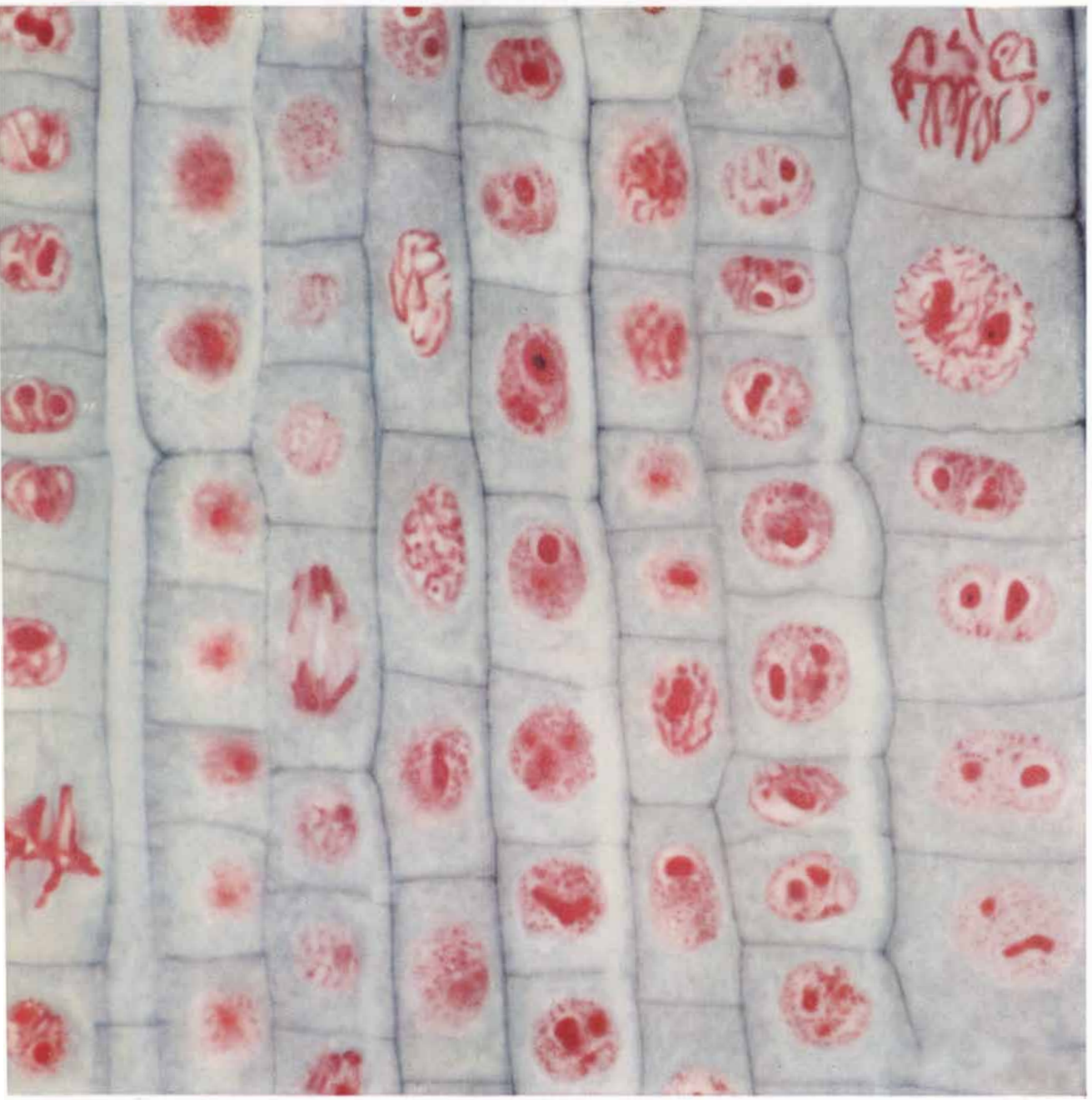
SCIENTIFIC AMERICAN



THE LIVING CELL

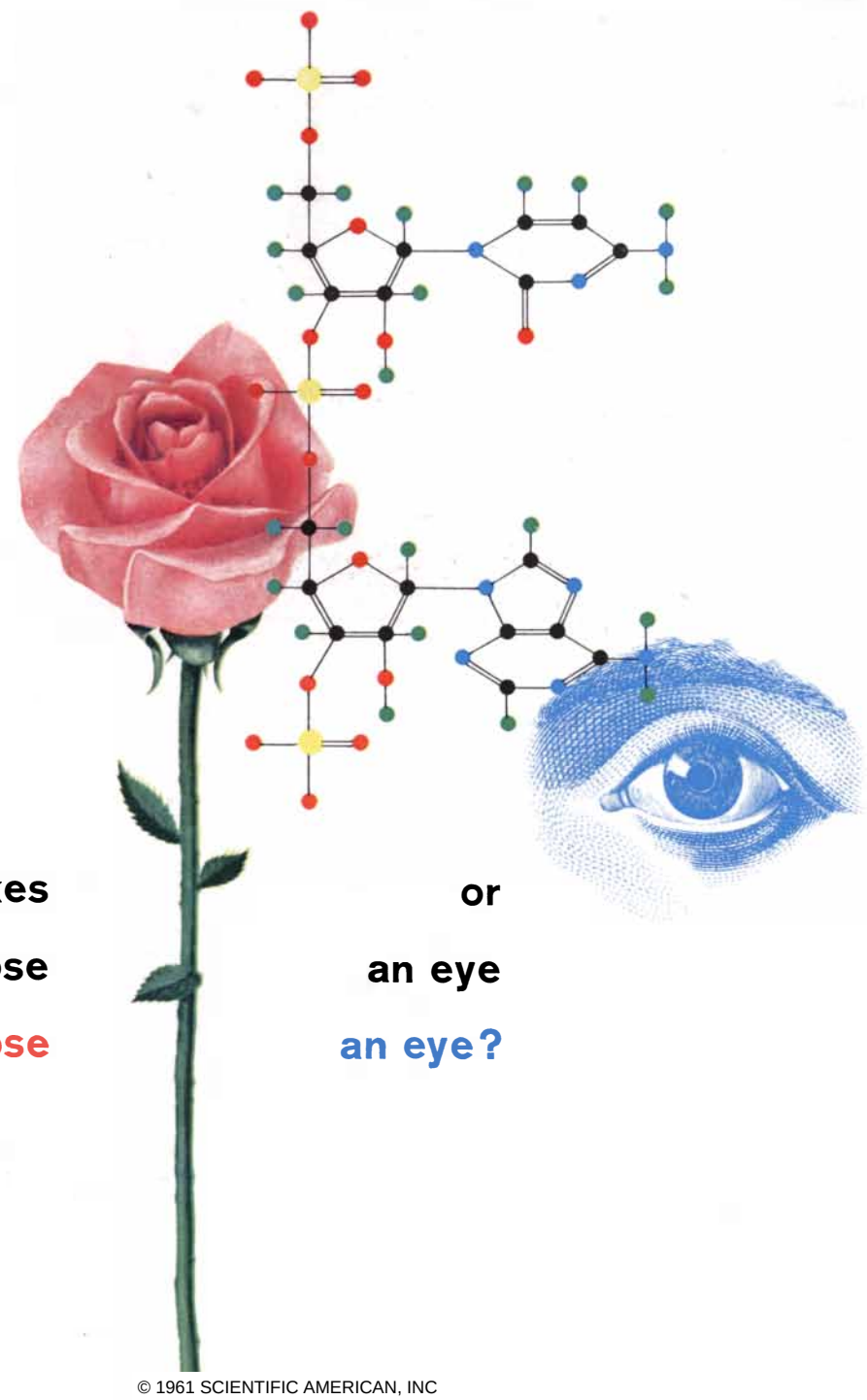
FIFTY CENTS

September 1961

IBM mathematicians have helped biochemists explore the mysterious pattern-makers that give life its myriad forms.

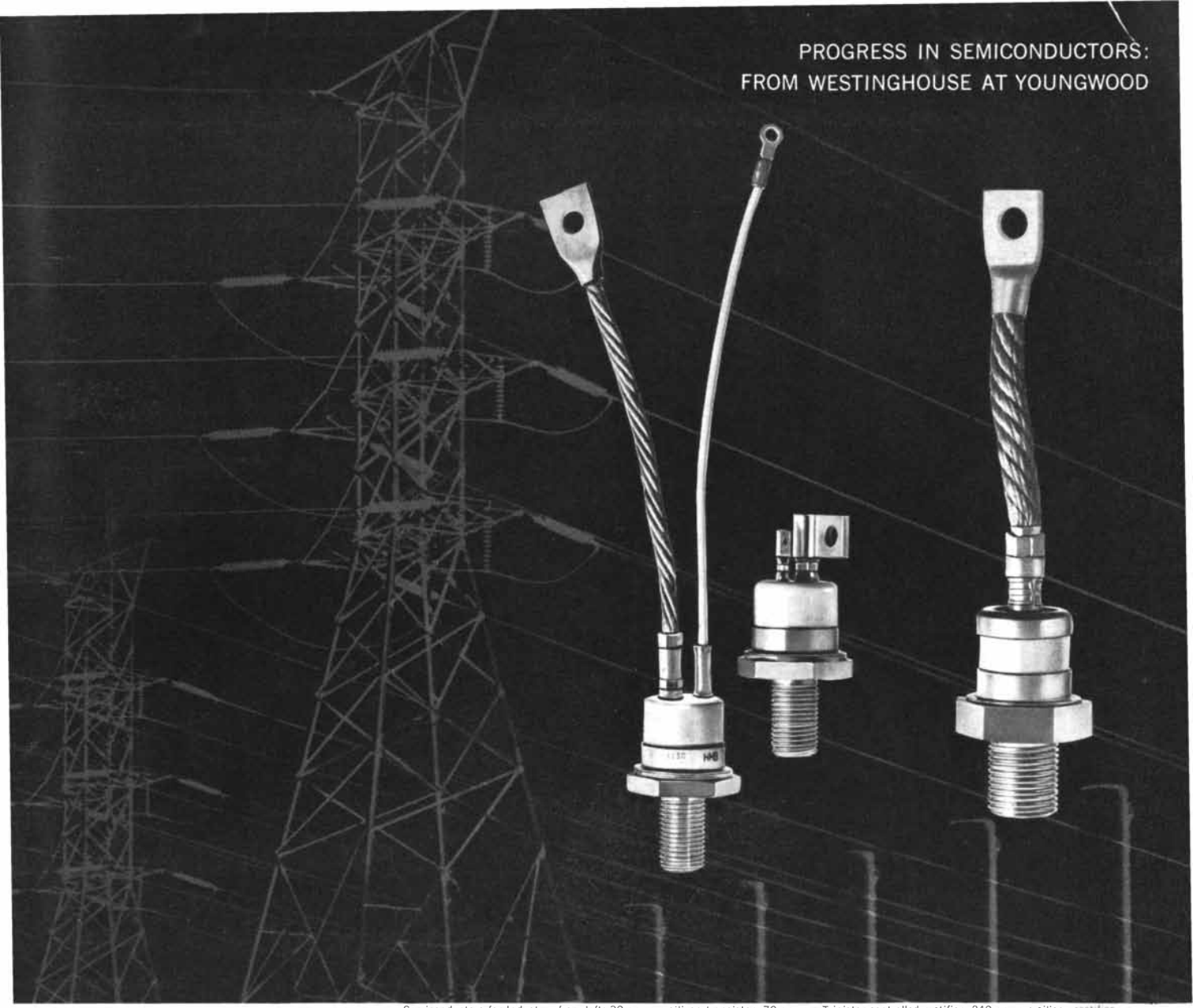
At the heart of every living cell lies a strange substance which makes the difference between an eye and a rose petal. Biochemists call it DNA. ■ To understand how living things grow when they are healthy (and what goes wrong when they are not), scientists are searching for the relationship between DNA and proteins in the cell. This means analyzing the molecular chains of thousands of different proteins, only a few of which are now known. ■ IBM mathematicians have cooperated with biochemists on the problem of protein analysis. They have applied principles of mathematical logic to masses of information developed in the laboratory. Using the computer as a tool, biochemists are hoping to piece together the identity and sequence of all the atoms in the protein chain. These methods could save years of laboratory labor and eventually help doctors diagnose diseases. ■ As scientists, engineers and businessmen reach for new advances in their fields, they often are faced with enormous data handling problems and look to computers and data processing systems for solutions.

IBM



what makes a rose a rose

or an eye an eye?



Semiconductors for Industry—from left: 30-ampere silicon transistor, 70-ampere Trinistor controlled-rectifier, 240-ampere silicon rectifier.

Westinghouse high-power semiconductors: new tools for American industry

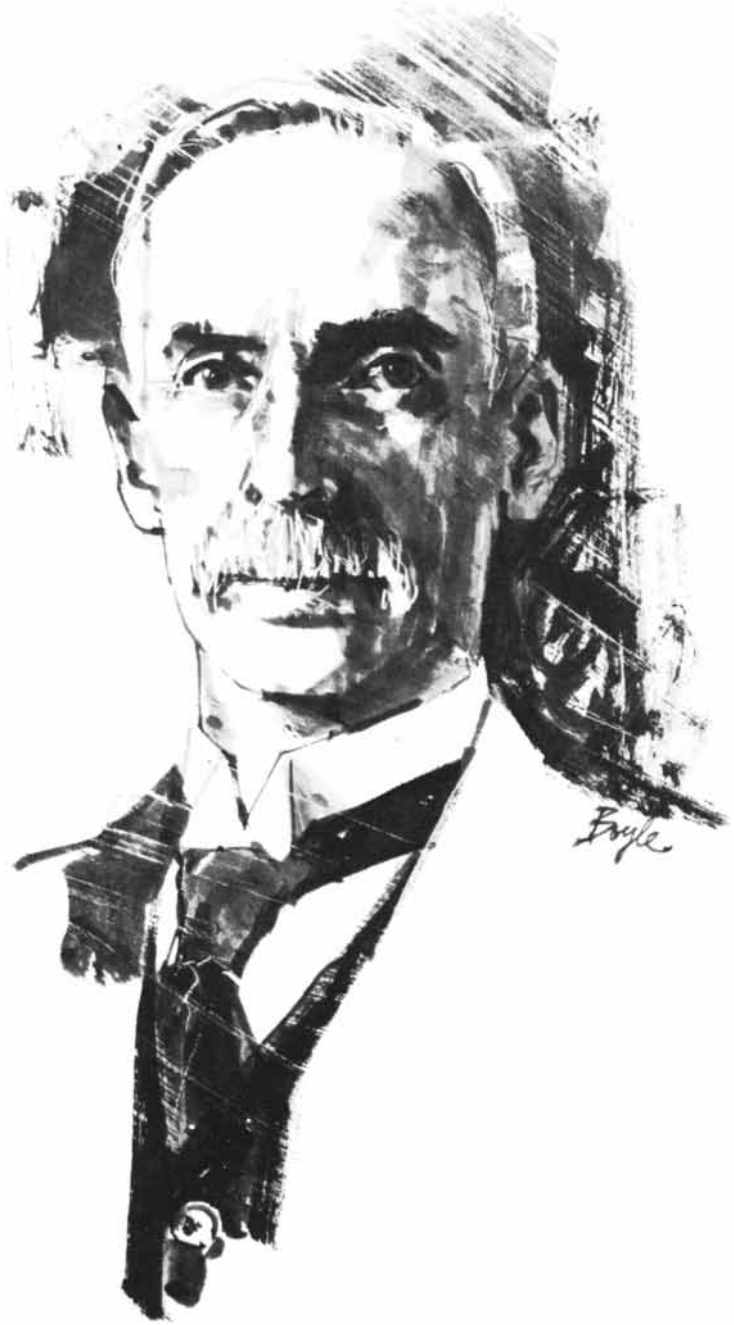
The word "semiconductors" usually brings to mind the glamorous products of our electronic age. Semiconductors mean pocket sized radios, marvelously compact hearing aids, electronic wrist watches, and many other ingenious new miniaturized products. They are the operating brains behind our complex data processing computers; they provide new standards of performance for military electronic gear; they are compact, efficient, and highly reliable devices. But all this is only part of the semiconductor story.

Westinghouse has added high power to semiconductors, a vital new dimension for industry. Westinghouse high-power silicon semiconductors—rectifiers, transistors, and Trinistor[r] controlled-rectifiers—are controlling speed, changing frequency, converting power, and performing a host of other electrical tasks for industry at multi-kilowatt power levels. They are upgrading system performance and cutting maintenance costs by replacing bulky magnetic and rotating apparatus. In all these applications Westinghouse high-power semiconductors have established a remarkable record of dependability in service.

Silicon rectifier cells to handle 240 amperes, transistors to operate at 200 volts, and Trinistor controlled-rectifiers to switch 20 kilowatt loads are available from stock. Westinghouse engineers are working on still higher power devices for industrial service. These development programs and new products result from a continuing Westinghouse awareness of long range industrial needs.

High-power silicon semiconductors can help to boost your plant production, cut costs or improve your process quality. They may even offer dramatic new product marketing possibilities for your company. For more information, contact; **Westinghouse Electric Corporation, Semiconductor Information Department, Youngwood, Penna.** SC-1050

You can be sure...if it's Westinghouse



John Atkinson Hobson...on creative thought

"The creative spirit is one and indivisible. It cannot live and work under servitude or external control. Disinterested thought cannot be drawn into the physical sciences and be kept out of politics and economic theory. If we are right in holding that the most urgent business of our age is to devise better laws of conduct in the arts of human government, within and beyond the limits of nationality, success depends upon stimulating in as many spots as possible the largest number and variety of independent thinkers, constructing and maintaining among them the best conditions of free intercourse and cooperation and finally enabling their creative thought to play freely in criticism and in reform upon the existing modes of political and economic life."

—*Free Thought in the Social Sciences*, 1926

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Established 1845 **SCIENTIFIC AMERICAN** September 1961 Volume 205 Number 3

ARTICLES

DEPARTMENTS

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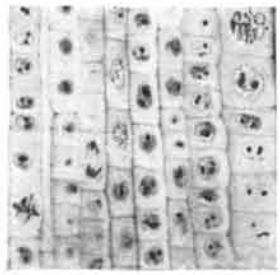

THE COVER

The photomicrograph on the cover of this issue, which is devoted to the living cell, enlarges the cells in an onion root tip 1,500 diameters. The cell nuclei and their contents are stained pink; the cell bodies, a pale green. Slide from which photomicrograph was made was prepared by J. P. Miksche of the Brookhaven National Laboratory.

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LIONEL: Instrumentation for Radiation Research

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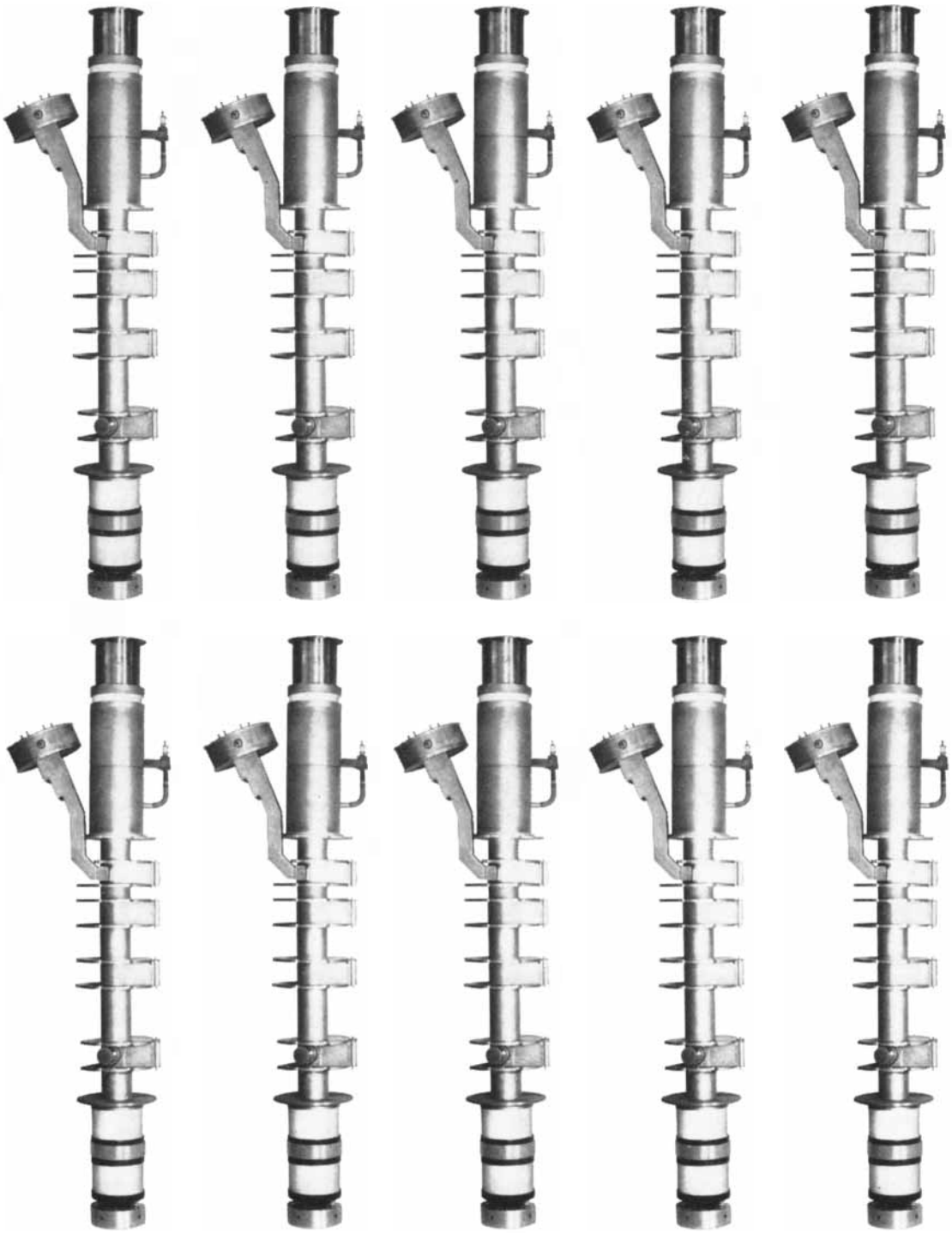
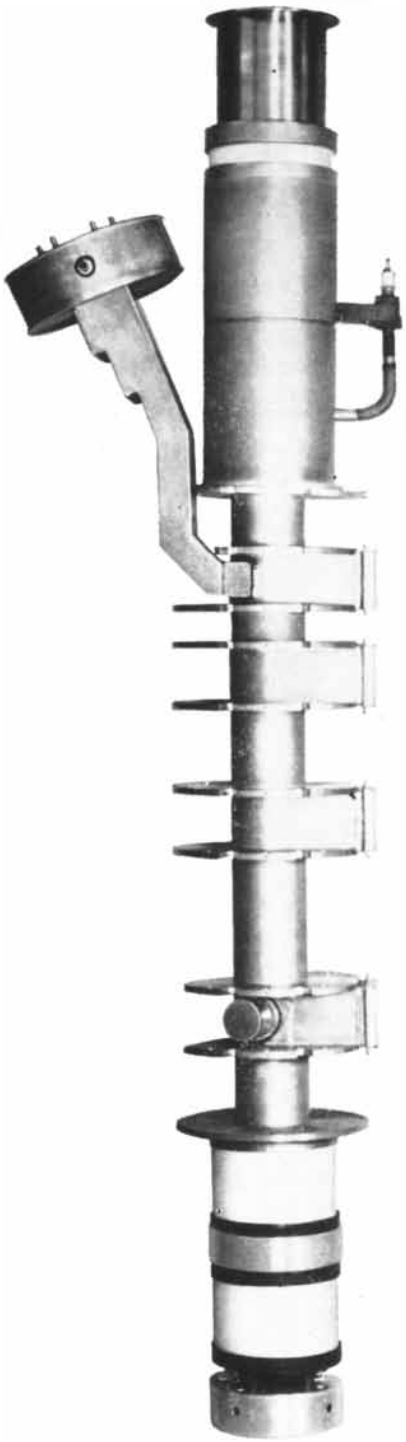


Today it would take ten super-klystrons to generate more than a megawatt of average power. But now Eimac is ready to do it



with one.

Today, the most powerful klystron available can produce 100KW of average power. But now Eimac is ready to develop a klystron with *ten times* this capability... a klystron that can generate more than one megawatt of average power!

Impossible? Not for the company that's designed, financed and built the world's largest high voltage DC power supply (325,000 volts at 10 amps steady current). Not for the company that's made more high power klystrons than any other manufacturer. Not, in short, for *Eimac*. Write for information about this super-klystron capability to: Power Klystron Marketing, Eitel-McCullough, Inc., San Carlos, California.

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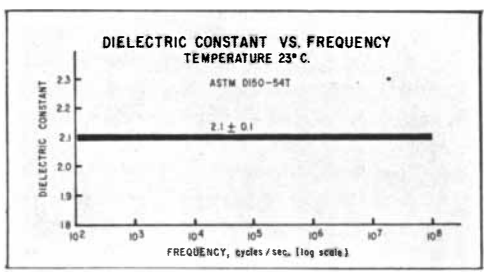
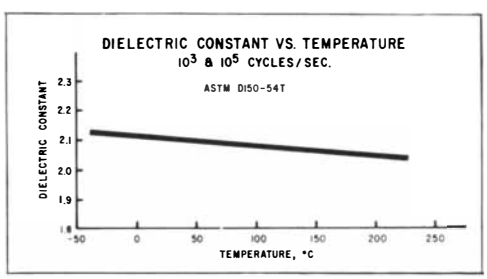
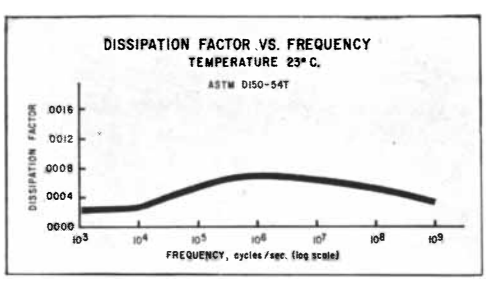
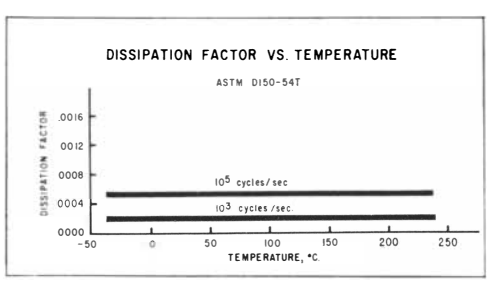
TEFLON® FEP FILM

Easy to process with outstanding electrical properties









Here's insulation news for electrical designers. "Teflon" FEP-fluorocarbon film is now available from Du Pont. Strong and stable—new FEP film is a true thermoplastic. It can be formed, laminated and heat-sealed to a wide range of substrates. There is even a cementable Type C film which is printable and pottable.

FEP film has all the outstanding electrical advantages of "Teflon" . . . even in thin gauges. The dielectric strength is as high as 4,000 volts for 1-mil film, 20,000 volts for 10-mil.* Dielectric constant stays essentially constant over a wide range of frequencies, temperatures and humidities. So does the dissipation factor. "Teflon" FEP film also has good corona resistance.

Already widely used in critical missile applications, "Teflon" FEP film opens the door to new areas of electrical product design and improvement. Investigate the unique properties of FEP film . . . now at new low prices effective July, 1961. Write: E. I. du Pont de Nemours & Co. (Inc.), Film Department, Wilmington 98, Delaware.

*ASTM D149-55T—Short Time Test
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Job Function _____

Proposed End Use _____

FINAL PRODUCTION TESTING. Zener diodes are checked by NLS M24s at final testing stations of Hughes Aircraft Company's Semiconductor Division.

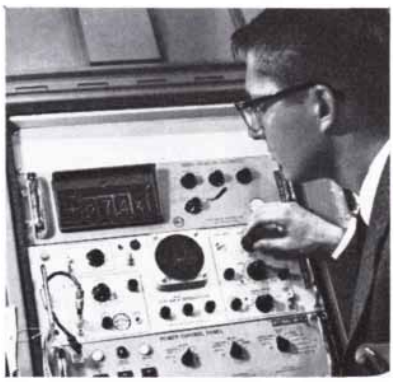
CHECKOUT OF MISSILE COMPONENTS. An M24 checks electronic components at Autonetics, a division of North American Aviation, Inc., as part of the High Reliability Program for Minuteman ICBM. The operator is shown measuring resistance. By turning a front panel knob on the M24, she can also measure DC voltage or DC voltage ratio.

MISSILE PRODUCTION TESTING. An NLS M24 Multi-Purpose Instrument performs an important part in the missile functional test system at Boeing Airplane Company's Missile Production Center in Seattle, Wash. The system automatically applies more than 400 go/no-go sequenced tests to ground-check missile flight reactions from launch to intercept. The M24 and the printout portion of the system monitor application of test stimuli and isolate malfunctions.

ELECTRO-CHEMICAL ANALYSIS. Savings of as much as $8,000 a year on one particular project are expected to result from use of an NLS 481 DVM at Diamond Alkali Company's plant in Deer Park, Texas. By accurately measuring small changes in voltage and voltage drop, it permits optimizing the efficiency of producing chlorine from sodium chloride brines by electrolysis.

ACCEPTANCE...

PETROLEUM RESEARCH AND DEVELOPMENT. This precision data logging system, incorporating an NLS V24 DVM, has served Esso Research Laboratories for more than two years in around-the-clock service. The V24 converts millivolt signals to digital form for operating a Friden Tape Punch. The system aids in making pilot plant studies of industrial processes.



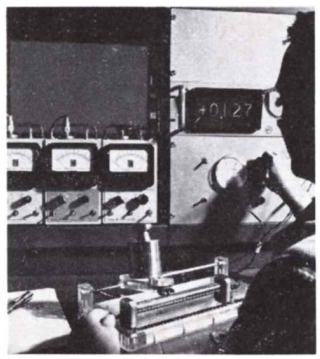
MISSILE TRACKING SYSTEMS. The Azusa Test Set, designed by General Dynamics/Astronautics, A Division of General Dynamics Corporation, includes an NLS V35 DVM. This set checks the power and transmitter portions of the airborne package of the system which is used for tracking all missiles launched from Cape Canaveral. Functions of the V35 include monitoring of 28-, 100- and 1,500-volt power supplies; calibrating telemeter transducers; and adjusting Klystron beam, bias and modulator voltages.

SPACE MEDICINE RESEARCH. In simulated space environment testing, this NLS V34 digital voltmeter is part of a system which detects and records minute changes in body weight, a key factor in determining physiological strain. The unique "No Needless Nines" logic of the V34 permits measurements at pre-selected time intervals with an accuracy of ±3 grams within a range of ±4,500 grams. AMF's Mechanics Research Division developed the overall system under direction of the Air Force's Aeronautic Systems Division at Wright-Patterson AFB in Ohio.

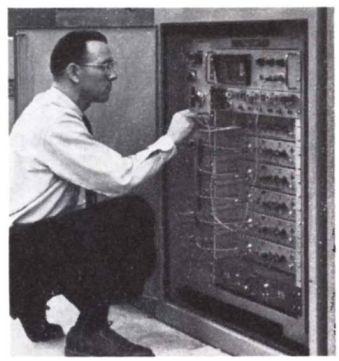
PRODUCTION TESTING. A 481—one of a battery of NLS DVMs—measures Zener diodes for separation into voltage categories at the Semiconductor Products Division of Motorola, Inc. Measuring speed for this operation was doubled by use of the NLS digital voltmeters.

MISSILE CHECKOUT. Two NLS DVMs team up on checkout of equipment for the GAM-77 Hound Dog Missile at the West Coast Laboratories of Mallory Electronics Company, A Division of P. R. Mallory & Co. Inc. The 481 (bottom) calibrates remotely settable timers for the Hound Dog and the V35 (top) is used for final checkout of these devices. "By using DVMs, we are able to eliminate human error in final inspection," said a Mallory executive.

QUALITY CONTROL OF ELECTRONIC COMPONENTS. More than 50 NLS 481 digital voltmeters are used in the Quality Assurance Program at the Semiconductor-Components Division of Texas Instruments Incorporated. The instrument pictured is measuring breakdown voltages of high-reliability germanium switching devices.



MATERIALS EVALUATION. Electronic Chemicals Division of Merck & Co., Inc., uses a 481 DVM to reduce testing time for determining resistivity of single crystal silicon.



A-TO-D CONVERSION IN INDUSTRIAL PROCESSING. A 481 DVM operates an analog-to-digital converter in a variance computer for Saran Wrap production at The Dow Chemical Company's Saran Wrap plant in Midland, Mich.

sign of superiority in digital voltmeters

If you measure or record voltage, consider the broadening applications of digital voltmeters as indicated by these examples. The NLS instruments shown here . . . and the thousands of others in action today . . . tell a story of acceptance that is three-fold:

1. The digital voltmeter—first unique instrument since the development of the oscilloscope and vacuum tube voltmeter—has become a *basic measuring and logging tool* since its origination by Non-Linear Systems, Inc., nine years ago.

2. NLS digital voltmeters have been *proved in use* by many of the most discriminating companies in the electronics and allied industries.

3. Most of these firms have *specified NLS again and again,* some owning more than fifty instruments . . . evidence of the acceptance of NLS, as well as the usefulness of the product it manufactures.

Our point: it makes sense to contact the most experienced manufacturer of digital voltmeters to meet your measuring and data logging needs. Select from the world's most complete line . . . by purpose . . . by price. NLS offers 16 basic models—all with exclusive features—from a low-cost "Industrial" type instrument to a $6,150 all-electronic DVM that makes 200 readings per second. For the most complete and authoritative information available on DVMs, contact your local NLS office or rep, or write NLS.

non-linear systems, inc. *Originator of the Digital Voltmeter*
DEL MAR, CALIFORNIA

LETTERS

Sirs:

I feel that it is necessary to comment further on the experiment by Miss Sonoko Ohwaki that you have brought to the attention of your readers ["Science and the Citizen"; SCIENTIFIC AMERICAN, April]. Ohwaki reports that the well-known geometrical illusions are either eliminated or reduced in stereoscopic presentation.

Edwin G. Boring has questioned Ohwaki's interpretation of the data and has suggested an alternative ["Letters"; SCIENTIFIC AMERICAN, June]. While I agree with Professor Boring, there is, in my view, another very much more serious criticism that invalidates Ohwaki's argument that illusions derive from processes in a single retina.

First, to get the record straight. It was not only E. Lau (*Psychologische Forschung*, Vol. 2, pages 1–2; 1922. Vol. 6, pages 121–126; 1924) who performed this type of experiment earlier, but also von St. Witasek at Graz in 1898 (*Zeitschrift für Psychologie*, Vol. 19, pages 81–174; 1899). A perusal of Witasek's paper would show the fallacy in Ohwaki's conclusion. Using the Zöllner illusion reproduced with Professor Boring's letter [*see top illustration on page 16*], in which parallel lines appear to converge, Witasek presented the parallel lines to one eye and the oblique "inducing" lines to the other and brought the

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two into retinal correspondence with a stereoscope. Instead of a steady fused image of the two sets of lines, Witasek observed considerable retinal rivalry between them. Either he saw the parallel lines or the oblique lines, but he was unable at first to see both. (Witasek asserted that he saw both sets of lines simultaneously after long practice, but no one has managed to confirm this.)

Retinal rivalry, first observed by P. L. Panum more than 100 years ago, is characteristic of that stimulus condition in which corresponding retinal points are stimulated by different or "incompatible" patterns. The phenomenon takes the form of an alternation, or rivalry, between the patterns of stimulation falling on each retina. Thus Witasek failed to get an illusion because, whereas the "test" element of the figure (parallel lines) was in view, the "inducing" element (oblique lines) was temporarily suppressed or inhibited.

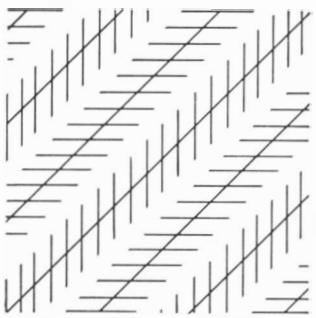
We have recently repeated Miss Ohwaki's experiment in this laboratory using an extended range of illusory patterns, and while her quantitative results have been largely confirmed, we have also observed the striking rivalry effects reported by Witasek. Among the patterns we used were the two reproduced here [*middle and bottom illustrations on page 16*]. One is a variant of a figure from E. C. Sanford (*A Course in Experimental Psychology*, 1894) and the other was used originally by William D. Orbison (*The American Journal of Psychology*, Vol. 52, pages 31–45; 1939). We presented these figures stereoscopically as well as to one eye only. In the stereoscopic presentation the lines in and around the square in both figures were either wholly or partly suppressed, and the observers reported a relatively bright square on a field of fragmented lines or circles. The square was very much more dominant than the other lines and disappeared less often. Similar suppression effects, with varying degrees of rivalry between test and inducing elements, were reported with a variety of classical illusions. For such rivalry to occur it is not essential that the two parts of the figure be superimposed as they are in the two figures shown. Less striking rivalry and suppression occur when test and inducing contours merely impinge or are slightly disparate.

We would not expect an illusion to occur when the inducing element is excluded from the pattern. This is precisely what happens in stereoscopic viewing. We do not observe the illusory effect because, as a result of an inhibitory process, the inducing element is suppressed while

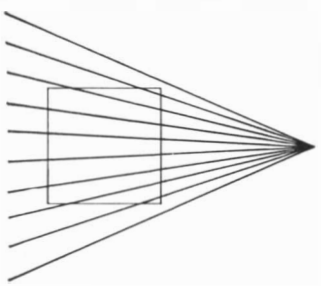
the test element is in view. Ohwaki, and Witasek before her, have shown this quite unequivocally. To argue, as Ohwaki does, that this absence or decrease in illusion is evidence of the peripheral origin of the geometrical illusions is unwarranted. This type of experiment is an excellent way to demonstrate retinal rivalry, but it does not tell us very much about the nature of illusions.

Ross H. Day

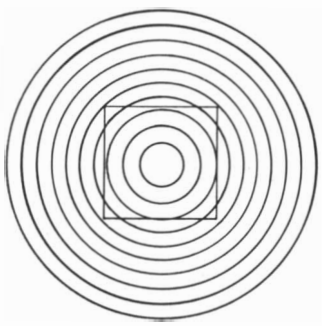
Department of Psychology
Brown University
Providence, R.I.



The Zöllner figure

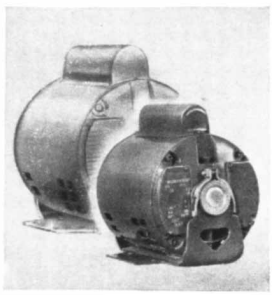


A variant of Sanford's figure



Orbison's figure

Tough, durable Mylar® cuts costs . . . improves product performance



1. Motor size and weight are reduced with no decrease in horsepower when thin, lightweight insulation of "Mylar" polyester film is used.

2. Wear-resistant book-jacket covers of "Mylar" keep books looking fresh and clean far longer . . . cut rebinding costs, increase service life.

3. Abrasion- and dirt-resistant cartons laminated with "Mylar" cut costs by lasting far longer than ordinary cartons—can even be washed.

For example, "Mylar"* polyester film gives many products extra resistance to chemicals and moisture . . . lengthens their life. Today, "Mylar", with its resistance to heat and cold, high tensile strength in thin gauges, is improving the performance of products as different as glazing film and tough, magnetic recording tape.

Can this unique plastic film and products made with it help you? For more information on "Mylar", write: Du Pont Co., Film Dept., Room #8, Wilmington 98, Del.

DU PONT
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*"Mylar" is Du Pont's registered trademark for its brand of polyester film.

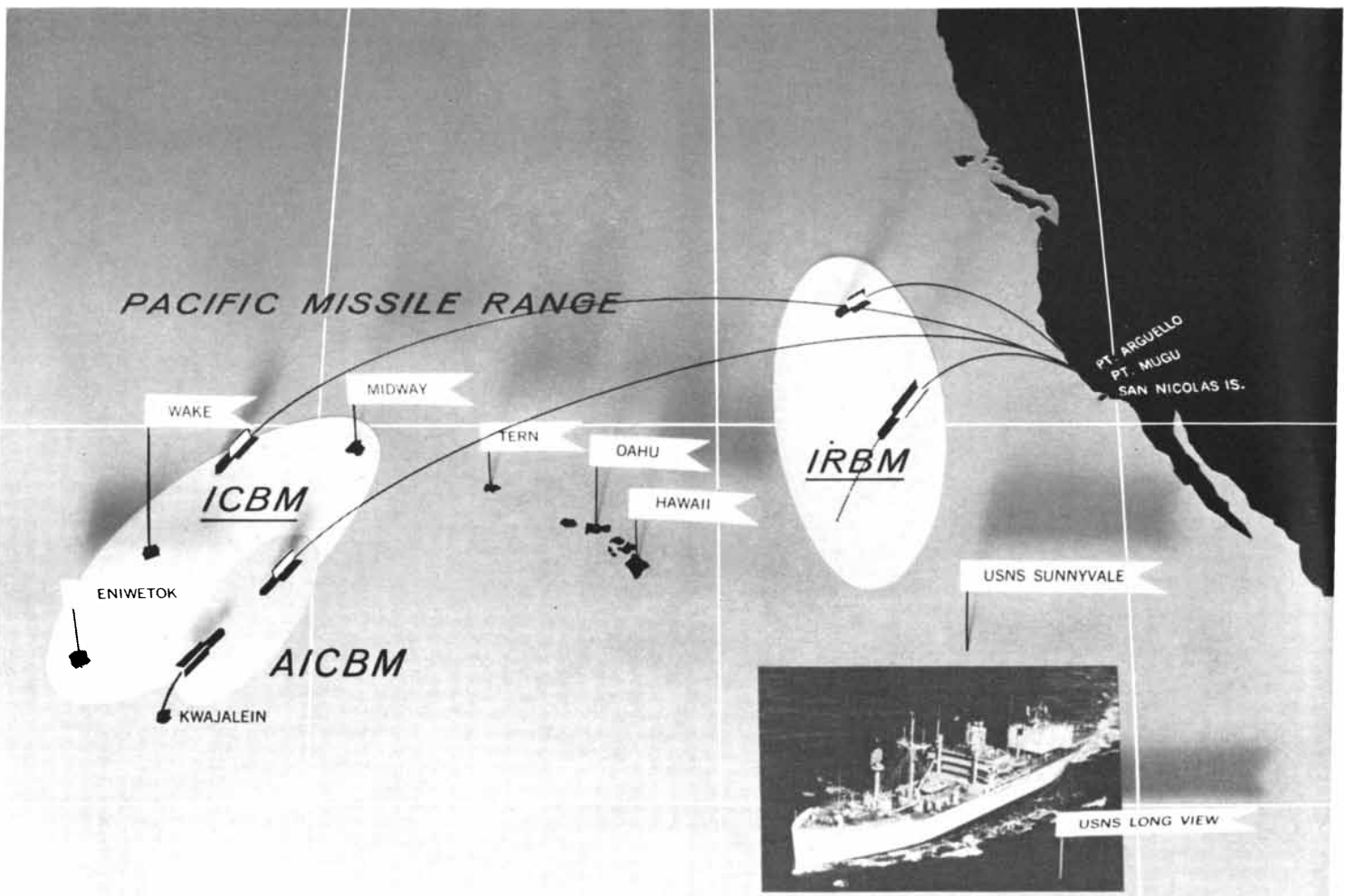
Better Things for Better Living . . . *through Chemistry*

DU PONT
MYLAR®
POLYESTER FILM

SEA SHOOT

Stretching from the California coast to the far Southwest Pacific is the U.S. Navy-managed Pacific Missile Range (PMR). This vast "shooting gallery" contains facilities for launching, tracking, and testing guided missiles—also for launching and tracking polar-orbit satellites and deep space-probe vehicles. ■ To operate and maintain the extensive line-up of PMR installations takes specialized technicians. A great many of them come from Bendix Radio Division, a down-range technical contractor for the Navy. As the map shows, Bendix and Navy personnel combine to provide the needed talents at island sites as well as aboard two satellite-recovery ships. ■ Prime Bendix operation and maintenance responsibilities are many and varied. Shipboard radar. Communications of all kinds. Combat Information Center flight controllers. ICBM impact detecting and accuracy measuring instrumentation. Telemetry equipment. Tracking equipment.

Five ranges make up the complex Pacific Missile Range. Three of them are shown here: ICBM (Intercontinental Ballistic Missile); AICBM (Anti-Intercontinental Ballistic Missile); and IRBM (Intermediate Range Ballistic Missile). Besides its island network of electronic instrumentation, PMR employs ships and aircraft. Pennants indicate installations manned by Navy-Bendix teams.



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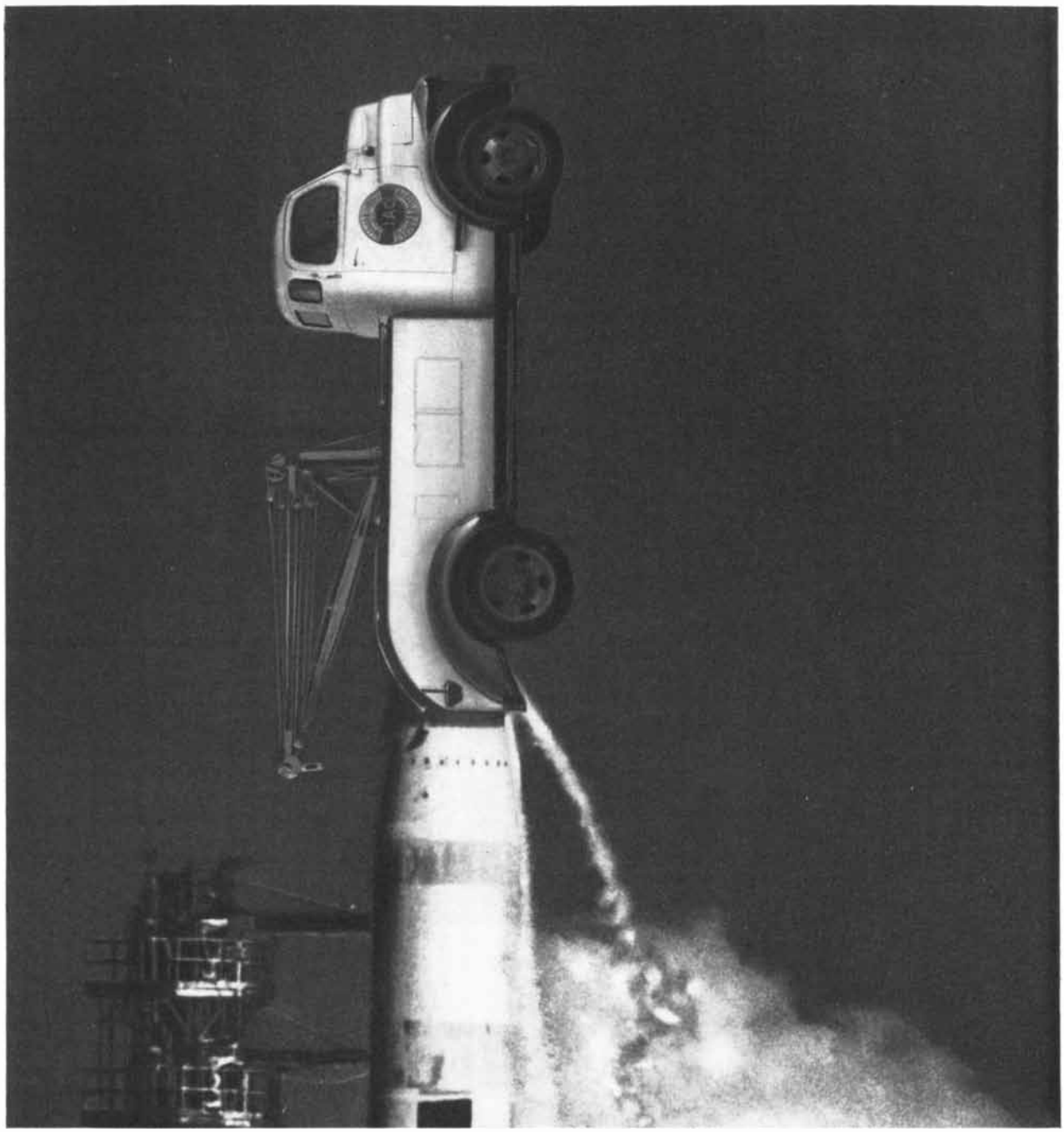

How do you service a satellite?

The instant a manned satellite goes into orbit, the question of service becomes critical. How do you handle routine or emergency maintenance and repair, for instance? What about getting replacement parts up there, supplying food and other necessities, or removing and replacing personnel?

At Northrop a special task force has been assigned to explore the complex technical problems involved and come up with practical recommendations. They are giving particular attention to such areas as the design of a general shuttle vehicle, close-in rendezvous and docking techniques, requirements for manned maintenance at all levels, and methods for transfer of men, materials and equipment under conditions of weightlessness.

Not all the problems are solved yet, even on paper. But a surprising number of practical answers have been found. That's Northrop's special strength . . . finding realistic answers to the problems of the space age, and translating them into working hardware.

NORAIR
A DIVISION OF
NORTHROP

*TYPICAL RETAIL PRICE

Must you pay the high price of miniaturization?

Electron-tube communication equipment, on the basis of a 25-30 watt output comparison, is priced as much as 32% lower than units employing solid-state devices. When this figure can amount to more than $247.00 per unit, the savings on large fleet purchases are obvious.

Where smallest size is required, solid-state devices will provide the answer. However, only in electron-tube equipment do you find such features as highest overload protection, simplified circuitry, time-proven design, and uniform operating characteristics over wide temperature ranges. Electron tubes don't require elaborate protective circuits or heat sinks, so that fewer components are required to perform a given function.

When maintenance is necessary, standardized tube characteristics assure that equipment will meet original performance specifications without costly hand selection of replacement components.

Tubes are less expensive than solid-state devices by a ratio of about 3 to 1. Off-the-air time is held to a minimum by the many convenient sources of supply and by the ease of plug-in replacement. G-E electron-tube communication units provide the lowest per-mile cost of operation and the highest performance per initial dollar of investment.

Before you buy your next electronic equipment, investigate and compare all the advantages of electron-tube circuitry.

To help you in your evaluation, send for your free copy of the 62-page comparative study, "Electronic Devices and Their Capabilities."

To: General Electric Company, Room 7118A
Receiving Tube Department, Owensboro, Kentucky

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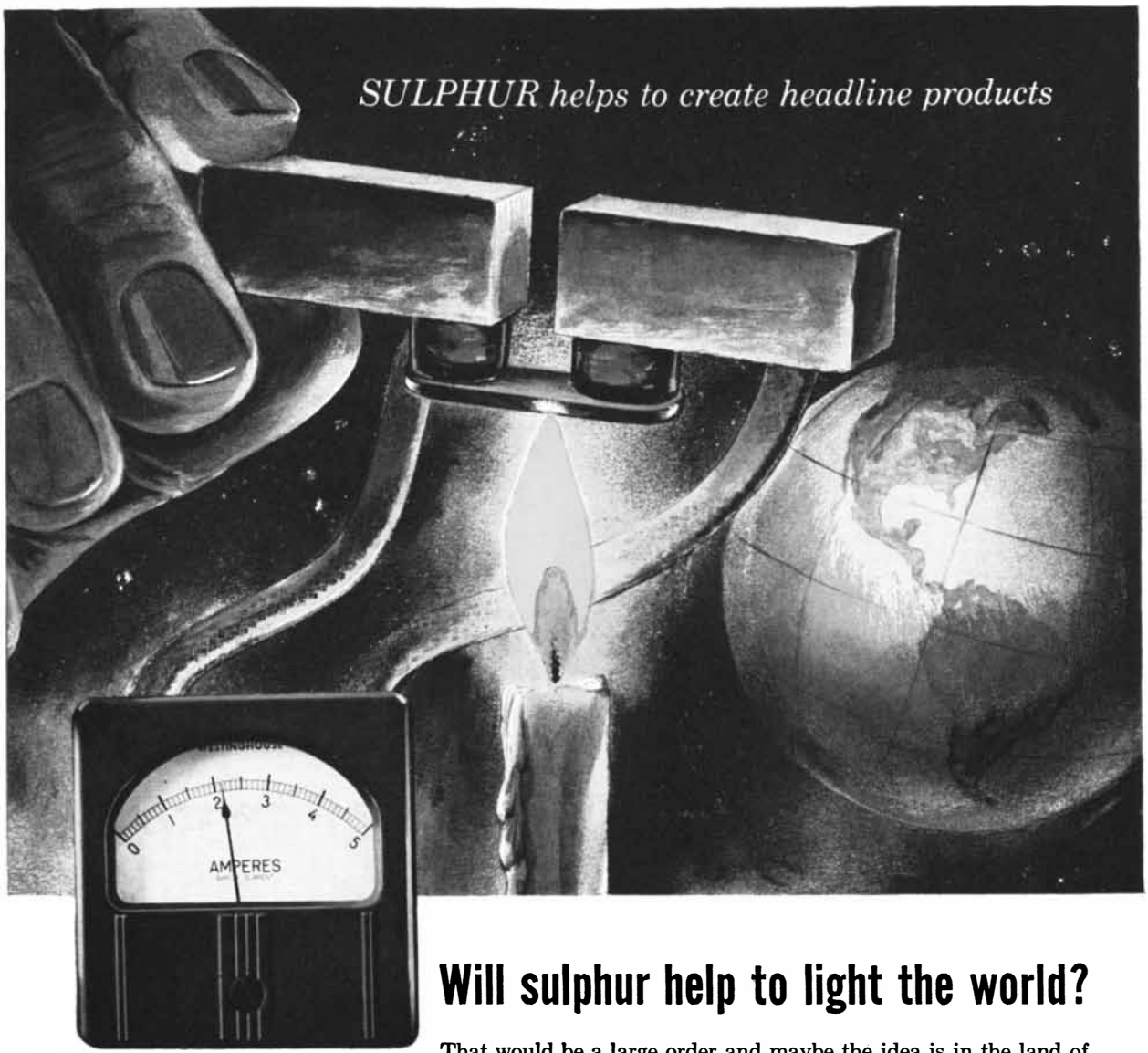
GENERAL ELECTRIC

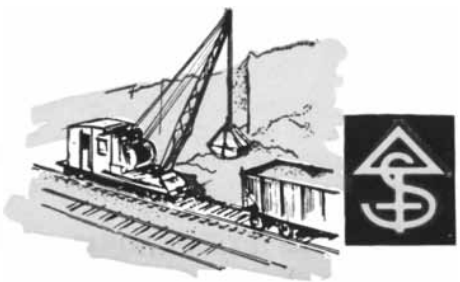


Will sulphur help to light the world?

That would be a large order and maybe the idea is in the land of fantasy but an interesting development involving sulphur has come from the Westinghouse Research Laboratories—electricity from a thermoelectric material heated to a very high temperature. The use of a thermocouple of dissimilar metals to measure temperature is, of course, not new and when so used generates a voltage. Today, through improved materials, the same concept is being developed to generate useful amounts of electric power. Recently, Westinghouse scientists discovered that two man-made rare-earth sulphides—Cerium Sulphide (Ce_2S_3) and Samarium Sulphide (Sm_2S_3)—can produce such power at very high temperatures.

Science has long been searching for the short cut between heat and power. This Westinghouse development has interesting possibilities.

As of the moment no 'tonnage' of sulphur is involved in this Westinghouse development but millions of tons of TGS Sulphur do go into industry annually from our producing properties in the States and Canada. Our regional terminal storage facilities for molten sulphur with short haul deliveries have greatly broadened the TGS service to industry.



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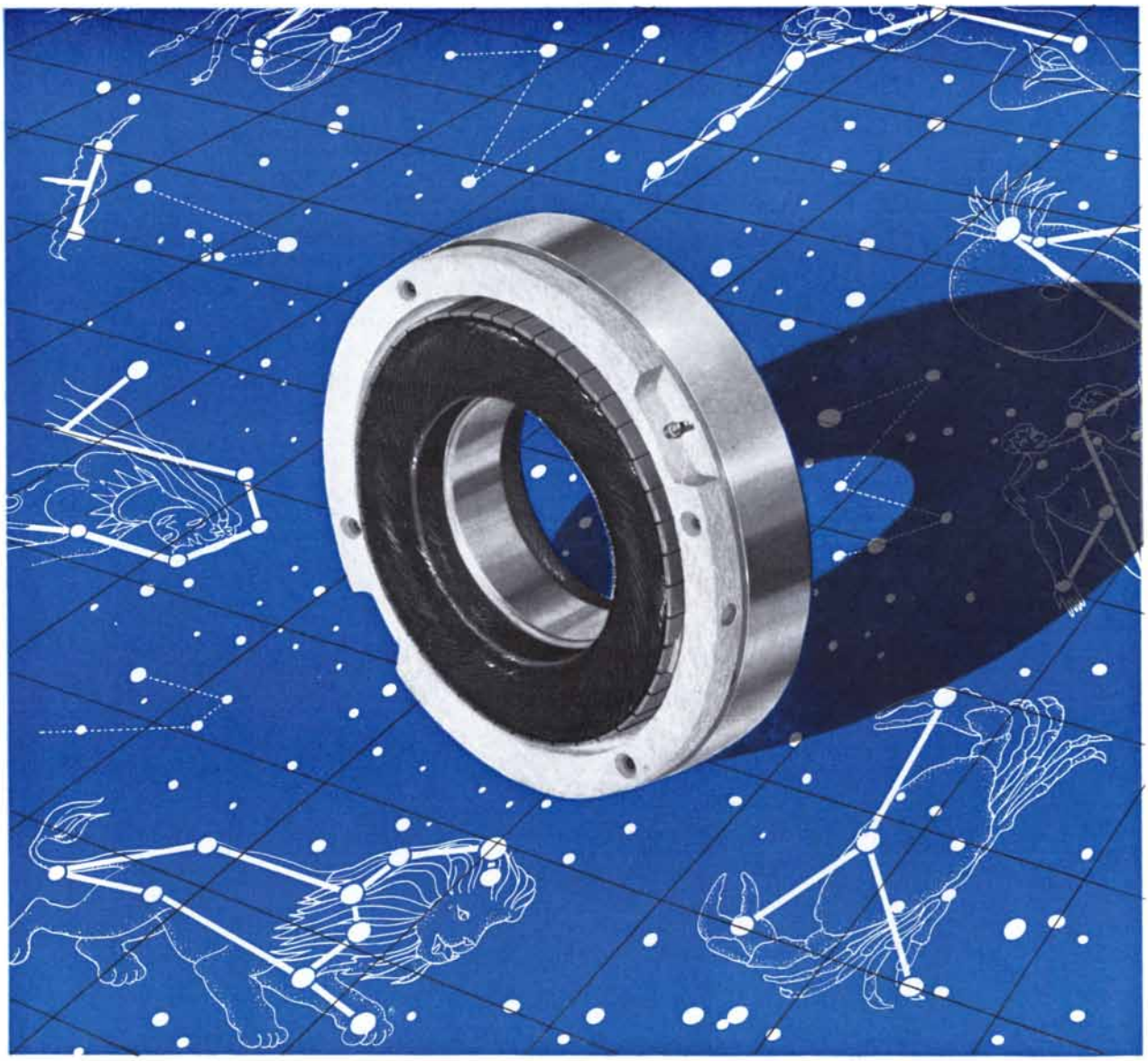

Guide to a space ride

Inland DC torque motors are integral components of many major U.S. missile guidance and ground support control systems. These direct-drive torquers provide efficient, low speed operation and produce exceptionally high torque to power ratios. Their gearless, pancake design eliminates backlash and other problems inherent in conventional motor design.

Inland products are used in various space instrumentation systems. For example:

- DC torque motors and rotary amplifiers are utilized in tracking antennas for Project Mercury.
- For a space exploration mission, Inland torque motors will help keep solar energy cells constantly aimed at the sun.
- For a new satellite, Inland torque motors and tachometer generators will keep cameras in constant focus on the earth.

Inland Motor Corporation is a subsidiary of Kollmorgen Corporation. Both coordinate their efforts in the design and production of instruments and systems involving optics, mechanics and electronics for industry and defense. For literature, Write Dept. 9-9.

Resumes invited from qualified optical engineers.

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CORPORATION
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50 AND 100 YEARS AGO

SCIENTIFIC AMERICAN

SEPTEMBER, 1911: "In our last issue we mentioned Beachy's new altitude record of 11,640 feet made at Chicago recently. This has since been exceeded by Garros in a Blériot monoplane. On September 4 this daring French aviator ascended to a height of almost 2½ miles (4,000 meters), or 12,954 feet. This startling performance would indicate that there is no limit to the height to which an aeroplane can soar. Garros reached an elevation almost as high as Pikes Peak, in Colorado. It has always been supposed that the monoplane was more difficult to drive to such great elevations than the biplane, but such has been demonstrated to be untrue and the monoplane now holds the palm for height as well as for speed."

"For several years Prof. H. Kamerlingh Onnes, of Holland, has carried out exceedingly interesting experiments on the enormous decrease of electrical resistivity that pure metals undergo at very low temperatures. He has now perfected his experimental facilities for the use of liquid helium and the results of his determinations of the resistivity of pure gold and mercury at liquid helium temperatures are given in abstract in the London *Electrician*. The author's recent experiments with gold have greatly strengthened his former conclusion that the resistance of pure gold vanishes at helium temperatures. Even more interesting are the experiments with mercury. The value of the mercury resistance used was 172.7 ohms in the liquid condition at 0 deg. C. At 43 deg. K. this had sunk to .084 ohm. At 3 deg. K. the resistance was found to have fallen below 3×10^{-16} ohm."

"The Otis Elevator Company has obtained a patent for an elevator that has a conveyer transporting between different levels in which the direction of movement is clockwise and contraclockwise. The elevator is in the form of a moving stairway, having ascending and descending series of steps that travel in spiral paths in opposite directions about a common center of curvature. The inventor is Charles Leeberger of New York City."

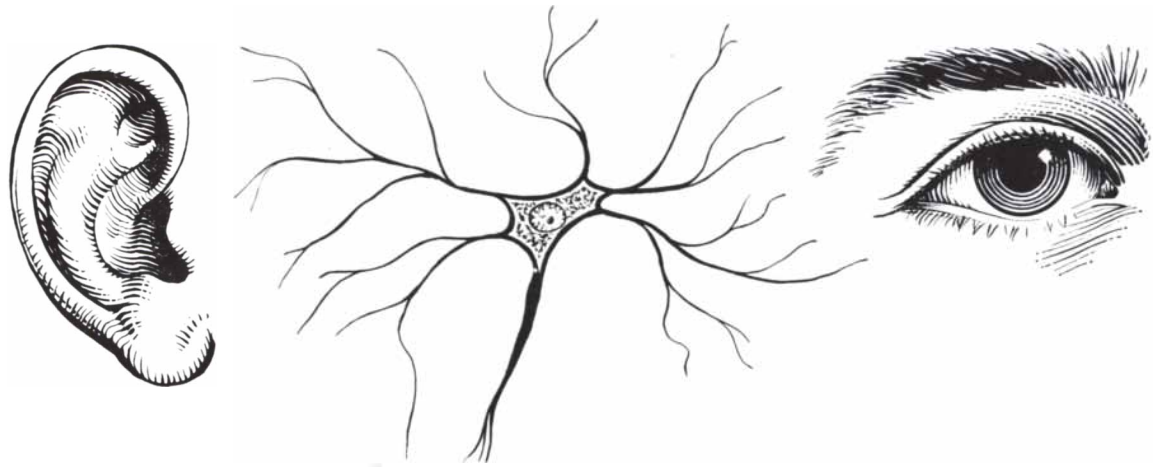
"Just as the accurate measurements of controlled phenomena have taught us much that is definite and much that is useful about the divisibility of matter, so also cleverly designed and skillfully executed experiments are giving us equally definite knowledge of the atomic nature of electricity, of the fact that there is a measurable and seemingly ultimate limit to the divisibility of an electric charge, and what the exact magnitude of the ultimate charge is. A few years ago it would have been almost silly even to have dreamed of accomplishing such an experimental feat. But Prof. R. A. Millikan of the Ryerson physical laboratory at the University of Chicago has most cleverly solved this seemingly impossible problem. Free gaseous ions of either sign have been captured at will, either singly or in multiples, and their magnitude has been so carefully measured, under conditions so free from assumptions, that the size of the electrical atom, the smallest quantity of electricity now attainable, is known probably to within one part in 500 of its actual value. Numerically this value is the absolute electrostatic unit multiplied by 4.891×10^{-10}, a quantity incomprehensibly small."

Scientific American.

SEPTEMBER, 1861: "The civil war in our country has had a most injurious effect upon the export trade of Great Britain with America. During the first six months of the present year British exports to the United States had fallen off about 40 per cent. The statistics of the British export trade with this country present some very striking features. In 1845 it amounted in value to little more than $31,500,000; in 1856 it rose to $105,000,000; in 1858 it fell to $65,000,000, and in 1859 it rose to nearly $110,000,000. It is expected that the exports will fall to $60,000,000 for the current year. The imports of Great Britain, on the other hand, have increased in an astonishing degree, and these are assumed to be signs of the growing prosperity of that country."

"The telegraph line now being put up to connect the Pacific with the Atlantic States is progressing satisfactorily. The *Alta Californian* states that if no accident

WHAT GOES ON HERE?



Bell Telephone Laboratories' new electronic "nerve cell" is a step toward finding out

One fascinating area of communications has long resisted exploration—what happens inside the nervous system when you see, or when you hear.

This area is of special interest to telephone science; knowledge of how the nervous system handles sound and picture signals can help determine what information is essential to perception. This in turn may lead to more efficient communication instruments and systems.

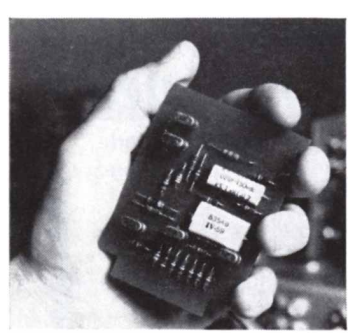
To probe the mystery of nerve activity, Bell Telephone Laboratories scientists have developed an electronic model of a living nerve cell or neuron. Consisting of transistors, resistors, capacitors and diodes, the "artificial neuron" exhibits many of the characteristics of a living neuron; for instance, "all-or-none" response and fatigue.

In one experiment at Bell Laboratories, a network of artificial neurons is subjected to a stimulus from light through a set of photocells. The network can distinguish specific patterns of light and dark, thus duplicating roughly some of the eye's basic reactions to light. Similar studies are underway to explore our hearing processes.

At present, too little is known about neural action to permit exact electronic duplication. But experiments with artificial neurons can provide suggestive clues, contributing to a stimulating interplay between electronics and neurophysiology which may help workers in both disciplines.

The human nervous system, including the brain, is the most efficient and versatile data processing system known; and data processing is an essential part of communications. The artificial neuron provides a new approach to investigating and understanding basic nerve network functions. It is a fresh example of how Bell Telephone Laboratories constantly explores new frontiers to improve America's communications system, now and in the years ahead.

Network of neurons is assembled by L. D. Harmon of Bell Laboratories, the initiator of this new research. Many kinds of assemblies are possible.



A single artificial neuron. It delivers electrical impulses when stimulated, like a living cell. Neurons are also being used for research into hearing.

BELL TELEPHONE LABORATORIES

WORLD CENTER OF COMMUNICATIONS RESEARCH AND DEVELOPMENT

happens to the teams employed in the work, the western half of the overland line between San Francisco and Salt Lake will be in working order before the first snow falls in the valley. On the eastern side the line is up to Julesburg, 200 miles west of Fort Kearney."

"When repeated charges of electricity are passed through a jar filled with atmospheric air or with pure oxygen gas, the oxygen acquires new properties. It emits a peculiar odor, it possesses extraordinary bleaching powers, and it has its affinities, or power of combining with other substances, very largely increased. Schönbein, who first discovered this fact, supposed that he had found a new substance, and he gave it the name of ozone, from the Greek *ozo*, odor; its most striking peculiarity being the odor that it emitted. We find in *La Répertoire de Chimie Appliquée* an account of some recent investigations that have revived the first idea of Schönbein, that ozone is not oxygen but a separate element. Messrs. Andrews and Tait, after a long series of observations, regard it as probable that oxygen is a compound substance, and ozone is one of its elements."

"We invite attention to a paper recently read by Mr. Bessemer on his process of refining iron and making steel. Six years ago the first experiments with this process attracted a great deal of attention throughout the world, it being regarded as holding forth the promise of working a complete revolution in the mode of refining iron, and very materially reducing the price of steel. The doubts in regard to the matter were such as are inseparable from all untried innovations, and the world has been watching the progress of the enterprise with very deep interest. The evidence, therefore, that Mr. Bessemer produces of the complete industrial success of the manufacture, and of the very superior qualities of his iron as well as of his steel, will attract general attention among mechanicians. The Bessemer steel seems to be the very best material for ordnance. It will be observed that Mr. Bessemer says that works sufficient to turn out steel enough to make forty 18-pounders per day may be erected for $25,000. Mr. Bessemer took out a patent in this country, but it was subsequently set aside in a case of interference with Wm. Kelly of Lyon's County, Ky., who was held to be the first inventor. Would not some of our enterprising iron manufacturers make a good operation by getting hold of this patent and starting a manufactory of the steel in this country?"

HOW ADVANCED IS THE ART OF ENERGY CONVERSION?

Chemical–Electrical: Fuel Cells. The direct conversion of chemical energy to electrical energy via fuel cells has for years been regarded as a great potential power source. The problem has been to translate theory into practical, producible devices. Recent prototype testing indicates this need may now be met.

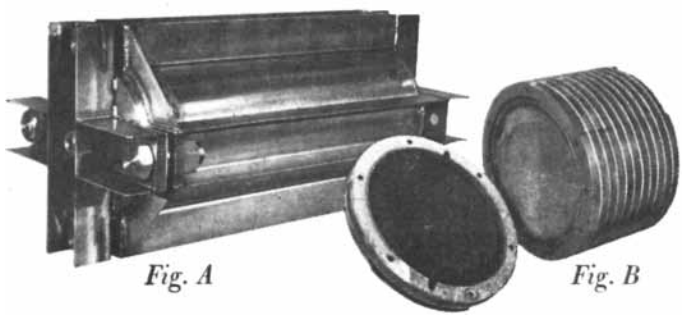


Fig. A *Fig. B*

■—The men at Leesona Moos Laboratories are responsible for a good deal of the early research on fuel cells. Present work is in two main areas: the hydrogen-oxygen Hydrox® cell, and hydrocarbon-air Carbox® cell. Thus far, prototypes of such cells have demonstrated good performance. Outputs with hydrogen equalling 150 watts per sq. ft. of electrode are readily achievable.

The Hydrox® cell can be designed as a regenerative unit which utilizes the same fuel and oxidant over and over, or as a non-regenerative unit which produces potable water as a by-product. The Carbox® cell, still under development, offers the advantage of more economical fuel.

■—*A typical Hydrox® Fuel Cell test battery is shown here. Fig. A shows the complete assembly and Fig. B indicates the internal fuel cell electrodes. It is but one of many configurations designed by Leesona Moos Laboratories.*

■—Leesona Moos Laboratories has been actively involved in the field of energy conversion for 13 years. Thermoelectric, electrochemical, and nuclear power sources, ranging from megawatt reactors to microwatt batteries, have been investigated. Some of these are offered as products, for example, the Dynox® solid state battery, Raypak® nuclear power pack, and Betachron® nuclear timer. An informative brochure on current state of energy conversion techniques with emphasis on fuel cells is available from Department 11.

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Maleic and phthalic anhydrides, and ethylene oxide, are products of reactions which offer a similar challenge. The catalyst carriers for these reactions must have heat resistivity, uniform size and porosity, and a purity not commonly found in ceramic materials. Norton pioneered their development, and has a fund of knowledge for anyone interested in catalysis.

In the chemical industry as in other fields, Norton is crystallizing ideas into products . . . through oxide chemistry, and through fundamental work in carbides, nitrides and borides. We are ready to work with you. Write NORTON COMPANY, Refractories Division, 548 New Bond St., Worcester 6, Massachusetts.

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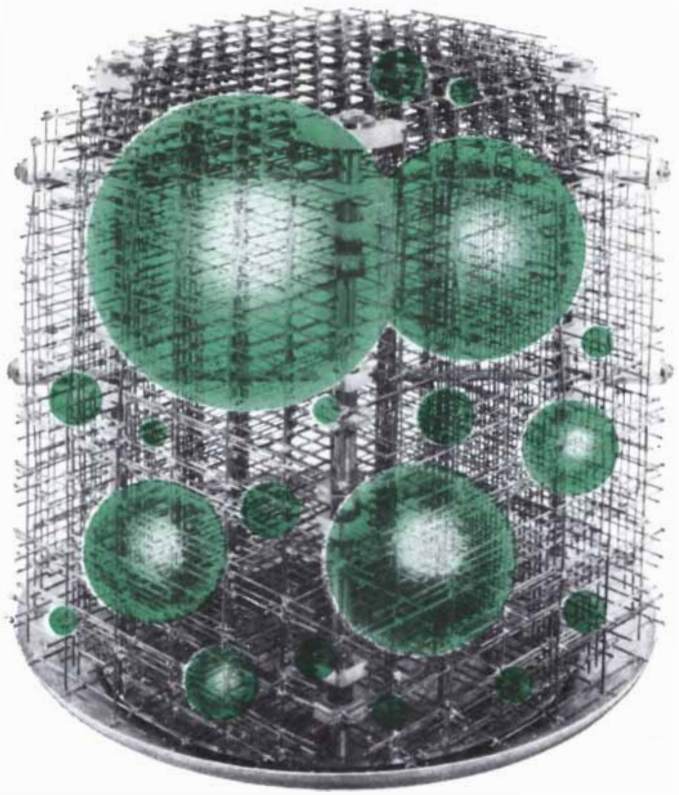
REFRACTORIES

Crystallizing ideas into products

Another measure of the competence of Liquidometer in advanced instrumentation



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whatever a liquid's state or attitude, whether still or in agitation, the volume indication is the same with the Liquidometer Matrix Liquid Quantity Gauge. A capacitor type measuring probe — intercellular in construction — is the heart of the system. In addition to actuating an indicator, output can be telemetered, used for control purposes, or fed into computers. Potential applications: measuring liquid oxygen for astronauts; gauging liquids in advanced rocket propulsion systems; all-attitude gauging of aircraft fuels. Technical details in Booklet 694.

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ARMY

Scientific and engineering groups at Thiokol, functioning as part of the Army Ordnance team, have developed propulsion systems of total reliability for a wide range of military requirements. Motors for Lacrosse, and for the developmental Sergeant and Pershing, the modern field artillery—powerplants for the Nike Hercules and Nike Zeus, defenders against air borne and ballistic missile attack . . . these are products of the joint Army-Thiokol effort. Additional capabilities for Army's advanced thinking are pro-

research through production

NIKE HERCULES
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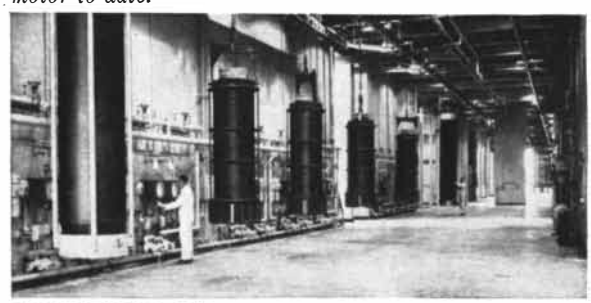
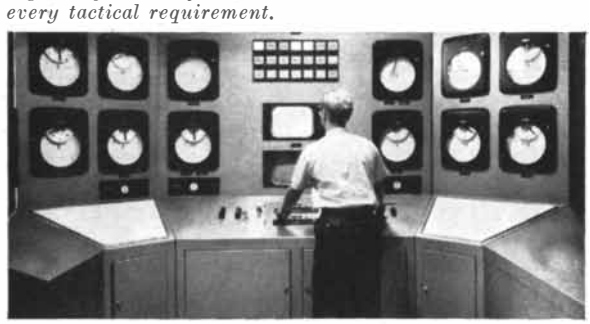
Western **Electric**
Missile: Douglas Aircraft

REDSTONE *The most powerful single solid rocket booster ever fired in the free world—450,000 lbs. thrust—was developed for the Army's Nike Zeus program at Thiokol's Redstone Division. The motor is a product of research from propellant formation to scale-up and development of largest thrust rocket motor to-date.*



LONGHORN *Production techniques of the most advanced nature are featured at Longhorn, to assure the military a steady flow of rocket motors of unvarying dependability. Through combined divisional efforts, Thiokol is producing reliable power-plants for the key air defense and anti-missile missiles, the Army's Nikes . . . Hercules, now operational and guarding major population centers . . . developmental Zeus, whose repeatedly successful R&D launchings underscore Thiokol capability to design and deliver rocket motors to meet every tactical requirement.*

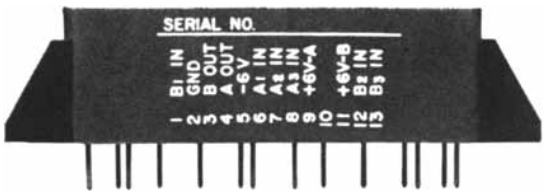


vided by other Thiokol Divisions. Utah, for large engine production — RMD, for sophisticated liquid systems -- Elkton, for diversified special motors.

Experiences gained through their development . . . basic laboratory research into high energy fuels and materials, new processing and evaluating methods, automatic production and quality control techniques, the most advanced and fluid research and manufacturing facilities . . . all have added immeasurably to the progress of Rocketry, U.S.A. All can be brought to bear in the most challenging future projects of the space age.

THIOKOL

THIOKOL CHEMICAL CORPORATION, Bristol, Pennsylvania
Rocket Operations Center: Ogden, Utah



In less time than it takes light to cross this room, a new product, **DELCO'S NEW** high speed **10 MC** silicon modules, could: (1) correct the course of a missile in flight; (2) make it possible for sonar pickups to track and compute the position of targets with microsecond accuracy; and (3) handle any number of other airborne guidance and control functions that previous modules—due to low speed or environmental or performance limitations —could not handle. Delco Radio's 10mc modules, with a maximum gate-switch speed of 40 nanoseconds, convert data 100 times faster —even under the most extreme environmental conditions.

These **SILICON** modules come epoxy encapsulated, and operate over a temperature range of −55°C to +100°C. And these same reliable **DIGITAL** circuits are available packaged on plug-in circuit cards. These Delco **MODULES** are environmentally proved to: **SHOCK,** 1,000G's in all planes. **VIBRATION,** 15G's at 10 to 2,000 cps. **HUMIDITY,** 95% at max. temp. **STORAGE AND STERILIZATION TEMP.** −65°C to +125°C. **ACCELERATION,** 20G's. Designed for systems using from one module to 100,000, and the module's rated performance considers the problems of interconnection. Data sheets are available. Just write or call our Military Sales Department.

Physicists and electronics engineers: Join Delco Radio's search for new and better products through Solid State Physics.

PIONEERING ELECTRONIC PRODUCTS THROUGH SOLID STATE PHYSICS

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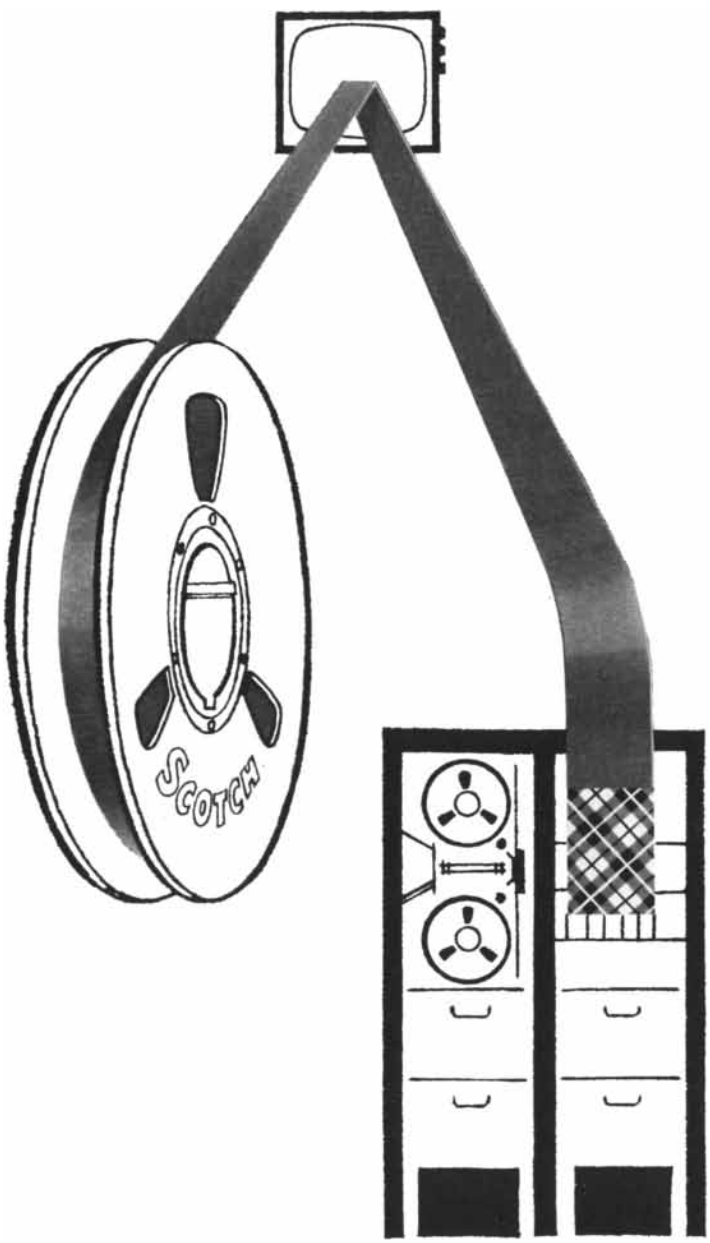
THE TAPE THAT CHANGED TV FOR ALL TIME

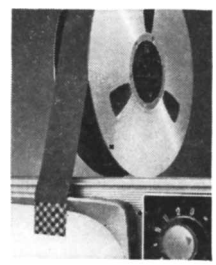
leads you right to rugged
SCOTCH® BRAND Heavy Duty Tape



THE TIE that binds television's top performer to instrumentation tape is strong—and it goes beyond the fact that the same expert team produces the best of both. "SCOTCH" BRAND Heavy Duty Tapes share a common heritage—and uncommon endurance—with "SCOTCH" BRAND Video Tape, the tape that puts a network TV show on the same "clock time" from Maine to California.

Similarities worth noting between the two: a similar high-temperature binder system, famous "SCOTCH" BRAND high potency oxides, a similar ability to resist tremendous speeds, pressures and temperatures while providing high resolution.

Let's look at the record of "SCOTCH" BRAND Video Tape and see what message it has for the user of instrumentation tape. On a standard reel of video tape like that shown here, some 1½ million pulses per second must be packed to the square inch—on a total surface area equal to the size of a tennis court. The tape must provide this kind of resolution while defeating the deteriorating effects of high speeds, pressure as high as 10,000 psi and temperatures up to 250°F.



The fact is that video tape must be essentially perfect. And it's a matter of record that thus far only the 3M experts have mastered the art of making commercial quantities of video tape that consistently meet the demands of the application.

Significantly, the high-temperature binder system developed for "SCOTCH" Video Tape is first cousin, only slightly removed, to that used in the Heavy Duty Tapes. It's this special feature that has given Heavy Duty Tapes their exceptional wear life.

The moral emerges: for tape that provides the best resolution of high and low frequencies under the severest conditions, turn to "SCOTCH" BRAND Heavy Duty Tapes 498 and 499.

They offer the high temperature binder system, plus the same high quality and uniformity that distinguish all "SCOTCH" BRAND Tapes. As the most experienced tape-makers in the field, 3M research and manufacturing experts offer tape of highest uniformity—from reel to reel and within the reel. Check into the other "SCOTCH" BRAND constructions: High Resolution Tapes 457, 458 and 459; High Output Tape 428; Sandwich Tapes 488 and 489; and Standard Tapes 403 and 408.

Your 3M Representative is close at hand in all major cities. For more information, consult him or write Magnetic Products Division, 3M Co., St. Paul 6, Minnesota.

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FOR INSTRUMENTATION

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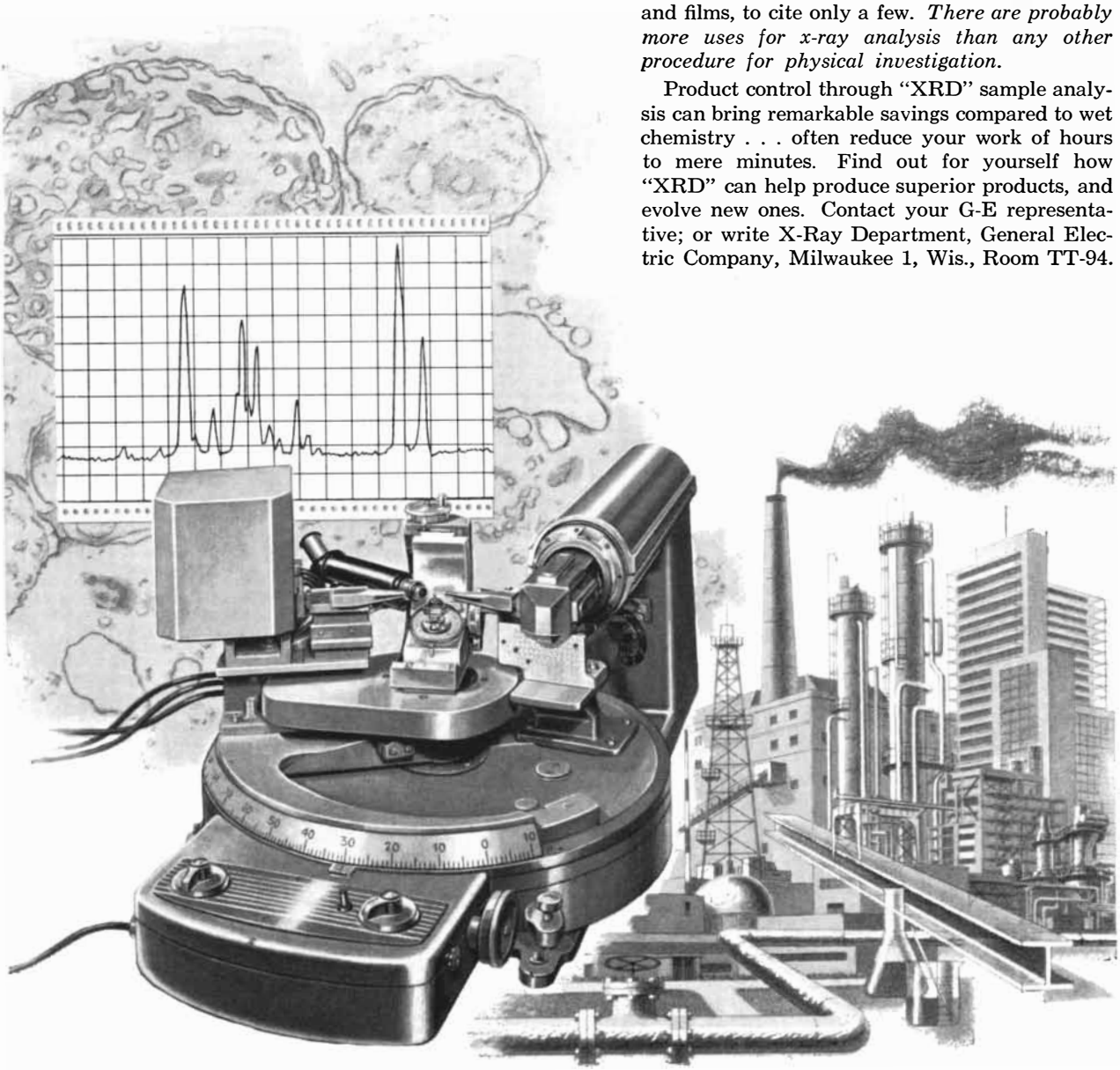
MAPPING THE MAKE-UP OF MOLECULES

...from proteins, in cancer research, to profitable products for industry!

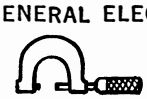
GENERAL ELECTRIC "XRD" X-RAY ANALYSIS EQUIPMENT ferrets-out basic answers impossible or difficult to obtain by other means. Witness one current application: helping map the frontiers of cancer research, through protein structure analysis. Solving this problem is expected to be a major step in understanding and perhaps preventing abnormal growth of living cells — cancer.

G-E x-ray diffraction and spectrometry equipment also supplies industry with proved, plant-practical tools for product control, development and research. Publicized results in new products include Nylon, magnetic TV tape, high-test gasolines, high-temperature alloys, synthetic fabrics and films, to cite only a few. *There are probably more uses for x-ray analysis than any other procedure for physical investigation.*

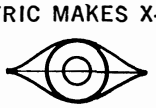
Product control through "XRD" sample analysis can bring remarkable savings compared to wet chemistry . . . often reduce your work of hours to mere minutes. Find out for yourself how "XRD" can help produce superior products, and evolve new ones. Contact your G-E representative; or write X-Ray Department, General Electric Company, Milwaukee 1, Wis., Room TT-94.



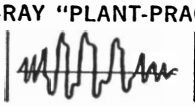
GENERAL ELECTRIC MAKES X-RAY "PLANT-PRACTICAL" FOR



MEASURING



INSPECTING



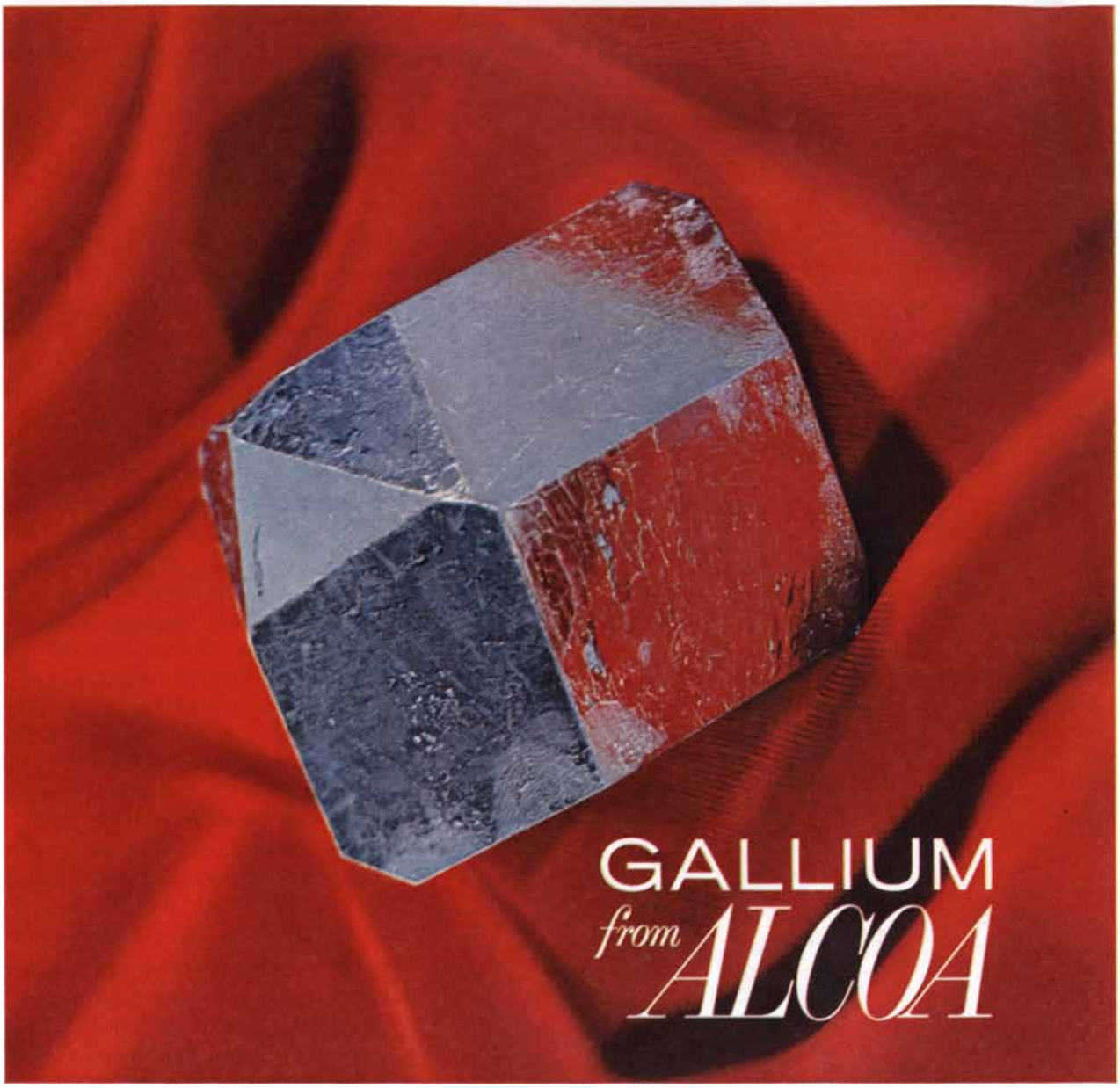
ANALYZING

IRRADIATING

Progress Is Our Most Important Product

GENERAL ELECTRIC

probably the purest metal ever produced by man . . .



A curious metal is gallium. It melts in your hand, but doesn't boil until 1,983°C. Like water, but unlike most elements, it expands when solidified. Gallium exists in nature, particularly in aluminous ores of the bauxite type. But because of low concentration, it is not economical to process these ores for gallium content alone. Discovered in 1875, this rare metal only recently has shown commercial promise.

Gallium is extremely anisotropic. The variation in electrical resistivity is thought to be greater than for any other known metal. Gallium is widely used in semiconductor devices such as tunnel diodes, high-speed switches and microwave diodes. Gallium alloys readily with most metals, which leads to applications as cathodes in specialized vapor-arc lamps, in dental alloys, as low-resistance contact electrodes.

Gallium is used as a sealant for glass joints in laboratory equipment, particularly mass spectrometers and vacuum equipment. It shows promise as a heat transfer medium in nuclear reactors. It is added in small amounts to certain selenium rectifiers because it emits electrons at fairly low temperatures. It is being evaluated as thermionic valve cathodes for the same reason.

Today Alcoa produces three grades: 99.99 per cent pure, 99.999 per cent pure and 99.9999 per cent pure (Ga-4, Ga-5, Ga-6)—probably the purest metal ever produced by man. Alcoa's spectrographic and electronic techniques are the most rigorous and highly developed in the industry.

Are you interested in gallium applications—tried or untried? Our research and development people are available for discussion. Please write Aluminum Company of America, 701-J Alcoa Building, Pittsburgh 19, Pa.

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THE AUTHORS

JEAN BRACHET ("The Living Cell") is professor of general biology at the Free University of Brussels, of which his father, the anatomist and embryologist Albert Brachet, had been the rector. As a medical student at the Free University, Brachet did research under the direction of Albert M. Dalcq, acquired an M.D. degree in 1934 and joined the faculty as an instructor in anatomy the same year. Brachet writes that he "preferred the satisfaction of doing original and independent research in biology to the responsibilities of medical practice . . . and decided to study the elementary forms of life, *i.e.*, cells and embryos. Such studies ultimately will lead to a better understanding of the origin of cancer and to a more logical therapeutic approach to disease." Brachet has held visiting professorships at the University of Pennsylvania, the Rockefeller Institute, the Pasteur Institute in Paris and the Indian Cancer Research Centre in Bombay.

ALBERT L. LEHNINGER ("How Cells Transform Energy") has since 1952 been DeLamar Professor of Physiological Chemistry and director of the department of physiological chemistry at the Johns Hopkins School of Medicine. He received his B.A. from Wesleyan University in 1939 and his M.S. and Ph.D. from the University of Wisconsin respectively in 1940 and 1942. After teaching at Wisconsin until 1945, Lehninger joined the faculty of the University of Chicago. In 1951 he went to the University of Frankfurt as an exchange professor, and in 1951 and 1952 he was a Guggenheim fellow and Fulbright research professor at the University of Cambridge. In 1948 Lehninger discovered that the enzymes involved in the citric acid and respiratory cycles of energy transformation in the cell are located in the mitochondria.

VINCENT G. ALLFREY and ALFRED E. MIRSKY ("How Cells Make Molecules") are respectively associate professor of molecular biology and Member of the Rockefeller Institute. Allfrey took a B.S. in chemistry at the College of the City of New York while working as a laboratory technician with Mirsky at the Rockefeller Institute. Following service with the Army Medical Corps in 1944 and 1945, Allfrey acquired an M.S. at Columbia University in 1948 and a Ph.D. there in 1949. Since joining the Rockefeller Institute in 1949 he has worked on the problems of isolating cell nuclei and on the genetic control of protein synthesis. Mirsky, who is editor of the *Journal of General Physiology*, received a B.A. from Harvard University in 1922 and a Ph.D. in physiology from the University of Cambridge in 1926. He went to the Rockefeller Institute in 1927.

