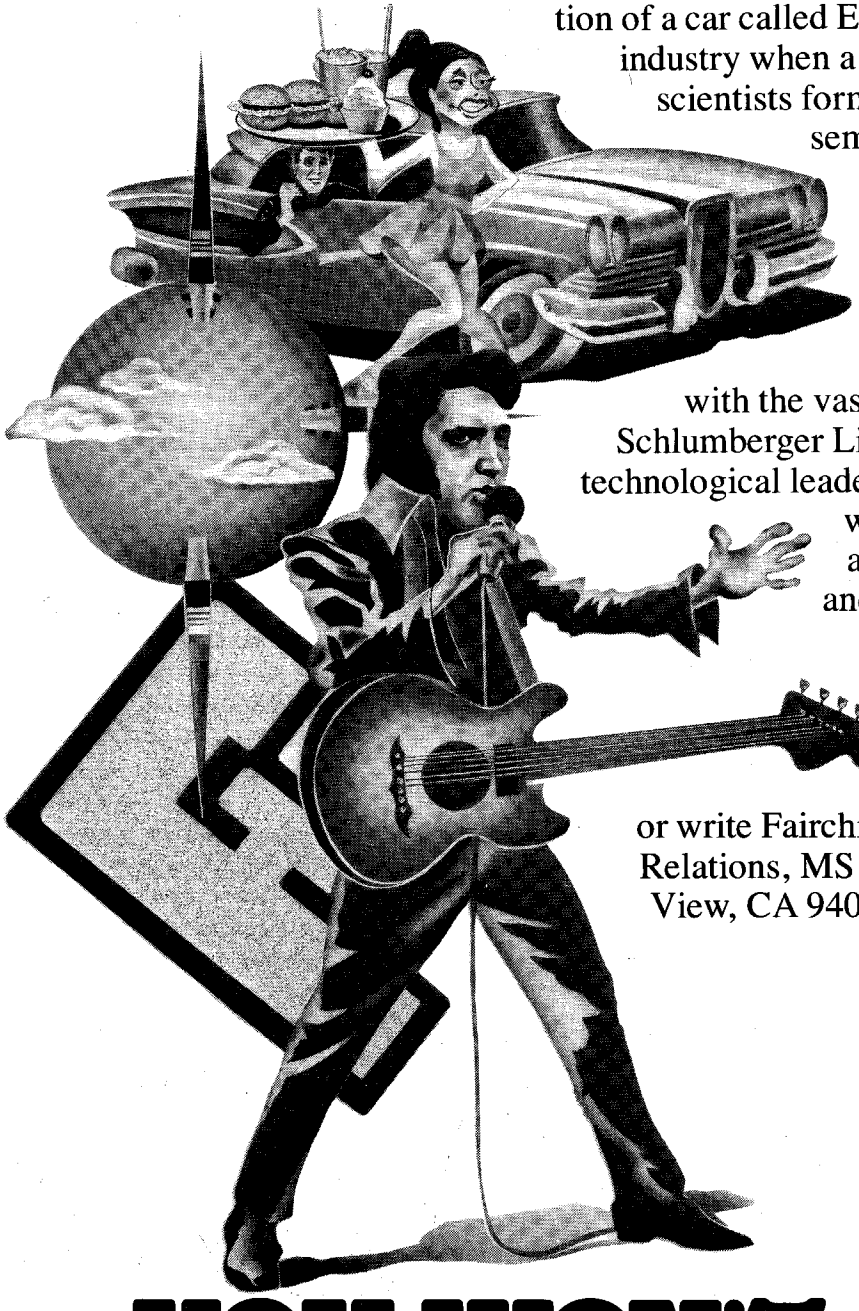

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Engineering & Science
MARCH-APRIL 1980

Drugs and the Brain

by HENRY A. LESTER

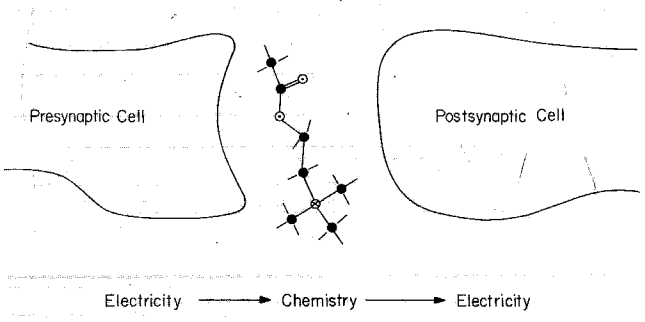
A Caltech neurobiologist discusses how some well-known drugs act upon the billions of nerve cells in the human brain

There are several useful definitions of a drug. It might, for instance, be the stuff obtainable from a pharmacist with a prescription from a physician. Or it might be something psychoactive, capable of influencing thought, perception, or behavior. These days, biologists have a rather general definition of a drug as any substance that affects the function of a living cell. In the spirit of this definition, we can identify thousands of drugs that we encounter or hear about in our society.

Here we are particularly interested in drugs that affect nerve cells. Most of the human body's ten billion or so nerve cells are found in the brain; and in the brain are located cells influenced by drugs such as Valium, strychnine, caffeine, L-DOPA, cocaine, Elavil, morphine, and of course LSD. Neurobiologists spend a good fraction of their time tracking down mechanisms of drug action, both because of the enormous therapeutic potential and because of the fascinating details that such investigations reveal about the way the nervous system functions.

Nerve cells have one predominant role — communication. They receive signals from the outside world; such signals become perceptions. They send signals to the outside world; such signals become the motion of muscles. And they communicate with each other. Indeed, most nerve cells in the brain just communicate with each other, elaborating and analyzing the signals to and from the external world. The language of this communication is the nerve impulse, a brief electrical event that travels throughout the branches of the nerve cell. All nerve cells in all animals apparently produce very similar impulses, lasting from one to ten milliseconds and measuring about a tenth of a volt in amplitude. How can this rather simple, brief electrical impulse, this universal code of the nervous system, allow the brain to perform all its diverse functions — perception, control of motion, emotion, cognition, the dance of the honeybees, the migration of birds? And how is this basically electrical code so sensitive to outside chemical influence?

The answer to both of these questions lies largely in the events that allow nerve impulses to travel between individual nerve cells and between groups of nerve cells. These events, which fascinate many modern neurobiologists, occur at a structure called the synapse, from the Greek for *contact*. In a highly schematic view of a synapse, there are two cells, the transmitting or *presynaptic* cell and the receiving or *postsynaptic* cell. When the impulse arrives at the synapse, it liberates a chemical substance called a transmitter. The transmitter then acts on the postsynaptic cell and reinitiates the electrical impulse. Thus, there is a chemical step in the hop that takes the impulse from one cell to another. It is because of this chemical step, and because this step occurs in the space between two nerve cells, that synaptic transmission is so highly susceptible to outside chemical influence.



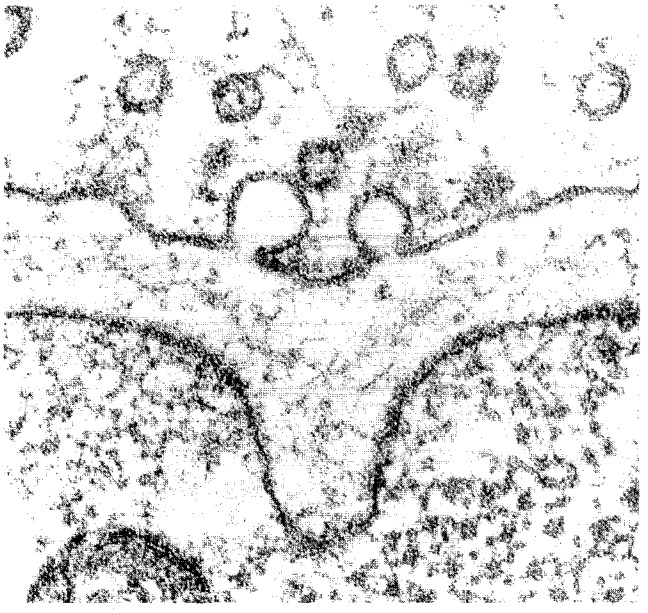
At the synapse, a chemical step transmits the electrical impulse from the presynaptic, or transmitting, nerve cell to the postsynaptic, or receiving, cell. The diagram above shows this step occurring via an acetylcholine molecule at the nerve-muscle synapse. In actuality, the molecule is much smaller relative to the nerve cells, and many such molecules participate at a single synapse.

There are dozens, perhaps hundreds, of transmitter substances in the brain and elsewhere in the nervous system. Each of these natural transmitters is associated with a constellation of drugs — some found naturally in the body, but most not — that modify synaptic transmission. Each synapse has only one transmitter, and a typical cell in the brain might receive signals at thousands or tens of thousands of synapses. Such a cell might, in turn, send signals to other nerve cells at other thousands of synapses. The brain may therefore be viewed as a network of nerve cells signaling each other chemically at synapses.

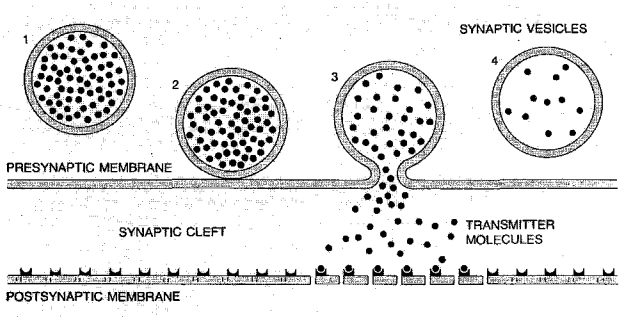
Imagine the path taken by a train of impulses that command a finger to move. The impulses arise in the brain, hop one or two synapses to reach the spinal cord, and hop one or two more synapses to reach the nerve that serves the arm and hand. One synapse remains — that between the nerve and muscle cells that move the finger. This nerve-muscle synapse, the last link in voluntary motion, is quite accessible to study. Neurobiologists now know a great deal about this synapse, and it serves as a reference point or model for other research on synapses. In some ways, the nerve-muscle synapse is the *E. coli* of neurobiology.

The preparations for synaptic transmission begin well before the impulse reaches the nerve-muscle synapse. The nerve (the presynaptic cell) is constantly packaging molecules of its transmitter, acetylcholine, into vesicles. The vesicles have a diameter of about 500 Angstroms, and each contains about 10,000 transmitter molecules plus a few other chemical species whose function still puzzles us. When the nerve impulse arrives at the synapse, a pulse of calcium apparently enters the nerve cell from the external fluid — essentially filtered blood — that bathes most of

Micrograph by John E. Heuser of the University of California School of Medicine in San Francisco.



This electron micrograph shows a synapse frozen by liquid helium at the moment the impulse arrives. Two synaptic vesicles, already fused to the presynaptic membrane are liberating their acetylcholine molecules into the space between nerve and muscle cells (center horizontal band). Other vesicles can be seen in the presynaptic (nerve) cell, which stretches across the top; the postsynaptic (muscle) cell is at the bottom. A schematic view of the electron micrograph (below) also shows the transmitter molecules binding to the receptors in the postsynaptic membrane.



the body's cells. Within less than a millisecond, the calcium in turn causes some of the vesicles to fuse with the presynaptic membrane. The vesicles then liberate their transmitter molecules into the space between the nerve and the muscle.

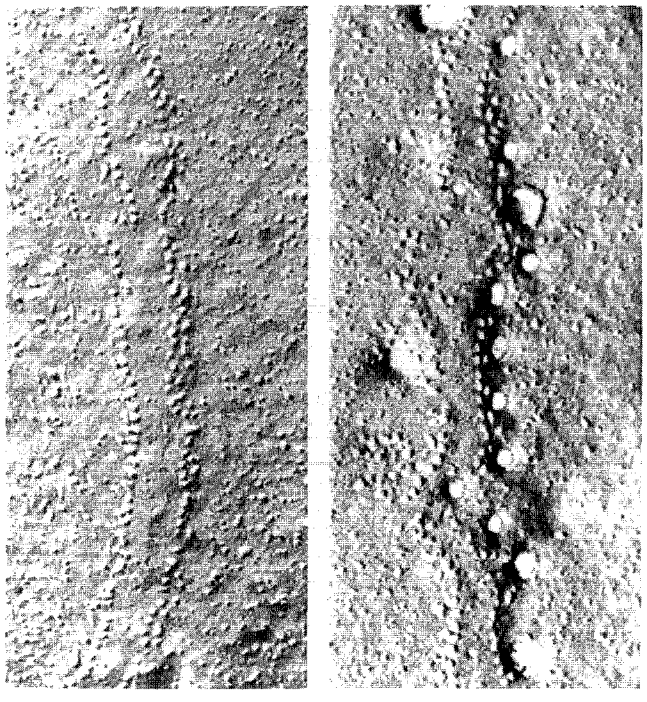
Some potent drugs interfere with the process of transmitter release. Botulism, one type of food poisoning, is caused by a bacterial toxin that apparently prevents the fu-

sion between vesicles and the presynaptic membrane. Transmitter is not released; the impulses never reach the muscle; and paralysis results. A complementary situation arises through the action of the black widow spider's venom. In this case, an "avalanche" of synaptic vesicles fuses with the membrane of the presynaptic cell; too much transmitter is released; and the spider's prey suffers muscular spasms.