DANIEL MAZIA ("How Cells Divide") is professor of zoology at the University of California. He received his A.B. in 1933 and his Ph.D. in zoology in 1937 from the University of Pennsylvania, where he did graduate work under the direction of L. V. Heilbrunn. After a year as a National Research Council fellow at Princeton University, working under E. Newton Harvey, Mazia went to the University of Missouri. There he became interested in the role of nucleic acids in chromosome structure and later in the functions of cell nuclei. He joined the faculty of the University of California in 1950. Mazia began doing research on the process of mitosis in 1952, when a former classmate of his at Pennsylvania, Katsuma Dan of Tokyo Metropolitan University, visited his laboratory. The result of their collaboration—the first isolation of the mitotic apparatus from a cell—was described by Mazia in his article "Cell Division," which appeared in SCIENTIFIC AMERICAN for August, 1953.

MICHAIL FISCHBERG and ANTONIE W. BLACKLER ("How Cells Specialize"), who have worked together in the Embryology Laboratory at the University of Oxford since 1959, will continue their joint research this year at the University of Geneva, where Fischberg has been appointed to the chair of zoology and directorship of the department of zoology, and Blackler to a visiting professorship. Fischberg was born in St. Petersburg in Russia and was educated in Switzerland, receiving his Ph.D. from the University of Zürich in 1946. After a year of postdoctoral research at the University of Basel, he went to the Institute of Animal Genetics in Edinburgh on a two-year research fellowship from the Swiss Academy of Medicine. Fischberg became Jenkinson Memorial Lecturer in Embryology and head of the Embryology Laboratory at Oxford in 1951. During this past year he was a visiting professor at the Rockefeller Institute. Blackler, who joined Fischberg's lab-

oratory in 1959, took his B.Sc. at University College London in 1953 and his Ph.D. there in 1956.

A. A. MOSCONA ("How Cells Associate") is professor of zoology at the University of Chicago. He received a Ph.D. in zoology from the Hebrew University in Jerusalem in 1950, spent two years at the Strangeways Research Laboratory of the University of Cambridge and from 1953 to 1955 was associate professor of physiology at the University of Jerusalem. Before joining the faculty at Chicago in 1958, Moscona had held a two-year research fellowship at the Rockefeller Institute.

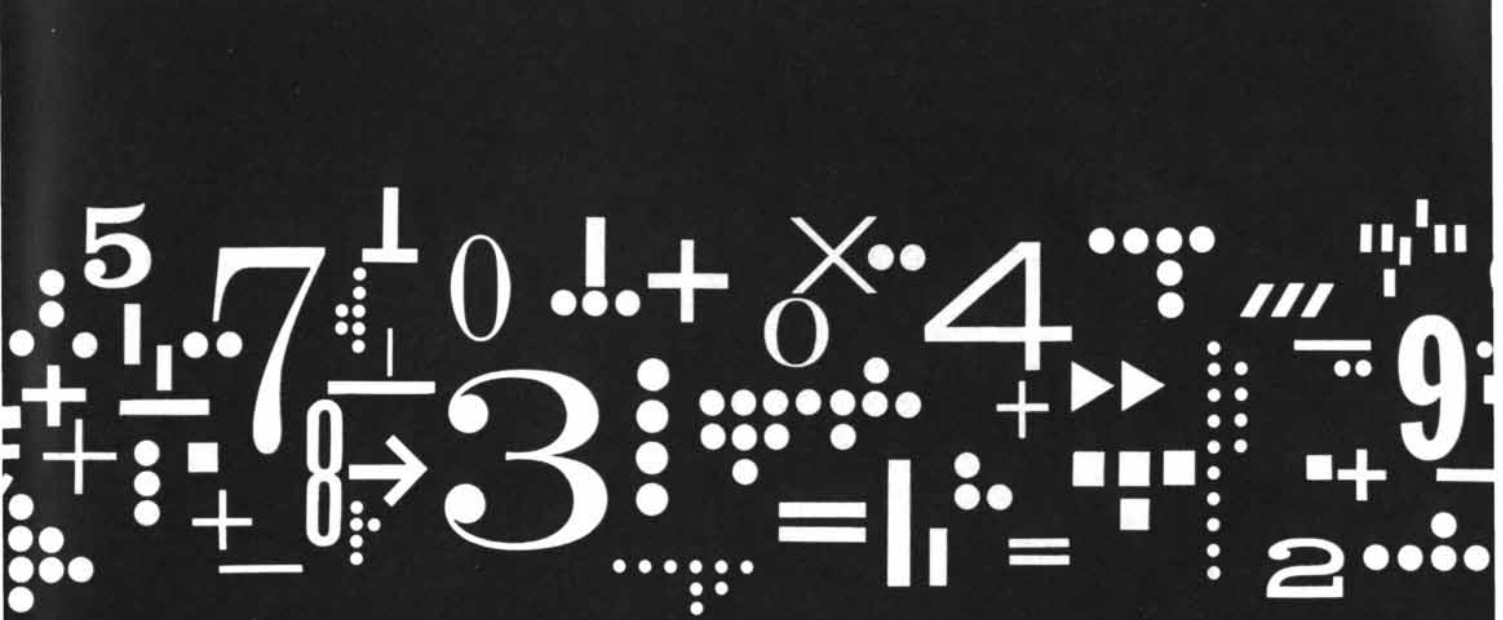
HEINZ HOLTER ("How Things Get into Cells") is head of the physiology department of the Carlsberg Laboratory in Copenhagen. Holter was born in Leonding in Austria, and he studied chemistry at the University of Vienna from 1923 to 1928. Although his Ph.D. thesis and first scientific papers dealt with problems of organic chemistry, he was more interested in biochemistry. He obtained a Rockefeller fellowship in biochemistry to do enzyme research in S. P. L. Sörenson's department at the Carlsberg Laboratory and arrived there in 1930 planning to stay only one year. Working with Kaj U. Linderström-Lang on enzymatic histochemistry, Holter became increasingly involved in studies of cell physiology, his current field of research. He founded the department of cytochemistry at the Laboratory in 1944, taking his present position in 1956.

TERU HAYASHI ("How Cells Move") is professor of zoology at Columbia University. Growing up in Atlantic City, N.J., during the depression, he "managed to get through the local high school and subsequently Ursinus College between odd jobs as a baker's apprentice, auctioneer's helper, aquaplane performer in water carnivals and announcer for bingo and other games of chance." His professor of physics at Ursinus, John Mauchly, a pioneer in the development of electronic computers, got Hayashi interested in an academic career. Switching from physics to biology, he studied under L. V. Heilbrunn at the University of Pennsylvania and then went to the University of Missouri, where, as a student of Daniel Mazia's, he took a Ph.D. in cell physiology in 1943. He joined the Columbia faculty later that year.

BERNHARD KATZ ("How Cells Communicate") is professor and head of the biophysics department of University College London. Born in Leipzig, Germany, in 1911, Katz acquired an M.D. degree at the University of Leipzig in 1934. From 1935 to 1939 he worked under the direction of A. V. Hill at University College, where he received a Ph.D. in 1938. Katz served with the Royal Air Force in the Pacific from 1942 to 1945 and then returned to University College. A Fellow of the Royal Society since 1952, Katz was Herter Lecturer at Johns Hopkins University in 1958 and Dunham Lecturer at Harvard University this past year. His article "The Nerve Impulse" appeared in the November 1952 issue of SCIENTIFIC AMERICAN.

WILLIAM H. MILLER, FLOYD RATLIFF and H. K. HARTLINE ("How Cells Receive Stimuli") have collaborated in studies of visual receptors and neural interaction at the Rockefeller Institute since 1955. Miller, assistant professor of biophysics, is a graduate of Haverford College and received his M.D. degree from Johns Hopkins University in 1954. He first began doing research on the eyes of invertebrates in Hartline's laboratory at Johns Hopkins. After an internship at Baltimore City Hospital, Miller joined the Rockefeller Institute in 1955. Ratliff, associate professor of biophysics, took a B.A. at Colorado College in 1947 and a Ph.D. in psychology at Brown University in 1950. He went to Johns Hopkins the following year on a National Research Council fellowship to study retinal interaction with Hartline. Before going to the Rockefeller Institute in 1954, Ratliff was assistant professor of psychology at Harvard University. Hartline joined the Rockefeller Institute as Member and professor in 1953. A graduate of Lafayette College, he took his M.D. degree at Johns Hopkins in 1927, did graduate work in physics at the same institution and from 1931 to 1949 was a staff member of the Johnson Research Foundation at the University of Pennsylvania. He went to Johns Hopkins in 1949 as professor and chairman of the newly established Jenkins Department of Biophysics.

F. FRASER DARLING, who in this issue reviews *Tropical Africa*, by George H. T. Kimble, is vice-president and director of research of the Conservation Foundation in New York. A noted animal ecologist, he was the author of "Wildlife Husbandry in Africa," which appeared in SCIENTIFIC AMERICAN for November, 1960.



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Modern data processing systems perform the near-miraculous as a matter of course. What they can't do is change the form in which data becomes initially available, or the requirements of its processing. That's why standard EDP systems are often "no fit" for unusual data handling problems.

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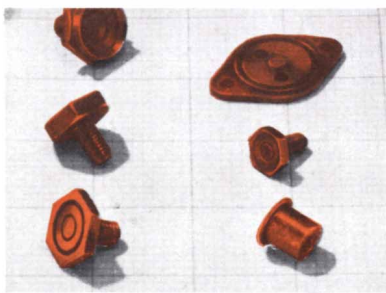
The chemical composition of this Anaconda alloy, 97.50% copper, 1.90% nickel, 0.60% silicon, produces many of the desired qualities inherent in Silicon Bronze or Everdur*. Most of the nickel and silicon in heat-treated Cunisil are present as an intermetallic compound of nickel silicide. This compound precipitates in submicroscopic particles during a relatively low temperature heat treatment; the alloy's distinctive properties result.

Cunisil is available as round rod, with or without final precipitation-hardening heat treatment, in the following sizes: straight lengths from 3/16" dia. to 1" dia.; coils from 3/16" dia. to 5/8" dia. Inquire about other sizes for special applications.

Anaconda copper for semi-conductor bases

Anaconda copper alloys are available for economical volume production of semiconductors and similar electronic components. These metals offer good machinability, high electrical and thermal conductivity, relatively high strength, and resistance to hydrogen embrittlement. The right combination of properties for most applications can be found in one of the following Anaconda alloys: DLP Copper-104 (deoxidized low phosphorus), OFHC* Copper-120 (oxygen-free high-conductivity), Amzirc* (Zirconium Copper)-134, Chromium Copper-999, Tellurium Copper-127.



Typical semi-conductor bases fabricated from Anaconda copper alloys

Anaconda specialists are available also—to help you select the right alloy and the right manufacturing method for your product requirements. Their technical know-how can provide fabrication economy, value analysis cost-cutting techniques, and help for any production problem.

For alloy information or technical assistance, get in touch with your Anaconda representative today or write Anaconda American Brass Company, Waterbury 20, Connecticut.

*Trademarks of American Metal Climax, Inc.

Copper-headed conductor rails win CABRA design award

Ringsdorff Carbon Corp. of East McKeesport, Pa., captured a recent CABRA award for use of copper in an outstanding engineering design. The metal: Anaconda ETP Copper-100 (electrolytic tough pitch). The design: compact conductor systems for a-c or d-c heavy-load applications. The Anaconda metal meets high conductivity requirements, contributes to conductor rail longevity, reduces maintenance costs. The Ringsdorff system provides operational economy for such heavy-current machinery as: monorails, traveling cranes, and ore bridges.

System fabrication is relatively simple. Over one basic steel shape, extruded copper is cold drawn to form the copper head. Head size is dictated by specific current requirements; capacities of up to 2000 amps can be attained. Ringsdorff carbon graphite materials, used as sliding contacts, exude a film to lubricate passage and protect conductor rails. Thus, over service periods of 25 years, wear on the copper head is negligible.

Copper-headed steel conductor rail and pantograph current collector with graphite carbon shoe are vital components of Ringsdorff Current Conductor System.

For this award-winning design, Ringsdorff selected copper for conductivity, steel for strength. A typical example of how the special properties of copper can be adapted—even teamed up with other materials—to fulfill industrial design requirements. Other examples, more Anaconda comments, and technical assistance for your metal selection and production problems—are yours for the asking. Contact Anaconda American Brass Company, Waterbury 20, Connecticut. In Canada: Anaconda American Brass Ltd., New Toronto, Ontario.

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A giant BMEWS antenna at Thule, Greenland. Vital diode crystals for the data processor were grown in an atmosphere of Airco nitrogen, monitored by an Airco-engineered system.

Faultless eyesight for America's Ballistic Missile Early Warning System depends on germanium diodes—tiny signal filtering "optics" for the data processor which are made by Clevite Transistor, Waltham, Mass. These germanium crystals are grown in a furnace atmosphere of nitrogen, and they must be of the highest quality.

Control of this quality in diode manufacture requires that the delivered gas be of utmost purity; and that this purity be held all the way from the liquid nitrogen receiver to furnace. An impurity of even a few parts per million in the nitrogen, and entrapped in the furnace-grown crystal, could cause miles of error in a field calculation.

To help make certain of the highest possible quality at the lowest possible cost, Clevite developed a gas monitoring system which Airco engineered and built to Clevite's specifications. The resulting system is so precise that it keeps watch on the purity of the Airco nitrogen right to the furnace entrance.

In every industry today, modern Airco processes based on gases are improving quality, boosting production, reducing costs.

Airco gases can give you heat...cold...special atmospheres . . . or can act as a raw material for a chemical reaction.

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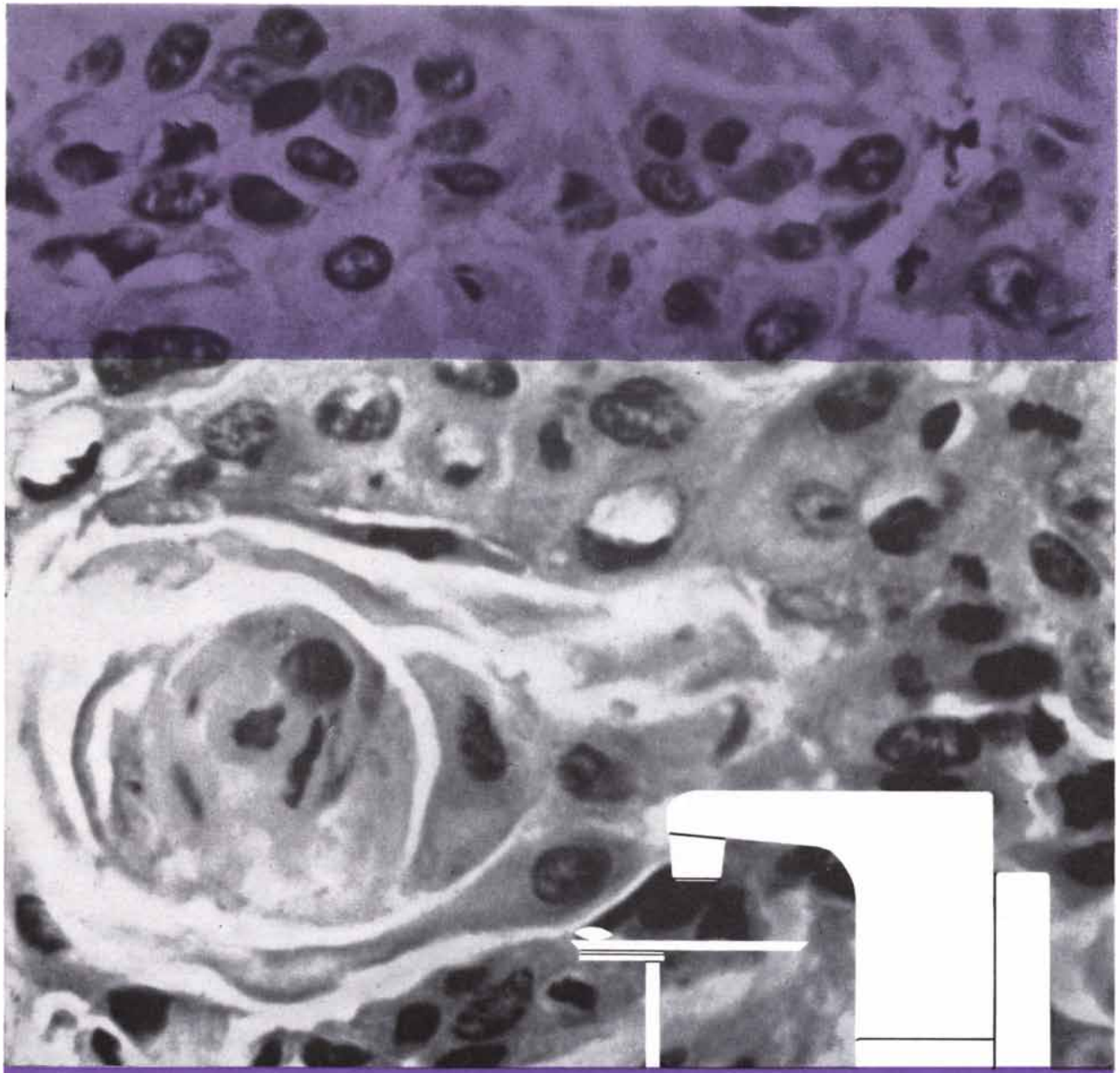

THERAPEUTIC RADIATION and the LINEAR ACCELERATOR

Significant advances are being made in methods for early detection of cancer. For example, the above photograph shows the cell structure of one form of lung cancer detected in an early stage by exfoliative cytology. ■ In radiation therapy, it is desirable that an accurately-defined dose of ionizing radiation be applied to the malignancy, with a minimum dose to the surrounding healthy tissue. ■ Specialized clinical linear accelerator systems of high reliability offer radiotherapists the advantages of convenient, rapid, and accurate treatment; the entire unit can be rotated 360° about the patient. ■ An X-ray beam produced from a small, highly-stable focal source at approximately 6 Mev provides a desirable distribution of dose. Differential bone absorption is minimized. Entrance and exit skin doses are low, and the dose at tumor depths is high. Penumbra and scatter to surrounding healthy tissue are low. ■ Varian Associates is currently producing three medical linear accelerator systems for delivery to U.S. hospitals.

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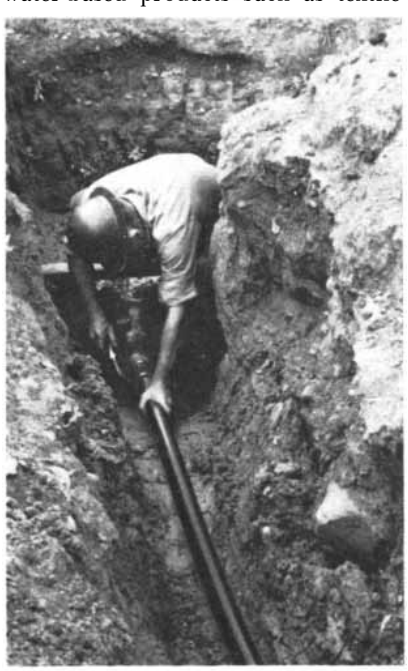
RADIATION DIVISION

News from Allied Chemical:

What's new in high polymers? What are the latest types? What methods are used to develop and modify these giant molecules so fascinating to contemporary chemists? Answers to such questions can be found in our new booklet, "High Polymers." In it you will read about polyethylene, for instance, an excellent example of polymer modification. First plastic to reach an output rate of a billion pounds a year, it is used in the familiar forms of packaging materials, squeeze bottles and unbreakable toys. Polymer research at Allied Chemical, by the way, has carried polyethylene far beyond these familiar uses. Our Plastics Division people have come up with an emulsifiable type to modify water-based products such as textile



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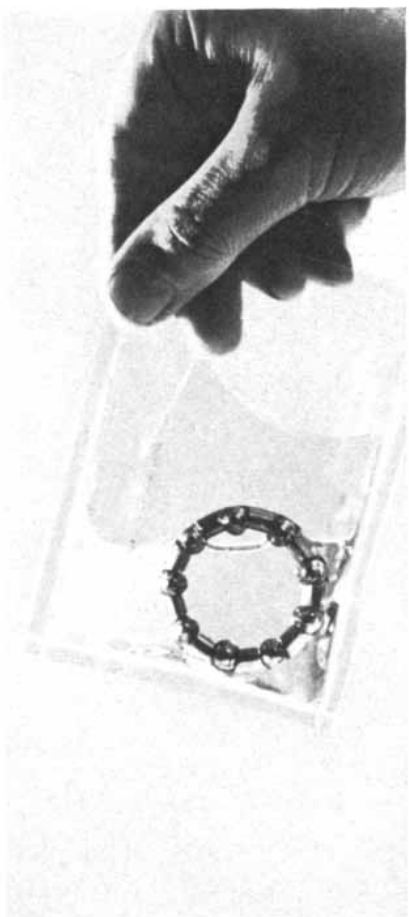

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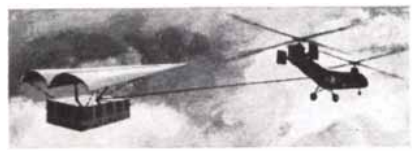

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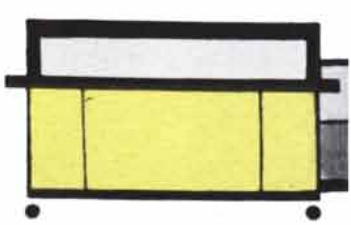

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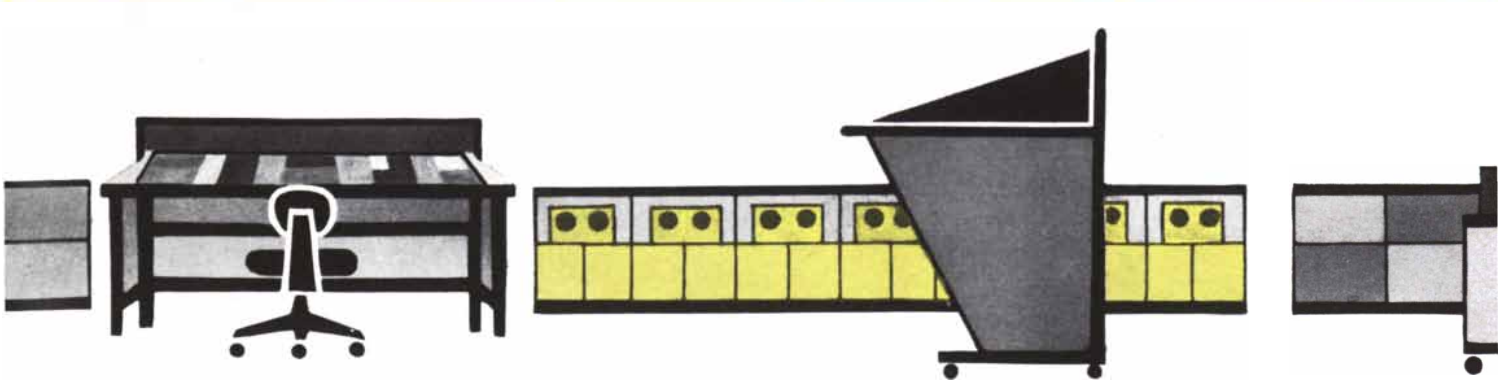

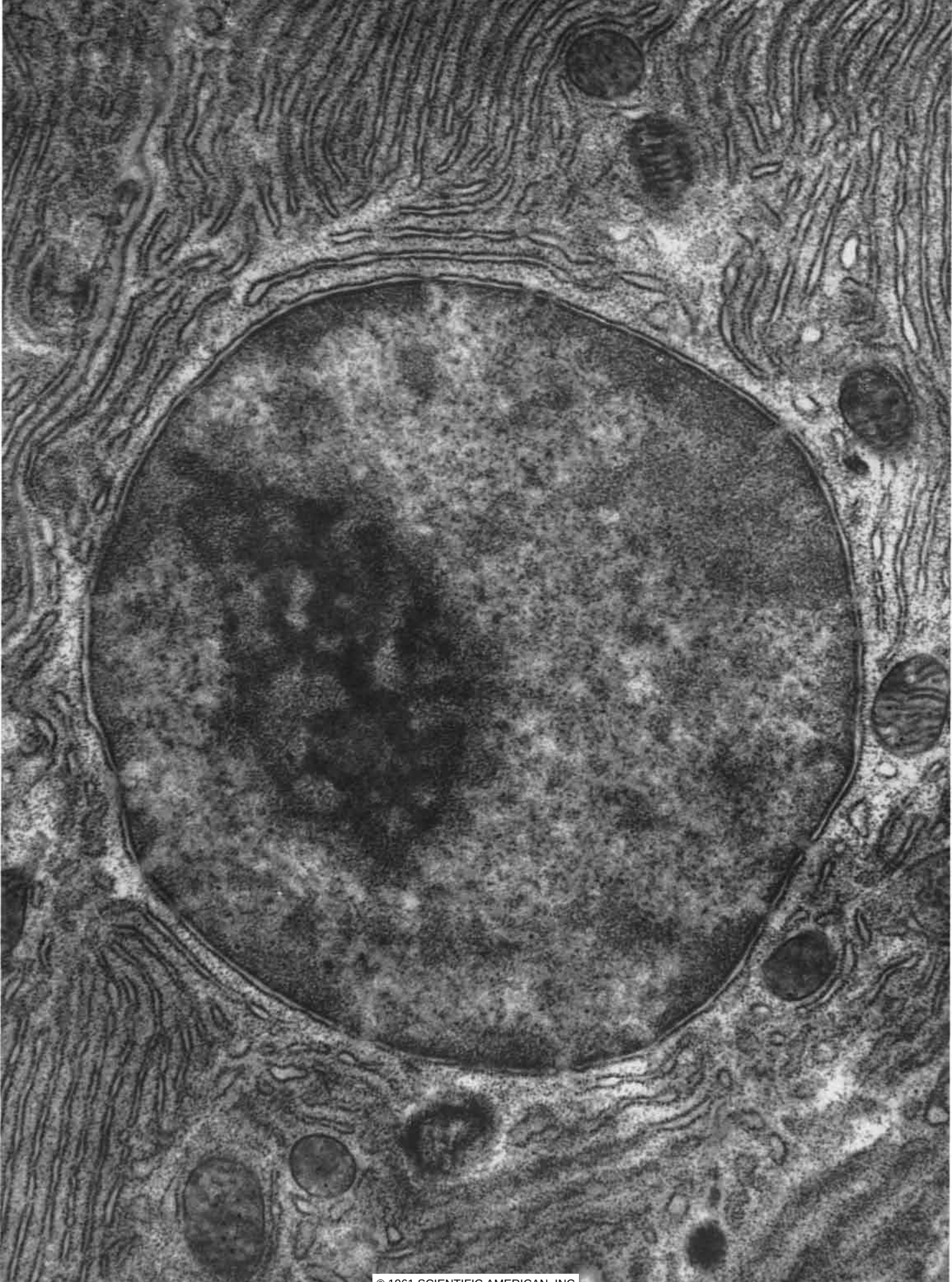

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The Living Cell

Presenting an issue on the fundamental particle of life. Anatomical and chemical views of the cell have now converged to show that it is not a droplet of protoplasm but a highly organized molecular factory

by Jean Brachet

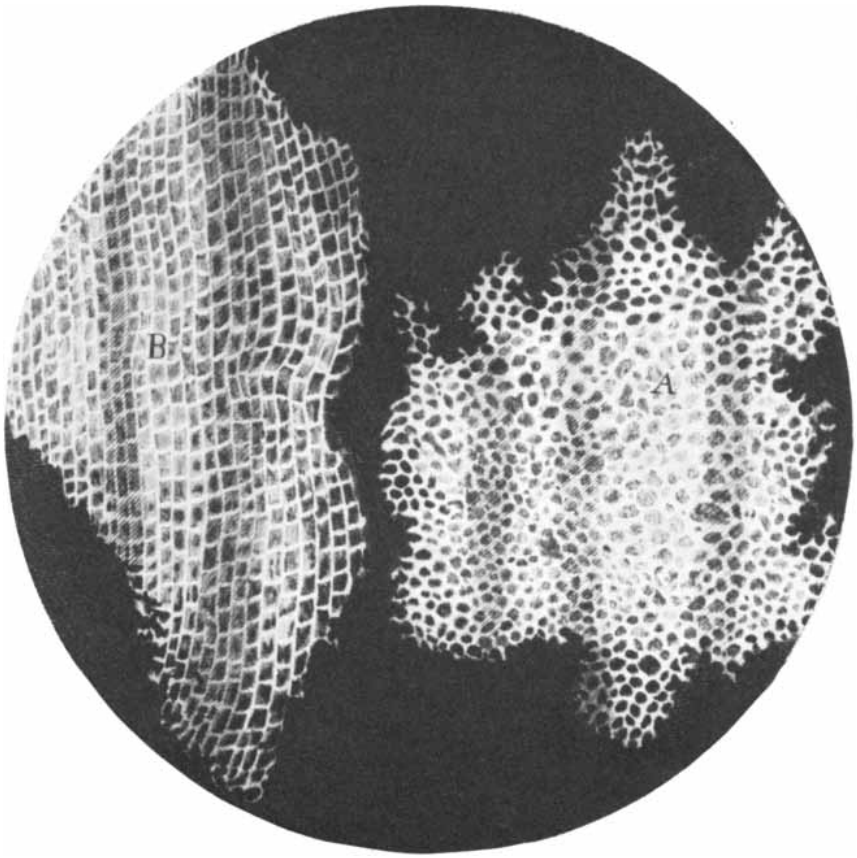
The living cell is the fundamental unit of which all living organisms are made. To a reader who finds this a commonplace, it may come as a surprise that the recognition of the cell dates back only a little more than 100 years. The botanist Matthias Jakob Schleiden and the zoologist Theodor Schwann first propounded the cell theory in 1839 out of their parallel and independent studies of the tissues of plants and animals. Not long after, in 1859, Rudolf Virchow confirmed the cell's unique role as the vessel of "living matter" when he showed that all cells necessarily derive from pre-existing cells: *omnis cellula e cellula*. Since cells are concrete objects and can easily be observed, the experimental investigation of cells thereafter displaced philosophical speculations about the problem of "life" and the uncertain scientific studies that had pursued such vague concepts as "protoplasm."

In the century that followed investigators of the cell approached their subject from two fundamentally different directions. Cell biologists, equipped with increasingly powerful microscopes, proceeded to develop the microscopic and submicroscopic anatomy of the intact cell. Beginning with a picture of the cell as a structure composed of an external membrane, a jelly-like blob of material called cytoplasm and a central nucleus, they have shown that this structure is richly differentiated into organelles adapted to carry on the diverse processes of life. With the aid of the electron microscope they have begun to discern the molecular working parts of the system. Here, in recent years, their work has converged with that of the biochemists, whose studies begin with the ruthless disruption of the delicate structure of the cell. By observing the chemical activity of materials collected in this way, biochemists have traced some of the pathways by which the cell carries out the biochemical reactions that underlie the processes of life, including those responsible for manufacturing the substance of the cell itself.

It is the present intersection of the two lines of study that provides the occasion for this issue of SCIENTIFIC AMERICAN, which is devoted to the living cell. The cell biologist now seeks to explain in molecular terms what he sees with the aid of his instruments; he has become a molecular biologist. The biochemist has become a biochemical cytologist, interested equally in the structure of the cell and in the biochemical activity in which it is engaged. As the reader will see, the mysteries of cell structure and function cannot be resolved by the exercise of either morphological or biochemical techniques alone. If the research is to be successful, the approach must be made from both sides at once. But the understanding of life phenomena that flows from investigation of the cell has already fully ratified the judgment of the 19th-century biologists who perceived that living matter is divided into cells, just as molecules are made of atoms.

A description of the functional anatomy of the living cell must begin with the statement that there is no such thing as a typical cell. Single-celled organisms of many different kinds abound, and the cells of brain and muscle tissue are as different in morphology as they are in function. But for all their variety they are cells, and so they all have a cell membrane, a cytoplasm containing various

NUCLEUS OF THE LIVING CELL is the large round object in the center of the electron micrograph on the opposite page. The membrane around the nucleus is interrupted by pores through which the nucleus possibly communicates with the surrounding cytoplasm. The smaller round objects in the cytoplasm are mitochondria; the long, thin structures are the endoplasmic reticulum; the dark dots lining the reticulum are ribosomes. Actually the micrograph shows not a living cell but a dead cell: the cell has been fixed with a compound of the heavy metal osmium, immersed in a liquid plastic that is then made to solidify and finally sliced with a glass knife. The electron beam of the microscope mainly detects the atoms of osmium, distributed according to the affinity of the fixing compound for various cell constituents. The micrograph was made by Don W. Fawcett of the Harvard Medical School. The enlargement is 28,400 diameters. The cell itself is from the pancreas of a bat.



DRAWING OF CELLS in cork was published by Robert Hooke in 1665. Hooke called them cells, but the fact that all organisms are made of cells was not recognized until 19th century.

PHOTOMICROGRAPH OF CELLS in the blood of a pigeon was made by J. J. Woodward, a U.S. Army surgeon, in 1871. Woodward had made the first cell photomicrograph in 1866.

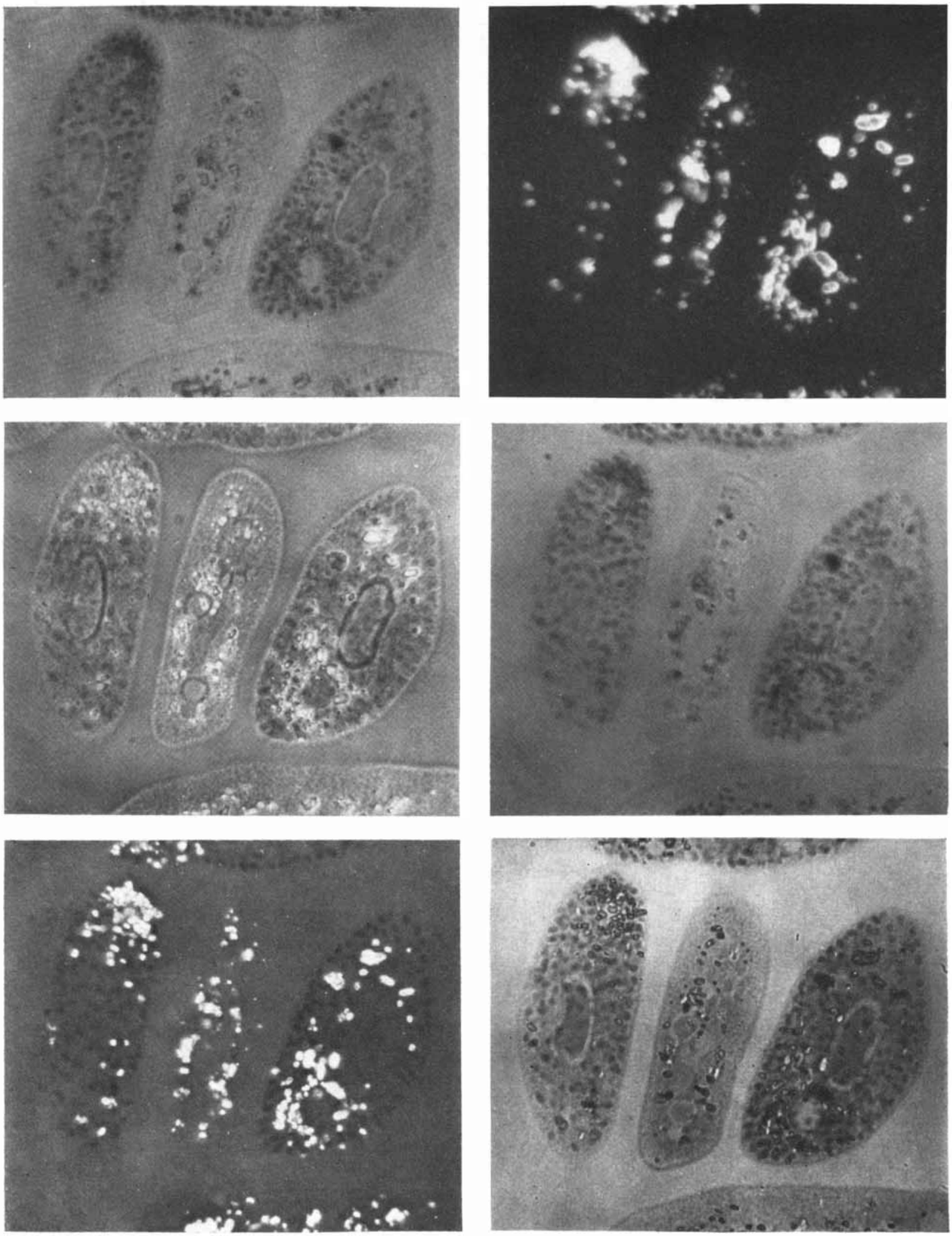
organelles and a central nucleus. In addition to having a definite structure, cells have a number of interesting functional capacities in common.

They are able, in the first place, to harness and transform energy, starting with the primary transformation by green-plant cells of the energy of sunlight into the energy of the chemical bond. Various specialized cells can convert chemical-bond energy into electrical and mechanical energy and even into visible light again. But the capacity to transform energy is essential in all cells for maintaining the constancy of their internal environment and the integrity of their structure [see "How Cells Transform Energy," page 62].

The interior of the cell is distinguished from the outer world by the presence of very large and highly complex molecules. In fact, whenever such molecules turn up in the nonliving environment, one can be sure they are the remnants of dead cells. On the primitive earth, life must have had its origin in the spontaneous synthesis of complicated macromolecules at the expense of smaller molecules. Under present-day conditions, the capacity to synthesize large molecules from simpler substances remains one of the supremely distinguishing capacities of cells.

Among these macromolecules are proteins. In addition to making up a major portion of the "solid" substance of cells, many proteins (enzymes) have catalytic properties; that is, they are capable of greatly accelerating the speed of chemical reactions inside the cell, particularly those involved in the transformation of energy. The synthesis of proteins from the simpler units of the 20-odd amino acids goes forward under the regulation of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), by far the most highly structured of all the macromolecules in the cell [see "How Cells Make Molecules," page 74]. In recent years and months investigators have shown that DNA, localized in the nucleus of the cell, presides at the synthesis of RNA, which is found in both the nucleus and the cytoplasm. The RNA in turn arranges the amino acids in proper sequence for linkage into protein chains. The DNA and the RNA may be compared to the architect and contractor who collaborate on the construction of a nice-looking house from a heap of bricks, stones and tiles.

At one or another stage of life every cell has divided: a mother cell has grown



VARIOUS KINDS OF LIGHT MICROSCOPY are used to photograph the same three paramecia. The photomicrograph at top left was made with a conventional light microscope and bright-field illumination; the one at top right, with dark-field illumination. The photomicrograph at middle left was made with a phase microscope at low contrast; the one at middle right, with a phase microscope at high contrast. The photomicrograph at bottom left was made with a polarized-light microscope; the one at bottom right, with an interference microscope of the AO-Baker type. The bright spots that appear in some of the photomicrographs are small crystals that are normally present in paramecia. All the micrographs were made by Oscar W. Richards of the American Optical Company.

and given rise to two daughter cells, according to the delicate process described by Daniel Mazia [see "How Cells Divide," page 100]. Before the turn of the century biologists had observed that the crucial event in this process was the equal division of bodies in the nucleus that accepted a certain colored dye and so were called chromosomes. It was correctly surmised that the chromosomes are the agents of heredity; in their precise self-replication and division they convey to the daughter cells all the capacities of the mother cell. Contemporary biochemistry has now shown that the principal constituent of the chromosomes is DNA, and an important aim of the molecular biologist today is to discover how the genetic information is encoded in the structure of this macromolecule.

The capacity for generative reproduction is not confined exclusively to the living cell. There are in the present world macromolecules called viruses that contain nucleic acids and proteins of great complexity and specificity. When they penetrate into suitable cells, they multiply just as cells do, but at the expense of the cell. They have a heredity, since they breed true when they replicate themselves, and they synthesize their own proteins. But, lacking the full anatomical endowment of the cell, they are unable to generate the energy required for their multiplication. Viruses are thus obligatory parasites of cells and take over the enzyme system of the infected cell in order to supply the energy they need. The cell must, however, furnish exactly the right complement of enzymes. This is why tobacco mosaic virus, for example, will not multiply in human cells and so is harmless to human beings.

Such single-celled organisms as bacteria, having the capacity to make their own enzymes and so to generate the energy required for their growth and multiplication, can live and multiply in a much simpler medium than that provided by the interior of a living cell. They are, therefore, not obligatory parasites. From the viewpoint of anatomy, however, bacteria are much simpler than cells, and the various bacteria are distributed over the range of complexity from the virus upward to the cell.

In addition to the capacity for energy transformation, biosynthesis and reproduction by self-replication and division, the cells of higher organisms possess other capacities that fit them for the concerted community life that is the life of the organism. From the single-celled fertilized egg the multicelled organism arises not only by the division of the daughter cells but also by their concurrent differentiation into the specialized cells that form various tissues. In many cases when a cell has become differentiated and specialized, it does not divide any more; there is a kind of antagonism between differentiation and growth by cell division.

In the adult organism the capacity for reproduction and perpetuation of the species is left to the eggs and spermatozoa. These gametes, like all other cells in the body, have arisen by cell division from the fertilized egg, followed by differentiation. Cell division remains, however, a frequent event in the adult organism wherever cells continuously wear out and degenerate, as they do in the skin, the intestine and in the bone marrow from which the blood cells arise.

During embryonic development the differentiating cells display a capacity for recognition of others of their own kind. Cells that belong to the same family and resemble one another tend to cluster together, forming a tissue from which cells of all other kinds are excluded. In this mutual association and rejection of cells the cell membrane appears to play a decisive role. The membrane is also one of the principal cell components involved in the function of the muscle cells that endow the organism with the power of movement, of the nerve cells that provide communication lines to integrate the activity of the organism and of the sensory cells that receive stimuli from without and within.

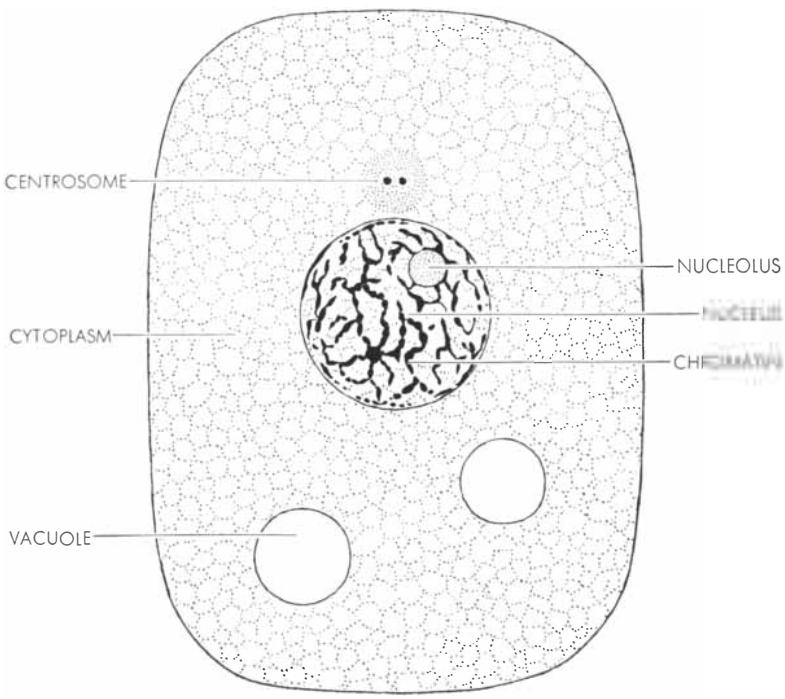
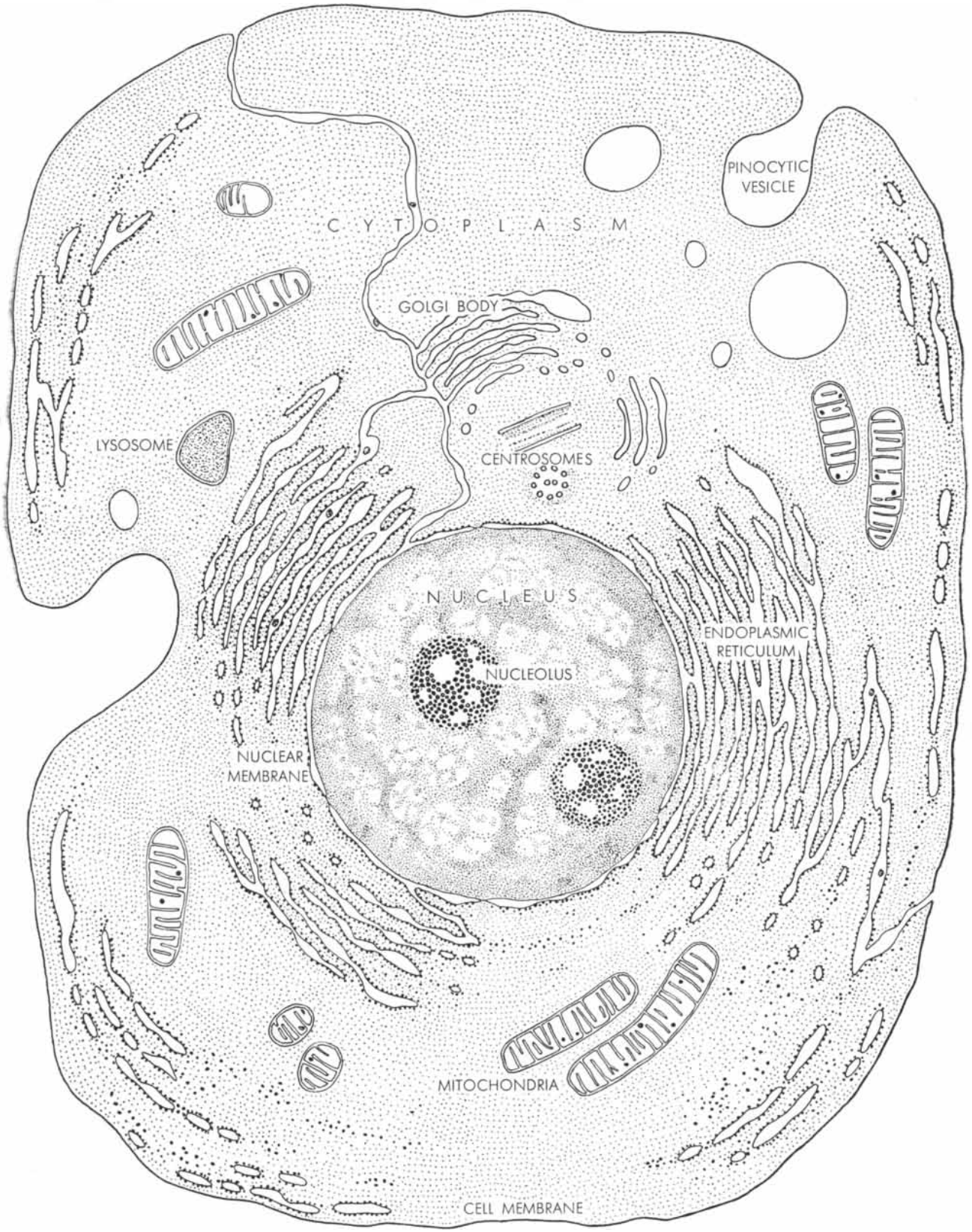


DIAGRAM OF A TYPICAL CELL (although there is no such thing as a typical cell) is based on what is seen in the conventional light microscope. Diagram is based on one that appears in 1922 edition of Edmund B. Wilson's *The Cell in Development and Inheritance.*

Although there is no typical cell, one may usefully put together a composite cell for the purpose of charting the anatomical features that are shared in varying degrees by all cells. Such a cell, based largely upon what is seen in electron micrographs, is presented on the opposite page; comparison of this cell with the corresponding cell drawn from photomicrographs made by Edmund B. Wilson of Columbia University in 1922 suggests the rapid advances that have been brought about by the electron microscope.

Even the cell membrane, which is only 100 angstrom units thick (one angstrom unit is one ten-millionth of a millimeter) and appears as little more than a boundary in the light microscope, is shown by the electron microscope to have a structure. It is true that electron micrographs have not yet revealed much



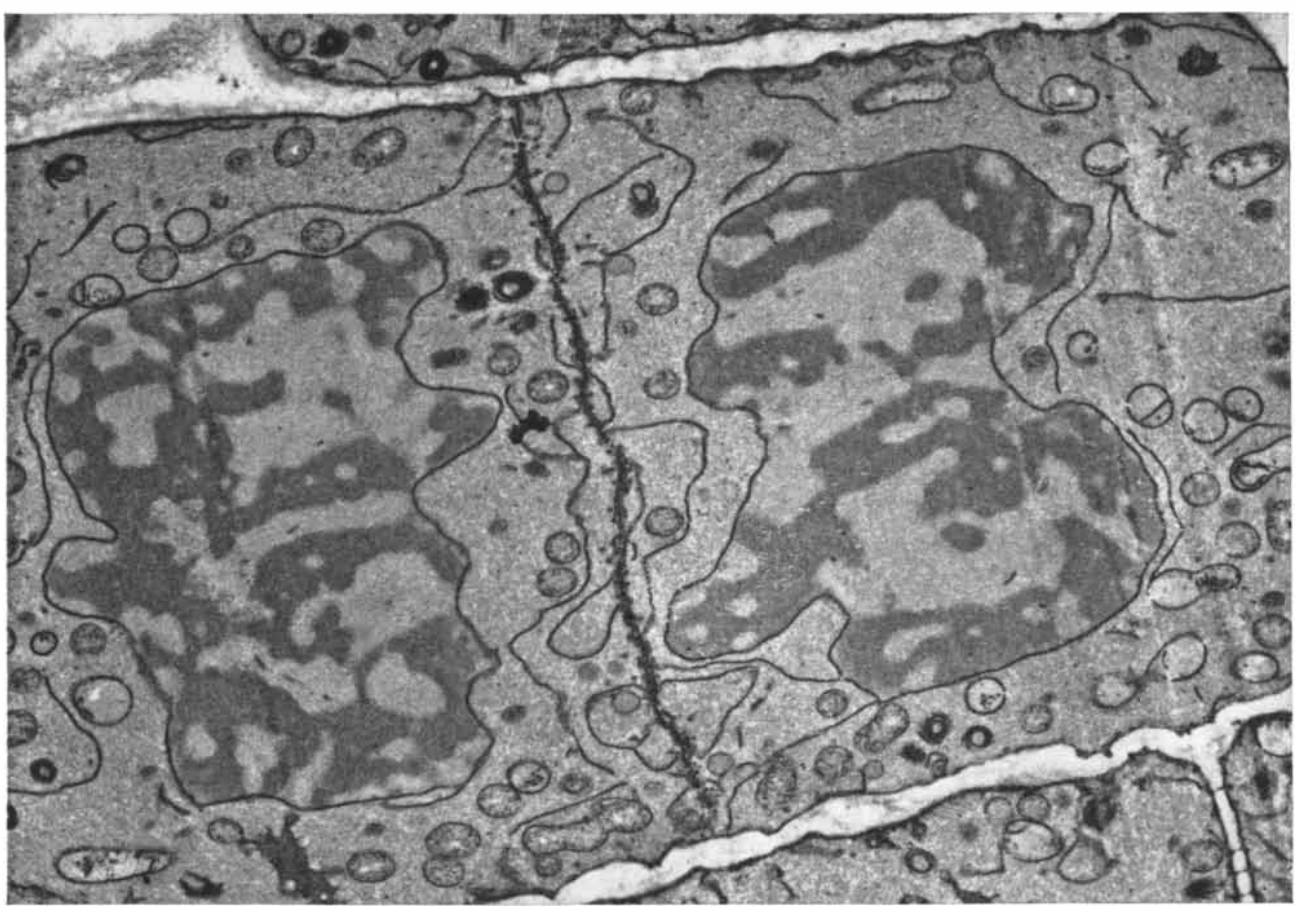
MODERN DIAGRAM OF A TYPICAL CELL is based on what is seen in electron micrographs such as the one reproduced on page 50. The mitochondria are the sites of the oxidative reactions that provide the cell with energy. The dots that line the endoplasmic reticulum are ribosomes: the sites of protein synthesis. In cell division the pair of centrosomes, one shown in longitudinal section (*rods*), other in cross section (*circles*), part to form poles of apparatus that separates two duplicate sets of chromosomes.

about this structure. On the other hand, such complexity as is shown clearly accords with what is known about the functional properties of the membrane. In red blood cells and nerve cells, for example, the membrane distinguishes between sodium and potassium ions although these ions are alike in size and electrical charge. The membrane helps potassium ions get into the cell and opposes more than a mere permeability barrier to sodium ions; that is, it is capable of "active transport." The membrane also brings large molecules and macroscopic bodies into the interior of the cell by mechanical ingestion [see "How Things Get into Cells," page 167].

Beyond the membrane, in the cytoplasm, the electron microscope has resolved the fine structure of organelles that appear as mere granules in the light microscope. Principal among them are the chloroplasts of green-plant cells and the mitochondria that appear in both animal and plant cells. These are the "power plants" of all life on earth. Each is adapted to its function by an appropriate fine structure, the former to capturing the energy of sunlight by photosynthesis, the latter to extracting energy from the chemical bonds in the nutrients of the cell by oxidation and respiration. From each of these power plants the yield of energy is made available to the energy-consuming processes of the cell, neatly packaged in the phosphate bonds of the compound adenosine triphosphate (ATP).

The electron microscope clearly distinguishes between the mitochondrion, with its highly organized fine structure, and another associated body of about the same size: the lysosome. As Christian de Duve of the Catholic University of Louvain has shown, the lysosome contains the digestive enzymes that break down large molecules, such as those of fats, proteins and nucleic acids, into smaller constituents that can be oxidized by the oxidative enzymes of the mitochondria. De Duve postulates that the lysosome represents a defense mechanism; the lysosomal membrane isolates the digestive enzymes from the rest of the cytoplasm. Rupture of the membrane and release of the accumulated enzymes lead quickly to the lysis (dissolution) of the cell.

The cytoplasm contains many other visible inclusions of less widespread occurrence among cells. Particularly interesting are the centrosomes and kinetosomes. The centrosomes, or centrioles, become plainly visible under the light microscope only when the cell approaches the hour of division, in which these bodies play a commanding role as the poles of the spindle apparatus that divides the chromosomes. The kinetosomes, on the other hand, are found only in those cells which are equipped with cilia or flagella for motility; at the base of each cilium or flagellum appears a kinetosome. Both of these organelles have the special property of self-replication. Each pair of centrosomes gives rise to another when cells divide; a kinetosome duplicates itself each time a new cilium forms on the cell surface. Long ago certain cytologists advanced the idea that these two organelles have much the same structure, even though their functions are so different. The electron



PLANT CELLS (onion root tip) are enlarged 6,700 diameters in this electron micrograph made by K. R. Porter of the Rockefeller Institute. The thin, dark line running from top to bottom of the micrograph shows the membrane between two cells shortly after the cells have divided. The large, irregularly shaped bodies to the left and right of the membrane are the nuclei of the two cells.

microscope has confirmed this suggestion. Each is a cylinder made up of 11 fibers, with two in the center and the other nine on the outside. This is the universal structure of all cilia and of flagella as well. The reason for the structure remains unknown, but it is undoubtedly related to the contractility of the cilia and flagella. It may be that the same "monomolecular muscle" principle underlies the action of the kinetosome and centrosome in their quite diverse functions.

The electron microscope has confirmed another surmise of earlier cytologists: that the cytoplasm has an invisible organization, a "cytoskeleton." Most cells show complicated systems of internal membranes not visible in the ordinary light microscope. Some of these membranes are smooth; others are rough, having tiny granules attached to one surface. The degree to which the membrane systems are developed varies from cell to cell, being rather simple in amoebae and highly articulated and roughened with granules in cells that specialize in the production of proteins, such as those of the liver and pancreas.

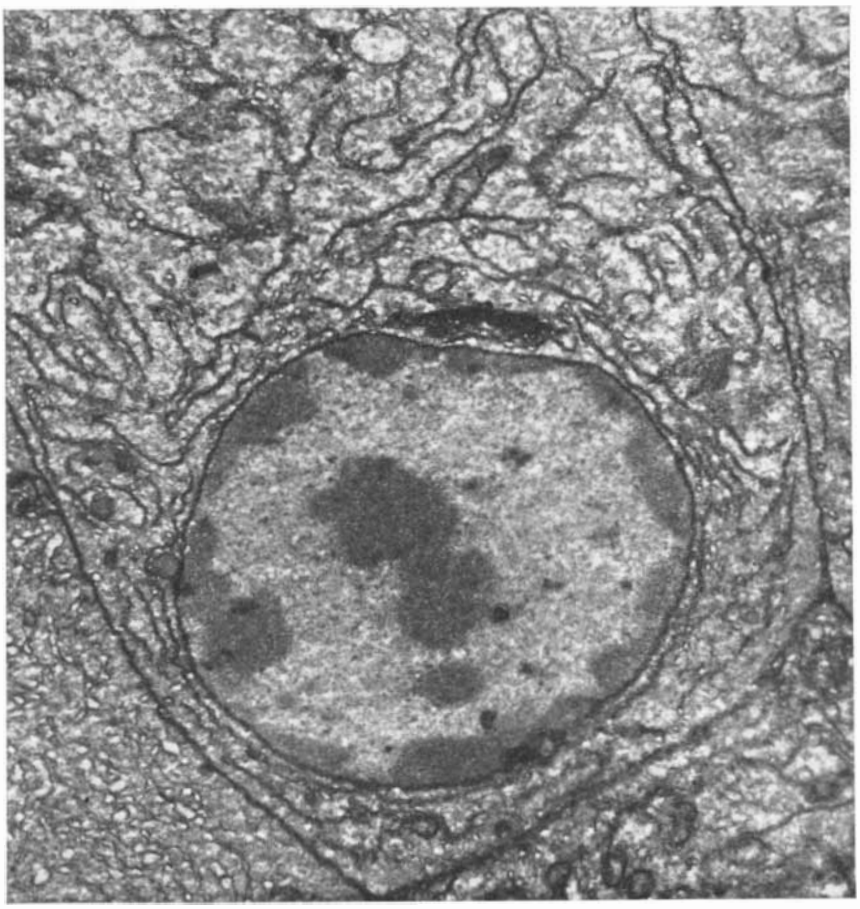
Electron microscopists differ in their interpretation of these images. The generally accepted view is that of K. R. Porter of the Rockefeller Institute, who has given the membrane system its name, the endoplasmic reticulum; through the network of canaliculi formed by the membrane, substances are supposed to move from the outer membrane of the cell to the membrane of the nucleus. Some investigators hold that the internal membrane is continuous with the external membrane, furnishing a vastly increased and deeply invaginated surface area for communication with the fluid in which the cell is bathed. If the membrane does indeed have such vital functions, then it is likely that the cell is equipped with a factory for the continuous production of new membrane. This might be the role, as George E. Palade of the Rockefeller Institute has recently suggested, of the enigmatic Golgi bodies, first noted by the Italian cytologist Camillo Golgi at the end of the last century. The electron microscope reveals that the Golgi bodies are made of smooth membrane, often continuous with that of the endoplasmic reticulum.

There is no doubt about the nature of the granules, which appear consistently on the "inner" surface of the membrane. They appear particularly in cells that produce large amounts of protein. As Torbjörn O. Caspersson and I showed some 20 years ago, such cells possess a high RNA content. Recent studies have revealed that the granules are exceedingly rich in RNA and correspondingly active in protein synthesis. For this reason the granules are now called ribosomes.

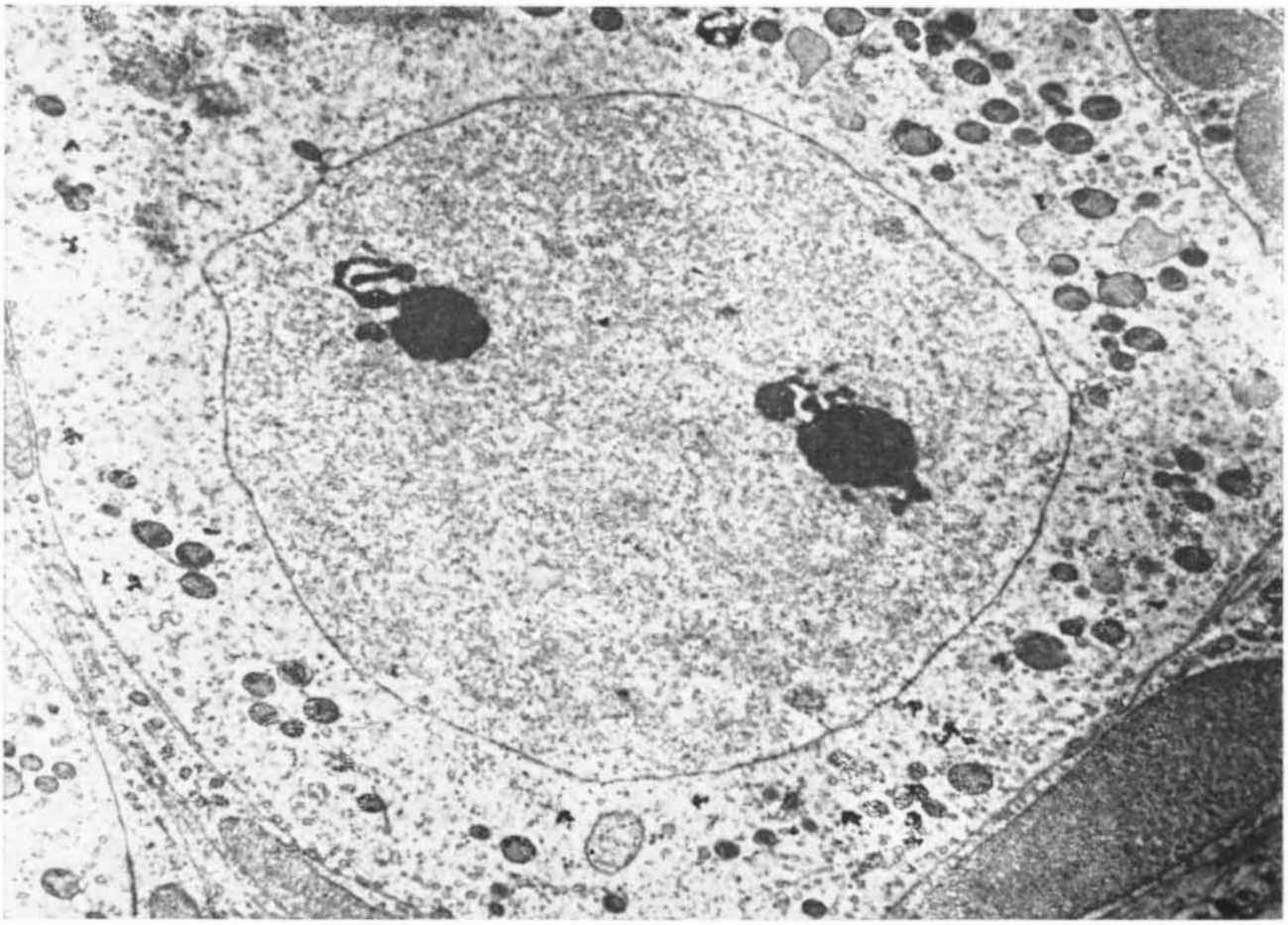
The membrane that surrounds the cell nucleus forms the interior boundary of the cytoplasm. There is still much speculation about what the electron microscope shows of this membrane. It appears as a double membrane with annuli, or holes, in the outer layer, open to the cytoplasm. To some investigators these annuli represent pores through which large molecules may move in either direction. Since the outer layer is often in close contact with the endoplasmic reticulum, it is also argued that the nuclear membrane participates in the formation of the reticulum membrane. Another possibility is that fluids percolating through the canaliculi of the endoplasmic reticulum are allowed to accumulate between the two layers of nuclear membrane.

Inside the nucleus are the all-important filaments of chromatin, in which the cell's complement of DNA is entirely localized. When the cell is in the "resting" state, that is, engaged in the processes of growth between divisions, the chromatin is diffusely distributed in the nucleus. The DNA thus makes maximum surface contact with other material in the nucleus from which it presumably pieces together the molecules of RNA and replicates itself. In preparation for division the chromatin coils up tightly to form the chromosomes, always a fixed number in each cell, to be distributed equally to each daughter cell.

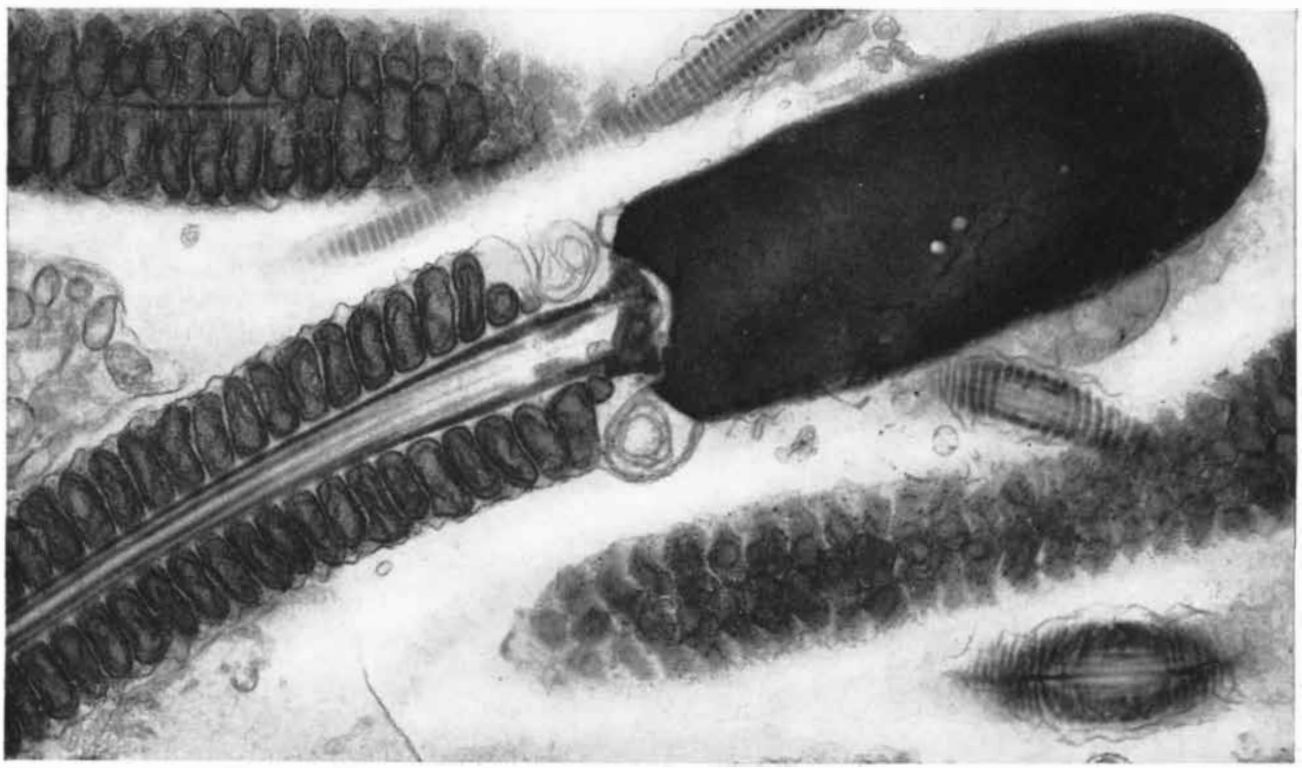
Much less elusive than the chromatin are the nucleoli; these spherical bodies are easily resolved inside the nucleus with an ordinary light microscope. Under the electron microscope they are seen to be packed with tiny granules similar to the ribosomes of the cytoplasm. In fact, the nucleoli are rich in RNA and appear to be active centers of protein and RNA synthesis. Finally, to complete this functional anatomy of the



ANIMAL CELL (hepato-pancreatic gland of the crayfish) is enlarged 12,500 diameters in electron micrograph by George B. Chapman of the Cornell University Medical College. The large round object is the nucleus; the smaller dark region just above it is the Golgi body.



EGG CELL of rabbit is enlarged 7,500 diameters. The large round object is the nucleus; the two prominent dark bodies within it are nucleoli. Electron micrograph was made by Joan Blanchette of Columbia University College of Physicians and Surgeons.



SPERM CELL of a bat is enlarged 21,500 diameters in electron micrograph by Fawcett and Susumu Ito of the Harvard Medical School. Nucleus (*top right*) constitutes almost all of sperm's head; arranged behind head are numerous mitochondria (*left*).

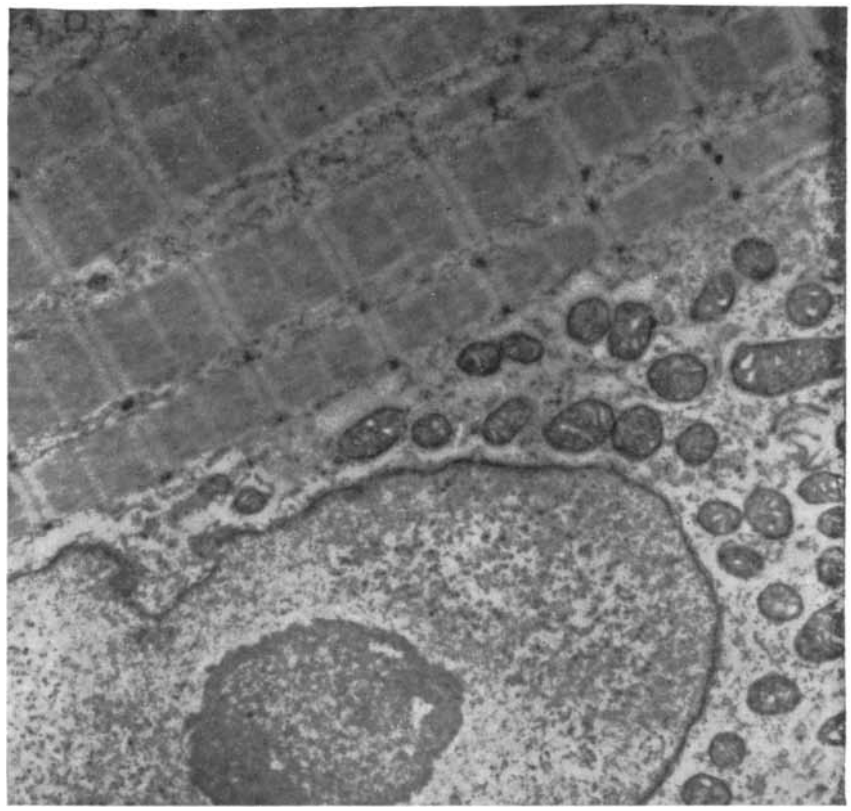
cell, it should be added that the chromatin and nucleoli are bathed together in the amorphous, proteinaceous matrix of the nuclear sap.

A remarkable history in the development of instruments and technique has gone into the drawing of the present portrait of the cell. The ordinary light microscope remains an essential tool. But its use in exploring the interior of the cell usually requires killing the cell and staining it with various dyes that selectively show the cell's major structures [*see the cover of this issue*]. To see these structures in action in the living cell, microscopists have developed a range of instruments—including phase, interference, polarizing and fluorescence microscopes—that manipulate light in various ways. In recent years the electron microscope, as the reader has gathered from this article, has become the major tool of the cytologist. But this instrument has a serious limitation in that it requires elaborate preparation and fixation of the specimen, which must inevitably confuse the true picture with distortions and artifacts. Progress is being made, however, toward the goal of resolving under the same high magnification the structure of the living cell.

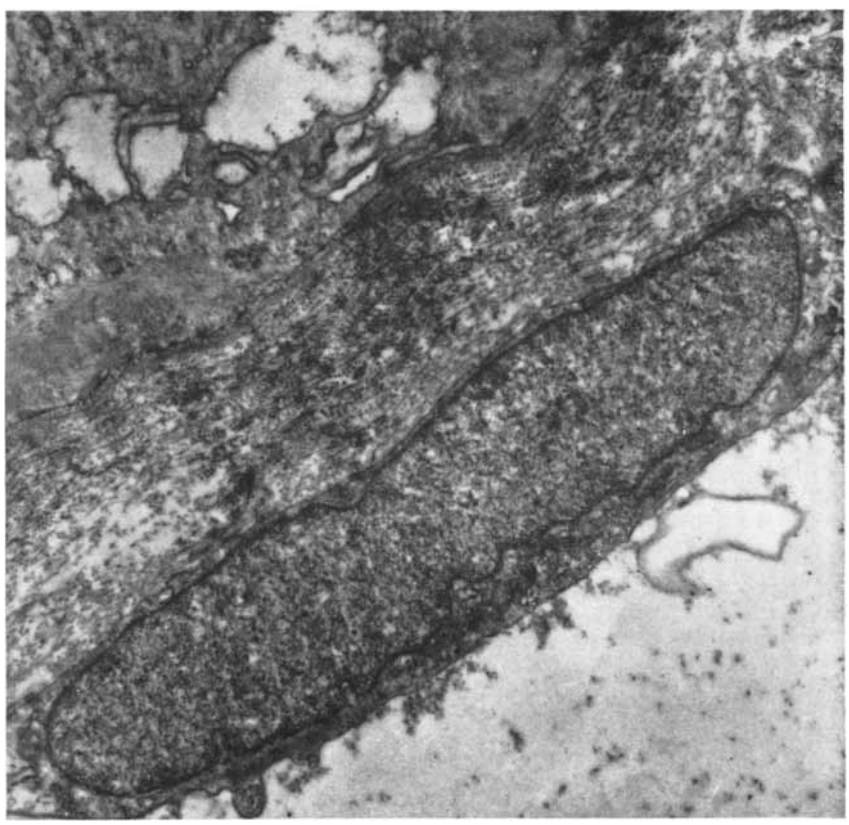
Biochemistry has had an equally remarkable history of technical development. Centrifuges of ever higher rotation speed have made it possible to separate finer fractions of the cell's contents. These are divided and subdivided in turn by chromatography and electrophoresis. The classical techniques have been variously adapted to the analysis of quantities and volumes 1,000 times smaller than the standard of older micromethods; investigators can now measure the respiration or the enzyme content of a few amoebae or sea-urchin eggs. Finally, autoradiography, employing radioactive tracer elements, allows the worker to observe at subcellular dimensions the dynamic processes in the intact living cell.

The achievements and prospects that have been generated by the convergence of these two major movements in the life sciences furnish the subject of the articles that follow. To conclude this discussion it will be useful to consider how the two approaches have been employed to illuminate a single question: the role of the nucleus in the economy of the cell.

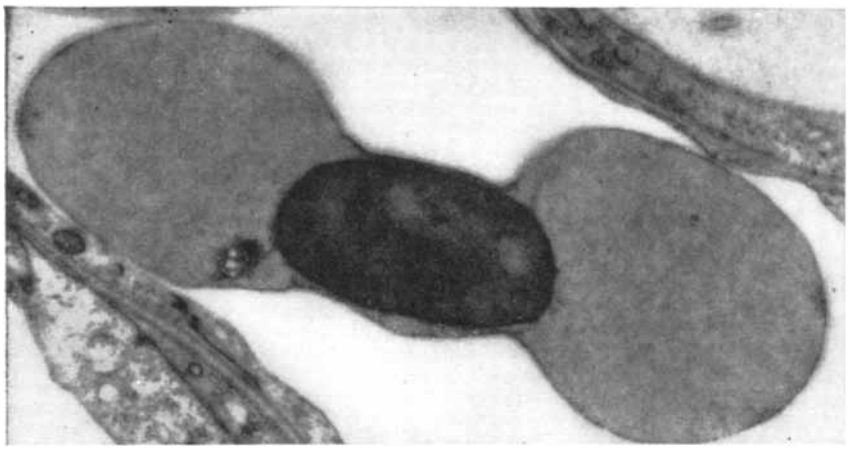
A simple experiment shows, first of all, that removal of the nucleus in a unicellular organism does not bring about the immediate death of the cytoplasm. The nucleate and enucleate



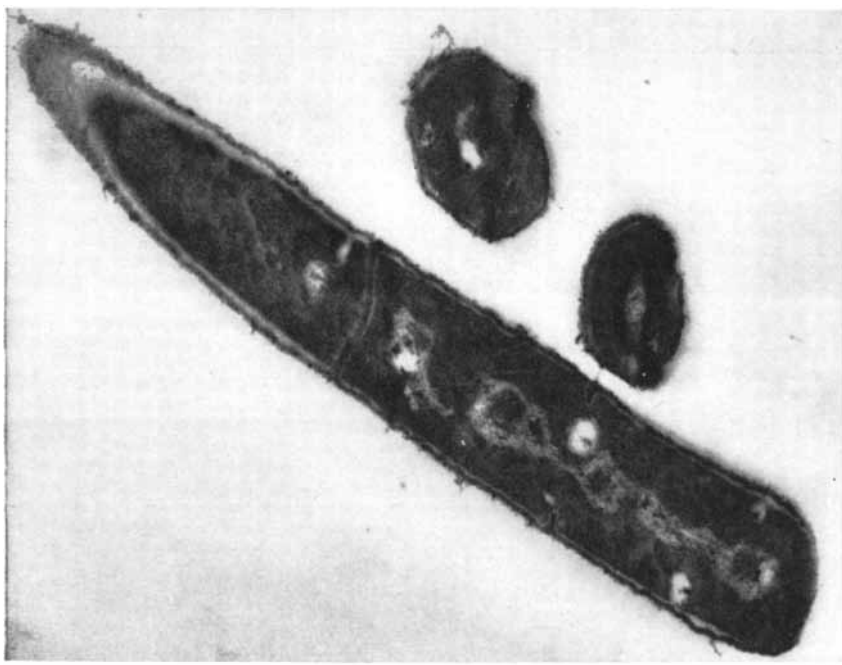
PART OF MUSCLE CELL of a salamander is enlarged 19,500 diameters in electron micrograph by George D. Pappas and Philip W. Brandt of Columbia College of Physicians and Surgeons. The nucleus is at bottom; around it are mitochondria. At top are muscle fibers.



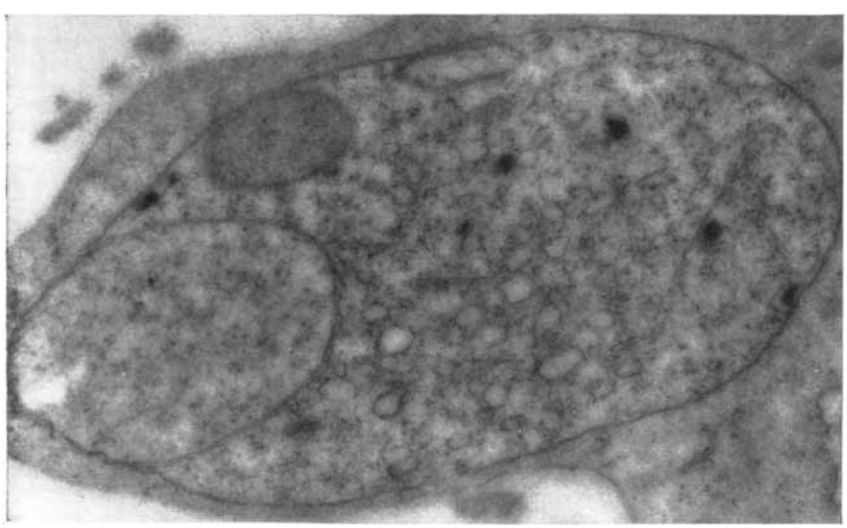
PART OF CONNECTIVE-TISSUE CELL of a tadpole is enlarged 14,500 diameters in electron micrograph by Chapman. Nucleus is oblong object; above it are fibrils of collagen.



RED BLOOD CELL of a fish is enlarged 8,000 diameters in electron micrograph by Fawcett. Large dark body in center is nucleus. The mature red cells of mammals have no nuclei.



BACTERIUM *Bacillus cereus* (*long object*) is enlarged 30,000 diameters in electron micrograph by Chapman and by James Hillier of RCA Laboratories. Bacillus has several nuclei.

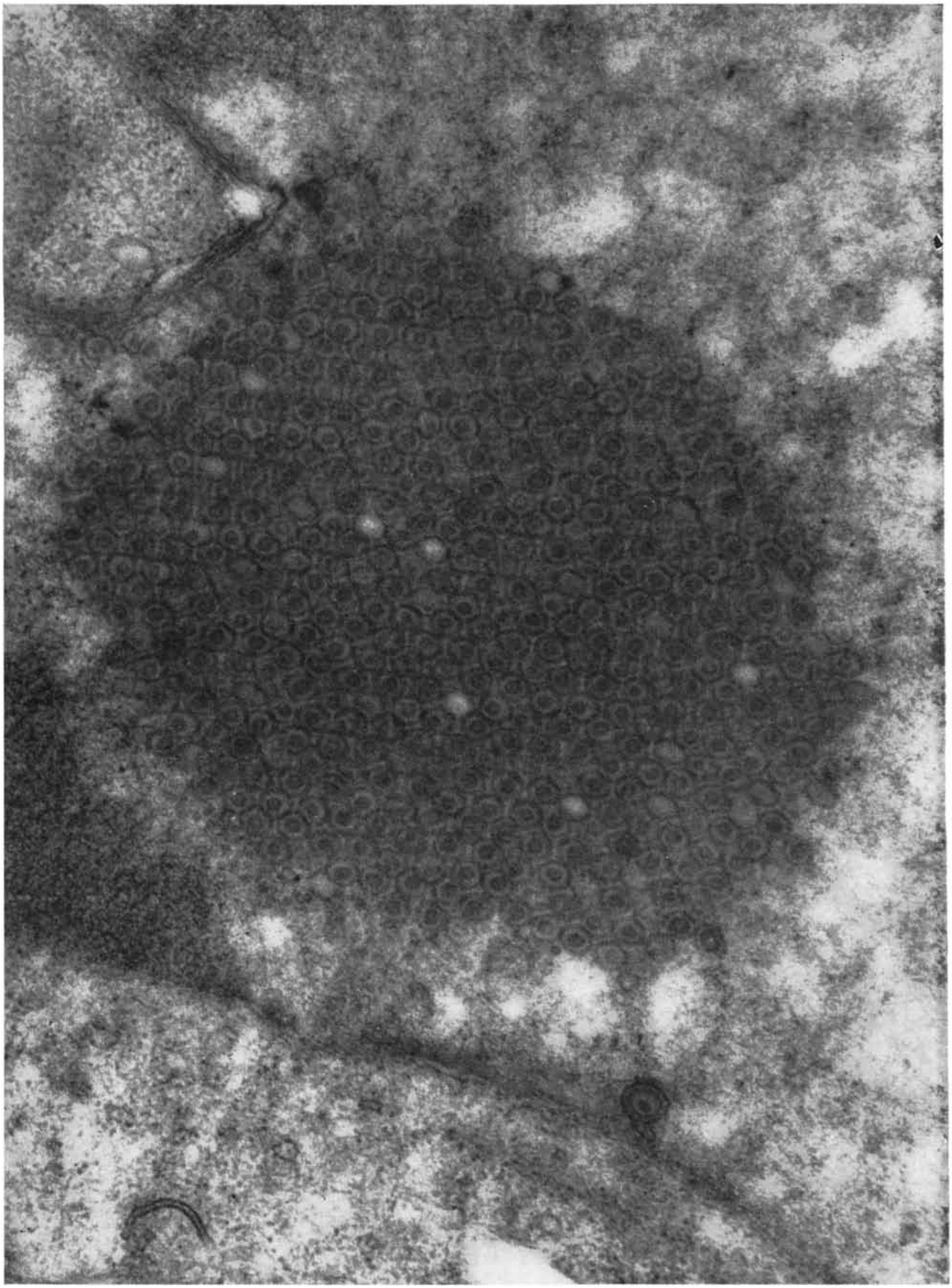


PROTOZOON *Plasmodium berghei* is enlarged 21,000 diameters in electron micrograph by Maria A. Rudzinska of the Rockefeller Institute. The nucleus is the large body at lower left.

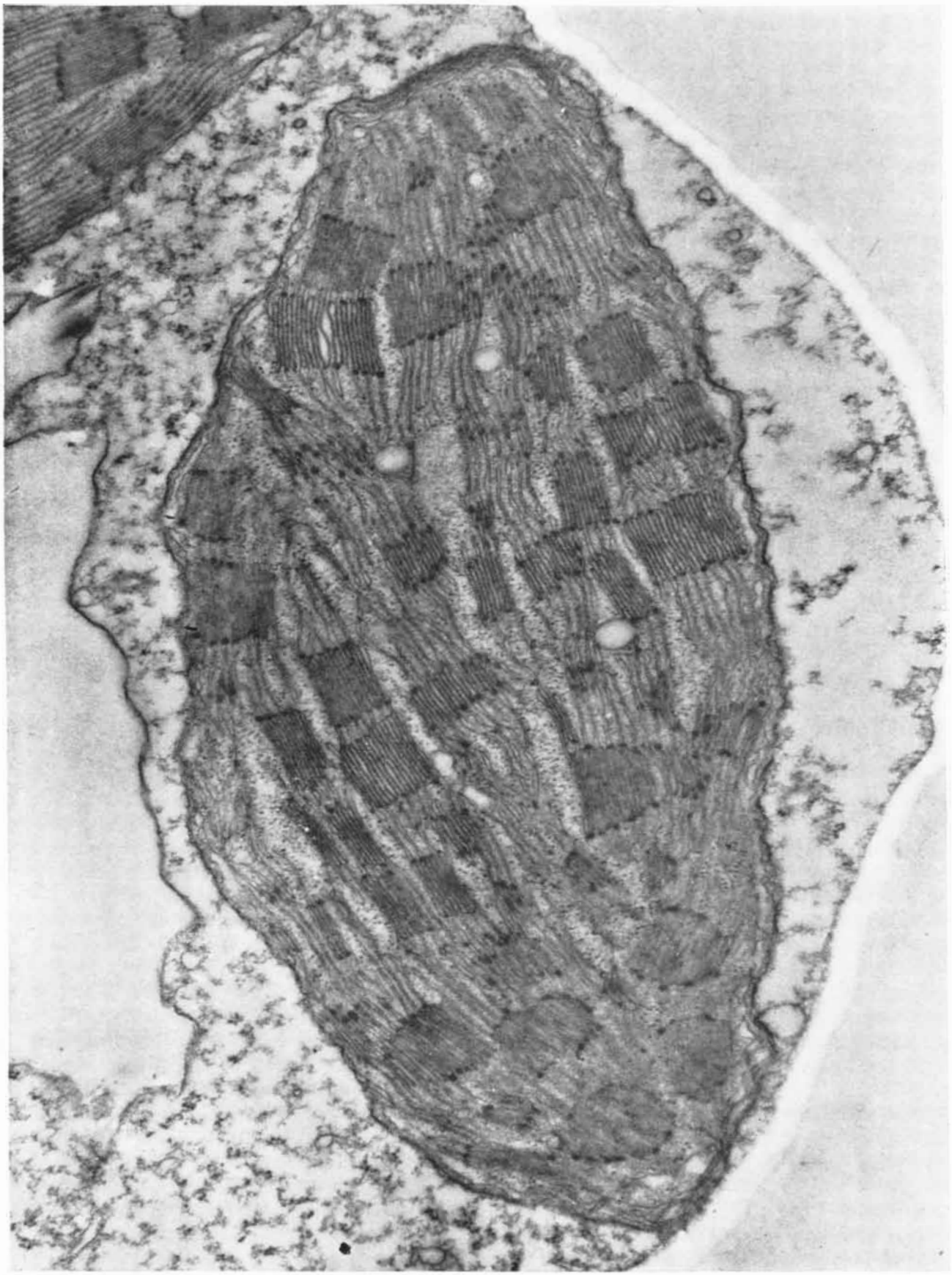
halves of amoebae, if kept fasting, attain the same survival time of about two weeks; the cilia of an enucleate protozoon such as the paramecium continue to beat for a few days; the enucleate fragments of the unicellular giant alga *Acetabularia* may survive several months and are even capable of an appreciable amount of regeneration. Many of the basic activities of the cell, including growth and differentiation in the case of *Acetabularia*, can therefore proceed in the total absence of the genes and DNA. In fact, the enucleate pieces of *Acetabularia* are perfectly capable of making proteins, including specific enzymes, although enzyme synthesis is known to be genetically controlled. These synthetic activities, however, die out after a time. One must conclude that the nucleus produces something that is not DNA but which is formed under the influence of DNA and is transferred from the nucleus to the cytoplasm, where it is slowly used up. From such experiments—employing the combined techniques of cell biology and biochemistry—a number of fundamental conclusions emerge.

First, the nucleus is to be considered as the main center for the synthesis of nucleic acid (both DNA and RNA). Second, this nuclear RNA (or part thereof) goes over to the cytoplasm, playing the role of a messenger and transferring genetic information from DNA to the cytoplasm. Finally, the experiments show that the cytoplasm and in particular the ribosomes are the main site for the synthesis of specific proteins such as the enzymes. It should be added that the possibility of independent RNA synthesis in the cytoplasm is not ruled out and that such synthesis can, under suitable conditions, be demonstrated in enucleate fragments of *Acetabularia*. From this brief description of recently observed facts it is clear that the cell is not only a morphological but also a physiological unit.

Perhaps the reader will wonder how such knowledge of this unit helps to answer questions under the more general headings of "life" and "living." All one can venture to say is that the results of investigation invariably point in the same direction: Life, in the case of the cell and its constituents, is more a quantitative than an "all or none" concept. This dissection of cells into their constituents does not, therefore, throw much light on the questions posed by philosophy. But without this dissection, without experimentation, we would know next to nothing about the cell. And, after all, the cell is the fundamental unit of life.



PARTICLES OF VIRUS *Herpes simplex* form a crystal within the nucleus of a cell. This electron micrograph, which enlarges the particles 73,000 diameters, was made by Councilman Morgan of the Columbia College of Physicians and Surgeons. Although viruses are exceptions to the rule that all living things are cells or are made of cells, they can reproduce only when they are inside cells.



CHLOROPLAST is the site of photosynthesis, whereby light energy is transformed into chemical energy to prime the life cycle of plants and animals. A chloroplast in a maize cell is enlarged 40,000 diameters in this electron micrograph made by A. E. Vatter of Abbott Laboratories. The "light" reactions involving chlorophyll and solar energy take place within the rectangular "grana."

How Cells Transform Energy

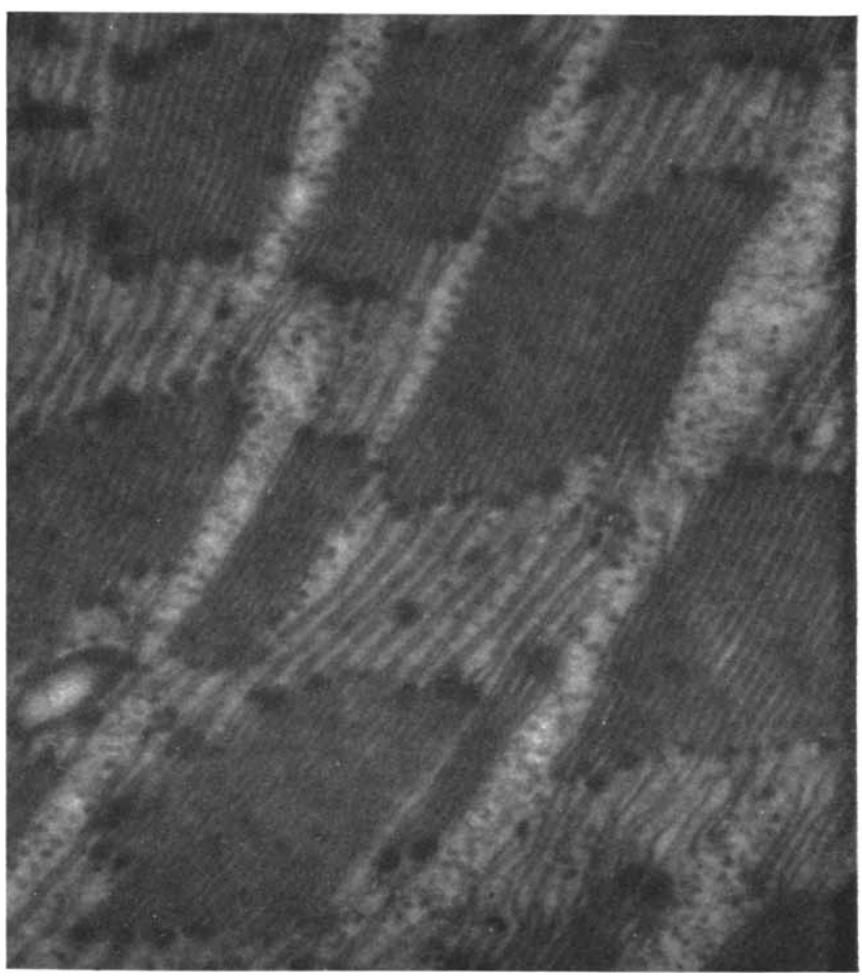
In the chloroplasts of plant cells the energy of sunlight is transformed into chemical fuels. In the mitochondria of animal cells these fuels are oxidized to run the cellular machinery

by Albert L. Lehninger

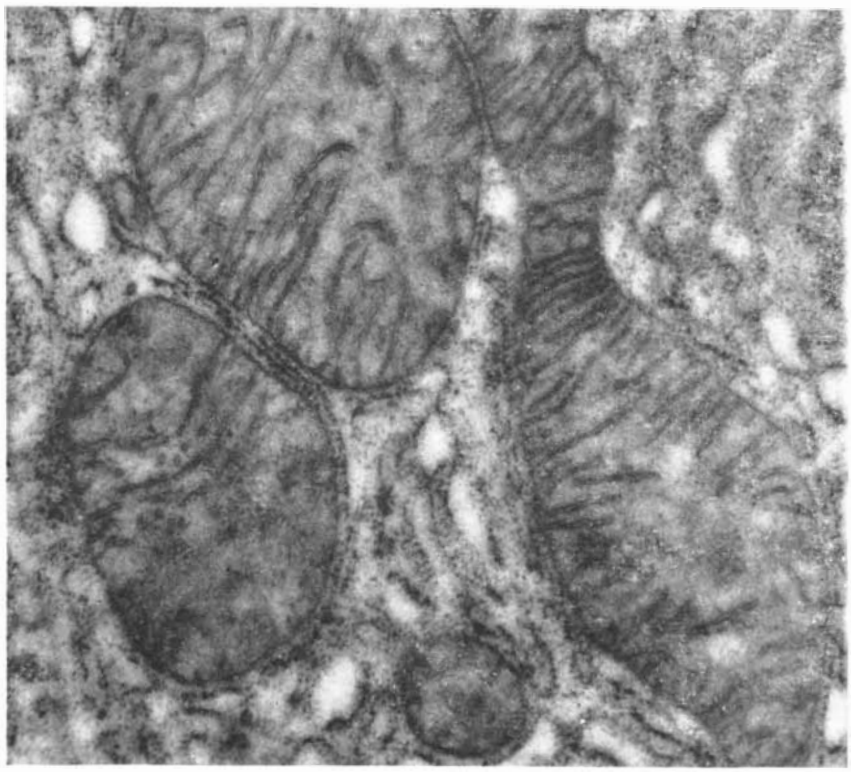
A living cell is inherently an unstable and improbable organization; it maintains the beautifully complex and specific orderliness of its fragile structure only by the constant use of energy. When the supply of energy is cut off, the complex structure of the cell tends to degrade to a random and disorganized state. In addition to the chemical work required to preserve the integrity of their organization, different kinds of cell transform energy to do the varieties of mechanical, electrical, chemical and osmotic work that constitute the life processes of organisms.

As man has learned in recent times to use energy from inanimate sources to do his work, he has begun to comprehend the virtuosity and efficiency with which the cell manages the transformation of energy. The same laws of thermodynamics that govern the behavior of inanimate substances also govern the energy transactions of the living cell. The first law of thermodynamics says that the sum of mass and energy in any physical change always remains constant. The second law states that there are two forms of energy: "free," or useful, energy; and entropy, or useless or degraded energy. It states furthermore that in any physical change the tendency is for the free energy to decline and the entropy to increase. Living cells must have a supply of free energy.