Once liberated from the presynaptic nerve cell, acetylcholine molecules probably require only a few microseconds to diffuse the 500 Angstroms or so to the membrane of the postsynaptic cell. Next, the transmitter molecules interact with special proteins embedded within this membrane at the synapse but nowhere else in the normal cell. These proteins, called receptors, are packed so tightly that there seems to be little room for other structures in the membrane. The receptors function to reconvert the chemical message back into an electrical one.

According to present concepts, each receptor molecule

Micrograph by John E. Heuser.



These electron micrographs show the presynaptic membrane as seen from outside the cell. In the view on the left, the synapse has been frozen without an impulse while the synapse on the right shows the membrane at the moment the impulse arrives. The white globs in the right-hand picture are the vesicles fused to the membrane, liberating their contents of transmitter molecules. The smaller bumps visible in both views, membrane particles, may be sites where the inward pulse of calcium flows to trigger the fusion.

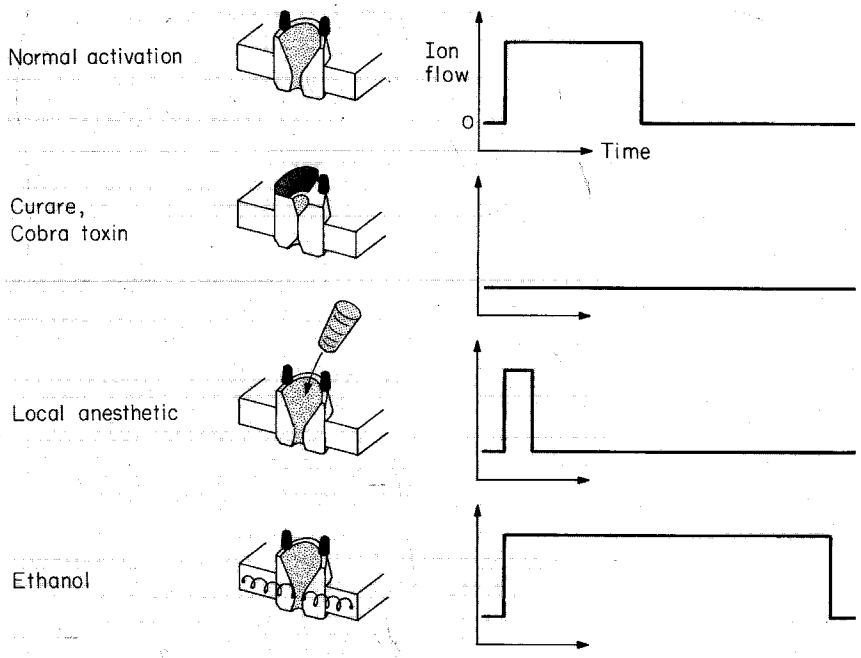
seems to guard a pore, or "channel," in the postsynaptic membrane. The pore opens if — and only if — two molecules of acetylcholine bind to one receptor molecule. The open channel seems to be a few Angstroms in diameter, and it allows ions (charged atoms) of sodium and potassium to flow in and out of the cell. The flow consists mainly of sodium ions, and its predominant direction is inward. This flow of positively charged ions constitutes an electrical current, which completes the chemical hop and triggers the impulse in the postsynaptic muscle cells. The impulse in turn signals a contraction of the muscle.

It has recently become possible to measure the electrical current associated with single acetylcholine receptor channels. The channels seem to switch rapidly between "open" and "closed" — there are no "half-open" or "nearly open" channels. Typically a channel remains open for about a millisecond, and during this time about 20,000 sodium ions flow into the cell from the outside fluid.

These receptor molecules and their channels constitute the research interest of my laboratory at Caltech. Ion channels are not restricted to the postsynaptic membrane of the nerve-muscle synapse. In fact, such channels occur in the membrane of every known nerve and muscle cell. Some ion channels allow only sodium to flow through; other types specifically allow potassium, chloride, or calcium ions. As for the signals that open and close them, receptors can be found that open channels in response to the specific binding of most neurotransmitter molecules. Some channels actually open and close in response to electric fields across the nerve cell membrane; these latter channels are responsible for the propagation of the nerve impulse within the nerve cell. We might summarize by saying, then, that the various ion channels seem to govern most electrical activity, and therefore most signaling, within the nervous system.

In the specific case of the channel associated with the acetylcholine receptor, we have a structure that is quite susceptible to drugs, and in the past few years studies on this channel have yielded a clearer picture of how some drugs act. Curare, for instance, is used by South American Indians on their poison darts. The curare molecule sits on the acetylcholine receptor and prevents one or both of the acetylcholine molecules from binding to it. As a result, the channel cannot open, no ions flow, and the impulse cannot be transmitted from the nerve to the muscle. The hunter's prey is paralyzed. The most toxic component from cobra venom has a similar action. Generally the cobra's prey dies of asphyxiation because the nerve message cannot reach its diaphragm muscles.

Local anesthetics such as Novocain (procaine) also act at



Several drugs act on the receptors of the postsynaptic cell — and they act in different ways. In the topmost figure on the left, two acetylcholine molecules bind to the receptors to open the channel for normal ion flow. Curare and cobra toxin molecules sit on the receptors, preventing the acetylcholine from binding, opening the channel, and transmitting the impulse. Local anesthetics allow the channel to open but plug it prematurely, while ethanol affects the springiness of the membrane, allowing the channel to stay open too long. The graph on the right indicates the flow of ions against time for each of the four cases.

acetylcholine receptor channels. A schematic view of events is that a local anesthetic acts like a cork. Acetylcholine can bind in the normal way, and the channel opens normally — and incidentally to the same extent as it might if only acetylcholine itself were present — but the local anesthetic now enters the channel and plugs it. As a result, ion flow — and the electrical message — is terminated prematurely. Local anesthetics block several types of ion channel in this fashion; the most important clinical blocking action is on the electrically excitable channels that propagate impulses within nerve cells. Pain impulses are thus prevented from reaching the brain, a fact that may be of some comfort to you the next time you find yourself in the dentist's chair.

Ethanol (alcohol) also influences the function of acetylcholine receptors. This drug seems to modify the springiness of the membrane that carries all of these receptors and channels. Once again, a channel might open normally and to the same extent as it would normally, but when ethanol is present, the modified membrane allows the channel to stay open substantially longer than usual. This drug certainly does not work primarily at the nerve-muscle synapse, but every nerve cell has ion channels, and a great many of them may be modified by alcohol. Some, like acetylcholine channels, remain open longer than usual; for others, the modified membrane forces the channel to close more rapidly than usual. At this point we cannot describe in detail how these actions on membrane channels lead to alcohol's profound behavioral effects or to addiction.

With the opening of receptor channels, the nerve impulse has almost completed its chemical hop from the nerve to the muscle. One final event is crucial. Acetylcholine molecules leave the receptors as the channels close again, and a very efficient enzyme, acetylcholinesterase, now destroys them. Enzyme molecules are located in large quantities exactly where they are required — in the space between the nerve and the muscle. As a result, the average acetylcholine molecule is destroyed within less than a millisecond after it leaves the receptor. Some insecticides and nerve gases work by blocking acetylcholinesterase. Such treatments allow acetylcholine molecules to hop from one receptor to another, forcing too many channels to open for too long. Too many postsynaptic impulses are initiated, and spasms result.

I have exploited the nerve-muscle synapse to discuss a few key concepts about synapses in general. First, transmitter molecules are liberated into the space between the two cells by electrical impulses; second, transmitter molecules then act upon the postsynaptic cell to generate further electricity; and third, transmitter molecules are then destroyed by an enzyme.

These events occur not only at the nerve-muscle synapse but at synapses in the brain as well. Nerve cells in the brain are, however, more complicated than the average muscle fiber. Each muscle fiber receives only one synapse, but some brain cells receive thousands. They fall into two major categories. One class of synapses *excites* impulses in the postsynaptic cell, as happens at the nerve-muscle

synapse. The second class *inhibits* the action of the first class.

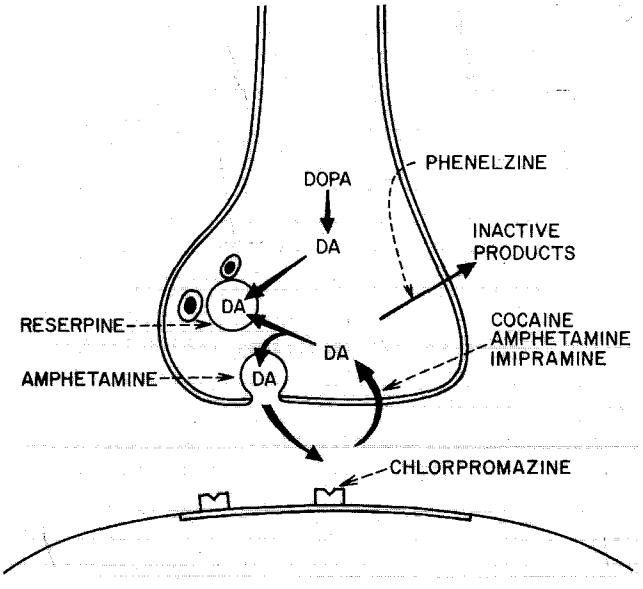
Inhibitory and excitatory synapses have very similar structures, although the cognoscenti can distinguish them in the electron microscope. The receptors and channels differ, however. The inhibitory synapses make an electrical short circuit for the excitatory synapses, decreasing their effect, much the way a car's headlights dim when the starter is operating. Any nerve cell in the brain is constantly computing the difference between the excitatory synapses and the inhibitory synapses, and the result determines the frequency of its impulses. If inhibition is stronger than excitation, the cell sends a fairly low frequency of impulses to other cells. If, on the other hand, excitation predominates over inhibition, the cell fires impulses at a high frequency, and substantial amounts of transmitter are liberated at synapses where our test cell is the presynaptic partner.

Inhibition plays a key role in information-processing, and more than half the brain's synapses may be inhibitory. Two of the known inhibitory transmitters are the amino acids, glycine and γ- (or gamma) aminobutyric acid (GABA). Glycine is an especially potent inhibitory transmitter in the spinal cord. The convulsant drug strychnine apparently blocks glycine receptors, perhaps in a fashion similar to the blockade of acetylcholine receptors by curare or cobra toxin at the nerve-muscle synapse. The result is that some nerve cells receive too little inhibition, excitation predominates, and convulsions occur.

The most commonly prescribed drugs in our society, Valium and its close relative Librium, may affect GABA receptors. Recent studies suggest that these chemicals cause the inhibitory channels to remain open longer than normal, similarly perhaps to the action of ethanol at the nerve-muscle synapse. As a result, GABA, the inhibitory transmitter, is much more potent than normal. How does modifying membrane channels lead to decreasing anxiety? At the moment we can't say.

Some details are known about two transmitter systems in the brain and about drug effects on these systems. Deep within the brain, one group of nerve cells produces a pigment that makes them appear darker than the surrounding structures; thus this group is called the substantia nigra — the black substance. These cells, which also produce the transmitter dopamine, send their branches to many other areas of the brain. At one such region, concerned with modifying voluntary motions of the body, dopamine is an inhibitory transmitter. In some diseased states, substantia nigra cells begin to die. The result is too little inhibition by dopamine at synapses concerned with the control of voluntary motion, and this leads to the tremor that characterizes Parkinsonism.

The simplest therapeutic strategy for Parkinsonism would be to inject the missing dopamine directly into the bloodstream; but such a treatment is ineffective because dopamine itself does not travel from the blood to the brain. However, knowledge of transmitter metabolism has led to a successful therapy. Clinicians exploit the fact that nerve cells make dopamine from the chemical DOPA, which does pass from the blood to the brain. The strategy, then, is to make increased use of the surviving substantia nigra cells by administering an excess of DOPA. These cells then make more than their usual share of dopamine and package it into synaptic vesicles. The synaptic vesicles fuse with the presynaptic membrane and liberate their contents of dopamine into the space between the presynaptic and postsynaptic cells, thus restoring the normal balance between the inhibitory effects of dopamine and the excitatory effects of other transmitters.



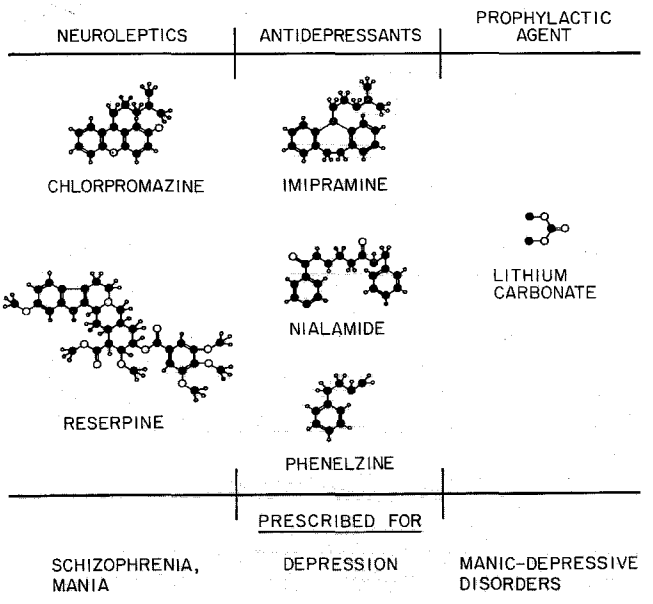
At different sites in the synapse various therapeutic drugs affect the action of dopamine, an inhibitory transmitter between nerve cells of the brain. Administration of DOPA allows increased production of dopamine (DA). Anti-depressant drugs imipramine (Tofranil or Elavil) and phenelzine also increase the amount of dopamine, phenelzine by blocking enzymes that inactivate it, and imipramine by interfering with the reuptake mechanism (as do cocaine and amphetamines). Reserpine and chlorpromazine work in the opposite way — to decrease the action of dopamine for treatment of schizophrenia. Reserpine prevents sufficient storage of dopamine in the synaptic vesicles, and chlorpromazine blocks the receptors.

The dopamine story has several other interesting chapters. In a small percentage of Parkinson's disease patients, DOPA therapy causes hallucinations and other symptoms of schizophrenia. These patients can be helped by other drugs, but such side effects remind us that substantia nigra cells release dopamine at synapses in many brain regions outside the one involved in Parkinsonism. Indeed, excess dopamine in some parts of the brain might cause forms of schizophrenia. This theory receives support from successful drug therapies that have been introduced over the last 25 years. For instance, chlorpromazine — the trade name is Thorazine — blocks dopamine receptors. As a result, even though too much dopamine might be released by a presynaptic cell at a synapse, if chlorpromazine is present the dopamine has less effect on receptors.

Apparently, chlorpromazine suppresses schizophrenic symptoms by restoring the normal balance between inhibition and excitation. Reserpine, from the snakeroot plant of India, was formerly in use for suppressing schizophrenic symptoms. This drug prevents efficient storage of dopamine in the synaptic vesicles of the presynaptic cell. Some of these synaptic vesicles are therefore empty when they fuse with the membrane. Less dopamine is released; the result, again, is a movement toward the normal balance between excitation and inhibition.

In some senses, schizophrenia can be contrasted with another class of mental disorders centering around depression. Some depressive states may arise because synapses have too little dopamine or the closely related neurotransmitter, noradrenaline (also called norepinephrine). Successful antidepressant drugs increase the level of these transmitters at synapses. Phenelzine, for instance (the trade name is Nardil), seems to block an enzyme that functions, like acetylcholinesterase at the nerve-muscle synapse, to inactivate the transmitter after it has bound to receptors. Thus phenelzine allows the remaining transmitter to have a greater effect, partially restoring the deficit.

Tofranil and Elavil, two other antidepressant drugs, enhance the effect of the remaining transmitter by interfering with another mechanism that normally terminates its action. The presynaptic cell can absorb the transmitter (dopamine or noradrenaline) into the cytoplasm. When this reuptake system is blocked, the transmitter again persists longer than usual. Interestingly enough, the reuptake system is also the site of action of the amphetamines and cocaine. These latter drugs produce a "rush" because they reach their targets within a few seconds — much more rapidly than the antidepressant drugs in clinical uses. Such differences provide a useful reminder that drug actions depend on a great many factors such as distribution, breakdown, and other effects in the body. For every drug that finds clinical use, a hundred may have been unsatisfactory because they acted too quickly, too slowly, or too broadly.



Of the above drugs, we know that five have large molecules and that they work by restoring normal levels of dopamine and norepinephrine action at brain synapses. Chlorpromazine blocks the receptors, and reserpine prevents sufficient storage of dopamine in the synaptic vesicles. The three in the center work in the opposite way — by blocking enzymes that inactivate or re-absorb dopamine and norepinephrine. The way lithium exerts its therapeutic effects is still unknown.

No one should infer that neurobiologists now understand completely the chemistry of mental disease and how to treat it. The use of the drug lithium is a case in point. This simple ion, which is quite effective against mania and manic-depressive disorders, strongly resembles sodium. It might, therefore, act at many different places in the nervous system, but we still have very little idea about the site where it produces its remarkable therapeutic effects.

One should also not infer that all transmitters act by opening channels in postsynaptic membranes. It is known that receptors for some hormones are coupled to enzyme molecules rather than to ion channels. The enzyme molecules produce a second transmitter molecule that acts *within* the receiving cell. This second transmitter is often cyclic AMP (adenosine monophosphate), which is made from the ubiquitous source of energy for physiological reactions, ATP (adenosine triphosphate). Cyclic AMP serves as an intracellular signal to activate second messengers in some parts of the nervous system. Like the transmitters themselves, the second messengers are usually de-

stroyed by an enzyme. This enzyme is highly sensitive to caffeine and theophylline, the drugs from coffee and tea. These beverages, then, prolong the action of intracellular transmitter molecules.

Papaver somniferum, the poppy that brings sleep, has been employed by man for thousands of years. Morphine, which is extracted from the opium poppy, is one of our most useful painkillers. Unfortunately, morphine is also addictive. Many factors make up addiction — some are sociological, some are psychological. Addiction is also observable at the level of cellular neurobiology. If a nerve cell is exposed repeatedly to morphine, the morphine loses its anesthetic effect. Increased doses become necessary because the cells become *tolerant* of the morphine. At the same time, the nerve cells change — in some fashion that is not understood — so that they cannot function normally without morphine; that is, they become *dependent* on morphine. These two interconnected phenomena, tolerance and dependence, underlie a large part of addiction.

Is there any hope for a nonaddictive painkiller that would not produce tolerance and dependence? To search intelligently for such a drug, we need to know more about morphine's action on the brain. Morphine is not present naturally in the brain, but morphine molecules do bind to cells of the so-called limbic system, a loosely connected ring of structures at the edge of the cerebral cortex. This system is importantly involved in perceiving pain. The straightforward hypothesis, then, is that these binding sites might also be sites of binding for a natural morphine-like substance produced by the brain. In other words, morphine might be mimicking a natural transmitter called into action to suppress pain during times of crisis or stress. Indeed, there is some evidence that such a transmitter is also released by acupuncture. Several research groups have therefore attempted to isolate and study the brain's own morphine-like substance.

The search, which began to show success about four years ago, exploited some similarities between nerve cells in the brain and those elsewhere in the nervous system. In addition to their action on the brain, morphine and its derivatives also suppress impulses in nerve cells of the digestive system, a fact appreciated by anyone who has cured the symptoms of an upset stomach by taking paregoric, which is an extract of opium. So the test for morphine activity involved soaking a bit of the intestine of a guinea pig in an organ bath. The tissue was stimulated with electrodes to produce impulses in the nerve cells that control the intestine's muscular activity. The strengths of the contractions were measured and provided a bio-assay for drugs that affect the nerve cells.

Morphine blocks the contractions, and a substance with similar effects was found in brain extracts. The substance is now called enkephalin, from the Greek meaning *from the brain.* Other pharmacological tests show that morphine and the enkephalins (there are a few, closely related molecules) act on the same receptors. Incidentally, the enkephalins are small proteins, unlike other transmitters I have described thus far. It is now becoming evident that many other transmitters in the brain are also small chains of amino acid residues.

Where are the cells that make the brain's own painkillers, the enkephalins? In large part they can be found in the limbic system, that region of the brain that suppresses our perception of pain. There is also enkephalin in the spinal cord, near the very first synapse that a pain impulse must pass to go from the outside world to the brain. At present we don't know where the enkephalins bind to their receptors or whether they open channels in postsynaptic cells. One possibility is that they inhibit the release of transmitter from the pain fibers at this first crucial synapse. This would prevent the pain signals from reaching the brain.

Thus far, the enkephalins do not constitute the sought-for nonaddictive painkillers, largely because, like most neurotransmitters, they are rapidly destroyed by enzymes that seem designed to terminate their action (as acetylcholinesterase inactivates acetylcholine). Therefore, direct injections of enkephalins have only a very weak action. Chemists have synthesized analogous molecules that are not subject to these enzymes. These relatives of the enkephalins do have painkilling action, but they also induce tolerance and dependence in the nerve cells — they are addictive. Despite these negative first results, there is good reason to expect further progress in this exciting new field.

An article on drugs and the brain would be incomplete without mentioning LSD, but we know embarrassingly few details about this drug. From molecular structures, we can say that LSD and psilocybin resemble serotonin, another known transmitter. It is possible to localize synapses where serotonin is the transmitter; and in animals given LSD these synapses become less active. So LSD and psilocybin might be blocking brain receptors for serotonin in the brain, but we have few clues as to how this might lead to hallucinations.

Neurobiologists seem to have made some progress since Freud asked, at the beginning of this century, whether psychiatrists and psychologists could put their science on a firm chemical basis. Freud would be pleased with the results so far, but he would certainly agree that the most exciting discoveries are yet to come. □

The Athenaeum–Fifty Years Young

by LEE A. DuBRIDGE

We owe a great debt to Allan and Janet Balch, who provided $500,000 so that Caltech could have the finest faculty club in the country — the Athenaeum — and to Gordon Kaufmann, the architect who made their dream a reality. Allan Balch was a New Yorker who earned part of his way through Cornell University by working in the college blacksmith shop. It was there that he met Janet Jacks, a young lady from California who brought her riding horse into the shop to be reshod. The Balches moved to California in 1896, and he became a Caltech trustee in 1925, serving as chairman of the board from 1933 until his death in 1943. Janet Balch was active in social and civic affairs, including in addition to Caltech the Los Angeles Symphony and Scripps College.

The original governing board of the Athenaeum consisted of Balch as president, and a group of distinguished friends of the Institute — historian William B. Munro, Walter Adams of Mount Wilson, Max Farrand of the Huntington Library, trustee Henry Robinson, and associates Albert B. Ruddock and James Page. The chairman of the House Committee was a brand-new young assistant professor of economics, Horace Gilbert. The other members were Mrs. Balch, Mrs. Josephine Hixon, Edwin Hubble, Mrs. Donald O'Melveny, and Earnest Watson.

According to a letter Watson wrote Gilbert in July 1930, the composition of this committee was cause for consternation. He said, in part:

> Help! Succor! Assistance! Our dear Athenaeum has turned into a women's club overnight. Women are to enjoy all the privileges of the club. Women are to live at the club if they so desire. Women have been put on all the committees. Women, to the number of three, have been added to our House Committee. With both you and Hubble gone for the summer, what is a poor, scared bachelor like myself to do? I

The Athenaeum

shall be outnumbered, outtalked, outvoted, and completely cowed before you even have a chance to return.

Apparently, a few years later things had worked out to Watson's satisfaction, for a 1937 Athenaeum bulletin listed no women as members of the House Committee. That, too, was a temporary situation, and for some years now women have again been on the roster. In fact, the current chairman of the committee is a woman.

Changes have taken place in other areas of Athenaeum management as well. In 1930 lunch cost 50 cents, dinner 75 cents, and a single room could be had for $2.00 per night. By 1937 price increases were regretfully announced: lunch 55 cents and dinner 85 cents. Many faculty members were reluctant to join the Athenaeum when they realized that there would be monthly dues, so — as a come-on gesture — dues for them were suspended for the first year. For some time thereafter they were only $2.00.

The first dinner for Athenaeum members was held on October 30, 1930. On November 4 there was an afternoon reception for undergraduate students and their friends, but for many years afterward no undergraduate — except for student waiters — ever saw the inside of the club again.

Among the other early celebrations was a dinner for Associates, a series of weekly lectures, and on February 4, 1931, the big Einstein dinner. Attendance that evening was limited to Associates and their wives, and the guests and press made much of the fact that three Nobel Prizewinners were on the program — Millikan, Michelson, and Einstein — and in addition astronomers George Ellery Hale and Edwin Hubble.

Charming as the Athenaeum was from the beginning, it was not without problems. Engineering professor Robert Daugherty used to recall that at Millikan's request he spent most of the evening of that first dinner in the basement trying to get the furnace to work. Not much later a door had to be installed at the head of the stairs leading from the lobby to the basement "in order to reduce the drafts and the the flies."

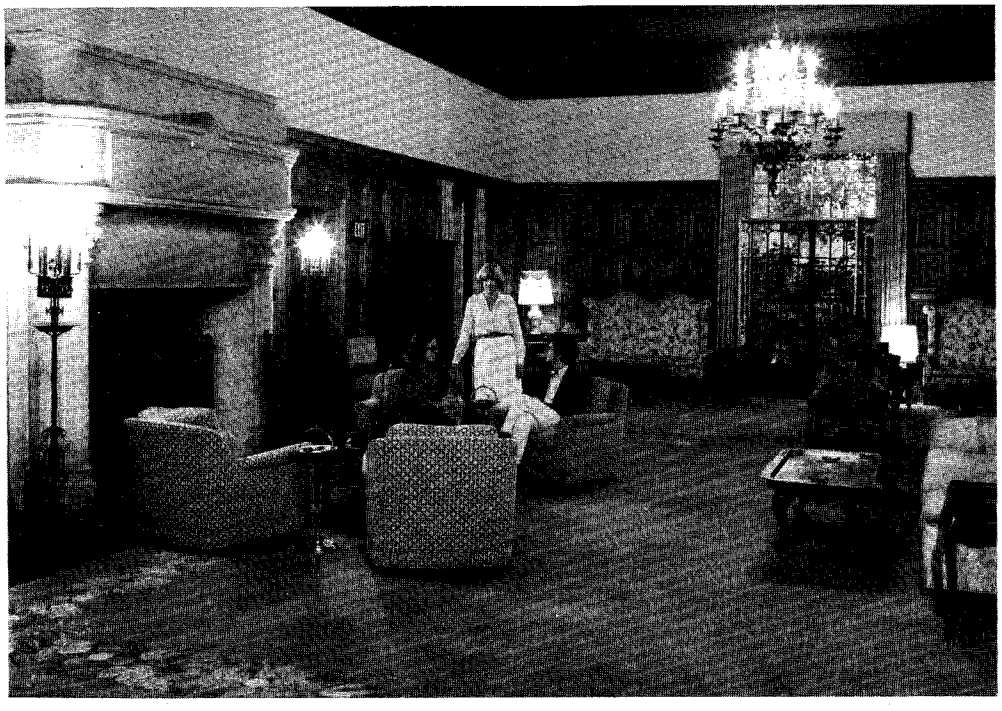
The 1930s were difficult for the Institute financially, and many a graduate student teaching assistant received his pay in the form of room and board at the Athenaeum instead of in cash. Several of these students took over a round table in the main dining room, and they were decidedly choosy over who should sit there. Being fond of Richard Tolman (then unmarried), they elected him an honorary member of their group. The round table boys also paid a lot of attention to the ladies they saw at the Athenaeum — mostly faculty wives — and they established a scale of pulchritude for them. At the top of the list was Luddye Michal, wife of the distinguished mathematician Aristotle Michal, and the unit of beauty was named the Michal in her honor. Unfortunately, the students felt it was much too grandiose to fit many of the ladies, so 1/100th of a Michal — a Kopek — was developed and applied to others. It is reported that certain of the ladies were even rated at a small fraction of that. No doubt they had beautiful minds.