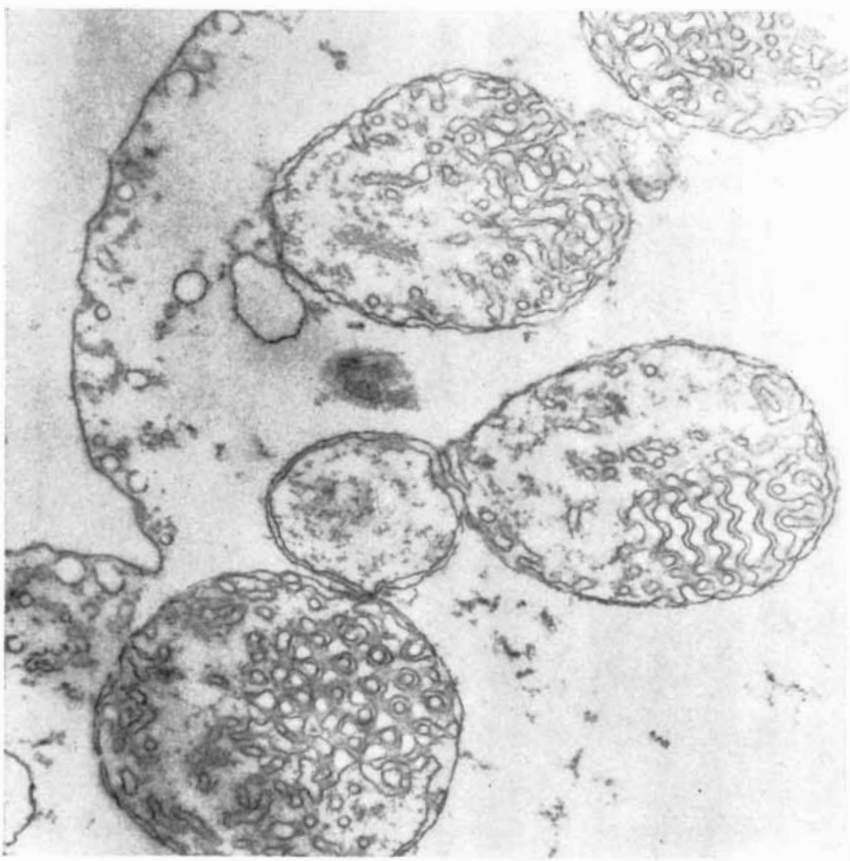
The engineer gets most of the energy he employs from the chemical bonds in fuel. By burning the fuel he degrades the energy locked in those bonds to heat; he can then use the heat to make steam and drive a turbogenerator to produce electricity. Cells also extract free energy from the chemical bonds in fuels. The energy is stored in those bonds by the cells that manufacture the foodstuffs that serve as fuel. The cell makes use of this energy, however, in a very special way. Since the living cell functions at an essentially constant temperature, it cannot use heat energy to do work. Heat energy can do work only if it passes from one body to another body that has a lower temperature. The cell obviously cannot burn its fuel at the 900-degree-centigrade combustion temperature of coal, nor can it tolerate superheated steam or high voltage. It must therefore obtain energy and use it at a fairly constant and low temperature, in a dilute aqueous environment and within a narrow range of con-



GRANA are enlarged 90,000 times in this electron micrograph by Vatter. They resemble stacks of coins in which chlorophyll is sandwiched between layers of protein and lipid. The lighter material around the grana is the stroma, in which the "dark" reactions take place.



MITOCHONDRION is the site of respiration, the energy-transfer process of animal cells. Four mitochondria of a rat pancreas cell are enlarged 33,000 times in this electron micrograph by George E. Palade of the Rockefeller Institute. The inner membranes of the mitochondria's double wall are involuted to form the characteristic cristae, or folds.



CRISTAE can be shelflike or tubular, as shown by this electron micrograph of mitochondria in a giant amoeba (*Chaos chaos*) by George D. Pappas and Philip W. Brandt of the Columbia University College of Physicians and Surgeons. Magnification is 27,000 diameters.

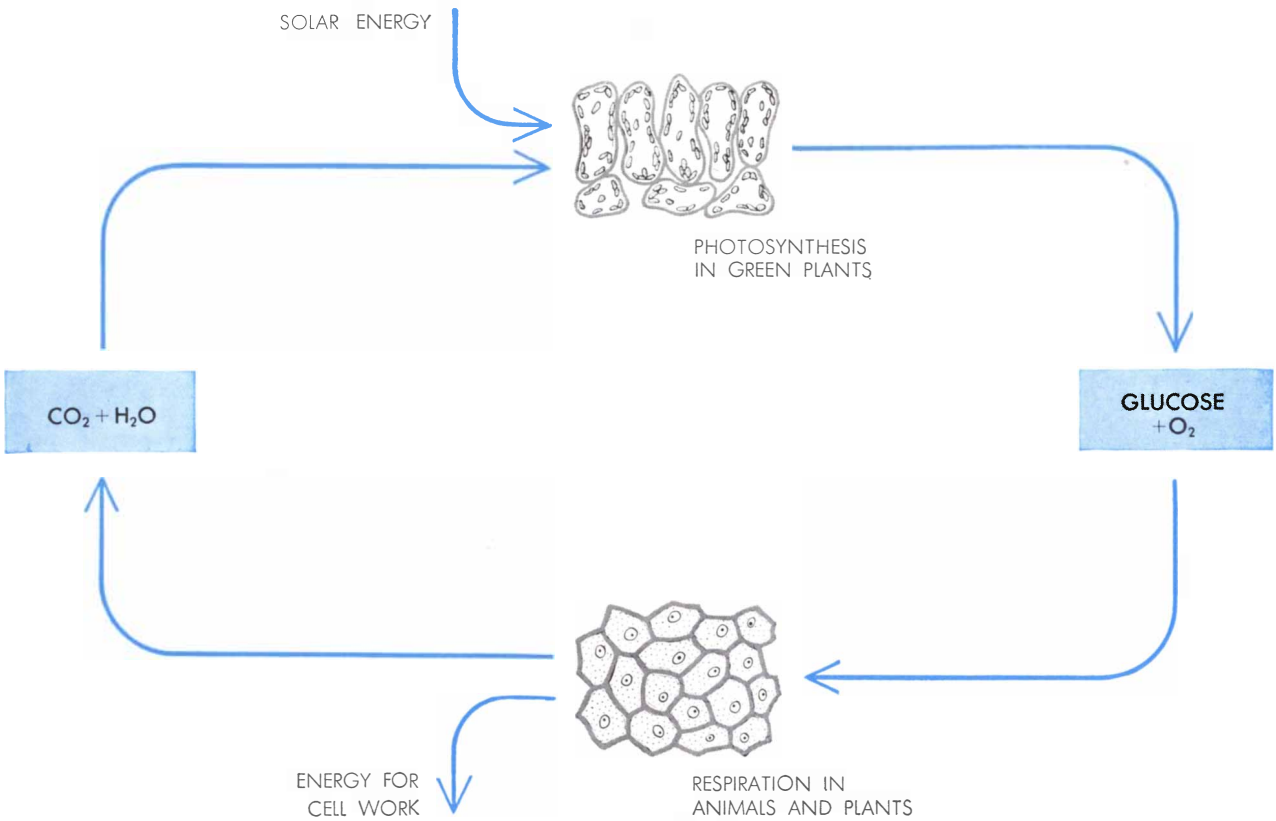
centration of hydrogen ions. To secure its primary energy the cell has during the eons of organic evolution perfected extraordinary molecular mechanisms that work with great efficiency under these mild conditions.

The energy-extracting mechanisms of living cells are of two kinds, and they separate all cells into two great classes. The first type of cell, called heterotrophic, includes the cells of the human body and of higher animals in general. This type of cell requires a supply of preformed, ready-made fuel of considerable chemical complexity, such as carbohydrate, protein and fat, which are themselves constituents of cells and tissues. Heterotrophic cells obtain their energy by burning or oxidizing these complex fuels, which are made by other cells, in the process called respiration, using molecular oxygen (O_2) from the atmosphere. They employ the energy so obtained to carry out their biological work, and they give up carbon dioxide to the atmosphere as the end product.

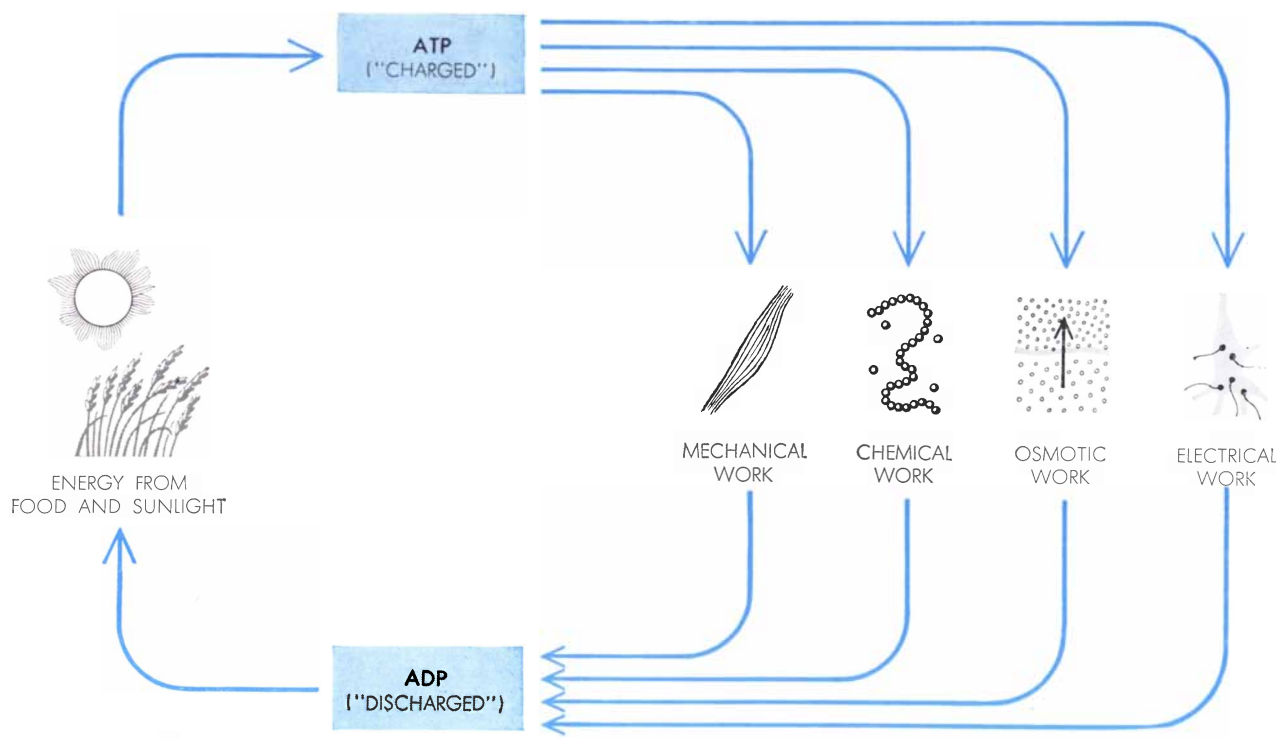
Cells in the other class get their energy from sunlight. Such cells are called autotrophic, or self-reliant. Principal among them are the cells of green plants. By the process of photosynthesis they harness the energy of sunlight for their living needs. They also use solar energy to incorporate carbon from atmospheric carbon dioxide in the elementary organic molecule of glucose. From glucose the cells of green plants and of other organisms build up the more complex molecules of which cells are made. In order to supply energy for this chemical work the cells burn some of the raw material by the mechanism of respiration. From this description of the cellular energy cycle it is clear that living things ultimately derive their energy from sunlight—plant cells directly and animal cells indirectly.

Investigations of the central questions posed here are converging on a complete description of the primary energy-extracting mechanisms of the cell. Most of the steps in the intricate cycles of respiration and photosynthesis have been worked out. Each process has been localized in a specific organ of the cell. Respiration is carried on by mitochondria, large numbers of which are found in almost all cells; photosynthesis is conducted by chloroplasts, the cytoplasmic structures that distinguish the cells of green plants. The molecular devices that make up these structures and perform their functions present the next great frontier to cell research.

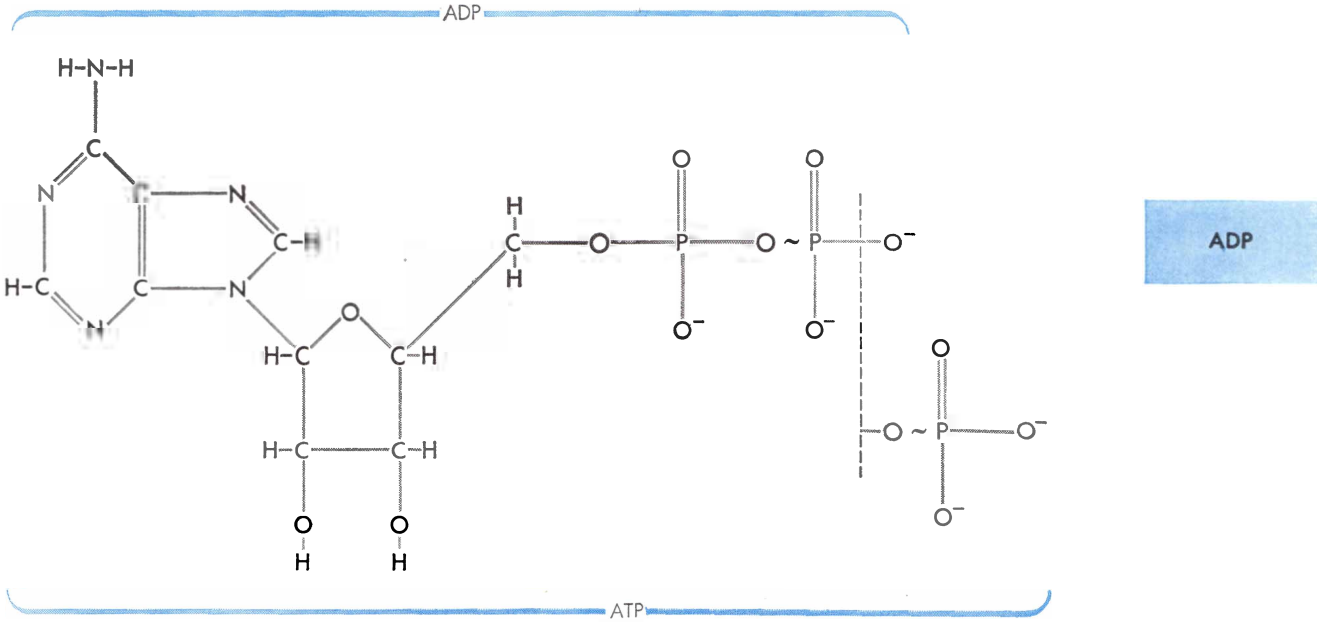
From the centers of respiration



CARBON AND ENERGY CYCLE of life is based on the sun as the ultimate source of energy. Solar radiation drives photosynthesis, which builds energy-rich glucose from energy-poor carbon dioxide and water. The glucose and other fuels synthesized from it are then broken down to carbon dioxide and water by animal cells, which use the energy extracted in the process to do their work.



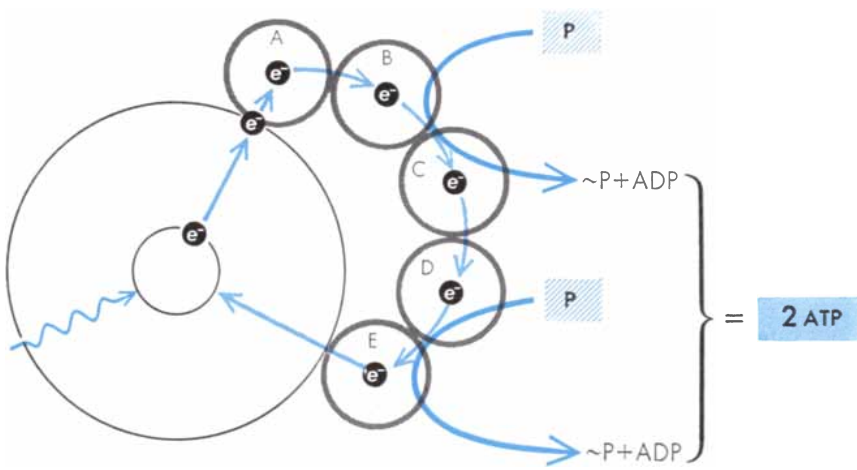
ADENOSINE TRIPHOSPHATE (ATP), the common carrier of energy in animal and plant cells, is formed in the mitochondria and chloroplasts. It supplies energy for muscle contraction, protein synthesis, absorption or secretion against an osmotic gradient and transfer of nerve impulses. "Discharged" adenosine diphosphate (ADP) thus formed is "charged" by solar or food energy.



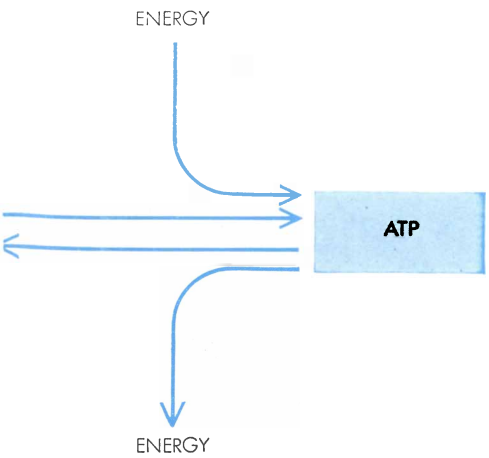
ATP MOLECULE has one more phosphate group than ADP, attached by a high-energy bond (*wavy line at right of formula*). Solar or food energy is required to make this bond and thus to charge ATP. The chemical energy of the bond is made available again when the ATP is discharged by losing its terminal phosphate, which is transferred to an "acceptor" molecule in the cell. This

and photosynthesis the same well-defined molecule—adenosine triphosphate (ATP)—carries the free energy extracted from foodstuffs or from sunlight to all the energy-expending processes of the cell. ATP, which was first isolated from muscle by K. Lohmann of the University of Heidelberg some 30 years ago, contains three phosphate groups linked together. In the test tube the terminal group can be detached from the molecule by the drastic, one-step reaction of hydrolysis to yield adenosine diphosphate (ADP) and simple phosphate. As this reaction proceeds, the free energy of the ATP molecule appears as heat and entropy, in accordance with the second law of thermodynamics. In the cell, however, the terminal phosphate group is not merely detached by hydrolysis but is transferred to a specific acceptor molecule. The free energy of the ATP molecule is largely conserved by "phosphorylation" of the acceptor molecule, the energy content of which is now raised so that it can participate in an energy-requiring process such as biosynthesis or muscle contraction. Left over from this "coupled reaction" is ADP. In the thermodynamics of the cell ATP may be considered as the energy-rich, or "charged," form of the energy carrier and ADP as the energy-poor, or "discharged," form.

It is, of course, one or the other of the two energy-extracting mechanisms that "recharges" the carrier. In respiration in animal cells the energy of foodstuffs is released by oxidation and harnessed to regenerate ATP from ADP and phosphate. In photosynthesis in plant cells the energy of sunlight is trapped as chemical energy and harnessed to drive the recharging of ATP. Experiments employing the radioactive isotope phosphorus 32 have shown that the inorganic phosphate passes into the terminal phosphate group of ATP and out again with great rapidity. In a kidney cell the terminal phosphate group turns over so rapidly that its half life is less than a minute, in consonance with the massive and dynamic flux of energy in the cells of this organ. It should be added that there is really no black magic associated with the action of ATP in the cell. Chemists are familiar with many similar reactions that permit the transfer of chemical energy in inanimate systems. The relatively complex structure of ATP has



CYCLIC PHOTOPHOSPHORYLATION is the process by which an electron in chlorophyll, raised to a high-energy state by a photon of light, provides the energy to make ATP. The excited electron is captured by the first of a chain of "carriers" (*A*) and passed on around a circuit of such molecules (*B through E*), losing energy along the way. Some of the energy couples phosphate to ADP. The cycle ends as the electron returns to chlorophyll.



"phosphorylation" raises the energy level of the acceptor molecule. The ADP-ATP reaction is shown in schematic form at the right.

apparently evolved uniquely in the cell to produce maximum control and organization of energy-transferring chemical reactions.

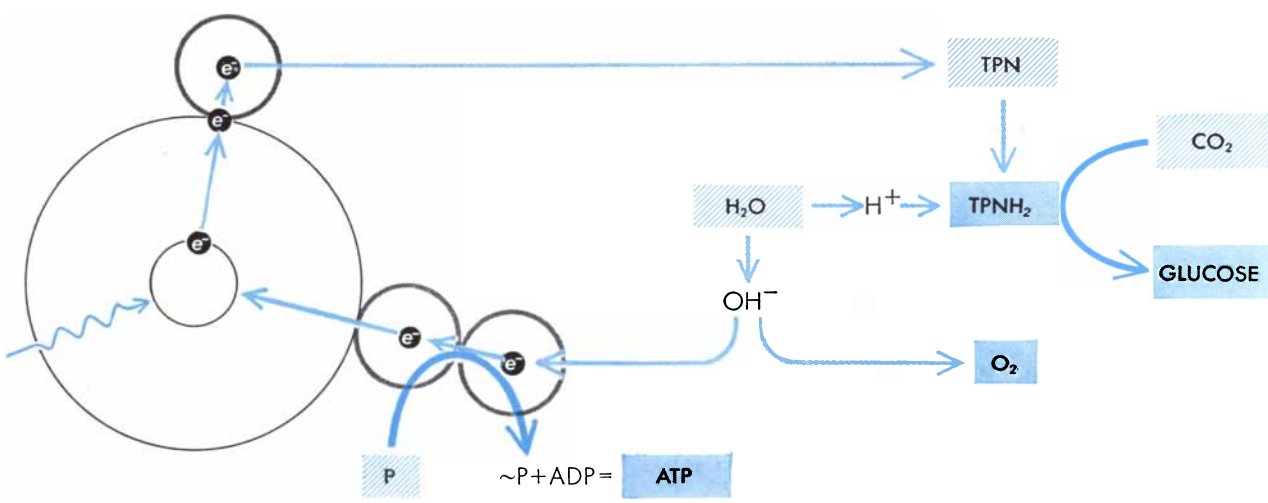
The role of ATP in photosynthesis has only recently been elucidated [see "The Role of Light in Photosynthesis," by Daniel I. Arnon; SCIENTIFIC AMERICAN, November, 1960]. This discovery supplies a major part of the explanation of how photosynthetic cells harness the ultimate energy source of all living things, solar energy, in the synthesis of carbohydrates.

The energy of sunlight comes in packets called photons, or quanta; light of different colors or wavelengths is characterized by different energy content. When light strikes and is absorbed by certain metallic surfaces, the energy of the impinging photons is transferred to electrons of the metal. This "photoelectric" effect can be measured by the resulting flow of electric current. In the green-plant cell, solar energy of a particular range of wavelengths is absorbed by the green pigment chlorophyll. The absorbed energy raises an electron from its normal energy level to a higher level in the bond structure of this complex molecule. Such "excited" electrons tend to fall back to their normal and stable level, and when they do they give up the energy they have absorbed. In a pure preparation of chlorophyll, isolated from the cell, the absorbed energy is re-emitted in the form of visible light, as it is from other phosphorescent or fluorescent organic and inorganic compounds.

Thus chlorophyll itself in the test tube cannot store or usefully harness the energy of light; the energy escapes quickly, as though by short circuit. In the cell, however, chlorophyll is so connected spatially with other specific molecules that when it is excited by the absorption of light, the "hot," or energy-rich, electrons do not simply fall back to their normal positions. Instead these electrons are led away from the chlorophyll molecule by associated "electron carrier" molecules and handed from one to the other around a circular chain of reactions. As they traverse this external path the excited electrons give up their energy bit by bit and return to their original positions in the chlorophyll, which is now ready to absorb another photon. The energy given up by the electrons has meanwhile gone into the formation of ATP from ADP and phosphate; that is, into recharging the ATP system of the photosynthetic cell.

The electron carriers that mediate this process of "photosynthetic phosphorylation" have not yet been fully identified. One of these molecules is believed to contain riboflavin (vitamin B_2) and vitamin K. Others are tentatively identified as cytochromes: proteins containing iron atoms surrounded by porphyrin groups similar in arrangement and structure to the porphyrin of chlorophyll itself. At least two of these electron carriers are able to cause some of the energy they carry to be captured, in order to regenerate ATP from ADP [*see illustration at bottom of opposite page*]. This appears to be the basic scheme of the conversion of light into the phosphate-bond energy of ATP, as it has been developed by Daniel I. Arnon and his associates at the University of California and by other workers.

The complete photosynthetic process, however, involves the synthesis of carbohydrate as well as the harnessing of



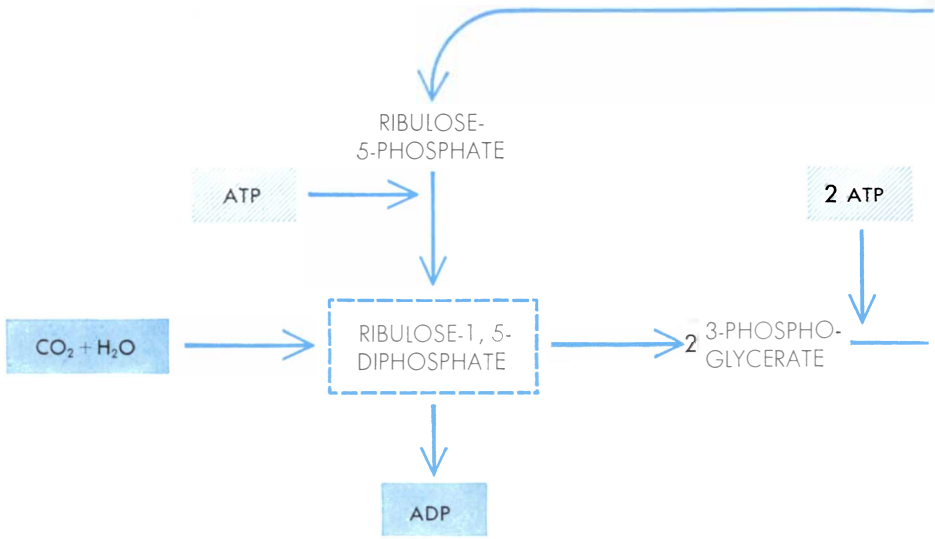
COMPLETE PHOTOSYNTHESIS requires an outside source of electrons and hydrogen ions (protons) to synthesize carbohydrate by "reducing" (adding electrons and hydrogen to) carbon dioxide. The source of electrons is chlorophyll and the source of protons is water. The reducing agent for carbon dioxide is "reduced triphosphopyridine nucleotide" ($TPNH_2$) formed by the action of protons and electrons on TPN, one of the carrier molecules. The leftover hydroxyl ions (OH^-) of water apparently lose electrons to restore the chlorophyll's supply. In this process oxygen gas, characteristic product of photosynthesis, is evolved and ATP is charged up.

solar energy. It is now believed that some of the "hot" electrons from excited chlorophyll, along with hydrogen ions derived from water, cause the reduction (that is, the addition of electrons or hydrogen atoms) of one of the electron carriers, triphosphopyridine nucleotide (TPN), which in its reduced form becomes $TPNH_2$ [*see illustration at bottom of preceding page*]. In a series of "dark" reactions, so named because they occur in the absence of light, $TPNH_2$ brings about the reduction of carbon dioxide to carbohydrate. Much of the energy necessary for this series of reactions is supplied by ATP [*see illustration at right*]. The pattern of the dark reactions was worked out largely by Melvin Calvin and his associates, also at the University of California. A by-product of the original photoreduction of TPN is the hydroxyl ion (OH^-). Although the evidence is not yet complete, it is thought that these ions donate their electrons to a cytochrome in the photosynthetic chain, releasing molecular oxygen in the process. The electrons continue down the carrier chain, contributing to the formation of ATP and finally settling—in their energy-depleted state—in the chlorophyll.

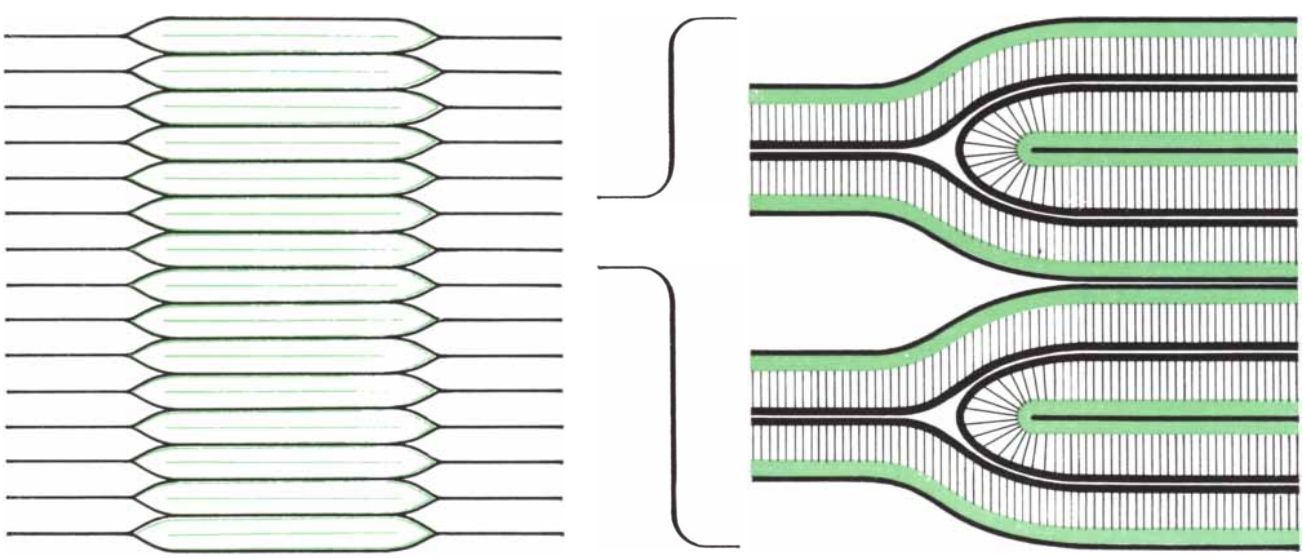
As the highly organized and sequential nature of the photosynthetic process suggests, the chlorophyll molecules are not randomly situated or merely suspended in solution inside the chloroplasts. On the contrary, the chlorophyll is arranged in orderly structures within the chloroplasts called grana, and the grana in turn are separated from one another by a network of fibers or membranes. Within the grana the flat chlorophyll molecules are stacked in piles. The chlorophyll molecules can therefore be looked on as the single plates of a battery, several plates being organized as in an electric cell, and several cells in a battery, represented by the chloroplast.

The chloroplasts also contain all the specialized electron-carrier molecules that work together with chlorophyll to extract the energy from the hot electrons and use that energy to synthesize carbohydrate. Separated from the rest of the cell, the chloroplasts can carry out the complete photosynthetic process.

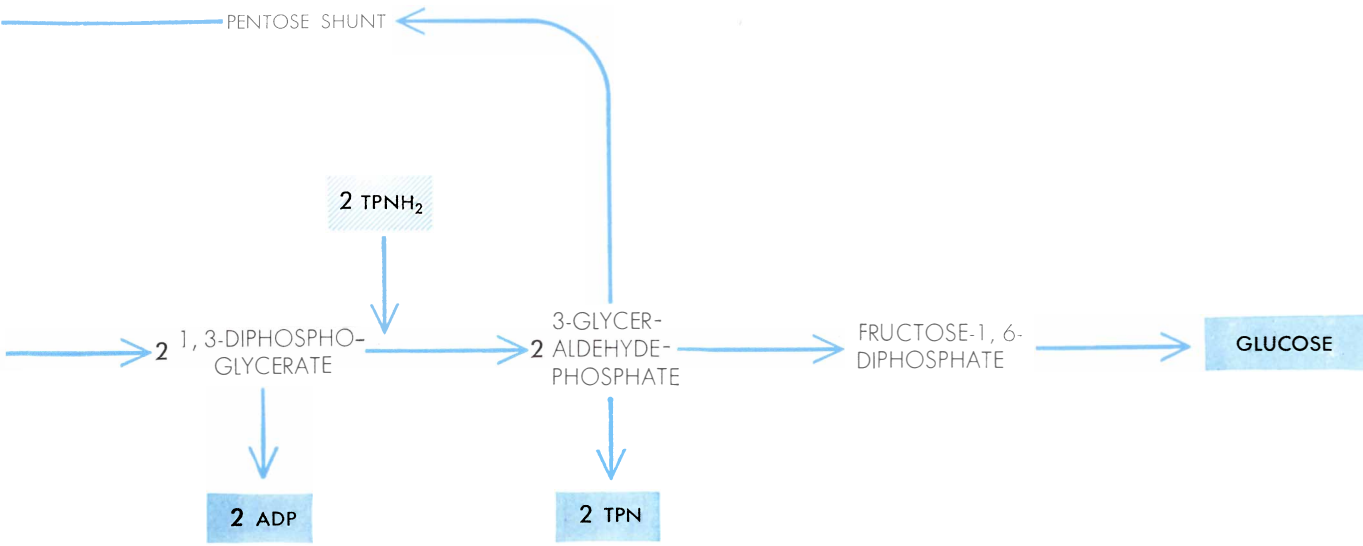
The efficiency of these miniature solar



SYNTHESIS OF GLUCOSE from carbon dioxide and water is a dark reaction—that is, it involves a series of reactions that do not directly require light. But it does require two compounds made by light, ATP and $TPNH_2$, as the energy supply and reducing agent respec-



STRUCTURE OF ONE GRANUM in a chloroplast is diagramed in successive magnifications. The chlorophyll (*color*) is concentrated within envelopes stacked to form the granum (*left*), with connecting fibers leading to adjacent grana. In the layers, two of which are magnified (*second from left*), the chlorophyll is sandwiched between membranes of protein, according to a hypothetical model proposed by Alan J. Hodge of the California Institute of Technology. In Hodge's model, based on electron microscopy and the "electron carrier" chemistry discussed in the text, the individual chlorophyll molecules are oriented (*third from left*) be-

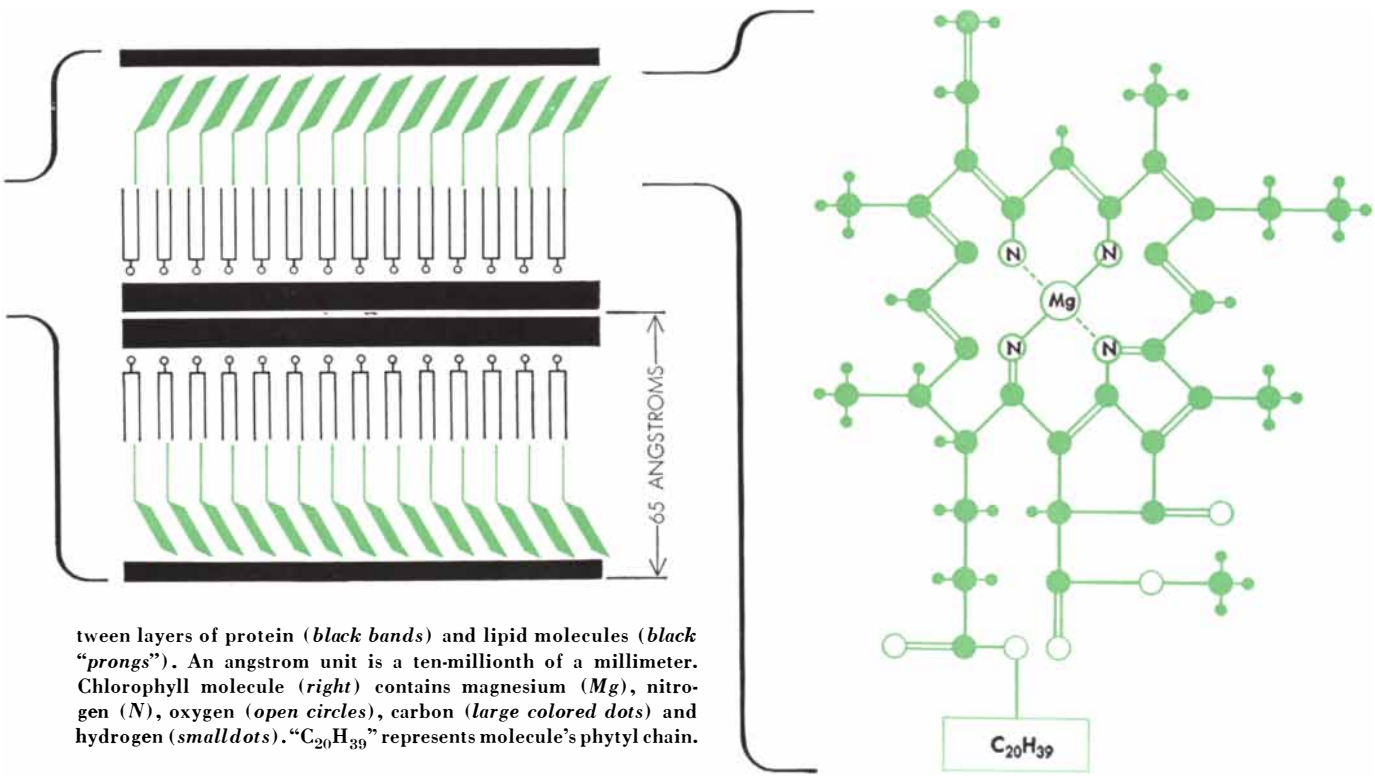


tively. In this complex cycle, shown here only in outline, the key intermediate is ribulose diphosphate, which picks up the carbon dioxide and makes two molecules of phosphoglycerate. This is reduced by $TPNH_2$ and rearranged in steps, ultimately to become glucose. Meanwhile the ribulose diphosphate is regenerated in a series of reactions abbreviated here as "pentose shunt."

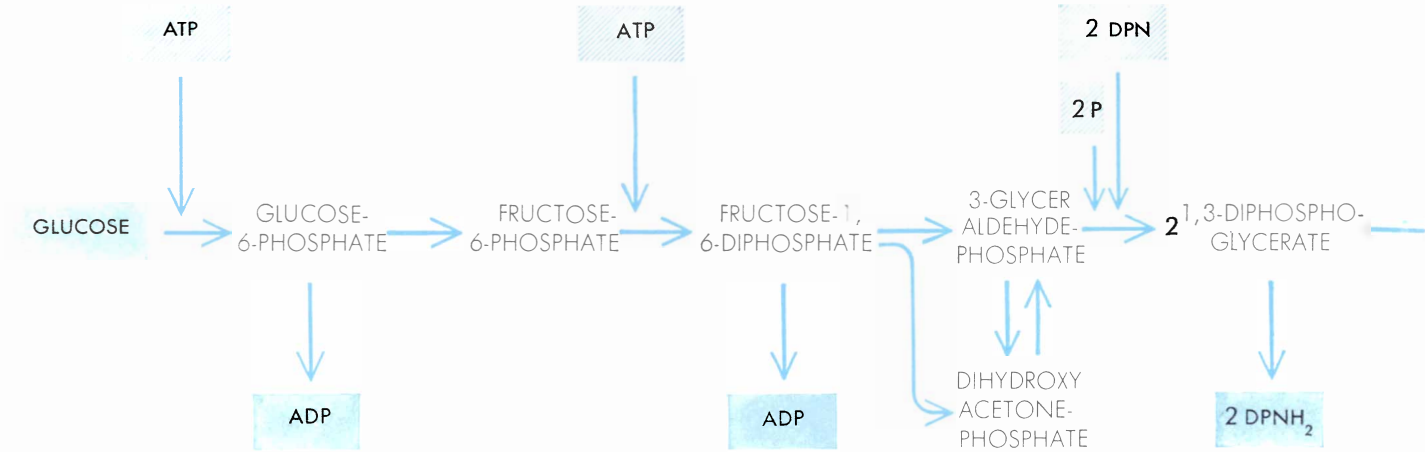
power plants is impressive. Though the exact figures are subject to controversy, it can be demonstrated under special laboratory conditions that the photosynthetic process converts as much as 75 per cent of the light that impinges on the chlorophyll molecule into chemical energy. On the other hand, the efficiency of energy recovery of a field of corn, given the random and uneven exposure of the leaves to sunlight and other conditions of nature, is considerably lower: on the order of only a few per cent.

The molecule of glucose, as the end product of photosynthesis, can therefore be visualized as having a considerable amount of solar energy locked in its molecular configuration. In the process of respiration heterotrophic cells extract this energy by carefully taking apart the glucose molecule step by step, conserving its energy of configuration in the phosphate-bond energy of ATP.

There are different kinds of heterotrophic cell. Some, such as certain marine microorganisms, can live without



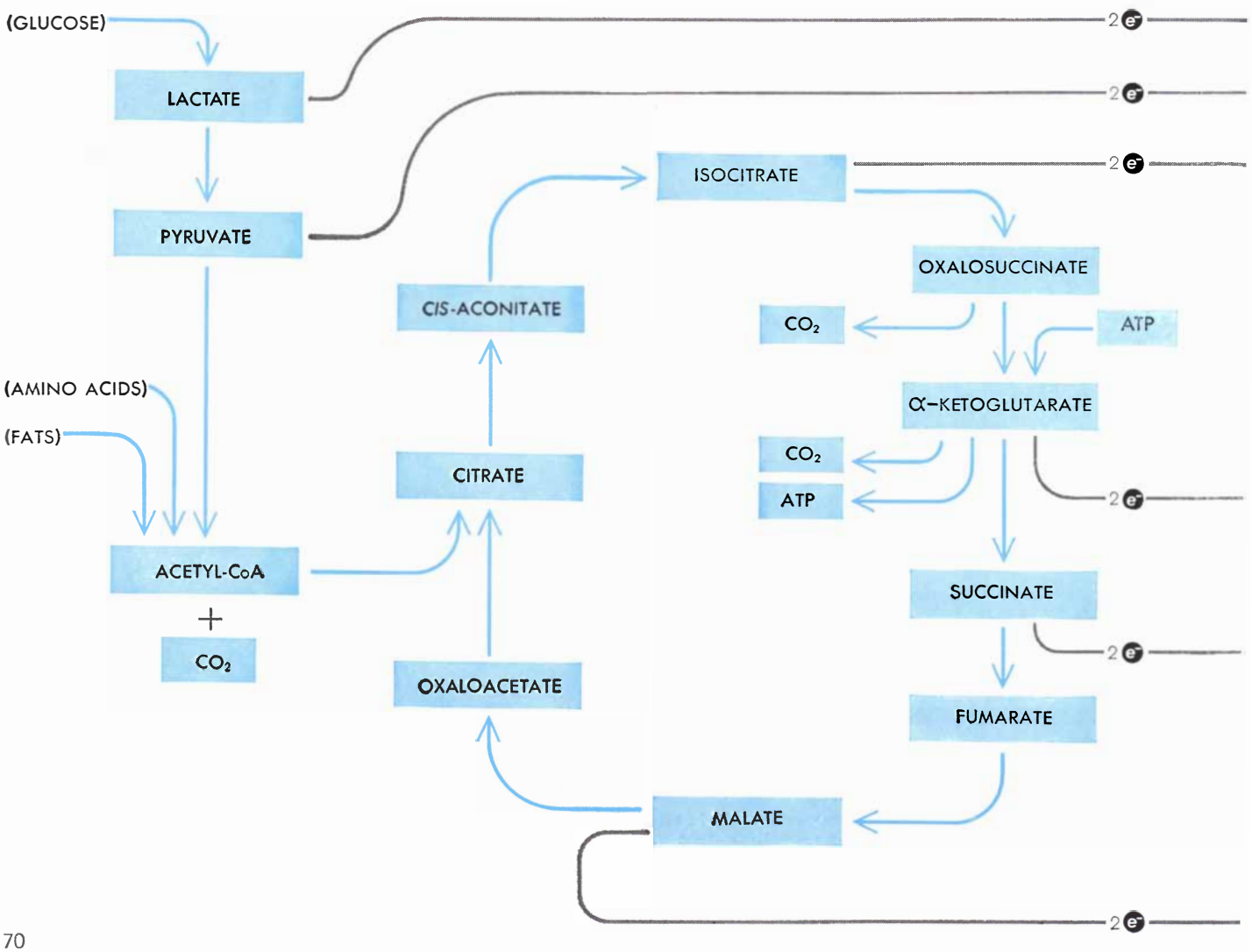
tween layers of protein (*black bands*) and lipid molecules (*black "prongs"*). An angstrom unit is a ten-millionth of a millimeter. Chlorophyll molecule (*right*) contains magnesium (*Mg*), nitrogen (*N*), oxygen (*open circles*), carbon (*large colored dots*) and hydrogen (*small dots*). "$C_{20}H_{39}$" represents molecule's phytyl chain.

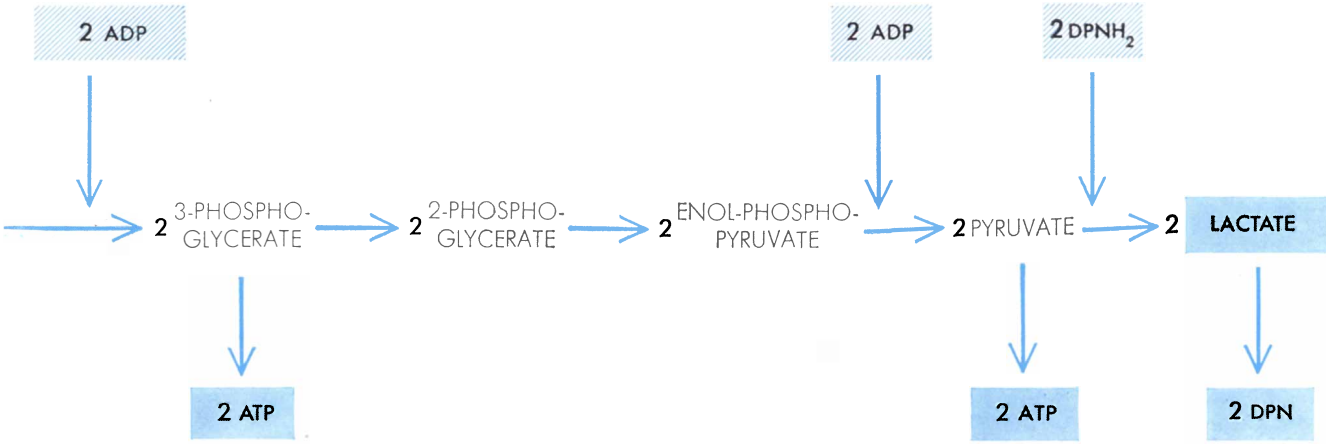


GLYCOLYSIS is the first step in energy recovery from glucose. As will show, many of the steps are the reverse of those in the dark comparison of this diagram with the upper one on pages 68 and 69 synthesis of glucose by plants. Six-carbon glucose is broken down

oxygen; some, such as brain cells, absolutely require oxygen; some, such as muscle cells, are more versatile, being able to function either aerobically or anaerobically. Furthermore, although most cells prefer glucose as the major fuel, some can live exclusively on amino acids or fatty acids synthesized from glucose as the basic raw material. The disassembly of the glucose molecule by the liver cell may be taken, however, as typical of the process by which most known aerobic heterotrophs obtain energy.

The total amount of energy available in a molecule of glucose may be quite simply determined. By burning a sample in the laboratory it can be shown that the oxidation of the glucose yields six molecules of water and six molecules of carbon dioxide, with the evolution of

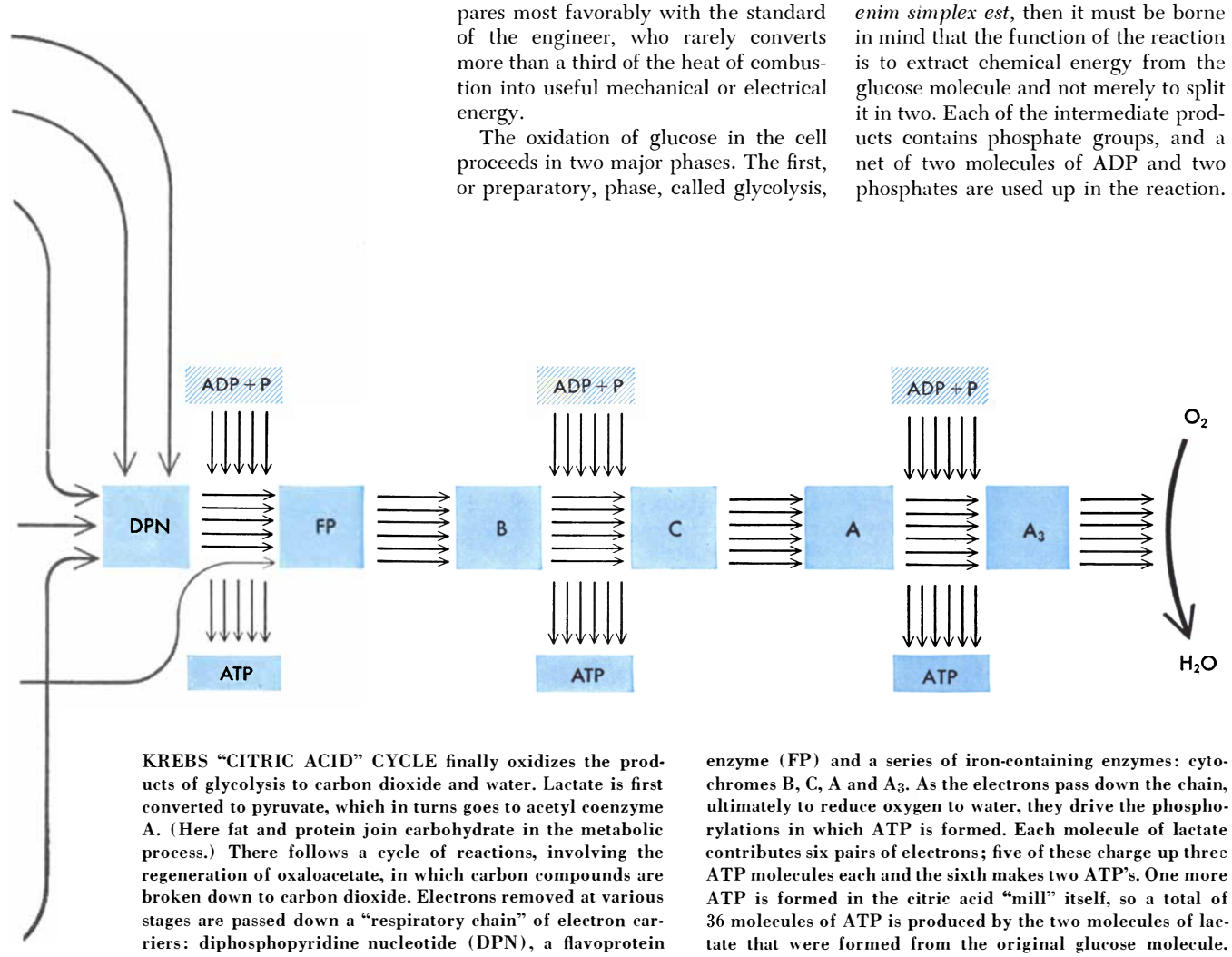




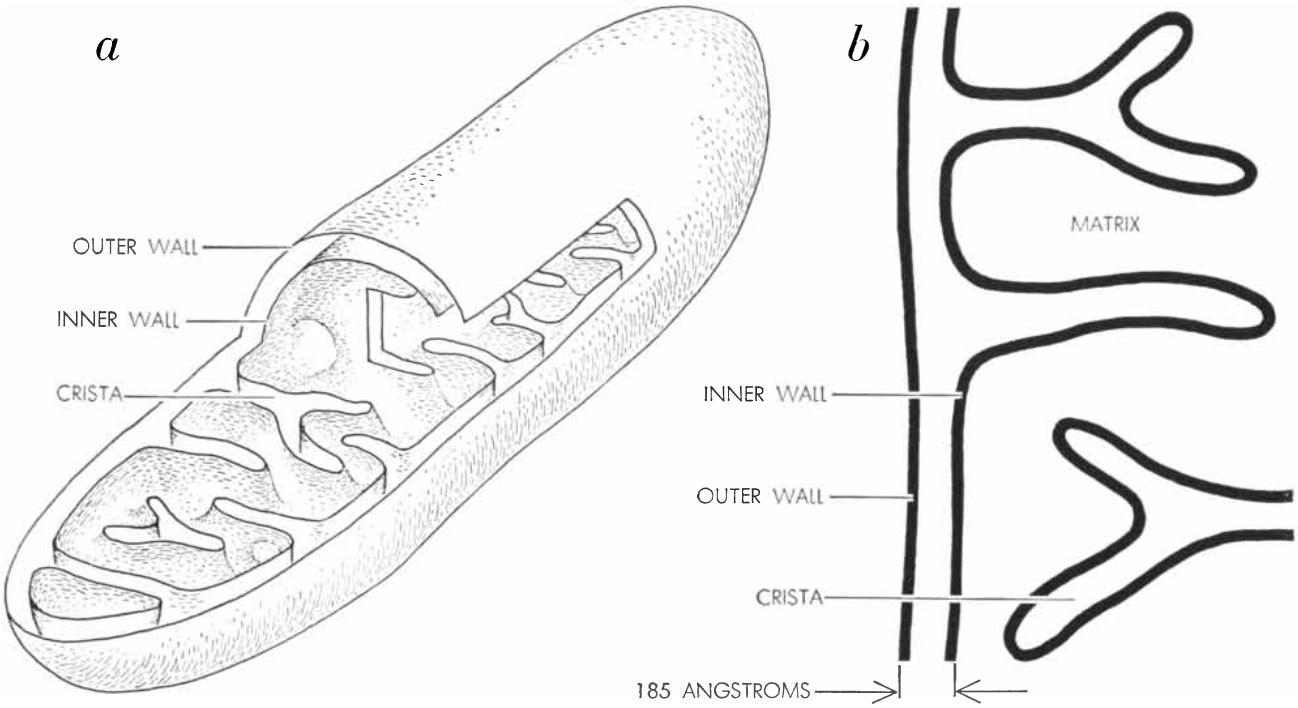
into two molecules of three-carbon lactate (or lactic acid; the ionic rather than the acid form of the intermediate compounds is shown in the diagrams). Two molecules of ATP are used up in glycolysis but four are formed, for a net gain of two molecules of ATP.

some 690,000 calories of energy per gram molecular weight (that is, per 180 grams of glucose) in the form of heat. Energy in the form of heat is, of course, useless to the cell, which functions under essentially constant temperature conditions. The step-by-step oxidation of glucose achieved by the mechanism of respiration occurs in such a way, however, that much of the free energy of the glucose molecule is conserved in a form that is useful to the cell. In the end more than 50 per cent of the available energy is recovered in the form of phosphate-bond energy. This recovery compares most favorably with the standard of the engineer, who rarely converts more than a third of the heat of combustion into useful mechanical or electrical energy.

The oxidation of glucose in the cell proceeds in two major phases. The first, or preparatory, phase, called glycolysis, brings about the splitting of the six-carbon glucose molecule into two three-carbon molecules of lactic acid. This seemingly simple process occurs not in one step but at least 11 steps, each catalyzed by a specific enzyme. If the complexity of this operation seems to contradict the Newtonian maxim *Natura enim simplex est*, then it must be borne in mind that the function of the reaction is to extract chemical energy from the glucose molecule and not merely to split it in two. Each of the intermediate products contains phosphate groups, and a net of two molecules of ADP and two phosphates are used up in the reaction.



KREBS "CITRIC ACID" CYCLE finally oxidizes the products of glycolysis to carbon dioxide and water. Lactate is first converted to pyruvate, which in turns goes to acetyl coenzyme A. (Here fat and protein join carbohydrate in the metabolic process.) There follows a cycle of reactions, involving the regeneration of oxaloacetate, in which carbon compounds are broken down to carbon dioxide. Electrons removed at various stages are passed down a "respiratory chain" of electron carriers: diphosphopyridine nucleotide (DPN), a flavoprotein enzyme (FP) and a series of iron-containing enzymes: cytochromes B, C, A and A_3. As the electrons pass down the chain, ultimately to reduce oxygen to water, they drive the phosphorylations in which ATP is formed. Each molecule of lactate contributes six pairs of electrons; five of these charge up three ATP molecules each and the sixth makes two ATP's. One more ATP is formed in the citric acid "mill" itself, so a total of 36 molecules of ATP is produced by the two molecules of lactate that were formed from the original glucose molecule.



STRUCTURE OF MITOCHONDRION is basically that of a fluid-filled vessel with an involuted wall (*a*). The wall consists of a double membrane (*b*), with infoldings of the inner one forming cristae. Each membrane is apparently constructed of a layer of pro-

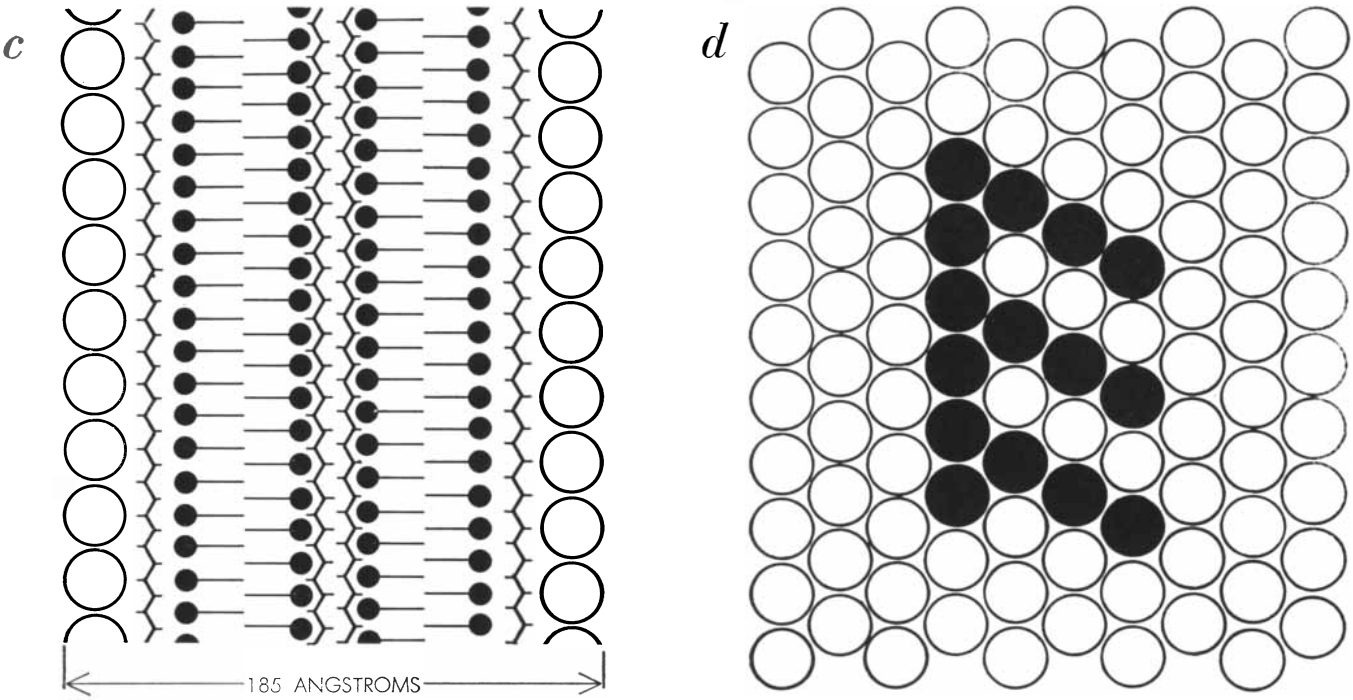
Ultimately the splitting of glucose not only yields two molecules of lactic acid but also generates two new molecules of ATP [*see illustration at top of preceding two pages*].

What does this mean in terms of energy? Thermodynamic equations show that the splitting of a gram molecule of glucose to lactic acid makes a total of 56,000 calories available. Since the charging of each gram molecule of ATP captures about 10,000 calories of energy, the yield at this stage is about 36 per cent, a respectable figure by engineering standards. The conversion of 20,000 calories represents, however, a small fraction—only 3 per cent—of the total of 690,000 calories bound in the glucose. Yet many cells, such as anaerobic cells or muscle cells in exercise (which are unable to conduct the process of respiration), function on this small yield.

With glucose now broken down to lactic acid, aerobic cells proceed to extract a major portion of the remaining energy by the process of respiration, in which the three-carbon lactic acid molecule is broken down to single-carbon molecules of carbon dioxide. The lactic acid, or rather its oxidized form pyruvic acid, undergoes an even more complex series of reactions, each step again being catalyzed by a specific enzyme system [*see illustration at bottom of preceding two pages*]. First the three-carbon compound is broken down to an activated form of acetic acid—acetyl coenzyme A—and carbon dioxide. The two-carbon acetic acid compound then combines with a four-carbon compound, oxaloacetic acid, to make the six-carbon citric acid. This is degraded again to oxaloacetic acid by a series of reactions, and the three-carbon atoms of pyruvic acid that were fed into this cyclic mechanism at last appear as carbon dioxide. This "mill," which oxidizes not only glucose but also fat and amino acid molecules previously broken down to acetic acid, is known as the Krebs citric acid cycle. It was first postulated by Sir Hans Krebs in 1937 in one of the great landmarks of modern biochemistry and honored by a Nobel prize in 1953.

Although the Krebs cycle accounts for the oxidation of lactic acid to carbon dioxide, it alone does not explain how the large amount of energy remaining in these molecules is extracted in useful form. The process of energy recovery that accompanies the action of the Krebs cycle has been an intensely active field of investigation in recent years. While the over-all picture can be described with some assurance, there are many details yet to be solved. In the course of the cycle, it appears, electrons are extracted from the intermediates by enzymes and fed into a series of electron-carrier molecules, collectively called the respiratory chain. This chain of enzyme molecules is the final common pathway of all electrons removed from foodstuff molecules during biological oxidation. At the last link in the chain, the electrons combine with oxygen to form water. The breakdown of foodstuffs by respiration therefore in essence reverses the process of photosynthesis in which electrons are removed from water to form oxygen. Moreover, it is striking that the electron carriers in the respiratory chain bear many chemical similarities to those of the corresponding chain in photosynthesis. They contain, for example, riboflavin and cytochrome structures similar to those in the chloroplast. The Newtonian simplicity of nature is thereby affirmed.

As in photosynthesis, the energy of the electrons passing along the chain to oxygen is tapped off and used to drive the coupled synthesis of ATP from ADP and phosphate. Actually this respiratory-chain phosphorylation, or oxidative phosphorylation, is better understood than the more recently discovered photosynthetic phosphorylation. One thing known with certainty is that there are three points along the chain at which ATP is recharged. For each pair of elec-



tein molecules (*spheres at "c"*) lined by a double layer of lipid molecules (*black-tailed spheres*). The respiratory-chain electron carriers and enzymes appear to be regularly spaced elements (*black spheres at "d"*) of the protein monolayers. The "matrix" is fluid.

trons split from lactic acid in the course of its oxidation in the Krebs cycle, therefore, an average of three molecules of ATP are formed.

From the total yield of ATP molecules it is now possible to calculate the thermodynamic efficiency with which the cell extracts the energy made available by the oxidation of glucose. The preliminary splitting of glucose to two molecules of lactic acid yields two molecules of ATP. Each molecule of lactic acid in turn delivers ultimately six pairs of electrons to the respiratory chain. Since three molecules of ADP are "charged up" to ATP for each pair of electrons traversing the chain, 36 molecules of ATP are formed in the respiratory process proper. On the rough estimate of 10,000 calories each, the 38 molecules of ATP incorporate in their phosphate bonds some 380,000 of the 690,000 calories contained in the original gram molecule of glucose. The efficiency of the combined processes of glycolysis and respiration can therefore be estimated as a minimum of 55 per cent.

The intricacy of the respiratory process in particular suggests again that the enzymatic machinery involved could not do its work if its component parts were randomly mixed together in solution. Just as the molecular devices of photosynthesis appear to be spatially oriented to one another in the chloroplast, so the organ of respiration in the cell, the mitochondrion, presents the same picture of structured order. There may be anywhere from 50 to 5,000 mitochondria in a cell, depending on its type and function. A single liver cell of the rat contains about 1,000 mitochondria. They are large enough (three to four microns long) to be seen in the cytoplasm with a light microscope. But their ultrastructure requires the electron microscope in order to be seen.

In electron micrographs it can be seen that the mitochondrion has two membranes, the inner one occurring in folds in the body of the structure. Recent research on mitochondria isolated from cells of the liver has shown that the Krebs-cycle enzyme molecules are located in the matrix, or soluble portion of the inner contents, but the respiratory-chain enzymes, in the form of molecular "assemblies," are located in the membranes [see "Energy Transformation in the Cell," by Albert L. Lehninger; SCIENTIFIC AMERICAN, May, 1960]. The membranes consist of alternating layers of protein and lipid (fatty) molecules, just as do the membranes of the grana of the chloroplasts. Indeed, there is a remarkable similarity in the structure of these two fundamental power plants of all cellular life, one capable of capturing solar energy in ATP and the other of transforming the energy of foodstuffs to ATP energy.

Modern chemistry and physics have recently been able to specify the three-dimensional structure of certain large molecules, such as those of proteins and of DNA, the molecules that carry genetic information. The next great step in cell research is to find out how the large enzyme molecules, themselves proteins, are arranged together in the mitochondrial membranes, together with the lipids, so that each catalyst molecule is properly oriented and therefore able to react with the next one in the working assembly. The "wiring diagram" of the mitochondrion is already clear!

If the classical engineering science of energy transformation is humbled by what is now known about the power plants of the cell, so are the newer and more glamorous branches of engineering. The technology of electronics has achieved amazing success in packaging and miniaturizing the components of a computer. But these advances still fall far short of accomplishing the unbelievable miniaturization of complex energy-transducing components that has been perfected by organic evolution in each living cell.

How Cells Make Molecules

The inherited master plan of the cell is contained in the molecules of deoxyribonucleic acid. They direct the manufacture of protein enzymes, which in turn engineer all the chemical reactions of life

by Vincent G. Allfrey and Alfred E. Mirsky

In our laboratory we have the portraits of Gregor Mendel and Friedrich Miescher side by side. Mendel in 1866 set forth evidence, from his observation of inheritance in the pea plant, for the idea that genetic information is carried in discrete units from one generation to the next. Miescher in 1869 isolated from the nucleus of cells a substance that he called nuclein and that is known today as deoxyribonucleic acid (DNA). He knew that he had in his hands a novel substance containing nitrogen and phosphorus, and he was well aware of its location within the nucleus. But he could have had no idea of what DNA does in the nucleus, because the role of the nucleus in heredity was at that time unknown, even to Mendel. It was well over half a century, long after the death of both men, before their work could be fused. The fusion required much more nucleic-acid and protein chemistry than there was in Miescher's time and a vast amount of new biology, including the unearthing of Mendel's work in 1900.

In the last three decades of the 19th century, work in biology, led by August Weismann, demonstrated the continuity of the germ plasm and showed that the nucleus of the cell plays a central role in heredity. Attention soon focused on the chromosomes. Since sperm and egg nuclei provide equal complements of chromosomes (except for the sex chromosomes) and since there is precisely equal cleavage and distribution of chromosomes at cell division, it seemed clear that chromosomes are concerned with the continuity that is essential in heredity. With the rediscovery of Mendel and the growth of genetics, biologists talked less about the germ plasm and more about the genes as discrete units of the germinal material. It became increasingly clear that each gene is derived from a pre-existing gene. The genes were located in the chromosomes, which now far more conclusively than before were shown to contain the materials determining heredity.

Meanwhile the chemistry of nucleic acids was making progress. But there was little contact between the two movements. The now standard color test for DNA was first demonstrated in 1914 by the German chemist Robert Feulgen in a test tube. Not until 10 years later did Feulgen use the test to stain cells and show that the chromosomes are the locus of DNA concentration in the nucleus. Yet it cannot be said that this experience led to the idea that DNA is the essential gene material.

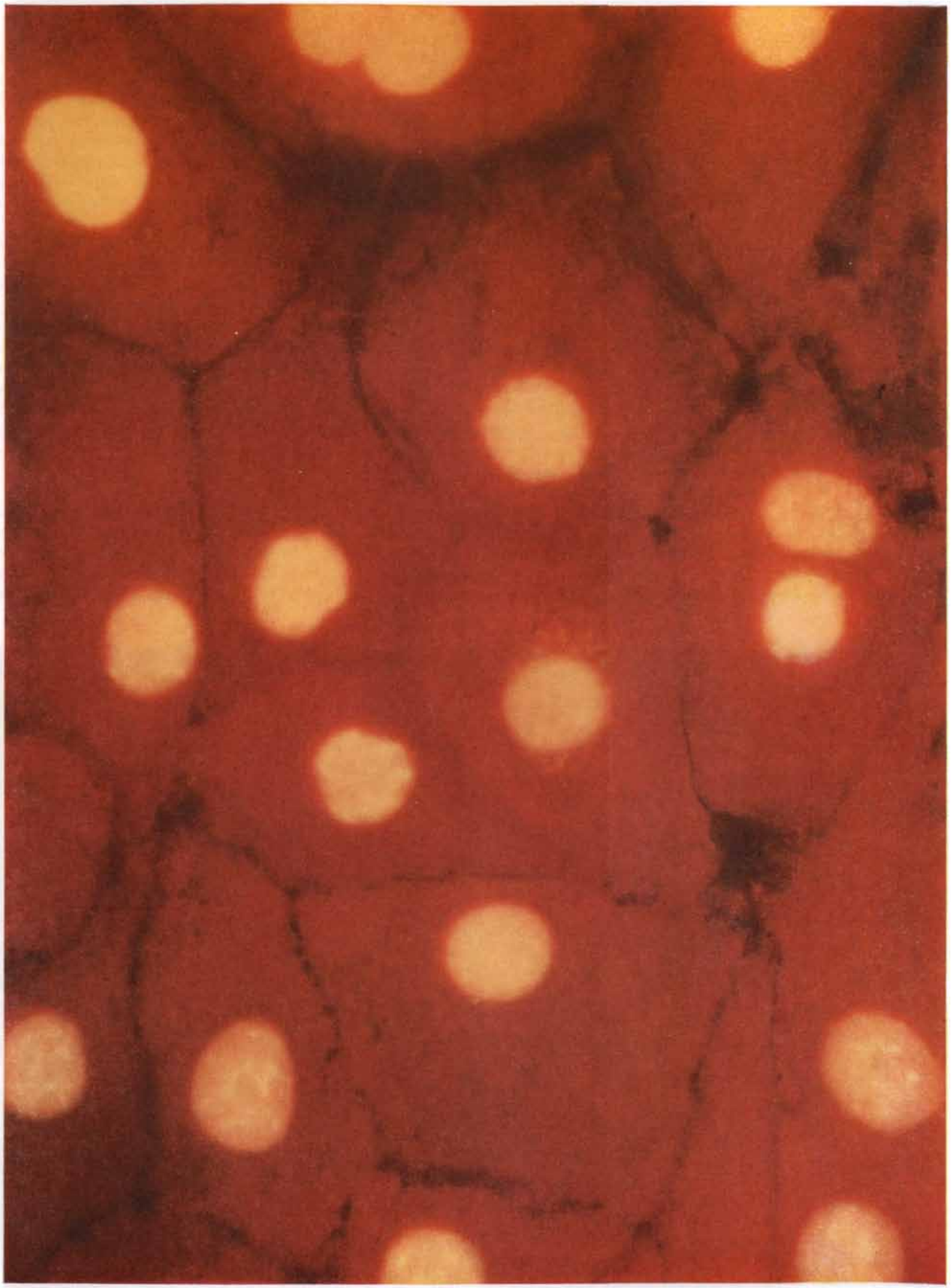
The evidence that genetic information is carried by DNA came in the late 1940's from a number of sources. André Boivin and Roger and Colette Vendrely of the University of Strasbourg and Alfred E. Mirsky and Hans Ris of the Rockefeller Institute measured the DNA content of nuclei in germ cells and various somatic cells and found that in a given organism the DNA content is constant per set of chromosomes. This constancy pointed to DNA as the essential material of the genes. In experiments on pneumococci Oswald T. Avery, Colin M. MacLeod and Maclyn McCarty of the Rockefeller Institute showed that hereditary traits can be transmitted from one strain of bacteria to another by transferring to cells of the latter DNA extracted from the former. Their experiments conclusively established DNA as the carrier of genetic information.

This development made a great impression on geneticists, for it went a long way toward answering one of their outstanding questions: What is the nature of the gene? The impact on biochemists was far greater; it revealed to them what the problems of biochemistry could be. The principle of genetic continuity, the rule that each gene comes from a pre-existing gene, was now transformed to the biochemical question: How does the molecule of DNA replicate itself? There was also the problem of the passage of genetic information from DNA in the chromosome to the fabric of the cell. As the carrier of genetic information, it was plain, DNA does much more than replicate itself. It plays an active role, directing the life of the cell. Biochemists could now study the molecular basis of gene action, tracing the effect of DNA in discrete observable events in the synthesis of the molecules of which the cell is made.

The fusion of biochemistry and cell biology has brought an accelerating growth of understanding over the past 20 years. It is now possible to answer at the molecular level some of the fundamental questions of genetics and cell biology that go back to the era of Weismann. Some of the most significant knowledge of DNA activity has come in recent months. It is difficult to believe that the discovery of this substance goes back to 1868!

When the chromosomes are coiled up tightly in stumpy rods, the DNA they contain is the repository of genetic information, but it is inert. When DNA is actively communicating its information to the cell, the chromosomes have an entirely different appearance. Then, in their "lampbrush" configuration, the chromosomes uncoil into delicate filaments forming a lacelike structure in which DNA and other components are readily accessible for interaction with the surrounding medium [*see illustration on page 82*].

Chemists have shown that the molecule of DNA consists of a long, un-



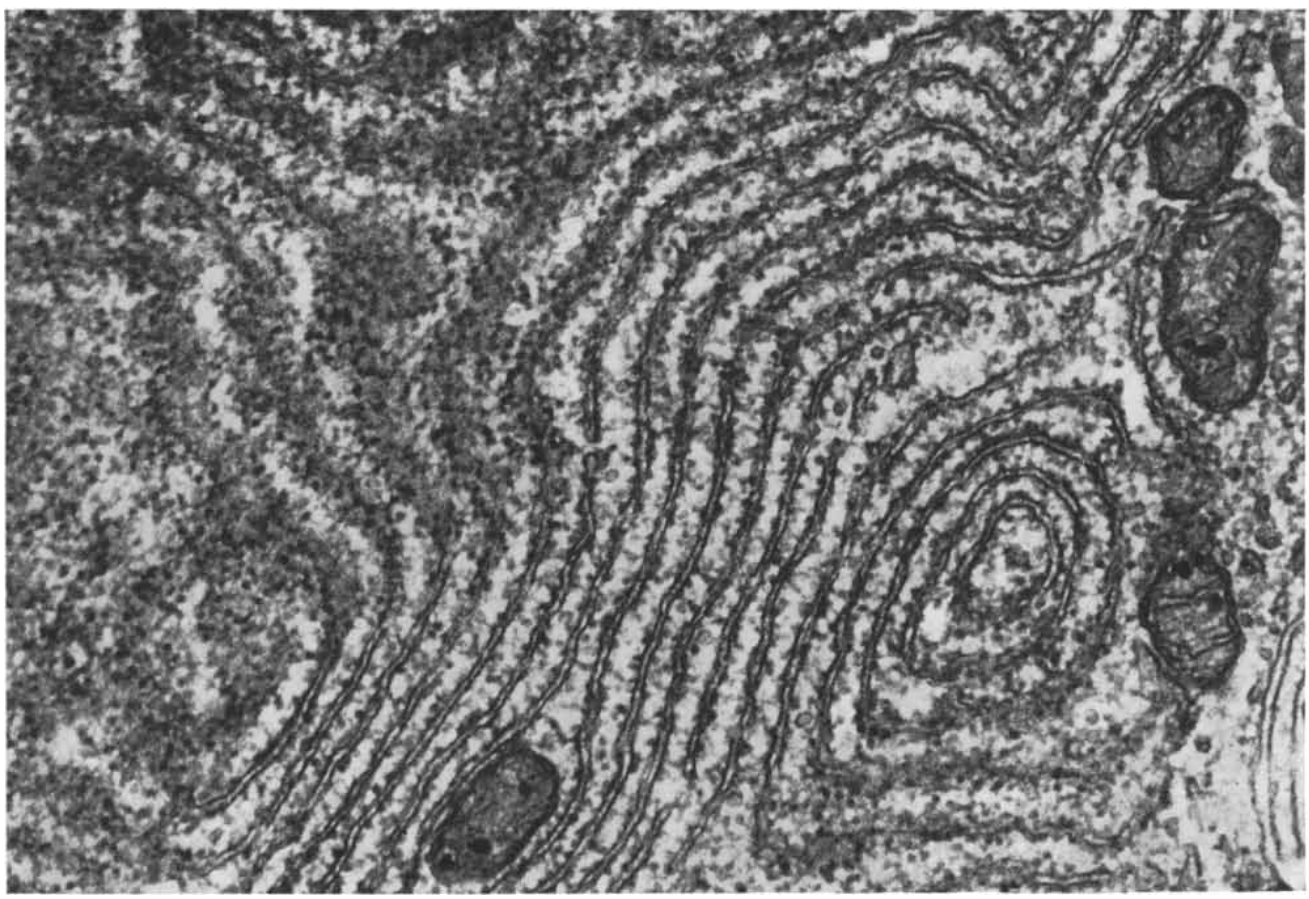
NUCLEIC ACIDS, the "blueprints" and "templates" of protein synthesis, are visualized in this photomicrograph of human amnion cells made by Suydam Osterhout at the Rockefeller Institute. Stained with acridine orange, the deoxyribonucleic acid (DNA) fluoresces yellow-green and is seen to be localized in the nuclei. Ribonucleic acid (RNA) fluoresces orange-red and is seen throughout the cytoplasm. There is RNA in the nucleus also, but it is obscured by the DNA. The magnification is 3,500 diameters.

branched chain, the backbone of which is made up of alternate five-carbon sugar (deoxyribose) and phosphate groups. To each sugar is attached a nitrogenous base; in most DNA's there are four such bases: adenine, guanine, thymine and cytosine. The unit in the chain, consisting of phosphate-sugar-base, is called a nucleotide. From X-ray crystallography, particularly the work of F. H. C. Crick and J. D. Watson, came the understanding that a DNA molecule consists not of a single polynucleotide chain but of two, twined around each other in a double helix and held together by hydrogen bonds between the bases. The companion bases are never identical but are always specifically complementary, with adenine joined to thymine and guanine to cytosine. This is demonstrated by experiments with simple, synthetic polynucleotides. Thus a synthetic DNA, or polynucleotide, made up exclusively of thymine bases (polythymidylic acid) binds a complementary chain made up exclusively of adenine bases (polyadenylic acid). In chains made up of all four bases, as in the natural molecule, the sequence of bases in one chain governs the sequence in the other; if the actual order of bases in one chain of a DNA were known, one could write down the order of its complementary chain. To complete the picture, Crick and Watson proposed that the genetic information carried by the molecule is encoded in the sequence of its bases.

The usefulness of this work to the classical concerns of genetics began to be demonstrated in 1957 when Arthur L. Kornberg, then at Washington University in St. Louis, brought about the synthesis of DNA in a cell-free system containing the four nucleotides, the enzyme polymerase and DNA. In the presence of polymerase the nucleotides linked together to form long chains of DNA. More important, Kornberg found that the polymerization of the four nucleotides will proceed only if a small amount of DNA is present to "prime" the reaction. He soon found that the over-all proportions of the bases in the product DNA paralleled the base composition of the primer used. Early this year Kornberg made the point more strongly. As primers he used a number of different DNA's prepared from virus, bacterial and animal sources, each DNA having its own characteristic sequence of nucleotides. Using a statistical method (known as nearest-neighbor nucleotide frequencies) to analyze the products of these reactions, he found that each primer DNA directs the polymerization so that the sequence of the nucleotides in the enzymatically synthesized DNA is the same as its own.

According to the Watson-Crick model, when DNA primes the making of more DNA, the double helix uncoils. Then along each chain a complementary chain is formed. In Kornberg's experiments the pattern of nearest-neighbor frequencies in every case showed the pairing of adenine to thymine and guanine to cytosine, just as in the model. A geneticist can now see how it is that each gene is derived from a pre-existing gene.

It was of course the more general activity of the genes—by which they bring about the expression of hereditary traits in the organism—that led to their discovery. The way to an understanding



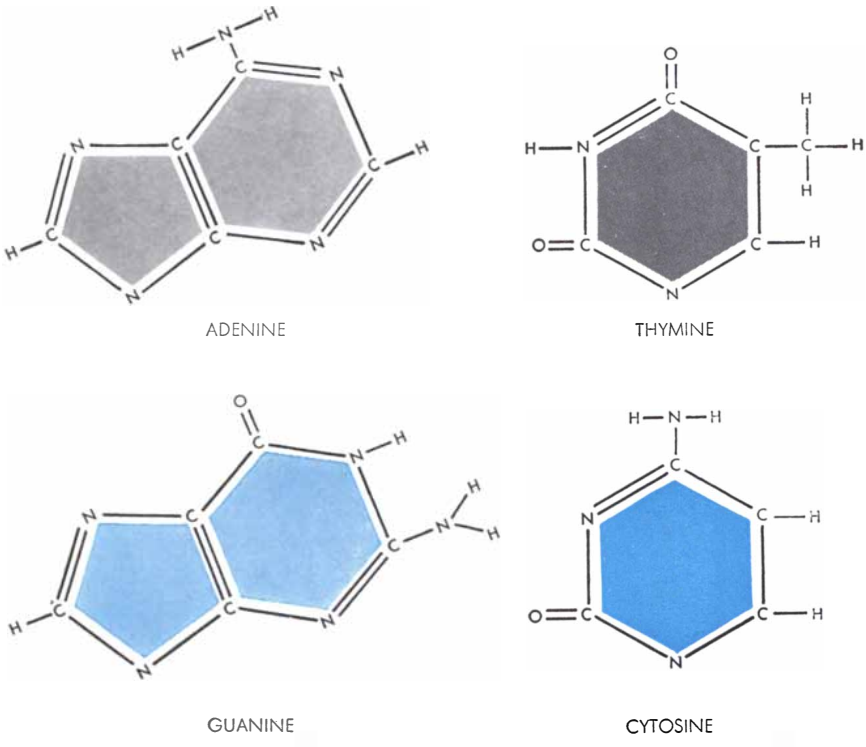
RIBOSOMES, the sites of protein synthesis, are shown in this electron micrograph made by Bernard Tandler of the Sloan-Kettering Institute. The cytoplasmic membrane system of a human submaxillary gland cell is enlarged 70,000 times. The ribosomes are the small, dark particles, each about .000015 millimeter in diameter, lining the membranes. The large oblong bodies are mitochondria.

of this activity at the molecular level—how DNA governs the biosynthetic processes of the cell—has become clear only in the last 10 years.

The heritable changes that geneticists first studied were necessarily those most readily observed. Many of these were changes in color. One of the early Mendelians was the English physician Archibald Garrod, who made a penetrating study of a rare hereditary disease in man characterized by the appearance of a black pigment, alcapton, in the urine. The pigment is formed because there is a derangement in the metabolism of the amino acid tyrosine; one particular reaction that normally occurs fails to occur. This failure, Garrod perceived as far back as 1909, is due to the absence of an enzyme that is normally present. The role of the normal gene, therefore, is to determine the production of a particular enzyme, and this is what the abnormal gene fails to do.

The idea that the action of a gene is concerned with the formation of a particular enzyme was ignored by most geneticists for some 30 years. It was revived by George W. Beadle and Edward L. Tatum when they showed the principle at work in heritable metabolic derangements of the red bread mold *Neurospora*. This time the idea made a deep impression on geneticists and biochemists, in part because the chemical nature of enzymes had meanwhile been revealed. Between 1926 and 1930 James B. Sumner of Cornell University and John H. Northrop of the Rockefeller Institute had shown that enzymes are proteins. The biochemical function of the gene was now to be looked for in the more general function of protein synthesis. It was firmly demonstrated in the early 1950's, when other examples of the determination of protein structure by genes were found in many animals, fungi and bacteria.

But the decisive new experiments were again, as in Garrod's time, on man—on human hemoglobin. Beginning with the hemoglobin of sickle-cell anemia, studied by Linus Pauling and his colleagues at the California Institute of Technology, quite a number of hereditary hemoglobin anomalies were discovered in an enterprising world-wide search. In several cases it was found that a gene mutation produces a single amino acid substitution in one location of the peptide chains, containing about 150 amino acids, that make up the hemoglobin molecule. So much precise information has by now been acquired linking genes and the amino acid composition in hemoglobins that there is no longer any doubt that genes determine protein synthesis.



DNA, the carrier of genetic information that serves as the "blueprint" for protein synthesis, has as its key components four nitrogenous bases. Their formulas are diagramed above and their arrangement in the complex DNA molecule is illustrated on the following two pages.

One of the best examples of the control of protein synthesis by the gene concerns the synthesis of DNA, the substance of the gene itself. When a bacterial virus that contains DNA enters a bacterial cell, a large quantity of virus DNA is soon synthesized. At the same time there is a five-to-ten-fold increase in activity of the enzyme polymerase, the enzyme that polymerizes mononucleotides and so produces DNA. But the polymerase in this case is the virus-induced polymerase, and it is distinctly different from the polymerase present in the bacterium before entry of the virus. This is to be expected since the genetic information for the new enzyme comes from virus DNA and not from the bacterial genes.

The understanding of how DNA directs protein synthesis in the cell involves among other things a vast lore of knowledge about protein synthesis and structure gained without reference to the cell. But the primary action of DNA also raises a logical problem that should be dealt with at the outset. Only four different nucleotides make up the long chains of DNA. Some 20 amino acids make up the long polypeptide chains of proteins. The genetic information in DNA is therefore spelled out in a four-letter alphabet. But the information in this molecular script is communicated to another in which the message must be translated into a 20-letter alphabet, the letters of which are entirely different from those in the four-letter alphabet. How is the information encoded and conveyed? The most plausible answer is that groups of three or four nucleotides are arranged in different sequences, each corresponding to a particular amino acid. By such an arrangement the four-letter DNA alphabet is able to determine the spelling out of protein structure in the 20-letter alphabet.

All cells synthesize protein, some continuously, others for only a part of their life cycle. The proteins they make are enormously varied, differing in size, shape, over-all chemical composition and physical properties. But whatever their function, and regardless of their size, shape, solubility or enzyme activity, all proteins have an underlying similarity in constitution: they are all made up of the relatively simple molecular units of amino acid. The synthesis of a protein from these smaller units is conceptually a simple process, involving the joining of the individual amino acids to form long chains. The length of the

chain and the sequence of the amino acids vary, of course, from one protein to another. But the essential unit of structure, the link that prolongs the chain, is ubiquitous; it is the peptide bond, the chemical union between the carboxyl group (COOH) of one amino acid and the amino group (NH_2) of the next amino acid in the chain.

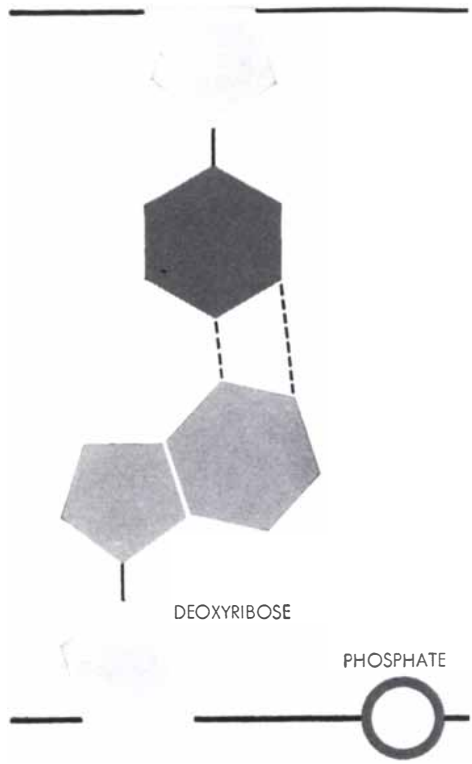
These bonds, connecting amino acids in various sequences, are the key linkages to be created in carrying out the synthesis of proteins or smaller polypeptides, either in the cell or in the laboratory. Since peptide bonds do not form spontaneously when amino acids are mixed, other chemical means have to be used to drive the formation of the bonds. The synthetic system of the cell begins with a reaction that "activates" the carboxyl group of the amino acids.

This reaction, originally discovered by Mahlon B. Hoagland of the Harvard Medical School in 1955, derives the energy necessary for the activation from adenosine triphosphate (ATP), the main energy currency of the cell [see "How Cells Transform Energy," page 62]. The ATP is cleaved to release two of its three phosphate groups; the remaining fragment, adenosine monophosphate (AMP), joins up with the acid group of the amino acid. In this way the amino acid is potentiated for the formation of the peptide bond. The enzymes that carry out this activation have great specificity: in general they react with only one type of amino acid. It is probable that most cells have activating enzymes for at least 20 amino acids. In animal cells these enzymes have been found in the nucleus as well as in the cytoplasm, and there is good evidence that they play a role in the synthesis of the nuclear proteins, including the proteins of the chromosomes.

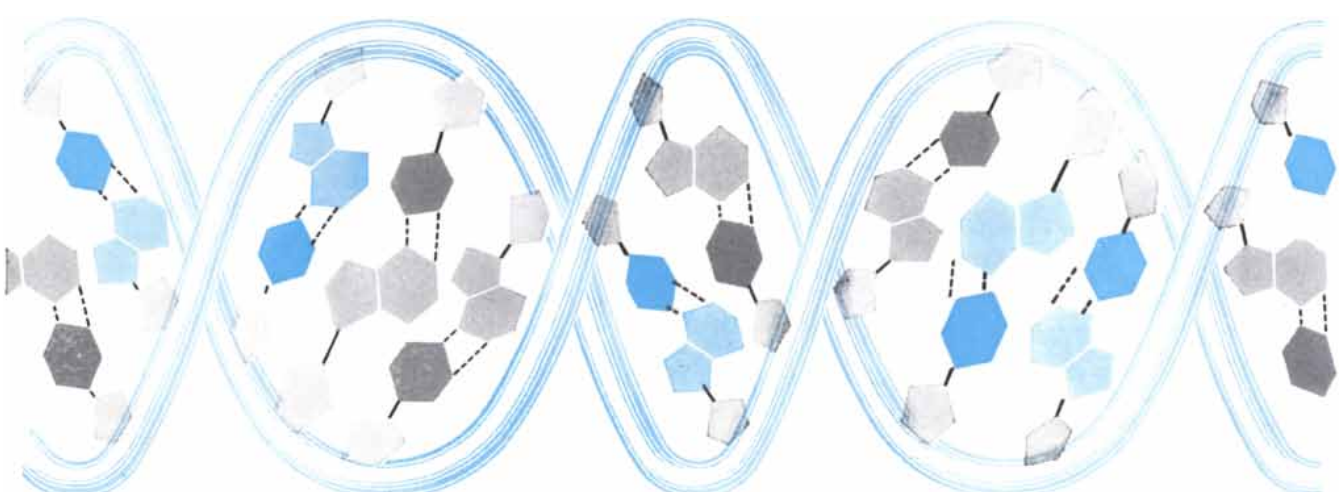
The activating enzymes mediate only the first step in a very complex and precisely ordered chain of reactions. The order is supplied by the information encoded in the DNA molecule. To convey the information from the DNA in the nucleus to the site of most protein synthesis in the cytoplasm, the cell employs another polynucleotide—ribonucleic acid (RNA)—as an intermediary. In RNA the sugar is ribose instead of deoxyribose; the main RNA bases are adenine, guanine, cytosine and, instead of thymine, uracil. As in DNA, the different nucleotides are linked together through their phosphate groups to form long chains.

The need for ribonucleic acid in protein synthesis was suggested 20 years ago, when Torbjörn O. Caspersson in Stockholm and Jean Brachet in Brussels showed that tissues that synthesize large amounts of protein, whether for growth or multiplication, are always rich in RNA. One of the highest RNA concentrations is found in the cells of the spinning gland of silkworms, which produce the proteins fibroin and sericin of the silk thread. In mammals, high RNA concentrations occur in such specialized cells as those of the pancreas and liver, in which many proteins are synthesized for transport to other parts of the organism.

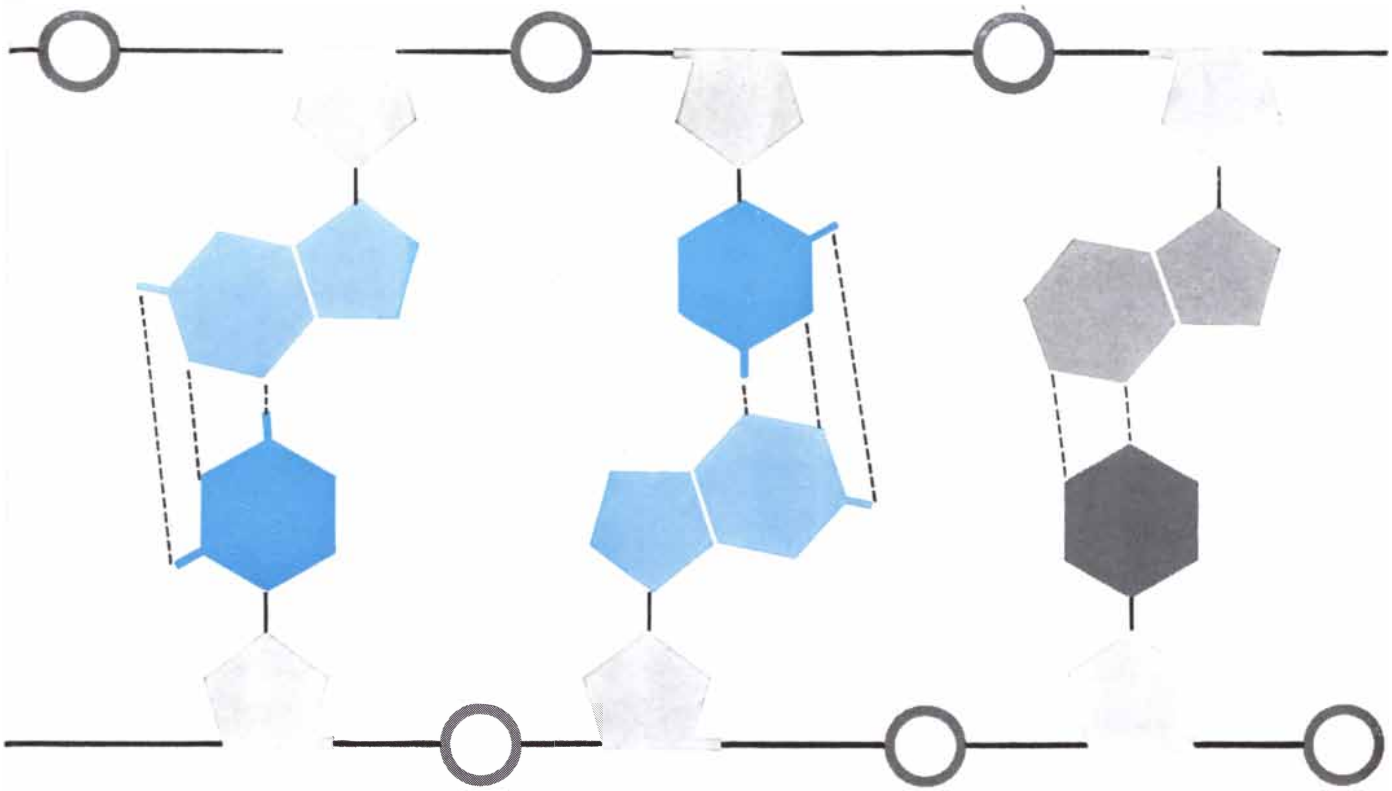
When cells synthesize protein on this scale, it is usually observed that the synthetic machinery is highly organized into a lamellar network of membranes and RNA-rich particles. The biochemical knowledge of these structures comes largely from studies of cell homogenates, from which different intracellular structures can be isolated by centrifuging at different speeds; that knowledge is now significantly supplemented by electron micrographs of the cytoplasmic membrane system [*see illustration on page 76*]. Particular interest attaches to the particles, which, in a liver cell, are



DNA MOLECULE is in the form of a long double chain of nucleotides—phosphate-linked deoxyribose sugar groups to each of



DNA MOLECULE, shown at the top of these pages as a straight ladder, is actually twisted into a double helix, according to the generally accepted Watson-Crick model. In this drawing the phosphate groups are not shown. The sugar and base molecules are shown diagrammatically; in the actual three-dimensional model the base pairs that make up the crosslinks all lie in parallel planes.



which one of the four bases is attached as a side group. Hydrogen bonds (*broken lines*) link pairs of bases to form the double chain. The bases are always paired as shown: adenine with thymine and guanine with cytosine. The sequence of pairs, however, can be varied infinitely. The sequence encodes the information that determines what kinds of protein shall be synthesized by the cell.

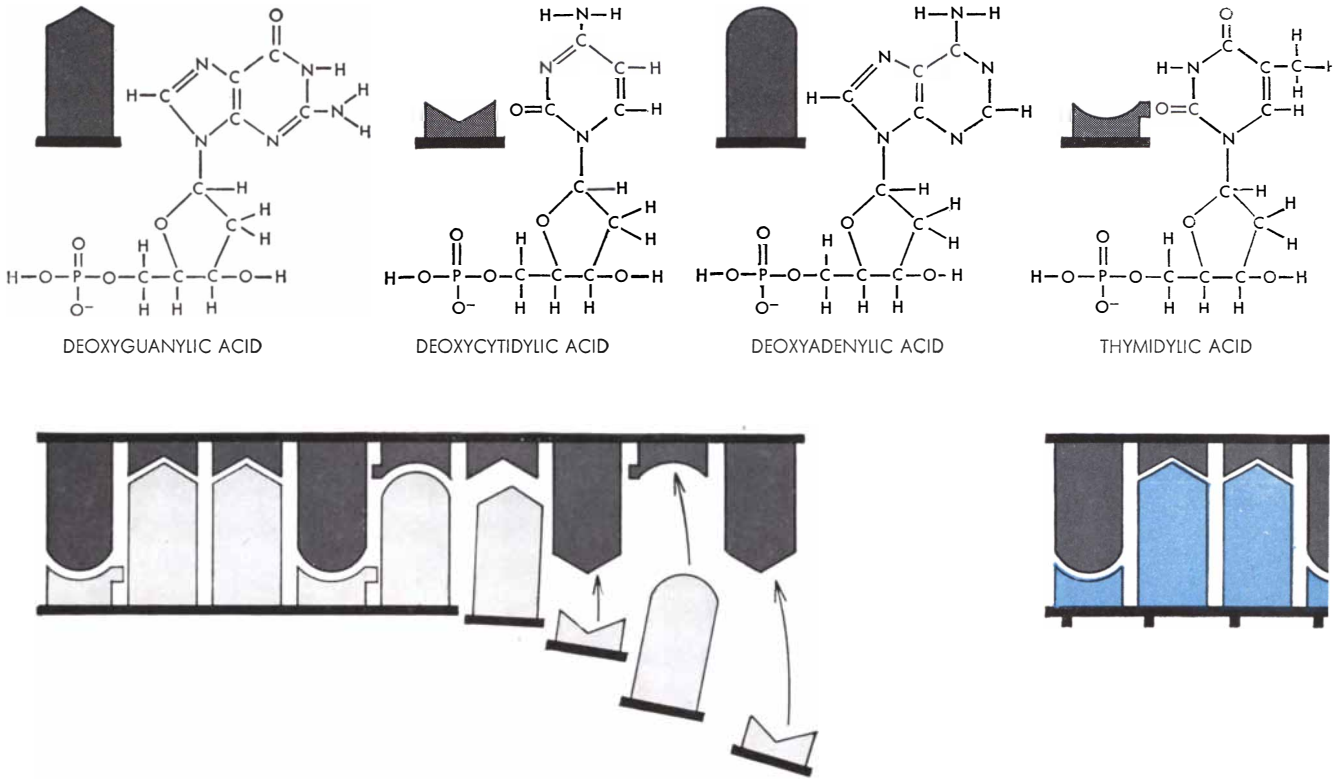
roughly spherical and about .000015 millimeter in diameter. In fully differentiated cells of the pancreas or liver, most of these particles are attached to membrane surfaces, but in embryonic tissues the particles appear free in the cytoplasm. George E. Palade of the Rockefeller Institute has suggested that the particles, not the membranes, are the primary sites of protein synthesis in these cytoplasmic systems. This view has been proved correct by biochemical studies of the particles themselves, isolated not only from pancreas and liver but also from tumor cells, plants, yeasts and bacteria. Most workers in the field now refer to the particles as ribosomes.

Whatever cell they come from, ribosomes are extraordinarily rich in RNA. Bacterial ribosomes, for example, have a molecular weight of nearly three million, of which at least 60 per cent is RNA. Ribosomes prepared from liver or yeast have a molecular weight of about four million, of which more than 40 per cent is RNA. Few purified ribosome preparations contain less RNA than this. Protein, often rich in basic amino acids, constitutes most of the remaining mass of the isolated ribosomes.

The first chemical indication that ribonucleoproteins play such a direct role in the synthesis of other proteins came from "tracer" experiments in which living animals were given isotopically labeled amino acids (that is, amino acids containing atoms of nitrogen 15 or carbon 14 instead of the nitrogen 14 or carbon 12 atoms usually present). Henry Borsook of the California Institute of Technology and Tore J. M. Hultin of the Wenner-Gren Institute in Stockholm in 1950 independently showed that when the cells of a labeled tissue were broken and fractionated, the highest concentration of labeled amino acids showed up in the microsome fraction. This fraction was subsequently shown by Philip Siekevitz and Palade to contain the ribosomal particles attached to membrane fragments. In 1953 Marie Maynard Daly and the authors made careful kinetic studies of the rate of nitrogen-15 amino acid uptake into different protein fractions of the pancreas cell. The results made it very likely that some of the protein attached to ribonucleic acid was a direct precursor of the enzyme proteins that are found free in the cell. Moreover, we found that an attack on the RNA by a specific enzyme, ribonuclease, stopped protein synthesis in isolated subcellular fractions. The experiments made on whole animals and in isolated cells were soon supplemented by studies of cell-free systems containing RNA, which would incorporate amino acids into protein in the test tube. The development of these systems was largely due to the experiments of Paul C. Zamecnik and his colleagues at the Massachusetts General Hospital.

Although many experiments suggested a direct role for RNA in protein synthesis, it has only recently been shown that the function of RNA is to supply the information necessary to organize the sequence of the amino acids in peptide chains. The argument is clinched by experiments in which a modification of the RNA has brought a change in the protein product. Working with a plant virus, Gerhard Schramm and his co-workers at the University of Tübingen succeeded in substituting a hydroxyl for an amino group in the viral RNA; the substitution led to the formation of a different viral protein. By growing bacteria in the presence of 5-fluoro-uracil, François Gros of the Pasteur Institute in Paris has caused this substance to replace the normal base uracil in the bacterial RNA; the bacteria thereupon synthesized an abnormal protein instead of the enzyme *beta*-galactosidase.

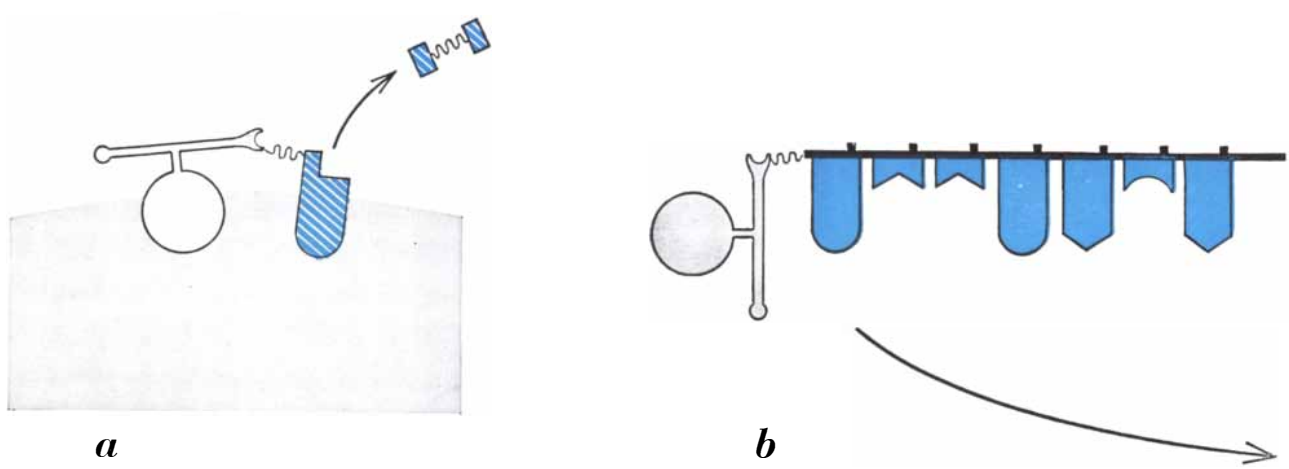
From all that is known, it is now supposed that RNA's in the ribosomes act as templates that determine the se-



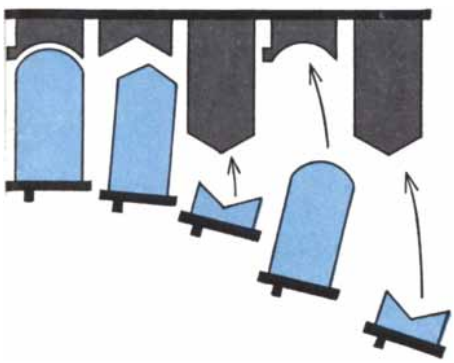
"BASE PAIRING" is the process by which DNA is replicated in cell division and by which it makes RNA, the closely related nucleic acid that in turn synthesizes proteins. The four nucleotides of DNA are symbolized (*upper left*) by four building blocks shaped as complementary pairs. RNA (*upper right*) differs only slightly: its sugar has an extra oxygen atom, and uridylic acid replaces DNA's thymidylic acid. The lower diagrams show how DNA can either replicate or form RNA carrying the same genetic information.

quence in which amino acids are linked together in protein chains. They reproduce in their nucleotide sequences the information encoded in the master templates of the DNA molecules in the cell nucleus.

But how do amino acids get to the RNA templates from their activating enzymes? Here too ribonucleic acids play a role. In 1957 several laboratories announced the discovery of low-molecular-weight RNA's that transfer activated amino acids to ribosomes. The function of these "transfer" RNA's is to get amino acids properly lined up on the RNA template of the ribosome. This view, put forward by Crick and others, assumes that there are 20 or so transfer RNA's, each specific for a particular amino acid and also capable of recognizing certain specific sites on the template. It is, of course, the nucleotide sequence in the shorter chains of these low-molecular-weight RNA's that capacitates them for



PROTEIN SYNTHESIS involves two kinds of RNA. "Template RNA" in the ribosomes organizes the sequence of amino acids to make protein. "Transfer RNA" carries the amino acids to the template. Transfer RNA is the intermediary: part of it can apparently recognize a specific amino acid and part is coded to seek the proper site on the template. The process begins (*a*) with activation of an amino acid by adenosine triphosphate (ATP), the cellular energy carrier (*hatched*). Two phosphate groups drop from ATP and, with

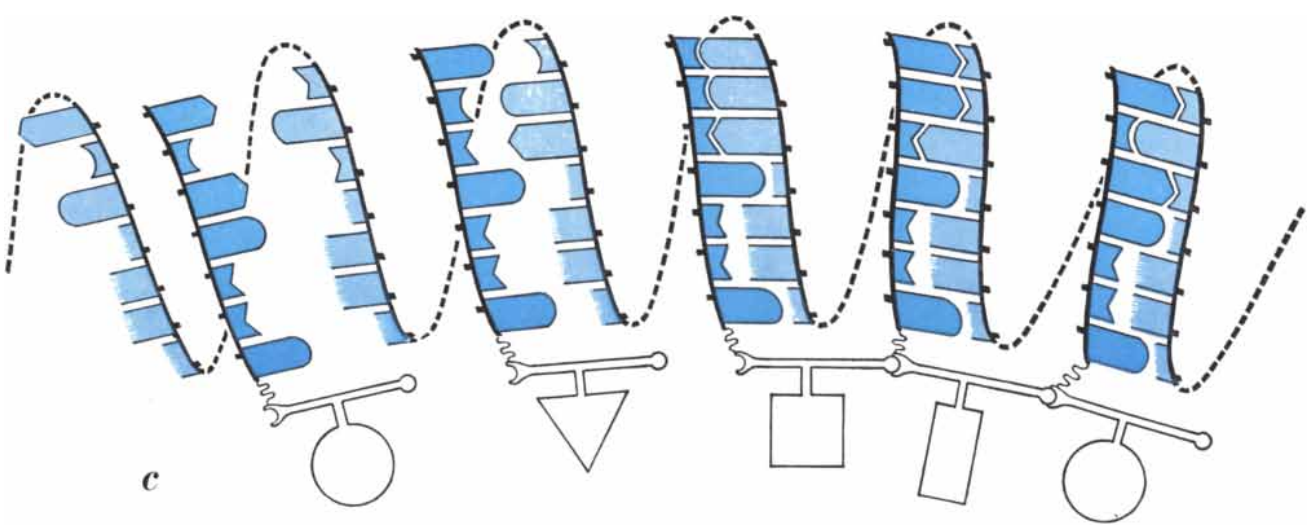


A single strand of DNA (*dark gray*) assembles new DNA nucleotides (*light gray*) or RNA nucleotides (*color*) that match its complementary strand.

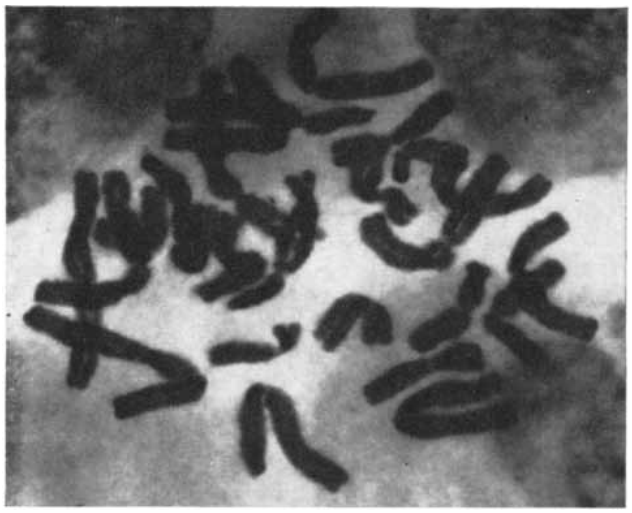
AMINO ACIDS are the constituents of proteins. Here four amino acids (of 20-odd that are known) are represented by building blocks. In the top row the symbols and formulas of the four are shown separately; in the bottom row they have been linked by peptide bonds, in which H_2O is dropped from adjacent COOH and NH_2 groups to form a fragment of protein.

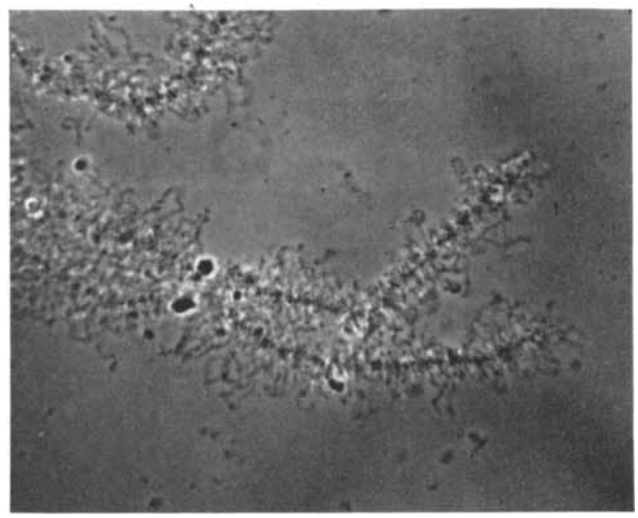
both of these highly specific reactions. According to this scheme the amino acids are transferred upon activation to the appropriate transfer-RNA chain. The transfer-RNA molecule then combines with its complementary sequence of nucleotides in the template RNA. This transfer reaction is known to be mediated by an enzyme requiring guanosine triphosphate. Other transfer RNA's, carrying other amino acids, take their appropriate places on the template, and the amino acids are now aligned and held in proper sequence to form the specific polypeptide chain of the protein.

Though this picture of transfer RNA as an adapter molecule is still tentative, something is known about the coupling of amino acids in the ribosome. Recent work on hemoglobin synthesis, by Richard Schweet of the University of Kentucky Medical School and by Howard M. Dintzis at the Massachusetts Institute of Technology, indicates that



the help of an enzyme (*gray*), the amino acid is attached to the remaining adenylic acid by a high-energy bond (*wavy line*). Then a transfer RNA molecule moves in (*dark-colored symbol at "b"*). Each transfer RNA has an adenylic acid at one end; that end takes over the bond to the amino acid. Finally, the transfer RNA carries the selected amino acid to a ribosome (*c*). There the coded section of the transfer RNA finds its place on the template (*light color*) and positions the amino acid to join with others in a protein chain.





DNA IN CHROMOSOMES is an inert repository of genetic information when the chromosomes are tightly coiled rods during mitosis (*left*). Between cell divisions, when DNA is doing its genetic work, the chromosomes are greatly extended, as in the "lampbrush" configuration (*right*). These photomicrographs of newt chromosomes were taken by H. G. Callan of St. Andrews University.

peptide-bond formation proceeds much like a zipper, starting with the amino acid valine at one end of the chain and closing bond after bond until the protein molecule is finished. New amino acids are added to the growing chain at the rate of about two per second, finishing the protein molecule (of 150 amino acids) in 1.5 minutes. This impressive feat, the synthesis of a finished protein molecule in less than two minutes, is testimony to the efficiency of the protein-synthetic mechanism of the cell.

One question now remains: How is the information encoded in the master template, DNA, transmitted to ribonucleic acids? The most suggestive clues come from experiments on enzyme systems that synthesize RNA. Samuel Weiss at the University of Chicago and Jerard Hurwitz at New York University have described enzyme systems isolated from animal cells and bacteria that utilize all four nucleotides (as triphosphates) for RNA synthesis. Although the nucleic acid being synthesized is RNA, DNA must be present for synthesis to occur. What is more remarkable, the nucleotide composition of the DNA determines what kind of RNA will be formed. The base-pairing rules of the Watson-Crick DNA model appear to apply with equal rigor to the formation of these DNA-RNA hybrids. DNA templates induce the synthesis of complementary RNA molecules only.

This control over RNA synthesis by DNA is also seen in living cells. Elliot Volkin of the Oak Ridge National Laboratory found in 1958 that when bacterial viruses infect bacteria, an RNA is formed that resembles the virus DNA and not that of the host in its base composition. Benjamin D. Hall and Sol Spiegelman of the University of Illinois then showed that the sequence of the nucleotides in the new RNA molecule is complementary to that of the RNA of the virus.

So the story comes full circle. Specific genetic information resides in the nucleotide sequences in DNA. By means of base-pairing mechanisms these sequences are copied to produce either new DNA molecules for new cells or the RNA templates needed for protein synthesis. Specific nucleotide sequences in the ribosome templates encode the amino acid sequence for particular proteins. The transfer RNA's recognize these sequences and bring amino acids into the proper alignment. Peptide bonds then form with great specificity and rapidity, putting together the protein molecules characteristic of the species. These proteins, many of them enzymes, are the tools with which the cell synthesizes the host of other molecules (purines, pyrimidines, amino acids, carbohydrates, fats, sterols, pigments and so on) necessary to its structure and function.

What has been said so far makes it clear that there is a transmission of genetic information from the DNA in the chromosomes to the sites of protein synthesis. Textbooks often show this flow as an arrow leading from the nucleus to the cytoplasm. There is no corresponding arrow from the cytoplasm back to the nucleus. Absence of the return arrow might suggest to a biologist that there is something essential missing in the scheme, for in all biological systems that have been carefully studied there is a feedback. In the cell there is indeed evidence for a feedback control directed from the cytoplasm to the chromosomes. In some cases the feedback comes quickly and lasts for only a short time. In the pancreas, for example, when the cells are stimulated so that their cytoplasm synthesizes digestive enzymes, tracer experiments show that within a few minutes there is a rise in the uptake of amino acids into proteins of the chromosomes. There are also less immediate and more enduring cytoplasmic influences on chromosomes. Among these are the profound changes associated with cell differentiation [see "How Cells Specialize," page 124].

But although protein synthesis in chromosomes has been shown to be subject to feedback control, there is at present no evidence that the sequence of bases in DNA can be altered by feedback. The chromosomes of germ cells have changed in the course of evolution so that they carry genetic information that is effective in adapting an organism to its environment. The DNA of a germ cell has been shaped by evolution so that it can determine the synthesis of enzymes and other proteins that make for a viable organism. The important point here is that the changes that have taken place during the course of evolution in the DNA molecules of the germ cells of an organism are not the direct result of a feedback from the cytoplasm to the chromosomes in the nucleus. Changes in DNA itself, according to the generally held views of biologists today, are due to mutation and selection.

Kodak reports on:

Tenite Butyrate men . . . the pallid virtue in a certain niggardliness . . . cutting down on copy breaks . . . when to remember our name and when to forget it

A phantom

Dozens of these phantoms have been manufactured out of our *Tenite Butyrate* for government, industry, universities, and hospitals by Alderson Research Laboratories, Inc., 48-14 33rd Street, Long Island City 1, N. Y. We know an interesting phantom when we see one and will forgive you for not knowing that the word means a dummy which simulates the human body in studies with ionizing radiation. (In perfecting the new medical x-ray films mentioned below to make them give the kind of rendition that a radiologist best understands, our phantoms were radiographed so frequently they almost spit fire.) The *Tenite* phantom here shown acts as an emitter for calibrating whole-body counters and such, its Tenite thyroid, liver, lungs, spleen, kidneys, and other organs filled with radioactive solutions that simulate the radiative properties of a radioisotope-treated organ. Alternatively the Tenite shell can be equipped with a human skeleton inside and a system of dosimeter ports for studies of absorption of radioactivity.

Sound tape, very sound

Eastman Sound Recording Tape has just started to enter the professional sound-recording market. The future will speak for itself, but for the present not a single reel of it is offered blank for home recording. (Digital recording tape is a different article.)

Eastman Tape differs from the best professional sound tape hitherto available only in uniformity, a pallid virtue but one not to be sneezed at because it made us what we are today in the motion-picture business, where a man who has to throw work away for technical inadequacy winds up slinking through back alleys.

Magnetic tape needs about the same thickness of coating as do the emulsions of a complicated color film, where much of the secret of success lies in niggardliness with thickness tolerance. Thickness variation of magnetic oxide coating shows up as spurious amplitude modulation. The oxide particles themselves closely match in size the silver halide crystals of a medium fine-grain photographic emulsion. The problems of preparing their surfaces for uniform distribution through a matrix are familiar to us. The answers turn out a little different from those first thought out, but satisfactory. Eastman Tape is no better than the best rolls of the best-regarded grade of the best-regarded other brand. Our methods, however, make *all* our rolls that good.

Eastman Sound Recording Tape *is currently sold only by Eastman Kodak Company, Motion Picture Film Department, 342 Madison Avenue, New York 17, N. Y.*

Has anybody seen Gwendolyn?

Lucky is the scientific worker who can afford a contemptuous attitude toward office routines. This item will bore him.

It deals with those copying machines that are now seen wherever there is paperwork. Their popularity is traceable to the introduction of the *Kodak Verifax* copier some 8 years ago. Now there are dozens upon dozens of makes of office copiers. The Verifax copier differs from the other inexpensive ones in permitting as many as five copies to be run off from a single sheet of sensitized material. The cost of making n copies is therefore $c_V = s_V + np_V$ where s_V is the cost of the sensitized material (which we call—and don't take this too hard—the "magic matrix") and p_V is the cost of a sheet of copy paper. With the others, the cost of making n copies is simply $c_A = n\ s_A$.

Here are some going rates for Verifax and other systems:

s_V	p_V	s_A	s_B	s_C	s_D
8¢	1¢	8¢	7¢	6¢	5¢

On this basis it becomes clear that if more than one copy is usually required, the Verifax copy is the best buy.

There are copiers which need no expendable sensitized goods. The cost or rental fee for these machines generally confines them to a central location where they can serve an entire organization of some size. This leads to the question of the reason for having a secretary. If you need her merely as a status symbol, we have nothing further to say to you on this subject. If, though, she has more directly useful work to do that justifies a weekly salary of $70 and she averages three 10-minute trips a day to the central copier, her walks for copies cost $225 a year. A Verifax copier could be placed next to her desk for less than $100.*

Simple though these great economic truths may be, we have gone so far as to prepare little cardboard calculators for convenience in making representations to the management. Request a free set from Eastman Kodak Company, Business Photo Methods Division, Rochester 4, N. Y.

A little x-ray news

More precious than rubies is confidence in the importance of what one does for a living. One thing we do for a living is to manufacture x-ray film. Unkind words are rarely spoken about society's need for x-ray film. Now we have news about x-ray film and need to make it seem important. Easy.

The first piece of news has it that *Kodak Industrial X-ray Film, Type M* is now obtainable with emulsion on one side only instead of both sides, the way x-ray film usually comes in order to double the strength of the image. Simple, yes; trivial, no. Ties in to the very large subject of mankind's current push for great structural strength in small mass. Load-bearing members are now getting so thin that putative flaws on their radiographs have to be checked out with a microscope. Since a microscope can focus on only one side of the film at a time, it's better to have the other side blank. Enough of this is being done now so that x-ray dealers are stocking the single-coated film of high contrast and fine grain.

Eastman Kodak Company, X-ray Division, Rochester 4, N. Y., will be glad to guide you to such a dealer.

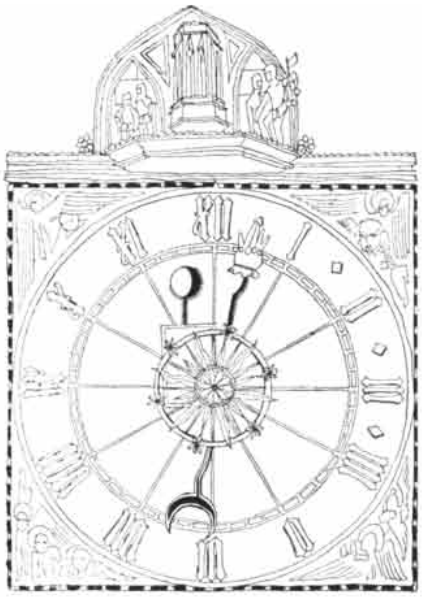
The second piece of news much exceeds the first in importance. The nuclear testing debate has gone on for years. As an intelligent citizen, you have been given estimates by various authorities of how much radiation you and your children can expect to soak up, barring disaster. You have been told how much to figure for medical and dental radiological examination over a lifetime. Meanwhile we have been quietly goofing up the statistics! We have been upping the response of the films. With the latest step, the same amount of examination requires half or a third as much radiation as had been estimated.

No action is required on your part. Just privately rejoice a little at how the deal has been sweetened a bit for you, statistically.

*Price subject to change without notice.

Kodak
TRADE MARK

This is another advertisement where Eastman Kodak Company probes at random for mutual interests and occasionally a little revenue from those whose work has something to do with science



The Cost of Science Education

If present trends in college and graduate school registration continue, the U.S. can double the number of students receiving doctoral degrees in science and engineering and the number of professional scientists and engineers in its labor force by 1970. To do so, however, it will have to increase expenditures for science and engineering education in colleges and universities from the 1961 level of $2.1 billion a year to $5.5 billion a year in 1970. In addition the institutions will need $2.7 billion instead of the present $900 million a year to carry on the basic research that is an essential part of university science education.

These estimates appear in a report entitled *Investing in Scientific Progress*, issued by the National Science Foundation as a follow-up to the so-called Seaborg Report, *Scientific Progress, the Universities and the Federal Government*, published by the President's Science Advisory Committee last fall. The new document was prepared by a group under Richard H. Bolt, professor of acoustics at the Massachusetts Institute of Technology now on leave to serve as associate director of NSF.

During the past 30 years, the report notes, the number of professional scientists in the labor force has grown an average of 6 per cent a year. If this rate continues, the total of 1,400,000 in 1960 will rise to 2,500,000 in 1970. The number of students earning doctoral degrees in science and engineering is rising even more rapidly—fast enough to reach 13,000 a year in 1970 (as compared with 6,600 in 1960) and to bring the total number of Ph.D.'s in the labor force to 168,000 (from 87,000 in 1960). Colleges and universities will need extensive help in coping with these increased numbers. Funds are required to increase science teaching staffs from 100,000 (1961) to 175,000 (1970); to provide $200 million worth of new teaching equipment and up to $360 million worth of new laboratory buildings a year; to make up an existing $800 million shortage in teaching plant; and to permit a proportionate increase in the university research establishment. Over the next 10 years, the report concludes, college and university expenditures for science teaching and research will have to be raised to a total of $8.2 billion a year.

Space Communications

In a major policy statement issued late in July, President Kennedy set down "guidelines" governing the creation of a space-satellite communications system. The statement declared that "private ownership and operation of the U.S. portion of the system is favored," subject to certain conditions. One is that the system must be truly world-wide, providing service to "the farthest corner of the globe" even if all corners are not profitable. Another condition is that foreign firms or governments must be allowed to participate in the venture. The U.S. Government promises to co-operate fully in establishing the system "for global benefit at the earliest practicable time." The Government will control the launching of all U.S. spacecraft needed for the project.

The statement settled the argument as to who should be allowed to participate in the venture. Owners and users must be "authorized carriers," meaning firms whose business is international communications (not rocket builders, unless they care to qualify themselves). According to the Federal Communications Commission there are now 10 such firms: American Cable and Radio Corp., American Telephone & Telegraph Co., Hawaiian Telephone Co., Press Wireless, Inc., Radio Corporation of Puerto Rico, RCA Communications, Inc., South Puerto Rico Sugar Co., Tropical Radio Telegraph Co., United States–Liberia

THE CITIZEN

Radio Corp. and Western Union Telegraph Co.

Two of the 10 firms, A.T.&T. and RCA, are already deep in development of communications satellites. Early next year the National Aeronautics and Space Administration will launch and track, for a fee of about $6 million, an experimental communications satellite developed by A.T.&T. Also next spring NASA will send up a communications satellite of its own, built by RCA and called the Project Relay satellite.

The A.T.&T. and RCA satellites belong to the class known as "active repeaters." They will receive signals beamed to them from transmitters on earth and rebroadcast the signals earthward, to be picked up by any suitably equipped station within line of sight. These first repeaters will travel in an orbit at an altitude of about 3,000 miles. A.T.&T. has proposed that a global system could be achieved with some 30 to 50 repeaters spaced randomly in belts about 7,000 miles high so that at least one would always be within sight of each of 26 ground stations. The system would cost about $500 million. A.T.&T. favors this system after weighing the advantages and disadvantages of "passive" satellites, such as *Echo I*, which merely reflect signals beamed at them from earth. The chief drawback of this concept is the large and costly ground equipment required to pick up the faint returning echoes.

A.T.&T. and others are also studying more advanced systems in which three large active repeaters (plus a stand-by for each) would be spaced equally around the equator at a height of 22,300 miles. At this altitude they will seem to be stationary over the earth. For example, a unit located over the Atlantic would be within constant sight of a segment of the earth that is bounded by New Mexico on the west and Athens on the east.

The big unknown in all the proposed systems is the reliability of launching vehicles and the reliability of repeaters once placed in orbit. A recent cost study made by William Meckling of the Rand Corporation shows that the satellite systems should be roughly competitive in cost with submarine cable systems if about 75 per cent of the launchings are successful and if the average oper-

ating life of the satellite repeaters, once they have been placed in orbit, is about two years.

More Time for Evolution

The first known toolmakers now appear to have lived 1,750,000 years ago, more than a million years earlier than was previously believed. Radioactive dating has suggested this age for *Zinjanthropus,* the "Nutcracker Man" of Olduvai Gorge in Tanganyika, and for an unnamed manlike animal discovered in the same place by L. S. B. Leakey of the Coryndon Museum.

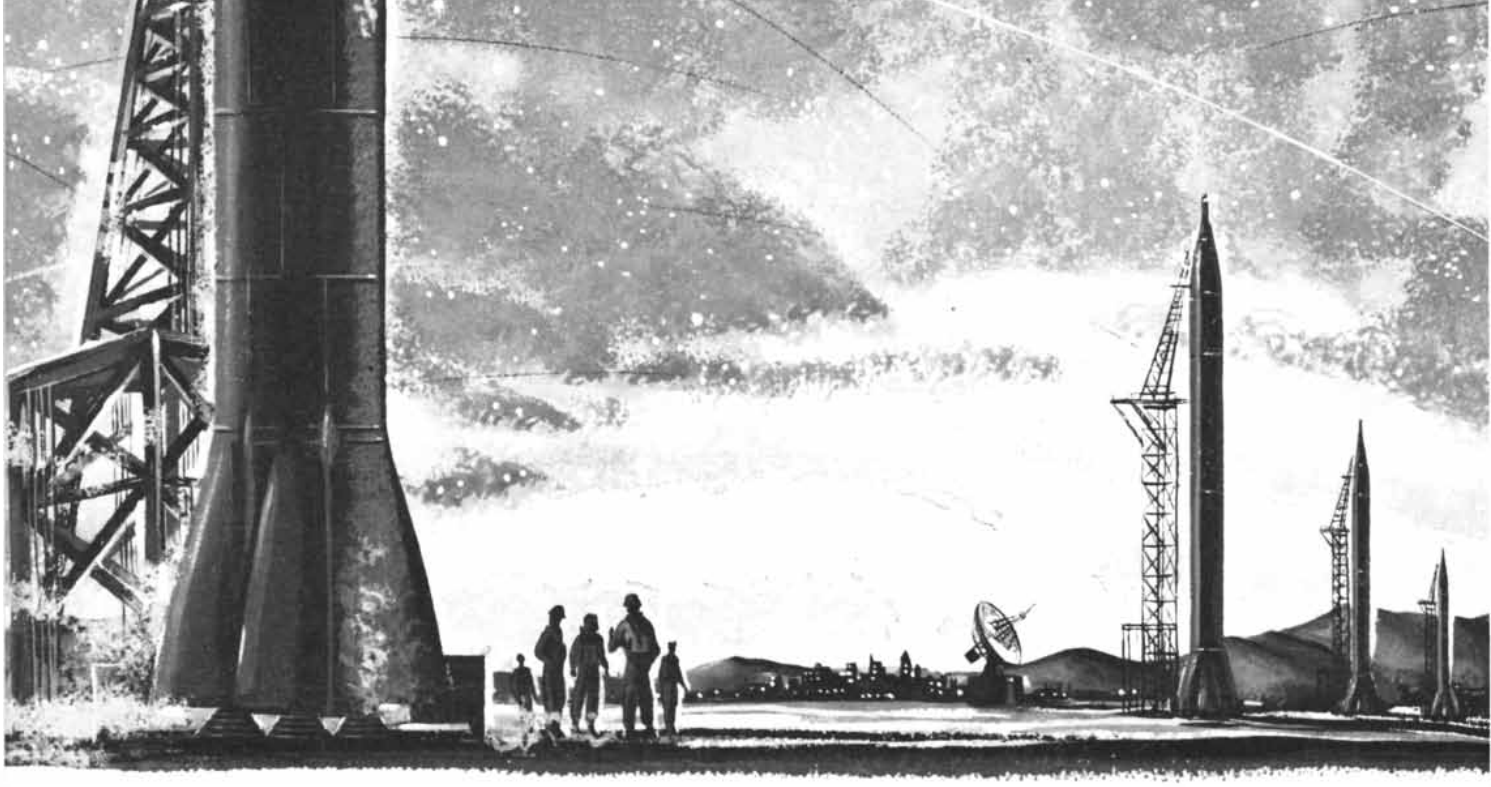
The dating was carried out by Jack F. Evernden and Garniss H. Curtis of the University of California. There is no way to date bone more than 50,000 years old, so they analyzed samples of rock from immediately above and below the level where the bones were found. By measuring the content of potassium 40 and its decay product, argon 40, in six samples Evernden and Curtis obtained an average age of 1,750,000 years, plus or minus "a couple of hundred thousand years." The younger samples showed signs of weathering, so the dates yielded by the older rocks may be more reliable and the finds may actually date back more than 1,750,000 years.

The unnamed specimen came from a slightly lower, and therefore older, stratum than did *Zinjanthropus.* The difference in age is not great—according to Curtis no more than 50,000 years—but the older individual is somewhat more highly developed than *Zinjanthropus.* Which of the two men was the maker of the many stone tools found in conjunction with both of them is still an open question.

The new date for the two Olduvai hominids puts the emergence of toolmaking back before the date of a million years usually given for the start of the Pleistocene, the era of ice ages and of the history of man. But many early Pleistocene dates are themselves in doubt. In any event, as T. Dale Stewart of the Smithsonian Institution commented, it seems more reasonable to fit human evolution into a span of 1.7 million years than to compress the entire process into little more than 500,000.

Dying Disease

Parkinson's disease, a crippling neurological ailment that afflicts substantially more than a quarter of a million Americans, should cease to be a major medical problem within the next 25 years. The prediction was made at a



EXPANDABILITY UNLIMITED...

Bendix G-20 COMPUTER *meets the dynamic demands of space-age computing*

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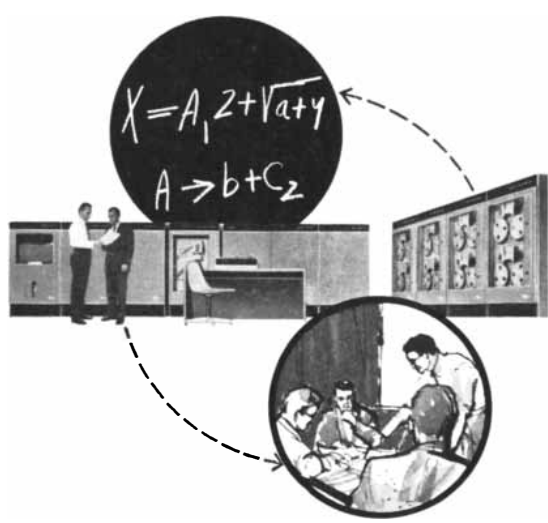

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meeting of the American Neurological Association by Robert S. Schwab and David C. Poskanzer, neurologists on the staff of the Massachusetts General Hospital. It is based on the curious fact that Parkinsonian patients seem to form a distinct group in the population who are aging together and will have died by about 1985.

Several years ago Schwab noticed that the average age of Parkinsonian patients under treatment at the Boston hospital and at centers in New York and Leeds, England, had risen seven years between 1948 and 1955. He and Poskanzer thereupon undertook a more detailed analysis of the records at these centers and at institutions in Kassel, Germany, and in Buenos Aires. The study showed a steady rise over the years in the average age of Parkinsonian patients in all five centers. Thus in 1938 the mean age was 44, in 1948 it was 55, in 1957 it was 65. In 1920 the typical Parkinsonian patient seen at the Massachusetts General Hospital was 21; 40 years later he was 39 years older. The rise in age applies to new as well as old cases.

The phenomenon suggests that most Parkinsonian patients were exposed to a common noxious agent at some time in the past. Schwab and Poskanzer believe it to have been the virus that caused the 1918 influenza pandemic, during which many cases of encephalitis also occurred. Most Parkinsonian patients, however, do not recall having had either encephalitis or influenza during or after the 1918 outbreak. In any event the Boston neurologists expect the incidence of Parkinson's disease to decline by two-thirds or more by 1985.

Explosions, Not Collisions

What is the origin of the prodigious quantities of radio energy emitted by the radio "stars" outside the Milky Way? A few years ago it was generally agreed that the power came from collisions between galaxies. Since then this explanation has begun to seem more and more dubious, and radio astronomers are now casting about for another mechanism.

Objections to the collision idea have been raised by a number of astrophysicists, notably V. A. Ambartsumian and I. S. Shklovsky in the U.S.S.R. and Geoffrey R. Burbidge of the Yerkes Observatory of the University of Chicago. For one thing, the frequency with which galaxies can be expected to bump into each other is too low to account for the number of known radio sources. For another, calculations indicate that the proc-

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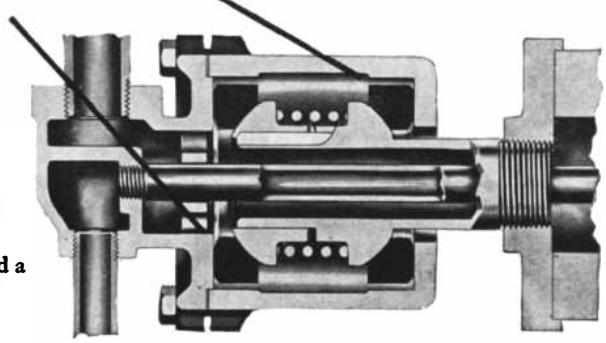

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ess that transforms collision energy into electromagnetic energy is too inefficient to produce the observed power.

If theoretical difficulties make the collision hypothesis unlikely, observation in some cases rules it out entirely. As the resolving power of radio telescopes has increased it has become possible to match a substantial number of distant radio sources with visible objects. Many of them turn out to be single galaxies—not pairs of galaxies, colliding or otherwise. A surprisingly large proportion of the newly identified sources are elliptical galaxies, some single, some double. These objects are almost devoid of gas and dust, the medium through which collision energy must be converted into radio emission. Thus even the double elliptical radio sources must draw their energy from some process other than collision.

In a recent issue of *Nature,* Burbidge proposes that most or all radio sources outside our galaxy are powered by chain-reacting supernovae. He argues that in a galaxy of closely packed stars (elliptical galaxies are of this type) radiation from one supernova explosion might heat up neighboring stars enough to make them explode; their radiation could in turn trigger more supernovae and so on. The time scale for each link in the chain, Burbidge calculates, might be as short as 150 years. The explosions would continue, thinning out the galaxy, until the stellar density became too low to support the chain reaction.

The whole cycle might last only a few hundred or a few thousand years. During the period and for some hundreds of years afterward the galaxies would be marked by strong and distinctive emission lines in their optical spectra. Burbidge suggests that certain of the radio sources be examined for these lines. Not all sources are expected to exhibit them, because a galaxy would continue to emit radio waves long after the optical effects of a chain reaction had died out.

Antipollution Law

President Kennedy has signed a bill giving the Federal Government increased powers and more money for curbing water pollution. Under the new law the Government can advance funds for projects on any navigable river; previously it was restricted to projects in interstate waters. It can even prosecute to halt nuisances in intrastate waters, although in such cases the consent of the state's governor must be obtained. And the sum available for aid in building sewage-treatment plants during the

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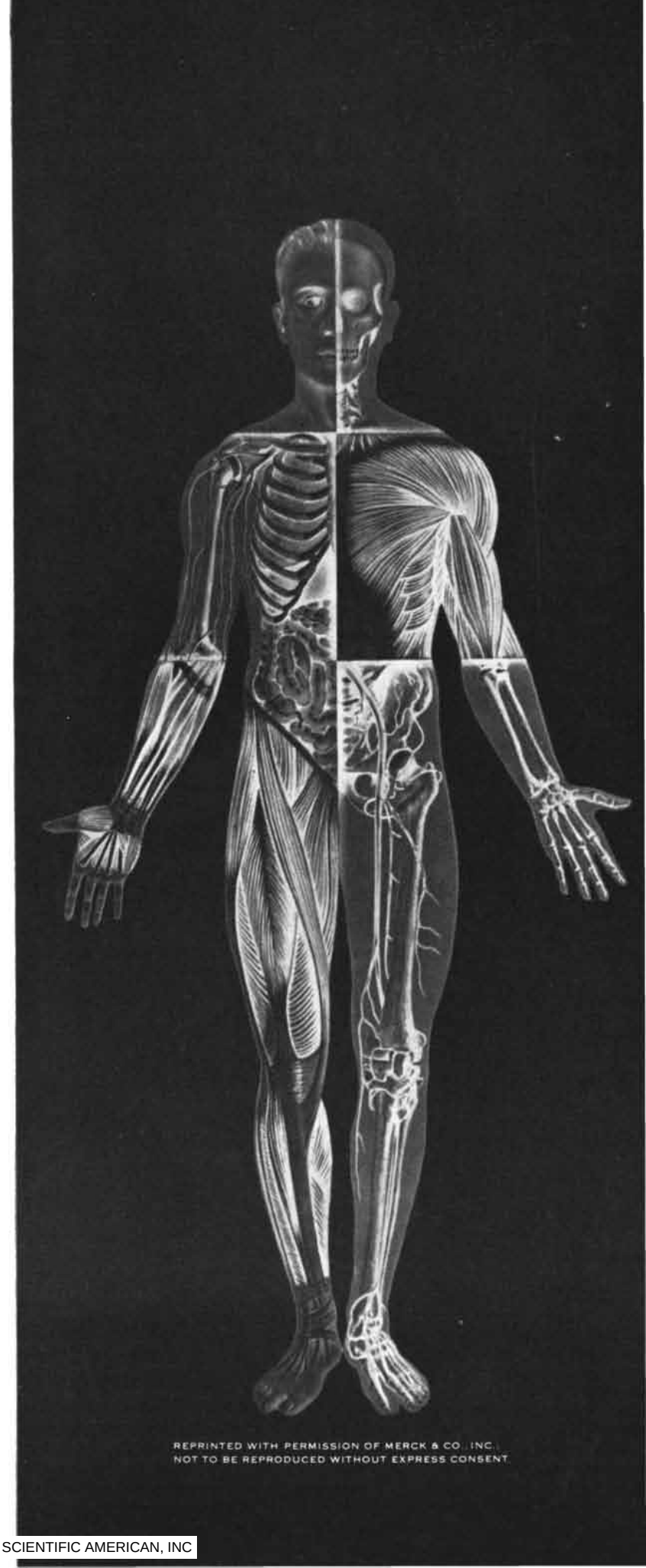

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next four years has been raised from $262 to $570 million.

The Public Health Service will administer the new law, as it did the old one. States and communities are to advance $7 toward any project for every $3 furnished by the Federal Government. The ceiling on grants to individual communities, however, is raised from $250,000 to $600,000 in order to make aid available to larger cities, and a project serving more than one community may receive up to $2.4 million. Half the funds provided by the law must go to communities with populations of less than 125,000. The first action scheduled under the new law was a conference among Federal, New York and New Jersey authorities, held in August, to plan the cleanup of Raritan Bay on the New Jersey coast.

Archaeologists in Aqualungs

Over the past few years aqualung divers have brought up a variety of relics from ancient shipwrecks, particularly off the French and Italian coasts. Although archaeologists are glad to get the material, they have been unable to learn as much from it as they would have if they had observed it in its original site. In the summer of 1960 a party from the University Museum of the University of Pennsylvania directed by George F. Bass undertook the first full-scale "excavation" of an old shipwreck. Preliminary reports of the expedition have now appeared in *Archaeology* and the *American Journal of Archaeology*.

The wreck, which was found by sponge divers, lay off Cape Gelidonya on the southwestern coast of Turkey. It dates back to about 1200 B.C., the approximate time of the Trojan War. The cargo, which weighed more than a ton, consisted chiefly of copper ingots and bronze tools, the largest hoard of Bronze Age metal and tools yet uncovered anywhere. Many of the tools were broken and were apparently being carried as scrap metal. Together with the copper were the oxidized remains of a quantity of tin—the earliest known industrial sample of the metal.

In addition to the cargo of metal the divers found several pieces of pottery, some Egyptian scarabs, polished stone maceheads, three sets of apothecary's weights, pieces of crystal, a lamp and a cylinder seal. In the section where the crew must have lived were the remains of a meal—olive pits and fishbones.

The ship itself had not been protected by a deposit of mud, so that very little was left of it. Judging from the disposi-

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SPERRY

tion of the cargo it must have been 25 or 30 feet long. A few pieces of doweled plank were preserved. They were about half an inch thick and two to six inches wide. The dowels were half an inch in diameter. The scanty remains tally with descriptions of ships in the Homeric poems, but there is not enough evidence to decide whether the vessel came from Syria, Cyprus or Greece.

Although the expedition was hampered by a short working day—the wreck lay in 90 feet of water, and divers equipped with aqualungs could stay at that depth for only 40 minutes in the morning and 28 minutes in the afternoon—the archaeologists explored the site as carefully and painstakingly as if it had been on dry land. After clearing away a growth of seaweed they mapped the wreck, triangulating positions from stakes driven into the bottom. They also photographed it in overlapping sections with an underwater camera held level at constant depth.

All the submerged material was encrusted with lime as hard as concrete. Rather than try to separate and clean the individual objects under water, the explorers broke up the deposit into large chunks with sledge hammers and chisels (without breaking so much as a piece of pottery), raised them to the surface and brought them back to land to clean. Sand overlying parts of the wreck was cleaned away with vacuum hoses. To avoid breaking any fragile objects a diver sifted the sand with his hands and then fanned it toward the mouth of the hose. The techniques developed at Cape Gelidonya, and improvements suggested by the experience there, should prove useful in investigating many of the other submerged relics of ancient maritime peoples.

Atlantic Undercurrent

A subsurface current flowing eastward along the Equator has been found in the Atlantic Ocean. Oceanographers are gratified rather than surprised at the discovery. Ever since a submerged equatorial flow—the "Cromwell Current"—turned up in the Pacific a few years ago, they have been expecting to find one in the Atlantic and possibly in the Indian Ocean as well [see "The Cromwell Current," by John A. Knauss; SCIENTIFIC AMERICAN, April, 1961].

The Atlantic current was identified by Arthur D. Voorhis of the Woods Hole Oceanographic Institution during a cruise of the research vessel *Chain*. It appears to flow along at a depth of about

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100 meters in a belt extending from one to two degrees south of the Equator to one to two degrees north, very much like the Cromwell Current. The speed of the Atlantic current, however, seems to be a little less—two knots versus two and a half to three for the Cromwell Current.

Detecting and measuring subsurface currents is a troublesome task. Voorhis accomplished it by towing velocity gauges, one just below the surfaces of the water and the other at a depth of 105 meters, as the *Chain* maneuvered in various directions. The submerged stream was detected by differences in the readings obtained with the two instruments. Additional cruises will be needed to chart the current over the whole of its course and to determine just how deep it goes.

Stain for Electrons

The pages of this issue of SCIENTIFIC AMERICAN testify to the remarkable success of the electron microscope in revealing the "ultrastructure" of living material. Yet electron microscopy is in its infancy, and it still lacks many of the refinements that contribute to the effectiveness of the light microscope. High on the list of requirements is a method of selective staining to delineate particular substances. Now a group at Yale University has announced a method by which it may be possible to stain specific proteins.

S. J. Singer and his colleagues prepare the stain by attaching molecules of ferritin to an antibody. Ferritin is a globular protein molecule containing several iron atoms. These atoms scatter electrons with high efficiency and therefore show up strongly in the electron microscope. Antibody is a substance synthesized by the body in response to an antigen, usually a foreign protein. Each antibody combines chemically with its antigen to form a stable compound.

In *The Journal of Biophysical and Biochemical Cytology*, Singer and a co-worker, Anita F. Schick, describe a series of experiments showing that antibody bonded to one or more ferritin molecules retains its ability to combine with its antigen. As a demonstration of the proposed staining procedure the chemists prepared antibody to the protein coat of tobacco mosaic virus by injecting the protein into rabbits. Recovering the antibody from the rabbits' blood, they treated it with ferritin and then sprayed the preparation on a sample of virus. Under the electron microscope the virus rods could be seen outlined by ferritin.

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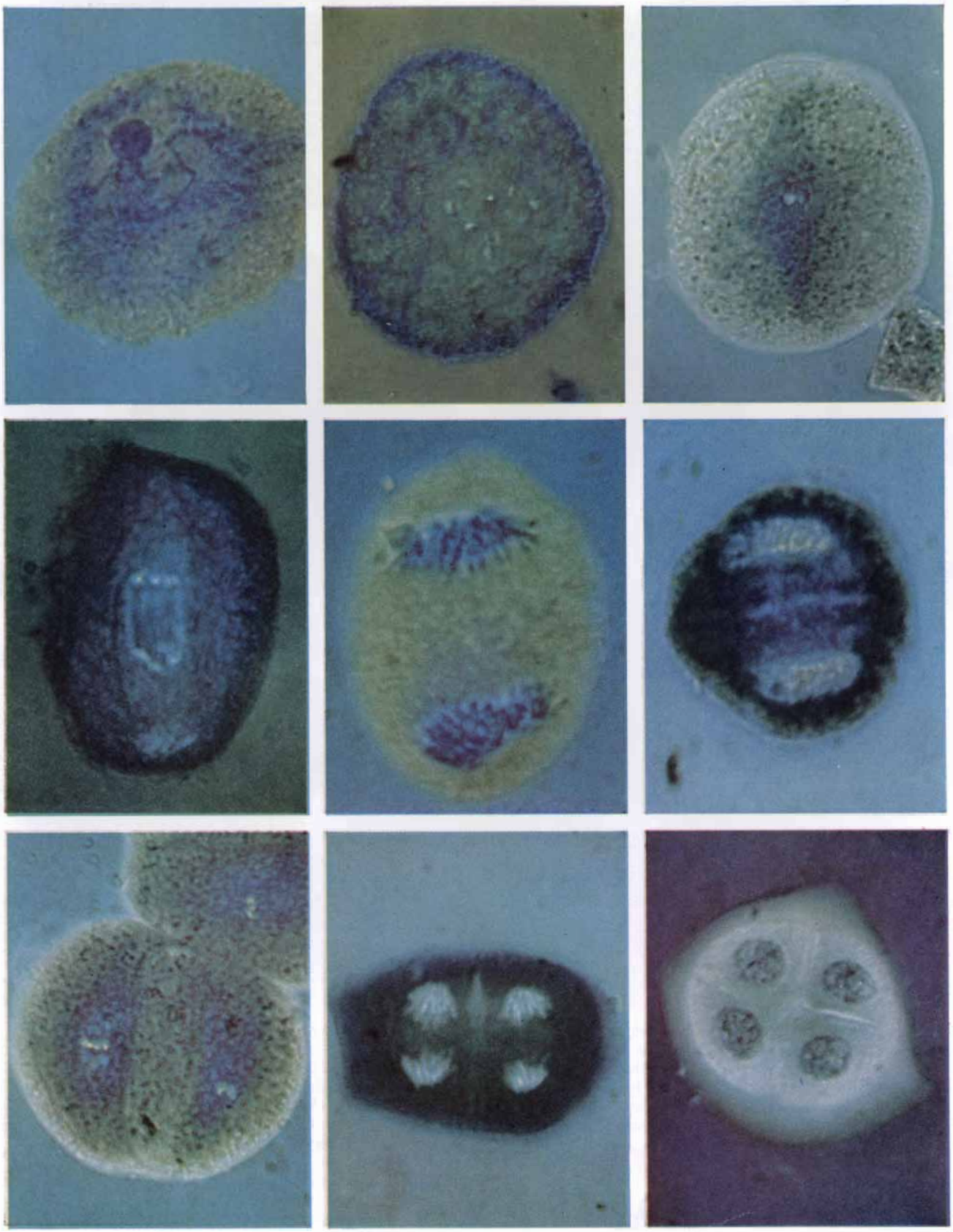


CELL DIVISION is shown in this series of interference-microscope photographs made by Arlene Longwell of the Children's Cancer Research Foundation in Boston. The first four photographs and the seventh show microsporocytes of corn; the remaining four, of wheat. The cells are seen undergoing meiosis, in which two successive cell divisions produce four germ cells. At start of first division (*top left*) chromosomes are seen as thin blue strands; they condense (*white spots at top center*), and spindle (*blue-green "diamond" at top right*) forms. After chromosomes move to spindle poles (*middle left and center*), cell wall forms between daughter cells (*middle right*). In second division chromosomes move to poles (*bottom left and center*), and germ cells form (*bottom right*).

How Cells Divide

All cells arise by division. In the process of mitosis each cell is apportioned a complete set of hereditary instructions when the chromosomes replicate and are separated by the mitotic apparatus

by Daniel Mazia

By the reproduction of cells, life thwarts time. Under the best circumstances the life span of individual cells is measured in days, weeks, months—at most in decades; the slope of time is the declivity of aging. But time can be reversed, with 100 per cent profit to boot, by the reproduction of a cell.

Each cell may begin its individual existence endowed with all the potentialities of its parent and may annihilate its individual existence in the production of two cells that inherit those potentialities unaged and undiluted. The daughters of these daughters may do the same and so on to immortality.

Although we shall be dealing here with the ideal case of the indefinite reproduction of cells, producing successive generations of identical individuals, it must be said that immortality need not be quite so monotonous in the real world. In organisms composed of many cells, some cells become different and subserve the needs of those special cells—the germ cells—which are responsible for the continuity from generation to generation. Such differentiated cells usually cease to reproduce and are therefore destined to age. Moreover, mistakes are made in the reproduction of cells; evolution turns such mistakes—mutations—into history.

The over-all reproductive cycle of a cell consists of the doubling of all the components of the cell, followed by a division that distributes the components to the daughter cells. The most fundamental part of the process, because it is the part responsible for the conservation of the character and potentialities of each kind of cell, is the replication of those molecules which carry the genetic code. The identification of the self-replicating molecule of deoxyribonucleic acid (DNA) as the agent of genetic continuity is one of the most impressive—and fateful—accomplishments of modern science [see "How Cells Make Molecules," page 74].

But the reproduction of cells and organisms is not completely described by, although it is controlled by, molecular replication. Imagine a giraffe reproducing by what might be called the fission method: each molecule in the giraffe would replicate, and the products would sort themselves out into two giraffes—a clumsy process to say the least. In the normal generative scheme a giraffe gives rise to a giraffe egg, which is capable of generating another giraffe. (We ignore the male, whose function is only to provide a little variety.) The generation of the new giraffe depends on the reproduction of cells, which also follows a generative scheme. Only a limited number of molecules, the most important of which are the nuclear genes, are capable of genuine self-replication. These molecules not only reproduce themselves but also control, anew in each generation, the production and assembly of the rest of the materials and structure of the cell.

The essence of the plan (as it applies to the cells of plants and animals generally and to certain one-celled organisms) is that the genetic material is packaged into a small number of chromosomes. The behavior of the chromosomal packages can be observed and interpreted rather easily. In the period between cell divisions, the so-called interphase, the genetic material is contained within a nuclear envelope, but in a highly extended and attenuated form. Normally we cannot recognize individual chromosomes in their longest and thinnest state with the light microscope, and we have not yet characterized them with any certainty with the electron microscope. The duration of interphase in plant and animal cells varies between 10 and 20 hours.

During the period of division, which occupies about an hour (with wide variations, of course), the genetic apparatus goes through a complex but intelligible series of acts. The chromosomes condense to compact bodies. In most cases the nuclear envelope disintegrates. The chromosomes are now part of a mitotic apparatus, the structure of which defines the logic of the process of mitosis. On the cellular scale the mitotic apparatus is a large body. It possesses definite poles, which represent the destinations of the chromosomes, and its "equator" determines the plane through which the cell will divide. By means of the mitotic apparatus the chromosomes are deployed in an exact way. They are first moved to the equator. Then sister chromosomes, the products of the reproduction of each chromosome at an earlier time, split apart and move to opposite poles. The cell now divides through the equator of the mitotic apparatus, producing two cells, each with a full set of replicas of the chromosomes that the parent cell received at the division in which it was born.

The chromosomes of each daughter cell now uncoil. A new nuclear envelope is formed around them, and they are ready to begin careers that will end when each becomes two cells in the same way.

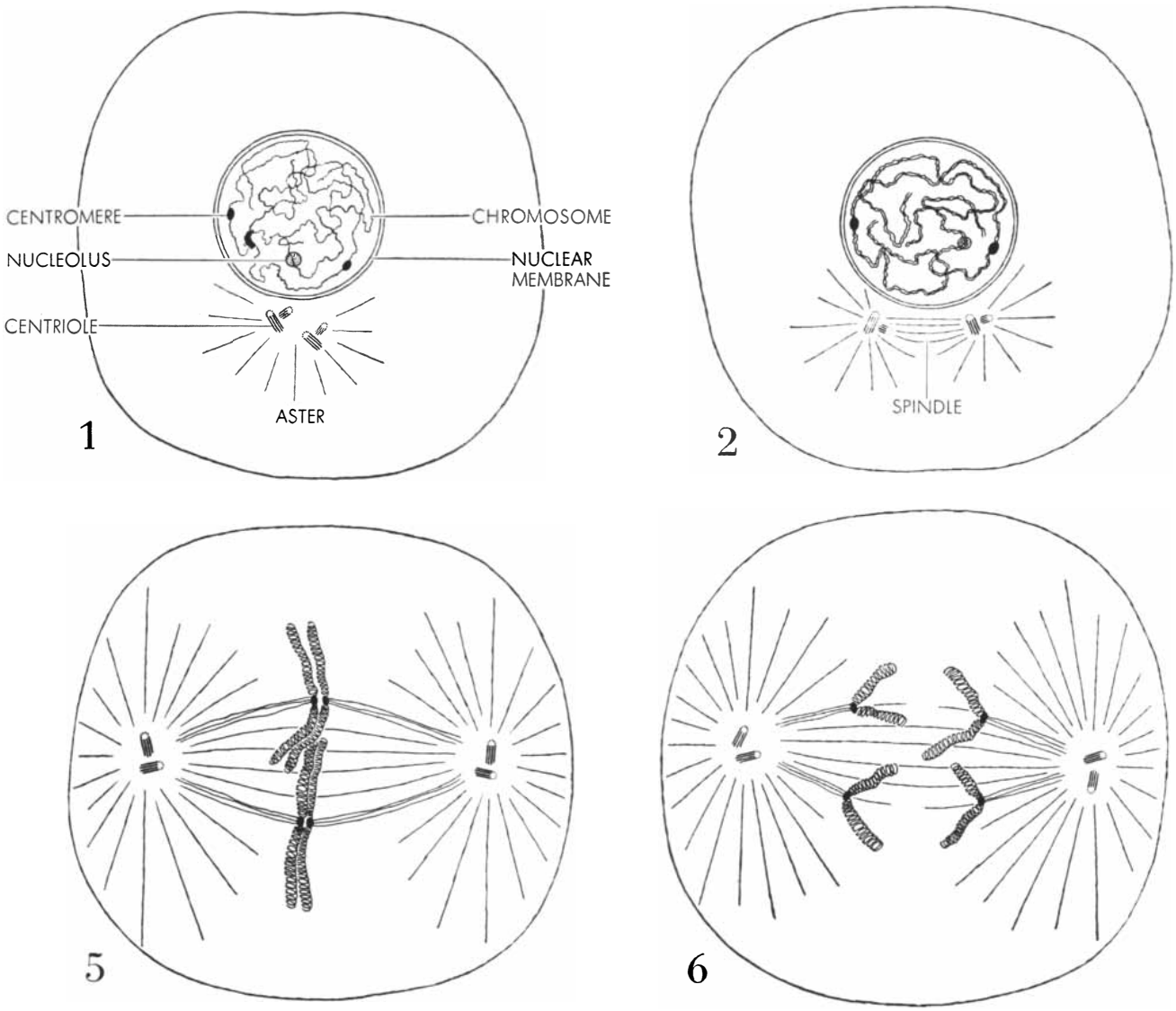
In an idealized version of the reproductive cycle of a plant or animal cell, we observe that it divides into halves, each daughter doubles in mass, seldom growing beyond the mass its parent had at the time of its division, then divides. Division creates the conditions for growth; growth culminates in division. It was quite logical, therefore, to assume that there was a causal connection between division and growth to some

critical mass. Unfortunately we must reject this idea, because closer observation has shown that a cell can divide even if it has not doubled its entire mass. An alternative is that certain of the events taking place between divisions can be thought of as specific preparations for division. So long as the cell completes these preparations, it can divide even though it may not have accomplished the normal doubling of other constituents. If this is the case, we cannot limit our study of division to the period when the cell is visibly engaged in the act, because some of the most important events may have taken place beforehand. What are the prerequisites of division?

It is now well known that in plant and animal cells the actual replication of the genetic material—the doubling of DNA—takes place only between divisions. This can best be shown by experiments in which a population of cells is fed for a brief interval with some radioactively labeled substance (usually thymidine) that is built into the newly formed DNA. The newly synthesized DNA is found only in the nuclei of cells that are in interphase—never in cells that are going through mitosis. Refinements of such experiments show that DNA synthesis occupies only a certain part of the period between divisions.

If a given cell is not destined to divide again, as is the case with the cells of many specialized organs (muscles and brain, for example), DNA synthesis does not begin. If it does begin, the rule is that it goes to completion; that is, the original amount of DNA is doubled. A less rigid rule is: If a cell does undertake DNA synthesis, not only is the doubling completed but also the cell will usually enter division. Studies of the intestinal cells of the rat, made by Henry Quastler and Frederick Sherman at the Brookhaven National Laboratory, have shown that every cell makes a crucial decision within the first few hours after division; either it enters DNA synthesis and will divide again or it adopts the career of a differentiated cell and will never divide again. The mechanism controlling this decision is still unknown. This is unfortunate, because it is surely one of the keys to the normal balance of cell division and differentiation and to the disturbance of this balance that is malignant growth.

The replication of the chromosomes merely gives us one cell with a doubled set of chromosomes. To make two cells,



MITOTIC DIVISION of a cell is depicted in these eight drawings. During interphase, the period between divisions (*1*), the chromosomes are thin, extended threads. Each of two "parent" centrioles is paired with a smaller "daughter" centriole. At some point before division the chromosomes replicate (*2*), the centrioles begin to separate and the spindle starts to form. In prophase (*3 and 4*) the chromosomes coil, becoming highly condensed, the nuclear membrane and nucleolus break down and the centrioles move apart to

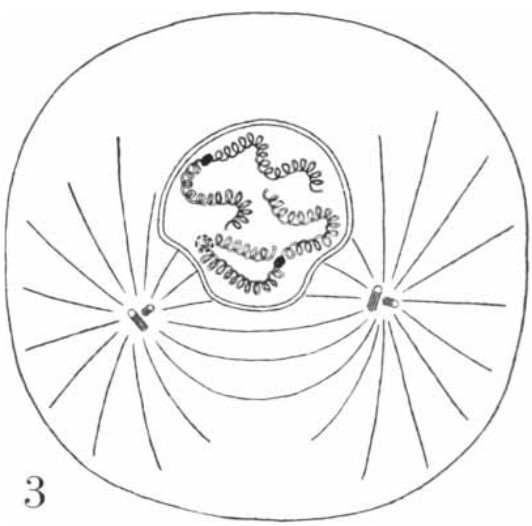
these chromosomes must move into an equator defined by poles; then sister chromosomes move to opposite poles. In many—perhaps all—cells, the poles that dictate the destinations of the chromosomes are not physical abstractions but definite, and most interesting, physical particles. What is more, the movements of the chromosomes depend on precise physical connections between the chromosomes and these particles.

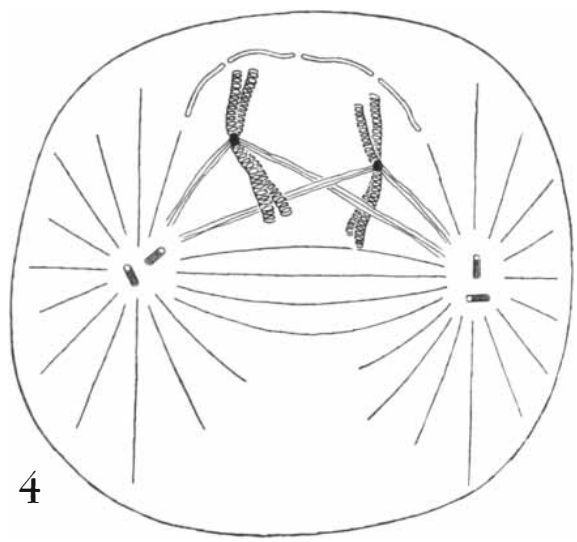
In animal cells, where such particles can always be found, they were first aptly named "polar corpuscles," but they are generally called centrioles. The centrioles originally could be identified only as small dots that were made visible by staining techniques; further clarification of their structure came only with the electron microscope. In 1956 Walter Bernhard and Étienne de Harven of the Institute for Cancer Research at Villejuif-sur-Seine, near Paris, described the centrioles of a cell in mitosis as cylindrical bodies about .3 to .5 micron long and about .15 micron in diameter, the walls of which consist of fine, parallel, tubular-appearing structures. Further work has shown that the cylinders are formed by nine groups of tubule-like bodies, each group often containing three of the tubules. The same particle can apparently serve in ways other than as a pole in mitosis; for example, the bodies found at the base of cilia and flagella have a fundamentally similar structure.

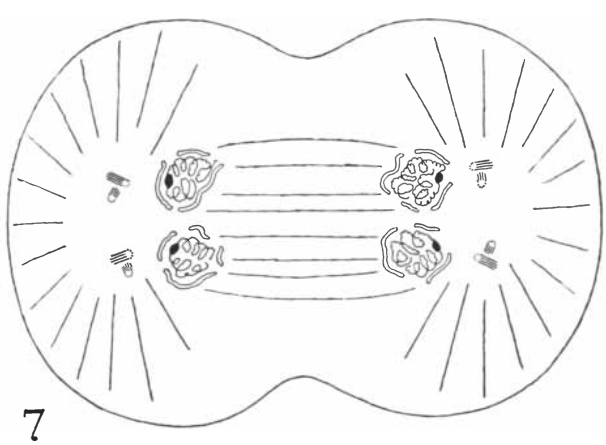
It must now be confessed that centriolar particles have not been seen in plant cells. Nonetheless the occurrence in plant cells of all the normal and abnormal features of mitosis that can be explained in terms of what we know about animal centrioles leads some of us to the opinion that equivalent particles will yet be discovered.

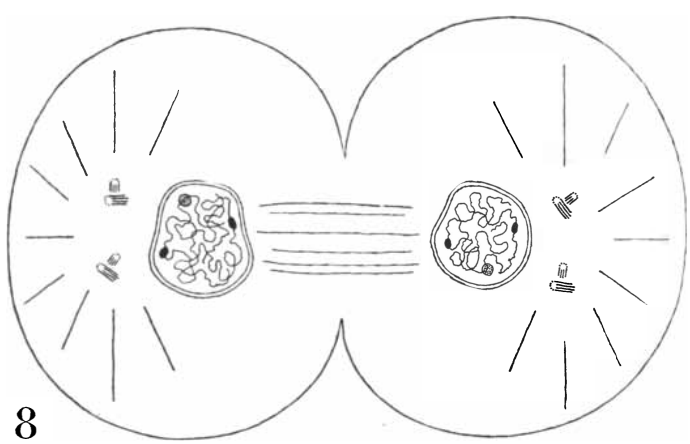
One of the prerequisites of division, then, is the production of centrioles, in animal cells at least. The most important statement we can make about this is that it is a reproductive process; centrioles are permanent and self-replicating structures. The centrioles generally are found in pairs, and it is a curious fact that the two centrioles of a pair commonly lie at right angles to each other. A cell inherits one set of them and makes two sets.

Something is known about the timing and the sequence of events. Experiments in our laboratory at the University of California had shown that mercap-









establish poles toward which the chromosomes will move. At the same time connections between the centromeres and the poles are being established. In metaphase (*5*) chromosomes move to the cell "equator." After splitting apart, sister chromosomes move toward poles during anaphase (*6*). In telophase (*7 and 8*) chromosomes uncoil, and the nuclear membranes and nucleoli of the daughter cells are formed. Each centriole has produced a new centriole. When division is completed, both cells will enter interphase (*1*).

toethanol, which is merely ethyl alcohol with a sulfur atom replacing a hydrogen atom, would block mitosis if applied before the time the chromosomes lined up and began to move. If cells were blocked for a sufficiently long time and then the block was removed, they consistently divided into four cells instead of two! Observation of what was going on inside the cells when they were blocked showed that the poles had split, each had given rise to two poles, and so the cell divided into four because it now had four poles. When the four daughter cells tried to divide, they could not do so at first because their mitotic apparatus had only one pole. (They then corrected the situation by going through an extra cycle of reproduction of centrioles, after which they could divide normally.) A simple interpretation of the observation is this: The poles of the mitotic apparatus are normally double; two actual poles contain four potential poles. While division is blocked by mercaptoethanol, the two units at each pole separate; the four potential poles become the actual poles of a four-way division.

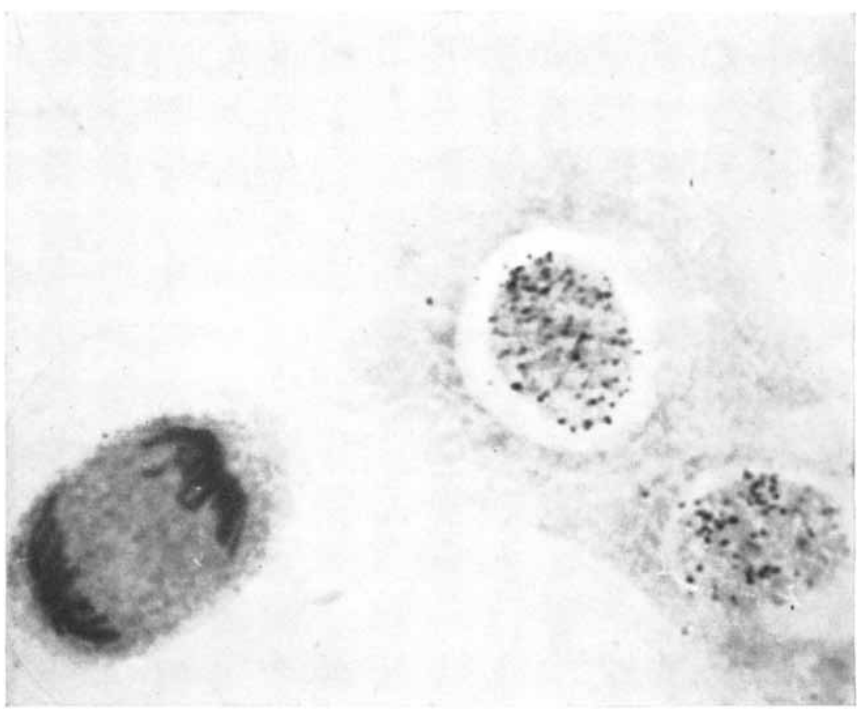
The experiment also told us that the mercaptoethanol did not suppress the separation of existing centriolar units but did block the formation of new ones. Using this fact, we were able to confirm the prevailing opinion that the replication of centrioles takes place long before division. If a four-way division following blockage by mercaptoethanol means that four potential poles are present, then the cells should be able to divide only in two if they are blocked earlier, before the centrioles have replicated. This turns out to be the case, and by systematic experiments we can determine at just what stage two potential poles give rise to four potential poles. By this test it was found that the decisive event in the generation of new centrioles takes place long before division; in fact, it seems to take place during the last part of the previous division. As the parent cell is dividing, it is conceiving centrioles for the next division.

From these experiments we conclude that the doubleness of the centriole depends on what may be called a generative mode of reproduction. On the molecular scale the centriole is a large three-dimensional body; it is difficult to imagine such a body making a copy of itself the way a strand of DNA does. But the first step could be the replication of a molecule carrying all the information for making a new centriole, just as the first step in the reproduction of a complex virus is the replication of the nucleic acid that will later assemble the other structures making up the complete virus. If some time must elapse between the conception of a new centriole and the completion of its development, then its fundamental doubleness can be taken as representing the coexistence of two generations. If we could see the production of new centrioles, we should expect to observe fully developed units with the new generation growing up beside them. This is exactly what has been seen in the electron microscope by Joseph G. Gall of the University of Minnesota [*see bottom illustration on opposite page*]. It is interesting enough that the reproduction of a particle takes place by the outgrowth of the daughter from the parent particle, but it is astounding that the new particle should invariably grow at a right angle to the old.

Once they have reproduced, the centrioles move apart. Their separation polarizes the cell for mitosis. When we have located the poles, we can tell where the chromosomes will go and through what plane the cell will divide. The separation takes place long before division in some kinds of animal cell; in others it occurs abruptly, just before the chromosomes begin their mitotic maneuvers. Superficially it has all the attributes of a repulsion; the polar particles move apart in a straight line. Measurements by Edwin W. Taylor of the University of Chicago indicate that this movement takes place in cells of newts at a constant velocity of about one micron per minute. We must not take the analogy of a repulsion literally. A more apt image is that the poles are pushed apart by the growth of fibers that continue to connect the poles and that together are called the central spindle. This is descriptively correct, but it remains to be explained how the growth of the central spindle is translated into an actual movement of the centriolar bodies.

The essence of the plan of mitosis is clear, and the precision is secured in a uniquely biological way. The centrioles double exactly, and the products separate to form two poles—no more and no less. The chromosomes reproduce exactly, and sister chromosomes are transported to sister poles. The rest of the story is a tale of complex molecular mechanics into which we are just beginning to gain some insight.

Since the act of mitosis involves the performance of work, it must also require the expenditure of energy [see "How Cells Transform Energy," page 62]. Experiments suggest that the ener-



CHROMOSOME REPLICATION takes place during interphase, as this autoradiograph made by J. Herbert Taylor of Columbia University demonstrates. Two Chinese hamster cells (*right*) in interphase have incorporated radioactive cytidine (*numerous dark grains*) in their nuclei. A third cell undergoing division (*left*) contains none. Since cells incorporate cytidine only during synthesis of RNA and DNA, replication of chromosomes (containing DNA) must occur between cell divisions. Cells are magnified here approximately 1,200 diameters.

getic expenses of division are met by a paid-in-advance accumulation of energy. Up to a point, as a cell proceeds toward division, it can be brought to a halt by depriving the cell of oxygen or by poisoning its oxidative enzymes with carbon monoxide. But when the cell reaches a certain point—about the time the chromosomes are coiling up—it is no longer possible to stop the division by throttling the oxidations. Michael M. Swann of the University of Edinburgh concludes that the preparations for division include the filling of an "energy reservoir" that is adequate to meet the requirements of mitosis. The chemical identification of the energy reservoir may be one of the important problems of research on cell division.

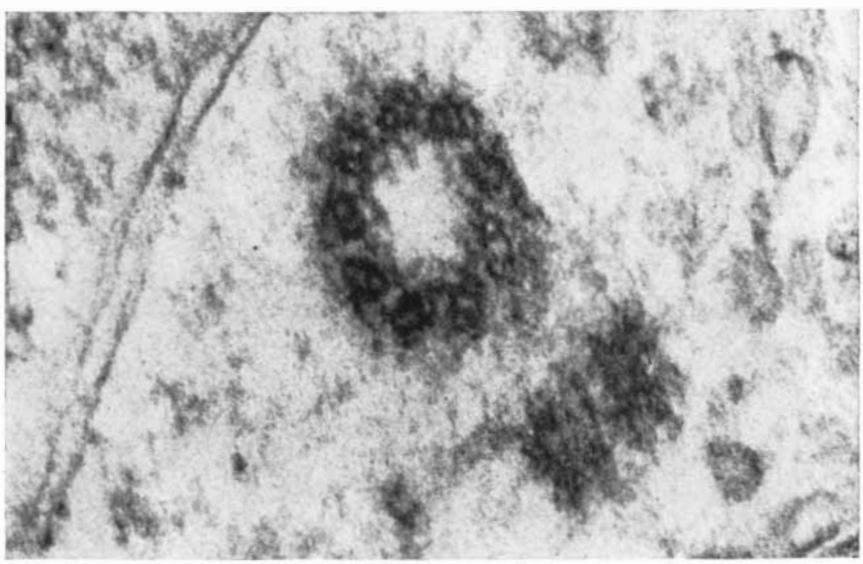
Once these molecule-building preparations have been completed, the cell ordinarily is committed to enter mitosis. Whether a further special "trigger" is required or whether the completion of the last of the synthetic preparations is itself the trigger, we do not commonly encounter cells that are stalled on the brink of mitosis.

If the essence of mitosis is the movement of sister chromosomes to sister poles, the inauguration of the process calls for the establishment of connections between chromosomes and poles. But before the connections are established a radical rearrangement of the structure of the cell takes place, the prophase, which is intelligibly a mobilization for action.

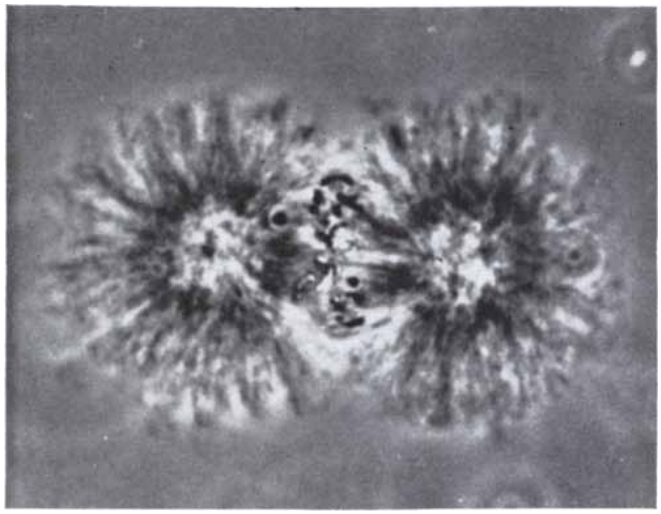
The chromosomes condense into visible threads. What we see suggests that this condensation is largely a matter of packing the chromosome strands into tight coils and then imposing still another order of coiling. As a coiled coil, the chromosome exhibits handsomely the theme of helical design that pervades the study of molecular order. Although we do not know the inner mechanisms of this large-scale coiling, its significance is clear enough. It converts a tangle of long and tenuous threads into compact masses that can be moved freely and without entanglement. Fully extended, the DNA in a human nucleus could make a thin thread some 10 million microns—a meter—long. Packaged into chromosomes, it is deployed as two sets of 46 chromosomes, each a few microns long.

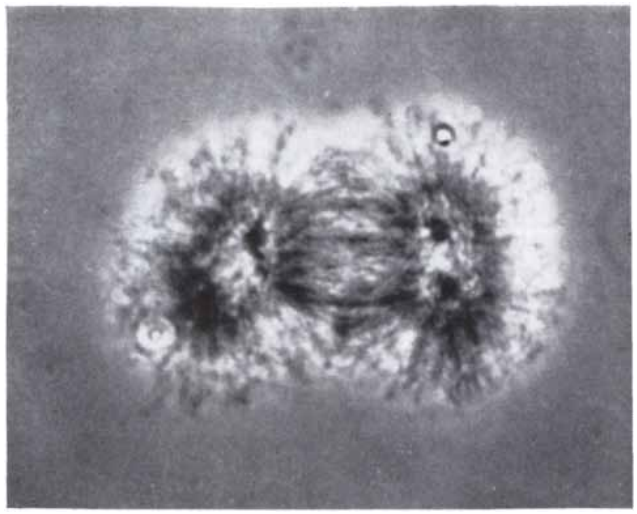
Toward the end of the period during which the chromosomes are coiling up, the nuclear envelope in many kinds of cell disintegrates. It is easy to understand this as the removal of a barrier between the chromosomes and the poles; it is more difficult to understand the

SISTER CENTRIOLES in a human tumor cell lie at right angles to each other. The cross section of one (*bottom*) shows that the centriole consists of nine groups, each containing three "tubules." Magnification of this electron micrograph, which was made by Walter Bernhard of the Institute for Cancer Research at Villejuif-sur-Seine, is 160,000 diameters.



REPRODUCTION OF A CENTRIOLE in a cell from the snail *Viviparus* is magnified 175,000 diameters in this electron micrograph made by Joseph G. Gall of the University of Minnesota. The short daughter centriole, which is seen in longitudinal section near lower right, grows out at right angles from the parent centriole, seen in cross section at center.





FOUR MITOTIC POLES are formed by centrioles in sea-urchin eggs when the movement of chromosomes during mitosis is blocked by the use of mercaptoethanol. The chromosomes (*seen in thin vertical grouping at center of photograph at left*) remain in the spindle as the centrioles split and separate (*second from left*). The centrioles then begin to move apart at right angles to the spindle

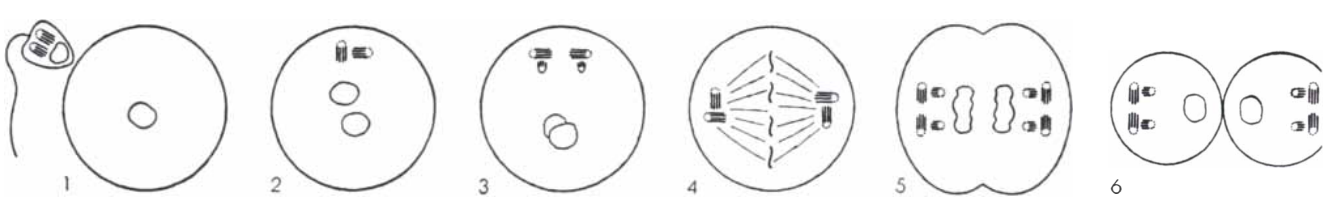
cases in which the envelope persists.

At the same time the body of the mitotic apparatus is assembling. We have described how the poles are established. The final destinations of the chromosomes are now fixed. Between the poles and around the nucleus we can often detect a gathering of a mass of material, still not well organized, that will be the mitotic apparatus. Descriptively we have every reason to say that the substances of the mitotic apparatus were originally spread through the whole cell but now are gathered in and concentrated by the centrioles, although we do not actually know how this comes about. In some kinds of cell we have the impression that the material of the future mitotic apparatus is collected inside the nucleus.

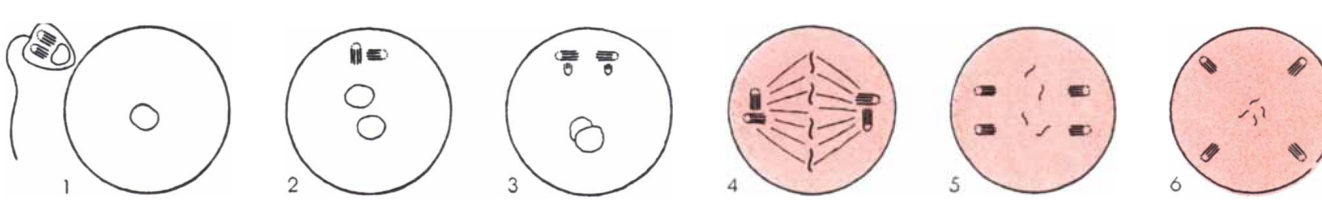
Only now—with the chromosomes neatly consolidated, the poles established and the substance of the body of the mitotic apparatus gathered—can the action begin. The chromosomes come under the control of the poles and begin to move. We describe this climax so cursorily because we know so little about it; actually it contains the essential mystery of mitosis.

The proper execution of the mitotic maneuvers demands strict obedience to a rule: All chromosomes must be engaged to a pole but it is prohibited that two sisters engage to the same pole. What we see suggests the establishment of physical connections—which we shall call fibers without invoking any special properties—between centrioles and chromosomes. We must also take into account another body: the centromere, or kinetochore. This is the anchor point on the chromosome at which its connection to its pole is made. The kinetochore has a constant position on each chromosome; and when we say that a chromosome in mitosis is V-shaped or J-shaped, it is because it consistently behaves as though it were being dragged by an attachment at its middle or toward one end. Clearly the kinetochore is that part of the chromosome which takes part in mitosis; the rest of the chromosome goes along for the ride. Yet we have no really detailed knowledge of this remarkable body.

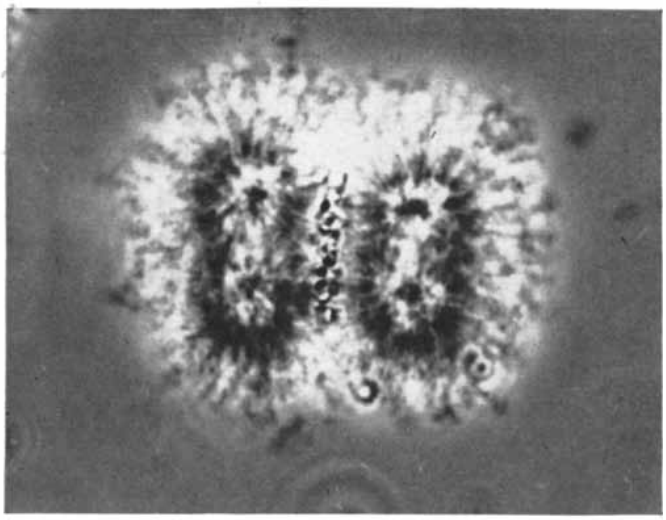
Once the chromosomes are engaged by the poles and begin to move, the movement proceeds in two steps. First the still-paired sisters move into the

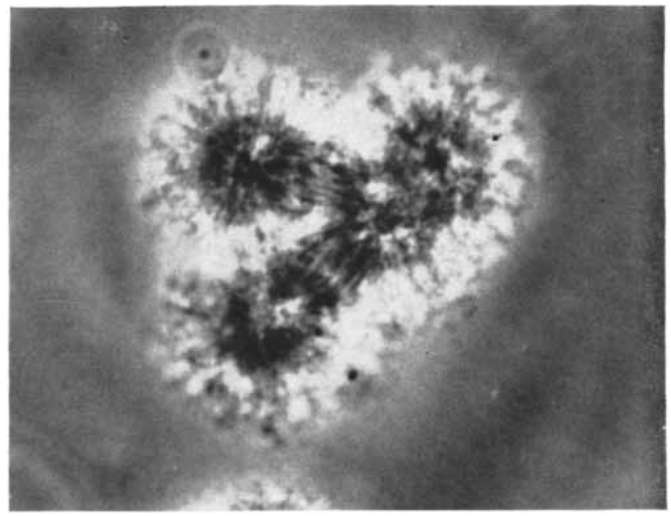


NORMAL CENTRIOLE REPRODUCTION is depicted here. After fertilization of egg (*1*) the parent-daughter pair of centrioles (*small cylinders in 2*) split, each producing a smaller daughter centriole (*3*). Centrioles form two mitotic poles (*4*). As cell di-



ABNORMAL CENTRIOLE REPRODUCTION was induced in sea-urchin eggs in an experiment performed by the author and his colleagues to show that a single mitotic pole (formed by a centriole) consists of two potential poles. In first part of experiment (*1, 2 and 3*) centrioles reproduced normally (*see first three drawings in illustration above*). Mercaptoethanol was then added (*4, 5 and 6*):





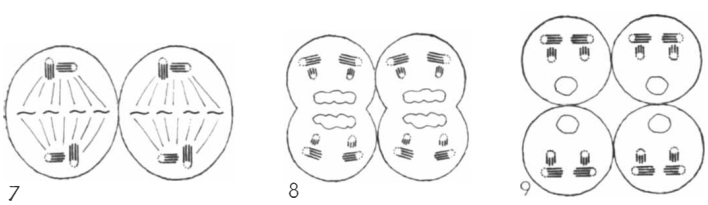
axis (*third from left*), moving farther apart to form a spindle with four poles (*right*). The shape of this mitotic figure is that of a pyramid with a triangular base. The magnification of these four phase-microscope photographs, which were taken in an experiment at the author's laboratory (*see illustrations at bottom of these two pages*), is approximately 1,100 diameters.

equatorial plane defined by the poles; then they split apart and move to the poles. We can understand this by the simple and instructive (but not necessarily faithful) image of a little puppet performance. The sister chromosomes, still paired and so connected by strings to both poles, are pulled into the equatorial–metaphase–position under equal tension from the two poles. When they split apart, the same tension carries them toward the two poles.

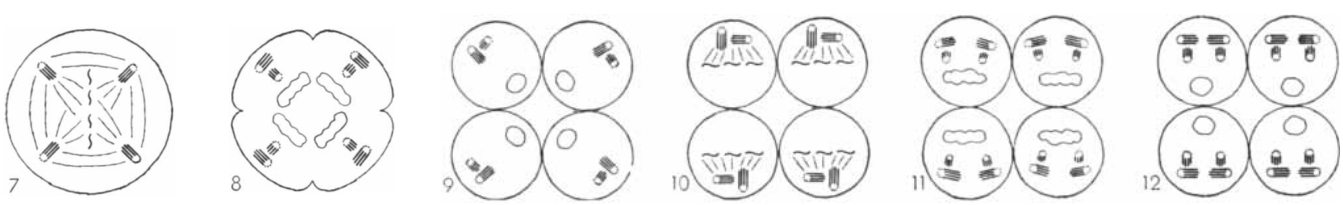
The separation of the sister chromosomes and their migration toward the poles–the anaphase movements–have been described and measured in great detail in recent years, thanks to better microscopes, the motion-picture camera, better methods of maintaining cells alive under the microscope and great expenditures of patience. On the cellular scale the distances traveled can be considerable: between five and 25 microns. The velocity of the movement is about one micron a minute; this works out to four hundred-millionths of a mile per hour, which is not a sensational speed. The chromosomes move in straight lines, usually converging on the poles. Often, as the chromosomes move to the poles, the poles themselves move farther apart, carrying the chromosomes with them. Commonly, but not always, the chromosome-to-pole movement precedes the further separation of the poles. The marveling observer has the impression that the chromosomes are pulled to the poles and then dragged by the poles as the poles push apart. The shapes of the chromosomes in movement, so often those expected of a flexible body being dragged through a liquid by a thread attached at one point, reinforce this impression.

Much of what has been said here is descriptive, but it is nevertheless intelligible. We perceive a consistent plan, followed in principle by a vast variety of cells, that does achieve the required end of genetic distribution. The meaning of each structure and step in relation to the others is clear, and the consequences of failure in any respect are predictable. Description is not necessarily "mere" description. Yet it is "mere" if we accept the objectives of contemporary cell biology, the ideal of which is a molecular (and submolecular and supermolecular) accounting for precisely those biological operations which, like heredity or mitosis, are already reasonably comprehensible in their own terms.

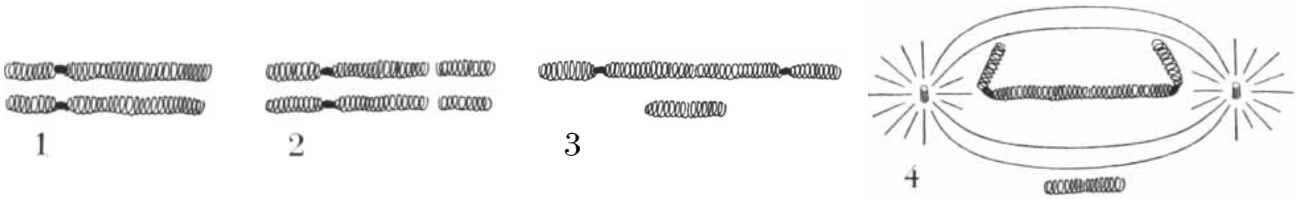
If mitosis is not desperately discouraging as a problem of molecular biology, it is because the complex operations are embodied in a definite structural assembly–the mitotic apparatus–that can be regarded as a gadget for perform-



vides (*5 and 6*), parent-daughter pairs split and produce four new poles. When daughter cells divide (*7, 8 and 9*), this process is repeated.



centrioles formed poles (*4*), separated without duplicating (*5 and 6*) and formed a tetrapolar spindle when the mercaptoethanol was removed (*7*). Four daughter cells formed and each centriole reproduced (*8 and 9*). Each cell, with half the normal number of centriolar units, formed a mitotic apparatus with one pole (*10*). Centrioles duplicated (*11*) and cells were ready to divide normally (*12*).

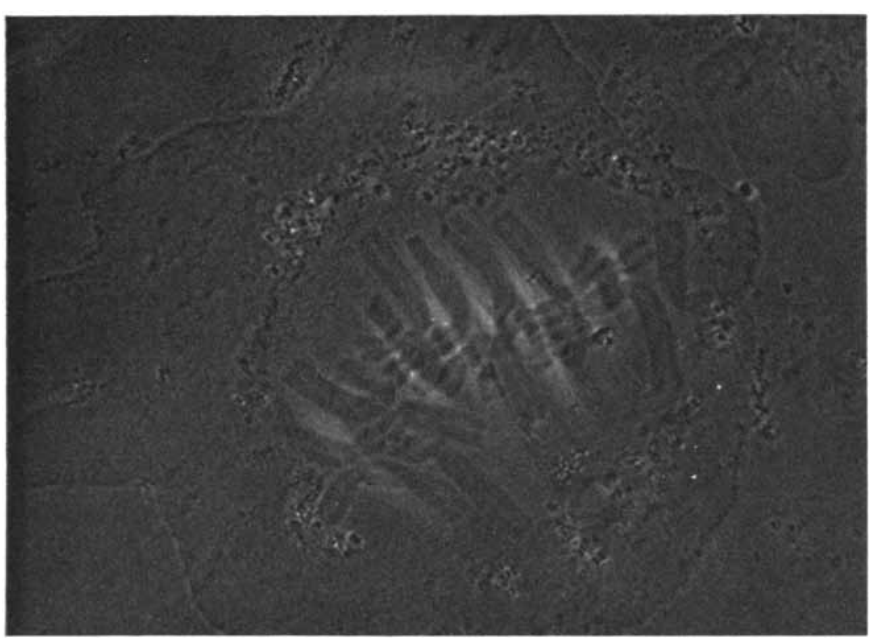


ROLE OF CENTROMERES, the sites (*small black ovals in 1*) at which chromosomes are connected to the poles of the mitotic apparatus, is illustrated by the experiment depicted here. If exposed to ionizing radiation, the chromosomes break (*2*). Broken ends always rejoin, but do so in various ways. As shown (*3*), the fragments with centromeres have joined together, as have those without centromeres. In mitosis (*4*) the former is pulled toward opposite poles; the latter does not take part in mitosis.

ing the operations. We can approach the physics and chemistry of mitosis through the study of the formation, structure and changes of the mitotic apparatus, without forgetting that mitosis is an operation of the whole cell.