The Athenaeum has, of course, had its ups and downs, some growing out of budgetary problems and some out of differences of opinion. Some managers have been more efficient than others. The quality of food has oscillated from barely acceptable to superb. Improving the dining room's noise level by the installation of carpeting on the floor and acoustic tile on the walls and ceiling made a gracious room even more gracious. And, after years of struggle over both principles and practicalities, a liquor license was procured. At last the surreptitious pre-dinner sherry parties in the upstairs suites could be abandoned in favor of openly consumed cocktails or wine from the well-stocked cellar.

Now at the age of 50, the Athenaeum has become not only a Caltech tradition but one of the best clubs in southern California — and, as always, surely rating several Michals on anybody's scale. □

The main lounge of the Athenaeum as it has appeared at three different periods in the last 50 years. Some of the furniture from the very first version (above) is still there — the octagonal table, the fire screen, and a pair of settees, for example — and pieces of the original rugs are still in use in Dabney Lounge. The tassels have long since been removed from the chandeliers. The hallmark of the lounge for most of its existence was its magnificent carpet, the Royal . . .

. . . Meshed rug in the picture above. Measuring 47½ by 28½ feet, it had to be turned under along the south wall to fit into the room. The story is that the rug was over a century old when it came to Caltech, having been woven for the palace of a Persian nobleman in the city of Masha. When that city was threatened by Bolshevik uprisings, the rug was smuggled out of the city, eventually was acquired by P. G. Winnett, president of Bullock's, and in due time was presented to Caltech. The portraits on the south wall are of Mr. and Mrs. Balch. Time and traffic finally caught up with the whole room, and in the early 1970s it was redecorated. Below, the Athenaeum lounge today.



William H. Corcoran

A Much-Honored Chemical Engineer

William H. Corcoran has collected enough honors during his career as a chemical engineer and educator to fill several pages on a resume. But the one that means most to him is a handsome plaque hanging beside the door of his office and inscribed, "To our fearless leader: We promise to love, honor, and obey mass, energy, and momentum balances throughout our lives. Class of '77."

This plaque, signed by all the members of Bill's senior course is, of course, a token of affection. It is also a kind of capsule comment on Bill's character. With his sincerely held and strongly enunciated beliefs and his firm commitment to advancing the causes to which he is dedicated, Bill is in many ways a fearless leader indeed. Fortunately, he also has a sense of humor that allows him to laugh at himself, and he never holds a grudge against those who don't see things his way.

The affection expressed by the plaque is probably one result of the pleasure Bill takes in teaching, but teaching is only one of the many roles he has filled during his 37 years as a chemical engineer — all with great enthusiasm. He has been president of the American Institute of Chemical Engineers (AIChE), Caltech's vice president for Institute relations and executive officer of its chemical engineering department, an executive in the biomedical engineering field, and a consultant to the biomedical industry. Now Caltech's Institute Professor of Chemical Engineering, Bill deserves his reputation for hard work and achievement.

Bill is one of those rather rare individuals in his generation who is actually a native of Los Angeles. His father, a California farmer, died when he was a year old, and he was raised by his mother, who worked as a credit manager for a wholesale grocery company, and his grandmother, a retired teacher. He attended Los Angeles public schools, including Norwood Grammar School and Fairfax High, where his fascination with the way things worked was stimulated by his biology and physiology teacher, Doris Siddall. Mrs. Siddall had the kind of pedagogical devotion that frequently led her to get up at 3 a.m. and travel by Pacific Electric car to San Pedro to collect fresh samples of sea life from the tide pools to illustrate her lectures. "Her style was a tremendous inspiration to me," says Bill.

Last year, after what he terms "40 years of thinking about it," he looked up Mrs. Siddall, now 87, and brought her to Caltech for a reunion, complete with lunch and a tour of the Institute's facilities. Meanwhile, he had other reasons to recall his high school days: In 1976 the Los Angeles School District honored him as one of its 50 outstanding graduates.

Back in the late 1930s, with college approaching, Bill weighed careers in medicine and chemical engineering, but believes now that he's fortunate in the decision he made. "If I'd become a doctor," he says, "I'd have lived and died with every patient."

In addition to studying at Caltech, Bill found time to write for the *California Tech*, play four years of intercollegiate baseball, and participate in all of the intramural sports, which meant spending almost every afternoon on the practice field. That was a matter of both pleasure and principle, and Bill continues to believe in the importance of keeping fit — a view he often expresses to his students.

From the day he enrolled, Bill found that "one of the great things about Caltech was its high density of interesting people," so he elected to stay on for graduate work after earning his BS degree in 1941. During his first year as a graduate student he met Martha Rogers, secretary to chemical engineering professor Bruce Sage. The couple became engaged six weeks after their first date, and they were married on Sadie Hawkins Day exactly a year later. Bill notes that among the many desirable traits Martha brought to the marriage — including, he happily proclaims, intelligence, wit, charm, beauty, and a love of all kinds of sports — she came equipped with a handy knowledge of chemical engineering terminology, thanks to her work in Sage's office.

The war interrupted Bill's graduate work, but beginning in the fall of 1942 he was on the campus as a research supervisor and development engineer for the National Defense Research Committee of the Office of Scientific Research and Development. He worked on interior ballistics and processing of propellant for artillery rockets and on the Manhattan Project for the firing mechanism of the atom bomb.

With the war at an end he returned to graduate studies,

completing his work in 1948 as one of the first two people to receive PhDs in chemical engineering from Caltech. He and Martha then left for Berkeley where he had a position as director of technical development for Cutter Labs.

Corcoran loved the atmosphere of industry. "It's creative," he says, "and there's a gratifying immediacy about the work. A chemical engineer in industry can go to the end of the production line and see the results of his efforts. Also, the hours, the pay, the support staff, and the equipment are usually better than at a university. To turn away from this requires a very special reason."

When he was asked to return to Caltech in 1952 as an associate professor, the very special reason prevailed — he couldn't pass up the opportunity to work with students. He also looked forward to the independence of an academic career. "I relish an opportunity to be myself," he explains. "In the industrial world, if a company has to make a 90-degree turn in direction, then its engineers have to turn 90 degrees with it or get out. At a university you have more freedom to choose your own direction."

The direction Bill chose has combined teaching, research, consulting, and commitment to the evolution of the chemical engineering profession. He has expressed his views and explained the results of his research via coauthorship of two books and more than 85 papers. His willingness to take on responsibility and hard work has led to his becoming, at various points in his career, a recognized leader in a dozen or more professional and educational organizations and committees. His contributions have won him numerous honors including the Lamme Award of the ASEE for excellence in his profession, the Western Electric Fund Award for excellence in teaching, the Founders Award from the AIChE for impact on his profession, and the Educational Achievement Award from the California Society of Professional Engineers. One other honor — and it ranks at the top with Bill — is the award from the Associated Students of Caltech for teaching excellence. Just recently he received the Engineer of the Year Award from the Institute for the Advancement of Engineering and was elected to the National Academy of Engineering.

In 1969, in addition to keeping a full load of teaching and research, he became vice president for Institute relations with responsibility for Caltech's development and public relations programs. That was no small commitment because it was a time when universities throughout the country were faced with skyrocketing costs and plunging incomes. Last July, after a decade in the fund-raising trenches, he relinquished that job to become Institute Professor of Chemical Engineering and to be responsible for examination of Caltech's and JPL's interactions in helping with the United States' energy program.

In his vice presidential role, Bill guided Caltech a long way toward the successful conclusion of a $130 million development program. A pedagogue all the way, he also did a lot of guiding of his staff on the need for clarity and precision in the use of the English language. "Please clean this up by getting to the point," "Please eliminate 'tangible' as an adjective in describing dollars," and "No self-respecting grammarian would ever start a sentence with 'it,' " were among his written directives. The staff preserved many of those memos and presented him with a scrapbook full of them when he retired from that position. It's a gift he treasures.

Handling two full-time careers, he also maintained two offices, one in Caltech's executive chambers on the third floor of Millikan and another in the chemical engineering building where he could be more easily accessible to the 30 or more students for whom he is adviser. "Don't ever try to con me by telling me you can't find me," he frequently told them. "I'm available all of the time." He meant it too. His staff soon learned that an appointment with an undergraduate ranked equally in importance with an appointment with a major donor, and that a trustee could be kept waiting if a student was undergoing a genuine personal crisis.

Whenever Bill has to be out of town, he leaves his students a telephone number where he can be reached. Call him collect, he says, if they have a problem that can't wait till he gets back. "Any time, day or night," he declares, adding, "but if you call after midnight, you'd better have a relatively good question."

Bill is known for his willingness to talk with his students about any problem from confusion over transport phenomena to a romance gone sour or how to budget their time. He advised one troubled young man to write down a schedule for how he planned to use his time during the coming week. When it revealed that the student was dating three girl friends, Bill suggested that he go the painful route of cutting down to one. Characteristically, Bill told him that his first priority was to stay healthy; his second was to attend to his studies; and extracurricular activities — even girls — would have to come third if he hoped to be successful at Caltech.

As a teacher, he dispenses prodigious amounts of work and tolerates no nonsense from procrastinators or goof-offs. But he also gives extensions of time when a student has a genuine problem, and he goes out of his way to help them find jobs. He has even served coffee and doughnuts on Friday mornings at an 8 o'clock class. "This isn't a

William H. Corcoran

bribe to get you here," he tells them. "I just want to wake you up."

Bill regularly reminds his students that, through their impact on energy, the environment, food production, medicine, and the like, they are going to play roles as leaders in society whether they want to or not. "I believe it's my responsibility to remind them that they don't live under a rock," he says, "that they can't simply concentrate on chemical engineering and ignore the rest of what's happening around them."

It was partly because of his desire to have students understand the economic and sociological aspects of engineering problems that in the late 1960s Bill developed an introductory course for sophomores that was built around the study of problems based on hemodialysis and artificial kidneys. The artificial kidney offers exceptionally fine examples of chemical engineering problems, Bill explains, and the costs of its maintenance and efficient use provide a good focus for the need to keep economics in mind while designing chemical systems. And finally, in dealing with human beings, students gain new insights into sociological needs and human problems.

In his current work with senior students, Bill stresses the importance of understanding the elements of design, which they apply through independent problems and case studies. In the third term the students simulate chemical processes, using Monsanto's FLOWTRAN programs. Bill doesn't give midterms or finals, considering them unproductive in a course devoted to problem-solving. He does expect that by the end of the year his students will understand the elements of design so thoroughly that they can explain the concepts in a clear, unambiguous way.

Bill's own PhD work was associated with heat transfer in fluids, and as a faculty member he has worked on the experimental measurement of the coefficients of diffusion for heat transfer and momentum and on applied chemical kinetics. He has conducted work on the pyrolysis of hydrocarbons and is now working on the reaction kinetics of desulfurization of fuel oil and coal. At the same time he has continued his interest in bioengineering and biomedical engineering and has been involved in the development of disposable hospital equipment, fermentation processes for penicillin and vaccines, and the development of mass parenteral solutions and peritoneal dialysis. Most recently he has done research on artificial heart valves.

There's no danger that all work and no play will make Bill a dull boy. He has, for example, found time for several excursions into musical comedy. He's been a regular in the Caltech Stock Company, a sturdy band of extroverted eggheads who masquerade as professors, faculty wives, and other members of the Institute community. The musicals have generally commemorated anniversaries, retirements, and the awarding of Nobel Prizes to Caltech luminaries, and Bill, picked for a solid baritone voice, has played such roles as a geologist, an illegal alien, a trustee, and a social worker.

"Some people think of Bill as an eminent educator," says Caltech's J. Kent Clark, professor of English, who has written the lyrics for all stock company productions. "But to me, Bill will always be a song and dance man. A tremendous talent was wasted when he went into fund raising."

In spite of the demands of his professional activities, Bill has always reserved time for his family. He and Martha have two children, Sally and Bill Jr., and four grandchildren. While his son was a teenager, Bill managed Senior League and Babe Ruth League baseball teams for boys. During the same period he and Martha taught a high-school-age Sunday school class at St. James Presbyterian Church, where they are members. They have also all worked together on the Corcorans' avocado and lemon ranch near Fallbrook, California. Bill enjoys farming as a hobby, but he is also seriously interested in the technology of agriculture.