Let us consider the fully formed mitotic apparatus at a crucial stage in mitosis: the metaphase, when the chromosomes have lined up on the equator but have not yet begun to move to the poles. The light microscope sees the chromosomes in a spindle, a body between the poles that has been thought to consist of fibers connecting pole to pole, fibers connecting chromosomes to poles, and a matrix of a rather undefined character. In animal cells the aptly named asters often radiate from the poles.

The mitotic spindle has been described as a gel, as a coherent body of limited rigidity and as a loose aggregate or network of chains or sheets of molecules. As J. Gordon Carlson of the University of Tennessee and others have shown, it can be pushed and poked about in the cell. That the spindle often appears as a transparent region against a more turbid background suggests that the assembly of materials to form the spindle excludes large particles such as mitochondria from that region, and this is confirmed by electron microscopy. The polarization microscope reveals that the molecular components of the spindle tend to be oriented along the pole-to-pole axis, in keeping with the impression of pole-to-pole and chromosome-to-pole "fibers." Recent advances in electron microscopy—especially in the preparation and fixing of cells for inspection in the microscope—go far toward confirming the impression. Pictures made by K. R. Porter of the Rockefeller Institute and by Bernhard and De Harven show fine straight filaments, usually double and sometimes occurring in bundles, running from the kinetochores to the vicinity of the centrioles. These are sometimes described as being tubules about 150 angstrom units in diameter. But this refers only to the image provided by the electron optics and does not mean that we actually are dealing with hollow pipes. It is these filaments that shorten as the chromosomes move to the poles and lengthen when the poles move apart. We are inclined to assign them an important part in the movement of the chromosomes. The picture remains, however, distressingly incomplete.



FIBERS OF MITOTIC APPARATUS and the chromosomes attached to them are seen in this polarization-microscope photograph made by Shinya Inoué of the Dartmouth Medical School and Andrew Bajer of the University of Cracow in Poland. The living endosperm cell containing them is that of the flowering plant *Haemanthus katherinae.* Sausage-like structures with faint lines running through their central axes are pairs of sister chromosomes. The thin bright lines perpendicular to the chromosome axes are the fibers, connected to specific chromosomal regions: the centromeres. Magnification is 1,500 diameters.

Obviously we shall not achieve a molecular analysis of mitosis before we know something about the molecules of the mitotic apparatus. The most straightforward way of going about this is to isolate the mitotic apparatus from dividing cells. For this purpose we require an abundant supply of cells in division, and this can be had. Marine organisms such as sea urchins produce great quantities of eggs. When such eggs are fertilized in the laboratory by mixing them with spermatozoa, they proceed to divide synchronously. Therefore one can obtain gram quantities of cells in division.

But the mitotic apparatus is notoriously evanescent. As a structure that assembles at the time of division and is dismantled when division has been accomplished, it is clearly not a permanent organ of the cell. Its chemical instability is revealed when one tries to isolate it; under most conditions it simply vanishes. In 1952 Katsuma Dan of the Tokyo Metropolitan University and I succeeded in isolating the mitotic apparatus [see "Cell Division," by Daniel Mazia, SCIENTIFIC AMERICAN, August, 1953]. It was evident from the first that a price of chemical damage had to be paid for the isolation of a stable mitotic apparatus; the aim of developing improved methods has been to reduce the price by seeking gentler procedures.

How could it be that the structure

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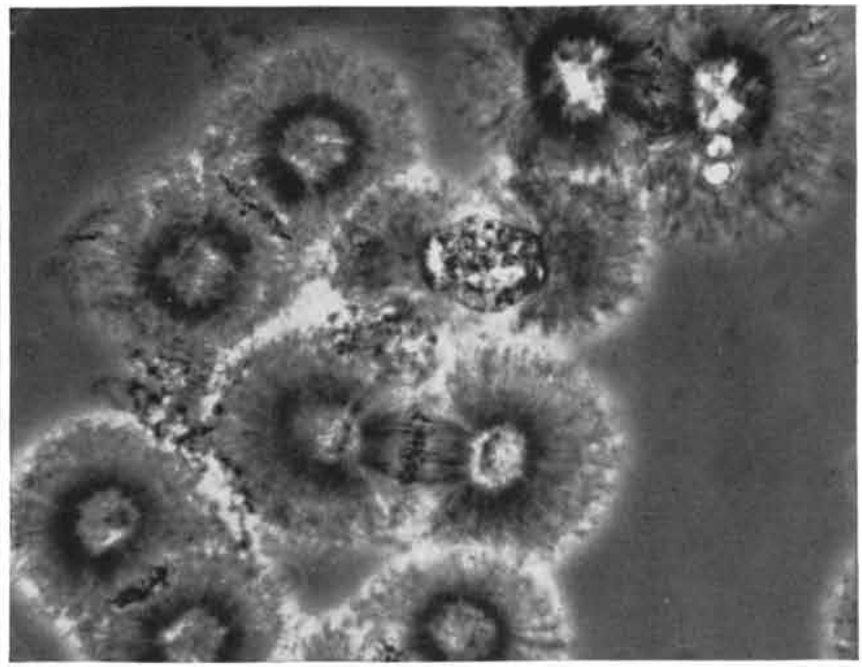


ISOLATED MITOTIC APPARATUSES from sea-urchin eggs are magnified 1,000 diameters in this phase-microscope photograph made by the author. In apparatus just below the exact center of the photograph the two light areas are mitotic poles; structure between them is the spindle. Chromosomes are seen as a thin, dark area at center of spindle.

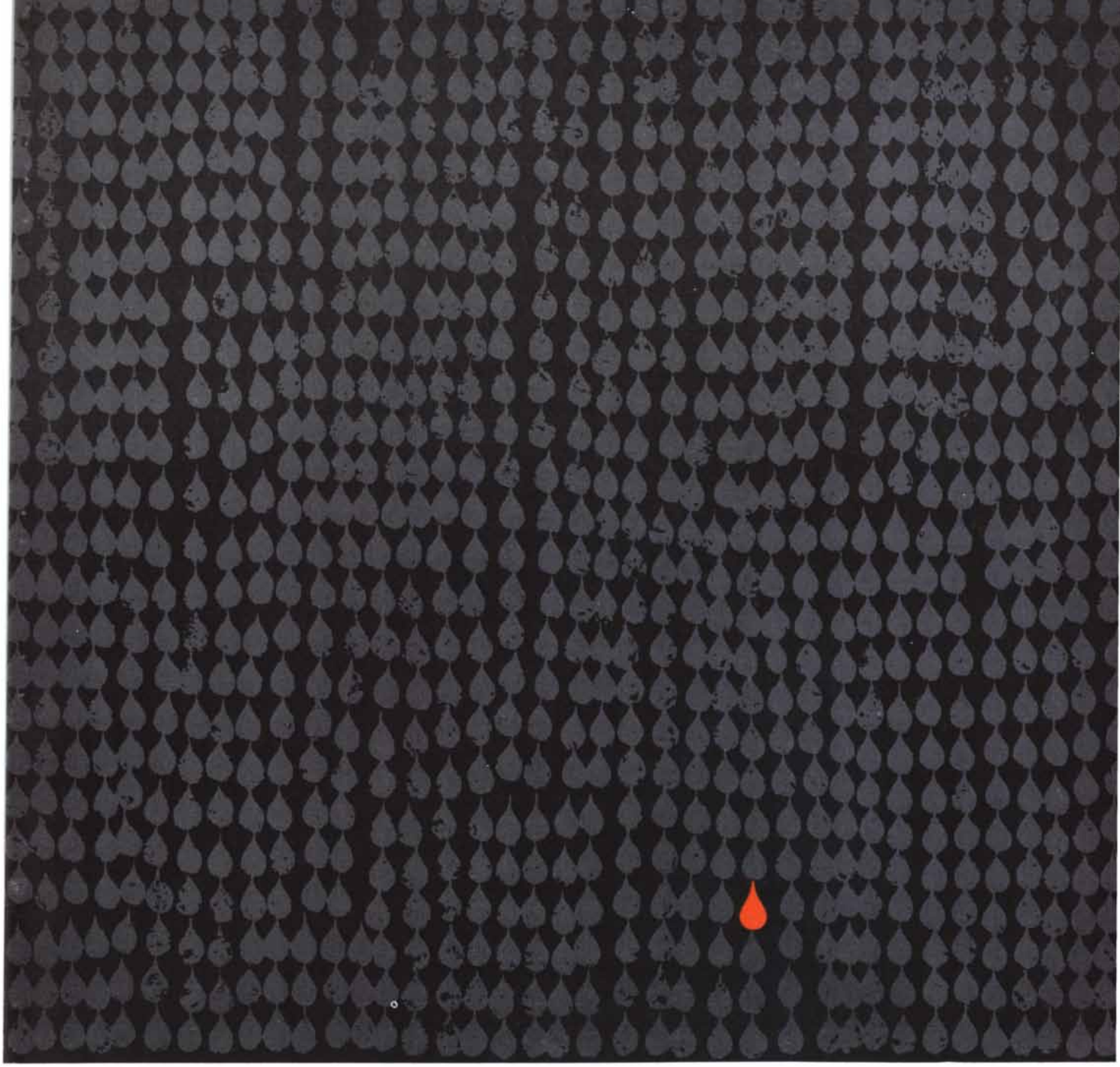
that held together within the cell was so incoherent once it was outside the cell? Obviously the cell was providing, in its internal environment, some protection for the structure. From evidence that sulfur bonds play an important role in holding the mitotic apparatus together in the cell and by a rather complex argument, I guessed that such protection might be given by a compound incorporating sulfur-to-sulfur bonds. The next compound tried was dithiodiglycol ($HOCH_2CH_2S–SCH_2CH_2OH$). J. M. Mitchison of the University of Edinburgh and I found that the addition of dithiodiglycol to a sucrose or dextrose medium did protect the stability of the mitotic apparatus, and the apparatus could be isolated merely by disrupting cells in such a medium. They could then be purified by further washing in the same medium. Such isolated preparations are being used in most of the current work in our laboratory at the University of California.

After eight years of study of the isolated mitotic apparatus, what have we learned? The reader who expects to be told how chromosomes are moved may skip the next few paragraphs. We have learned something about the kinds of molecule that are present in the apparatus and how they are put together; perhaps this is all that can be expected from studies of isolated parts of cells.

The mitotic apparatus contains a great deal of protein. John Dale Roslansky and I found that it represents an investment of at least 10 per cent of all the protein in the dividing sea-urchin egg. Is this protein synthesized at the time of division or is it preformed and then assembled at the time of division? Hans Went, now at Washington State University, attacked the question by an immunological method, asking whether the isolated mitotic apparatus contained any proteins—detected as antigens—that were not already present in the cell before division. Thus far no such antigens have been found, so we infer that the synthesis of the proteins of the mitotic apparatus is one of the prerequisites of division. A cell must anticipate division by providing these molecules.

Arthur M. Zimmerman, now at the Downstate Medical Center of the State University of New York, has made a careful study of these proteins. So far the picture has been surprisingly simple in the sense that most of the protein in the isolated mitotic apparatus seems to be of one kind, although there must be many other kinds that are present in smaller amounts.

The mitotic apparatus also contains ribonucleic acid (RNA), and much of the RNA seems to be associated with the major protein. The function of this RNA is a puzzle. RNA is usually identified with protein synthesis, but the mitotic



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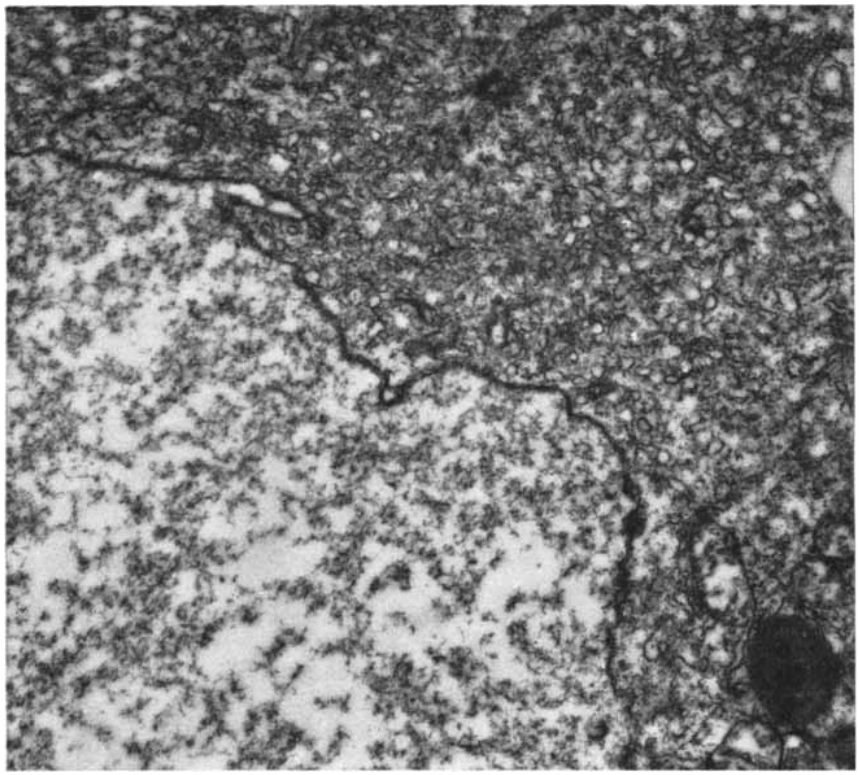
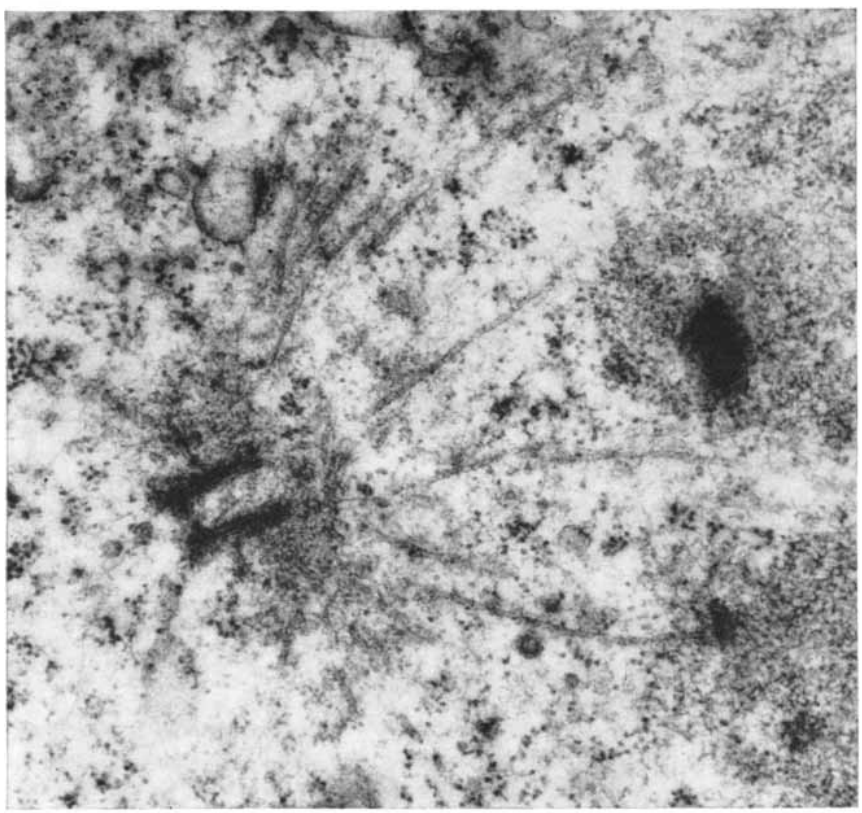


EARLY STAGE in the assembly of the mitotic apparatus of a sea-urchin egg is magnified 16,000 diameters in this electron micrograph made by Patricia Harris of the University of California. The apparatus is beginning to form around a centriole (*small dark C-shaped structure at top center*), which will be at one pole of the future apparatus. At such an early stage the nucleus (*large light gray area*) is still surrounded by the nuclear membrane.



CENTRIOLE AND CHROMOSOMES, seen respectively at left and at right (*amorphous gray areas*), are connected by spindle fibers in a chicken-spleen cell. One fiber is attached to centromere (*small black area at lower right*). Micrograph was made by Jean André of the Institute for Cancer Research at Villejuif-sur-Seine. Magnification is 53,000 diameters.

apparatus does not seem to be manufacturing protein. The RNA associated with the mitotic apparatus may have something to do with the assembly of this structure and not merely of its molecules. It is tempting to imagine that genetic information is involved in the architectural activities of the cell as well as in the shaping of the bricks.

Our recent work has also shown the presence in the mitotic apparatus of a considerable amount of lipids, the fatty molecules that are so prominent in other kinds of structure, such as the external and internal membrane systems of the cell, the mitochondria and so on. Perhaps the lipids account for the presence in electron micrographs of so many vesicles, membranes and tubular-appearing structures in the mitotic apparatus.

Our early experiments were guided by the theory that the molecules in the mitotic apparatus were held together by disulfide bridges, chemical bonds between sulfur atoms on neighboring protein molecules. It was proposed that the assembly of the apparatus was essentially a process of establishing such bridges. More recent work, particularly in Dan's laboratory in Tokyo, has shifted the emphasis from disulfide bonds to interactions that still involve sulfur-containing groups but which are not necessarily fully oxidized disulfide bonds such as are formed in such stable structures as hair and vulcanized rubber. Using a method that combines a colored compound specifically with the thiol groups (—SH groups) of proteins, Dan and a student of his, N. Kawamura, were able to show that the assembly of the mitotic apparatus is an ingathering toward the centrioles of proteins having a particularly high content of thiol groups, and that when the mitotic apparatus goes through the period of transport of the chromosomes to the poles (the anaphase), these thiol groups disappear, only to reappear at the next division. We would like to know how the congregation of proteins rich in thiol groups is related to the assembly of the mitotic apparatus, and whether the disappearance of these groups, perhaps by oxidation, is part of the chemistry of the chromosome movement itself. It is tantalizing to have so much evidence that the sulfur-containing groups are particularly important in mitosis without knowing just how or why.

The chemistry of movement in biological systems has provoked biologists throughout the recent history of the life sciences. The most influential idea is that movement somehow involves the re-

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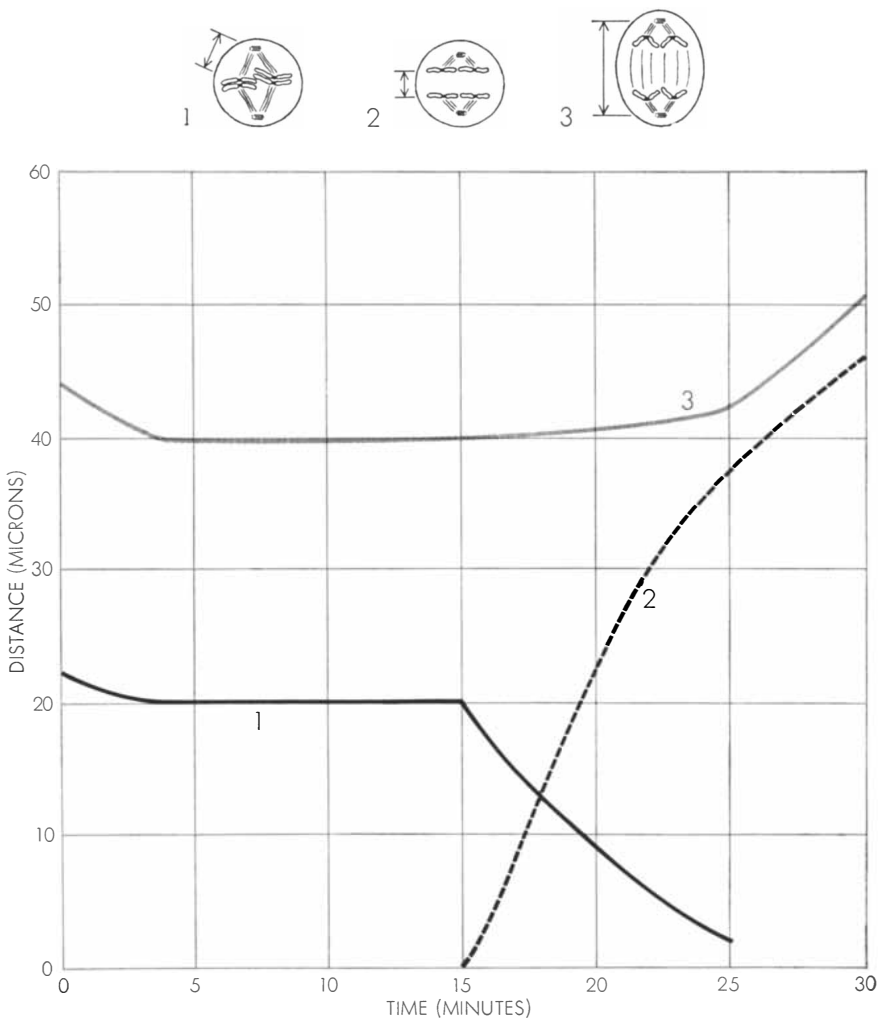
action of the motile system with adenosine triphosphate (ATP) and the splitting of phosphate groups from the ATP. Proteins involved in movement—and not just proteins in muscle—are expected to react with and split ATP [see "How Cells Move," page 184]. The early methods of isolating the mitotic apparatus did not, however, yield any material capable of this reaction. Using the newer sucrose-dithiodiglycol medium, Ray M. Iverson (now at the University of Miami), Rowland C. Chaffee (now at the University of California in Riverside) and I have discovered an active enzyme in the mitotic apparatus that splits ATP. So far as the observations go, they do favor the prediction that proteins of the mitotic apparatus would, like the contractile proteins of muscle, react with and split ATP.

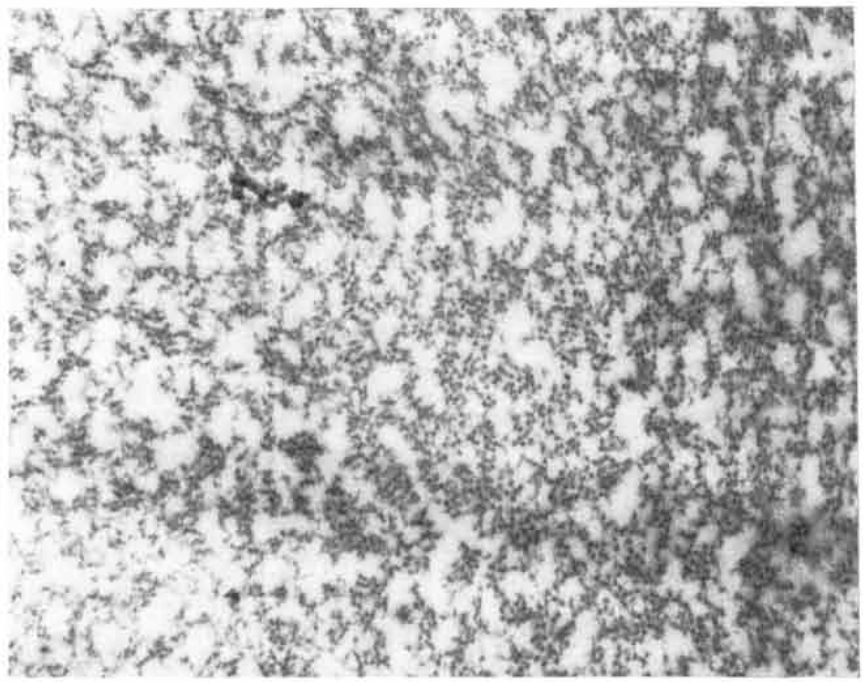
We may let our love of unity take us still a step further, asking whether the mitotic apparatus is a system of contractile fibers—a little muscle. Fibers connecting chromosomes to the poles, and also fibers running from pole to pole, were seen long ago in microscope preparations of dead cells and are now seen with the electron microscope, but until they were observed in living cells in mitosis they could be discounted as artifacts of the preparation methods. The observations of live cells in polarized light by Shinya Inoué of the Dartmouth Medical School, who has designed advanced polarization microscopes for this purpose, leave little doubt that the fibers of the mitotic apparatus are real [*see bottom illustration on page 108 and illustration at top of pages 118 and 119*].

But a crude image of a system of contractile fibers will not take us far. The chromosome-to-pole fibers shorten to a fraction of their original length, if not to the point where they simply vanish. The

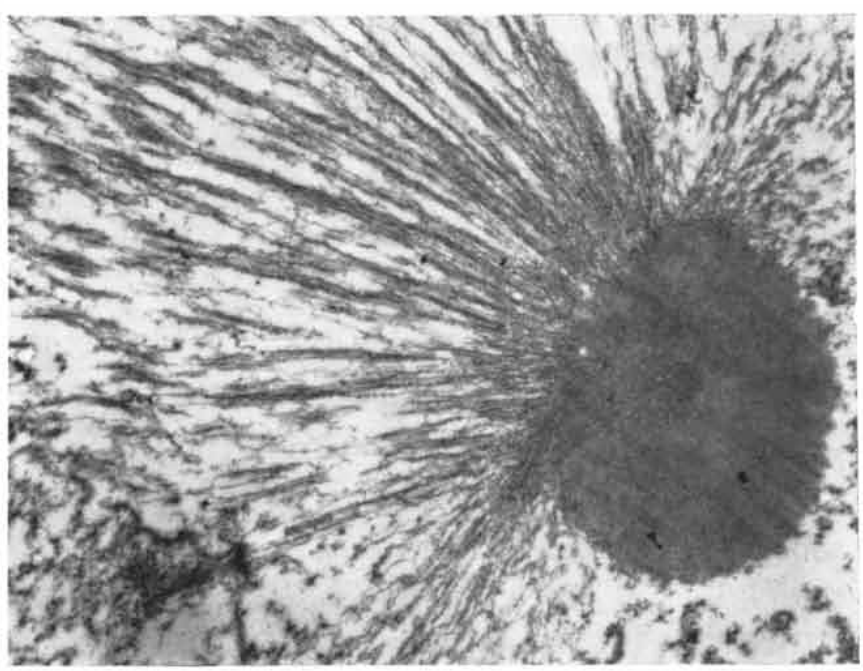


CELL MOVEMENTS IN MITOSIS are here plotted in three curves that show the changes in distance between chromosomes and poles (*1*), between sister chromosomes (*2*) and between poles (*3*). Curves are keyed to drawings at top, which indicate the distance plotted. On the time scale at bottom "0" marks beginning of anaphase, when chromosomes are aligned at the cell "equator." The sister chromosomes separate after 15 minutes (*1 and 2*).

pole-to-pole fibers grow longer, sometimes much longer. As the fibers become shorter or longer they do not become thicker or thinner, nor do they become less straight. The filaments seen in the electron microscope [*see illustrations below*] seem to retain the same diameter although they grow shorter or longer. In fact, we wonder if the "contraction" of fibers in the mitotic apparatus is not a shortening due to the actual removal of molecules and if the elongation is not a growth in one dimension, the addition of mole-



CROSS SECTION of central spindle (that part of the spindle connecting the mitotic poles) of *Barbalunympha*, a flagellate protozoon, is here magnified 18,000 diameters. The individual fibers appear to be tubular when they are viewed in cross section. This electron micrograph and that below were made by Joan Erickson Cook of the University of California.



LONGITUDINAL SECTION seen here shows structural details of the mitotic apparatus of *Barbalunympha*. The main mass of fibers radiating from the end of the large centriole (*right*) runs to the other pole (*not shown*). A centromere (*small dark crescent at lower left*) connects a chromosome (*small gray area farther to left*) to several fibers. Scalloped line passing between them is the nuclear membrane. Magnification is 12,000 diameters.

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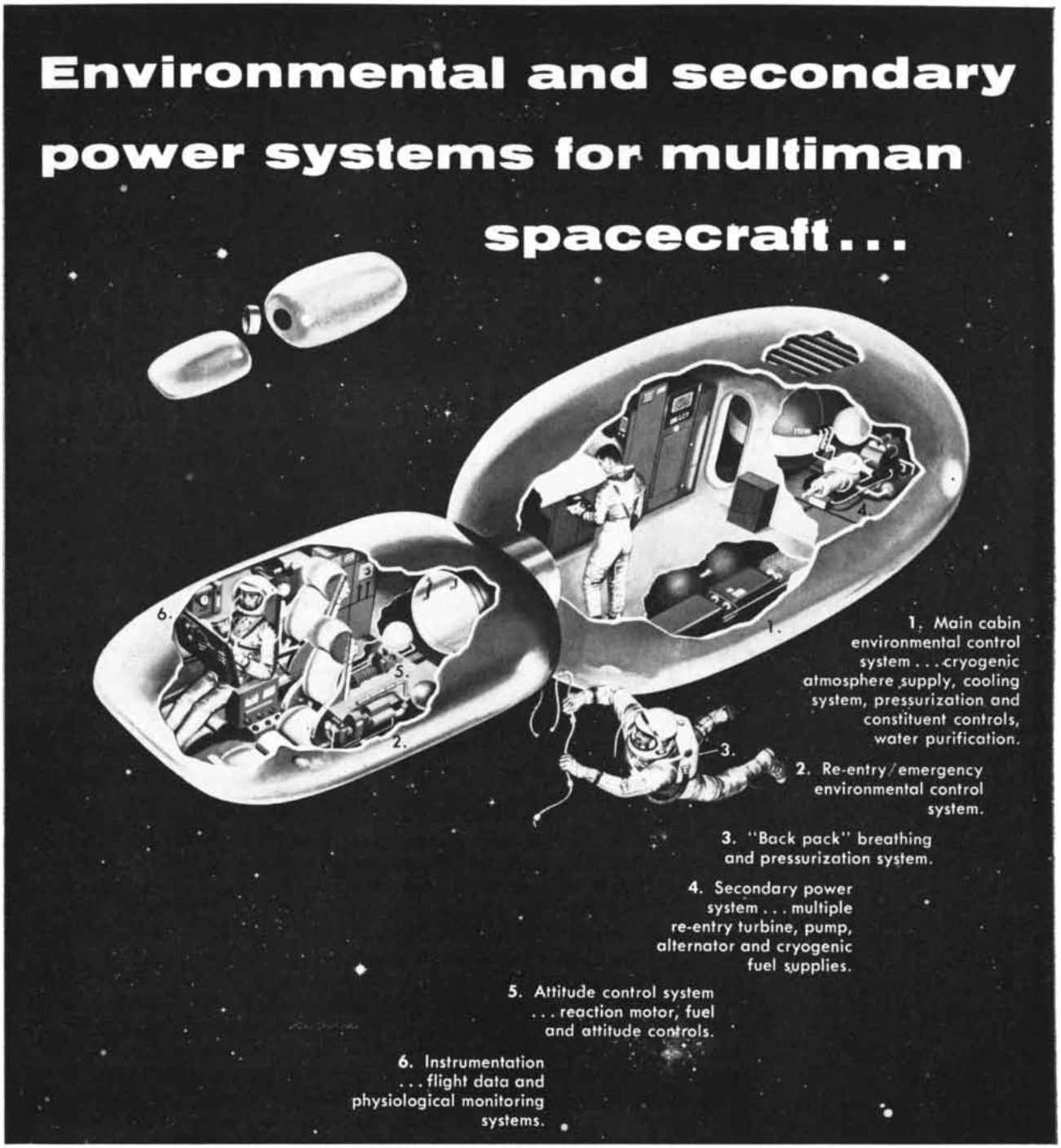

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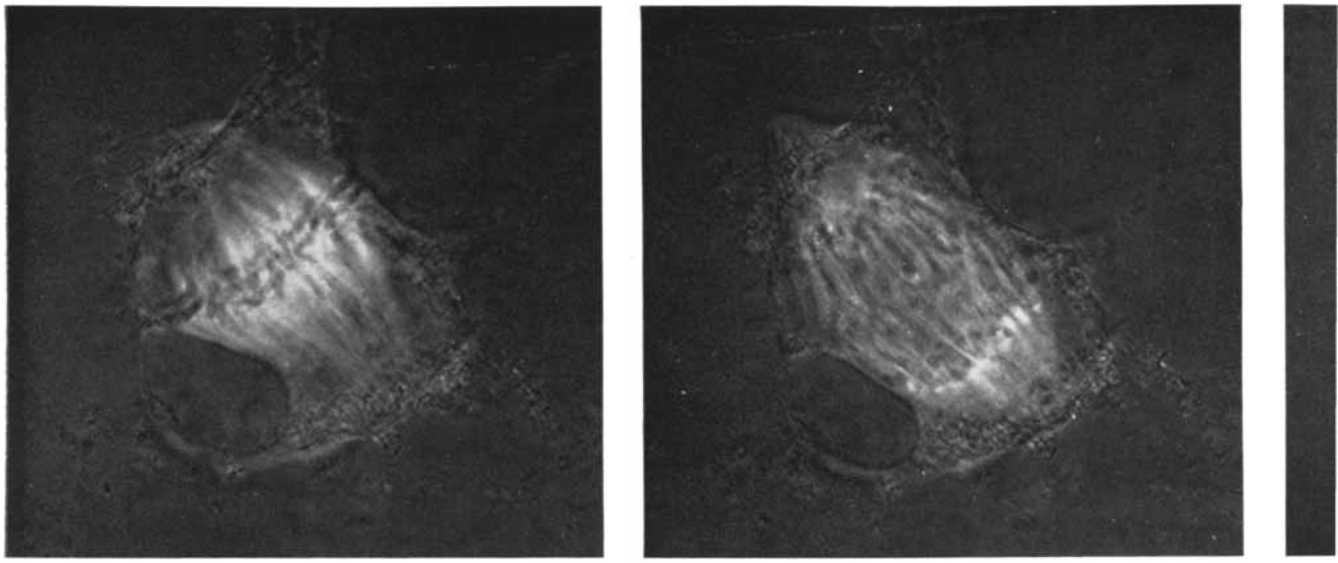
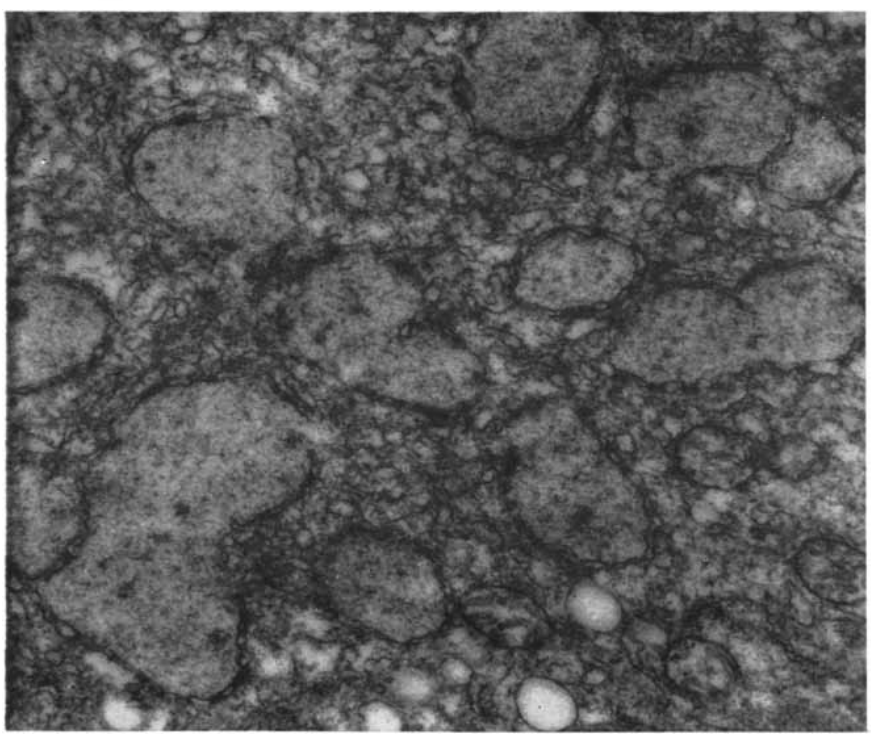


CHROMOSOME MOVEMENT in living endosperm cell of *Haemanthus katherinae* is seen in these three polarization-microscope photographs from a film sequence made by Inoué and Bajer. During metaphase (*left*) the chromosomes are aligned at the equator of the spindle. The chromosomes then move toward the mitotic poles (*second from left*) with their "arms" trailing, as though

cules. The question would be whether or not the removal or interpolation of substance could be carried out in such a way that the fibers could pull or push a mass. The growth itself can be accounted for by a model proposed by Inoué. He sees the molecular elements of the mitotic apparatus as being in two states: oriented (fibrous) and disoriented. Their transition from one state to the other is bound by an equilibrium such that the proportion of the material in the oriented state changes in response to the conditions in the cell as a whole.

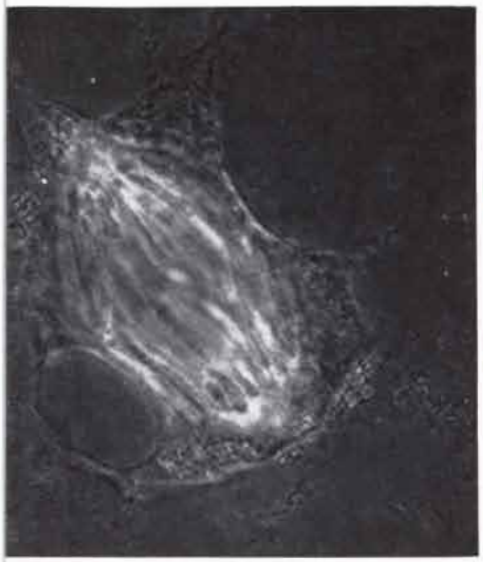
Once the chromosomes have separated into two groups, the organization of two interphase nuclei, with their attenuated chromosomes contained by the characteristic envelope, begins. Only a few details of the reconstruction of nuclei are known; for instance, electron microscopy gives us the impression that the nuclear envelopes are not brand new but are made by assembling fragments of membranous material from the surroundings.



NUCLEAR MEMBRANE (*doubled lines surrounding small gray areas*) first re-forms around individual chromosomes as they approach mitotic pole at end of division. As chromosomes "flow" together, separate membranes form one. This electron micrograph of a cell from a sea-urchin embryo was made by Patricia Harris. Magnification is 20,000 diameters.

To the observer at the microscope the most remarkable event of cell division is the pinching of an animal cell into two, or the appearance in a plant cell, as though from nowhere, of a wall between the nuclei that have just gone through mitosis. The most ingenious theories have been proposed; for example, the idea that the cell surface forms a contractile belt around the equator, or that the cell surface can expand and push into the equatorial plane.

The requirement of a successful theory is that it explain how the poles of the mitotic apparatus can dictate the laying down of new cell membrane at the equator, whether the appearance is that of a furrowing of the original membrane or the building of a partition from within. If the mitotic apparatus is pushed to one side or rotated by 90 degrees, the plane of division will be displaced correspondingly, as has been shown recently by K. Kawamura at the University of Tennessee. Yet the completion of the act of division does not seem to require the immediate co-operation of the mitotic apparatus. Y. Hiramoto of the Misaki Marine Station in Japan has been able to remove the mitotic apparatus from dividing sea-urchin eggs, literally sucking them out of the cell by means of a very fine pipette controlled by a micromanipulator. If the



they were being pulled by their centromeres. The centromeres reach the poles (*right*). Magnification is 1,200 diameters.

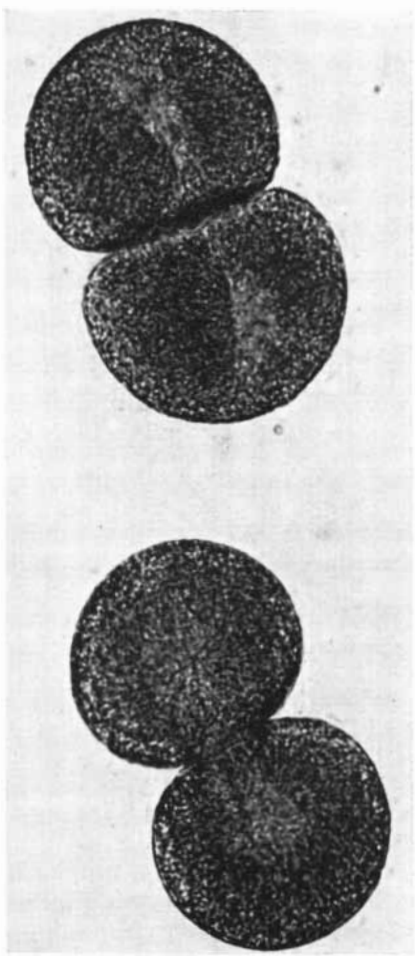
apparatus was removed some time before the cell body began to divide, no division occurred. But if the operation took place just before division, at the time when the chromosomes were moving to the poles, then division proceeded. On the other hand, division does not depend on the chromosomes. We know this from various experiments in which the mitotic apparatus goes through its performance after the chromosomes have been removed.

An account of mitosis and cell division sounds more like the libretto of an Italian opera than like a page from Euclid. Cell reproduction is not a unit process, and it is not to be described by an equation. Its essence is the doubling of all the potentialities of a cell—the generation of twoness. The twoness is not only doubleness of quantity but the twoness of separation and independence. Indeed, we have seen that all the doubling of molecules takes place before mitosis, and only then is the material of one cell remolded into two cells.

Basically, biological increase is a scale-of-two process. A single cell can only attain a limited degree of growth. The limit seems to be a restriction of the domain of living mass that can be administered by a single nucleus. The limitation is not an exhaustion of the capacity for growth; if, after a cell has reached its maximum size, a piece is amputated, the cell will grow back to the maximum size but no larger. The genetic material of a plant or animal cell, measured as DNA, can only double, and it cannot increase further until the chromosomes have gone through the mitotic cycle. If

the mitotic apparatus is damaged by drugs such as colchicine, the split chromosomes will not separate and will be retained in a single nucleus. The "polyploid" cell thus produced can grow to a size that is proportional to the number of sets of chromosomes present. If normal mitosis takes place but cell division fails, the cell with two nuclei can also grow to twice the normal size. If the whole division cycle is normal, each of the daughter cells can grow to the size attained by the parent cell.

Reproduction as the generation of twoness is not merely another interesting biological phenomenon. In it we can find reasons for everything else that happens in living things. Indeed, the biologist, unlike some other brands of scientist, can allow himself such a term as "reasons" because he does have a standard of judgment: the unambiguous criterion of survival.



DIVISION FURROW, which pinches cells in two at the end of mitosis, is depicted in sea-urchin eggs. The furrow in the egg at top is almost complete; the furrow in the egg at bottom is at an earlier stage. The mitotic apparatus is still faintly visible. This photomicrograph, made in the author's laboratory, enlarges cells 800 diameters.

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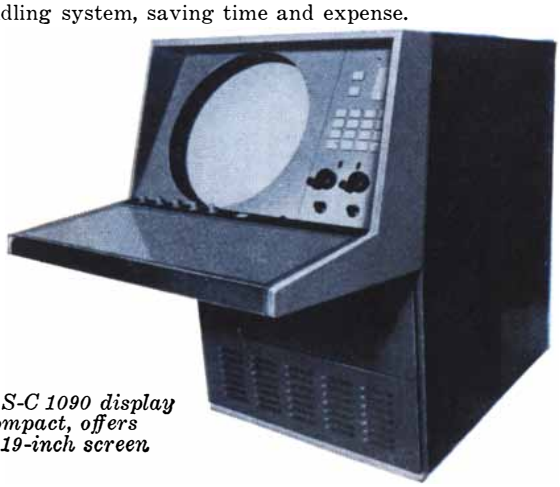

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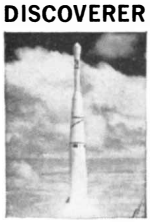

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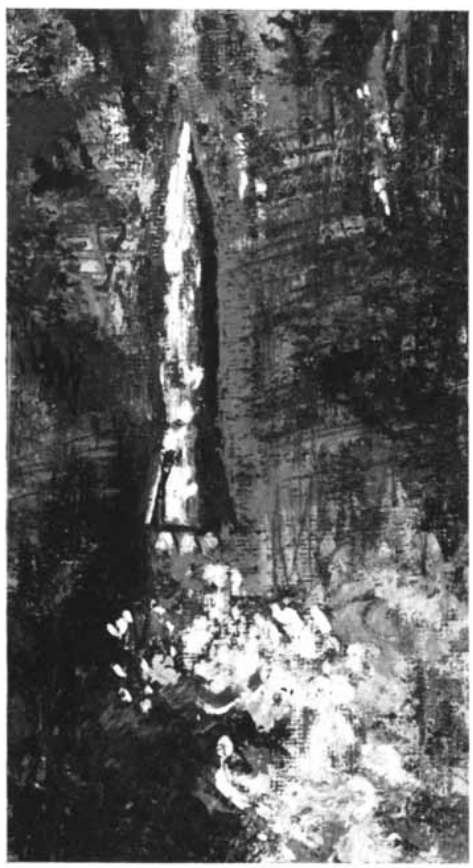

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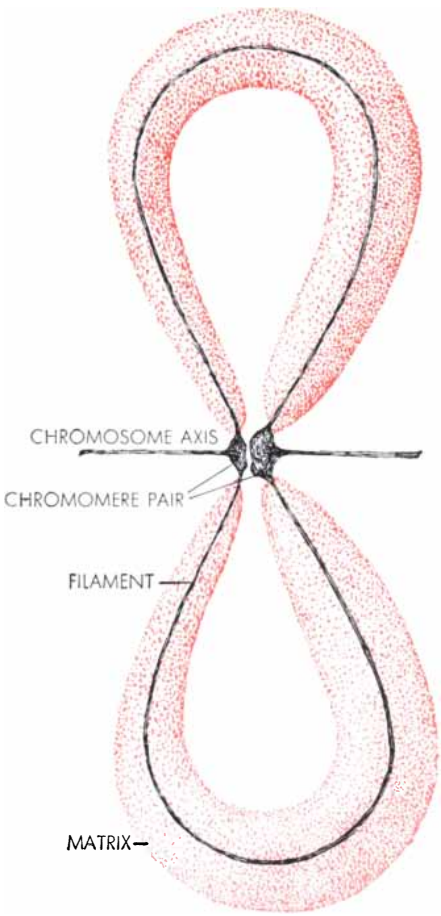
How Cells Specialize

The egg cell of a multicellular organism differentiates into all the specialized cells of the adult organism. It is now believed that this differentiation begins in the egg itself

By Michail Fischberg and Antonie W. Blackler

Long before men knew anything about cells, much less molecules, they were familiar with one of the most tangible mysteries in nature: out of a simple-looking egg emerges a living organism, complete and perfect in every detail and unimaginably complex. Each organ is normally just the right size and in the right place and contains the right kinds of cell to carry out its specialized function. Today we are scarcely less mystified. How does the undifferentiated cell of a cleaving egg turn into the specialized cell of heart, liver, nerve, bone or muscle?



CHROMOSOME LOOPS at locus of a lampbrush chromosome are formed by filaments (with surrounding matrix) that connect a pair of chromomeres. The chromosome axis, chromomere pair and filaments consist of DNA; the matrix, of RNA and protein.

Although the complex riddle of differentiation yields its secrets most unwillingly, great progress is now being made. This progress is mainly due to rapid advancements in biochemistry, the development of new techniques and the choice of organisms particularly suited for the study of the problem of differentiation. But perhaps most important of all is a change in the philosophical approach to the problem. One formerly thought too much in terms of the isolated role of the cell nucleus, or the role of the cell cytoplasm, or the role of the environment of the cell. Today we have become much more aware of the dynamic interplay among the three variables and we have learned to observe all three as the embryonic organism develops.

Having said this, however, we will limit our discussion to examples and experiments that demonstrate the roles and mutual interactions of the cell nucleus and cytoplasm in process of differentiation. The nature of the nucleus and the cytoplasm has been presented elsewhere in this issue [see "The Living Cell," page 50]. We are not suggesting that the role of the cell environment is negligible in the cases that we shall present; only that it appears to be secondary to that of nucleus and cytoplasm. Its role, in any case, is not dominant, as it often is in the development of slime molds or in the differentiation of cells in tissue culture.

We shall start by describing how an egg cell develops, for we now believe that the foundation of the future embryo is already laid down while the egg is growing and before the mature egg is even fertilized.

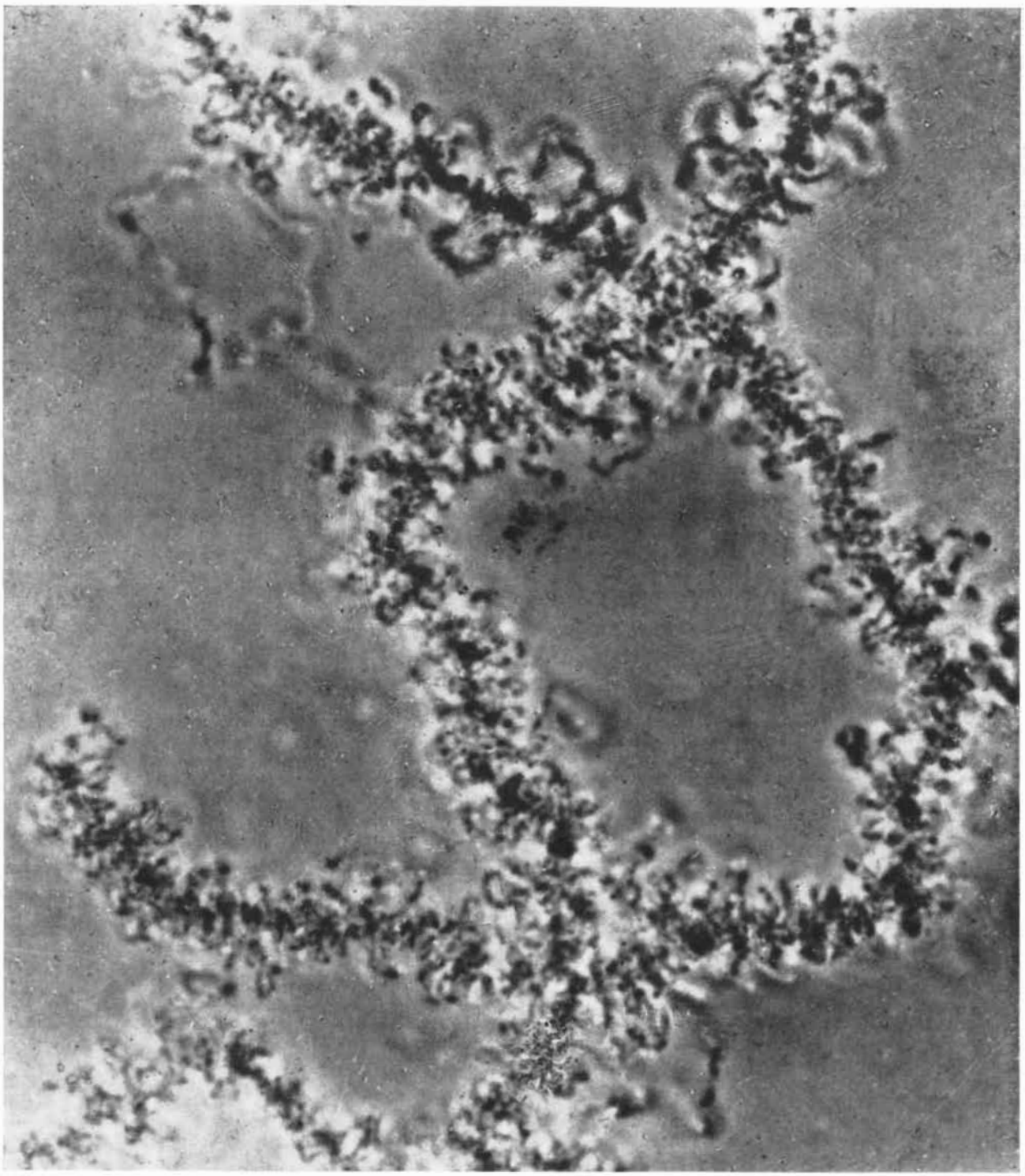
Before a future egg cell begins to grow it looks like any other undifferentiated cell in that it lacks the characteristics by which it would be assigned to a particular specialized cell type. In the frog it measures about 17 microns in diameter, or about twice the diameter of specialized cells. By the time the frog egg has matured its diameter has increased to about 2,000 microns, or two millimeters. This means the volume has increased 1,600,000 times. This tremendous increase in volume is due to the uptake of raw material from the ovarian environment and the use of this material in the synthesis of egg substrate. In some animals highly complicated molecules, the product of synthesis of other cells (usually the "nurse" cells or follicle cells), are taken up into the egg cell and incorporated. In frogs and other amphibia, however, it appears that the incoming material is largely in the form of simple molecules and that these are actively synthesized into more complex substances by the nucleus and cytoplasm of the egg cell itself.

Cytoplasm, nucleus, nucleoli and the nuclear membrane all increase in mass during egg development, so evidently the simple precursors from the environment are taken up by all these cell components and at least stored in them. Research with radioactive precursors has shown that strong synthesis occurs in the nucleus as well as in the cytoplasm. Within the nucleus very active synthesis takes place on the chromosomes, in the nuclear sap and probably also in the nucleoli.

The substances synthesized in the growing egg cell are mainly glycogen, lipids, proteins and nucleoproteins,

which are proteins combined with the nucleic acids, DNA and RNA [see "How Cells Make Molecules," page 74]. The proteins are partly in the form of clear cytoplasm rich in RNA and partly in the form of yolk particles called platelets, which come in various sizes and whose role is obscure. Mitochondria and many enzymes are found in abundance. In the eggs of some species DNA has also been found in the cytoplasm. It is probable that the main groups of chemicals in growing eggs are themselves tremendously heterogeneous since much of the complex chemical synthesis takes place at the sites of the 10,000 to 20,000 genes, each of which may give rise to a different substance. Let us, therefore, take a closer look at the chromosomes, where the genes reside.

The chromosomes of egg cells that have entered the growth period are not the densely spiralized, rodlike struc-



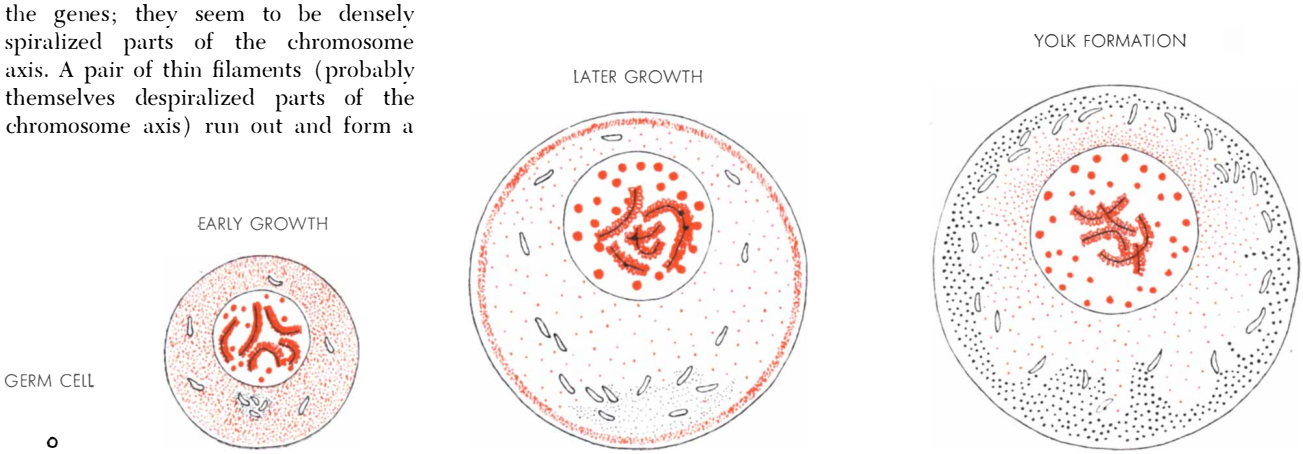
LAMPBRUSH CHROMOSOMES are named for their brushlike appearance, which results from the presence of numerous chromosomal loops (*small, dark wavy lines*) along the chromosome axes. This homologous pair of chromosomes, enlarged some 20,000 diameters, is from the oöcyte nucleus of a newt. This phase-microscope photograph was made by H. G. Callan of St. Andrews University.

"COMPOSITE" CHROMOSOME shows the wide variations that occur among chromosome loops of lampbrush chromosomes, particularly in the size of the loops and in the matrix and

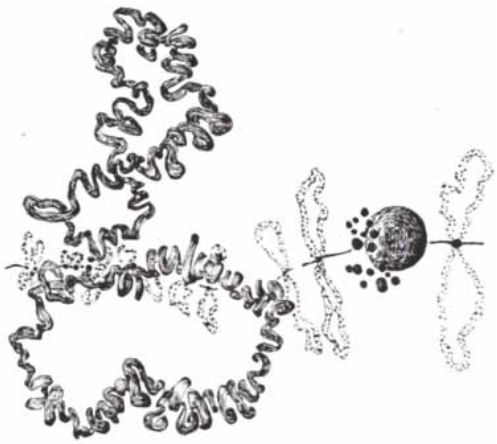
tures commonly seen at the time of mitotic division. Rather, they are largely despiralized and therefore very long and thin. Early in egg growth they consist of a single axial filament and later of a double filament, which contains at short intervals pairs of thicker and denser swellings: the chromomeres. The chromomeres are so plentiful that they agree roughly with the expected number of genes and they may even be the genes; they seem to be densely spiralized parts of the chromosome axis. A pair of thin filaments (probably themselves despiralized parts of the chromosome axis) run out and form a loop on each side of the chromosome and then return to it, entering the second chromomere of each pair [*see illustration on page 124*]. The over-all appearance of the chromosomes in this stage of egg growth has led to their being called "lampbrush" chromosomes.

The vast majority of the chromomeres possess lateral loops, which come in many lengths and varieties. H. G. Callan of St. Andrews University in Scotland and Joseph G. Gall of the University of Minnesota have found that the shape of the loop and the nature of the matrix surrounding a particular loop are characteristic for a given chromomere, which is always found in the same position along the axis of a particular chromosome. The chromosome axis, the chromomeres and the lateral loops consist of DNA, now regarded as the substance of which genes are composed. The matrix surrounding the lateral loops, however, consists of RNA and protein. These two substances, but not DNA, are abundantly synthesized at these loops during the whole period of egg cell growth.

Callan and Gall have shown that RNA (and probably protein) produced at the lateral loops of lampbrush chromosomes detaches itself from the loops and comes first to lie free in the nuclear sap and later passes through the porous nuclear membrane into the cytoplasm. The RNA in the cytoplasm increases during the early and middle stages of



GROWTH OF FROG EGG CELL is marked by increased heterogeneity of cell components (*keyed to legend at right*). Size and number of RNA globules are greatest in "Later growth" and "Yolk formation" phases. The cell cytoplasm is packed with RNA granules in "Early growth"; granules are fairly evenly distributed in "Later growth," except for a peripheral ring that disappears in "Yolk formation." At "End of growth" the granules are distributed in a smooth and weakening gradient from the upper to the lower pole.



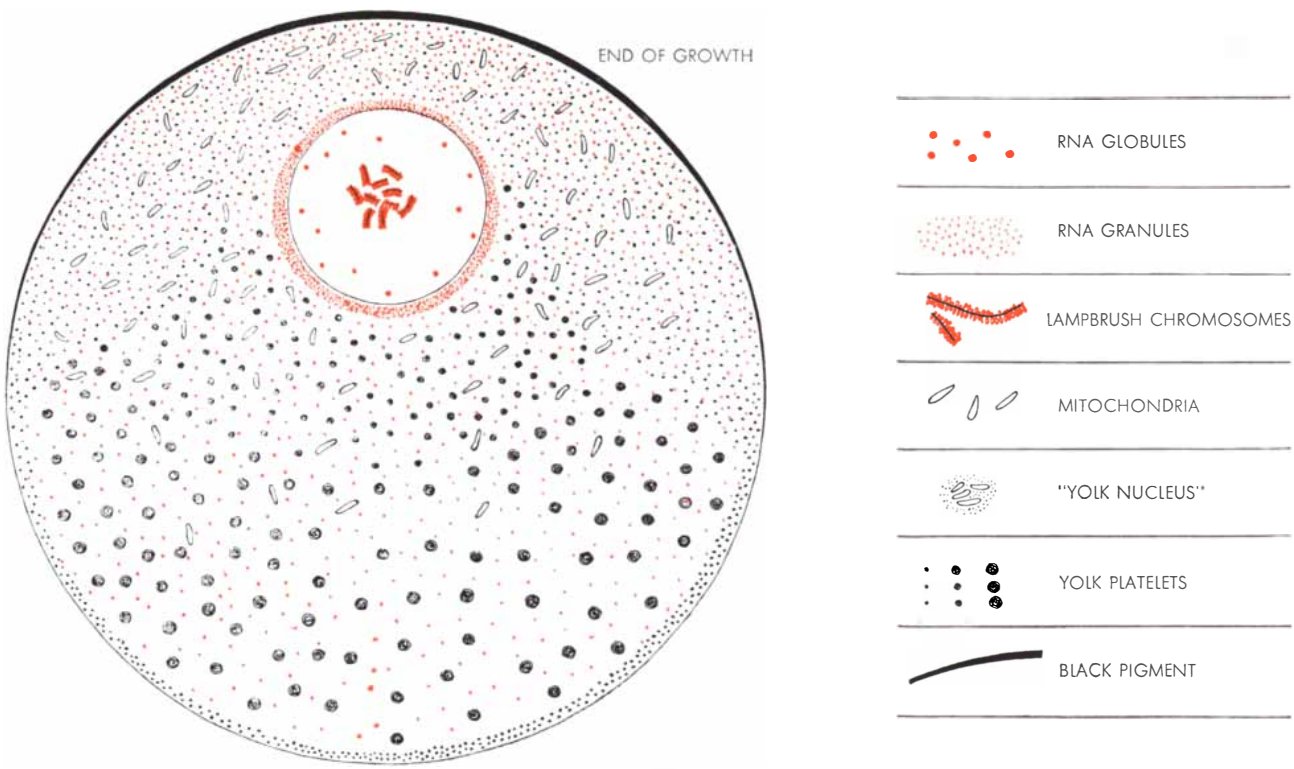
matrix inclusions. The loops depicted here do not all belong to the same chromosome.

egg growth, and much protein is synthesized at the sites of the cytoplasmic RNA granules. It is possible, therefore, that the number of different species of RNA and protein molecules in an egg cell equals the number of synthesizing genes present. Until methods for distinguishing among different species of RNA and proteins have improved one can only guess at the heterogeneity of the egg contents.

It is not difficult to see, in any case, that the mature egg has polarity, which means that its contents are distributed nonuniformly and in an orderly and specific way. The nucleus lies near what can be called the upper pole and the clear cytoplasm, the RNA granules and mitochondria are concentrated near this pole and decline toward the lower pole in quantity. The pigment on the surface shows a similar distribution, whereas the yolk granules are larger and more densely packed near the lower pole, becoming smaller and more widely spaced toward the upper pole. We can therefore speak of gradients in the cytoplasmic substances. These gradients run parallel to the egg axis and are radially symmetrical about it. In other words, all the points on a particular plane parallel to the "equator" of the egg have the same cytoplasmic composition but differ in composition from points on all other planes. As a consequence all the meridional slices going from the upper pole of the egg to the lower one (like segments of an orange) contain the same substances distributed in the same way.

This radial symmetry, observable in the eggs of many species, is eventually changed to bilateral symmetry. Depending on the species of animal producing the egg, this happens either shortly before or shortly after fertilization [*see illustration on next page*]. The change in symmetry is caused by a change in the distribution of the cytoplasmic components and is often linked to a change in the outermost (cortical) layer of the egg. Certain cytoplasmic substances sometimes accumulate in the form of a crescent on one side of the egg. Further development of these eggs shows that the plane that divides the body of the developing embryo into a right and left half passes through the broadest region of this crescent, roughly parallel to the equator, and through the two poles. In amphibia the broadest region of the crescent always becomes the dorsal or upper part of the body, while the region where the thin tips of the crescent come together develops into the ventral part, or underbelly. The head of the animal develops on the ventral side of the upper pole, and the tail comes to lie in the region between the lower pole and the lower edge of the crescent.

We see, then, that the future embryo is fully predetermined in the uncleaved egg by the distribution and peculiarities



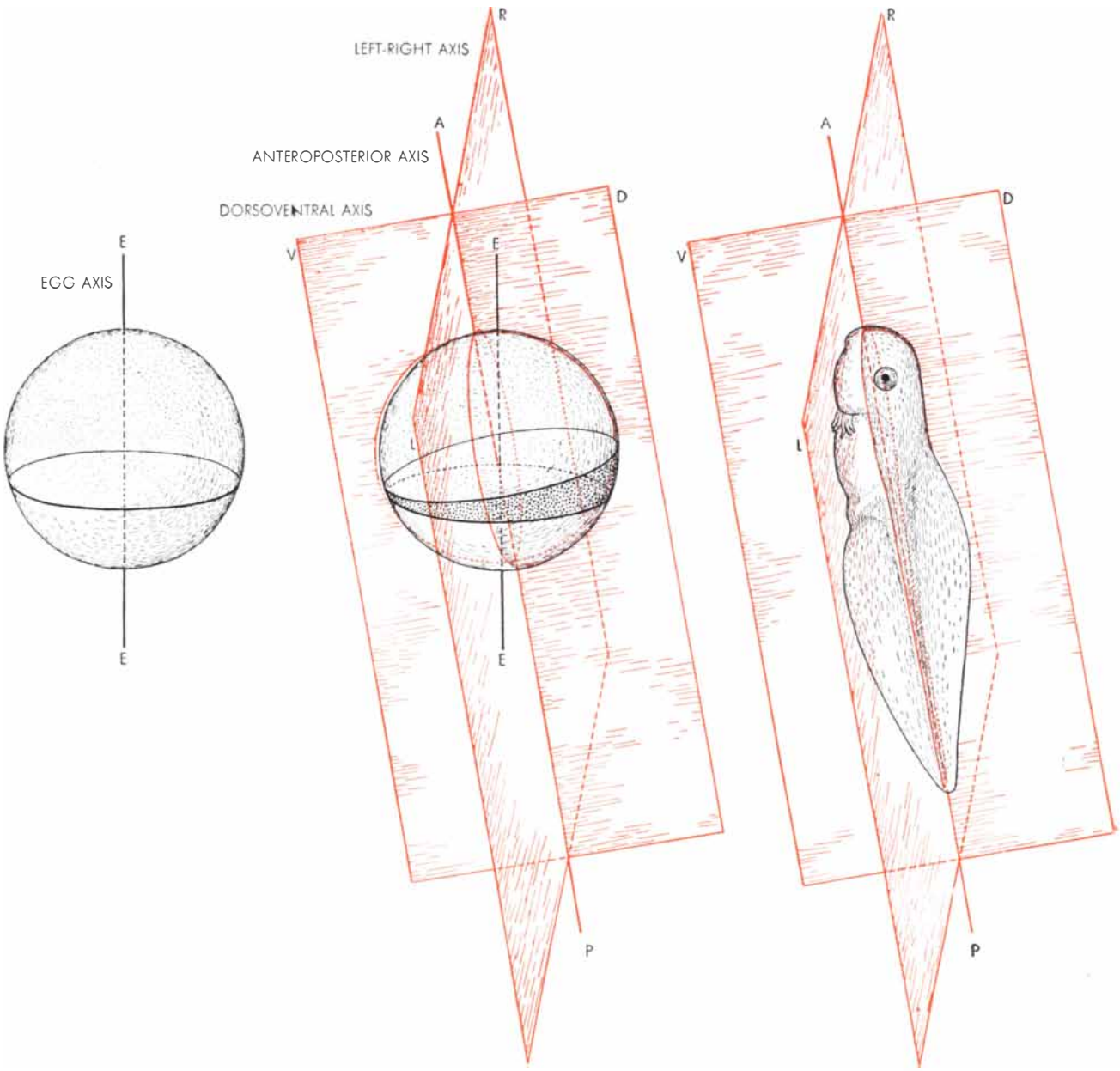
Throughout cell growth lampbrush chromosomes become increasingly condensed in center of nucleus. Mitochondria are equally distributed in "Early growth" except for concentration in the yolk nucleus; at "End of growth" they are distributed in a smooth and weakening gradient from the upper to the lower pole. Smallest yolk platelets appear in "Yolk formation." At "End of growth" platelets are distributed throughout the cell, increasing in size from top to bottom. Black pigment appears only at "End of growth."

of its cytoplasmic components. This predetermination is so clear in the eggs of many species that certain areas in the uncleaved egg can be easily recognized as those which are going to give rise to the brain, the intestine, the muscles or the future germ cells. And, as we have noted, the predetermination in some species is clearly evident even before the egg is fertilized. Fertilization is normally required, of course, before cleavage will take place.

During subsequent development, after fertilization, the chromosomes of the egg and sperm are incorporated into a single nucleus, which then divides by mitosis, leading to the first cleavage. As cleavage progresses, each daughter nucleus is accordingly surrounded by a distinctively different matrix of cytoplasmic substances as the spatially organized heterogeneity of the egg cytoplasm is stabilized by the appearance of cell membranes.

However, all the nuclei derived by mitosis from the one nucleus of the fertilized egg are initially, at least, identical. Being identical, they all have to act in the same manner. They can act differently only if they are ordered or stimulated to do so by a variable factor, namely their environment, particularly the immediate cytoplasmic environment. Unless one is willing to believe that the cytoplasm has full responsibility for differentiation, one has to believe that the cytoplasm, which varies from one part of the egg to another, influences identical nuclei to act in different ways. This assumption is not only a logical necessity but has found strong experimental support, as we shall now see.

Some insect larvae (mainly the larvae of the order Diptera) have salivary glands consisting of a small number of large cells with enormous chromosomes. This is one of those cases in which



RADIAL SYMMETRY of a frog egg (*left*) changes to bilateral symmetry (*middle*) with the development of a "crescent" (*one side of which is defined by the heavily stippled area*). The tadpole (*right*) that will develop when such an egg is fertilized will also show a corresponding symmetry, as can be seen by comparing the main axes of both the egg and the tadpole. As depicted here, the "Left-right axis" (*L-R*) and "Dorsoventral axis" (*D-V*) have been extended to form planes that cut through egg and tadpole.

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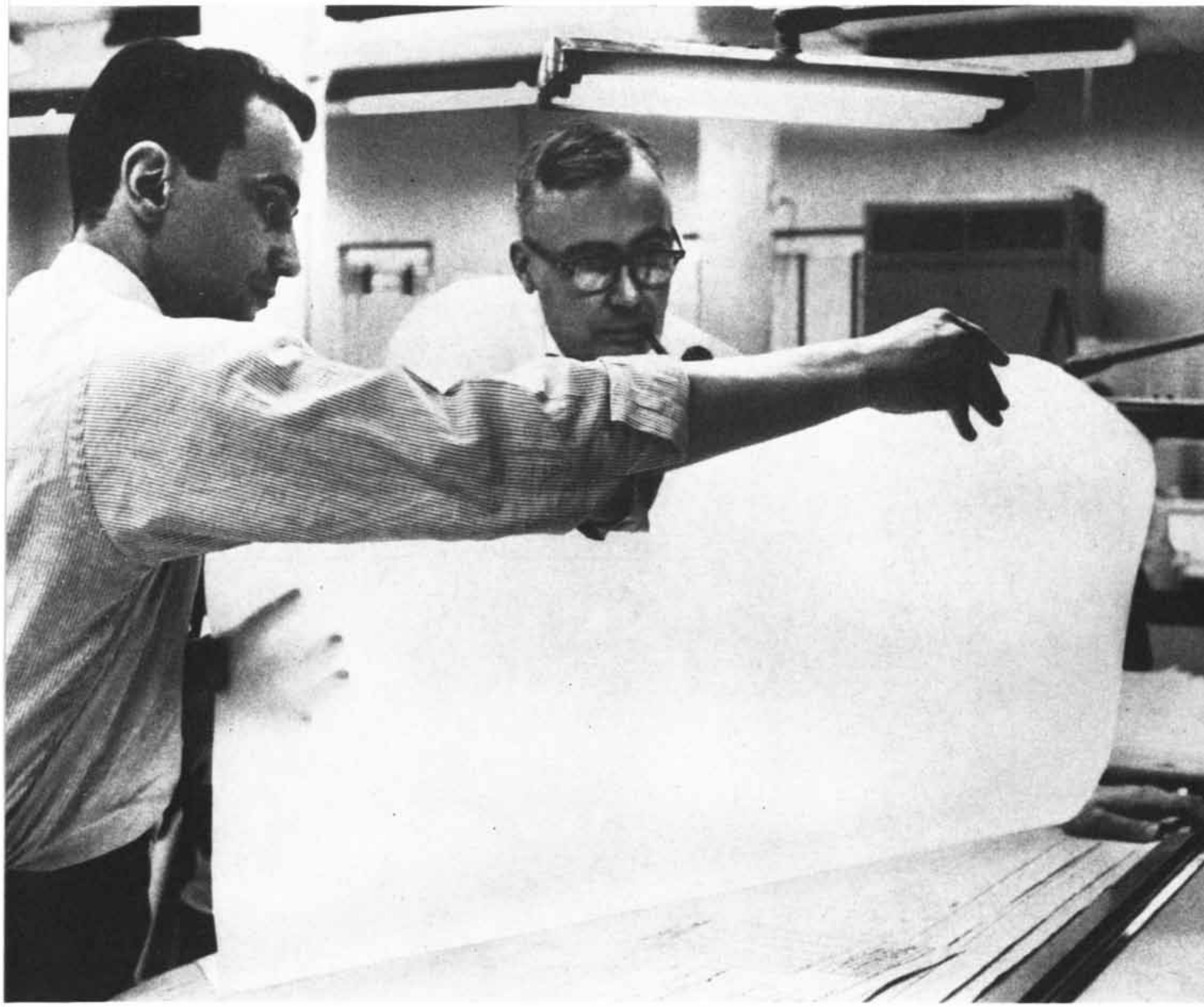

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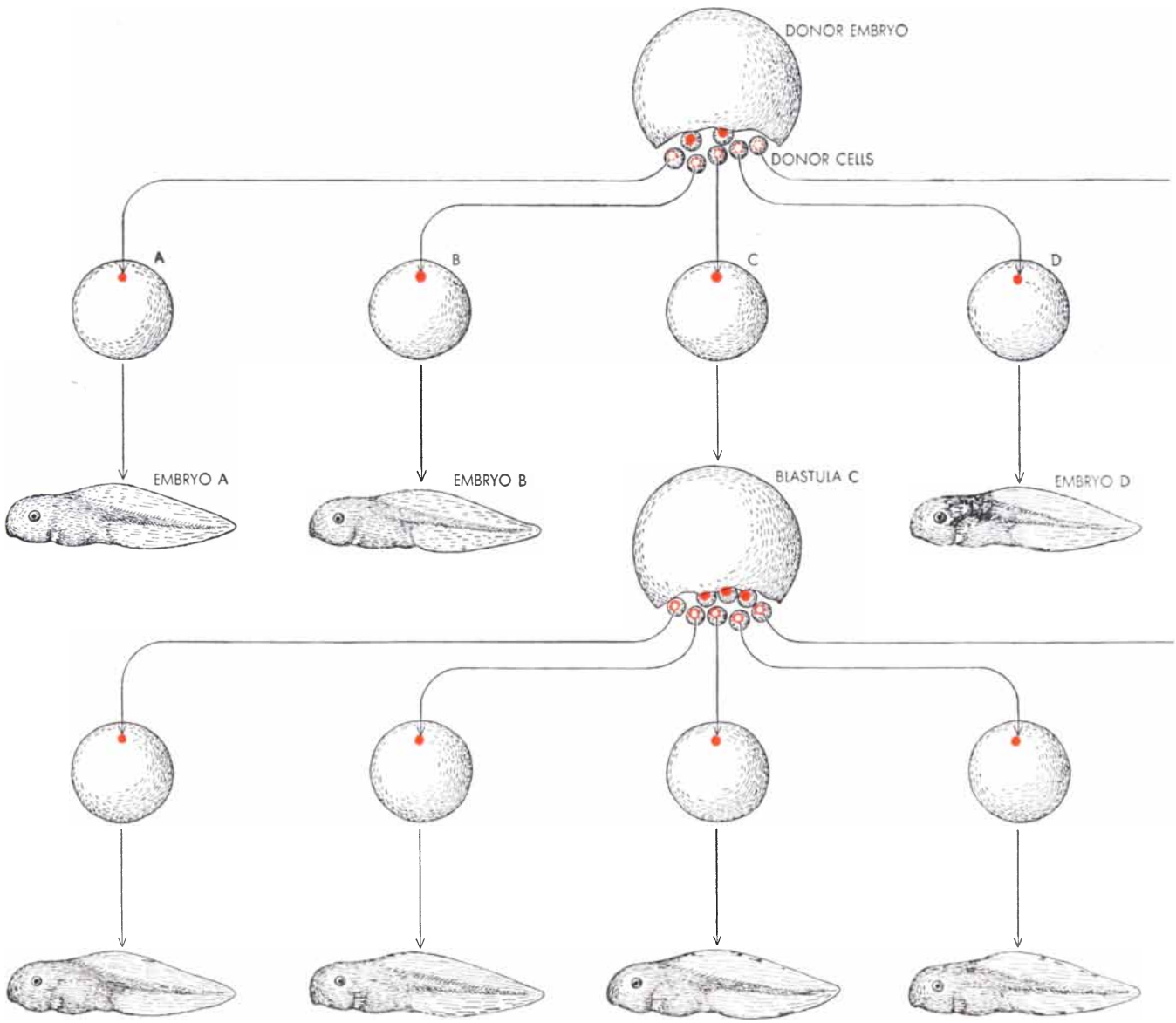
growth is achieved not by an increase in cell number but by an increase in cell size. Very large cells apparently cannot function with the usual number of chromosomes, and the chromosome number is therefore increased in proportion to cell size. The giant salivary gland chromosomes are really bundles of about 500 to 1,000 despiralized chromosomes that stick together in such a way that the identical parts—the chromomeres—of all the homologous chromosomes lie side by side. As a result all the chromomeres of a particular gene site form a disk, as do the chromomeres at other sites. These disks are separated by disks of the nonchromomeric parts of the sausage-like chromosomes, so that the giant chromosome looks as if it were made up of a large number of dark and light bands of varying thickness [*see illustration on page 138*].

Careful studies by M. E. Breuer and Clodowaldo Pavan of the University of São Paulo and by W. Beermann and his colleagues at the University of Tübingen have shown that chromomeres can swell up into so-called Balbiani rings, or puffs. They have also found that the puffs are the sites of strong synthesis of RNA and proteins. These observations are particularly exciting because the occurrence of the puffs follows a specific pattern. In mature larvae of a particular species only certain recognizable chromomeres will show puffs in all the specimens. But in young larvae other chromomeres, or gene sites, will be puffed up. It is reasonable to conclude that different genes puff up and become active at different stages of an organism's development.

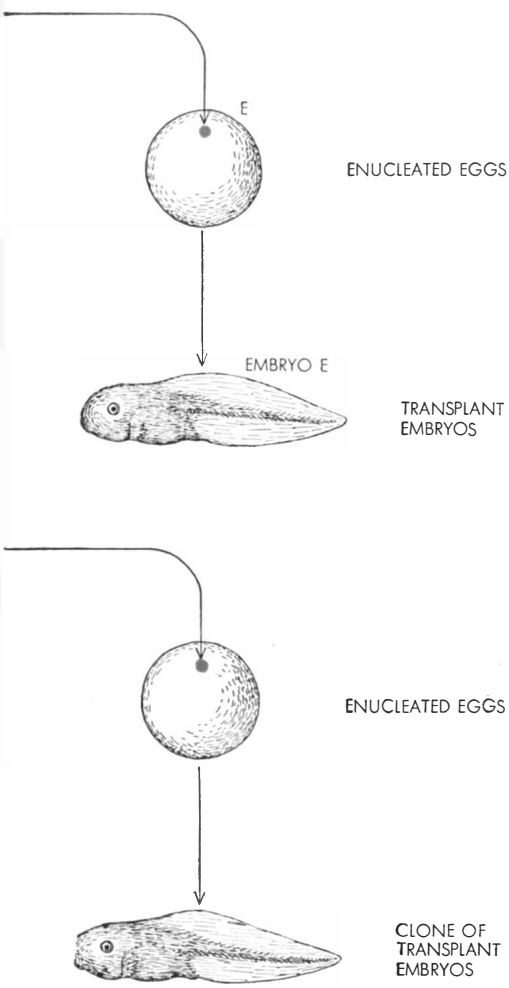
This activity of chromomeres is not only specific with respect to age but also with respect to cell type. Salivary glands, at least in chironomid Diptera (midges), possess two types of secretory cell, and each type has its own pattern of swellings, which also undergoes changes during development. It appears, therefore, that specific factors in the cytoplasm call forth the activity of particular genes. Furthermore, it is likely that the cytoplasm varies from one cell type to another and changes progressively (prob-



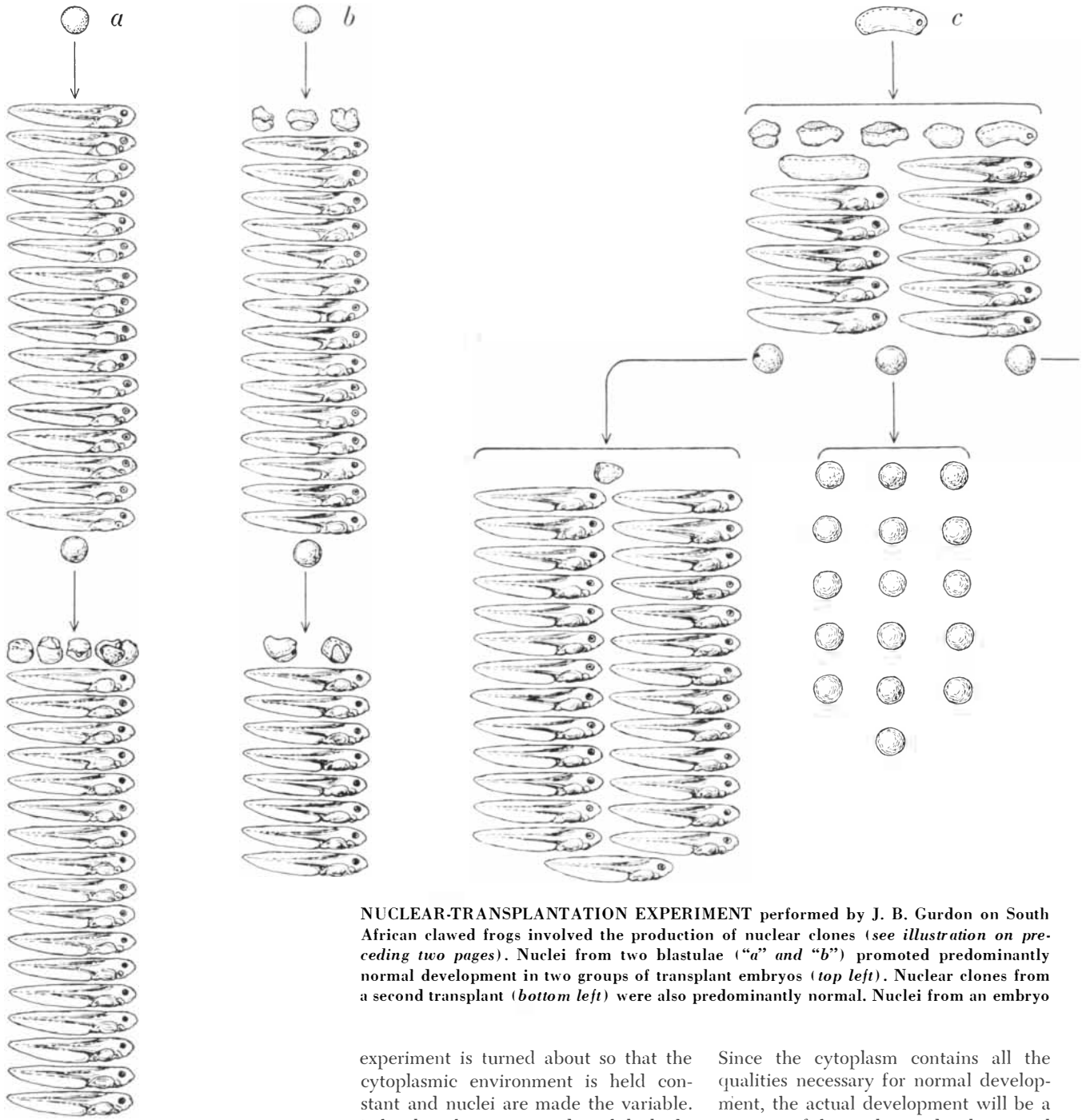
PRODUCTION OF NUCLEAR CLONES makes it possible to test various assumptions concerning the specialization of cells (*see, for example, the experiment illustrated on pages 132 and 133*). Nuclei (*colored dots*) from donor cells of a partially developed frog embryo are injected into "Enucleated eggs," *i.e.*, eggs from which the nuclei have been removed. These produce five normal "Transplant embryos." Nuclei from cells of "Blastula C" are injected into another set of enucleated eggs. The resulting "Clone of

ably as a result of specific gene activity) during development.

Some support for this idea is provided by new and original experiments conducted by H. Kroeger at Oak Ridge National Laboratory. He changed the environment of salivary gland chromosomes by transferring the nuclei from glands of advanced larvae into a preparation containing the cytoplasm characteristic of developing eggs. He found that the swellings of certain chromomeres of the salivary gland chromosomes disappear in the new environment and that other chromomeres are induced to produce puffs. There is even a certain amount of correlation between the puffing and the developmental stage of the



transplant embryos" consists of five genetically identical individuals whose chromosome complements are all descended from chromosomes of one nucleus (*C at top*).



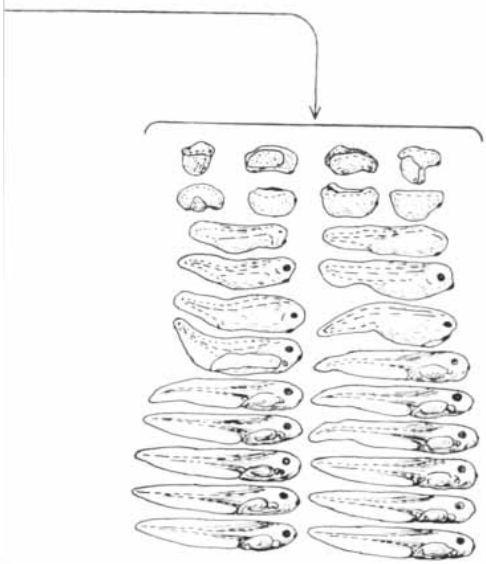
NUCLEAR-TRANSPLANTATION EXPERIMENT performed by J. B. Gurdon on South African clawed frogs involved the production of nuclear clones (*see illustration on preceding two pages*). Nuclei from two blastulae ("*a*" *and* "*b*") promoted predominantly normal development in two groups of transplant embryos (*top left*). Nuclear clones from a second transplant (*bottom left*) were also predominantly normal. Nuclei from an embryo

eggs providing the new environment [*see illustration on page 136*].

The work on the salivary gland chromosomes is of the greatest importance to our views on how cells specialize. It provides a rare insight into the relationship of cytoplasmic environment and nucleus. The fact that the work deals mainly with advanced stages of development does not prevent it from serving as a model suggesting how differentiation can arise in early development.

Let us now see what happens if the experiment is turned about so that the cytoplasmic environment is held constant and nuclei are made the variable. It has long been accepted, with little direct evidence, that the chromosomes in all the cells of an organism are identical, regardless of how the cell itself is specialized. To test this assumption one can, by means of delicate techniques, extract the nucleus (containing all the chromosomes) from an unfertilized frog egg and replace it with a nucleus obtained from one of the partially specialized cells of a developing frog embryo. The cytoplasm of the egg and the injected nucleus will then undergo development and give rise to what is called a transplant embryo. Fertilization is not necessary because the injected nucleus is already the descendant of a fused egg and sperm nucleus. Since the cytoplasm contains all the qualities necessary for normal development, the actual development will be a measure of the quality or developmental potential of the injected nucleus.

Robert W. Briggs of Indiana University and Thomas J. King of the Institute for Cancer Research in Philadelphia, and the authors in collaboration with J. B. Gurdon of the University of Oxford, carried out such experiments with different species of frog and obtained in principle the same results. They found that if the nuclei were obtained from embryos in the early (blastula) stage of development, the new transplant embryos in most cases produced normal tadpoles [*see illustration on these two pages*]. If, however, nuclei of advanced embryonic stages are transplanted, few-



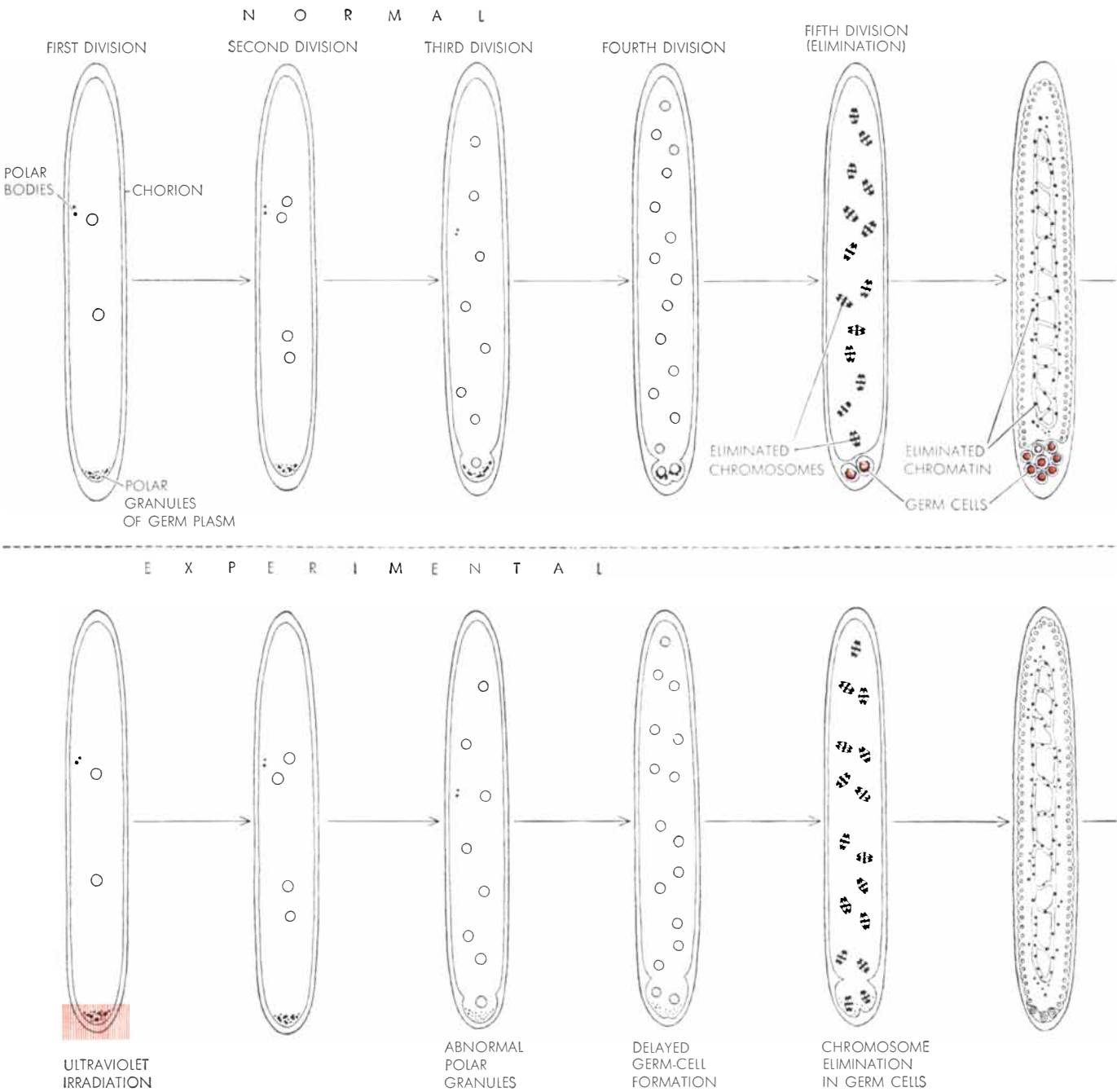
at a later stage ("*c*") promoted a variety of normal and abnormal embryos from which three nuclear clones were produced: predominantly normal (*at left, under "c"*), undeveloped (*middle*) and abnormal (*right*).

er nuclei are able to participate in the production of normal embryos. Most of the transplant embryos either do not cleave normally and die or are arrested at later and abnormal developmental stages. The conclusion from this last experiment is that nuclei change during development and differentiation. They seem to lose their totipotentiality and become more limited in their ability to promote normal development.

One of the most striking characteristics of these experiments is that nuclei taken from a single future organ—say, the gut—of a single embryo do not give rise to similar transplant embryos but to a great variety of embryos. This includes arrested blastulae, a wide range of abnormal embryos and a few normal tadpoles. Accordingly, one can conclude

not only that nuclei differ from one organ to another but also that even single organs are made up of cells containing quite different nuclei. In other words, a developing organ of an embryo is made up of a heterogeneous population of nuclei. If nuclei of newly hatched tadpoles are transplanted in the way described, the resulting transplant embryos show greater uniformity. This decline in variation of the transplant embryos could indicate that the nuclei become more similar because most of them have by now undergone the same kind of changes, whereas in experiments with embryos the nuclei were caught at different phases of change. On the other hand, the nuclei of tadpoles may be so limited in their potentialities that they lead usually only to arrest at the earliest stages of development.