Bill's own love for sports — as a spectator and participant — remains undiminished, and he follows USC football religiously. (One student, being stalked by Bill for an overdue paper, claims to have diverted him by launching into a discussion of the fine points of Saturday's game.) He can describe the contributions of a quarterback with the authority he would use to explain which free radical is essential in a chemical reaction.

On vacation in Hawaii for three weeks each September, he switches from sports spectator to participant, indulging himself in lots of golf and swimming over a mile in the ocean each day. At home he enjoys badminton and bicycling with Martha, and he recently experimented with the latest California fad — a pair of roller skates.

Although Bill's schedule is always brim full, there are lots more activities that he'd like to take on — mastering a musical instrument, for example, and becoming proficient in Spanish. He's already studied Latin, French, and German. Bill also loves to read and wishes he could do a lot more of it.

Does he feel frustrated at all the challenges and demands and lack of time to do what he wants to? Not at all. In the first place, he says, "I am doing exactly what I want to do at the age of 60. Everything that's happened to me has been good; I don't know why I've been so damn lucky!"

–by Winifred Veronda, editor of Caltech News

Max Delbrück

—How It Was

Max Delbrück was born in Berlin in 1906, first came to Caltech in 1937, received the Nobel Prize in 1969, and became Board of Trustees Professor of Biology, emeritus, in 1977. He began his scientific studies in astronomy, changed to theoretical physics and then to biology, becoming – through his work on phage – a leader of molecular biology by the mid-1940s. The outbreak of World War II prevented his return to Germany, and he spent the years 1940 to 1947 at Vanderbilt University teaching physics and doing research in biology. In 1947 he returned to Caltech, and he has been a member of its faculty ever since.

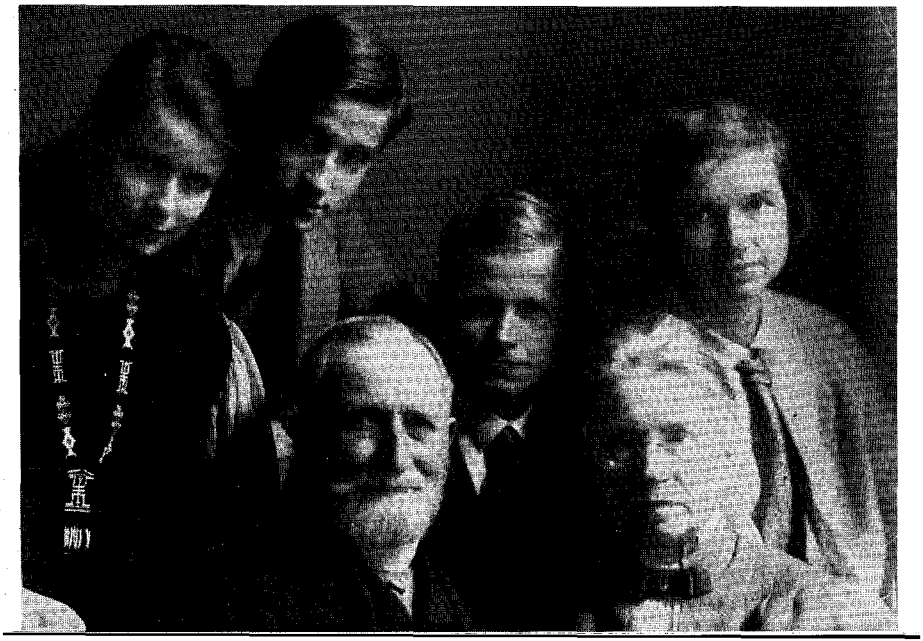
It would be hard to write a less adequate description of the career of one of the most distinguished and humane scientists of this century, and fortunately the Oral History program of the Caltech Archives has made it possible to flesh out such a bare bones account. Six interviews conducted by Carolyn Kopp cover such topics as Delbrück's family and early education, his university education and postgraduate work, his early career in Germany, his phage work and the phage group, observations on Caltech and on physicists and biology, and his postwar visits to Germany – all sprinkled with fascinating anecdotes. In fact, having to omit more than half of the material so that excerpts would fit in E&S *turned out to be an exercise in making hard choices. We present here the first installment (of two).*

Max Delbrück: My father, Hans Delbrück, was a professor of history at the University of Berlin and 58 years older than I, so he was practically my grandfather, and I never knew him in the part of his life when he was still struggling. His specialty was the history of the art of war and material criticism of the sources. He was also editor of a monthly called the *Preussische Jahrbücher* — that's a monthly somewhat analogous to the *Atlantic Monthly*. He singlehandedly edited that for at least 30 years and wrote a column commenting on German politics. There's a book on my father called *Hans Delbrück as a Critic of the Wilhelminian Era*, and that's what he was.

I was the youngest of seven children, four sisters and three brothers over a span of 16 years. My four sisters, Lore, Hanni, Lene, and Emmi, are all still alive. My oldest brother, Waldemar, was killed in action in the First World War; I knew very little of him because he was sent to a boarding high school, and then he was at the University, and then he was in the war and was killed; he was 14 years older than I. My other brother, Justus, was four years older and of him I saw an enormous amount; we shared a room for quite a number of years of my adolescence, and my relation to him was a very great mixture of admiration and competition and all things that siblings can have. Now looking in retrospect he was an exceptionally kind and friendly and by no means a domineering and intellectually threatening person, but my whole soul was concentrated on trying to compete not only with him but with the other siblings, and the older ones in our close friends' families, since I was the youngest in all these contexts.

My mother was, I think, 15 years younger than my father. She was 42 years older than I, and so I did not know her as a young woman. I have heard her described as on the timid and shy side. She, I think, also was the youngest of her family, and she got married when she was 19 or something and my father was 35, and

Berlin, 1927. Hans and Lina Delbrück with four of the seven Delbrück children, from left, Emmi (Bonhoeffer), Max, Justus, and Lore (Schmid).



she was expected to be and was very submissive. She also was of fragile health, which is no surprise, having had a large number of children and having gone through very difficult times during the First World War. You see, I was born eight years before the war, so my recollections essentially start with the first war and the hunger periods during that time.

CK: What about your next-door neighbors, the Harnacks?

MD: Our nearest relatives who lived next door, the Harnacks, were similar to our family. Like my father, the old man Harnack, Adolf von Harnack, was also very much in public life and also had historical interests. He was a church historian and public servant. He was director of the Prussian State Library and of all Prussian libraries, and most important, he became president of the Kaiser Wilhelm Society when it was founded in 1910. The Harnacks had numerous children that were on the average ten years older than we were, and the Harnacks and the Delbrücks assembled almost every Sunday night either at the Harnacks or at the Delbrücks. It started out very informally, and everybody talked with everybody and also played games, but gradually it led to these more serious conversations about politics and history, and the others had to pipe down.

This whole section of the suburb of Berlin was just crawling with professors with large families; Karl Bonhoeffer, professor of psychiatry, around the corner, and the Max Planck family a little ways down, and the mathematician Hermann Amandus Schwarz, and quite a few others — professors with large families intermingled with moderately successful businessmen. Some of the houses were quite palatial, but the houses that the Harnacks and the Delbrücks and Bonhoeffers built were straightforward accommodations for large families, nothing very fancy about them.

CK: Were you close to your parents?

MD: I was very close to my mother, and I had a very ambivalent relation to my father, of which I was not conscious when I was a child, but in retrospect it was just absolutely classically Freudian. Not until many, many years later did I resolve this subconscious hatred and jealousy mixed with admiration and fear and respect.

CK: Can we talk a little bit about the intellectual and cultural environment in your home? Besides history and politics, was there much interest in the arts, literature, philosophy, science?

MD: In science, there was no knowledge and no interest and no competence at all. In art I would say it was very modest and conventional. In music neither my father nor my mother was musically gifted or trained, my father not at all and my mother had very modest competence in singing and piano playing. But some of my sisters and I played a little bit of various instruments, and there was occasionally chamber music. My father had a great interest in philosophy, and his hero was Hegel for philosophy of history.

CK: Economically was your family pretty well off until the war?

MD: I think they must have been until 1914 moderately well off. My father had his salary and his income as editor, and my mother had a dowry from her father, so there was a modest degree of affluence, and apparently the life until 1914 was pretty free and very hospitable. As the war came and life became more and more of a nightmare in every respect, of course all this darkened. In a way the First World War was much worse than the second one because I think many more people were killed. I think three-quarters of the young men in the family were killed. So that was all very sad, and in addition then there came these pretty severe food and coal shortages and then the total mess in 1918. So this relatively affluent residential suburb after the war became almost a ghost town.

CK: And the Second World War? There were others lost?

MD: Ernest Harnack participated in the German Resistance during the war and was executed by the Nazis. On the Bonhoeffer side there was, of course, a much greater involvement in the Resistance, and that has been widely documented. They lost two sons and two sons-in-law in the aftermath of July 20, 1944.

My brother Justus was imprisoned by the Nazis but got out during the fall of Berlin. Then the Russians came and arrested him, and he died in a diphtheria epidemic in one of the camps. We didn't find out until two years later.

CK: Why don't we back up again to your childhood and talk a little bit about the development of your own interest in science and other areas. Did you have the sense that science was what you wanted to do?

MD: I think I did have a special interest in math, but I don't know whether that preceded my interest in astronomy or followed it. The last two or three years in high school I certainly proclaimed myself an astronomer. I had a two-inch telescope, and I read popular books on astronomy, and I had a little astronomy club with a pal who had similar interests. Also one of the

The Delbrück house in Berlin-Grunewald, built in 1906, destroyed by bombing in 1943.

Bonhoeffer sons, Karl Friedrich, knew much more about astronomy, being a real scientist. He quickly found out that I really didn't know much, and he told me a fair amount, and from that developed our friendship. He took a great liking to me, and I, of course, admired him. I was very pleased that an older friend took an interest. (Almost all through my student years I had older friends, from whom I learned a great deal. I shifted universities for quite awhile, and in each situation I think I developed a particular friendship with some older person.)

So I proclaimed myself an astronomer and then I almost became an astronomer. My interpretation of this, in retrospect (and this retrospect dates back now 40 years or something) is that I did that because I found it a convenient way to establish my identity for myself — that I knew something where nobody else knew anything. And it's true — none of the Harnacks, none of the Delbrücks, and only this very much older Bonhoeffer was a scientist. So here I had my own thing which I could claim to know.

CK: Did your parents encourage this interest in astronomy and science?

MD: My father was very tolerant of it and my mother was very helpful in it. Tolerant is maybe the right expression because I really made myself a tremendous nuisance. I had my telescope set up on a little balcony which was adjacent to my parents' bedroom, so during the night to get to this telescope I had to go through their bedroom. I remember a number of winter and summer nights where it was necessary for me to look at my telescope at 2:00 in the morning. Of course I had a sleep that could only be awakened by the *loudest* of alarm clocks, so I had this enormously loud alarm clock which awakened everybody in the house except me. And then finally I roused myself and crawled through my parents' bedroom thinking they were asleep. I'm sure my mother was worrying herself stiff that I would freeze to death out there. She made me a special, very warm dressing gown.

CK: Was science taught in school as well as mathematics?

MD: We had a very modest amount of physics and practically no chemistry. We had actually one small group who were taught a little bit of chemistry sort of as an aside by one of the teachers. I didn't learn anything from that. We had in earlier years some absolutely miserable biology courses, unbelievably bad biology courses. Just something about the classification of animals and plants, *unbelievably* bad; nobody had an appreciation of biology. Biology at that time was not considered an interesting science. I mean, the 19th century was essentially a century of systematics. Experimental embryology had begun to exist at the beginning of the century but hadn't penetrated into any high school texts by the 1920s. Biochemistry didn't exist. Nor genetics. It was all very descriptive.

CK: And Max Planck lived nearby?

MD: Yes, Planck lived down the street but none of the family knew what he had done, even that he had gotten the Nobel Prize, or not sure whether he had. It was all very vague. I mean everybody knew that Planck was secretary of the Academy of Sciences and so on, that he was somehow a great scientist, but what on earth he had done nobody knew.

CK: The first university you went to — Tübingen in 1924 — did you go there with the intention of studying astronomy?

MD: That I did. Hans Rosenberg was there; he was sort of an astrophysicist, which at that time was a science just beginning. He had a little observatory, and I think we were a total of three students of astronomy. Of course I had just come from high school; I was 17½ and had to take lots of other courses besides — mathematics and physics. I took mathematics courses quite seriously and I took the physics courses much less seriously and I took one chemistry course. I mean I didn't take it — I went to one lecture and actually I think attended one or two chemistry lab sessions, but this wasn't my cup of tea at all. And so I never learned any chemistry while I was a student. I had to learn physics and chemistry the hard way later on. I learned more about science from older students, not from any of the professors.

I was at Tübingen for one semester; then I went to Berlin, then to Bonn, then back to Berlin, and then finally to Göttingen. In Berlin I could study free of tuition because my father was a professor there.

CK: Scientifically I would think Berlin would be a very exciting place with Einstein and Planck; or by then was Planck considered somewhat out of it?

MD: Planck was out of it. Einstein never had students, and Max von Laue had students but was not an exciting teacher. He was too uptight in his personality. He was a very fine person, but he was not easy.

CK: Do you remember being interested in Einstein's theory of general relativity?

MD: Well, yes. Interested but quite incapable of mastering the technical aspects of it at that time. Gradually I got around to learning enough mathematics that goes with it to get a fair understanding.