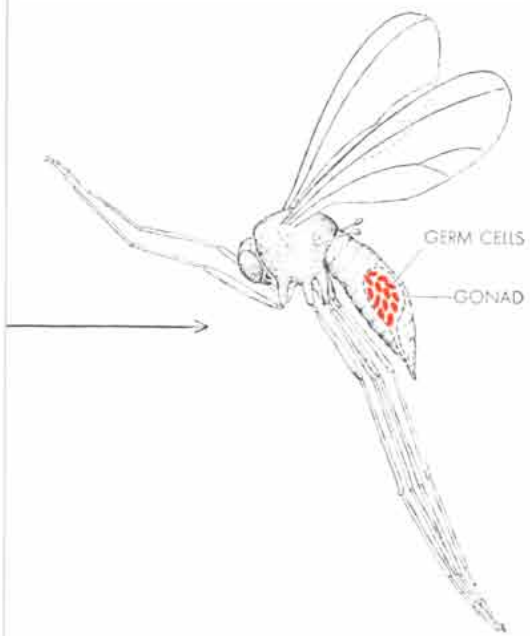
Another question is: Are the observed nuclear changes of a reversible nature or are they stable, irreversible and hereditary? This question can be answered by the production of "nuclear clones" [*see illustration on pages 130 and 131*]. A nucleus of a donor embryo is injected into an unfertilized, enucleated egg. This develops without further nuclear differentiation into a blastula. The cells of this blastula are then dissociated and their nuclei are injected singly into unfertilized eggs. The embryos developing from this second transfer form a clone of embryos, each containing

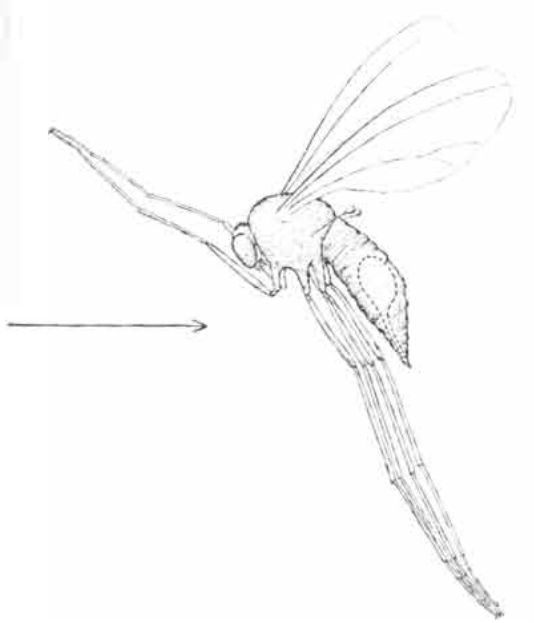


GERM-CELL SPECIALIZATION in gall midge *Mayetiola destructor* is contrasted under normal and experimental conditions. In normal development (*top*) nucleus of fertilized egg divides into two nuclei (*small circles in "First division"*), then four and so on. In "Third division" and "Fourth division" two nuclei move to posterior pole of egg; the cytoplasm contracts so as to separate the nuclei from the rest of the egg. In "Fifth division" the remaining 14 nuclei undergo a mitotic division in which only eight sets of chromosomes in each nucleus separate to the poles; the other 32 pairs eventually dissolve in the cytoplasm of the cell. The germ cells develop normally and adult gall midge is fertile (*top right*). In an experiment (*bottom*) discussed in the text the germ plasm

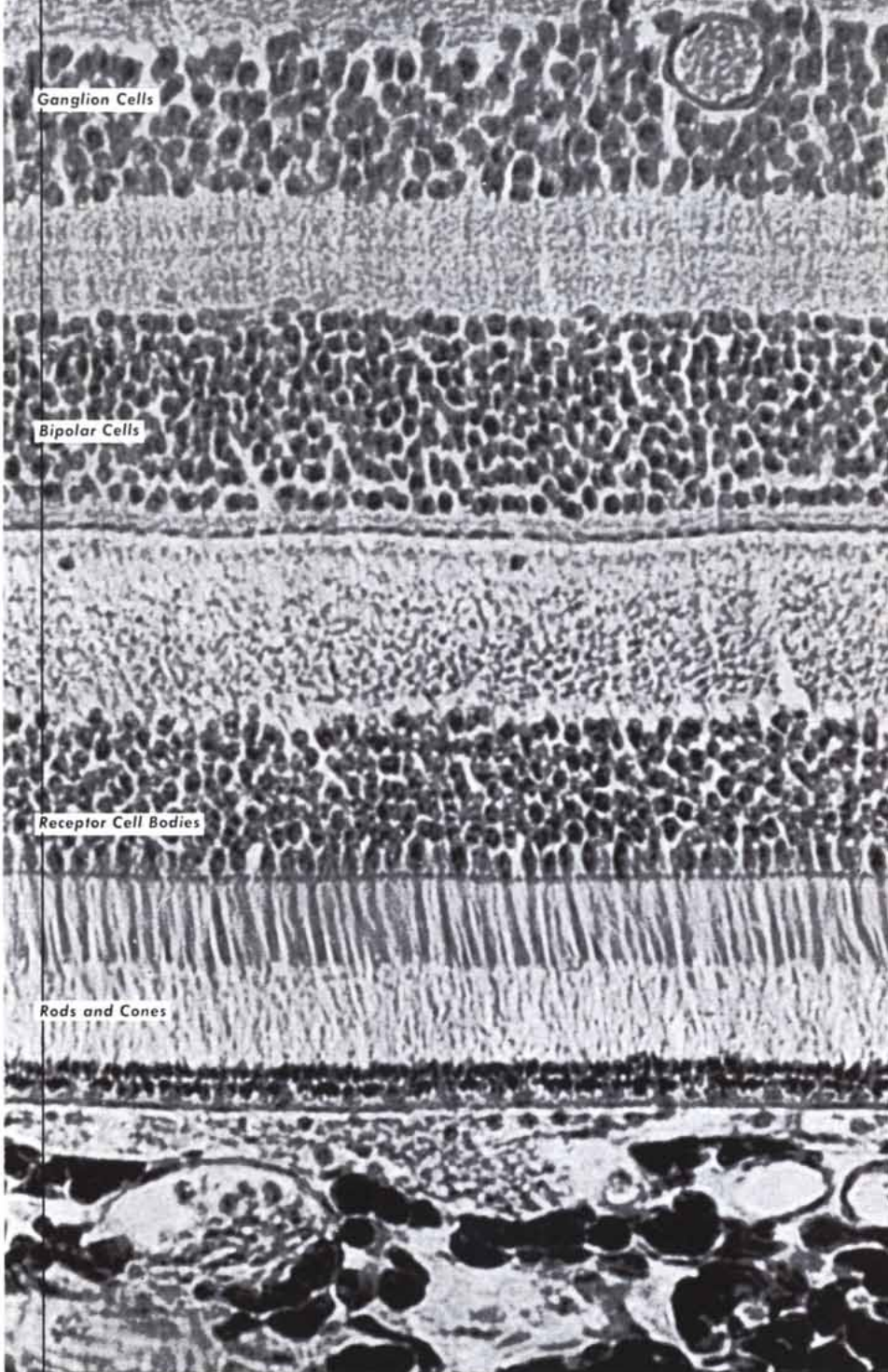
nuclei that are derived from the one initial nucleus used in the first transfer, and are therefore of identical genetic constitution. The experiment is repeated to produce a number of such clones.

The similarity within a clone is in remarkable contrast to the variation found among different clones. Each clone represents the quality of only one tested nucleus and the differences among clones represent differences among individual nuclei. The experiment indicates that the





was irradiated with ultraviolet light (*bottom left*), thus retarding germ-cell formation. As a result the two posterior nuclei also underwent mitotic division and lost 32 of their chromosome sets. Gall midge that developed (*bottom right*) was consequently sterile.



Photomicrograph courtesy of Dr. Kenneth T. Brown

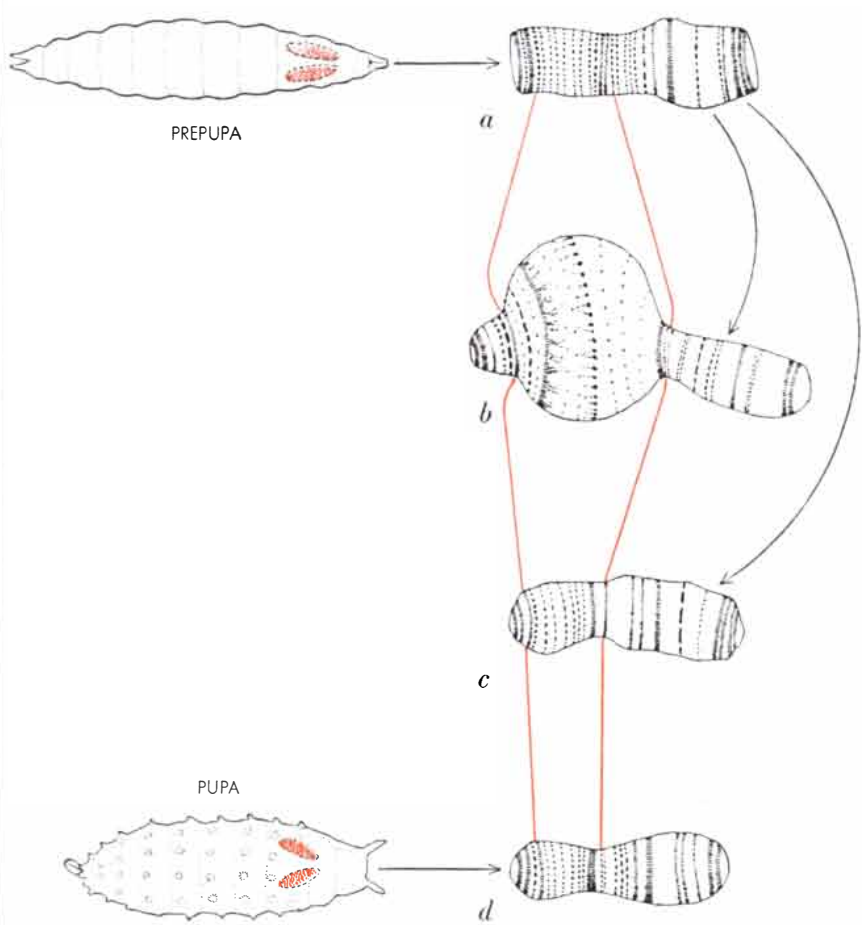
nuclear changes due to natural differentiation are relatively stable and of a heritable nature. It also strengthens the belief that the variation observed after the first transfer is a true one and not a result of damaging the nuclei during handling.

The stable, heritable and apparently irreversible nature of these nuclear changes poses, of course, a number of new questions. For example, one would like to find out which of the nuclear components is the site of the change. Is it the nuclear membrane, the nuclear sap, the nucleolus or the chromosomes embodying the genes? The chromosomes would seem the likeliest site, because so far as we know they are the only nuclear structure showing continuity throughout both mitosis and heredity. But a definite answer cannot be given until experiments now in progress shed some light on the problem.

Some years ago it would have been almost unthinkable to consider that nuclei might, during differentiation, change in their genetic qualities. Recently more and more cases of irreversible nuclear changes induced by cytoplasmic factors have been brought to our attention. They include examples from protozoa, ascarides, frogs and gall midges. In the last the changes occur at the level of chromosomes and are clearly visible under the light microscope.

Adult gall midges are unusual in that they have a large number of chromosomes in the germ cells and a small number in the somatic cells, which make up the whole body except the germ line. We shall describe how this difference in chromosome number is established in one species, *Mayetiola destructor* [*see illustration on preceding two pages*].

As in other insects, no cell membranes are formed during the earliest development. The zygote nucleus, containing about 40 chromosomes, divides into two, then four, then eight nuclei. Because of the lack of cell membranes, the nuclei are free to distribute themselves evenly



EXPERIMENT performed by H. Kroeger involved chromosome Number 2 from the salivary gland of the fruit fly *Drosophila busckii*. The chromosome is depicted here as it appears at the prepupal (*a*) and pupal (*d*) stages of the fly's development; and as it appeared after transferal to the preblastoderm (*b*) and blastoderm (*c*) egg contents of *D. melanogaster*.

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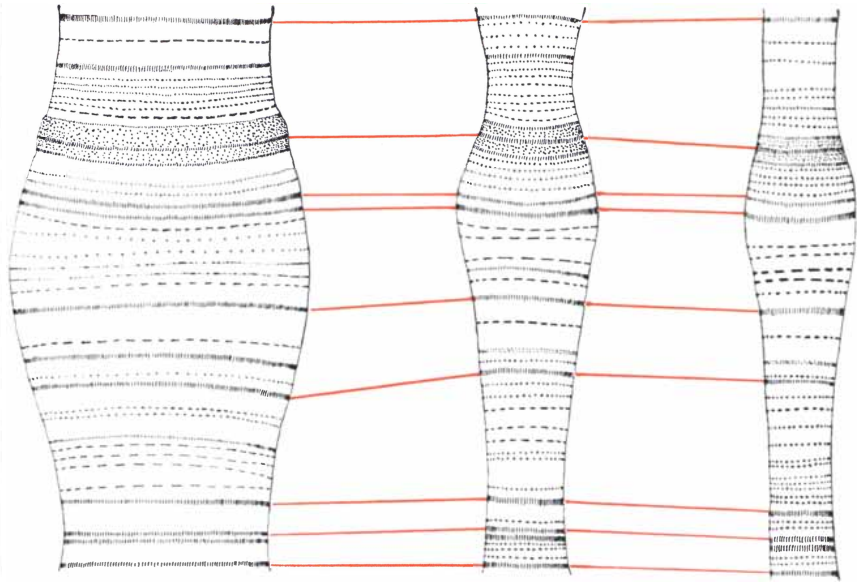


GIANT CHROMOSOME NUMBER 3 of larva of the midge *Chironomus* varies in shape and slightly in banding pattern depending on the type of cell in which it is found. Identical sections here are from the salivary gland (*left*), Malpighian tubule (*middle*) and rectum (*right*).

through the cytoplasm of the egg. At the eight-nucleus stage one of the nuclei moves all the way down to the posterior pole of the egg and comes to lie in the vicinity of a particular cytoplasm, the germ plasm, which always accumulates at this pole.

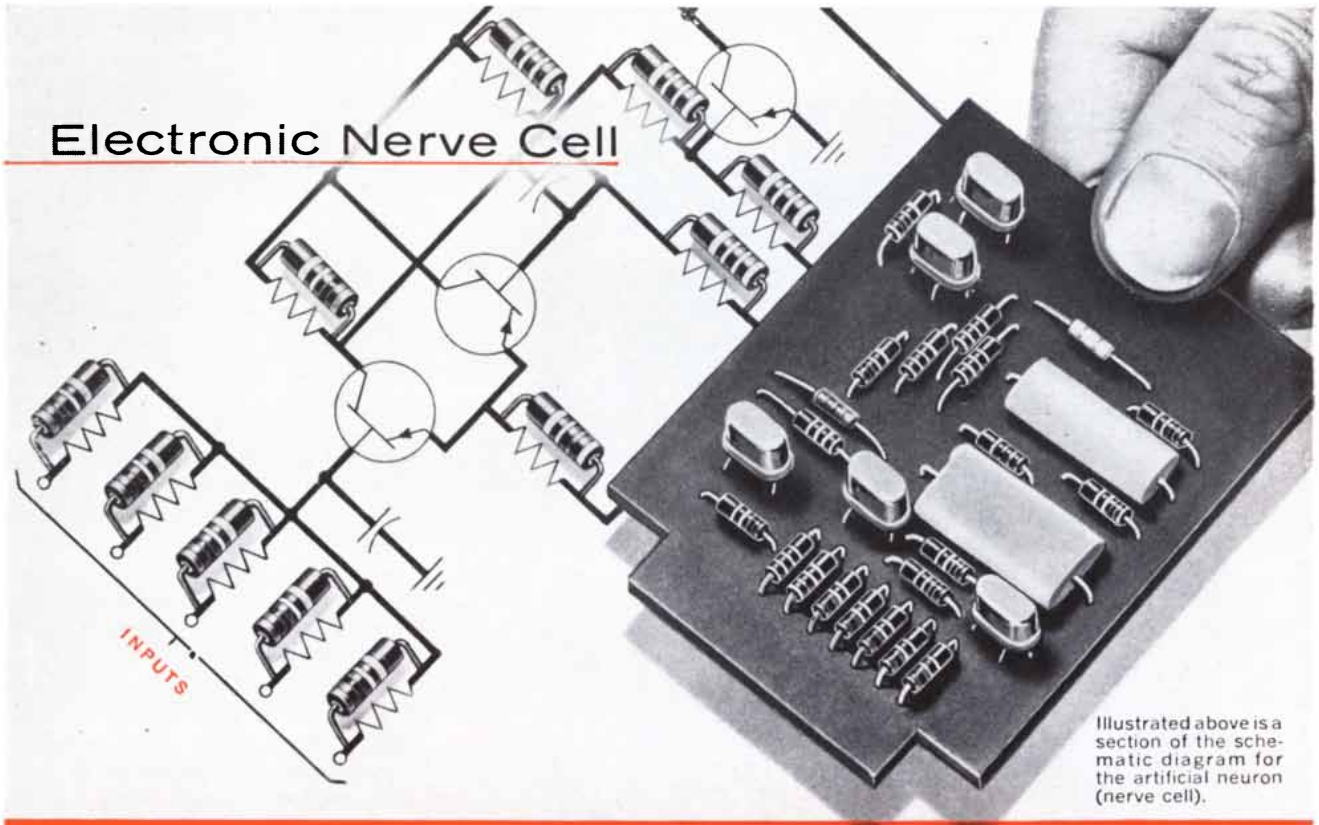
During the next mitosis all eight nuclei divide again, so that 16 are present. At the same time the cytoplasm near the posterior pole constricts in such a way that two cells are formed, containing the two most posterior nuclei and all the germ plasm. This cleavage cuts off the two newly formed cells from the rest of the egg. These two cells are destined to become the primary germ cells, and all the future eggs or spermatozoa, as well as the nurse cells, will derive from them.

At this moment the peculiar fifth division begins in all 14 nuclei lying in the somatic part of the egg, but the two primary germ cells are exempt from this mitosis. When it is time for the duplicated chromosomes to start moving apart (at the anaphase stage), it becomes clear that the mitosis is most unusual. Only eight of the 40 chromosomes of each nucleus separate along their whole length into two chromosomes and move toward the opposite poles of the mitotic spindle. The remaining 32 fail to separate at their ends and remain immobile in the equatorial plane of the spindle. Meanwhile the eight chromosomes at each pole of the spindle form two small daughter nuclei. The 32 chromosomes left behind soon begin to dissolve and the material derived from them gradually disperses throughout the cytoplasm and is not seen again. In this way 32 chromosomes are eliminated from somatic cells.

The primary germ cells are exempt not only from this mitosis but also from chromosome elimination. During subsequent divisions of the germ cells the full chromosome number is maintained and the germ line is formed. The small nuclei (which contain eight chromosomes) go on dividing and give rise to the small nuclei of all the somatic cells.

It is evident that the presence or absence of a cytoplasmic factor determines the behavior of the nuclei during the fifth mitosis. Close observation of the future germ-cell nuclei shows that the germ plasm, rich in RNA and mitochondria, wraps itself intimately around the nuclear membranes of these nuclei after the fourth mitosis. One has the impression that the germ plasm protects the nuclei from the influence of the neighboring cytoplasm, an impression that is strengthened by the formation of cell membranes cutting this pair of cells off from the rest of the egg.

To study the cause of chromosome elimination, C. R. Bantock of the University of Oxford irradiated with ultraviolet light the extreme posterior ends of gall-midge eggs, the ends containing the germ plasm, before the future germ-cell nuclei had migrated into them. The remainder of each egg, containing all the nuclei, was carefully shielded from irradiation. In eggs so treated the posterior nuclei migrated normally into the germ plasm, but now, instead of being pro-



Illustrated above is a section of the schematic diagram for the artificial neuron (nerve cell).

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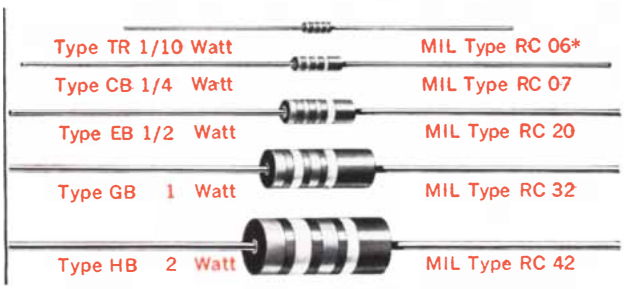

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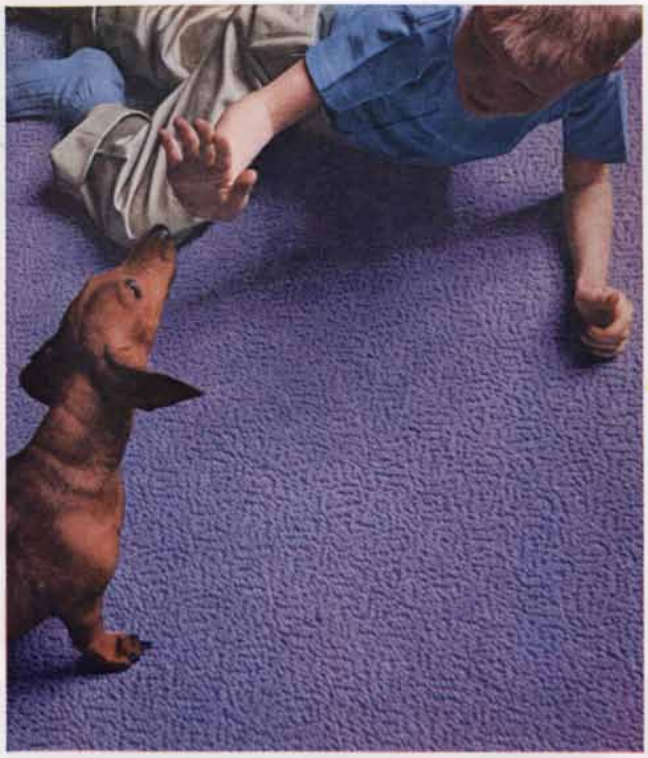
tected in some fashion, they shared the same fate as the other nuclei—that is, their chromosome number was reduced from 40 to eight. The primary germ cells, in spite of losing 32 chromosomes, still gave rise to the beginning of a germ line. If the embryos were allowed to develop, they produced adult male and female midges that looked normal but were actually sterile. Histological examination of the gonads of gall midges obtained from ultraviolet-treated eggs revealed that the reproductive cells failed to develop.

It appears, therefore, that the germ plasm normally prevents chromosome elimination. This might be due to an inhibition of the fifth mitosis in the future germ-line nuclei or to another protective mechanism merely coinciding in time with this inhibition. The absence of reproductive cells in gall midges hatched from irradiated eggs indicates that the missing chromosomes are necessary for the development of such cells. The strong effect of the irradiation suggests furthermore that the protective factor of the germ plasm is composed of RNA, because it is particularly sensitive to ultraviolet light.

Bantock's work on the gall midge provides a clear example of nuclear-cytoplasmic interactions. It shows that egg formation can proceed normally only with the participation of the whole chromosome complement of the species, whereas somatic differentiation can take its normal course with a severely reduced chromosome number (eight) provided that the egg cytoplasm contains gene-products of the genes active during egg formation.

Just as the germ plasm prevents chromosome elimination in the gall midge, it probably plays a comparable role in protecting the germ cells in other and more complex organisms from specialization and loss of their totipotentiality. In frogs a germ plasm of similar chemical composition has been discovered and here too ultraviolet irradiation of the germ plasm causes partial or total sterility of frogs developing from such treated eggs.

In summary, differentiation is most likely to result from nuclear-cytoplasmic interactions that cause progressive individuation of the cytoplasm and increasing specialization of the nuclei of particular cells. The original question of how cells specialize has not been solved, but we hope we have shown that complexity of the cytoplasm in the mature egg cell cannot fail to lead to specialization.



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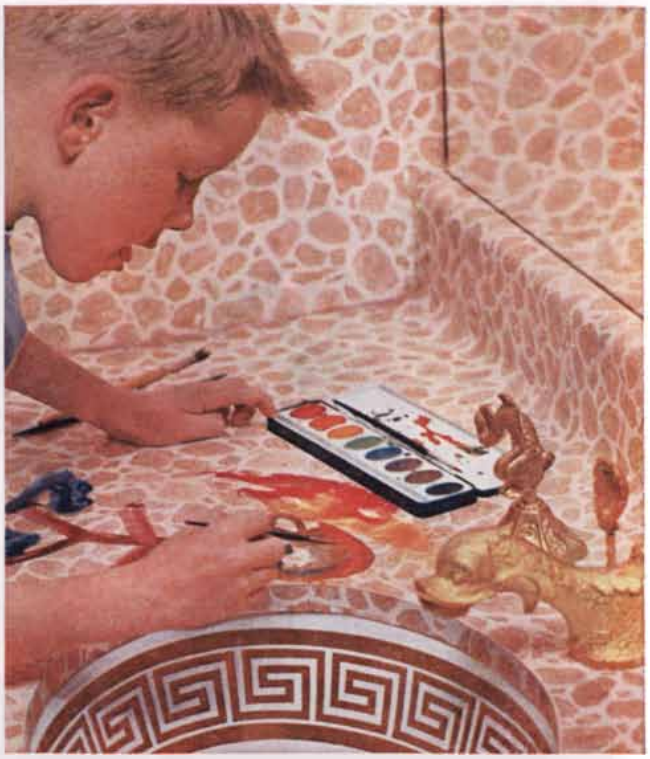

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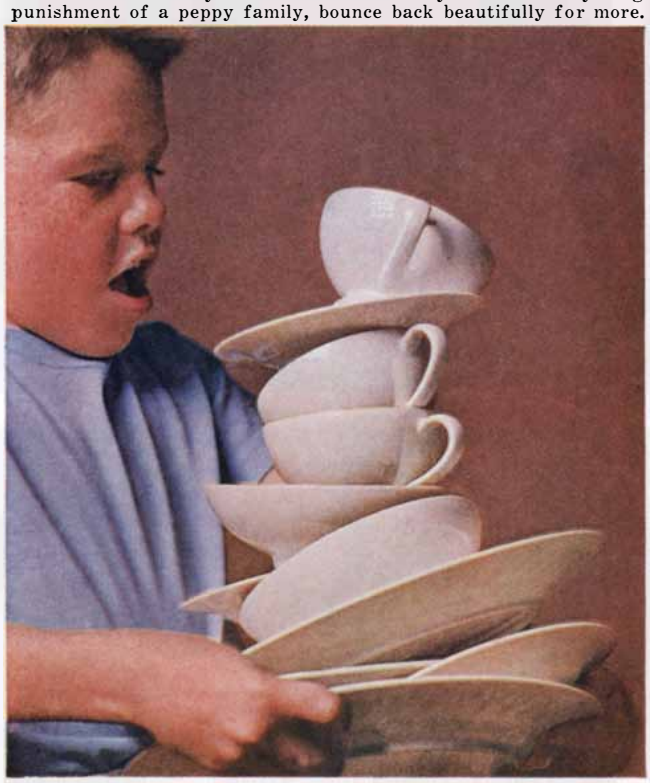

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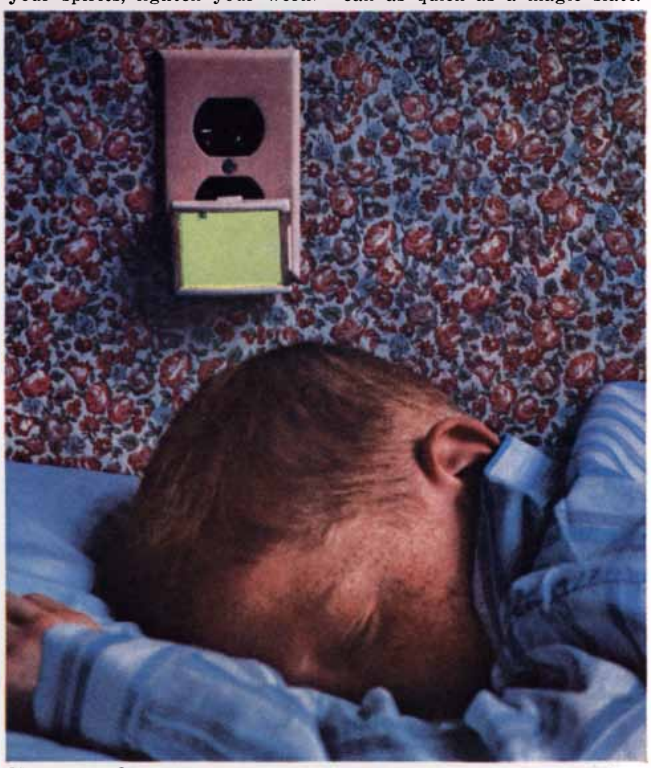

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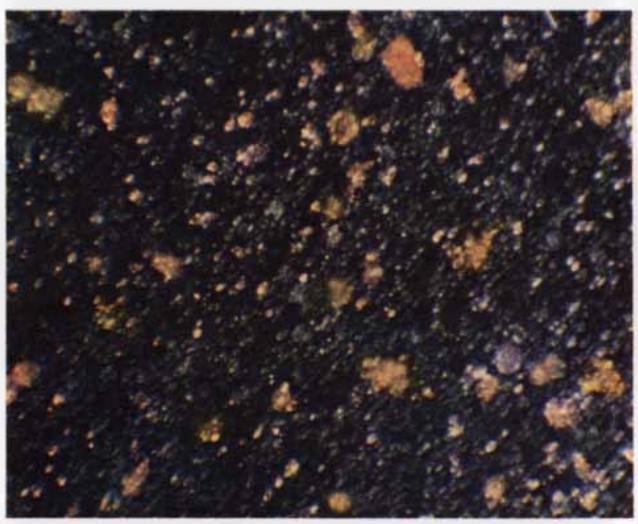
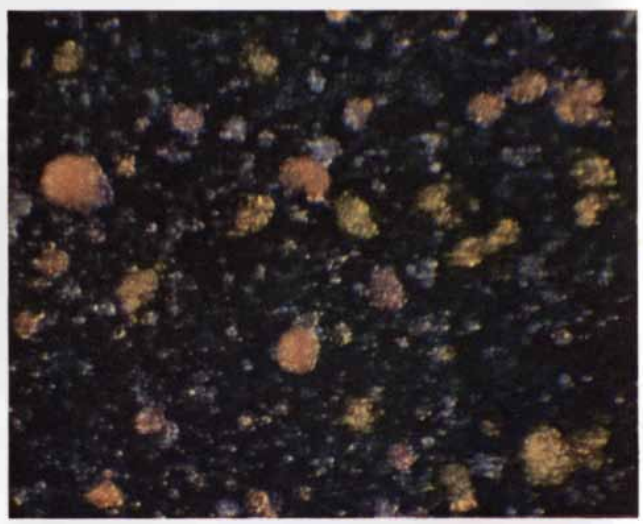
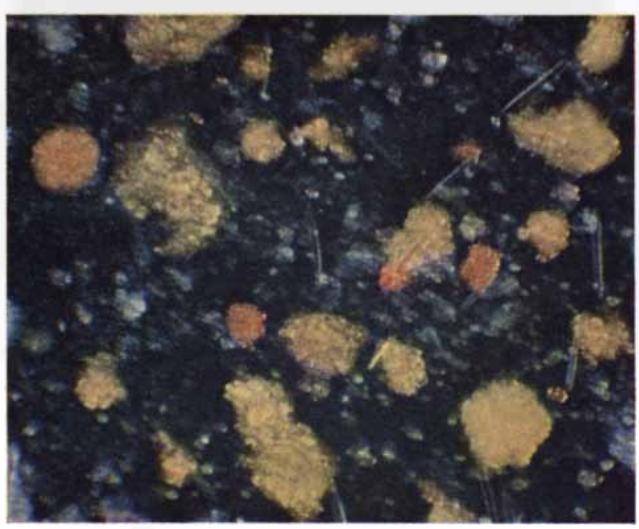
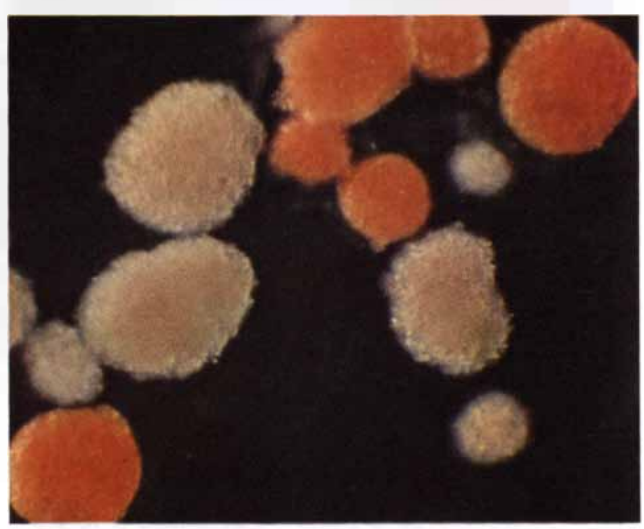








CELLULAR AGGREGATION is demonstrated in author's laboratory at the Marine Biological Laboratory in Woods Hole, Mass., using naturally orange sponge *Microciona* and yellow sponge *Cliona*. Solutions containing cells from each are in beakers at top. Cells are mixed together (*photomicrograph at middle left*). In the course of 12 hours they creep along the floor of the dish in which they have been placed and clump together by species, finally forming tiny orange sponges and yellow sponges (*bottom right*).

How Cells Associate

The cells of many-celled organisms are marshaled and held together by specific physical and chemical factors. These factors are studied by dispersing the cells of a tissue and allowing them to recombine

by A. A. Moscona

To explain how cells join with one another to form the tissues and organs of multicellular organisms, the biologist must answer questions that are as basic and pressing in their way as those that surround the nature of the chemical bond. In the absence of the intercellular bonds that hold cells together, the human body would collapse in a heap of disconnected, individual cells, many of them quite indistinguishable from certain free-living protozoa. Were it not for the high specificity of these bonds and the selectivity with which cells interact with one another, there would be no tissues or organs, only nondescript clumps of cells. To devise an approach to these questions—to submit masses of cells to experimental test as they proceed to associate, interact and synthesize tissues—challenges the ingenuity of the investigator.

The study of cell association proceeds along the parallel paths of analysis and synthesis. Since the turn of the century workers in this field have been developing techniques of tissue culture that make it possible to study tissue cells in the simplified environment of laboratory glassware and, by one means or another, to cause the tissues to dissociate into cells. Biochemical analysis has sought to identify the substances involved in the bonding and interaction of cells; morphological analysis, facilitated by the electron microscope, has concentrated on the connection between function and structure. But it is the relatively novel and direct method of synthesis—the experimental synthesis of tissues from free cells under controlled conditions—that offers particular promise in this field. Only by such frontal approach can one put hypothesis to the test and find out how cells actually associate.

In nature, as the fertilized egg proliferates into a mass of rapidly dividing cells, the cells first bunch together in no clearly apparent order. But the lack of order is only superficial. The cells have fundamentally identical genetic endowments. Their initial diversification must arise, therefore, in large measure from their different positions in the embryo. There is an impressive body of evidence for this. In the early embryo, for example, one can graft cells from a skin-forming area to the eye-forming one. The grafted cells develop in harmony with their new site, acquiring their neighbors' "eyeness" as their persisting identity, recognized as such by their kind and by other cells. If they are thereafter transferred to other sites, they remain unchanged.

While the embryonic cell may thus "learn" a specific functional identity in response to influences in its environment, it also retains an intrinsic identity established by its genetic endowment. Oscar E. Schotté and Hans Spemann performed an experiment many years ago that strikingly demonstrates this principle. In amphibians the ectodermal tissue (the outer of the three primary embryonic layers) of the mouth forms the teeth. But it does so only if it is in contact with the mouth endoderm (the inner embryonic layer). A "signal" from the endodermal cells triggers a sequence of events in the ectoderm that leads to the formation of teeth. Actually the matter is more complex; the endodermal signal apparently reciprocates a prior stimulus from the ectoderm. So before any noticeable appearance of teeth several "messages" may have been exchanged by the cells in this region. In the early embryo it is possible to transfer ectoderm from any part of the body to the mouth region and make it form teeth by placing it in proper association with the endoderm. Schotté and Spemann took advantage of the fact that newts have bony teeth and frogs have horny teeth to see what would happen if they transplanted frog ectoderm cells to the mouth endoderm of the newt. It turned out that the frog cells get the "message" to form teeth but, being frog cells, they form horny teeth. The learned identity acquired in this experimental association is interpreted by the cells in accordance with their genetic endowment.

The movement of cells from one place to another in the embryo constitutes an essential and conspicuous feature of normal development. Singly and in groups, cells move to new sites where, in association with new neighbors, they form new structures. The mammalian kidney, for example, arises from two separate and initially distant components. A little pocket of cells on each side of the cloaca elongates into a finger-like process, destined to form the ureters, and extends into the body cavity toward a mass of mesodermal (middle layer) cells that at this stage shows no definite structure. As soon as the two groups of cells come into contact, however, they begin to change rapidly. The ureter branches and sends out secondary processes; the mesodermal cells with which these processes make contact are organized into kidney tubules. These changes come quite promptly, as if by an exchange of signals between the two groups of cells. Proximity and association are necessary to the interaction. If the cell groups are kept separate, they do not produce their typical responses. In one strain of mice a genetic defect keeps the two kidney components from making contact, and the kidney does not form.

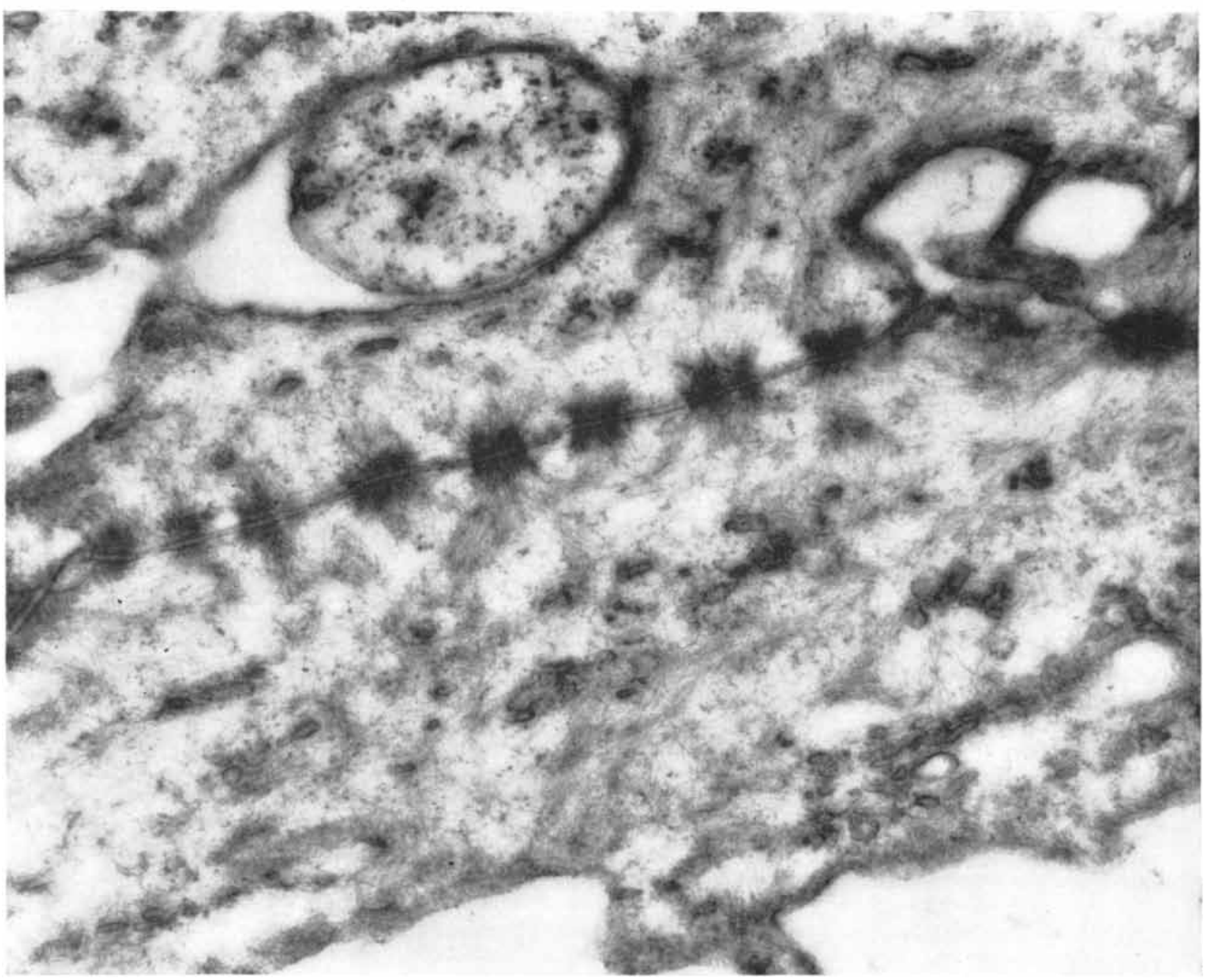
Next to nothing is known about the

signals that are supposed to be involved in such "inductive" interactions. Jean Brachet and H. de Scoeux, working at the Catholic University of Louvain, found many years ago that the messages did not get across when they interposed a strip of cellophane between two prospectively reactant masses of cells. Cellophane allows the passage of only very small molecules. On the other hand, L. W. McKeehan of the University of Chicago used thin strips of agar, through which larger molecules can diffuse, and observed interaction between two tissues. Clifford Grobstein of Stanford University has performed similar experiments with the two components of mouse kidney isolated in tissue culture; he has found that cellophane blocks their interaction, whereas a filter that passes larger molecules permits the interaction to proceed.

The simplest and perhaps likeliest deduction from these experiments is that the tissues, as they associate, react toward one another through the medium of certain metabolic products. These products may provide both the signals and the means of linking the cells in a specific manner. It must be emphasized, however, that at present, with one possible exception, no such products have been isolated from the cells of any higher organism; moreover, there are acceptable alternative explanations for the experimental results.

But it would seem that some means of intercommunication between cells in a developing system must exist. The cells act as if they were capable of mutual recognition and of specific responses to messages conveyed by their neighbors. There is support, on general biological grounds, for the idea that the messenger is chemical in work on slime molds initiated by Kenneth B. Raper of the University of Wisconsin and continued by John Tyler Bonner of Princeton University, by Maurice and Raquel Sussman at Brandeis University and others. The slime molds live part of their life cycle as free amoebae; under certain conditions they come together and form aggregates that differentiate into "fruiting bodies." Their aggregation is directed by a substance (named acrasin) that has been isolated by Brian Shaffer of the University of Cambridge and that is being investigated in a number of laboratories. It emanates from the initial cluster of amoebae and attracts other cells to them. Here is an established case of chemical communication and guidance in the interaction of cells.

It is not too farfetched to assume that all cell contact implies interaction through the production of specific reaction products. The Australian biologist Sir Macfarlane Burnet suggested recently that production of antibodies by cells in adult organisms might present a



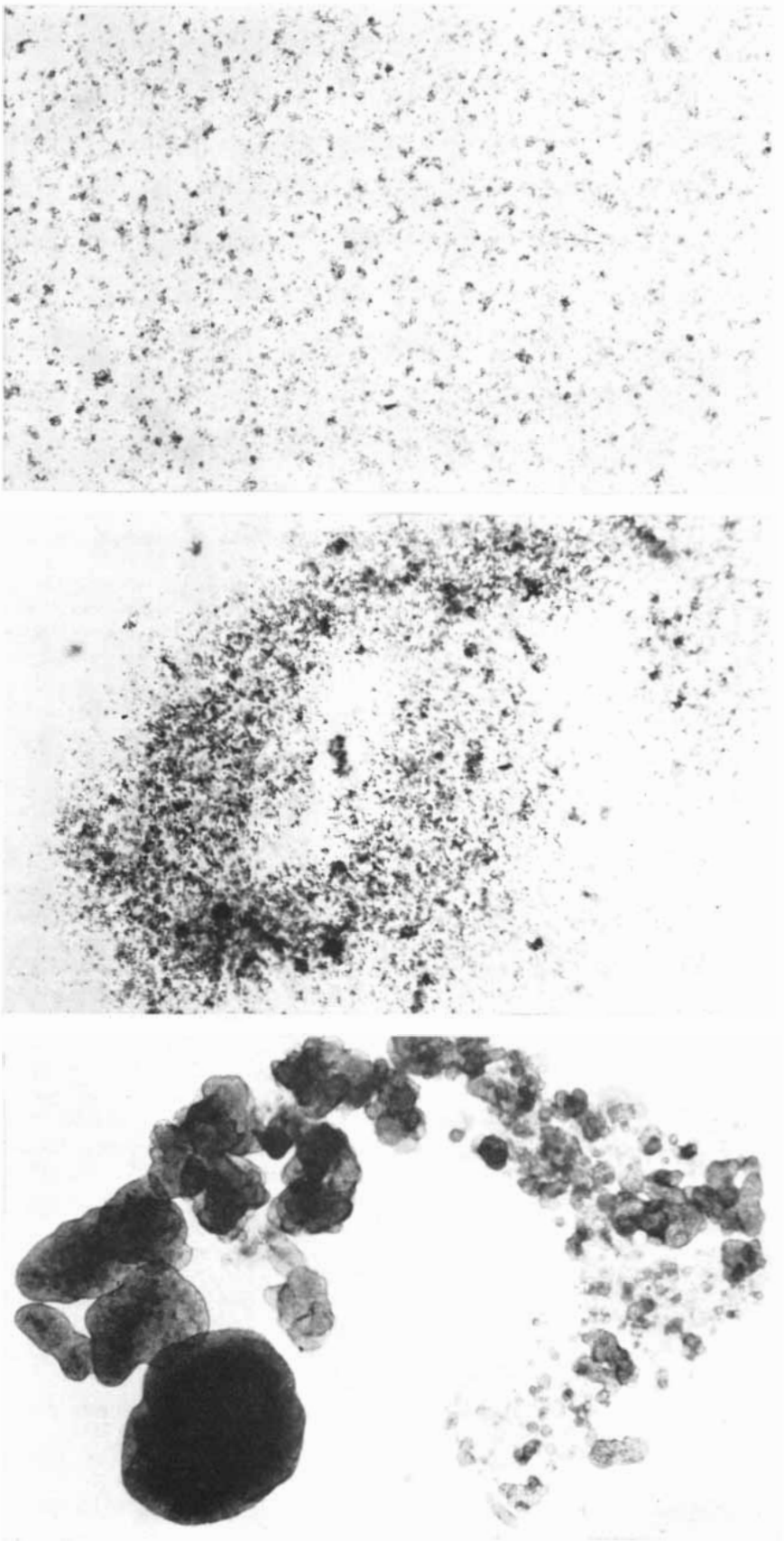
BRIDGES BETWEEN CELLS (desmosomes) are apparently special devices for mutual attachment of cells across their membranes. In this electron micrograph by K. R. Porter of the Rockefeller Institute more than a dozen such bridges (*dark, squarish areas*) connect two skin cells from a salamander larva. The cell membranes run horizontally across picture. Magnification is 35,000 diameters.

model, and perhaps an extreme case, of specific cellular response to chemical signals. The interactions among embryonic cells are, of course, different in detail from the true antibody reaction, and the subtlety and intricacy of these processes are probably of a different order. But it is precisely such subtle chemistry that could provide embryonic cells with the means of mutual communication and integration.

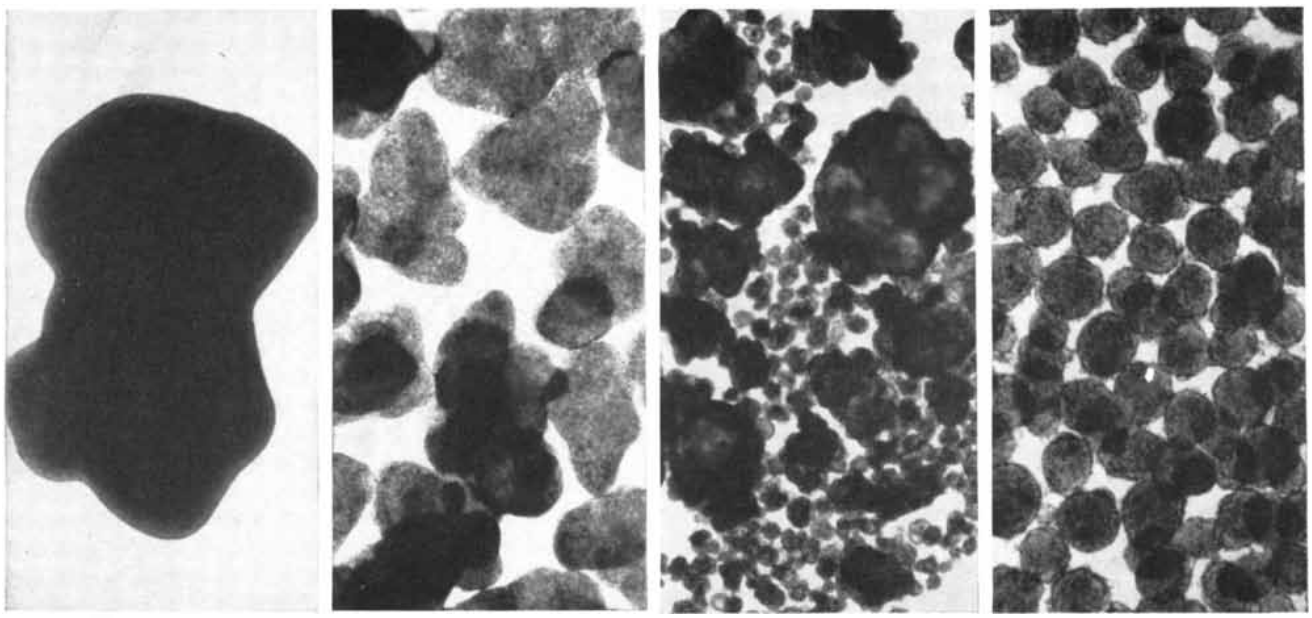
As for the intercellular bond, the term must not be taken as implying that the cells are firmly stuck together or even in direct contact with one another. Electron micrographs made by K. R. Porter of the Rockefeller Institute, by Don W. Fawcett of the Harvard Medical School and by others have suggested that cells may have special devices for mutual attachment on the outer surface of their membranes [*see illustration on opposite page*]. Furthermore, there is always some distance between cells in contact; this space may be extremely narrow or quite wide, and it seems to be filled with a cementing substance. Unlike brick-binding mortars, these intercellular cements have remarkably flexible and dynamic properties. Although they bind the cells, they permit them to move about and regroup without actual dissociation or loss of contiguity.

This dynamic linking is a cardinal feature of cell contact at all levels of multicellular organization. Consider the case of the everted hydra, described by R. L. Roudabush of Iowa State College in 1933. This tiny, vase-shaped animal can be made to turn itself inside out like the finger of a glove. Its internal digestive cells are then on the outside and the skin cells inside. The cells sense this change, and the hydra promptly proceeds to revert to normal. With the intercellular bonds destabilized, the cells migrate, gliding past each other from wrong side to right side. Throughout the process the hydra retains its over-all configuration, keeping its identity as an organization despite the flux of its constituent parts.

It is in terms of such flexibility of contact and such perception of position by the cells that one must visualize the nature of the intercellular bonds. Variations and changes in the stability of cell contacts are part and parcel of any organism—embryonic or adult. Pigment cells begin their embryonic development in the so-called neural crest; they soon lose their contact with this tissue and move out, singly and in groups, to find positions throughout the integument. Their migrations are clearly not random: they reach specific destinations and form



AGGREGATION IN ROTATING FLASK is illustrated in this series of photographs by the author. At top is a suspension of cells from the retina of a seven-day-old chick embryo. In middle is the initial stage of aggregation in a gyrating flask with cells and intercellular material accumulating in the vortex of the liquid culture medium. At bottom a later stage shows compact aggregations at the "head" of the spiral, with continuing aggregation toward the "tail." Magnification in these photographs is approximately 30 diameters.



SPECIFIC AGGREGATION PATTERNS characterize each type of cell population. These aggregations were made by (*left to right*) liver cells, retina cells, kidney cells and limb-bud cells, all rotated for 24 hours at 70 revolutions per minute. The first three types came from seven-day-old chick embryos, the last from a four-day chick embryo. Enlargement is approximately 30 diameters.

typical pigmentation patterns. Other cells leave the neural crest in loose swarms, "homing" toward certain sites in the head of the embryo, where, in conjunction with the cells of that region, they form the lower jaw.

Changes in cell-contact stability continue to play an important part in the life of the organism past the embryonic stage. The steady supply of blood cells involves the continuous disconnection of precursor cells from the bone marrow and their entry as free cells into the circulatory system. Similarly, sperm and egg cells free themselves, as they mature, from their tissues of origin. Elsewhere stability is greater, but definitely relative. Living cells cannot be disengaged from their places in the skin by mere pinching. But when the skin is cut, cells rapidly dissociate from the periphery of the wound, move into the gap, fill it and reestablish stable contacts.

Few questions about cell association yield to fruitful study in the intact organism. It is necessary to separate the cells and tissues from the complexity of the organism in order to control the conditions of observation and experiment. The first steps in this direction necessarily involved the tissues of lower organisms. At the turn of the century Curt Herbst, working at the Zoological Station in Naples, found that young sea-urchin embryos would fall apart and dissociate into single cells when placed in sea water from which he had removed the calcium. He then made the even more interesting discovery that the cells would coalesce and re-form into an embryo when calcium was restored to the water. Calcium has since proved to be an important element in the binding of cells, but not always so dramatically as in the sea-urchin embryo. In general calcium acts more directly as a cell binder in early embryos; later on it seems to operate in conjunction with organic materials to which the primary role seems to shift. There are, however, many invertebrates whose tissues fall apart in the adult state when deprived of calcium. In 1927 James Gray of the University of Cambridge isolated living ciliated cells from the mantle tissue of mussels by placing fragments of the mantle in calcium- and magnesium-free sea water.

An experiment by H. V. Wilson of the University of North Carolina in 1907 pointed to even deeper questions. By gently pressing a marine sponge through a fine sieve he found that he could dissociate it into free cells. He then noticed that as soon as the dispersed cells settled through the sea water onto the dish they started to coalesce. The resulting clumps, when suitably cultured, grew into small but complete sponges. At first it was thought that the sponges regenerated from cells called archeocytes, which, along with skin and digestive cells, make up the loosely associated tissues of the sponge. But further observation showed that all three types of cell persisted following dissociation and that they reassociated in the new aggregations.

Work by later investigators, particularly by Paul S. Galtsoff at the Marine Biological Laboratory in Woods Hole, Mass., and by Tom Humphreys of our laboratory at the University of Chicago, has added new dimensions to these early findings. When cells of different sponge species, preferably of different color for easy recognition, are dispersed and then mixed together, they separate and reaggregate by species, forming separate clusters [*see illustration on page 142*]. The cells, in other words, are able to identify one another, to give out and register some kind of signal and so associate preferentially with their kin.

A sponge is in some respects a differentiated colony of cells rather than a true multicellular organism. One might question whether the capacity of sponge cells for mutual recognition and sorting out represents a phenomenon of general significance, found in other cellular systems and particularly in higher organisms. Certainly in the case of mammalian tissues it would be difficult to answer the question one way or another in the absence of techniques for dissociating them into individual cells. Some years ago, however, I found that the cementing substances in these tissues will yield to digestion by trypsin and certain other enzymes that break down proteins without serious injury to the cells. Practically any tissue of embryonic origin can now

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be dissociated and reduced to a suspension of its constituent cellular units. The cells may then be maintained in suitable nutrient media in a germ-free, temperature-controlled environment. It was now possible to conduct studies of the bonding and interaction of the tissue cells of mammals, birds and other higher organisms.

The next step—the resynthesis of complete systems from individual cells—also proved to be feasible. We found that, like sponge cells, the dispersed cells of mammalian or bird embryos will readily aggregate into clusters, migrating over the surface of the culture dish and forming stable connections. Cells from different kinds of tissue were even observed to sort themselves out by cell type in forming these clusters.

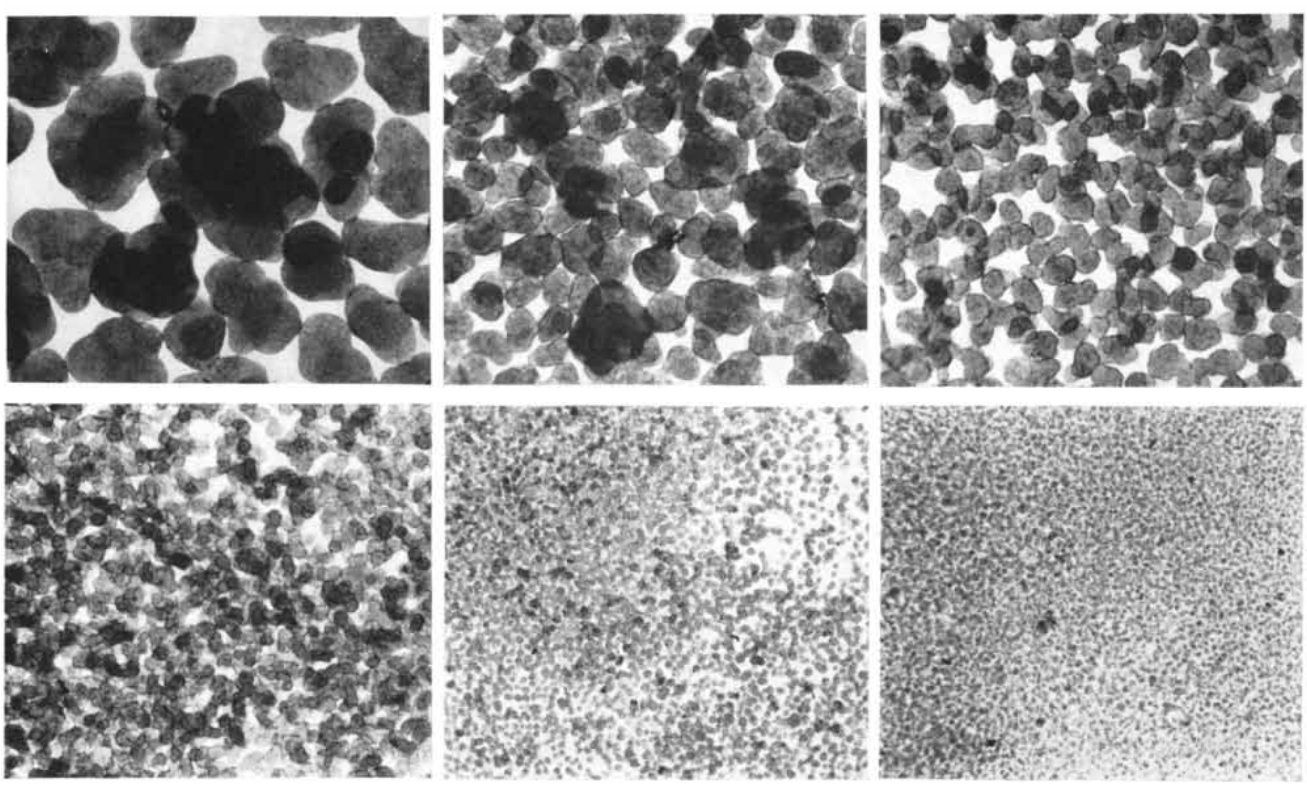
The technique lent itself to the study of many previously unanswerable questions, but it fell short of being an exact and adequately controlled procedure. For one thing, it depended primarily on active movement by the cells, a highly variable capacity susceptible to a host of poorly understood conditions. The results in consequence varied unpredictably from one experiment to another.

How could one harness cell aggregation and make it into a critical tool for the study of interactions among cells? The solution turned out to be extremely simple. Most of the irrelevant chance factors that dominate the situation in a stationary cell culture can be neutralized by setting the culture in motion and thereby suspending the cells in a controlled field of force. To do so we place the culture flasks on a horizontally gyrating platform that rotates the flasks 70 times a minute. In each flask the spinning liquid forms a vortex in which the cells concentrate rapidly. They soon link into clusters, within which they construct tissues.

The formation of these clusters depends on and reflects a dynamic equilibrium among the major factors in the system: a balance between the concentrating and shearing-flow forces in the liquid; the differential capacities of the cells to cohere; and the effects of the suspension medium on the cohesiveness of the cells. In this relatively simple system all the pertinent factors—the speed of rotation, the size of the flasks, the character and volume of the medium, the kind and concentration of cells and so on—can be effectively controlled. Thus if the rotation speed and the medium are made the constants of the experiment, the results will reflect the native cohesiveness of the cells in the population tested. The more cohesive they are, the larger and fewer will be their aggregates; the less their cohesiveness, the smaller and more numerous their aggregates. In experiments employing this system we have obtained strikingly consistent results. The rate of aggregation, the number, size distribution, shape and internal structure of the aggregates are always the same when cells of a given kind are aggregated under the same set of conditions.

Such experiments yield an aggregation pattern that is characteristic of the cells in question and of the particular set of conditions under which they are tested. These patterns can be readily described in terms of numbers, ratios and rates. The traditionally elusive subject of cell-bonding can now be reduced to laboratory prose. Moreover, since the patterns are reliably repeatable and sensitive to changes in conditions, they serve as useful base lines for the bioassay of the effects under study in a given experiment.

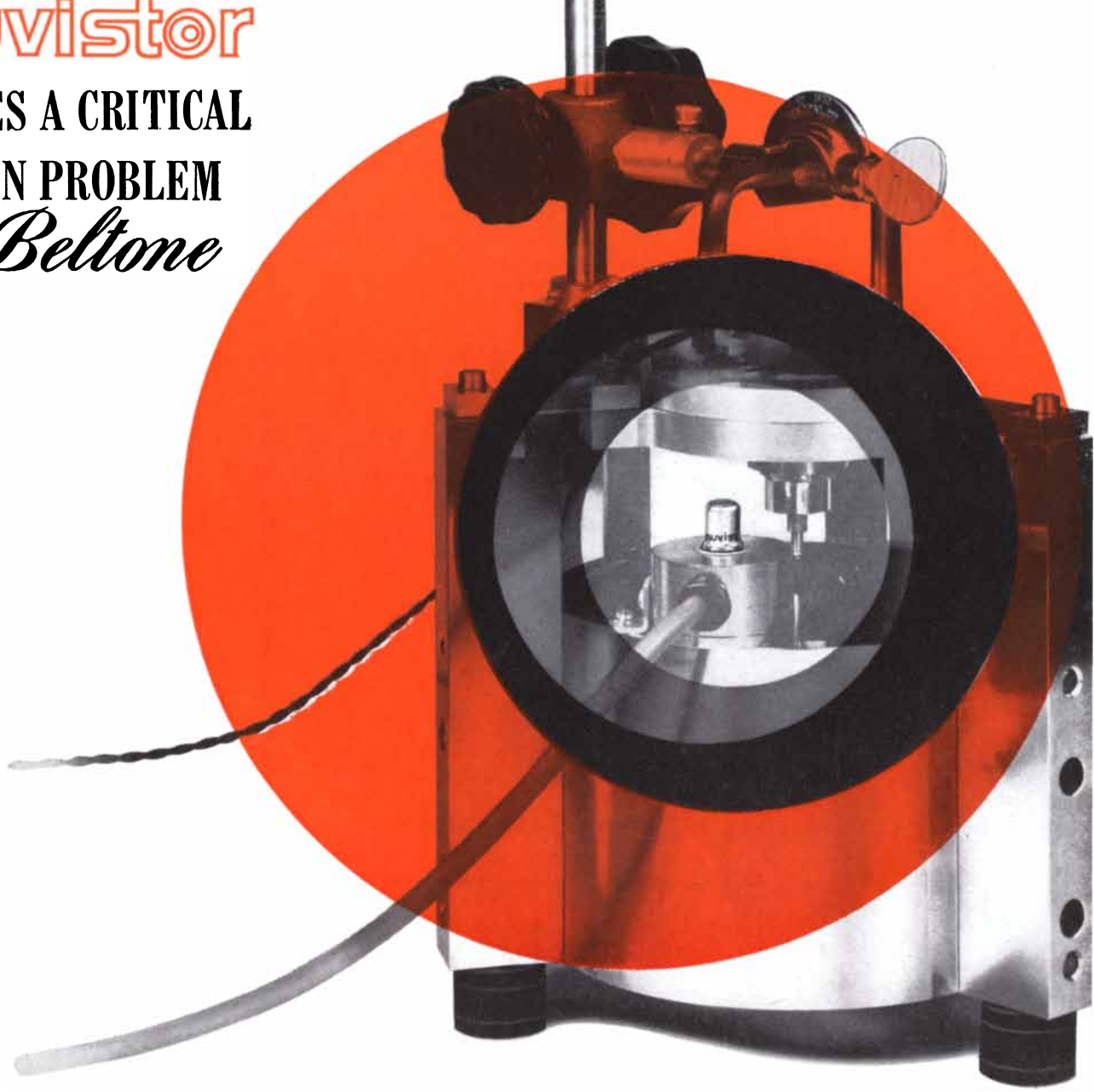
We soon found that aggregation patterns vary with different types and mixtures of cell. Under otherwise identical conditions, different kinds of cell "crys-



AGGREGATIONS ARE SMALLER when older cells are used. In these photomicrographs the concentration of dissociated retina cells was the same in every case; all were rotated for 24 hours at 70 r.p.m. The cells, however, were taken from chick embryos aged 7, 9, 11, 14, 17 and 19 days respectively. At 19 days the cells simply do not form aggregations. Lowering the temperature or increasing the rotation rate, while all other experimental conditions remain the same, has a similar effect on the size of the aggregations.

nuvistor

SOLVES A CRITICAL DESIGN PROBLEM FOR *Beltone*



The Instrument That Simulates The Human Mastoid . . .

This remarkable new instrument, an "Artificial Mastoid" developed by BELTONE Hearing Aid Company of Chicago, is the first readily reproducible laboratory device that accurately simulates the mechanical impedance of the human head, as determined by the National Bureau of Standards.

Contributing to the instrument's high accuracy is the RCA nuvistor tube used as a cathode-follower type amplifier. After trying several other devices BELTONE selected the RCA nuvistor tube for this critical application because the nuvistor tube offered high input impedance, small size, low noise, low dissipation, and most important—absence of mechanical resonance in the range of 125 to 8000 cycles per second.

The BELTONE "Artificial Mastoid" is used to calibrate the output of bone conduction vibrators and audiometers that test hearing loss. According to BELTONE the unique advantages of nuvistor design helped them produce the most accurate calibrating device yet achieved for audiometers used in clinical diagnosis of hearing difficulties. The nuvistorized BELTONE "Artificial Mastoid" is a truly significant contribution to medical science.

Nuvistor was the answer to BELTONE's design problem; it may well be the answer to yours. For the complete nuvistor story, see your RCA Field Representative. For technical information write to Commercial Engineering, RCA Electron Tube Division, Harrison, N.J.

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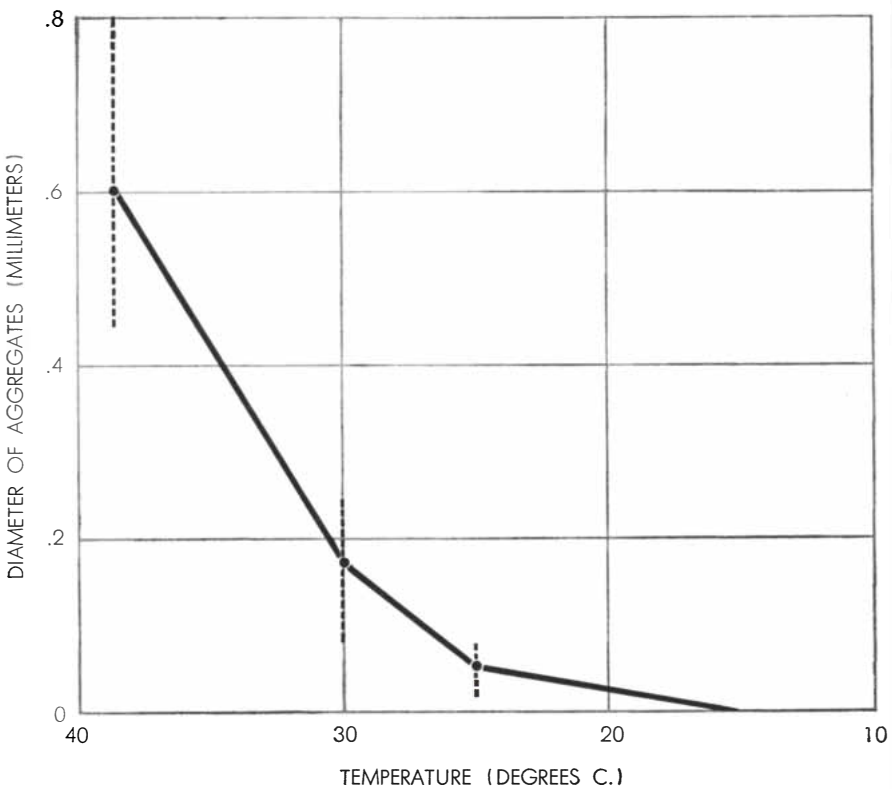
tallize" into distinct and characteristic aggregates. Some kinds of cell consistently form a single mass; others produce numerous clusters of predictable shapes and sizes. Remarkably, those patterns that showed themselves to be characteristic of particular kinds of tissue proved to be similar for cells from different species. Whether from mouse or chick embryo, cells of the same tissue aggregate into very similar patterns. Their collective reactions seem to be guided by signals legible to both species.

For cells in general we also soon found that certain factors operate with uniform effect. The relationship of the embryonic age of the cells to their capacity for aggregation proved to be particularly striking. Under otherwise equivalent conditions, cells dissociated from tissues of older embryos are less cohesive than their counterparts from younger embryos. For each kind of cell, aggregation patterns provide a characteristic age profile. With increasing age in the donor embryo, the dissociated cells produce smaller and more numerous aggregates and eventually fail to aggregate. Cells dissociated from adult animals usually do not recohere at all.

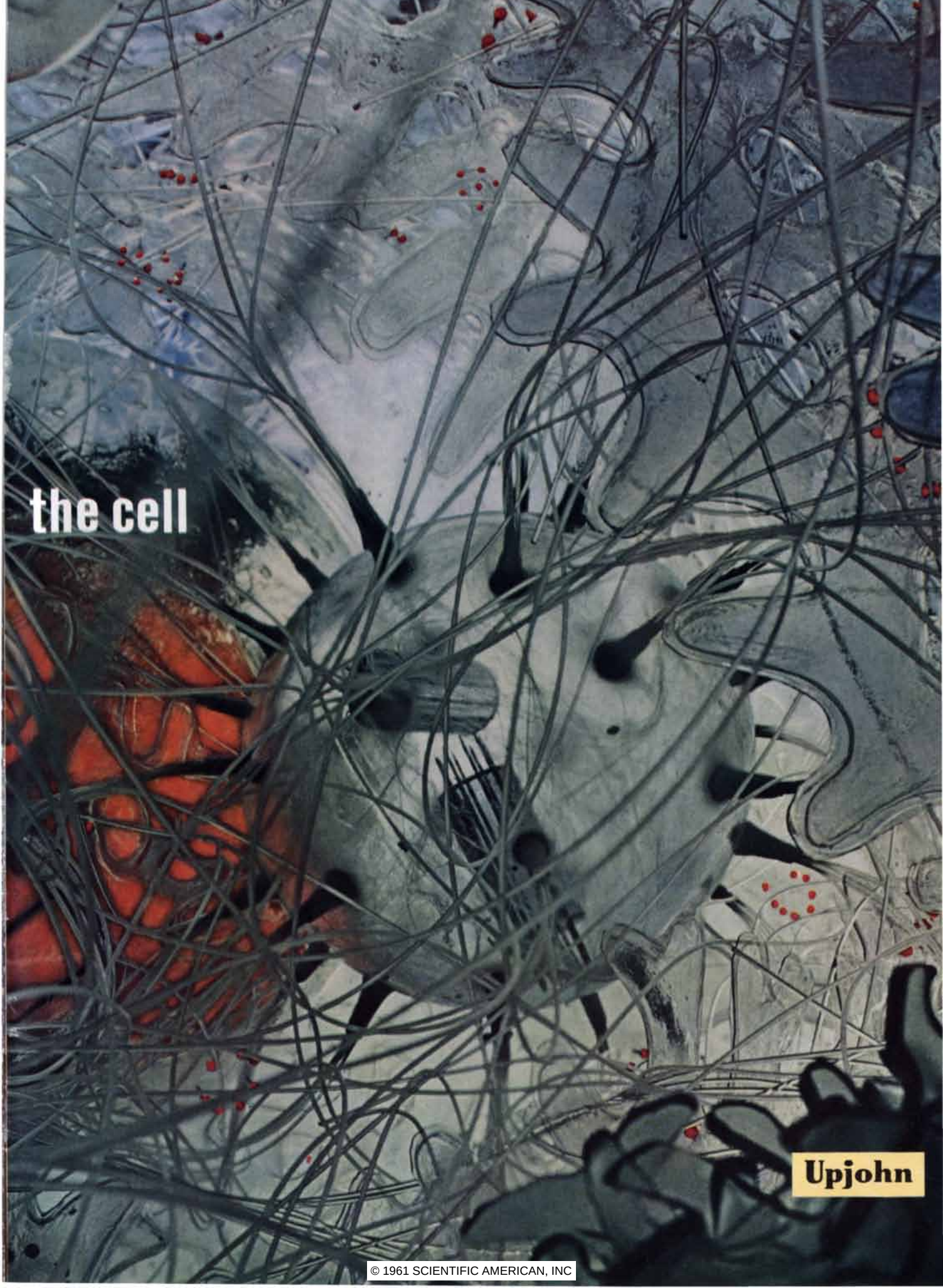
The precise meaning of this effect of aging is not clear. There are grounds for believing that it reflects the loss by the cells of their ability to produce either the right kind or the right quantity of cell-linking substances. It may be that, as cells mature and acquire specialized functions within their stabilized associations, their metabolic machinery is gradually switched over from those processes that manufacture cell-linking materials to more pressing activities. As a result, when they have been isolated and denuded of their coatings, such cells can no longer recohere effectively. In contrast, embryonically young cells exhibit the capacity to manufacture those materials and to recohere.

If the recohesion of cells does depend on metabolic processes, then it should be possible to inhibit it simply by lowering the temperature at which the experiment is performed, because metabolic processes are known to be dependent on temperature. This has proved to be the case. Cells that aggregate readily at the usual body temperature of 38 degrees centigrade cohere less effectively at lower temperatures; they remain separate indefinitely at 15 degrees C., even when brought together by rotation. Transferred back to 38 degrees C. after two or three days, such cooled cells aggregate well.

We do not know which of the many



EFFECT OF LOWER TEMPERATURES on the size of aggregations of seven-day chick-embryo retina cells is plotted on this graph. The largest aggregations appear at 38 degrees centigrade; no aggregation occurs after 24 hours of rotation at 15 degrees C. The vertical broken lines show the range of size of the aggregations that build up at each temperature.



The interplay of plastics and packaging

A complex of technology and art, packaging has gained from the versatility of plastics. The adaptation of Tenite plastics to packaging functions holds promise for improvements in other product fields.

The egg and the coconut, cited in offhand discussions as being ideally packaged for their environments, seem ill-fitted to the complicated methods of modern distribution. The eggshell, unfortunately, can do little more than hold the egg together in the nest. And the coconut, for all its ability to float across the sea to a friendly beach, might be improved by a tear-tape.

A package today must perform several functions beyond mere containment—one reason why plastics have become so popular with package designers. Man-made, plastics can also be man-tailored. For example, Eastman's laboratory has developed twenty-six formulations of Tenite Polyethylene for extrusion into packaging film alone, combining such variables as stiffness, gloss, transparency, and the ability to be heat-sealed on high-speed machines.

Protecting the packaged contents is an obvious essential, and plastics perform some remarkable protective functions. A hypodermic needle in a molded polyethylene container stays both sterile and sharp in its heat-sealed package, which also holds the needle firmly to protect against impact damage [1]. Since polyethylene is impervious to moisture vapor, a polyethylene coating on paper will protect frozen foods from "freezer burn" caused by loss of moisture. Some products even need protection from their packages. For example, the multi-wall paper bags Eastman uses for shipping polyethylene have an inner coating of Tenite Polyethylene to prevent contamination of the product by paper fibers [2].

Packaging for movement and storage is a step beyond protection, and here the light weight of plastics is important. Polyethylene, for years the lightest solid plastic (it floats on water), has yielded in this respect to polypropylene. Drums for chemicals are molded of Tenite Polyethylene not only because it is highly inert and withstands impact, but because the light weight

means shipping economy [3]. Special formulations of both Tenite Polyethylene and Tenite Polypropylene resist stress-cracking, a phenomenon occurring when a material is under stress in the presence of a chemical that normally does not affect it. Tenite Polypropylene shows remarkable resistance to repeated flexing. Because laboratory test bars have been flexed over a million times without cracking, it is said to have a "built-in hinge."

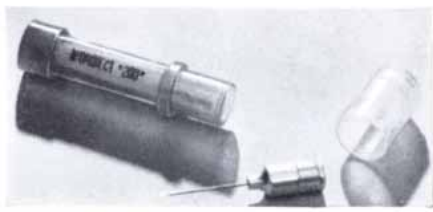
Even the preparation of food servings has come within the purview of plastic packaging. The heat resistance of Tenite Polypropylene suggests its use as film for the boilable cook-in pouch. Another Eastman plastic, Tenite Polyester, is made into a film bag in which corn, oil, and salt are sealed, to be popped later under three minutes of heat from infra-red lamps.

The mechanics of packaging challenge any material, and the adaptability of plastics is a special virtue. In fact, their capabilities have helped advance package design, as in the case of blister packaging—plastic sheet thermoformed to fit the contents and attached to a cardboard backing. With Tenite Acetate, Eastman helped to pioneer this packaging method, which also employs Tenite Butyrate and Tenite Propionate today.

All together, Tenite plastics include formulations to be molded, extruded, or applied as coatings to other packaging materials; to be printed, heat-sealed, or laminated. Where color is important, Eastman can supply over 42,000 colors and effects from its color laboratory [4]. And along with all their other advantages, these plastics have proved economical—a governing factor in the acceptance of a material in the packaging field.

Continuously adapting Tenite plastics to the shifting technology of packaging has given Eastman a fund of information and materials useful in the design of other products. Thus, the stress-cracking resistance of polyethylene makes it practical for pipe to convey chemicals; the moisture resistance of polyethylene led to its use in coating burlap for Army Ordnance huts to protect stored equipment; the easy formability of sheet of Butyrate makes it practical for a miniature planetarium [5].

We'll be glad to show you how the people at Eastman, with ingenuity and experience, can make plastics fit your ideas for product improvements or new developments. And for a comprehensive picture of Tenite plastics in packaging, get the 20-page booklet "TENITE PLASTICS VIEWS—PACKAGING" by writing to EASTMAN CHEMICAL PRODUCTS, INC., subsidiary of Eastman Kodak Company, KINGSPORT, TENNESSEE.



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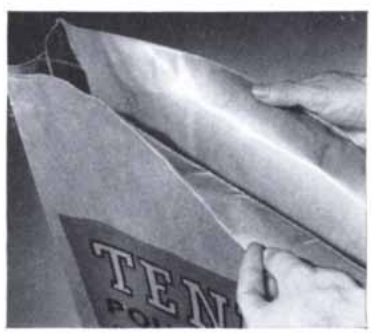

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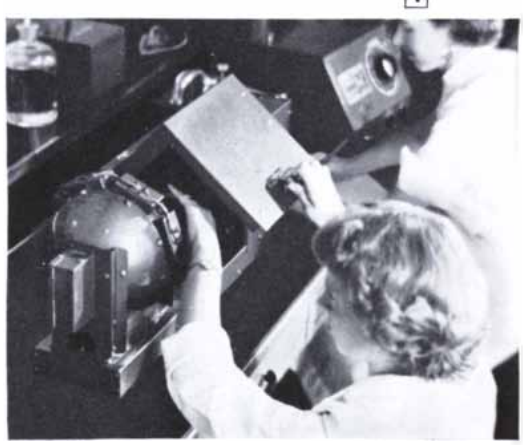

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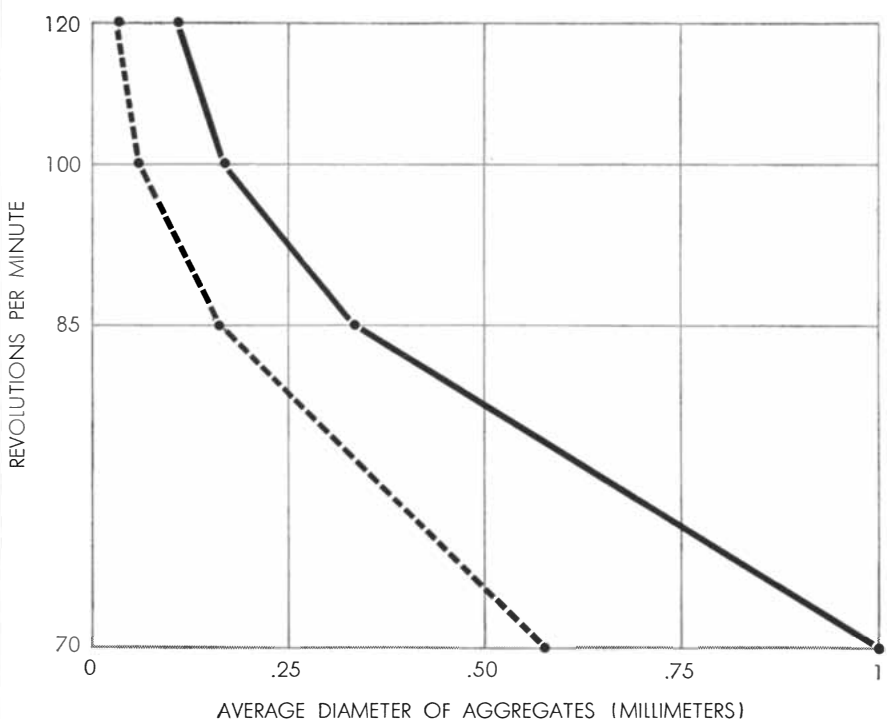
Adaptable plastics by Eastman

temperature-dependent metabolic activities that are depressed by cooling are involved in the production of cell-binding materials. But the answer, we are confident, is only a matter of time. The important point is that the problematical issue of cell-bonding can now be approached by means of concrete tests and experiments. Given the right temperature and otherwise favorable conditions, cells of suitable embryonic age construct tissues of the kind from which they have come. Aggregated liver cells make liver lobules; kidney cells reconstitute kidney tubules and corpuscles; intestinal cells produce digestive tissue; skeletal cells, cartilage and bone; retinal cells, sensory epithelium; heart cells, lumps of beating heart tissue; and so on. Although they are arbitrarily bunched by rotation, the cells rapidly organize orderly fabrics in the pattern of their original tissue. Like parts of an animated jigsaw puzzle, they re-establish a new whole in accordance with the original blueprint. At the Rockefeller Institute, Paul Weiss and Cecil A. Taylor recently grafted such aggregated cells back to embryos; the lumps became joined to the circulatory system of the embryo and developed into remarkable facsimiles of their original organs.

As in experiments with stationary cultures, mixtures of cells in rotating flasks sort themselves out by cell type. One can, for example, readily coaggregate intermingled skeletal and kidney cells. At first the cells are lumped by the spinning liquid into chaotic conglomerates, but soon they segregate by kind—skeletal cells congregating in the middle as nodules of cartilage, kidney cells lining up on the surface. Throughout these cellular maneuvers the aggregates maintain their over-all configuration. The situation obviously resembles the case of the everted hydra or of the embryo that retains its over-all configuration in spite of the extensive movement of its constituent cells.

As might be expected, the final patterning of such composite aggregates reflects their cellular composition. Depending on the nature of their partners in the common aggregate, cells of the same kind may settle inside or outside. By testing various combinations of cells one discovers a kind of hierarchical order—a "who goes where" in aggregations of various kinds. Preference as to site and competition for physiological need obviously play an important role in the patterning of aggregates. The differential diffusion and availability of various constituents of the medium, of oxygen and carbon dioxide, also contribute to the outcome. But the patterning of aggregates also reflects the ability of the cells to "recognize" each other, to dis-



FASTER ROTATION makes the aggregations smaller, as shown by these curves. The broken curve represents chick-embryo retina cells; the solid curve, chick-embryo liver cells. The optimal aggregation size is achieved at 70 r.p.m. The vertical scale on this graph is logarithmic.

The stockholders of Chance Vought Corporation and Ling-Temco Electronics, Inc., on June 30, 1961, approved plans for combining these two companies into a vast new company — Ling-Temco-Vought, Inc., to be effective August 31, 1961.

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Robert McCulloch
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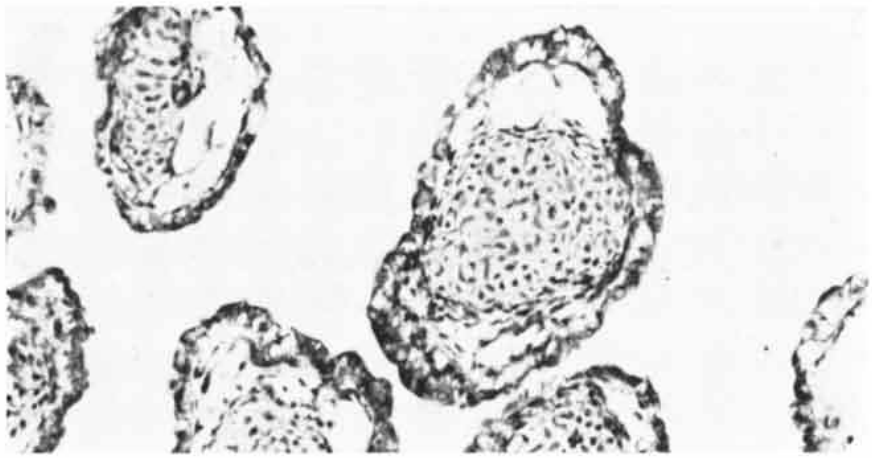
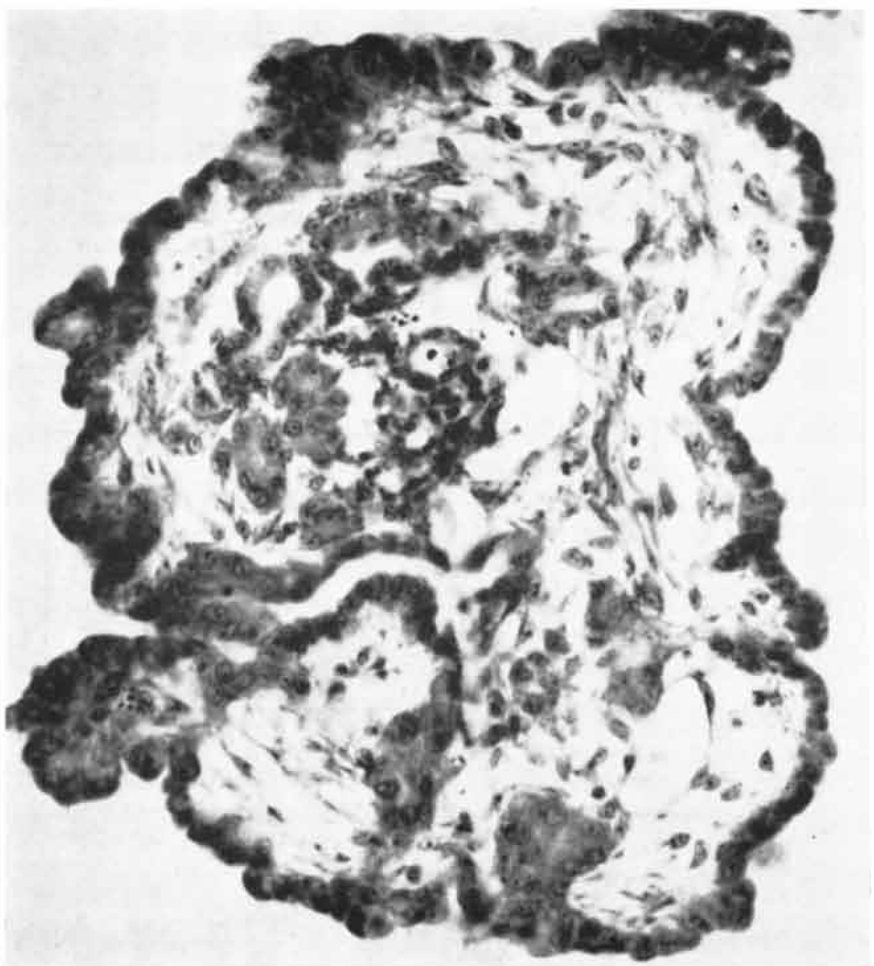
criminate between self and nonself, to sort out and to associate in accordance with functional kinships.

One of the more remarkable aspects of such communication-by-contact in embryonic cells is that the signals characteristic for cells of a given tissue are not unique to a given species. One can coaggregate cells from mouse and chick embryos, either from different or from similar tissues. The cells from the dissimilar tissues aggregate separately, as might be expected. But cells of similar kind co-operate in the construction of



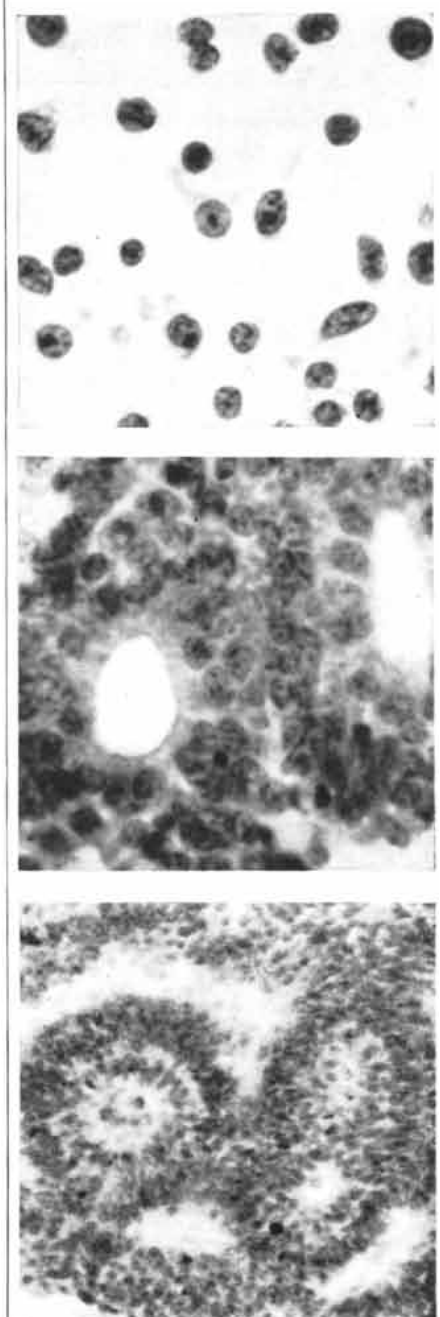
CHARACTERISTIC COMPOSITE AGGREGATIONS form when two different kinds of cell are mixed together in a rotating flask. In the resulting aggregations the cells sort out according to kind. Shown here are sections through such organized aggregations. They are composed of cartilage-forming cells surrounded by kidney cells taken from chick embryos.



KIDNEY CELLS from the chick embryo form a complex organ-like aggregation after 24 hours of rotation in a flask. This is a highly enlarged section of such a kidney-cell aggregation.

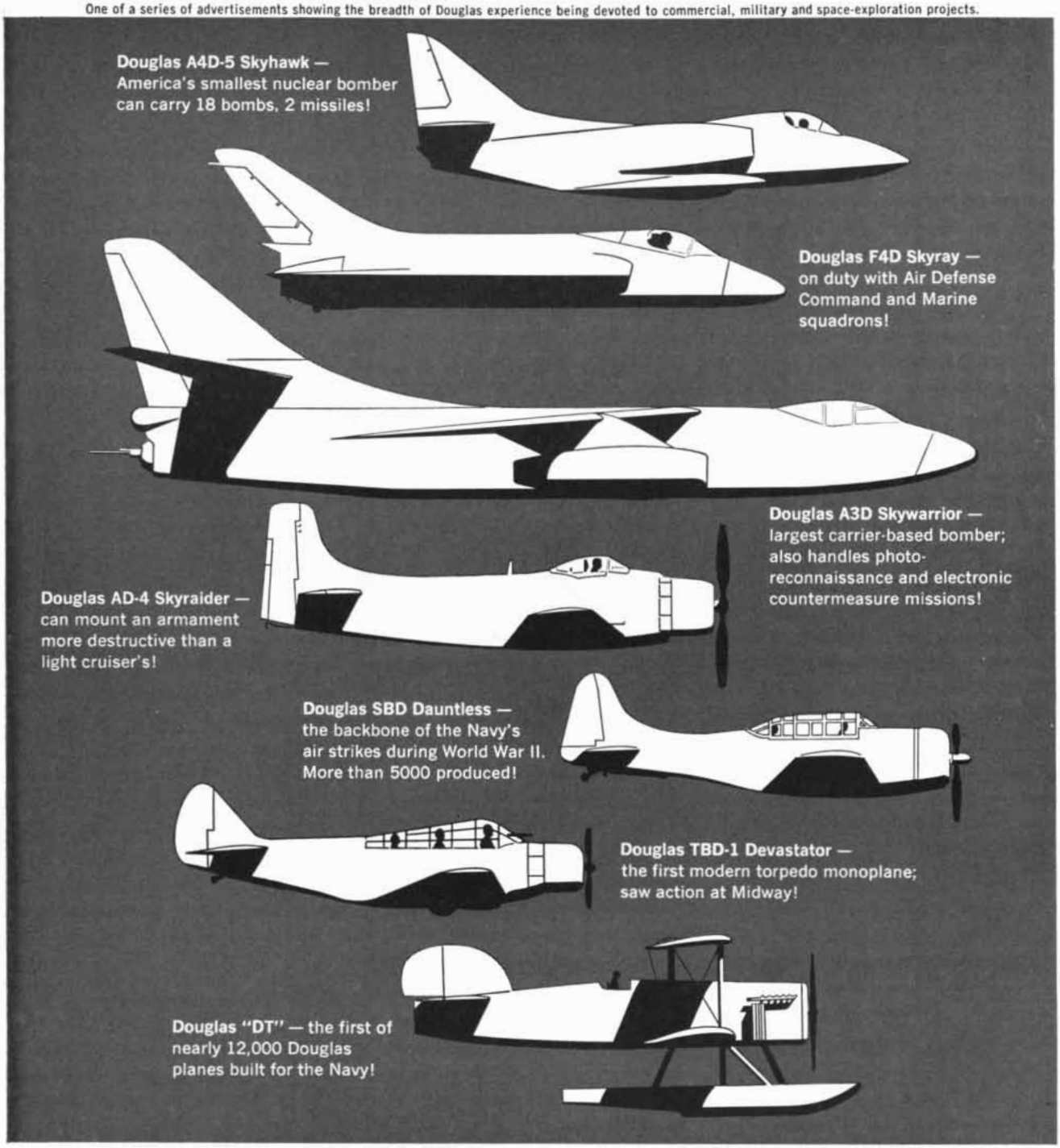
chimeric fabrics, incorporating the cells of both species. Coaggregated kidney cells from the two species produce tubules of mouse and chicken cells. Liver, cartilage, retina and other cells likewise join in the formation of bi-specific tissues. The means by which these cells recognize each other and become effectively linked into tissues evidently transcend differences between species.

It occurred to us that one might learn



RETINA CELLS from seven-day chick embryo are already differentiated into types that will make up retina and its nerves. At top are stained dissociated cells. In middle is section through aggregation formed in 24-hour rotation. At bottom 56-hour aggregation shows advanced reconstruction of the tissue.

One of a series of advertisements showing the breadth of Douglas experience being devoted to commercial, military and space-exploration projects.



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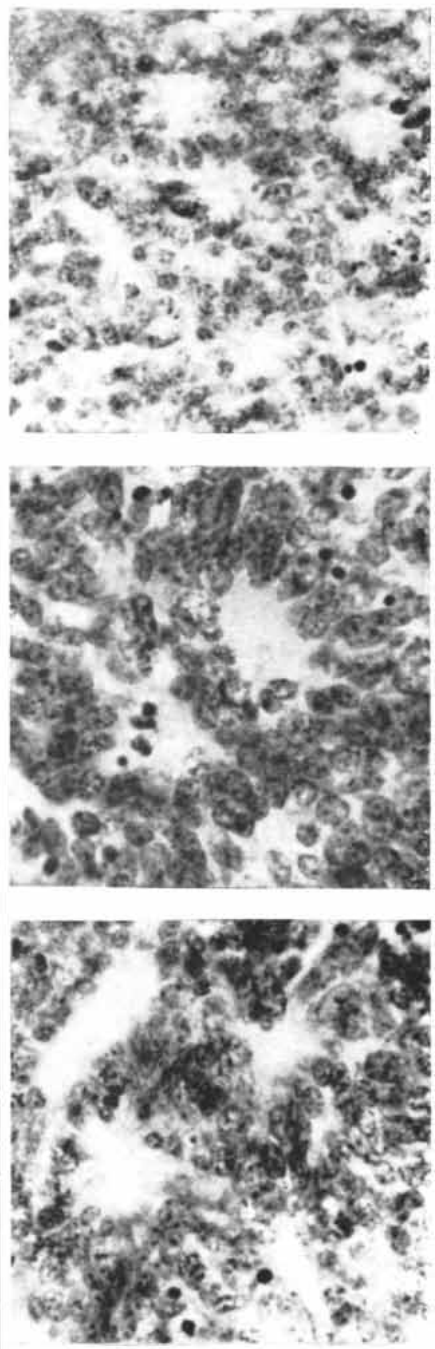
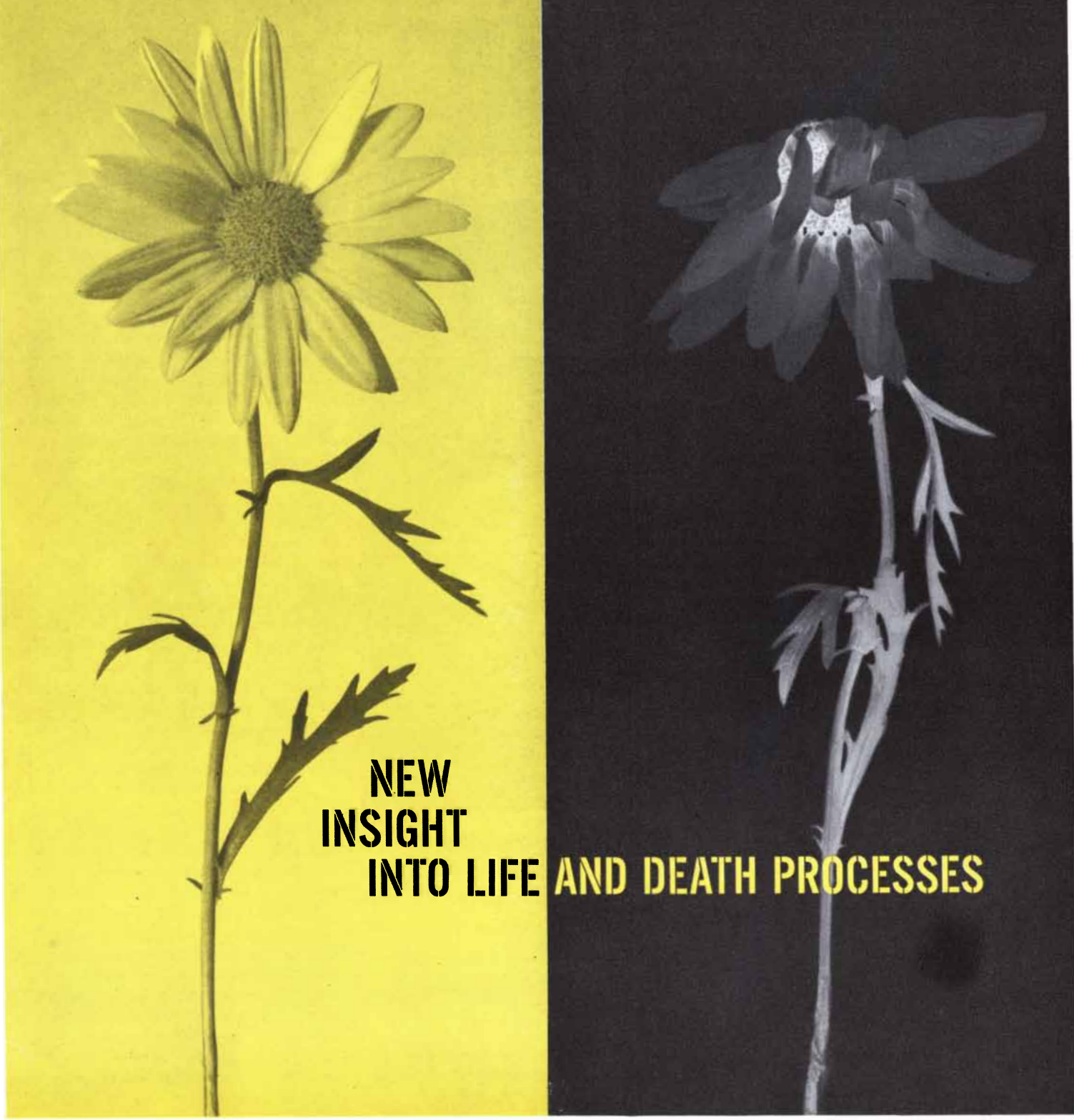
more about communication among cells by trying to interfere with its specificity and effectiveness. We found that when dissociated cells are maintained in the dispersed state for some time (the time required varies from days to weeks, depending on the kind of cell and the conditions in which they are kept), they lose two significant capacities progres-



CELLS OF TWO SPECIES will form aggregations. These are sections through aggregations of chick-embryo retina cells (*top*), mouse-embryo retina cells (*middle*), which have larger nuclei and stain darker, and mixed cells of both (*bottom*). Coming from the same kind of tissue, the mouse and chick cells interweave into a common fabric.