They had good experimental physicists in Berlin but the thing was that the university was right in the center of this very big city, and it took from our house where I lived about 40 minutes to get there and 40 minutes to get back. The amenities in those days for big-city universities were very poor; they had practically no public rooms at all; you just had to go there to the lecture and then go home again.

CK: What was the state of astronomy when you were a student?

MD: Actually, in Germany astronomy was altogether pretty bad at that time. It had been *ruined* by the overambition of the generation of astronomers 50 years earlier. The first parallax of a star had been measured in 1837 by the German astronomer Bessel, and that was a tremendous triumph. The Germans had taken great pride in improving these methods more and more, not only measuring parallaxes but also the proper motions of the stars and making catalogues of the stars. Fifty years of this had ruined German astronomy, because all the young people who trained there, all they did was sit

every night for hours and hours in unheated observatories and measure transits of stars. It really had a disastrous effect on the intellectual quality of the German astronomers.

And I came in just as there were a few people who decided it was time to really apply more sophisticated physics to astronomy — Rosenberg in Tübingen, Hopmann in Bonn, and Hans Kienle in Göttingen. Göttingen, of course, was a much more exciting place than the others because the mathematics was absolutely tops. It was the place where David Hilbert was and quite a galaxy of other mathematicians; in physics it also was tops because Max Born and James Franck were there.

CK: How was the intellectual atmosphere at Göttingen different from that at the other universities that you had attended?

MD: Well, of course, it was just after the breakthrough of quantum mechanics which had happened in 1925. In 1925 Werner Heisenberg had discovered quantum mechanics, and a flood tide of publications on this subject came out, most of which were out of date by the time they were published — everybody who was "in" had seen them circulate in preprint form. There was a very considerable influx of foreigners; Paul Dirac was there, J. Robert Oppenheimer was there, Yoshikazu Sugiura from Japan, H. P. Robertson from here at Caltech, E. V. Condon — are just a few of the names that I remember. So you really had a feeling that you were close to where things are really happening, which is a feeling students do not usually have in most places.

CK: Was it Heisenberg's paper, or the impact of his ideas that stimulated you to go to Göttingen?

MD: No, I went to Göttingen still as an astronomer, because of Kienle. . . I guess I *had* heard while in Berlin, while working at the Einstein Tower observatory, I had heard about Heisenberg's paper, *rumors* that a breakthrough had happened in this quantum thing. And I think Heisenberg came to give a seminar at Berlin in the winter of 1925-26. I went to the seminar — didn't understand a word — but I remember as I walked into the building — the grimy old building, the physics institute in downtown Berlin, the lecture hall on the third floor, enormous staircases — as I walked in there, at the same time Einstein came in from one side and Walther Nernst from the other side. And I heard Nernst ask Einstein (whispering), "Do you think there's anything to this?" And Einstein said, "Ja, ja, I think it's a very good paper, very important." So they walked up there and the place was *packed*, standing room only. In the front row on the right were sitting Einstein and Planck and Nernst and von Laue. In the second row, the associate professors and on down, standing room only for the others.

In Göttingen I essentially did not pal around with the physicists in the beginning but more with mathematicians and astronomers, which changed only when my attempts to write a thesis in astronomy on novae failed. I was trying to understand the theories that were just being advanced, which was quite impossible for me, because the mathematics was beyond me and because they were in English and I didn't know any English at the time. It was far too ambitious a project and didn't lead anywhere.

As a result of trying to understand this astrophysical theory of the interior of the stars, I had had to learn a good deal of quantum mechanics, and therefore had started palling around with some of the theoretical physicists, among them Pascual Jordan and Eugene Wigner and Walter Heitler. In fact, I wrote a minute little paper on group theory in quantum mechanics, which was just filling out a proof that Wigner had somehow skipped in his paper. And then I asked Heitler whether he didn't know of a quick topic for a PhD thesis. He suggested that since he and Fritz London had just made a quantum mechanical theory of the hydrogen molecule, which explained reasonably satisfactorily the strong bonding of the two hydrogen atoms in terms of what was called an exchange integral, it might be interesting to look into the lithium molecule. So I thought that's fine, that looks like something manageable. And that turned out to be a nightmare, because this is wave mechanics and perturbation theory; it involves calculating integrals over the space of the two electrons involved — that means six-dimensional integrals with wave functions around two different centers.

Well, by hook or by crook I finally put a thesis together. I have not dared look at it again, and I understand that quite a few other papers have been written on this problem meanwhile, and maybe by now they know the answer to the problem.

CK: When you finished your doctoral dissertation do you remember how you felt, whether you felt like this was really exciting science and you wanted to pursue it?

MD: No, I didn't feel that my dissertation was exciting science. No, I didn't feel that I was doing very well. I had not felt that I had been doing well in astronomy, and I did not feel that I was doing well in physics; and I was just hoping that something would happen that I *was* doing well and was willing to carry on with.

Then I got a job at Bristol University in England. Max Born, my official professor, recommended me to teach some quantum mechanics to a professor of theoretical physics there — John E. Lennard-Jones. I must have gone to Bristol in about September of 1929 not knowing more than a dozen words of English. Bristol was an attractive place in the sense that the physics department there had just gotten a large sum of money and had expanded and had hired several young fellows, mostly from Cambridge, who were experimental physicists; they had good facilities there and were very spirited. One was C. F. Powell who rose to great fame as the discoverer of the pi meson, and several other important things in elementary particle physics, for which he got the Nobel Prize. He was my roommate and a very good friend.

CK: Then you had a postdoctoral fellowship to study with Niels Bohr and Wolfgang Pauli?

MD: Yes. Somehow by hook and by crook I got this Rockefeller fellowship to go to Copenhagen and Zurich. I guess by hook and by crook means I must have

Max Delbrück and roommate C. F. Powell (with groceries) in Bristol, 1932.

Colloquium in Copenhagen, 1936. In front row (from left), Niels Bohr, Paul Dirac, Werner Heisenberg, Paul Ehrenfest, Max Delbrück, and Lise Meitner.

been recommended by Max Born and by Karl Friedrich Bonhoeffer. So in the early spring of 1931 I arrived in Copenhagen and was immediately taken in hand by George Gamow. In fact I roomed with him for awhile. I came to Copenhagen without much of an idea of what I was going to work on, and I fell in with Gamow and did a little work on nuclear physics.

So I spent the summer there, and in the fall I moved on to Zurich and there I shared an office with Rudolf Peierls, Pauli's assistant. From Pauli I went back to Bristol for half a year.

CK: How did you come in contact with Bohr's ideas about complementarity?

MD: During the time I was in Copenhagen and during all those years, Bohr incessantly worked and reworked his ideas on the deeper meaning of quantum mechanics. Quantum mechanics had been discovered as a technique in 1925 by Heisenberg, matrix mechanics, and in 1926 the other technical form of quantum mechanics had been discovered by Erwin Schrödinger — wave mechanics; the interconvertibility of these two forms of quantum mechanics had been shown very quickly.

In 1927 Heisenberg had formulated the uncertainty principle as the real root of meaning of the quantum of action, and Bohr in a lecture at Como had given his version of what the deeper meaning was, and had formulated what was called the "complementarity argument." The essence of this argument was that for any situation in atomic physics, it is impossible to describe all aspects of reality in one consistent space-time-causal picture. The various experimental approaches that you use will reveal one or another aspect as reality, but these various experimental approaches are *mutually exclusive*; that means they are such that you cannot get the information that you get out of one arrangement, and simultaneously use the other arrangement to get other information. So these various experimental arrangements stand in a mutually exclusive relationship. The nature of the formalism of quantum mechanics is to permit you to derive the predictions for the outcome of the experiment of one kind from the results of experiments made with the mutually exclusive arrangement (if they are done successively); these predictions are of a statistical, probabilistic nature.

This feature of atomic physics, expressed in the way Bohr expressed it, or in the more popular way that Heisenberg expressed it as an uncertainty relation, was, of course, a total shock to everybody concerned; in fact, so much a shock that Einstein never got over it. During the rest of his life Einstein tried somehow to get back to the classical picture where reality is just one reality, and if you can't get at the full reality with present methods, then presumably there must be other methods to get at reality; whereas Bohr was insistent on saying that this limitation to the classical picture of reality was not a preliminary stage to be replaced by a return to classical notions, but was an advance over classical notions — that we now had arrived at a new dialectical method to cope with the feature of reality that was totally unexpected. That was the formulation of Heisenberg in 1927, and Bohr in maybe the same year, maybe the next year. But Bohr continued to elaborate and restate his position year in and year out until he died 30 years later — *innumerable* lectures.

CK: Were you interested in the idea of complementarity when he first . . .

MD: Enormously. I was interested — well, anybody who was *at all* interested in quantum mechanics couldn't help but be fascinated. It also motivated me to look at the writings of Kant on causality to see how Kant, who was so clever and thoughtful, could have overlooked this possibility. So for the first time, and with a real motivation, I looked at Kant, and it was very clear that this situation was just utterly removed from anything that Kant had thought of — so there was no doubt that the physicists had been *pushed* into an epistemological situation that nobody had dreamed of before.

Bohr then very vigorously asked the question whether this new dialectic wouldn't be important also in other aspects of science. He talked about that a lot, especially in relation to biology, in discussing the relation between life on the one hand, and physics and chemistry on the other — whether there wasn't an experimental mutual exclusion, so that you could look at a living organism either as a living organism or as a jumble of molecules; you could do either, you could make observations that tell you where the molecules are, *or* you could make observations that tell you how the animal behaves, but there might well exist a mutually exclusive feature, analogous to the one found in atomic physics.

He talked about that in biology and in psychology, in moral philosophy, in anthropology, in political science, and so on, in various degrees of vagueness, which I found both fascinating and very disturbing, because it was always so vague. It was vague largely because the basic situation wasn't clear enough, and also in many respects Bohr wasn't sufficiently familiar with the status of the science. So it was intriguing and annoying at the same time. It was sufficiently intriguing for me, though, to decide to look more deeply specifically into the relation of atomic physics and biology — and that means learn some biology. So when the question

Max Delbrück

came up of what job I would take after this year in Copenhagen with Bohr and in Zurich with Pauli (and another half year in Bristol), and I had the choice of either going to Berlin to become an assistant of Lise Meitner at the Kaiser Wilhelm Institute for Chemistry, or to Zurich to be an assistant of Pauli, I chose to go to Berlin because of the vicinity of the K. W. Institutes for Biology.

I came to Berlin in the fall of 1932, but during that summer I went back for a short visit to Copenhagen, where I heard that Bohr was giving a big lecture, opening a world congress of light-therapy physicians in the Riksdag, the parliament building. So I went there, and after five other people had greeted the solemn assembly of several hundred of these characters (with the prime minister sitting in the front row and the Crown Prince of Denmark, all in morning coat), Bohr finally was called upon to give the opening lecture. He got up, promptly lost his way behind the rostrum, and finally found the lectern. In his usual way he whispered away, almost inaudible; so it was impossible to decide whether he was speaking English or Danish, and fiddling, fidgeting away. After he had talked awhile, while fidgeting around he must have actuated a mechanism which caused a hydraulic mechanism to lift the lectern, and he gradually disappeared behind the lectern, very slowly — it was really like a Charlie Chaplin movie. It was slow enough and long enough for the Crown Prince to notice it, and poke the prime minister in the ribs, and everybody was watching with utter fascination whether this would stop or not, and finally Bohr took it and pressed it down and continued. From then on, of course, everybody riveted their attention on him to see whether this was going to happen again. This was the great lecture entitled "Light and Life," which was published quite a bit later. In it he went out on a limb to predict such a complementarity; for once he was spelling things out so explicitly that later on it could be said that his prediction was wrong. It was a very good thing that he did, because it certainly challenged me to take it seriously, and constituted my motivation to turn to biology. □

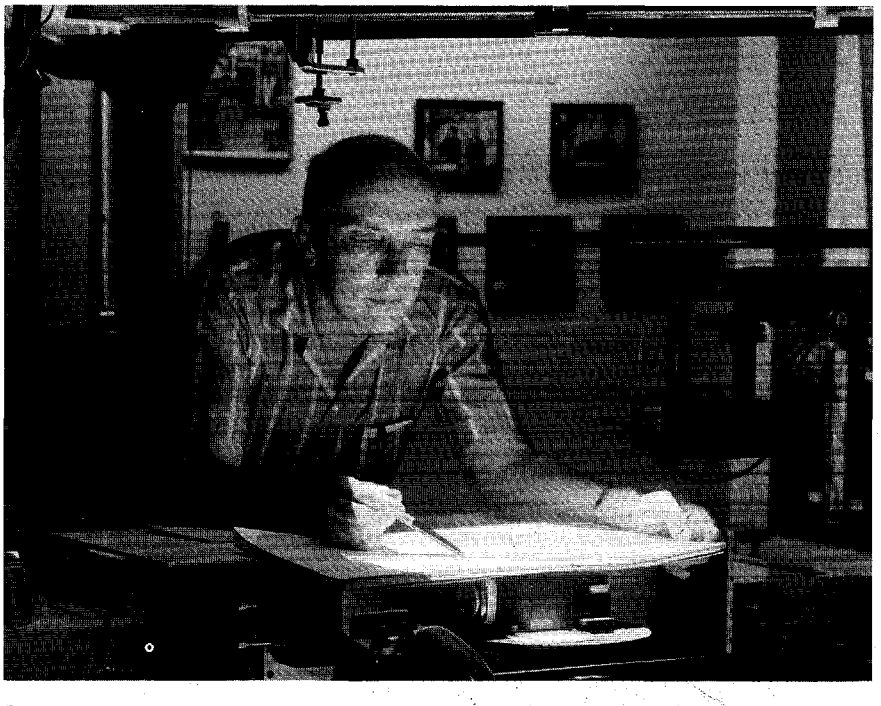
Research in Progress

An Eleven-Year Twitch

Sunspots were first observed by Galileo, and their 11-year cycle was noted in the mid-19th century, but the reason for this repeating period of solar activity has remained one of the sun's biggest mysteries. Recent evidence uncovered by Robert Howard and Barry J. LaBonte links this cyclic activity to solar-mass movements, offering a solution to the mystery. Howard is a staff member and LaBonte a research fellow of the Hale Observatories, which are operated jointly by Caltech and the Carnegie Institution of Washington.

What *is* known about sunspots is that they contain highly magnetized material and are associated with violent storms, the largest of which appear as solar flares. At the beginning of the cycle, sunspots appear at the intermediate latitudes (about 35°) in both hemispheres and increase in frequency and size as they drift toward the equator over an 11-year period. As this activity then vanishes at the equator, small new sunspots show up closer to the poles as the start of the next cycle. The polarity of the magnetic field of this new group of sunspots is opposite to that of the previous ones, creating a cycle of 22 years.

–continued on page 28



Robert Howard checks a solar image at Mount Wilson's 150-foot Tower Telescope.

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WE'RE SEARCHING FOR SOMETHING MORE

. . . continued from page 26

Howard and LaBonte analyzed velocities (measured from the wavelength shifts of an absorption line of iron) representing horizontal east-west motions of solar material in 12 years of data from the magnetograph of Mount Wilson's 150-foot Tower Telescope. A series of calculations from these data, including subtracting other motions, and a sensitive method of constructing maps of the east-west flows led to a contour plot of the velocity differentials. An obvious organized pattern could be seen — a traveling torsional wave with alternating horizontal zones of slow and fast rotation originating at the poles and drifting over 22 years toward the equator, where they disappear.

Four zones (two fast and two slow) start from each pole in that interval. LaBonte and Howard theorize that, as the torsional wave reaches the intermediate latitudes, the differential velocity of the fast and slow zones increasingly "stretches" the subsurface magnetic fields, causing them to erupt to the surface as sunspots. The sunspot regions form in a latitudinal strip centered on the poleward shear boundary of the fast zone.

When solar activity is at a minimum (when sunspots have disappeared at the equator and are just beginning to appear closer to the poles), a new fast zone originates at each pole. About 11 years later this zone reaches sunspot latitudes, and sunspots begin to form along its poleward boundary with the slower zone. After another 11 years it merges at the equator with the corresponding zone from the other hemisphere and disappears. So two full cycles of the torsional oscillation are always present in each hemisphere.

This is the first evidence that the sunspot cycle is not a random process, but a large-scale, deep-seated phenomenon arising from a fundamental property of the sun — the subsurface wave oscillation. The two astronomers conclude that the solar magnetic cycle is not generated by the drift of fields across the surface; it is driven from underneath by the torsional oscillations. Investigations into the phenomenon will continue, but this evidence provides an important clue to a mystery that has endured for nearly 400 years.

A Second Left-Handed DNA Helix:

One Good Turn Deserves Another

Since it was first proposed by Watson and Crick in 1953, the right-handed DNA double helix has been almost an article of faith among molecular biologists. That faith was put to the test last fall when Wang, Rich, and coworkers at MIT discovered that the double-helical DNA hexamer d(CpGpCpGpCpG), a six-base-pair sequence of alternating cytosine and guanine or CGCGCG, is in fact a *left-handed* helix, and has a zigzag backbone such that the repeating unit of the helix is two base pairs rather than a single step. (A. H.-J. Wang, G. J. Quigley, F. J. Kolpak, J. L. Crawford, J. H. van Boom, G. van der Marel, and A. Rich (1979). *Nature* 282:680-686.)

Caltech graduate student Horace Drew and Professor of Chemistry Richard Dickerson have found a similar but not identical left-handed helix in crystals of the DNA tetramer d(CpGpCpG), a four-base-pair sequence or CGCG, prepared under high-salt conditions. They have found a possible mechanism for the transition between low-salt (MIT) and high-salt (Caltech) helices involving the binding of ions in the groove of the helix. If valid, this represents the first detailed single-crystal study of a conformation change in DNA induced by the binding of small ions or molecules.

The MIT group has christened its structure the Z helix after its zigzag backbone. The Caltech helix also has a zigzag backbone — the differences are more subtle than that — but it has been named the A_L helix to differentiate it from the low-salt version and to call attention to its formal resemblance to the right-handed A helix. The A_L double helix, formed by making Watson-Crick base pairs between two strands of CGCG running in opposite directions, is shown in Figures 1 and 2. The zigzag backbone that is common to both Z and A_L helices arises because of an alternating geometry of the bonds between bases and deoxyribose sugar rings: *syn* (rings turned toward the Watson-Crick base pairing) at guanines and *anti* (rings turned away from the base pairing) at cytosines. This feature alone probably limits left-handed helices of this type to alternating sequences of purines (adenine and guanine) and pyrimidines (thymidine and cytosine), since the *syn* conformation, although tight but acceptable for purines, leads to energetically unfavorable close contacts between atoms in pyrimidines.

The difference between the A_L and Z helices lies in the geometry of the backbone chain and the puckering of the deoxyribose sugar rings. Classical right-handed A helices have C3′-*endo* sugar puckering, meaning that carbon atoms (numbered from the atom connecting to the base) C1′, C2′, C4′, and the oxygen (O) of the sugar ring are essentially planar, and atom C3′ projects out of the ring on the same side of the plane as the attachment of atom C5′ to C4′ (Figure 3). The classical B helix has C2′-*endo* puckering, meaning that only the C2′ atom is out of the ring plane in the same direction. The low-salt hexamer structure from MIT has an alternation of C2′-*endo* at cytosines and C3′-*endo* at guanines. In the high-salt tetramer, the sugar puckering at cytosines is C2′-*endo*, but that at guanines is C1′-*exo* (that is, projecting on the opposite side from the C5′-C4′ bond) instead. Figure 3 shows that this is only a slight deformation of C2′-*endo*, so to a first rough approximation the A_L helix has uniform sugar puckering along the chain rather than alternating conformation. An ideal left-handed A helix would be expected to have C2′-*endo* puckering at every position, which is why the Caltech helix has been called the A_L helix.

Not only can a CG polymer of DNA adopt two different helical conformations;

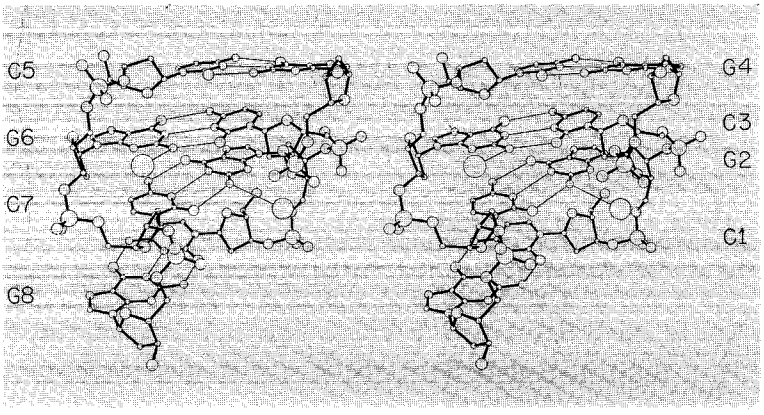


Figure 1. Stereo drawing of the double-helical CGCG molecule, looking into the groove of the helix. One of the two tetramer molecules has its cytosine (C) and guanine (G) bases numbered 1-4 to the right of the right-eye image, and the other has its bases numbered 5-8 to the left of the left-eye image. This view corresponds to a view into the narrow groove of right-handed helical DNA. Spheres in order of decreasing size represent Cl^-, P, O, N and C atoms.

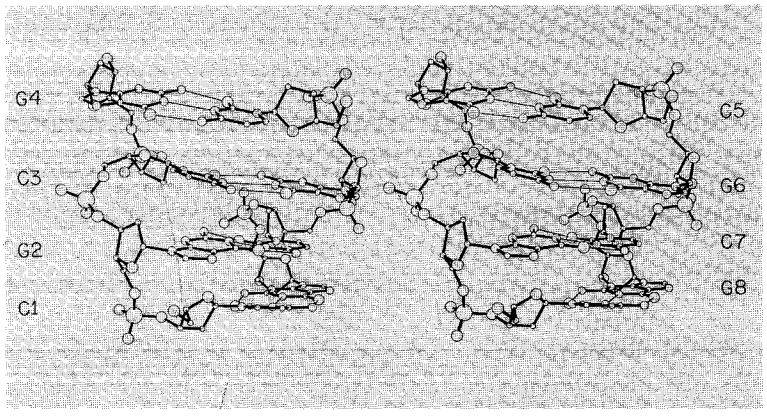


Figure 2. Stereo drawing of CGCG viewed from the outside of the helix, in what formally corresponds to the wide groove of a right-handed helix. Each guanine has the oxygen atom of a neighboring deoxyribose pointed toward its six-membered ring, and the base pairs are puckered in a manner suggesting steric repulsion between sugar oxygen and the guanine ring.

it can go from one to the other in the crystalline state. Drew established in 1978 that two different crystal forms of CGCG were obtained by crystallizing it from low- and high-salt conditions (H. R. Drew, R. E. Dickerson, and K. Itakura (1978). *Journal of Molecular Biology* 125:535-543), and that crystals could be induced to change from one form (and one x-ray diffraction pattern) to the other by changing the surrounding crystal medium, without leading to destruction of the crystals. The low-salt form of CGCG has not yet been solved here, but it appears likely that it will turn out to be a Z helix like the MIT hexamer.

The difference between the two structures can be accounted for in terms of binding of chloride ions. Drew found several Cl^- ions in his crystal structure, two especially significant ones being 3.4 Å away from the N2 amino groups on guanine rings G2 and G6. (These are the largest two circles in Figure 1.) The phosphate groups linking G2 and C3 on one chain, and G6 and C7 on the other, are turned out, away from the chloride ions as if they were being repelled by their mutual negative charges. (Figure 4, right.) The C3′-C4′ torsion angle is 122° and the sugar has C1′-*exo* puckering. In the MIT low-salt hexamer, these phosphate groups are rotated inward and connected to the guanine amino groups by hydrogen-bonding water molecules. (Figure 4, left.) The torsion angle decreases to 82°, and the sugar conformation becomes C3′-*endo*. Drew and Dickerson propose that the origin of the salt-induced structure change in CG tetramers and hexamers lies in the displacement of bridging waters by anions under high-salt conditions, resulting in repulsion of the phosphate backbone.

Left-handed DNA helices are not new: They have been proposed in the past by

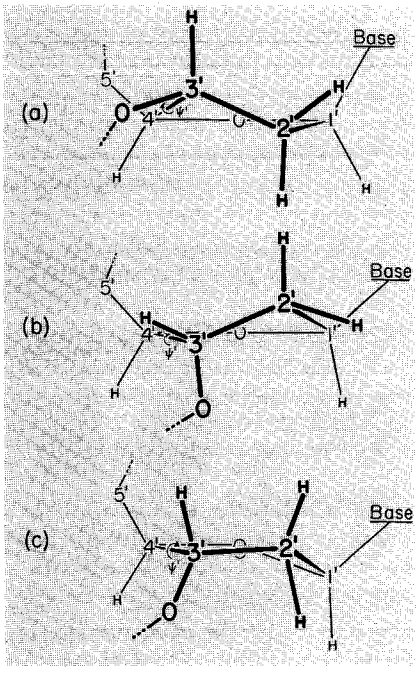


Figure 3. Deoxyribose sugar puckering and torsion angle ψ'. (a) C3′-*endo*, with $\psi' = 82°$. (b) C2′-*endo*, with $\psi' = 144°$. (c) C1′-*exo*, with $\psi' = 120°$. Conformations (b) and (c) are closely related, and less like (a).

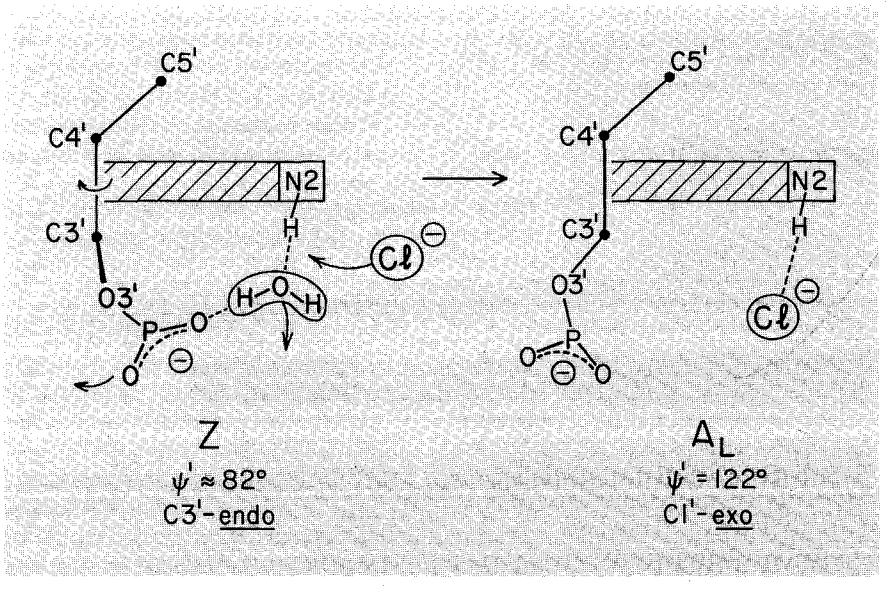


Figure 4. Proposed mechanism for salt-induced conformation change in a left-handed poly (CG) helix. C3′ and C4′ are atoms in the sugar ring and C5′ and O3′ are continuations of the helix backbone. The shaded slab represents an edge view of a guanine double ring with a $-NH_2$ amino group at position 2 on the rings (N2). In the Z helix this group and a backbone phosphate are bridged by a water molecule, but in the A_L helix a chloride ion bound to the amino group at N2 repels the phosphate and changes the helix backbone geometry.

people who worried about the topological difficulty of unwinding a long helix for duplication and readout. (This turned out to be a red herring.) But no one thought of incorporating an alternating *syn/anti* geometry into a zigzag backbone with two base steps per helix repeat, and the structures that were proposed looked like right-handed Watson-Crick structures which some atomic-level weight lifter had wrenched bodily in the wrong direction. As so often happens, Nature turns out to be much more imaginative than its chroniclers are.