NEW INSIGHT INTO LIFE AND DEATH PROCESSES

Although the innermost secrets of life and death still remain a mystery, continuing investigations are helping us gain better insight into these fundamental processes. One of the newer techniques being used successfully to study these phenomena is EPR (Electron Paramagnetic Resonance) Spectroscopy.

Several recent experiments using EPR to detect the presence of free-radicals have helped confirm new theories concerning the nature of the life and death processes which previously had been based on rather inconclusive evidence.

For example: EPR has been used to study photosynthesis, an important life process in **Chlorella pyrenoidosa** (an algae). It was demonstrated that more than one pigment must be activated by light for efficent photosynthesis to occur. And in another experiment, the results of EPR analysis were used to show a strong correlation between the death process and free radical concentration in freeze-dried **Serratia marcescens** (a common bacteria).

Perhaps EPR analysis can be of value in your investigations. If you would care to discuss possible applications, please contact the INSTRUMENT DIVISION.

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sively and concurrently. Their cohesiveness decreases, and their precision in distinguishing between self and nonself in the organization of tissue drops markedly. These time-related changes raised the question of whether they are not also causally related; that is, whether the materials on the surfaces of cells and between them that link them together might not also play a key role in their interaction and communication.

It seemed not unlikely that these materials are bound to change in response to the novel conditions to which the cells are exposed when they are maintained in the dispersed state. The specificity of the materials could thereby become inactivated or blunted, and this would impair the ability of the cells to interact effectively. These were thin speculations, but we decided to test them by trying to reactivate modified cells by coaggregating them with freshly dissociated cells of their own kind. The fresh cells would presumably be effective producers of the cell-surface materials. When coaggregated by rotation with freshly obtained cells of the same kind, the modified cells did recover their ability to construct tissues. But when coaggregated with fresh cells of a different kind, the modified cells were largely left out of the aggregates. If they were included, they formed no clear structures.

Such findings lend themselves to different interpretations. Until we know more about the whole problem, they are at best suggestive. As such they focus attention on the possible role of cell-surface and intercellular materials in communication among cells and in their developmental association. Wherever such materials could be adequately examined they have been found to contain protein-bound carbohydrates. This fact is of considerable interest since it would seem to place them in the same chemical family with certain other cell products that have highly specific functions: the substances that determine blood groups, that compose antibodies, that are involved in the mating of microorganisms and that influence the selective susceptibility of tissue cells and bacteria to viruses. Could it be that the chemically similar materials that bind cells together also equip them with the means for mutual recognition and specific association? If so, then these cell-binding materials would be mortars of an extraordinary kind. Produced by the bricks themselves, they would serve also to co-ordinate the construction of the tissue, the organ and the organism.

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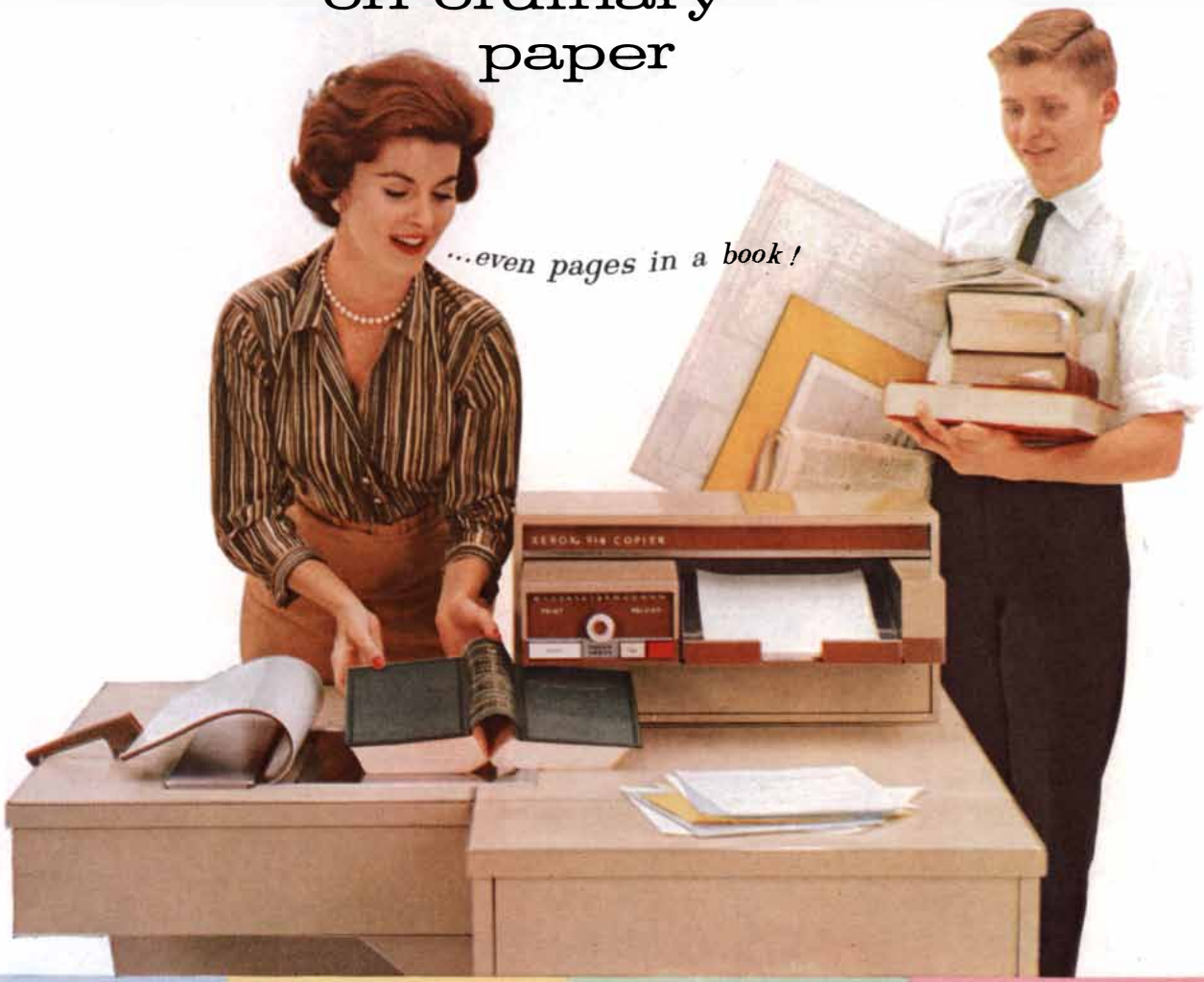

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PROGRESS

IN THE PHYSICAL SCIENCES

is dependent on precise measurement of infinitesimally small voltages and currents, electrical energy such as that involved in the measurement of ions in air.

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How Things Get into Cells

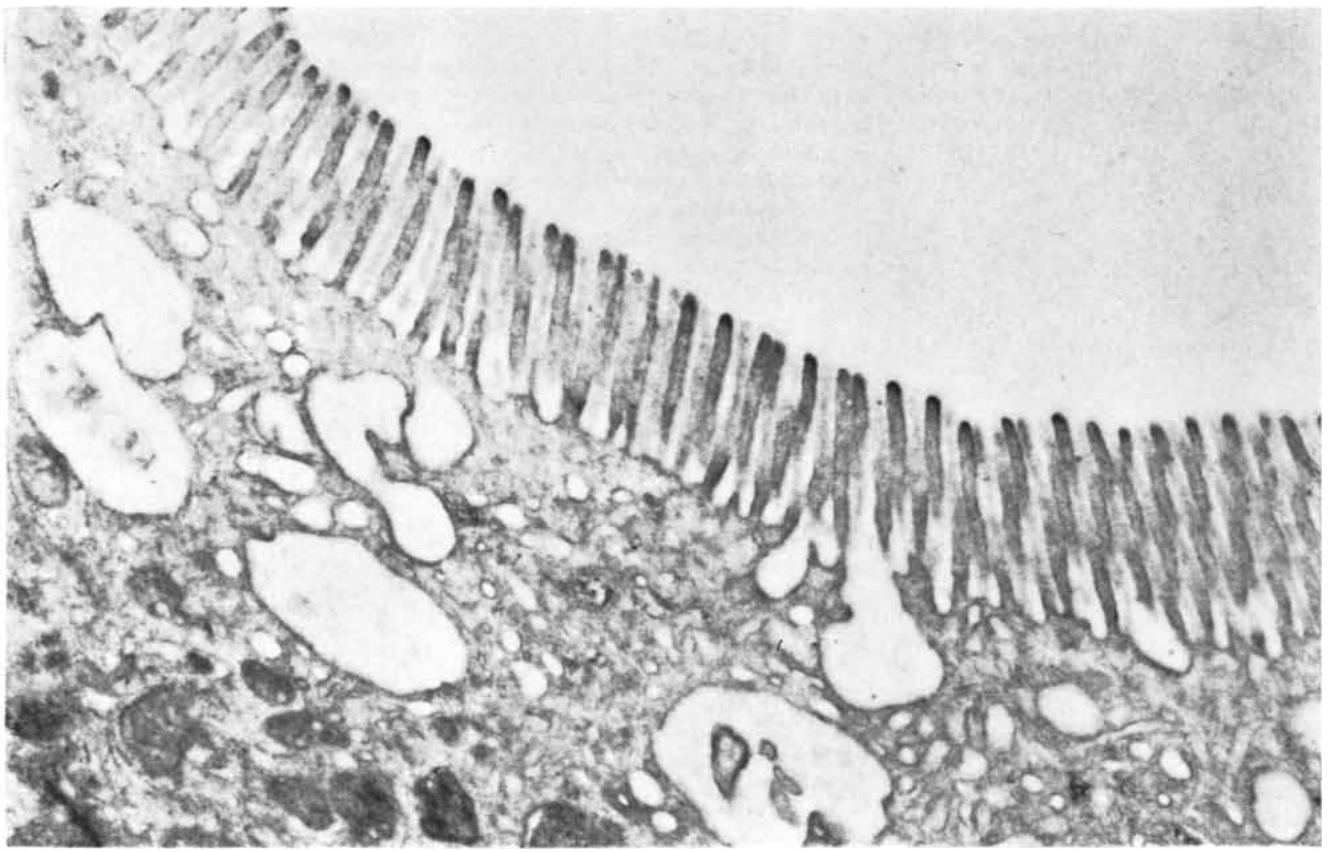
It seems that some things passively flow through the cell membrane under various pressures, others are somehow actively pumped across the membrane and others are engulfed when the membrane folds inward

by Heinz Holter

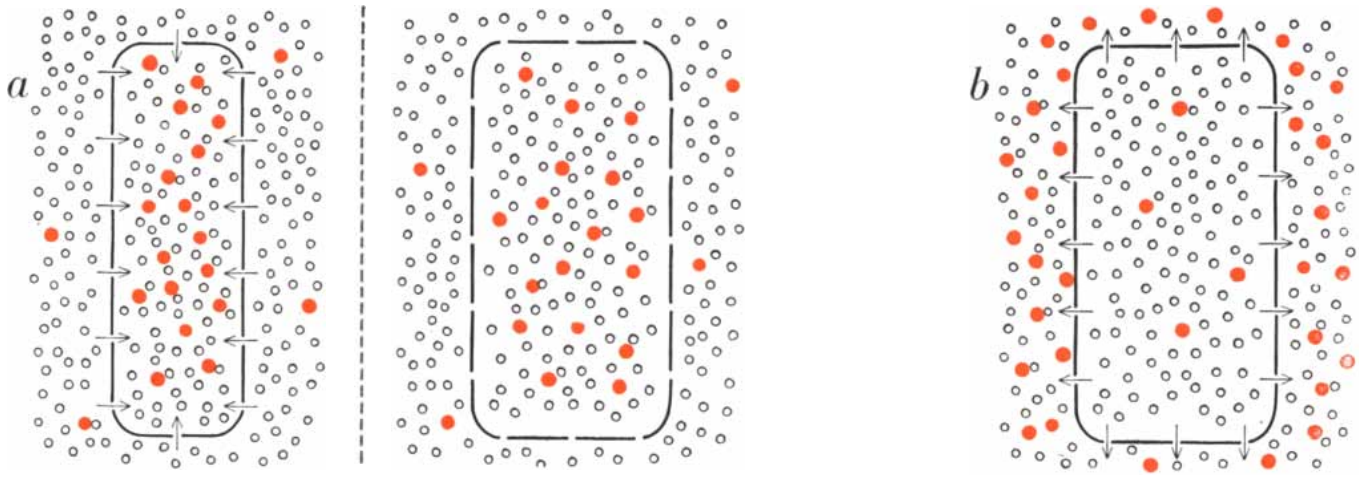
Most cells live in an environment unsuited to the maintenance of that fine interior balance of water, salts and organic matter on which life depends. The interchange of substances between the outside world and the cytoplasm must be at all times meticulously regulated. The barrier that thus isolates the interior of the cell is the cell membrane, a surprisingly flimsy structure only about ten millionths of a millimeter thick.

Many substances are able to permeate this barrier directly, and the traffic runs in both directions. Within its tiny dimensions the membrane itself possesses a structure and chemical composition, as yet only dimly understood, that make it selectively and variably permeable. If the forces that drive substances across the membrane are supplied by the environment of the cell, one speaks of "passive transport." If the energy originates in the cell's own metabolism, the movement is due to "active transport." This interaction between the cell and its environment not only serves to maintain all the substances inside the cell within the concentration range proper to life; in some cells, such as nerve cells, it is central to the function they serve in the body [see "How Cells Communicate," page 209].

Many cells also bring substances into their interior by the indirect process of ingestion. This process is known as



INGESTION BY CELLS transports substances across the cell membrane. This electron micrograph by Sam L. Clark, Jr., and D. Wochner of Washington University shows the process of pinocytosis ("drinking by cells"). Between the papillae of the "brush border" of mouse intestine cells, pinocytic microvesicles extend into the cells, where they are pinched off with their contents. The resulting vacuoles migrate into the cells and somehow release their contents. Magnification is approximately 6,500 diameters.



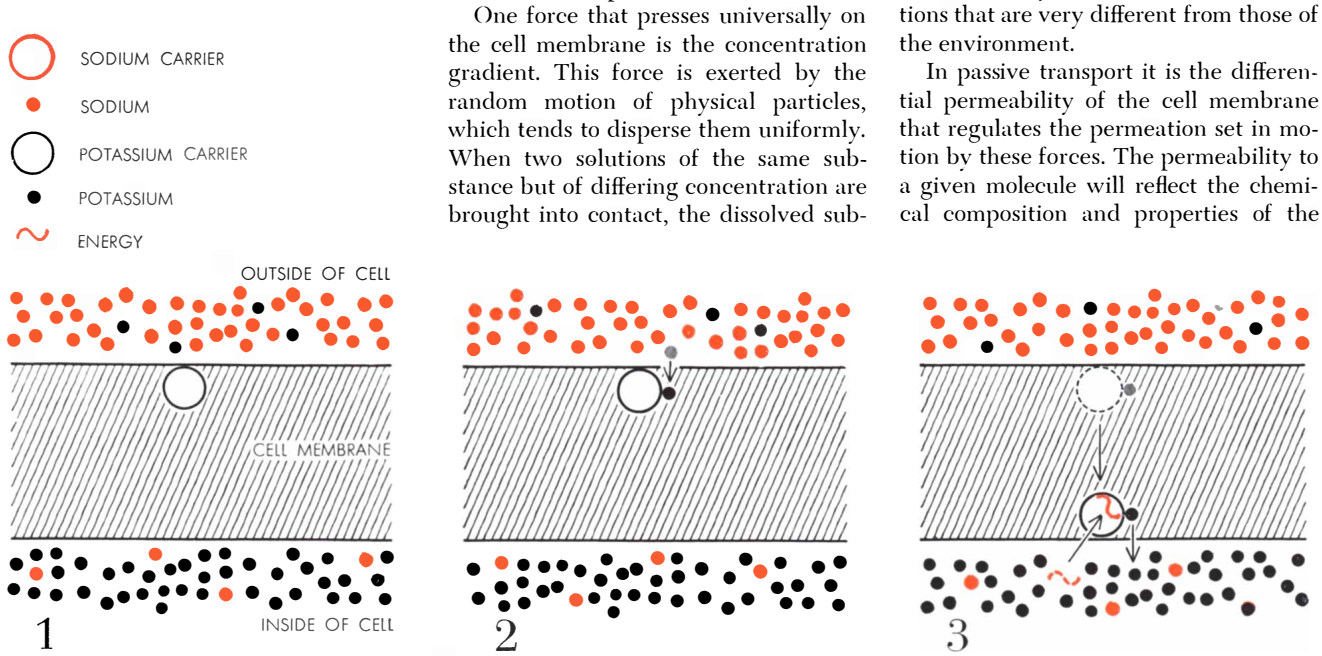
FORCES OF PASSIVE TRANSPORT across cell membrane are represented in these highly schematic diagrams. At far left the cell contains more of a dissolved substance (*colored dots*) than the culture medium, creating a concentration gradient. Because the cell membrane is permeable to water but not to the solute, water (*open circles*) flows in by osmosis, causing the cell to swell. When the culture medium contains more of the solute than the interior of the cell (*b*), water flows out, causing the cell

phagocytosis or pinocytosis, from the Greek roots for "eating" and "drinking" and for "cell." The membrane forms pockets, or invaginations, that draw material on the outside toward the cell interior; the membrane then envelops this sample of the external environment in a vacuole or vesicle that pinches off and floats free in the cytoplasm.

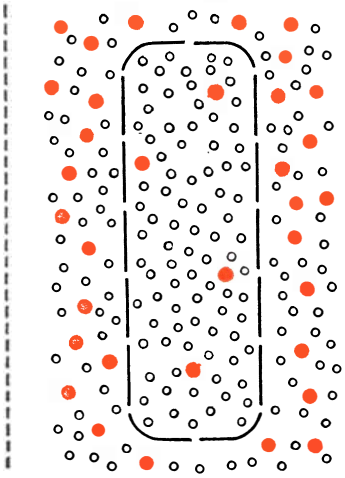
However much this process resembles the simple act of swallowing, it must be described as indirect because it raises the question: What does "inside" mean? From the macroorganismic view of the human being we are inclined to the superficial notion that as soon as we have swallowed a morsel it is inside us. But this is not quite true. The interior of the digestive tract is topologically speaking outside the body; the real uptake of food begins when it enters the cells of the intestinal wall. So a substance within the cell that has been ingested by pinocytosis or phagocytosis must be regarded as still "outside" because it remains enveloped in the membrane that engulfed it. In order to enter the cell proper and become a metabolically accessible component of the cytoplasm such materials must somehow permeate the membrane.

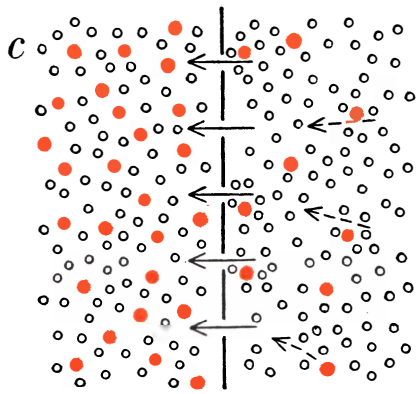
One force that presses universally on the cell membrane is the concentration gradient. This force is exerted by the random motion of physical particles, which tends to disperse them uniformly. When two solutions of the same substance but of differing concentration are brought into contact, the dissolved substance or solute will diffuse from the centers of higher concentration until its concentration is the same everywhere. This will happen even if the two solutions are separated by a membrane, provided that the membrane is permeable to the solute. When the membrane is permeable to the solvent but not to the solute, the concentration gradient appears as the familiar force of osmosis; the solvent now moves across the membrane from the lower to the higher concentration of solute. Across the membrane of the cell the concentration gradient and osmotic forces are considerable, because the cell contains many substances in concentrations that are very different from those of the environment.

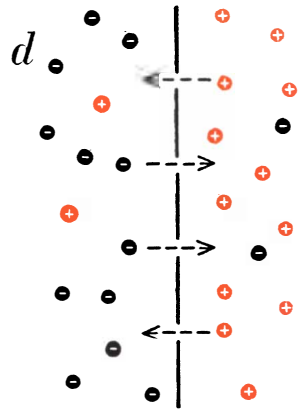
In passive transport it is the differential permeability of the cell membrane that regulates the permeation set in motion by these forces. The permeability to a given molecule will reflect the chemical composition and properties of the



MODEL OF ACTIVE TRANSPORT proposed by T. J. Shaw of the University of Cambridge employs hypothetical carriers for sodium and potassium. The free potassium carrier cannot move across the membrane (*1*) until it forms a compound with a potassium ion (*2*). Then the carrier migrates from the outside wall of the membrane to the inside wall (*3*), where it gives up the potassium ion to the interior of the cell and receives energy from the cell. The energy turns it into a sodium carrier (*4*), which cannot cross the







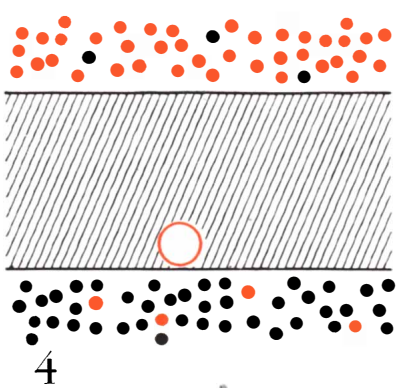
to shrink. Solvent drag occurs (*c*) when a flow of solvent (*open circles*) across the cell membrane pulls along a few molecules of the solute (*colored dots*) even against a concentration gradient. The force of an electrical potential across the cell membrane also causes passive transport (*d*). The solution on one side of the membrane contains a high concentration of negative ions, whereas that on the other side has more positive ions. This creates a potential gradient that causes ions to migrate across the membrane.

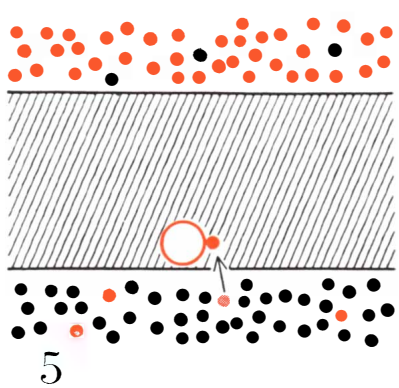
molecule as well as its size, and the membrane not only will exclude certain substances completely but also will allow others to cross it at different rates.

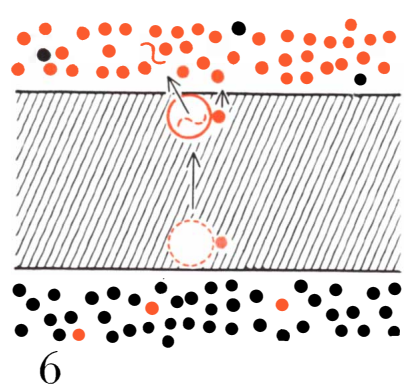
Depending on the environment to which they are adjusted, cells of various kinds will exhibit widely different permeabilities. The common amoeba and the human red blood cell, for example, show a more than 100-fold difference in permeability to water. On the scale of the permeability constant—expressed in terms of the number of cubic microns of water crossing one square micron of cell membrane in one minute driven by an osmotic pressure difference of one atmosphere—the amoeba stands at only .026, which is very tight indeed. The adaptive value is apparent: organisms living in fresh water encounter the greatest possible gradient between the outside and inside of the cell and must restrict the entry of water in order to save the energy necessary to pump it out again. The red blood cell has no need of such protection because it is normally surrounded by blood plasma, a medium in relative osmotic balance with the interior of the cell. Placed in water, the cell begins to swell immediately and, because its membrane is not elastic enough to stand the inrush of water, quickly bursts.

If, as is usually the case in nature, the molecules of the solute are dissociated into ions that carry an electric charge, a new force comes into play. It is well known that many—perhaps all—cell membranes have the ability to maintain differences of electric potential between inside and outside. Such differences set up a potential gradient that acts along with the concentration gradient as a driving force for passive transport across the cell membrane. A third force in passive transport is that of solvent drag. It comes into play only if a solution can flow in bulk across a membrane; in other words, if the membrane is porous. Solute particles diffusing in the direction of flow are then speeded up, whereas particles diffusing against the flow are slowed down. This drag effect is generally of little importance, but in special cases it may be considerable.

The three driving forces of passive transport may act singly or together. But whether a concentration gradient, an electric potential gradient or a solvent drag is the moving force, the movement always goes in a "downhill" direction, and the membrane acts as a passive barrier. Cell biology, however, knows of many important instances in which the transfer of substances across the membrane cannot be accounted for by any of these forces. The movement in these cases is "uphill," against the forces of passive transport, and so must involve expenditure of energy generated by the cell's metabolism. In this active mode of





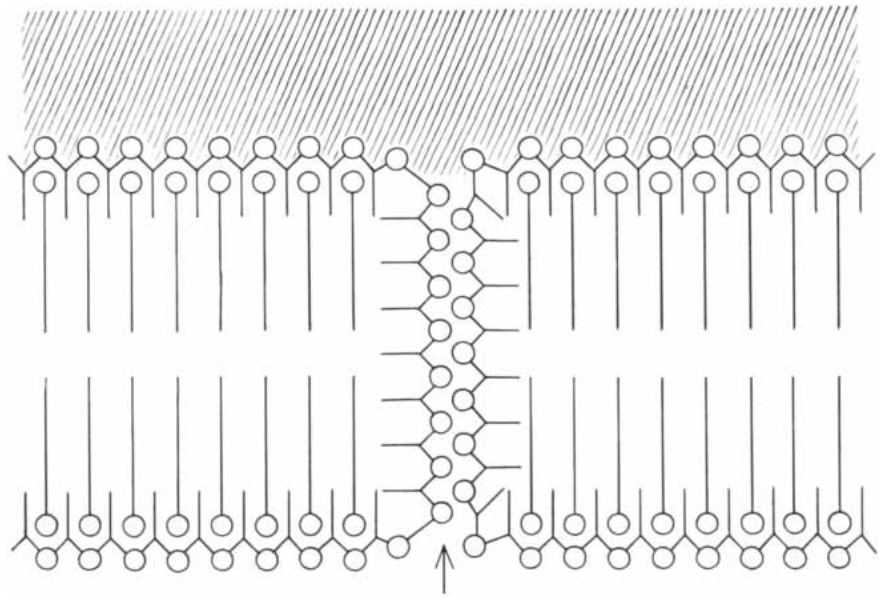


membrane until it in turn combines with a sodium ion (*5*). The carrier migrates to the outside wall of the membrane and releases the ion (*6*). It also gives up energy, probably through the mediation of an enzyme, to become once again a potassium carrier (*1*). This is called active transport because the cell supplies energy to operate the system against the large concentration gradients of sodium outside and potassium inside the cell. The gradients cause sodium to "leak" slowly into the cell and potassium to leak out.

transport the membrane is no mere passive barrier but functions as a dynamic organ.

Until recently all the information about the structure of the cell membrane came exclusively from permeability studies and was therefore of a quite indirect nature. It was observed, for example, that many substances that are soluble in lipid (fatty) solvents penetrate the membrane easily. This suggested the idea that the cell membrane must contain a layer of lipids; substances soluble in lipids could penetrate the membrane by being dissolved on one side and released on the other. But it was also observed that water-soluble molecules can pass the cell membrane. This made it necessary to assume some sort of sievelike structure, with pores or nonlipid patches or both, and patches with electrical charges to account for the peculiarities of the passage of ions. Finally, a protein component was added to the lipid layer in this hypothetical scheme in order to account for certain other observations, particularly the low surface tension, or "wettability," of the membrane, which excludes a purely fatty composition.

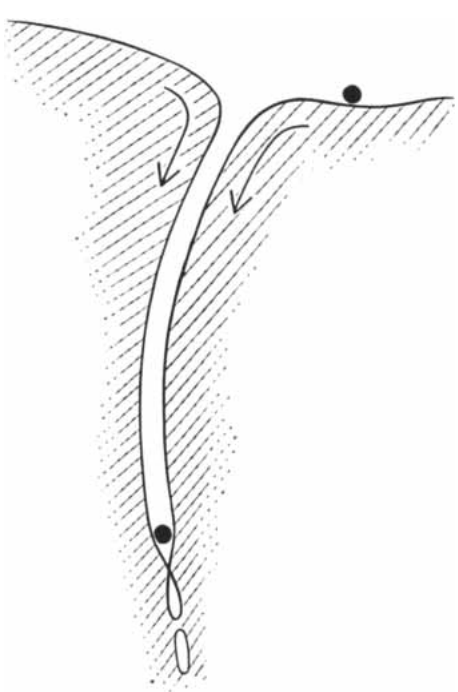
These observations and hypotheses were pulled together in a model of the cell membrane proposed by J. F. Danielli of King's College in London in 1940. According to this model the membrane consists of a double layer of lipid molecules covered by two protein layers. The lipid molecules are oriented parallel to one another at right angles to the plane of the membrane, with the nonpolar (uncharged) ends of the lipid molecules pointing toward one another and the polar groups pointing toward the surfaces of the membrane. Adsorbed to the polar ends are layers of protein, consisting of protein chains that form a network on the outer and inner surfaces of the membrane and so endow it with a certain degree of elasticity and mechanical resistance as well as low surface tension. Because the length of the lipid molecules is about 30 angstrom units (one angstrom unit is one ten-millionth of a millimeter) and the thickness of a monomolecular protein layer is some 10 angstroms, Danielli fixed the total thickness of the membrane at about 80 angstroms.



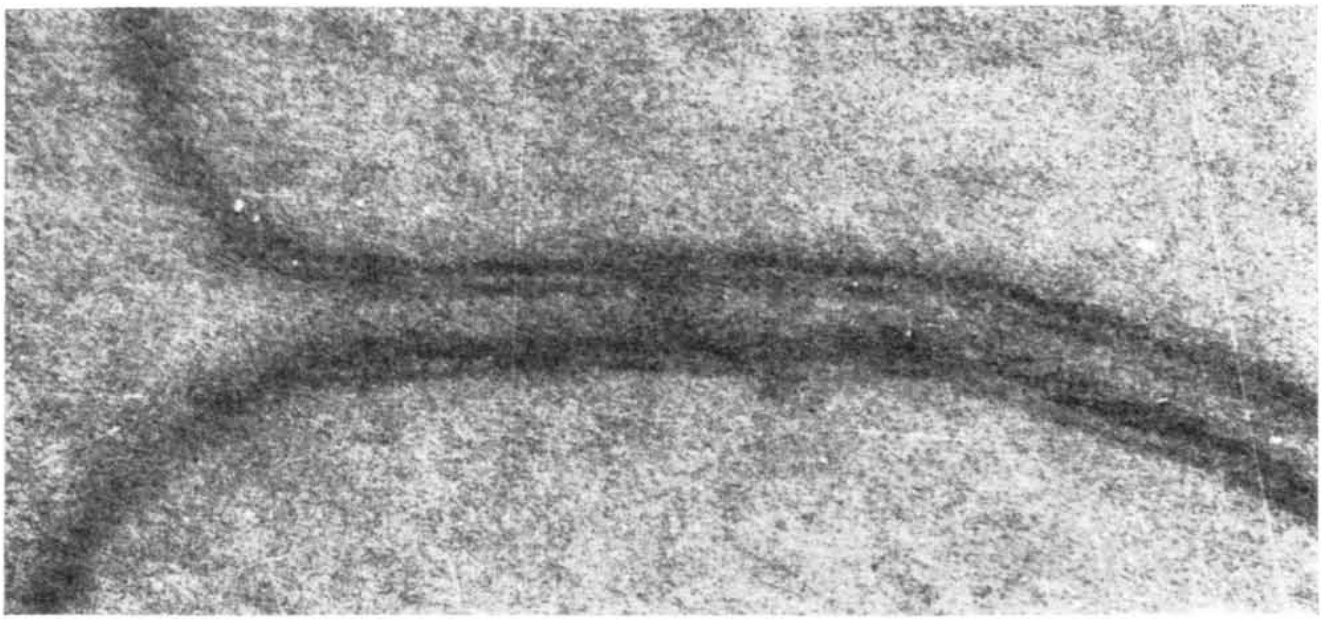
MODEL OF CELL MEMBRANE proposed by J. F. Danielli of King's College in London shows double layer of lipid molecules oriented parallel to each other. A protein layer covers them and lines a pore (*arrow*). Polar (electrically charged) ends of molecules are represented by circles. The hatched area is mucus, which is thought to coat most cells.

Danielli's model of the membrane has now been beautifully supported by the results of electron microscopy. The "unit membrane" developed from electron micrographs by J. David Robertson of the Harvard Medical School has the appearance and dimensions predicted by the model and has been observed in many types of cell. It shows two electron-dense lines, about 20 angstroms thick, which could very well correspond to the two postulated layers of protein; they are separated by a lighter 35-angstrom core corresponding to the lipid layer. The total thickness of 75 angstroms comes satisfactorily close to that of the model.

Without upsetting the symmetry of the model, it appears that the picture must be amended to provide for a difference in the chemical nature of the inside and outside surfaces of the membrane. This would permit the chemical gradients across the membrane suggested by some observations. Moreover, many cells wear a carbohydrate-con-



PROCESS OF PINOCYTOSIS according to current hypothesis involves adsorption of particles, molecules or ions on cell surface. The loaded cell membrane then slides or flows along, forming a recess extending toward the inside of the cell. This transports the adsorbed substance inward. In amoeboid type of pinocytosis (*single diagram at left*) the recess is a long channel from



MEMBRANES OF TWO CELLS in a mouse nerve fiber are enlarged 400,000 diameters in this electron micrograph by J. David Robertson of the Harvard Medical School. Each membrane is approximately 75 angstrom units thick and consists of two dense lines each 20 angstrom units wide separated by a light area 35 angstroms across. The gap between the cells is nearly 150 angstroms. The two dense lines of each membrane correspond to Danielli's protein component; the light area between them may be the lipid region.

taining overcoat of mucoprotein, which is of different thickness in different types of cell. This layer may or may not influence permeability, but it probably has an important function in pinocytosis.

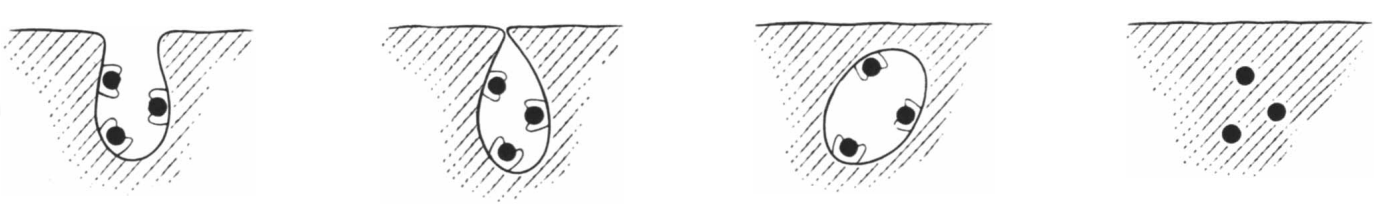
In addition to these cross-sectional features, permeability studies indicate that the membrane varies in structure laterally. Cell membranes show, for example, filtration effects in admitting particles up to a given size and blocking others, and this suggests the presence of pores. So far the electron microscope has failed to prove the existence of pores. But this is not surprising, because the pores are assumed to be very small and far apart, accounting for only one thousandth or so of the total area of the membrane. If one speaks of the membrane as a sieve, it is a sieve with very few holes in it [see "Pores in the Cell Membrane," by Arthur K. Solomon; SCIENTIFIC AMERICAN, December, 1960].

Still more important, in order to explain the high selectivity with which many cells discriminate between substances, one must assume that different patches of membrane have different chemical specificity. Certain enzymes, for example, have been shown to be localized on the surfaces of the cells. Apparently their function is to convert substances that are otherwise insoluble in the membrane into soluble derivatives that can permeate the membrane. There are many cases in which one substance is allowed to penetrate the cell while another, closely related and similar in size and electrical properties, is rejected.

The flimsy structure of the cell membrane therefore appears as an elaborate apparatus that is designed for active intervention in the movement of substances into and out of the cell. Such an apparatus is plainly necessary to the process of active transport that handles so much of the traffic. To accomplish this uphill movement the cell must work against the forces of passive transport. But intensive research by many investigators has so far failed to disclose the mechanism by which the necessary energy is transferred from the cell's metabolic machinery to the transport process. Probably different energy-transfer mechanisms come into play.

The liveliest interest in this field centers on the active transport of ions. Biologists have been aware of the existence of potential differences across cell membranes for more than 100 years; for nearly that long they have realized that the membrane potential influences the transport and distribution of ions. But they have only recently begun to understand that membrane potentials are themselves set up and maintained by the active transport of ions.

The importance of the problem is indicated by the fact that many cells con-



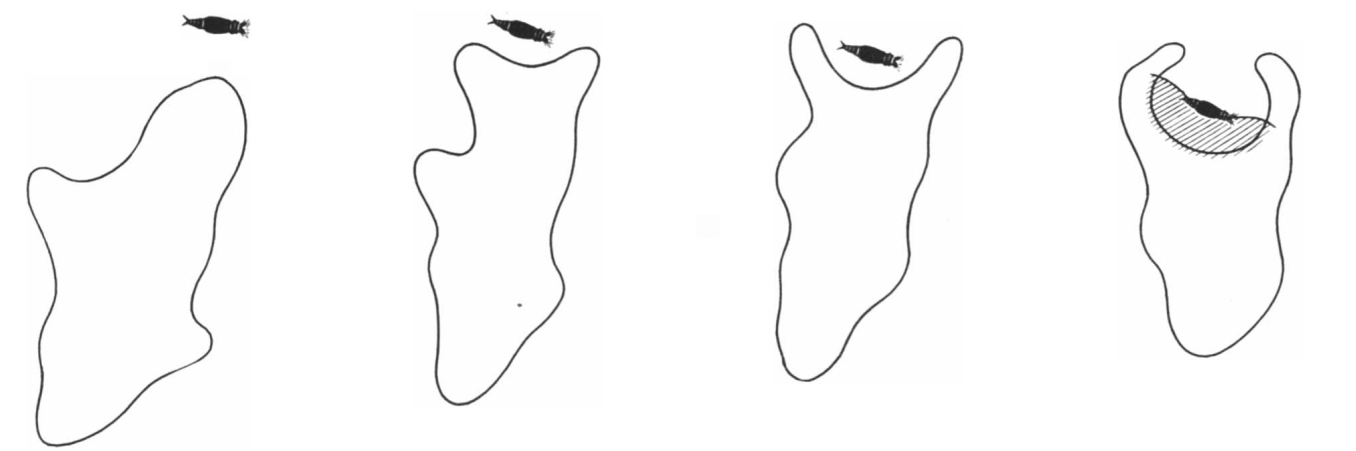
which small vesicles are pinched off to form tiny vacuoles. In submicroscopic pinocytosis by other types of cell (*series of six diagrams*), vesicles are pinched off directly from the cell surface. The "hairs" holding the particles are hypothetical. The disappearance of the vacuole wall (*far right*) is also a theoretical concept. It is not known how substances actually leave the vacuole.

tain in their cytoplasm much more potassium than sodium and yet must live in a medium in which the ratio between those two ions is just the reverse. Blood plasma, for instance, contains 20 times more sodium than potassium, whereas the red cell contains 20 times more potassium than sodium. The membrane of the red cell shows a passive permeability to both sodium and potassium ions that is low but definite. If this permeability were allowed to express itself, the sodium would leak into, and the potassium would leak out of, the cell. To maintain the difference in ionic composition, therefore, the cell constantly extrudes sodium and accumulates potassium against an aggregate 50-fold concentration gradient.

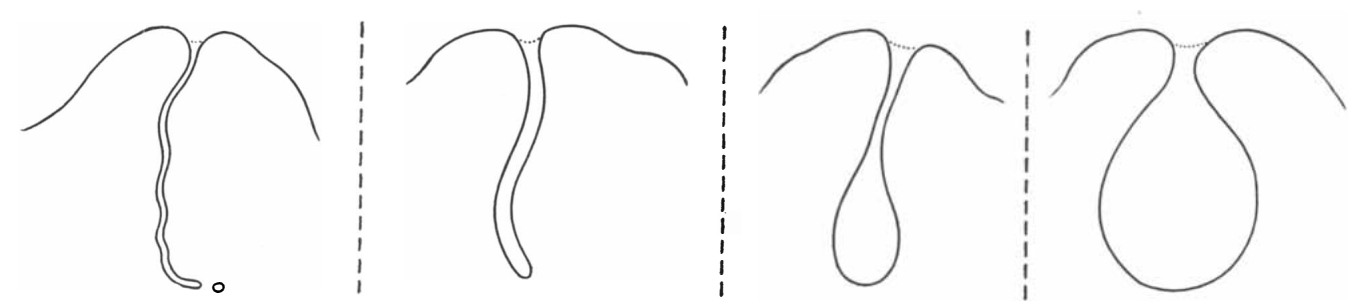
Most of the models proposed to explain active transport assume the existence of some kind of carrier molecule. This still hypothetical carrier is supposed to form a compound with the ions on one face of the membrane; the compound then passes through the membrane to be destroyed, releasing the ion, at the other. The movement of the compound, as distinct from the ion, is assumed to be downhill, following a chemical concentration gradient.

One such model, put forward by T. J. Shaw of the University of Cambridge in 1954, not only explains the movement of potassium and sodium ions across the membrane but also furnishes a link between them. In Shaw's model the potassium and sodium ions (K^+ and Na^+) are transported across the membrane by

PINOCYTOSIS CHANNELS in *Amoeba proteus* were drawn in 1934 by S. O. Mast and W. L. Doyle of Johns Hopkins University. The channels appear in small pseudopods and are often convoluted. They disintegrate into vacuoles or droplets at the inner



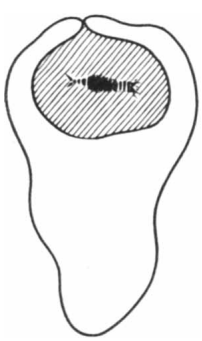
PHAGOCYTOSIS BY AMOEBAE resembles some types of pinocytosis. Here the amoeba is engulfing a tiny multicelled organism, a rotifer. The amoeba approaches its prey, extends large pseudopods and a membrane (*hatched area*) around it. Finally a large



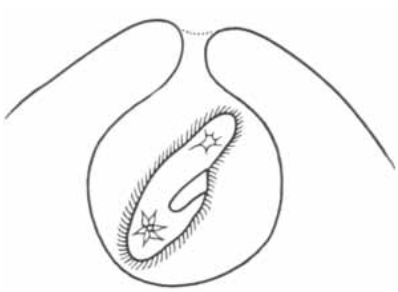
PINOCYTOSIS CHANNELS in amoebae are compared with phagocytosis vacuole (*far right*). Four types of channel are, from left, those formed in salt solution, wider channel, "bottle" channel in solution of tobacco mosaic virus and a cavity formed in a solu-

lipid-soluble carriers (X and Y) that are specific for the two ions. The compounds formed (KX and NaY) can move across the membranes by diffusion, whereas the free carriers cannot. At the outside surface of the membrane the sodium carriers are converted to potassium carriers, losing energy in the process. At the inside surface the potassium carriers are reconverted to sodium carriers, thanks to the supply of energy (probably furnished by energy-rich phosphate compounds) from the me-

end. The amoeba ingests these and then absorbs the substances contained within them.



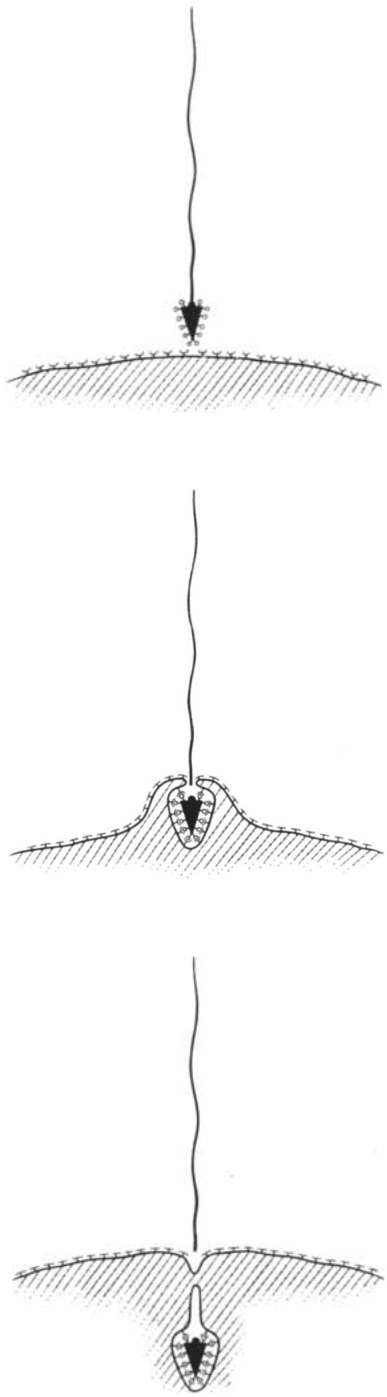
vacuole completely encloses the rotifer and the amoeba prepares to digest its prey.



tion of the chemical methionine. The phagocytosis vacuole contains a paramecium.

tabolism of the cell. This ingenious model contains many assumptions difficult to prove experimentally, and it is by no means universally accepted. Nevertheless, it may serve to illustrate the intricacy of active transport.

Long before biologists were troubled by processes involving such elegant manipulation of the physical forces that prevail across the cell membrane, they had observed cells in the plainly intelligible act of "eating." In the late 19th century Elie Metchnikoff of the Pasteur Institute in Paris saw white blood cells engulfing bacteria and gave them the name "phagocytes." In 1920 Asa A. Schaeffer of Temple University drew the classical picture of an amoeba catching its prey [*see middle illustration on preceding two pages*]. It was not until 1931 that Warren H. Lewis of Johns Hopkins University observed the somewhat less obvious process of pinocytosis. Studying tissue-culture cells by means of time-lapse photography, he saw membranous fringes at the periphery of the cells undulating so intensely that once in a while a part of the membrane would close up like a clenched fist and trap a small portion of the surrounding medium in a vesicle. The whole action seemed to Lewis so much like the process of drinking that he coined the word "pinocytosis."



FERTILIZATION as visualized by Albert Tyler of California Institute of Technology involves pinocytic engulfment of the sperm by the egg. Interaction of complementary substances on the surfaces of the sperm and the egg causes the egg to admit one sperm. Other sperm are then excluded.

With the exception of a confirmatory report of a similar phenomenon in amoebae by Samuel O. Mast and W. L. Doyle of Johns Hopkins in 1934, Lewis' discovery attracted little attention. Pinocytosis remained more or less a curiosity until in the 1950's the electron microscope showed that ingestion is a much more universal process in cellular life [see "Pinocytosis," by Ronald C. Rustad; SCIENTIFIC AMERICAN, April].

In amoebae and tissue-culture cells pinocytosis is within the range of microscopic visibility. In the scale of dimensions accessible to the electron microscope a great number of cell types show the formation of submicroscopic vesicles. Physiologically speaking, one of the most interesting examples is that of the "brush border" cells in the epithelium of the kidney and the intestine: the vesicles that bring substances into the cell form at the base of the villi from which the cells get their name [*see illustration on page 167*]. The essential feature of pinocytosis or phagocytosis is the same in all cells: an area of the cell membrane detaches itself from the cell surface to form a vacuole or vesicle, which leaves the periphery of the cell and migrates toward the interior.

The size range of the vesicles formed by pinocytosis is wide. In amoebae and tissue-culture cells the average diameter of a newly pinched-off pinocytosis vacuole is one to two microns (a micron is a thousandth of a millimeter); the vesicles discernible in the electron microscope may range from .1 to .01 micron. These vesicles often change their orig-

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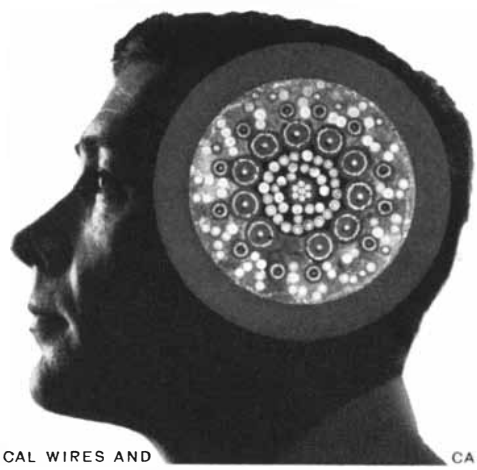

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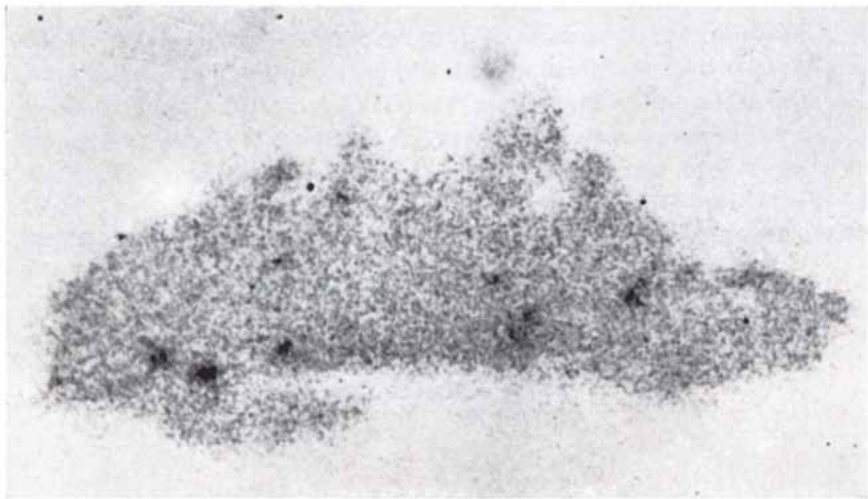

SECTION OF AN AMOEBA after pinocytosis of a protein solution containing radioactive glucose shows much of the radioactivity still confined to the pinocytosis vacuoles (*heavily blackened areas*), although much is evenly distributed (*gray*). The author and his colleagues made the autoradiograph by placing the section on a photographic negative.

inal size by fusing with one another. Since most cells contain an array of other vacuoles and granules, the pinocytosis vesicles soon become unrecognizable unless they are marked by a "tracer" of some kind. The vacuoles formed in phagocytosis are, of course, much larger, accommodating whole bacteria, protozoa and bits of tissue debris in the case of phagocytes.

Simple experiments with amoebae show clearly that pinocytosis does not occur in all media and at all times but is induced by the presence of certain substances in the medium. In pure water amoebae do not pinocytose, at least not enough to be detected in the microscope. If sugar or some other carbohydrate is added to the water, nothing happens. But if salts, proteins or certain amino acids are added to the water, pinocytosis sets in. Cicily Chapman-Andresen, in our group at the Carlsberg Laboratory in Copenhagen, has found that amoebae are able to sustain the activity for about 30 minutes at a time, regardless of the nature of the inducer, and in this period will form about 100 channels. When that number of channels has been formed and the corresponding number of vacuoles has been ingested, pinocytosis stops and does not begin again until after a three- or four-hour period. Chapman-Andresen interprets this as meaning that after 30 minutes of pinocytosis the surface membrane available for invagination has been exhausted.

She has also helped to settle an old question by showing that phagocytosis and pinocytosis can be regarded as essentially the same sort of physiological process. In this experiment the amoebae are first allowed to phagocytose as many food ciliates as they will take from a solution teeming with these organisms. Upon transfer to a pinocytosis-inducing solution they will form only a few channels, less than 10 per cent of the normal number. And vice versa: amoebae that have pinocytosed to exhaustion will not feed when transferred to a droplet containing their food organisms. So it seems that the availability of the same membrane is the limiting factor in both cases.

H. Stanley Bennett of the University of Washington proposed in 1956 that pinocytosis is induced by the adsorption of the inducer molecules or ions on the surface of the cell membrane. This idea has been fully verified by several investigators. There is not much doubt that in amoebae the adsorbing sites are furnished by the mucus coat that covers the surface of the amoeba. Inasmuch as a mucous substance is supposed to cover many other cells, it will be interesting to find out whether it serves the same function in all cases.

The vesicle that carries the inducing substance into the cell also brings along some of the fluid medium. Chapman-Andresen and I performed a "double label" experiment to determine which of the two—the inducer or the fluid—is physiologically more significant. We exposed amoebae to a solution that contained a radioactively labeled protein as an inducer and a sugar with a different radioactive label as an indicator of the amount of ingested fluid. If the protein was the principal nutrient ingested as well as the inducer of ingestion, then we expected that the vesicles would contain relatively more protein than the outside medium. We found that this was

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indeed the case. But we were surprised by the magnitude of the effect: a more than 10-fold concentration of the protein relative to the sugar. The total amount of protein taken up in 30 minutes corresponded to about 25 per cent of the total mass of the amoeba. This is a considerable meal, and it indicates that the uptake of the surface-adsorbed substance is what mainly matters to the cell in pinocytosis.

But the nutrient contained in the vesicle must still be regarded as outside the cell, for the envelope that encloses it is a portion of the external membrane. The question remains whether and how this mode of communication with the environment delivers raw materials to the metabolic machinery of the cell. The simplest means of transfer from the vacuole to the cytoplasm would be the disappearance of the membrane itself under the influence of cytoplasmic enzymes. But the electron microscope does not support this suggestion; the vesicle membrane has never actually been seen to disappear.

Because the membrane persists, the study of its permeability properties becomes the main task in the investigation of pinocytosis. There is no doubt that the pinocytosis vesicles lose water to the cytoplasm. This manifests itself as a visible shrinkage of the vacuoles. John M. Marshall, Jr., of the University of Pennsylvania School of Medicine and I have shown that in amoebae the shrinkage is accompanied by a progressive concentration of the vacuolar contents. Centrifugation shows that in the first hours after pinocytosis the vacuoles become heavier and heavier compared with the surrounding cytoplasm. Eventually the pinocytosis vacuoles wind up as cytoplasmic granules of approximately the size and centrifugal behavior of mitochondria.

It has been demonstrated, furthermore, that the vacuolar membrane is permeable not only to water but also to low-molecular substances such as glucose. Chapman-Andresen and I, using radioactive glucose, found that the glucose so ingested quickly spreads from the vacuoles and is homogeneously distributed in the cytoplasm. The glucose enters the cell's normal metabolism as if it had been taken up by diffusion through the cell surface; its metabolic product, radioactive carbon dioxide, soon shows up among the amoebae's excretion products. Chapman-Andresen and D. M. Prescott have made similar findings with regard to certain amino acids. There is therefore no doubt that a

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cell can be "fed" substances of small molecular size by pinocytosis. Experiments with large molecules have not yet been made.

These results seem to indicate that some change in the permeability of the membrane occurs. The change is not discernible in the electron microscope; the membrane seems to be the same before and after pinocytosis. It is reported, however, that the mucous coat from the external surface peels off the vacuolar lining and collects, together with the adsorbed material, as a central mass in the vacuole.

At the same time another and possibly important event takes place. Small secondary vesicles form, pinch themselves off from the primary vacuole and migrate into the cytoplasm. The significance of this process for the distribution of the contents of the primary vacuole cannot yet be judged. But one effect is obvious: such permeation processes as can work across the membrane of the microvesicles must be greatly facilitated by the enormous increase in intracellular-membrane area. The secondary vesicles could also serve a selective function, carrying certain substances away from the primary vacuole and leaving others behind.

The main difficulty with pinocytosis as a basic process in cellular physiology is its lack of specificity. It is true that a high degree of specificity is observed in the performance of phagocytes when they have been sensitized by antibodies to engulf particular bacteria. Albert Tyler of the California Institute of Technology has postulated that fertilization involves a pinocytotic engulfment of the sperm by the egg, an act initiated by the interaction of specific substances at the surfaces of the two cells. But by and large the mechanical uptake of adsorbed material and fluid from the external environment must be rather undiscriminating. On many occasions the cell may have to cope with useless or even obnoxious substances so ingested.

A more selective mechanism must exist somewhere. It is easiest to imagine that the selection is accomplished, passively or actively, at the membranes that surround the vacuoles and vesicles inside the cell. If this view is correct, pinocytosis ought to be regarded not as alternative to membrane transport but rather as a supporting process. Its essential feature would be the creation of large interior interfaces where the forces of passive and active transport can set to work with even higher efficiency than at the cell surface proper, and with less danger of substance losses by leakage.

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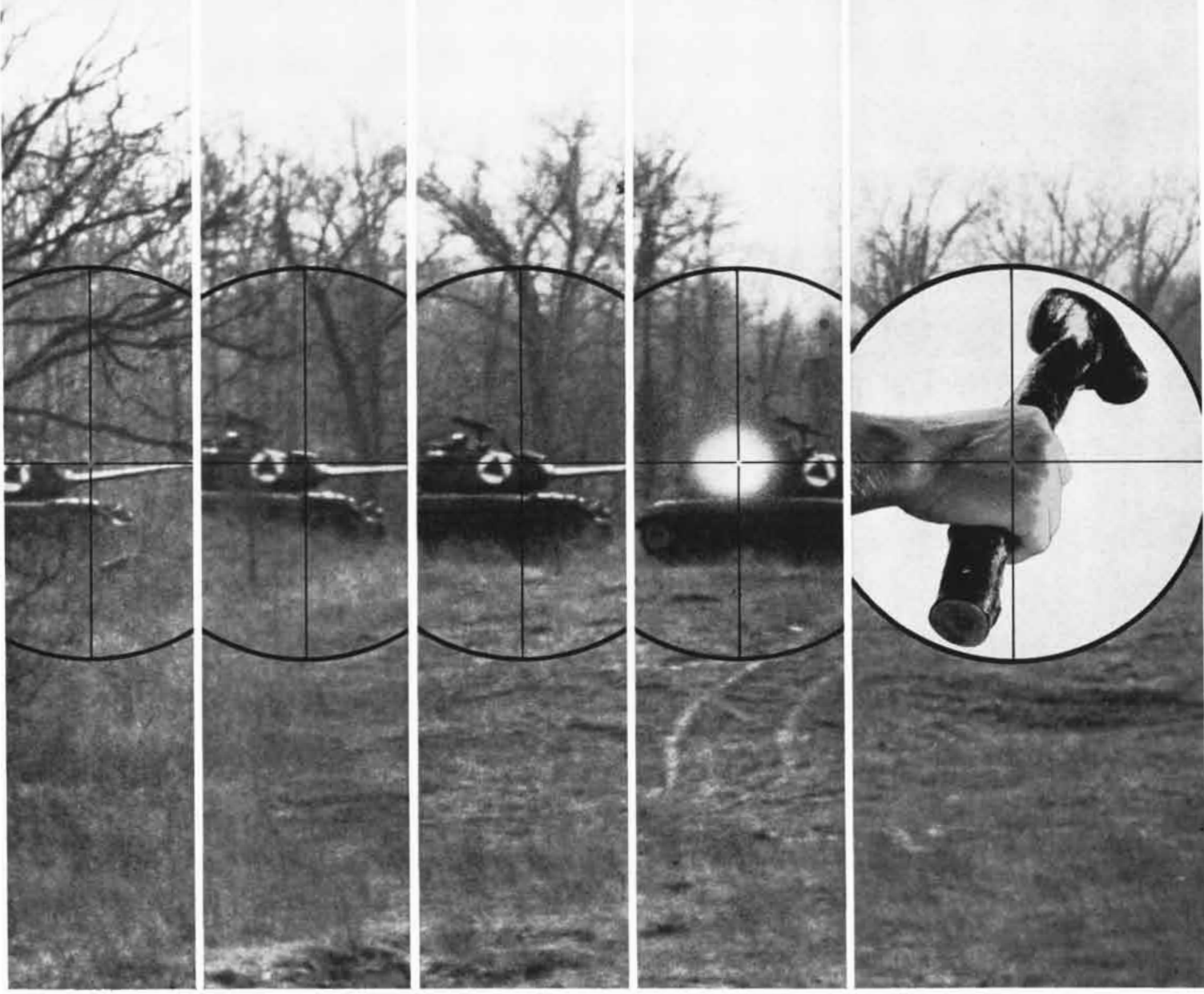

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How Cells Move

A paramecium moves by the beating of its cilia; an amoeba, by the streaming of its cytoplasm; a muscle, by its over-all contraction. All these processes appear to share an underlying molecular unity

by Teru Hayashi

Life is movement. This definition, though incomplete, is perhaps as good as any. One is tempted to add that the movement is "constructive," or even "purposeful," but such qualifications raise definition problems of their own. So let us just say that where there is life there is movement. By this criterion we need not hesitate to describe cells as living and viruses as nonliving. Until it meets a living cell a virus is as inert as any stone.

Activity is a manifestation of the energy of living things. Generations of biologists have sought to answer the question: How does an organism move? Early workers understandably concentrated their attention on the activity of muscle, a word from the Latin for "little mouse." Later, when it was recognized that organisms are composed of cells, the search for the secret of motion moved down to the cellular level. Today we try to reach down to the level of the molecule, still seeking the final answer, which continues to elude us.

In large, complex organisms such as ourselves, the muscle cells are the cells most highly specialized for producing movement. Striated muscles activate our limbs, cardiac muscles make the heart beat, and smooth muscles push food along its digestive course. Less familiar are the movements exhibited by other cells within our bodies and by many one-celled organisms. The sperm cell, for example, is powered by a single whiplike flagellum. The paramecium and a number of other one-celled organisms are propelled through their liquid environment by fine, hairlike extensions called cilia. If the cell is stationary, as are the ciliated epithelial cells of the trachea, the cilia propel a liquid film past the cell, thereby keeping the surface of the cell washed clean. At a deeper level there is a constant turbulence within every living cell—a churning of the cell contents termed protoplasmic streaming. When this streaming results in the locomotion of the entire cell, the cell exhibits amoeboid movement. In nonmoving cells protoplasmic streaming carries a constant supply of molecular building materials to sites where large molecules are synthesized, carries these large molecules to other sites and in general provides the cell with an internal transportation system. The beautifully precise turning and positioning of the chromosomes in cell division are also a manifestation of movement within the cell [see "How Cells Divide," page 100].

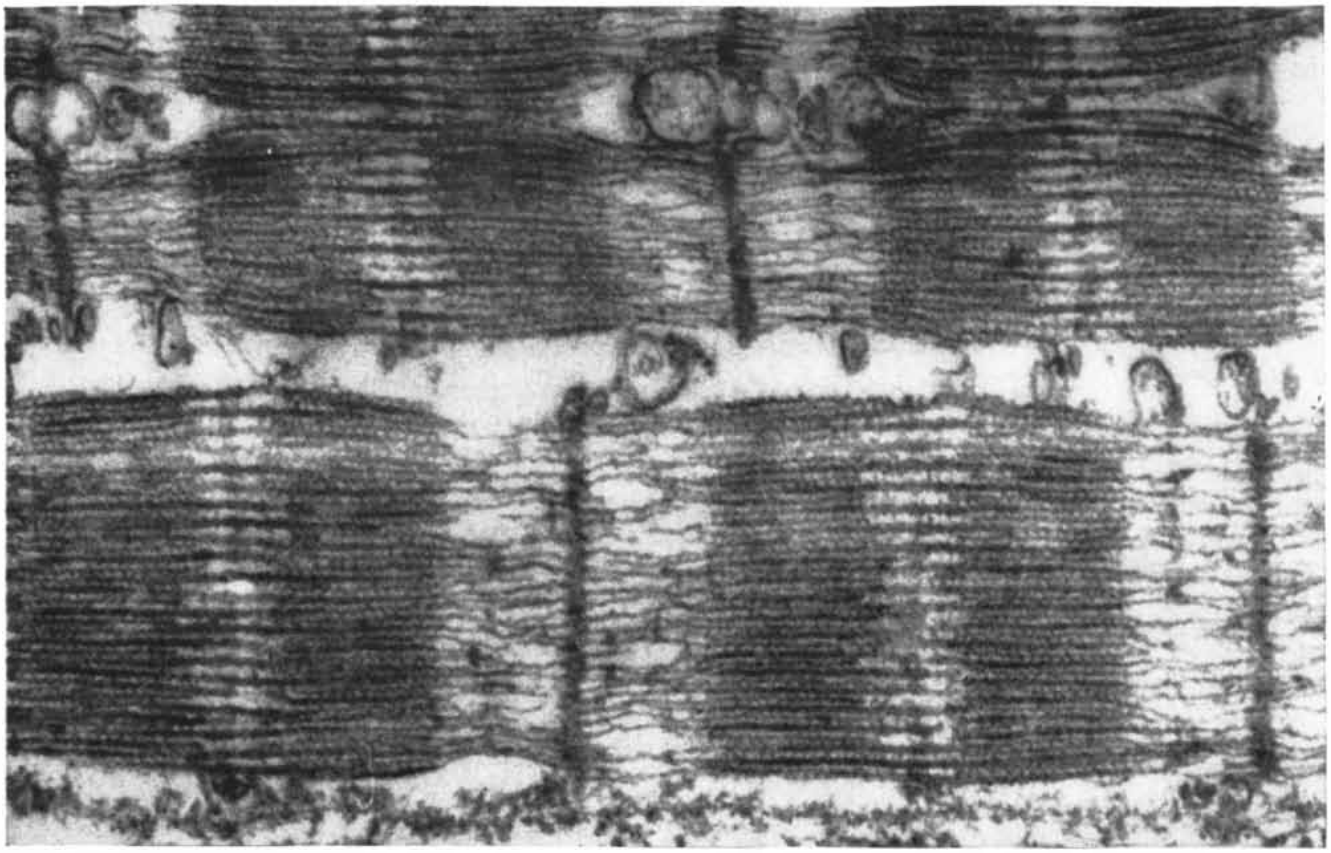
The simplest form of protoplasmic streaming occurs in the plant cell, which has a rigid cell wall with the protoplasm in thin layers just inside the wall. The innermost part of the cell is filled with a watery solution in a space called a vacuole. Close examination of the huge rhizoid (rootlike) cell in the water plant *Nitella* reveals that the thin protoplasmic layer is composed of a cortical gel layer, immediately inside the cell wall, and the more fluid endoplasm, or interior protoplasm. The endoplasm is the layer in motion; it circulates around the sides of the cell in a uniform direction, a movement called cyclosis [*see top illustration on page 186*].

A more complex type of streaming is found in the locomoting amoeba, in which the endoplasm flows forward in the direction the cell is moving. At the advancing end the endoplasmic material moves to the sides of the cell in a "fountain" flow, where it becomes transformed into the stiff, nonmoving material of the cortical gel. At the rear end of the cell the opposite series of events is taking place; the gel material is transformed into the flowing endoplasm that provides the forward-moving stream. In its simplest form, then, the amoeba moves by means of a flow of endoplasm through a tunnel of cortical gel, the tunnel wall being built up continuously at the front end of the cell from the flowing material and being torn down at the rear end to supply the material for the flow.

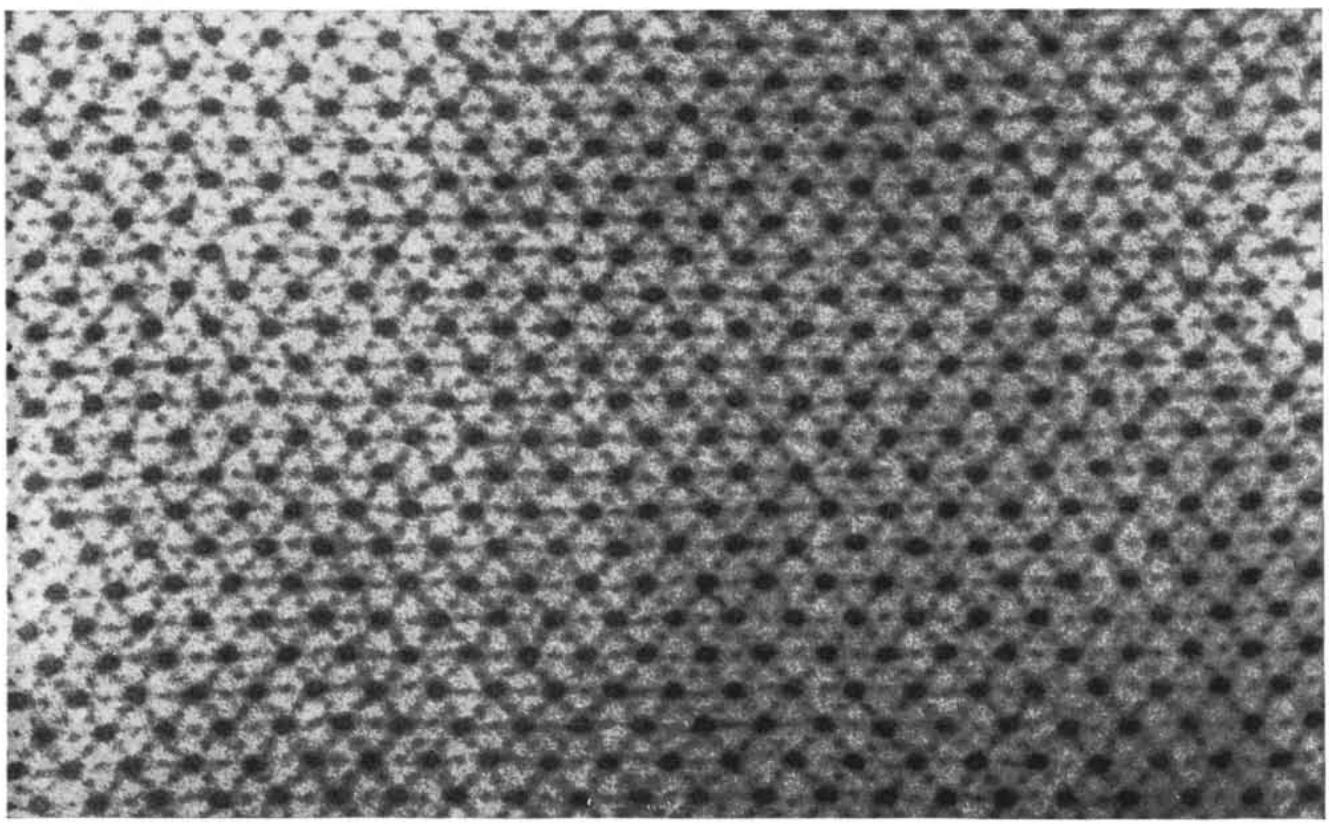
A still more complex movement takes place in the slime molds, such as *Plasmodium*, which are large masses of protoplasm containing many nuclei not separated from each other by cell membranes. The streaming of the protoplasm is similar to that in the amoebae but is complex because many streams exist simultaneously, moving in different directions.

Exquisite techniques for studying protoplasmic streaming have been devised by such workers as Robert D. Allen of Princeton University, R. J. Goldacre of the Chester Beatty Research Institute of the Royal Cancer Hospital in London and Noburô Kamiya of Osaka University in Japan, each of whom advocates a different hypothesis to explain protoplasmic flow. All agree that endoplasm flows passively, that there is an outside motive force urging it along. Where they disagree is on the nature of the force. Let us see how Kamiya and his associates have tried to settle the matter.

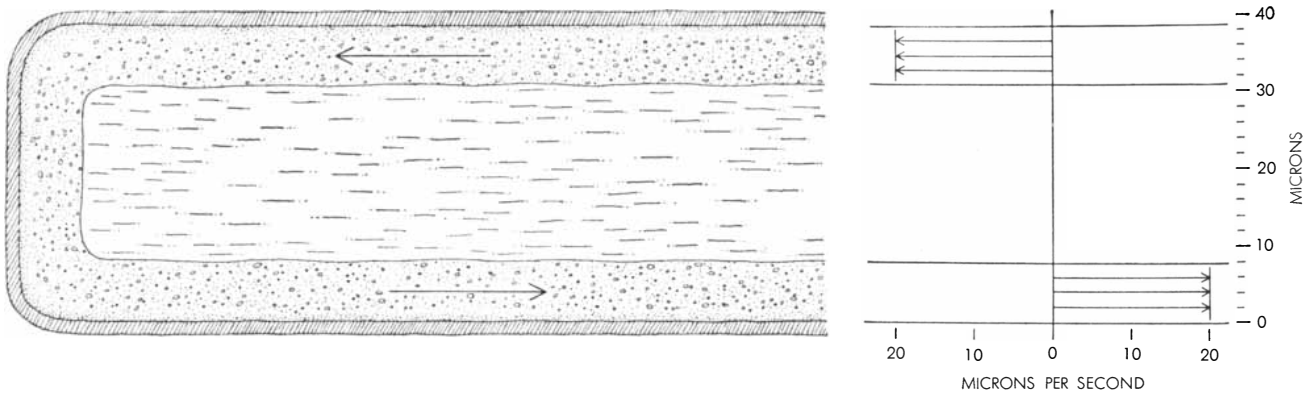
If a small mass of *Plasmodium* is divided into two parts but with a very thin connecting strand remaining, the protoplasm will flow from one side to the other for a while, then reverse and flow in the opposite direction, in an oscillatory motion. If the connecting strand is fine enough, the flow within it at any moment is simple and unidirectional. Taking advantage of this, Kamiya and his students constructed a double cham-



MOVEMENT IN STRIATED-MUSCLE CELL results from action of thick and thin filaments, seen here in an electron micrograph by H. E. Huxley of University College London. Dense *A* bands, bisected by *H* zones, mark overlap of thick and thin filaments. Light *I* bands, bisected by *Z* lines, are regions occupied by thin filaments alone. This is a very small part of one fibril of a rabbit muscle cell.



END VIEW OF FILAMENTS from an insect flight muscle shows regular hexagonal array of thick filaments (*larger spots*) and thin filaments (*smaller spots*). The electron micrograph, made by Jean Hanson of King's College in London and Huxley, enlarges the filaments approximately 250,000 diameters. This cross section shows only a part of one of the many fibrils that make up one fiber.



PROTOPLASMIC STREAMING, or cyclosis, in the rootlike cell of the water plant *Nitella* is diagramed. The outside wall of the cell is rigid. Just within is the very thin cortical gel layer. Next is the fluid endoplasm, which streams circularly (*arrows*) at 20 microns per second. The inner part of the cell is the vacuole, filled with a watery solution. The long cell is only 42 microns thick.

ber with a small opening in the wall between the chambers [*see illustration below*]. The two protoplasmic blobs were placed one in each chamber and connected by a single thin strand through the opening in the middle wall, so that the mold would now flow from one chamber to the other for a time, then back again. To the two chambers Kamiya attached devices to measure the rate of flow in the strand, the pressure causing the flow and the rate of oxygen consumption. Provision was also made for introducing chemical agents into the chambers during the measurements.

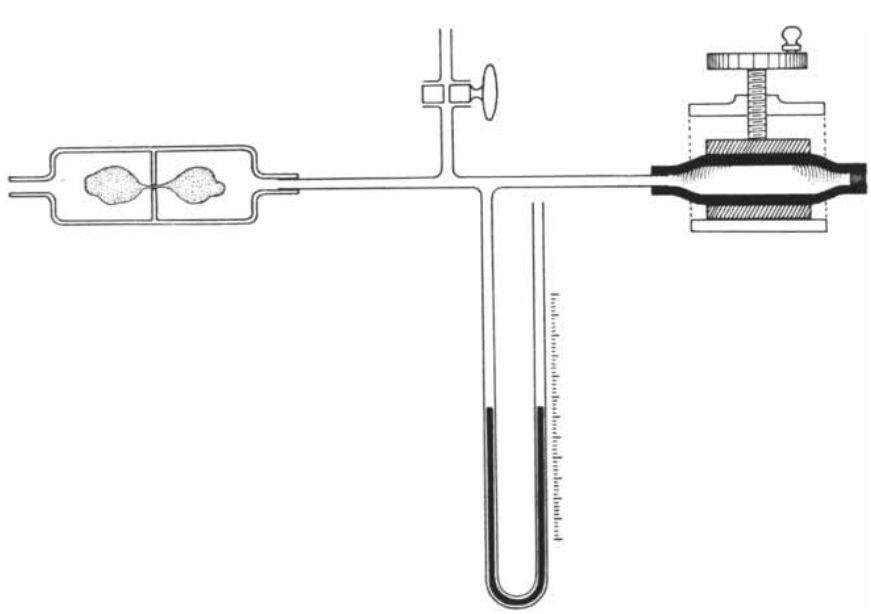
Here are a few of the results drawn from many precise experiments. First, the flow through the strand has the same characteristics whether it is the natural flow or a flow enforced with applied pressure. This indicates that the motion of the endoplasm is indeed a passive one, caused by local changes in pressure. Second, this motive force in the form of pressure differences has been measured and found to be about two pounds per square inch, a considerable force notwithstanding the small dimensions of the cell. Kamiya has also found that the energy for this movement comes from fermentation—that is, by the nonoxidative breakdown of glucose—rather than from the oxidative respiratory process that supplies energy for other functions.

Reviewing the information, Kamiya hypothesizes that the motive force causing the pressure change can be either a contraction of the cortical gel layer on one side of the *Plasmodium* or a shearing action that propels the endoplasm sideways across the surface of the cortical gel layer. Kamiya points out that the latter mechanism would also explain the cyclosis in *Nitella*.

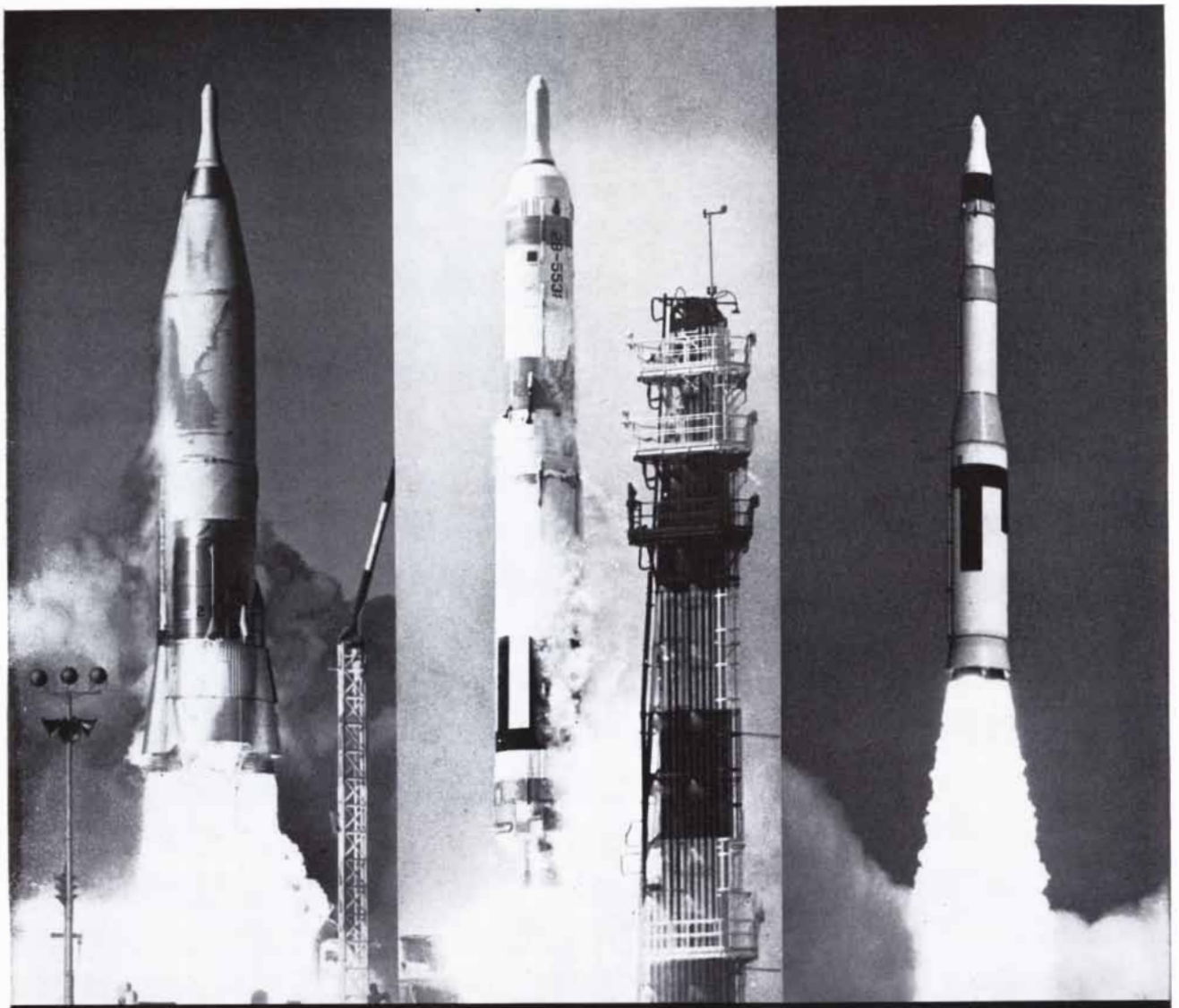
Contraction of the cortical gel has also been invoked by those studying the amoeba; there is a century-old hypothesis that contraction of the cortical gel in the rear end of the advancing amoeba pushes the endoplasm forward. Goldacre favors this view on the basis of many ingenious experiments. Allen, on the other hand, finds his own observations incompatible with that hypothesis and maintains instead that a contraction of the cortical gel in the region of its formation, which he calls the "fountain zone," pulls the endoplasmic material forward.

Thus three mechanisms have been put forward to explain protoplasmic streaming in general and amoeboid movement in particular: (1) gel-endoplasm shearing or sliding, (2) rear-gel contraction and (3) front-gel contraction [*see illustrations on page 189*]. The actual parts of the cell engaged in one or more of these actions must be of molecular dimensions, because the best and most recent electron micrographs of the cells involved do not reveal any mechanical structures in the cortical gel region that could help us to decide among these choices.

Whereas visible parts are markedly lacking in streaming protoplasm, they exist in abundance in cilia and flagella. Vastly improved techniques in electron



STUDIES OF STREAMING in the slime mold *Plasmodium* are carried out in this apparatus by Noburô Kamiya of Osaka University. The slime mold is in two compartments (*left*) and has a thin connecting strand. Rubber bulb with screw attached (*right*) and mercury manometer (*center*) control and measure pressure of the flow in streaming.



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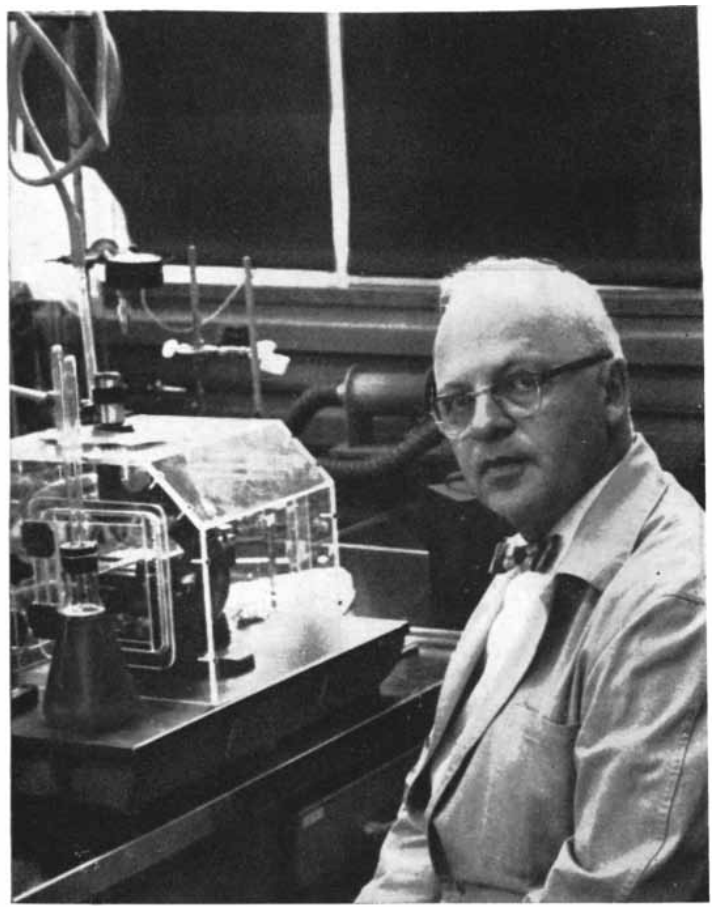
His problem:

To develop time-temperature curves for a wide variety of living cells

Name of this scientific American:
Dr. Ralph Buchsbaum,
University of Pittsburgh



Because heat is a universal environmental factor, scientific exploration into the world of living cells requires an accurate knowledge of the time-temperature tolerances exhibited by various cells. A family of curves which defines these tolerances is now being developed at the University of Pittsburgh under the direction of Dr. Ralph Buchsbaum.

A Home Away From Home

In order to study the chemical, physiological and morphological relationships of living cells, one must create an environment which makes observation possible, yet keeps the cell in a normal state of health while studies are being made. Further, the environment must be such that it can be controlled as desired by the observer.

Early attempts in the study of cells involved a transplant—or more specifically, an explant—of tissue into a medium which could support life for the cell under study. This method, however, had certain disadvantages. For example, the immediate responses of cells could not be observed because several hours were required for the first cells to migrate out from the explant. In addition, the concentration of an experimental drug used could not readily be maintained, the drug could not easily be removed, the effects could not be observed on a single cell over the entire experimental period and, finally, repeated doses could not be given to the same cell.

The Perfusion Chamber

One of the first men to develop a practical alternate was Dr. Buchsbaum of the University of Pittsburgh. Dr. Buchsbaum developed a perfusion chamber in which the isolated cell is continuously bathed in a flow of nutrients which sustain cell life. Using this device, it is now possible to alter the environment of a cell in any desired manner over any required period of time—and observe the results.

At present, Dr. Buchsbaum is using a perfusion chamber and appropriate instrumentation in order to develop a family of time-temperature curves for a variety of cells. In a typical case, the temperature of the cell is gradually elevated to a given level, held at that level for a pre-determined period, and then brought back on a planned temperature descent to the original temperature state. In this fashion, Dr. Buchsbaum not only can determine the temperature tolerance of different cells, but also accurately determine effects of the time factor. Motion pictures help to clarify further the nature of these events.

Although many media are used in these experiments, the most common contains all essential components of body fluids which ordinarily bathe the cell in the intact, living organism—components which include a water solution of salts, sugar, amino acids, etc.

The Need For Precise Measurement And Control

Initial instrumentation requirements for this project called for a flexible system capable of tempera-

ture measurement and control to an accuracy of less than 0.5°C. In addition, the system had to offer a means of programming temperature control at a known rate.

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Precise information of the kind being developed by Dr. Buchsbaum will permit a better understanding of the temperature-tolerances of whole organisms—as well as better insight into the healing process which follows burns and freezing.

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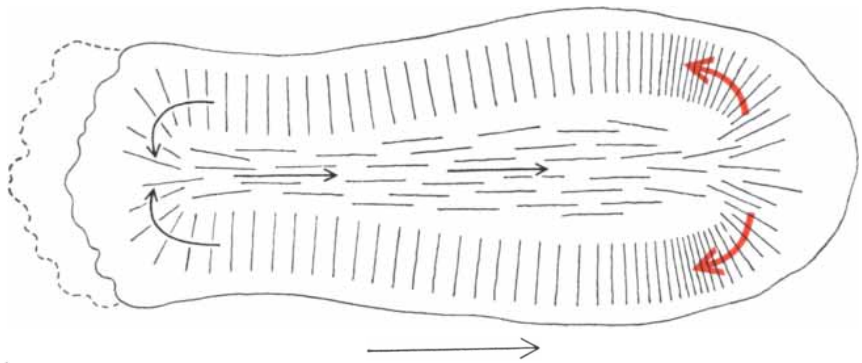
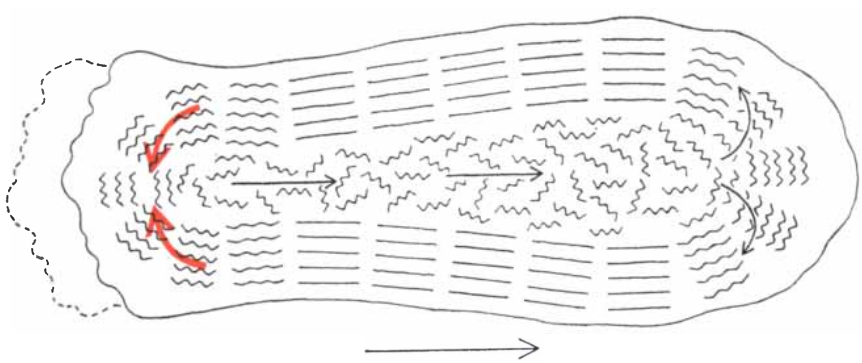
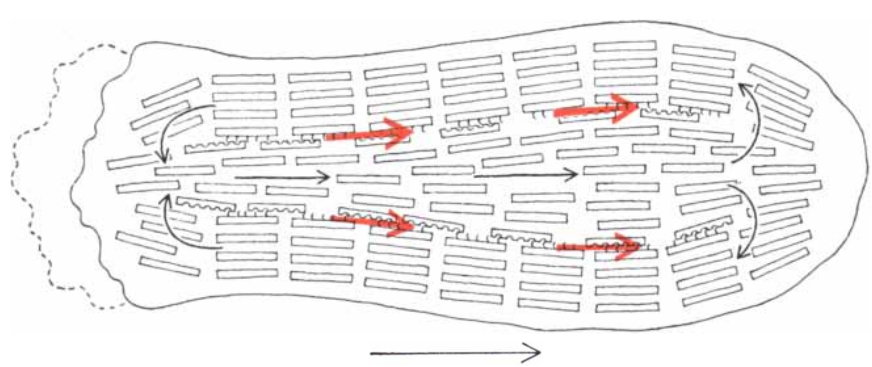
microscopy have revealed a wealth of exquisite fine structure in these "diverse incredibly thin feet," as Anton van Leeuwenhoek described them in 1676. In particular we have learned that these two types of motile "hair"—cilia and flagella—share the same basic structure. Barely visible under the ordinary light microscope, these fine hairs are built up of two center filaments surrounded by a ring of nine outer filaments in what is called a "9 + 2" arrangement [*see illustration on page 196*]. The nine outer filaments appear to be double structures,



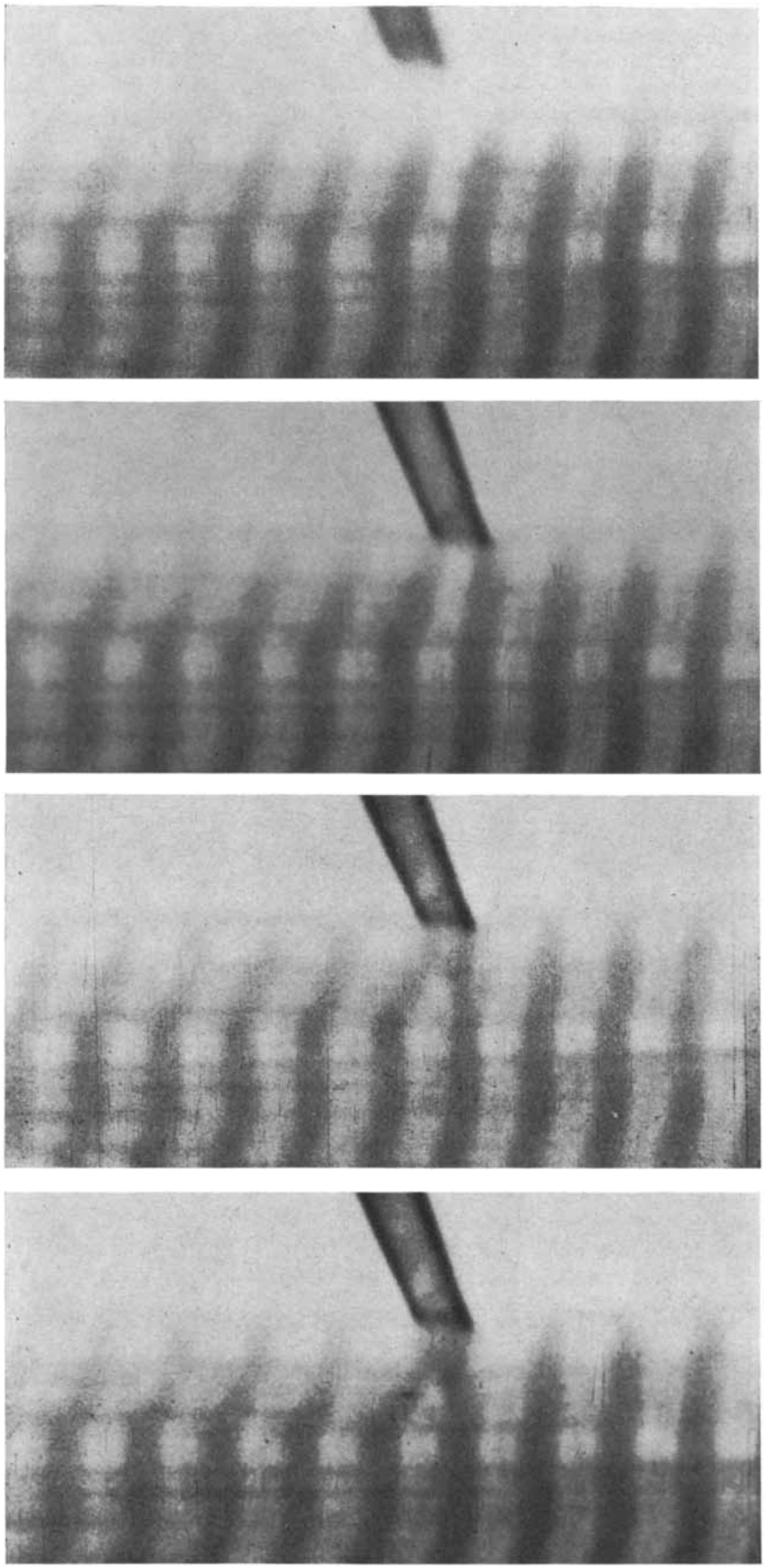
THEORIES OF AMOEBOID MOVEMENT are diagramed on this page. Robert D. Allen holds that semiliquid endoplasm streaming up center of the cell is pulled forward by contraction of the cortical gel near the head (*above*). Red arrows in each diagram indicate point at which force is applied. In all three diagrams endoplasm is turning to gel at head.



CONTRACTION AT TAIL, where gel is liquefying into endoplasm, accounts for movement, according to theory supported by R. J. Goldacre. The contraction would squeeze the endoplasm forward, in the manner of toothpaste being squeezed from a tube. Wavy lines are contracted molecules of endoplasm, which is more liquid than in Allen's theory.