What relevance do these left-handed helices have to DNA *in vivo?* The answer is not clear. It is easy to explain why these two zigzag helices can only form with alternating pyrimidine/purine copolymers such as CGCG; it is less easy to see why even such alternating copolymers should prefer the left-handed helix over a conventional right-handed one. It has been suggested that something similar to a zigzag left-handed helix occurs in chromosomal DNA in short regions of alternating CG sequence, as a means of relaxing total helix coiling. Several carcinogens and other alkylating agents are known to alkylate (attach methyl or other alkyl groups to the ring atoms) the guanine and cytosine rings along their edges that in right-handed helices are buried in the major groove but in left-handed helices are pushed to the helix surface (nearest the viewer in Figure 2). Rich has suggested that a low but measurable susceptibility of chromosomal DNA to such modification might represent a low but finite amount of left-handed helical regions. Such drastic changes in the middle of a helix might function as markers or recognition sites for proteins.

Drew's structure is part of a longer range study in Dickerson's laboratory designed to help answer the question: To what extent is the helical structure of DNA modified by the particular base sequence, and might this be a factor in recognition of specific DNA sequences by repressors and other control proteins? Graduate student Ben Conner is working on the structure of CCGG, which is not expected to be left-handed. Drew and Visiting Professor Richard Wing from the University of California at Riverside are collecting data on a self-complementary DNA 12-base-pair sequence — CGCGAATTCGCG, which is of biological interest because it contains the recognition site for the *Eco*RI restriction enzyme, one of a family of enzymes that makes sequence-specific cuts in DNA. A left-right-left helix sense change may be possible in this molecule. Research chemist Mary Kopka is attempting to crystallize the 21-base-pair *lac* operator, which controls expression of the lactose gene, and a sequence variant, both in its double-stranded form and in single-strand hairpins. All of these sequences have been synthesized by or under the guidance of Dr. Keiichi Itakura of the City of Hope National Medical Center in Duarte. Postdoctoral fellows Peter Dembek from Poland and Shoji Tanaka have worked at Caltech to help prepare some of the sequences, under a joint Caltech/City of Hope collaborative arrangement. These structures, and others now being planned by Itakura and Dickerson, will help shed light on the sequence-structure-recognition problem with DNA.

Letters

Eppy Log

Tucson, Arizona

EDITOR:

I read with considerable interest and nostalgia Winchester Jones's fanciful tale of Professor Paul Epstein's driving habits as related to him by Professor Fritz Zwicky ("Have You Heard Winch Jones Tell This One?" *E&S,* November-December, page 22). It brought to mind an *actual* event that led me at the time to believe that Eppy was indeed protected by divine providence.

It happened sometime in 1943 or 1944, when Pacific Electric street cars ran on tracks along Colorado Blvd. and into downtown Los Angeles. Eppy invited me to attend with him a committee meeting of the American Friends of Hebrew University in L.A. I met him at his home near the campus, and when we got into his car, he told me that his wife usually does the driving but that she's busy this evening. I was a bit frightened by his erratic driving along the (then) Arroyo Seco freeway, but when we were in L.A. I became certain that I would not survive the ride. The high point came when, with unconcerned innocence, he decided to pass a Pacific Electric car by driving on the tracks to the left while another P.E. car was approaching from the opposite direction. I closed my eyes, held my breath, and prayed!

When I came home that evening, my wife tells me, I was still pale and shaking. That was my first and last ride with Eppy.

LEON BLITZER, PhD '43
Professor of Physics
University of Arizona

Cover Story

In its November-December issue, E&S *ran a cover picture and a story about the stone capitals on the colonnade that runs between Ricketts and Fleming houses on the campus. To our delight "A Capital Idea" brought us several responses and even a little fan mail, some of which we'd like to share with our readers. The first letter is from the man who executed the stone figures.*

Keaau, Hawaii

EDITOR:

I have studied the pictures carefully, and they are made from what we classed as waste molds. They were structural as well as ornamental and were cast of structural concrete. This could not be worked on after casting as the aggregate was too hard and would shatter instead of cut. The interior cast stone was given more attention. The mantel in Fleming was French Caen stone, but the other three house mantels were my cast stone. I also did some 23 flights of stairs.

As an incident of record, when Gordon Kaufmann (the architect) was doing the Santa Anita Race Track buildings, I hit him up to be sure and put some cast stone on the job for me. His answer was: "My God, Hood, I just can't do it because I have to take $40,000 of my fee out in Santa Anita stock!" His stock paid 100 percent the first year, and he designed a fountain for me.

JOHN H. HOOD, '21

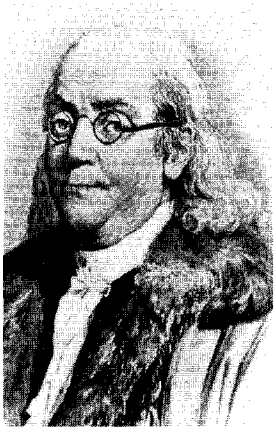
Los Angeles

EDITOR:

A brief note to express my admiration for the persistent investigation and the fine writeup on your article, "A Capital Idea." You certainly were successful in digging out comparative pictures. I feel strongly that Gordon Kaufmann or one of his aides had such people in mind when they designed the molds.

Congratulations also on taking over as editor of *E&S.* It is quite a job, and I am happy to see the magazine so successful, as I was the founder and the editor for the first years (1937-38) of the Caltech *Alumni Review,* which subsequently became *Engineering and Science.*

ALBERT W. ATWOOD JR., BS '32, MS '33



Pasadena

Your readers' choice figure looked a lot like Paul Epstein, who just happened to have his picture on page 23.

ROBERT E. SHERIDAN

Anderson, Missouri

My choice for the readers' choice figure in the ornamental capitals story on page 14: Benjamin Franklin.

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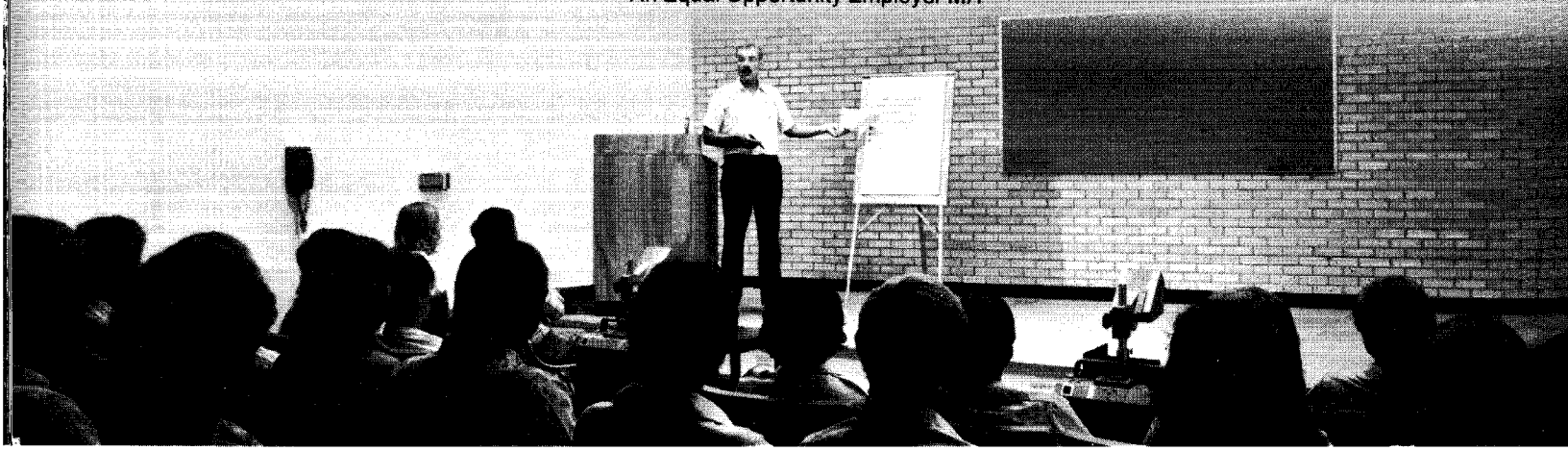

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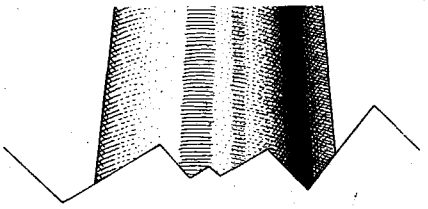
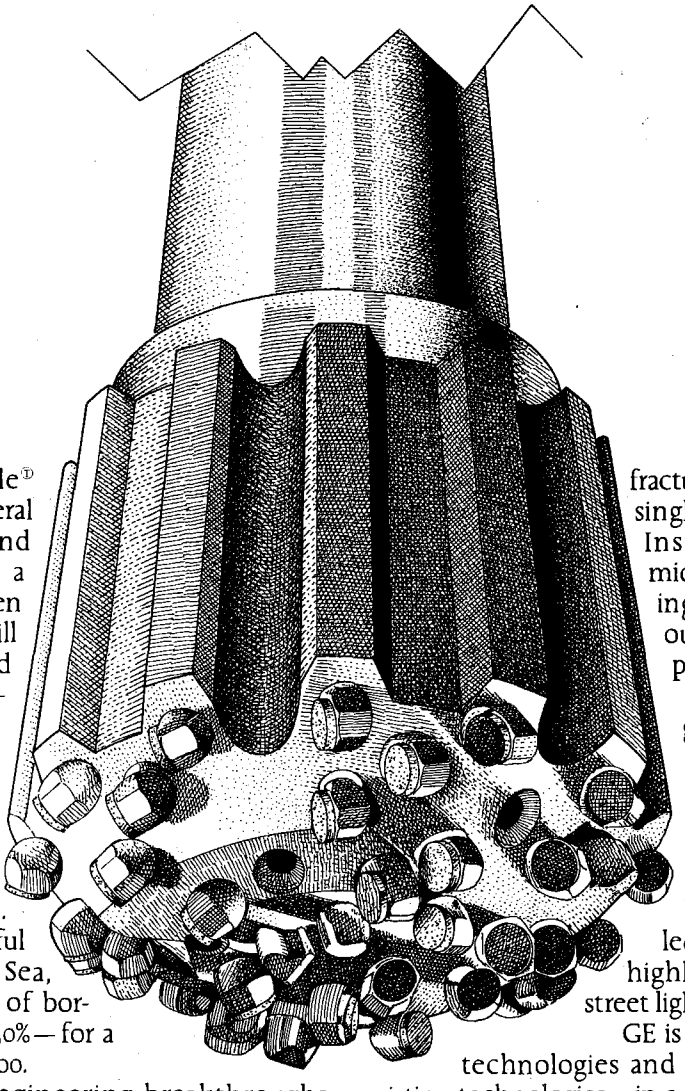


With this drill bit, GE is putting diamonds back into the earth.



The diamond is Man-Made® diamond developed by General Electric. Man-Made diamond crystals are pressed into a polycrystalline "blank." When this blank is attached to drill bits like the one pictured here, it provides a highly efficient cutting tool to probe deep into the earth.

Drill bits which include diamond blanks can as much as double the penetration rates of steel bits in drilling for oil and gas. In one of the most successful applications in the North Sea, these drill bits cut the cost of boring through shale by nearly 30%—for a total saving of close to $300,000.

Two remarkable engineering breakthroughs were required for the development of these drill bits. First came the synthesis by GE of Man-Made diamond itself. Pioneering the technology of heating and pressurizing carbon established GE as a leader in superpressure science.

The polycrystalline diamond blank microfractures because of its structure. Natural cleavage planes of mined diamond (right) cause it to break off in larger pieces.

Then GE invented the technology which compacts the small, powdery Man-Made diamond into far larger disks (as large as 12 mm. in diameter by as much as 1 mm. thick). Since these disks are composed of many nonaligned crystals, they resist the massive destructive fracturing which occurs in large, single-crystal natural diamond. Instead, these disks tend to microfracture, constantly exposing new cutting edges without destroying the diamond product.

Creating new engineered materials is an important example of research in progress at GE. Recent developments include a proprietary epoxy catalyst that's cured by ultraviolet light. GE work in ceramics led to the Lucalox® lamp—a highly energy-efficient form of street lighting.

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