GEL-ENDOPLASM SHEARING or sliding is third theory. Chemical "ratchets" on the inner edge of the gel would push forward individual molecules of endoplasm. The flow of these molecules would carry along the endoplasm molecules nearer the center. As in top and center diagrams, endoplasm turns to gel at the head and gel turns to endoplasm at the tail.



MUSCLE-FIBRIL CONTRACTION is demonstrated in sequence from a motion picture by A. F. Huxley. At top a microelectrode approaches fibril. It touches and electric current is turned on. Contraction can be seen as two dark *A* bands come together, pinching the light *I* band. The last photograph shows maximum contraction. Fibril is from frog muscle.

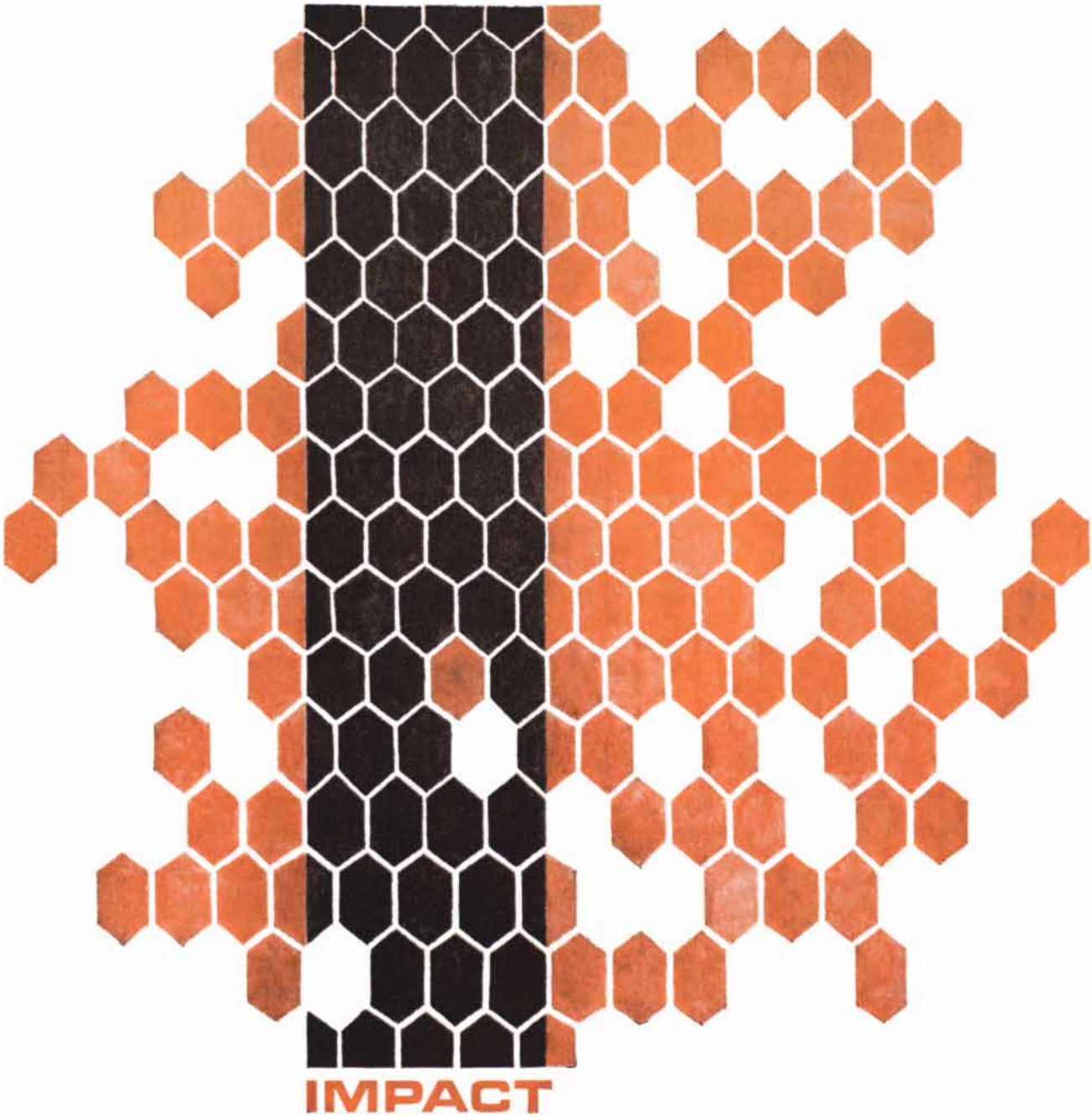
whereas the two central ones appear to be single. The widespread occurrence of this arrangement demands that any explanation of ciliary movement must include a role for these filaments.

The classic study of ciliary movement was made by Sir James Gray of the University of Cambridge with motion-picture micrography. The most common type of ciliary beat consists of an effective stroke and a recovery stroke [*see top illustration on page 192*]. In the effective stroke the cilium sweeps rapidly as a stiff, slightly curved rod, the only region of true bending being near its base. We can easily see that such a stroke —which resembles the power stroke made by a swimmer—will efficiently move the cell through its watery medium or move the medium past the cell. In the recovery stroke the cilium starts bending near the base and the bending proceeds as a wave toward the tip. The direction of this bending carries the cilium back to its original position.

J. R. G. Bradfield of the Cavendish Laboratory at the University of Cambridge has advanced an ingenious, if speculative, mechanism to account for the two kinds of stroke. He proposes that five of the outer filaments on one side of the cilium contract simultaneously and throughout their entire length to produce the effective stroke. The other four filaments are idle during this stroke but then contract slowly, beginning at the base, to produce the recovery stroke. The two central filaments, Bradfield believes, may act as telegraph lines to carry the message for contraction rapidly up the cilium so that the total contraction required for the effective stroke can be realized. Therefore even the apparently simple beating of a single cilium would seem to involve the complexity of message transmission. And when the cilia of many adjacent cells beat together rhythmically, as they do in the trachea and elsewhere, the co-ordinating signals must be more complicated still.

The undulant motion of some flagella, which may be as much as 50 times longer than cilia, is similar to that of cilia but more involved. Waves of bending arise at the attached end and move toward the tip, exerting a pushing force on the medium and driving the cell forward. In many cases the progressing cell rotates, causing the undulating flagellum to assume the shape of a coil. This movement would seem to require localized co-ordinated contractions, presumably of the internal filaments.

Although there is yet no direct evidence for contraction in cilia and flagella,



The impact of electronics on medicine has evolved a whole new concept in therapeutic and diagnostic techniques. As a manufacturer of active components for electronic circuitry, Tung-Sol has contributed to one of the newer weapons in the fight against cancer—the microwave linear electron accelerator (LINAC).

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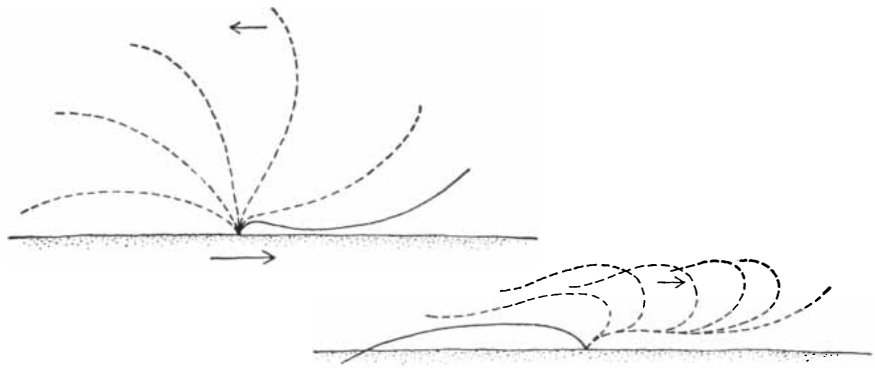
no alternative mechanism seems appealing. (One old proposal visualized the cilium as a tiny hose that lashes in reaction to water forced through it by the cell.) The chief support for the contraction hypothesis comes from the examination of muscle cells, which provide much more favorable objects for study.

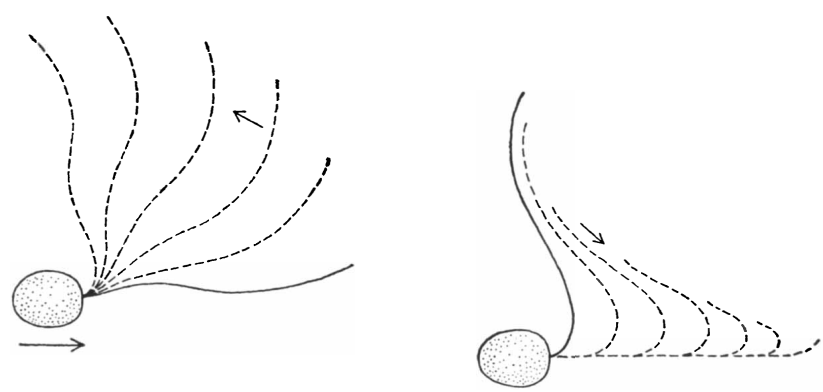
In a splendid demonstration of the power of the electron microscope, H. E. Huxley of University College London and Jean Hanson of King's College in London have elucidated for us the ultrafine structure of muscle cells in the rabbit. The muscle cell, usually termed muscle fiber, is a long, thin cylinder encased in a thin membrane. This cylinder contains fine threads called myofibrils that run lengthwise throughout the full length of the cylinder. The small spaces between the myofibrils are apparently filled with that watery solution of various substances which is the liquid portion of protoplasm. This fluid can probably penetrate the fibrils easily, since the individual fibrils do not have membranes surrounding them. The fibrils themselves are bundles of even finer filaments of two kinds, a thick and a thin variety, packed in a precise geometric array [*see illustrations on page 185*]. The entire fiber has a diameter of only 50 microns, a thread barely visible to the naked eye; the fibrils are one to two microns thick, and the thick filaments are only 100 angstrom units in diameter, or perhaps large enough to hold three protein molecules side by side.

The action of muscle involves many things, including the message to action brought by the motor nerve, the spreading of this message over the surface of the muscle fiber, the relaying of this message to the actual contractile parts of the cell, the contracting action itself and the energy sources for the action. The essential action, however, is simply shortening or contraction, and so we shall be concerned simply with the question: How does muscle shorten?

Any proposed mechanism for action must agree with certain well-established observations, due in large part to the work of A. V. Hill and his students at the University of Cambridge. First,



MOTION OF A CILIUM on an organism moving toward the right involves a sweeping effective stroke (*left*) followed by a graceful recovery stroke (*right*). Cilia are quite short.



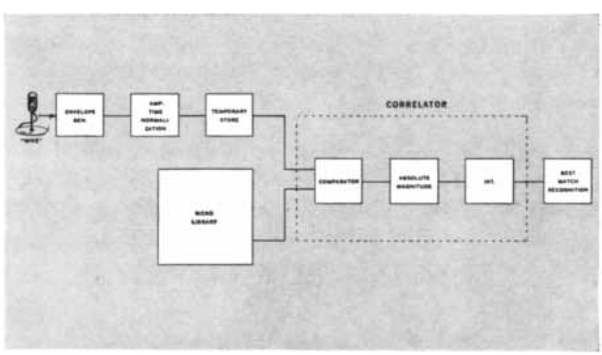
MOTION OF A FLAGELLUM propels the organism *Monas* to the right. Effective stroke is at left, recovery at right. Flagella are longer than cilia and can move in several ways.

BULOVA ANALOGUE TECHNIQUES APPLIED TO PATTERN RECOGNITION

Bulova's unusually creative team of electronic scientists and engineers play an ever increasing role in the state of the art advances in analogue techniques. Consider the nature and application of these Bulova techniques as they relate to spoken word recognition.

Advances in digital techniques used in pattern recognition have tended to obscure the prior art of analogue pattern recognition. Work with the analogue approach was successfully applied to the matching of maps and similar data as early as 1950. However, since that initial success, no major new application to these principles has developed.

At the present time, pattern recognition has taken on a much broader area of application than previously and is now applied to such things as automatic readers, spoken word recognition and photographic interpretation. Bulova Research & Development Laboratories is extending this analogue approach to these modern requirements; the first effort is being devoted to spoken word recognition.



Spoken word recognition can serve two functions: (1) it can be used for coding to conserve transmission bandwidth or (2) as automatic vocal control. Although both are concerned with analysis, the major difference between these applications is that only the bandwidth reduction problem involves synthesis.

One of the analogue approaches to word recognition assumes the use of a standard word library in the form of waveforms. The comparison of a wave form derived from a spoken word and the library word results in recognition. The concept, as shown in the diagram, utilizes waveform duration and amplitude normalization, a form of cross correlation and a criteria of best match. Experimental equipment, consisting basically of closed loop tape recorders and necessary electronic analogue computing equipment, has been set up for evaluation of this analogue technique. The first tests as performed on speech waveforms, compared envelopes. The comparison was based on obtaining the

absolute magnitude of the difference between the spoken word waveform and the library waveform. The minimum of the integral of this difference establishes the choice. In other words, the criteria is a best match based on

$$\int_0^t \left| f(t) - g(t+\tau) \right| dt$$

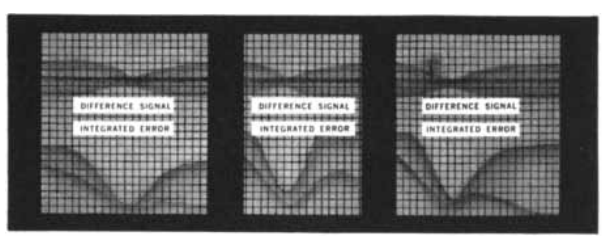
where f (t) represents the envelope of the spoken word
g (t) represents the envelope of the library word

As shown in the block diagram, the envelope is placed in temporary storage after amplitude and duration normalization. Repetition of the input envelope results in the generation, out of the correlator, of the series

$$\sum_i \int_0^t \left| f(t) - g_i(t+\tau_i) \right| dt$$

The value of i which produces the minimum term as j is varied indicates the best match and thus produces the word-identification.

Tests of this system have been performed in our laboratory with encouraging results. The attached figures are recordings of the correlator output as a function of correlation time for the two words "nine" and "five". Each pulse amplitude is proportional to the magnitude of the difference integral and it can be seen that a significantly better match is obtained for "nine" vs "five" as compared to "nine" vs "five".



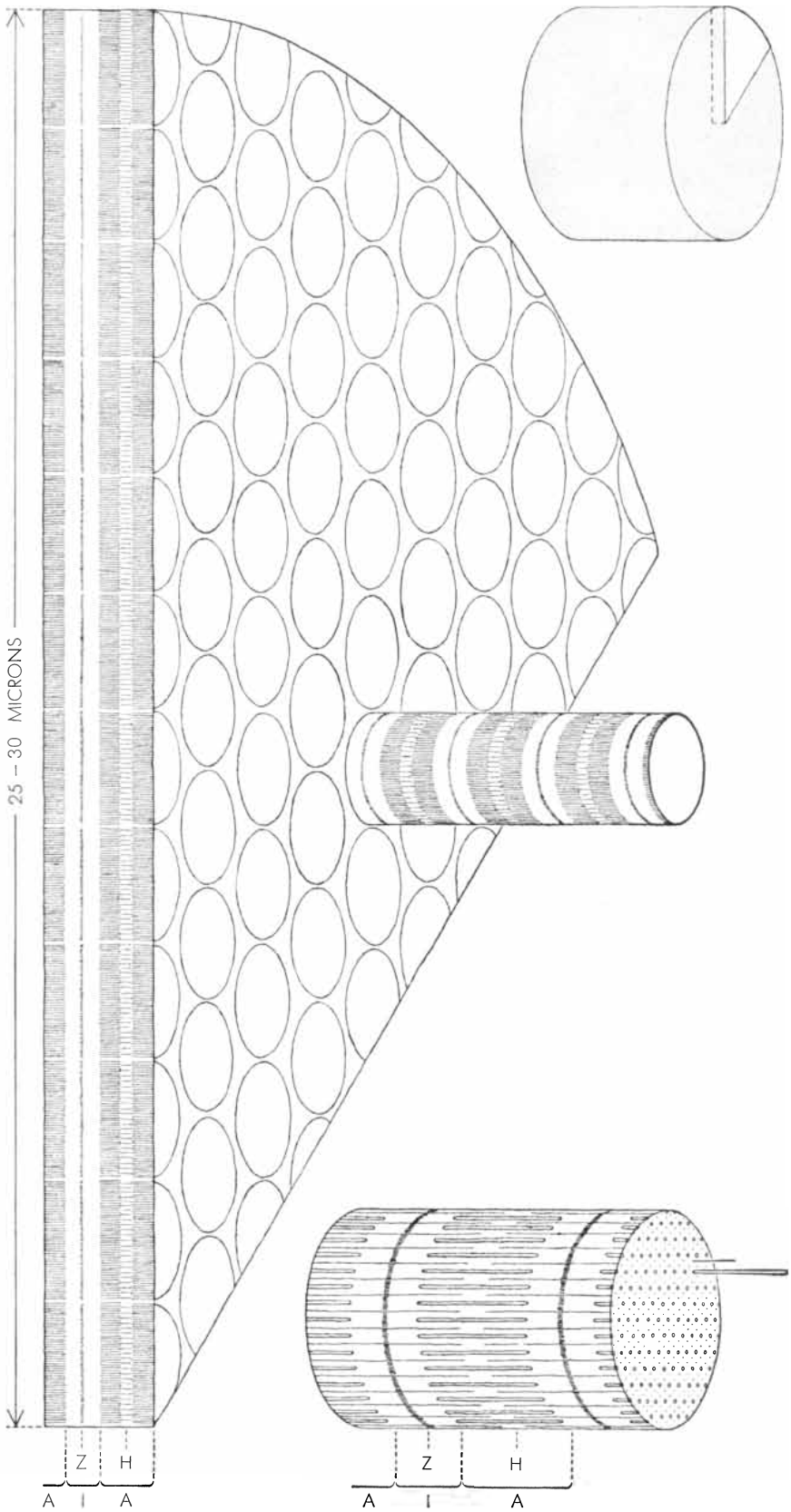
STANDARD "NINE" VS S. R. "NINE" 4-5-61

STANDARD "NINE" VS B. F. "FIVE" 4-5-61

STANDARD "NINE" VS B. F. "NINE" 4-5-61

The reliability of any speech recognition technique depends on the degree of independence of the identifying parameter on the information property of speech. It is the intent to apply the analogue matching technique to various envelope characteristics of speech to test the efficiency of this approach relative to this criterion. Envelopes can be developed which are proportional to amplitude, frequency, zero crossings and their derivatives. Experimental evaluation of these envelopes will lead to a simple, real-time, spoken word recognizer.

Bulova's developments in the fields of electronics and analogue techniques offer significant advances in the state of the art to meet the growing needs of both industry and the Military.



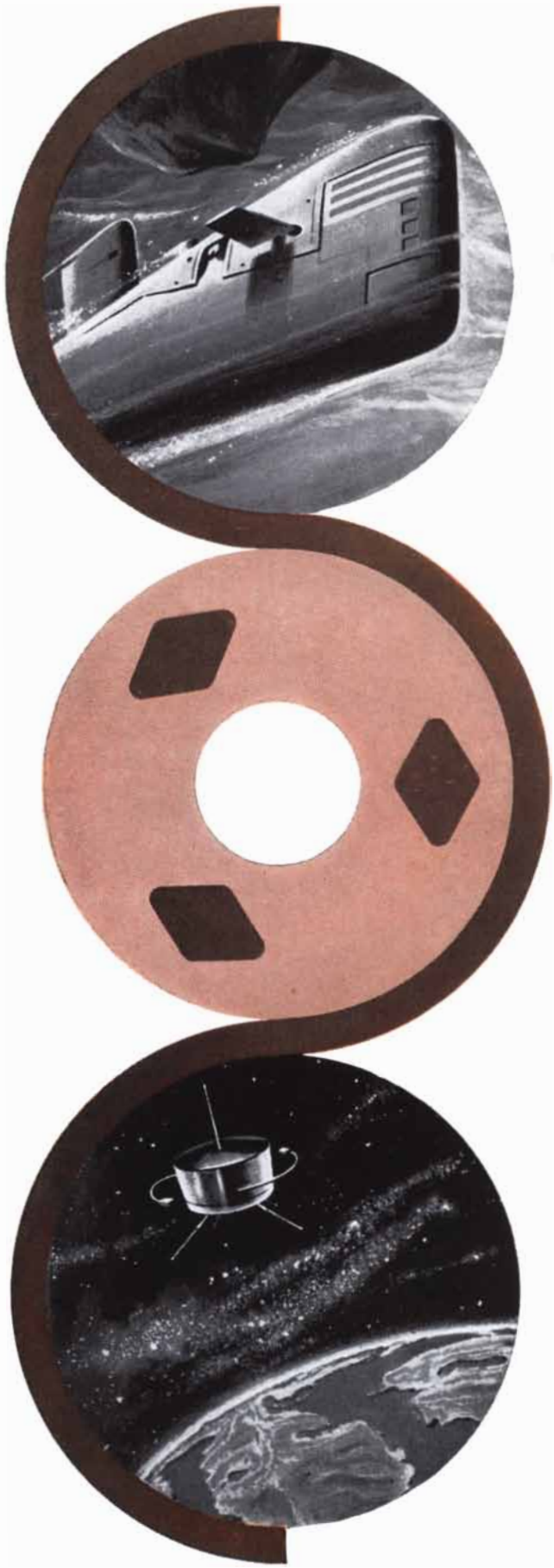
SECTION OF STRIATED-MUSCLE FIBER, highly schematic, shows how fiber is related to fibrils and to the filaments that cause the striations. The large, pie-shaped segment has been cut from a single fiber, as shown at top right. One such fiber is a long thread barely visible to the naked eye. The circles in the wedge are the numerous fibrils that pack a fiber. One of them projects. At bottom a single fibril is enlarged to show how interdigitating filaments make up the striations. One thick and one thin filament project from the fibril.

when muscle shortens, it gives off heat, and the amount of heat is directly proportional to the amount of shortening. Second, the tension that the active muscle can develop is at a maximum when the muscle reaches a certain length; if the muscle is stretched beyond that length, or allowed to contract to a shorter length, the tension decreases from the maximum. Finally, when the muscle is contracting, it is in an "active state" in which it strongly resists being stretched. When relaxed, the muscle is plastic and easily extensible.

From such observations it is plausible to infer that the muscle cell contains a group of contractile elements in a chemical relationship with its surrounding cell material, a picture that has been fully borne out in electron microscope studies. It is generally agreed today that the fibrils represent the contractile elements of the muscle cell.

In 1954 A. F. Huxley (no relation to the H. E. Huxley mentioned earlier) and his associates at the University of Cambridge reported the first of a series of observations of the muscle fibril during contraction, using beautifully simple and direct methods. They placed a tiny electrode against the surface of a muscle and stimulated it with carefully regulated shocks that caused only a limited local reaction, which they observed with an interference microscope. Motion pictures of the reaction showed conclusively that during contraction certain striated regions of the muscle (the so-called *I* and *A* regions) move together [*see illustration on page 190*].

From these and similar studies, therefore, the two Huxleys independently and simultaneously proposed that contraction takes place when the two sets of filaments, the fine and the thick, telescope into each other. They suggest that the force that makes the filaments slide past each other comes from an interaction between the thick and thin filaments—a sort of chemical, make-and-break ratchet capable of clawing one set of filaments past the other. The proposed mechanism seems quite compatible with many of the detailed facts obtained from physiological studies. In only a few muscles, however, does the electron microscope show two sets of interdigitating and geometrically perfect filaments; they have been found only in the rabbit, the frog and in the flight muscles of a few insects. No indication of such an organization appears, for example, in the best electron micrographs of smooth muscle of the viscera. Similarly, no filament structure is found in amoebae, and although



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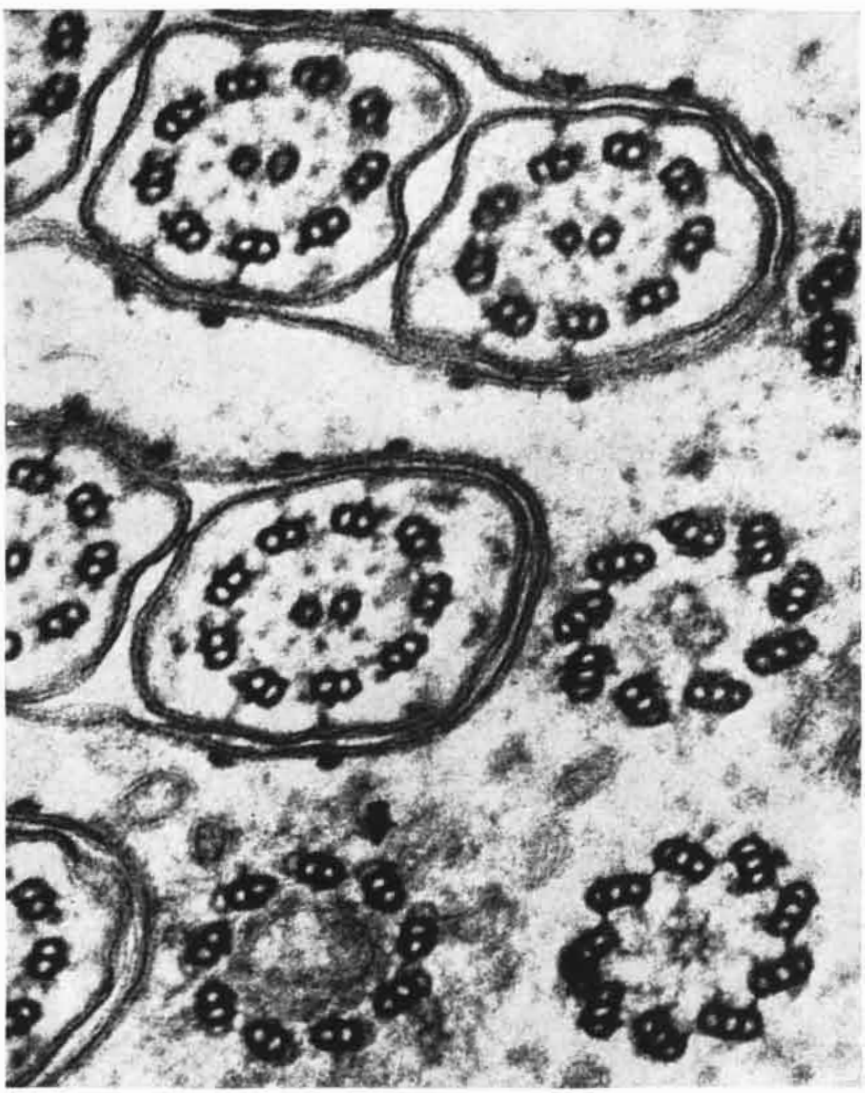
filaments are found in cilia, they are not arranged in an interdigitating manner.

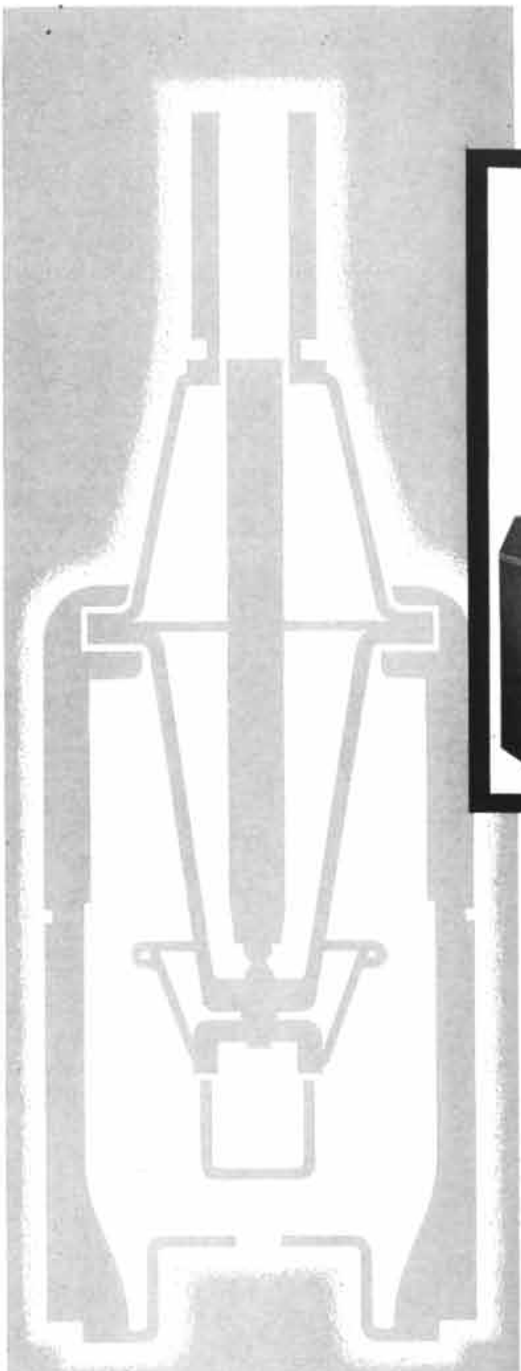
To mention the movement of amoebae and cilia in the same breath with muscle action may seem rather farfetched. Yet if we recall the various hypotheses that have been presented, we note that movement is ascribed either to contraction or to a sliding of one thing past another in all cases, so that perhaps it is not unreasonable to look for a common basis for all biological movement. To do this we must move from the structural level of the cell toward the molecular level.

A small boy, confronted by a ticking watch, is driven by curiosity to take it apart to see how it works; the physiologist has similarly tried to take apart the complex machine we know as the muscle cell. There are different degrees of taking things apart, however. We may take something apart a little or take it apart completely, and perhaps attempt to put the completely dissociated structure back together again, even if only partly. Physiologists refer to partly or wholly disintegrated muscle as a simplified system, and the study of such systems has been extremely fruitful.

The original simplified system is the one devised around 1949 by Albert Szent-Györgyi (now at the Institute for Muscle Research in Woods Hole, Mass.), who worked with the same rabbit muscle later studied by the Huxleys. He tied a freshly dissected muscle cell to a frame at its natural length and then



"9 + 2" ARRANGEMENT of filaments in flagella is clear in this electron micrograph by I. R. Gibbons of Harvard University and A. V. Grimstone of the University of Cambridge. Sections with membranes around them are flagella of the organism *Pseudotrichonympha*; other sections are the bases of flagella. Each of the filaments in the outer ring is double.



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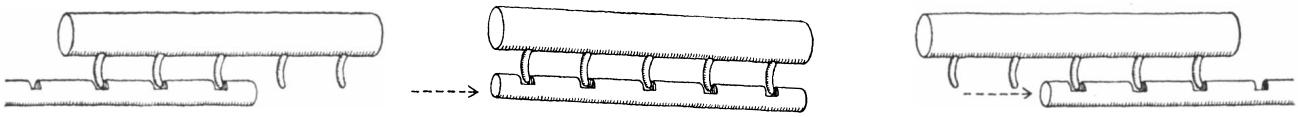
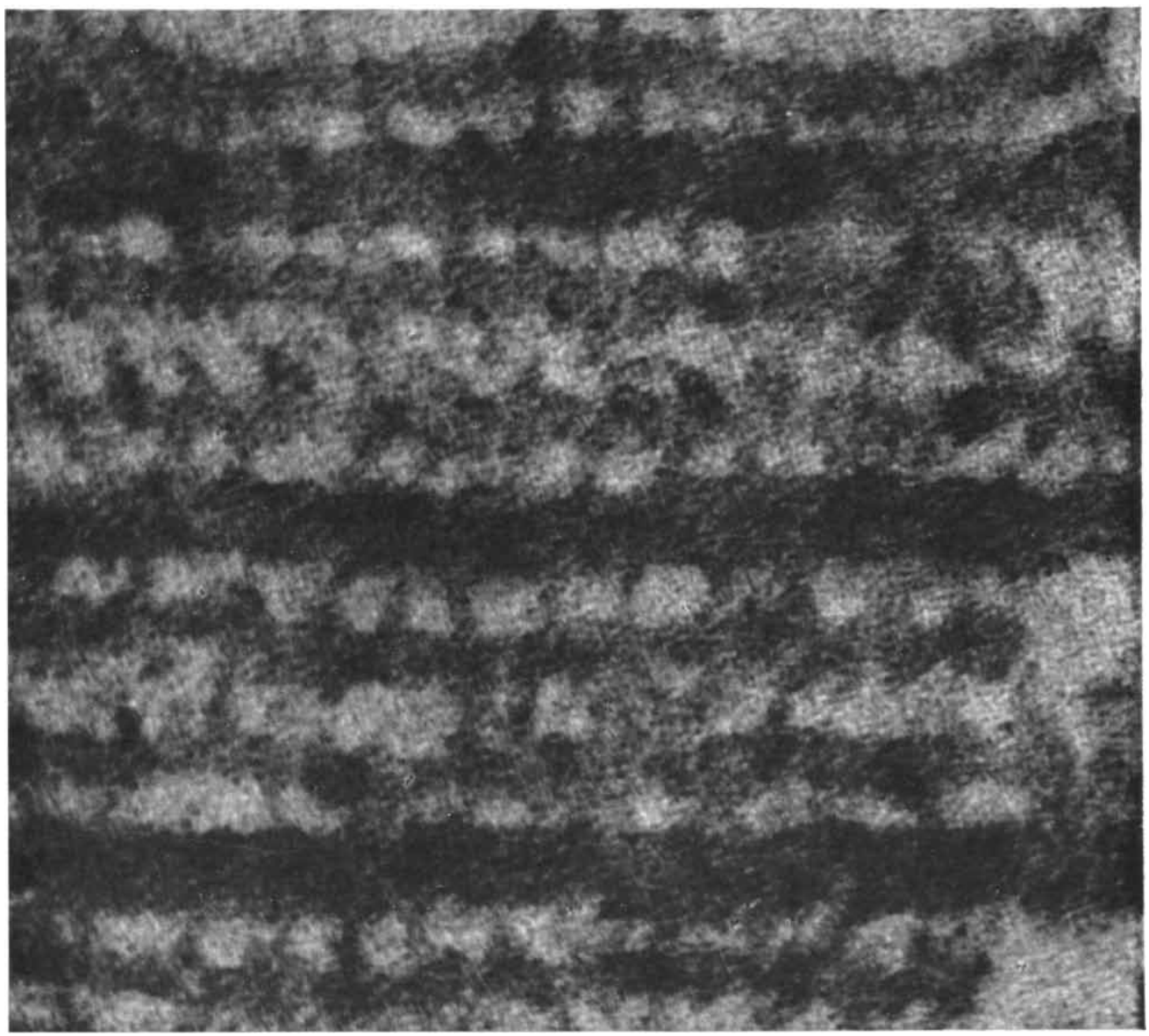


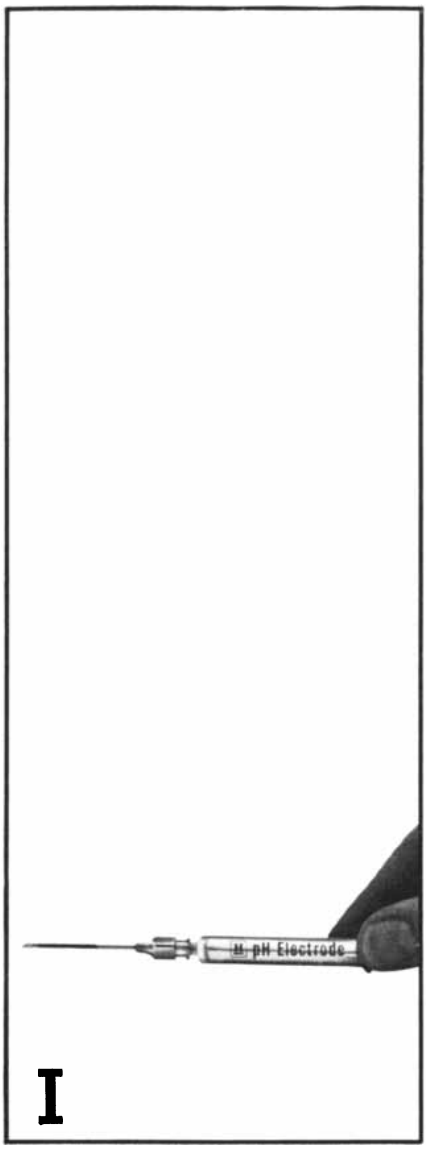
POSSIBLE RATCHET ACTION in striated muscle is diagramed. Thick and thin filaments of relaxed muscle are at left. As muscle contracts it reaches maximum tension (*center*); further contraction lowers tension because fewer ratchets are engaged (*right*).

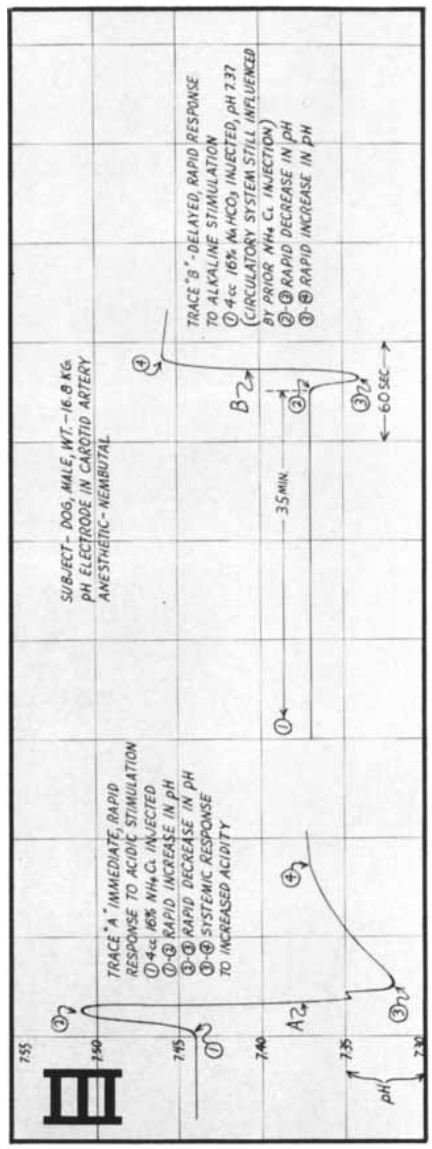
soaked it in a cold solution of glycerine overnight. The muscle cell is killed by this treatment, and many of its components are leached out. Its structural integrity remains, however, and it can be preserved in a freezer for months if kept in the glycerine solution. If this unmistakably dead muscle cell is warmed to room temperature in a dilute salt solution and exposed to the action of adenosine triphosphate (ATP), a remarkable thing happens: the dead cell contracts. ATP, of course, is the substance that provides the energy for many cellular functions [see "How Cells Transform Energy," page 62].

If muscle cells are primed to move by ATP, why not other cells that are capable of motion? This thought occurred to H. Hoffmann-Berling at the Max Planck Institute for Medical Research in Heidelberg. He glycerinated sperm cells and young connective-tissue cells (fibroblasts), which exhibit a form of amoeboid movement. When ATP was applied to these dead cells, each moved in its characteristic fashion: the fibroblast cells



CROSS BRIDGES connect thick and thin filaments of striated rabbit muscle, as seen in this electron micrograph by H. E. Huxley. This is part of the *A* band, enlarged some 900,000 diameters. The bridges may be the ratchets in a system that moves filaments.





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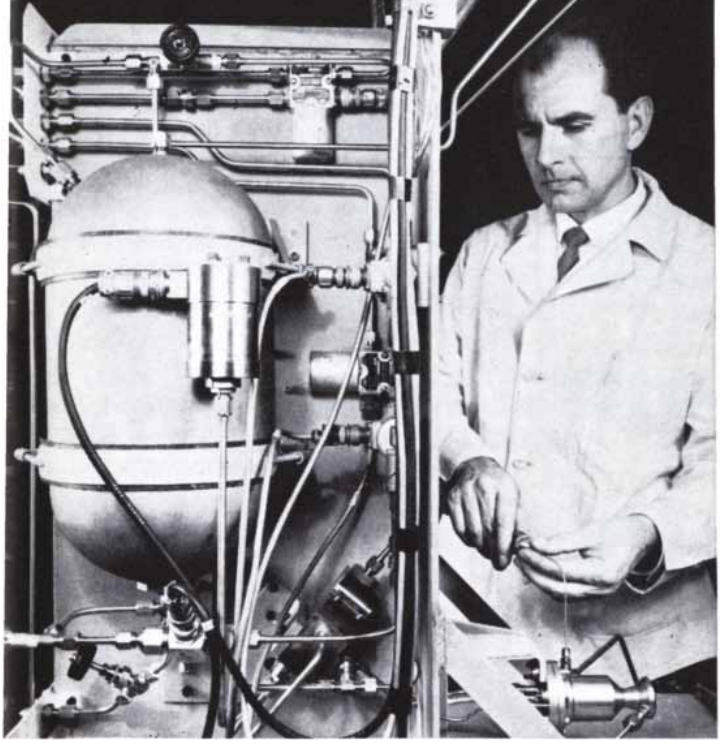
pH study courtesy T. W. Nielsen, Ph.D., Department of Physiology, University of Colorado Medical School

contracted and the sperm tails lashed vigorously. Similar studies have since been made on a variety of cilia and flagella, cancer cells and tissue-culture cells; many are activated by ATP. These dramatic results furnish a strong argument for the idea that cell movement in general has a common molecular basis.

When the muscle cell is taken apart completely, two important and interesting proteins are found: actin and myosin. These two substances make up the bulk of the structural material of the muscle cell. In the test tube they combine to form actomyosin, and they were originally studied in this form. In 1939 V. A. Engelhardt and M. N. Ljubimova of the Institute of Biochemistry of the Academy of Sciences in Moscow found that actomyosin is an enzyme capable of releasing the chemical energy of ATP. Soon afterward Szent-Györgyi reported that a reconstituted gel of actomyosin will contract suddenly when ATP is applied. It has since been shown by H. H. Weber at the Max Planck Institute for Medical Research and in our laboratory at Columbia University that artificial fibers formed of actomyosin can contract, perform work and develop tension with much the same characteristics as living muscle. The conclusion seems inescapable that actin and myosin form the molecular basis of muscle contraction.

Elaborating on this view, H. E. Huxley has adduced evidence to show that the myosin is located in the thick filaments of the fibril, whereas actin seems to be localized in the thin filaments. He visualizes that the interaction of these proteins in the two different filaments provides the ratchet mechanism for pulling the filaments past each other.

If there is a common molecular mechanism for cell movement, then contractile proteins similar to actomyosin should be present in other types of cell. The confirmation of this reasoning has not been easy; whereas muscle cells are specialized for movement and therefore contain large amounts of actomyosin, movement is just one of many functions carried out by the amoeba and the slime mold, and they would not be expected to contain much contractile protein. In 1952, however, Ariel G. Loewy, then at the University of Pennsylvania, succeeded in isolating from slime mold a contractile protein that has properties strikingly similar to those of actomyosin. Thus it would seem that the motive force for protoplasmic streaming is provided by the action of contractile protein. In support of this view, Kamiya's group has



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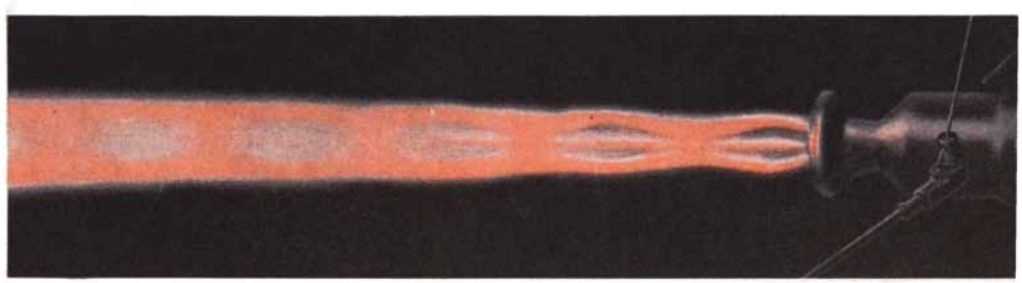
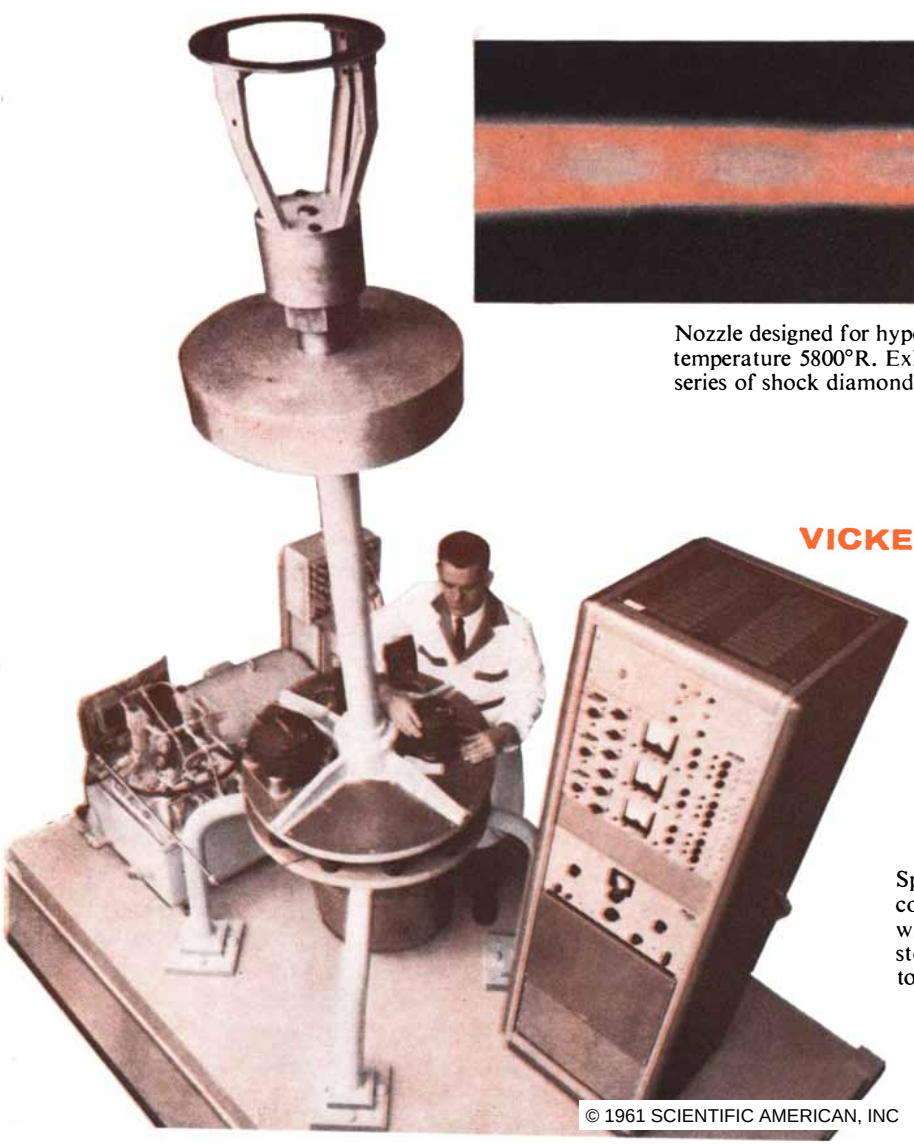


Nozzle designed for hypergolic bipropellant shown under test, flame temperature 5800°R. Exhaust flame is characterized by well defined series of shock diamonds.



Space vehicle simulator used in development of attitude control systems weighs 2 tons, yet can be set in motion with a finger touch. Entire unit is supported on a 3-inch steel ball that floats on a hydrostatic bearing and is free to move in three planes: pitch, yaw and roll.

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shown that ATP extracted from *Plasmodium* will react with rabbit actomyosin fully as well as with the ATP obtained from rabbit muscle.

What of ciliary or flagellar movement? In 1958 Engelhardt and a co-worker reported finding an actomyosin-like protein in sperm cells, which they have named spermosin. So far this is the only isolation of a contractile protein associated with flagellar movement. It has been shown, however, that flagella broken off from various types of cell contain enzymes capable of releasing the energy of ATP, and Leonard Nelson of Emory University has ingeniously combined chemistry and electron microscopy to show that the splitting of ATP is restricted to the outer nine filaments of the 9 + 2 arrangement.

We see, therefore, that the intensive study of simplified systems leads us to two general and important conclusions. The first of these is that the basis of muscle movement is a combined protein called actomyosin, which is capable of producing a contraction when provided with energy by ATP. The second is that this concept of a molecular basis for contraction can be extended to other types of cellular movement.

It may be recalled that the hypotheses advanced to account for the various types of movement inside cells involve either a contraction or a sliding of one substance past another. We can now appreciate that the difference between these alternatives may be more apparent than real, and that contraction may involve a sliding. For those cells which do not possess oriented filamentous structures, the sliding-contraction may be of molecular dimensions. Such an idea is, of course, highly speculative, but the widespread attention being given to the actin and myosin molecules may demonstrate the reality of the sliding-contraction mechanism or may lead to a totally new concept.

There are always hazards in assuming that substances observed to behave in a certain way in a test tube behave the same way inside a living cell. And sometimes paradoxes arise. To illustrate, a number of investigators have posed the following question: If actomyosin is the machinery of contraction and ATP the fuel for this contraction, the contracting muscle should show a depletion of ATP; is this true?

To answer the question it is possible to carry out an experiment with identical muscles, one from each hind leg of a frog. One muscle serves as a control; the

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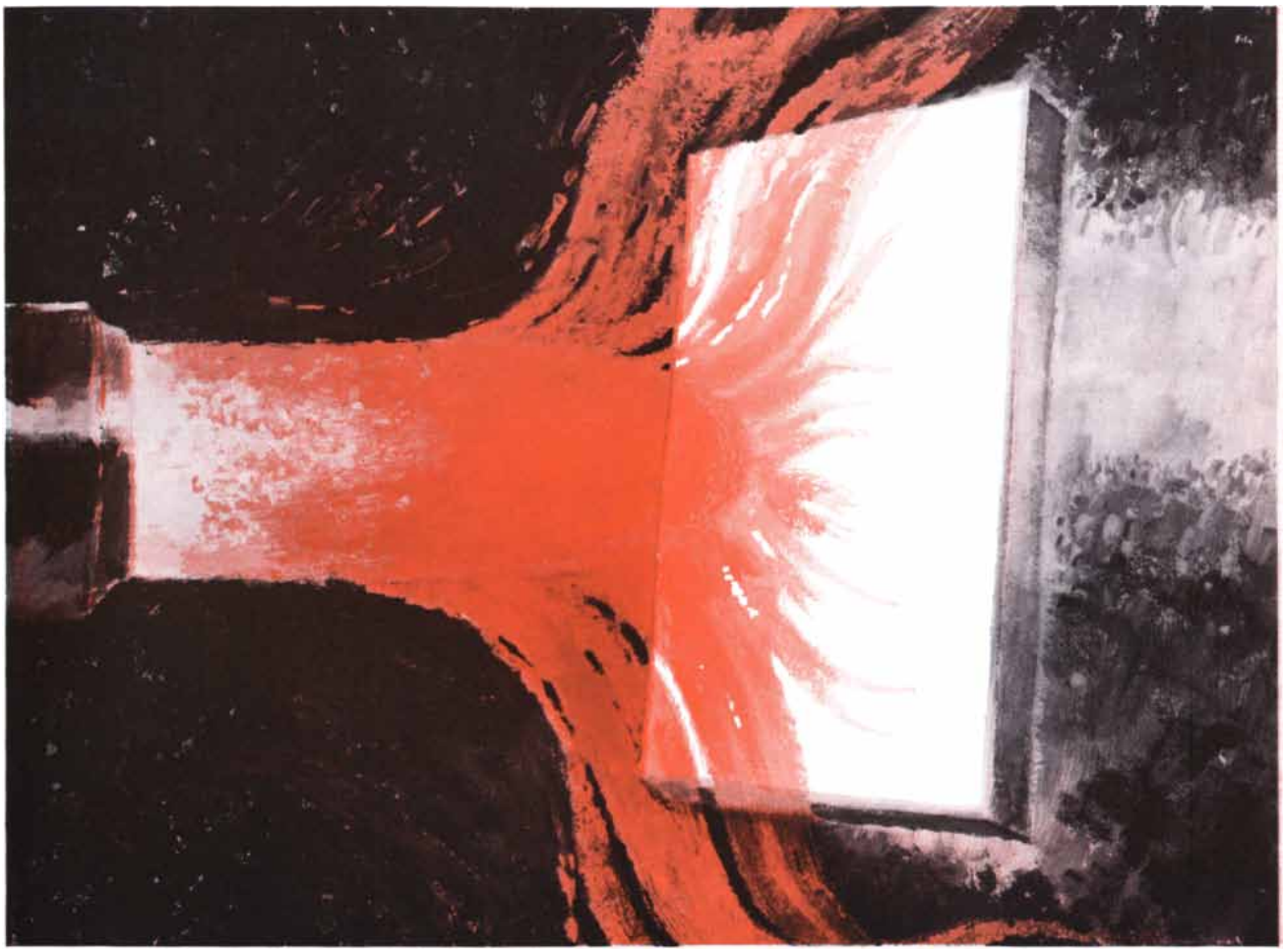

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other is stimulated to contract. Both are then frozen quickly and analyzed for their chemical content; the technique has been refined so that the chemical change caused by a single twitch of the muscle can be detected. The results are discomforting because they show that very little ATP disappears, certainly not enough to account for the energy exhibited by the muscle. However, another energy-rich biochemical compound—creatine phosphate—does disappear.

The facts seem irreconcilable. Actomyosin contracts with ATP and not with creatine phosphate. On the other hand, it is the creatine phosphate that disappears in active muscle and, as Francis D. Carlson of Johns Hopkins University has recently shown, it disappears in amounts that are directly proportional to the number of contractions the muscle performs.

Yet all may not be lost. Carlson has drawn up a plausible scheme to reconcile these facts. Briefly, he proposes that the energy from creatine phosphate is funneled through a "compartmentalized" ATP, which in turn feeds the energy into the actomyosin. This ATP, then, works like the middle man in a bucket brigade, receiving a bucket of energy from creatine phosphate, passing it to the muscle and immediately obtaining another load of energy. The energy-laden ATP does not get used up because it is constantly re-formed.

It turns out, indeed, that a candidate for the role of compartmentalized ATP can be found in muscle. The candidate is the relatively little-studied protein actin, each molecule of which has an ATP molecule bound to it. A number of investigators are now looking into the matter and we may learn before long whether or not actin meets the requirements of Carlson's hypothesis.

Assuming that the story runs smoothly to its denouement and we are finally able to describe in detail how actin, myosin and ATP produce contractile movements in cells, is this the end of the problem? It would be pleasant to think so. But scientific problems have a way of eluding solution. There is a sense in which "the more we find out, the less we know," which is merely to say that the resolution of one problem usually opens up a number of others. Once we understand biological movement on the molecular level we may wish we could understand it on the submolecular, or atomic, level. Such is the charm and fascination of scientific inquiry.

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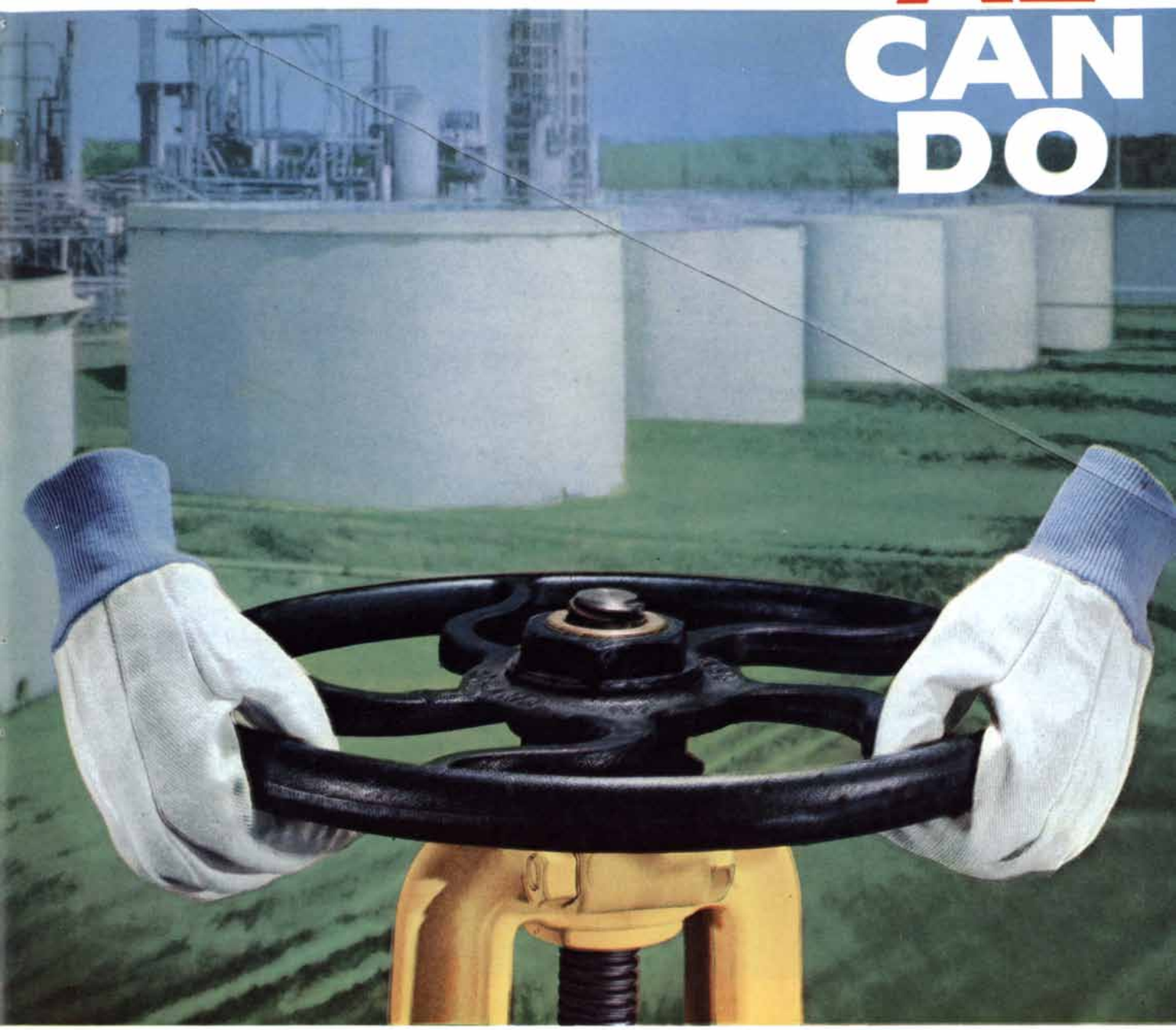

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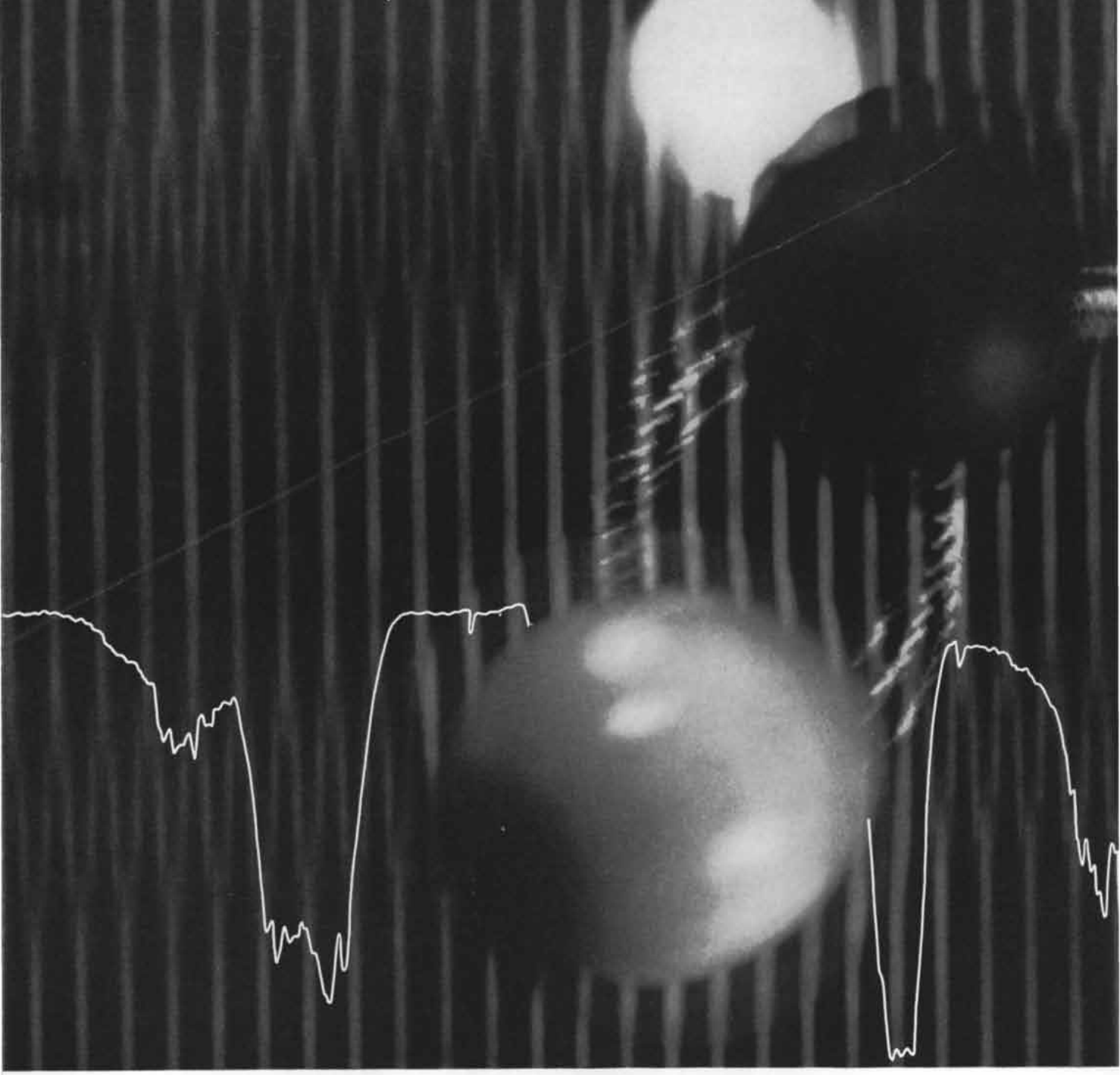

SHAKING A MOLECULE TO SHOW ITS STRUCTURE

A molecule acts very much like a collection of weights held together by springs. Each part vibrates at frequencies peculiar to it alone. When excited by infrared at one of these natural frequencies, the molecule absorbs energy and oscillates more strongly. As the molecule undergoes stretching, bending and deforming vibrations, individual atoms, groups and bond structures are revealed. The pattern of vibration recorded by an infrared spectrophotometer is as distinctive as a fingerprint.

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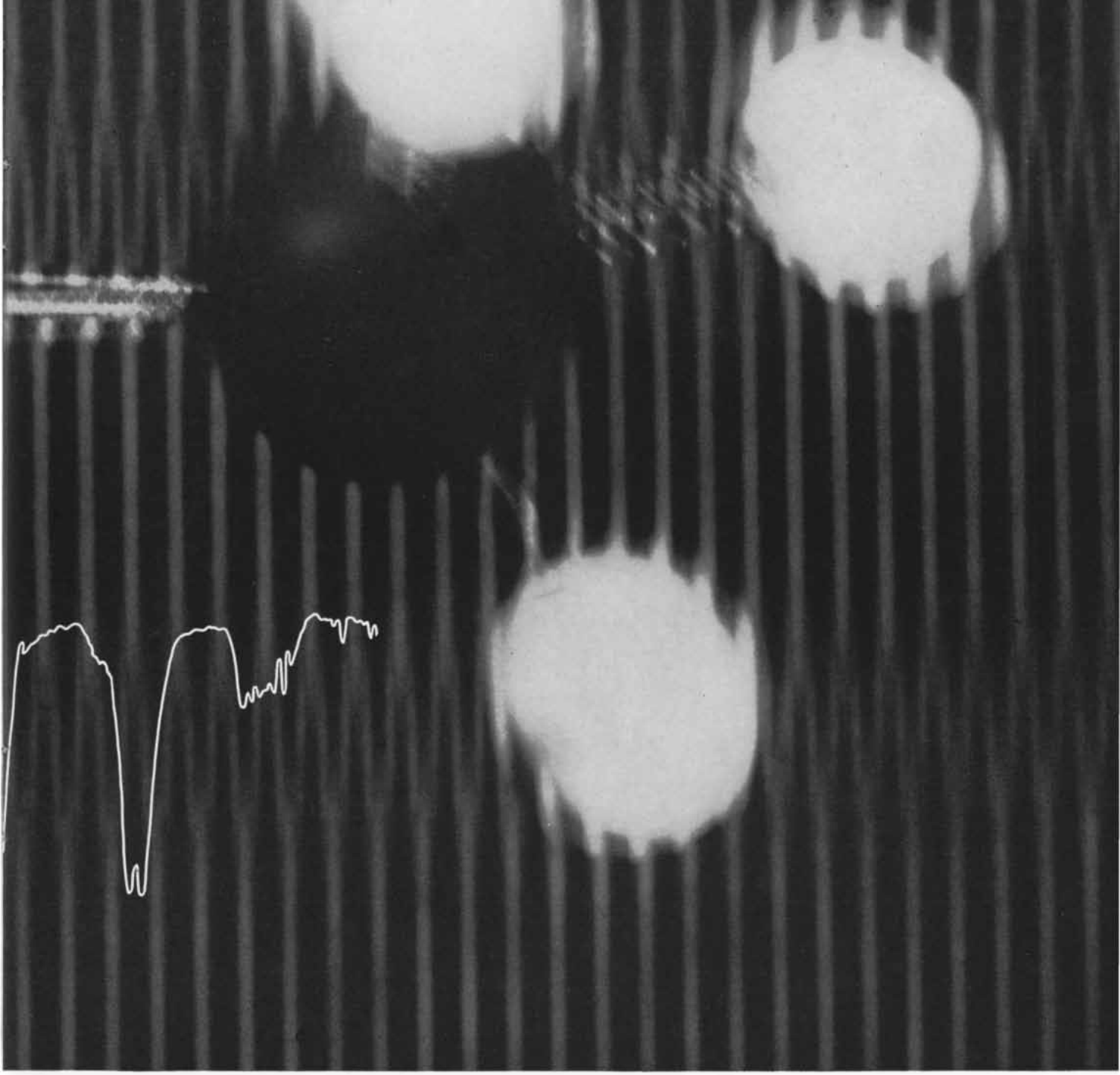
In the spectrum of the acetaldehyde molecule shown above, the structure of the chemical is clearly displayed. For example, the deepest dip in the curve unmistakably identifies the double



bond of the carbonyl group. The record was made with a Perkin-Elmer Infrared Spectrophotometer. This instrument has become an indispensible quantitative and qualitative tool of chemists, scientists and engineers. It is used to analyze molecular structures, check quality, identify substances in a wide range of industries including chemical, petrochemical, plastics, food, pharmaceutical, cosmetics.

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How Cells Communicate

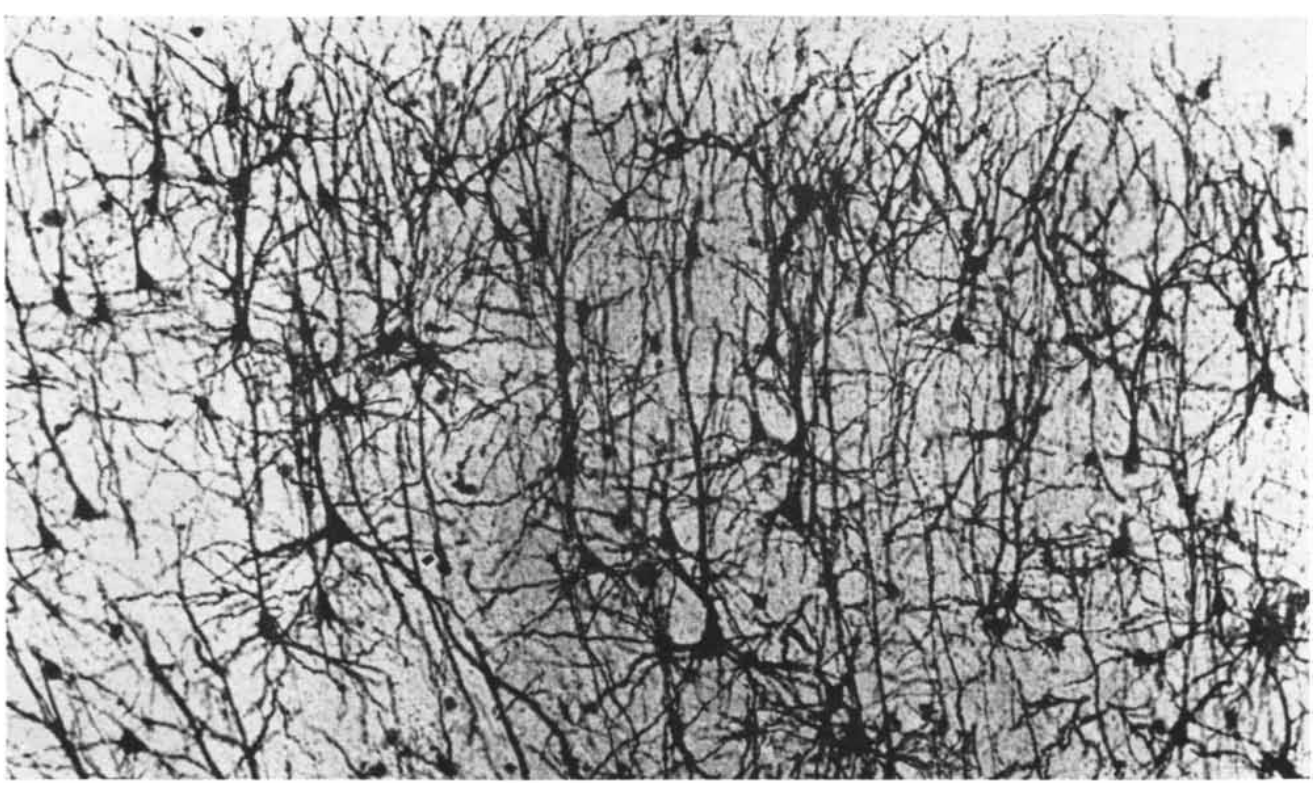
The activities of cells in multicellular animals are co-ordinated by "chemical messengers" and nerve cells. During the past few years the character of the nerve impulse has been considerably clarified

by Bernhard Katz

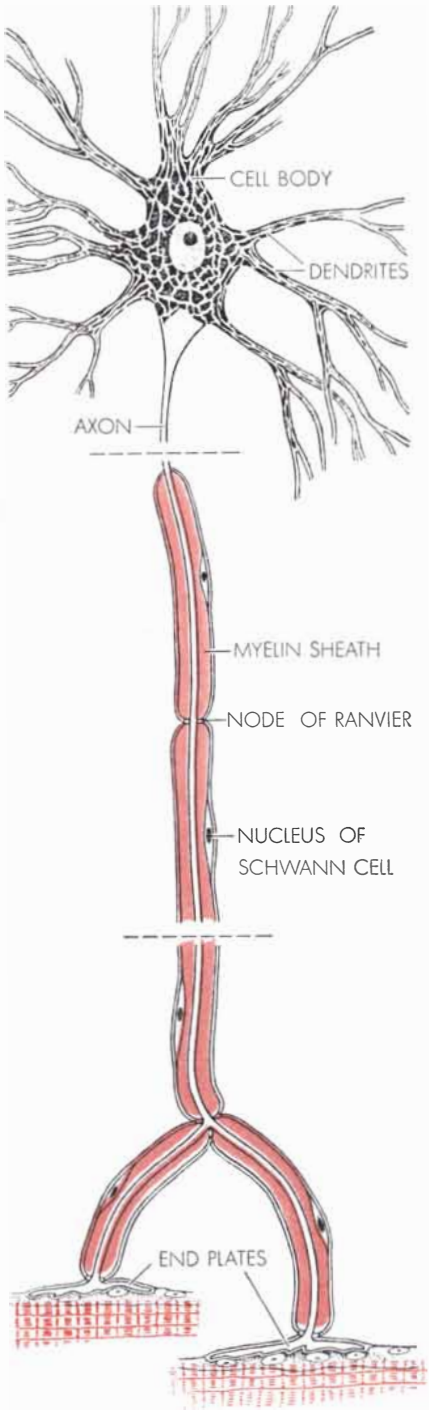
In the animal kingdom, the "higher" the organism, the more important becomes the system of cells set aside for co-ordinating its activities. Nature has developed two distinct co-ordinating mechanisms. One depends on the release and circulation of "chemical messengers," the hormones that are manufactured by certain specialized cells and that are capable of regulating the activity of cells in other parts of the body. The second mechanism, which is in general far superior in speed and selectivity, depends on a specialized system of nerve cells, or neurons, whose function is to receive and to give instructions by means of electrical impulses directed over specific pathways. Both co-ordinating mechanisms are ancient from the viewpoint of evolution, but it is the second—the nervous system—that has lent itself to the greater evolutionary development, culminating in that wonderful and mysterious structure, the human brain.

Man's understanding of the working of his millions of brain cells is still at a primitive stage. But our knowledge is reasonably adequate to a more restricted task, which is to describe and partially explain how individual cells—the neurons—generate and transmit the electrical impulses that form the basic code element of our internal communication system.

A large fraction of the neuronal cell population can be divided into two classes: sensory and motor. The sensory neurons collect and relay to higher centers in the nervous system the impulses that arise at special receptor sites [see "How Cells Receive Stimuli," page 222],



CEREBRAL CORTEX is densely packed with the bodies of nerve cells and the fibers called dendrites that branch from the cell body. This section through the sensory-motor cortex of a cat is enlarged some 150 diameters. Only about 1.5 per cent of the cells and dendrites actually present are stained and show here. The nerve axons, the fibers that carry impulses away from the cell body, are not usually shown at all by this staining method. The photomicrograph was made by the late D. A. Scholl of University College London.



MOTOR NEURON is the nerve cell that carries electrical impulses to activate muscle fibers. The cell body (*top*) fans out into a number of twigs, the dendrites, which make synaptic contact with other nerve fibers (*see top illustration on opposite page*). Nerve impulses arising at the cell body travel through the axon to the motor-plate endings, which are embedded in muscle fibers. Myelin sheath is formed by Schwann cells as shown at bottom of opposite page. By insulating the axon the myelin wrapping increases the speed of signal transmission.

whose function is to monitor the organism's external and internal environments. The motor neurons carry impulses from the higher centers to the "working" cells, usually muscle cells, which provide the organism's response to changes in the two environments. In simple reflex reactions the transfer of signals from sensory to motor neurons is automatic and involves relatively simple synaptic mechanisms, which are fairly well understood.

When a nerve cell, either motor or sensory, begins to differentiate in the embryo, the cell body sends out a long fiber—the axon—which in some unknown way grows toward its proper peripheral station to make contact with muscle or skin. In man the adult axon may be several feet long, although it is less than .001 inch thick. It forms a kind of miniature cable for conducting messages between the periphery and the central terminus, which lies protected together with the nerve-cell body inside the spinal canal or the skull. Isolated peripheral nerve fibers probably have been subjected to more intense experimental study than any other tissue, in spite of the fact that they are only fragments of cells severed from their central nuclei as well as their terminal connections. Even so, isolated axons are capable of conducting tens of thousands of impulses before they fail to work. This fact and other observations make it clear that the nucleated body of the nerve cell is concerned with long-term maintenance of the nerve fibers—with growth and repair rather than with the immediate signaling mechanism.

For years there was controversy as to whether or not our fundamental concept of the existence of individual cell units could be applied at all to the nervous system and to its functional connections. Some investigators believed that the developing nerve cell literally grows into the cytoplasm of all cells with which it establishes a functional relationship. The matter could not be settled convincingly until the advent of high-resolution electron microscopy. It turns out that most of the surface of a nerve cell, including all its extensions, is indeed closely invested and enveloped with other cells, but that the cytoplasm of adjacent cells remains separated by distinct membranes. Moreover, there is a small extracellular gap, usually of 100 to 200 angstrom units, between adjoining cell membranes.

A fraction of these cell contacts are functional synapses: the points at which signals are transferred from one cell to the next link in the chain. But synapses are found only at and near the cell body of the neuron or at the terminals of the axon. Most of the investing cells, particularly those clinging to the axon, are not nerve cells at all. Their function is still a puzzle. Some of these satellite cells are called Schwann cells, others glia cells; they do not appear to take any part in the immediate process of impulse transmission except perhaps indirectly to modify the pathway of electric current flow around the axon. It is significant, for example, that very few scattered satellites are to be found on the exposed cell surfaces of muscle fibers, which closely resemble nerve fibers in their ability to conduct electrical impulses from one end to the other.

One of the known functions of the axon satellites is the formation of the so-called myelin sheath, a segmented insulating jacket that improves the signaling efficiency of peripheral nerve fibers in vertebrate animals. Thanks to the electron microscope studies of Betty Ben Geren-Uzman and Francis O. Schmitt of the Massachusetts Institute of Technology, we now know that each myelin segment is produced by a nucleated Schwann cell that winds its cytoplasm tightly around the surface of the axon, forming a spiral envelope of many turns [*see bottom illustration on opposite page*]. The segments are separated by gaps—the nodes of Ranvier—which mark the points along the axon where the electrical signal is regenerated.

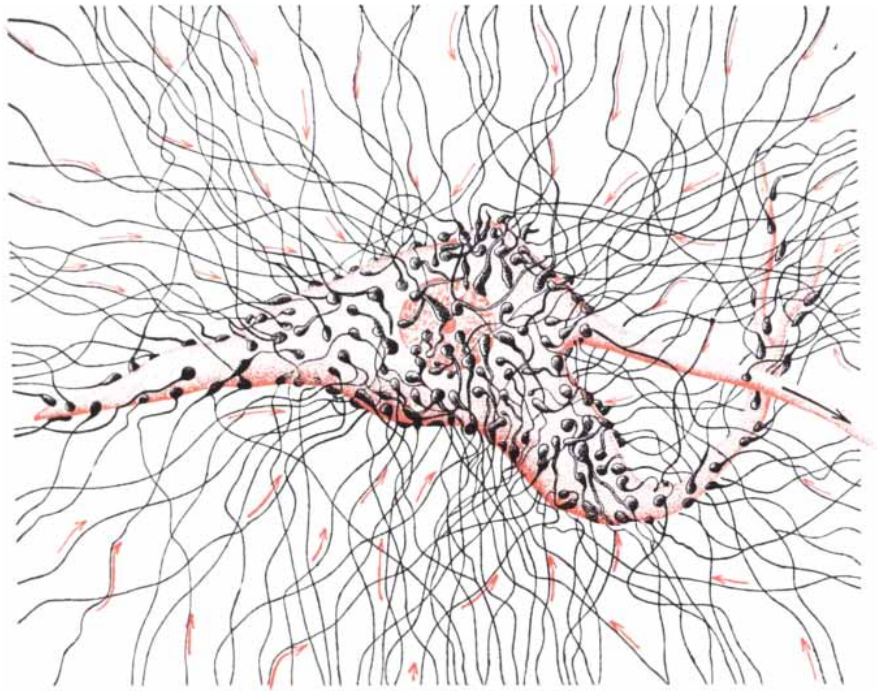
There are other types of nerve fiber that do not have a myelin sheath, but even these are covered by simple layers of Schwann cells. Perhaps because the axon extends so far from the nucleus of the nerve cell it requires close association with nucleated satellite cells all along its length. Muscle fibers, unlike the isolated axons, are self-contained cells with nuclei distributed along their cytoplasm, which may explain why these fibers can manage to exist without an investing layer of satellite cells. Whatever the function of the satellites, they cannot maintain the life of an axon for long once it has been severed from the main cell body; after a number of days the peripheral segment of the nerve cell disintegrates. How the nerve cell nucleus acts as a lifelong center of repair and brings its influence to bear on the distant parts of the axon—which in terms of ordinary diffusion would be years away—remains a mystery.

The experimental methods of physiology have been much more successful in dealing with the immediate processes of nerve communication than with the

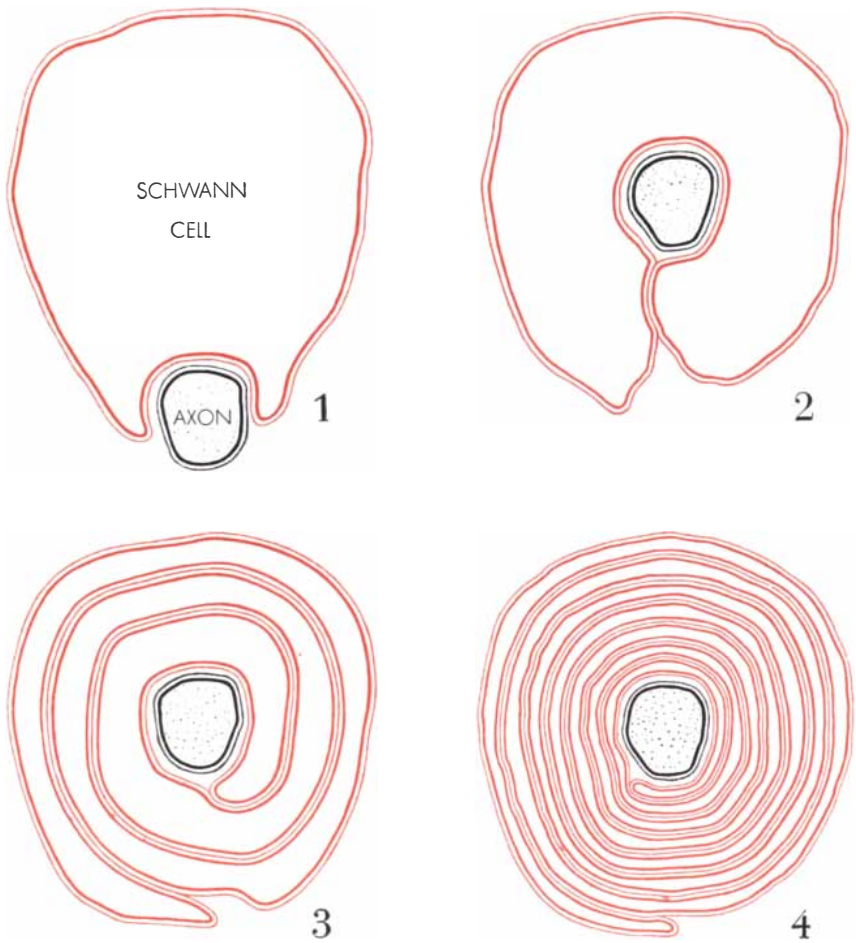
equally important but much more intractable long-term events. We know very little about the chemical interactions between nerve and satellite, or about the forces that guide and attract growing nerves along specific pathways and that induce the formation of synaptic contacts with other cells. Nor do we know how cells store information and provide us with memory. The rest of this article will therefore be concerned almost solely with nerve signals and the method by which they pass across the narrow synaptic gaps separating one nerve cell from another.

Much of our knowledge of the nerve cell has been obtained from the giant axon of the squid, which is nearly a millimeter in diameter. It is fairly easy to probe this useful fiber with microelectrodes and to follow the movement of radioactively labeled substances into it and out of it. The axon membrane separates two aqueous solutions that are almost equally electroconductive and that contain approximately the same number of electrically charged particles, or ions. But the chemical composition of the two solutions is quite different. In the external solution more than 90 per cent of the charged particles are sodium ions (positively charged) and chloride ions (negatively charged). Inside the cell these ions together account for less than 10 per cent of the solutes; there the principal positive ion is potassium and the negative ions are a variety of organic particles (doubtless synthesized within the cell itself) that are too large to diffuse easily through the axon membrane. Therefore the concentration of sodium is about 10 times higher *outside* the axon, and the concentration of potassium is about 30 times higher *inside* the axon. Although the permeability of the membrane to ions is low, it is not indiscriminate; potassium and chloride ions can move through the membrane much more easily than sodium and the large organic ions can. This gives rise to a voltage drop of some 60 to 90 millivolts across the membrane, with the inside of the cell being negative with respect to the outside.

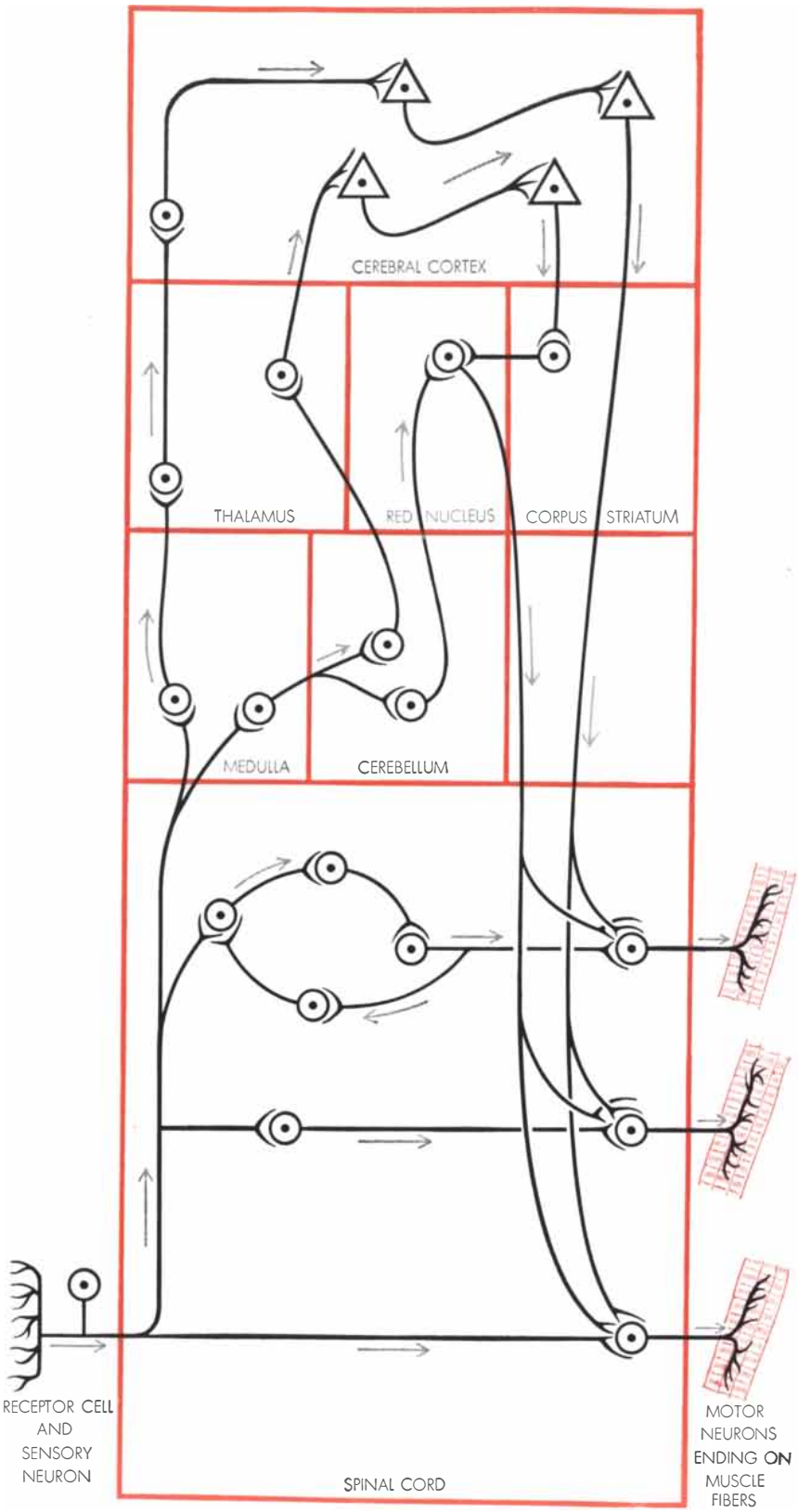
To maintain these differences in ion concentration the nerve cell contains a kind of pump that forces sodium ions "uphill" and outward through the cell membrane as fast as they leak into the cell in the direction of the electrochemical gradient [*see illustration on page 216*]. The permeability of the resting cell surface to sodium is normally so low that the rate of leakage remains very small, and the work required of the



MOTOR-NEURON CELL BODY and its dendritic extensions are richly covered with synaptic knobs, which grow at the endings of other nerve fibers. Normally many such fibers must carry impulses to the knobs before the motor neuron will generate signals of its own.



MYELIN SHEATH is created when a Schwann cell wraps itself around the nerve axon. After the enfolding is complete, the cytoplasm of the Schwann cell is expelled and the cell's folded membranes fuse into a tough, compact wrapping. Diagrams are based on studies of chick-embryo neurons by Betty Ben Geren-Uzman of Children's Medical Center in Boston.



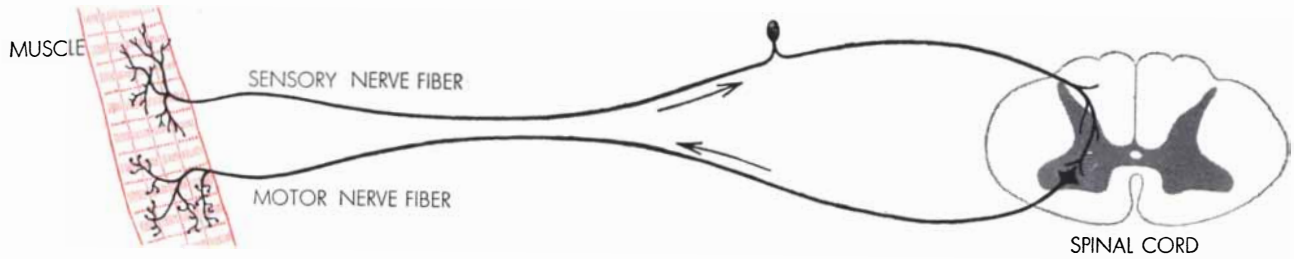
SIMPLIFIED FLOW DIAGRAM OF NERVOUS SYSTEM barely hints at the many possible pathways open to an impulse entering the spinal cord from a receptor cell and its sensory fiber. Rarely does the incoming signal directly activate a motor neuron leading to a muscle fiber. Typically it travels upward through the spinal cord and through several relay centers before arriving at the cerebral cortex. There (if not elsewhere) a "command" may be given (or withheld) that sends nerve impulses back down the spinal cord to fire a motor neuron.

pumping process amounts to only a fraction of the energy that is continuously being made available by the metabolism of the cell. We do not know in detail how this pump works, but it appears to trade sodium and potassium ions; that is, for each sodium ion ejected through the membrane it accepts one potassium ion. Once transported inside the axon the potassium ions move about as freely as the ions in any simple salt solution. When the cell is resting, they tend to leak "downhill" and outward through the membrane, but at a slow rate.

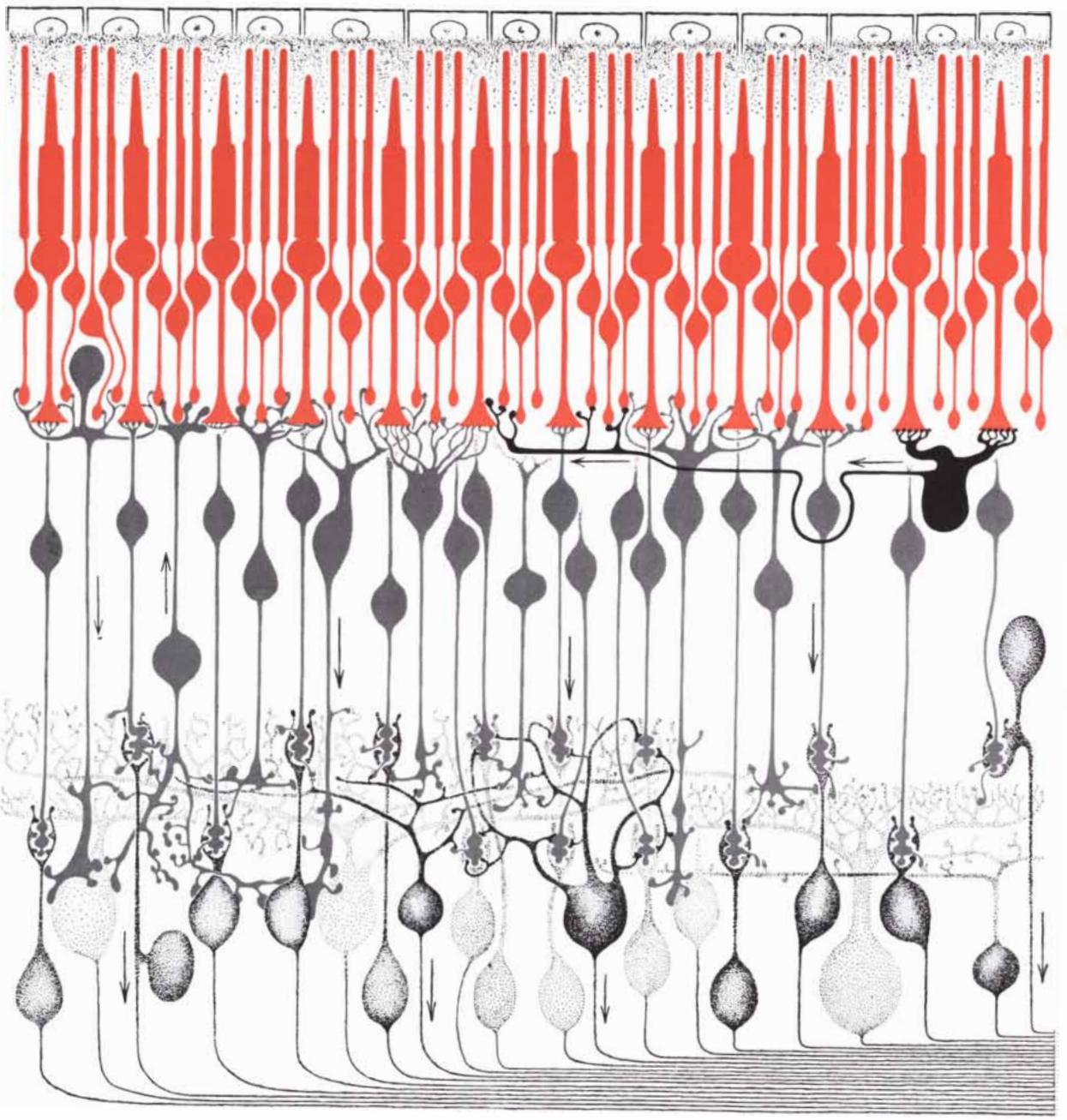
The axon membrane resembles the membrane of other cells. It is about 50 to 100 angstroms thick and incorporates a thin layer of fatty insulating material. Its specific resistance to the passage of an electric current is at least 10 million times greater than that of the salt solutions bathing it on each side. On the other hand, the axon would be quite worthless if it were employed simply as the equivalent of an electric cable. The electrical resistance of the axon's fluid core is about 100 million times greater than that of copper wire, and the axon membrane is about a million times leakier to electric current than the sheath of a good cable. If an electric pulse too weak to trigger a nerve impulse is fed into an axon, the pulse fades out and becomes badly blunted after traveling only a few millimeters.

How, then, can the axon transmit a nerve impulse for several feet without decrement and without distortion?

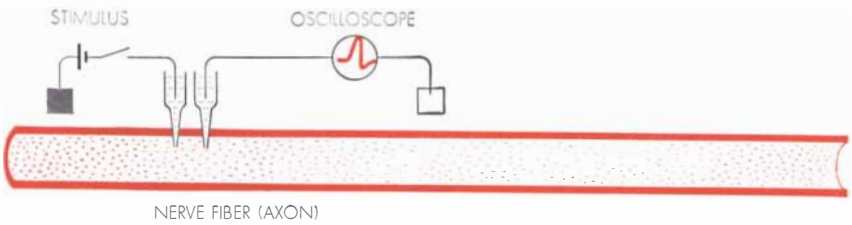
As one steps up the intensity of a voltage signal impressed on the membrane of a nerve cell a point is reached where the signal no longer fades and dies. Instead (if the voltage is of the right sign), a threshold is crossed and the cell becomes "excited" [*see illustrations on page 214*]. The axon of the cell no longer behaves like a passive cable but produces an extra current pulse of its own that amplifies the original input pulse. The amplified pulse, or "spike," regenerates itself from point to point without loss of amplitude and travels at constant speed down the whole length of the axon. The speed of transmission in vertebrate nerve fibers ranges from a few meters per second, for thin nonmyelinated fibers, to about 100 meters per second in the thickest myelinated fibers. The highest speeds, equivalent to some 200 miles per hour, are found in the sensory and motor fibers concerned with body balance and fast reflex movements. After transmitting an impulse the nerve is left briefly in a refractory, or inexcitable,



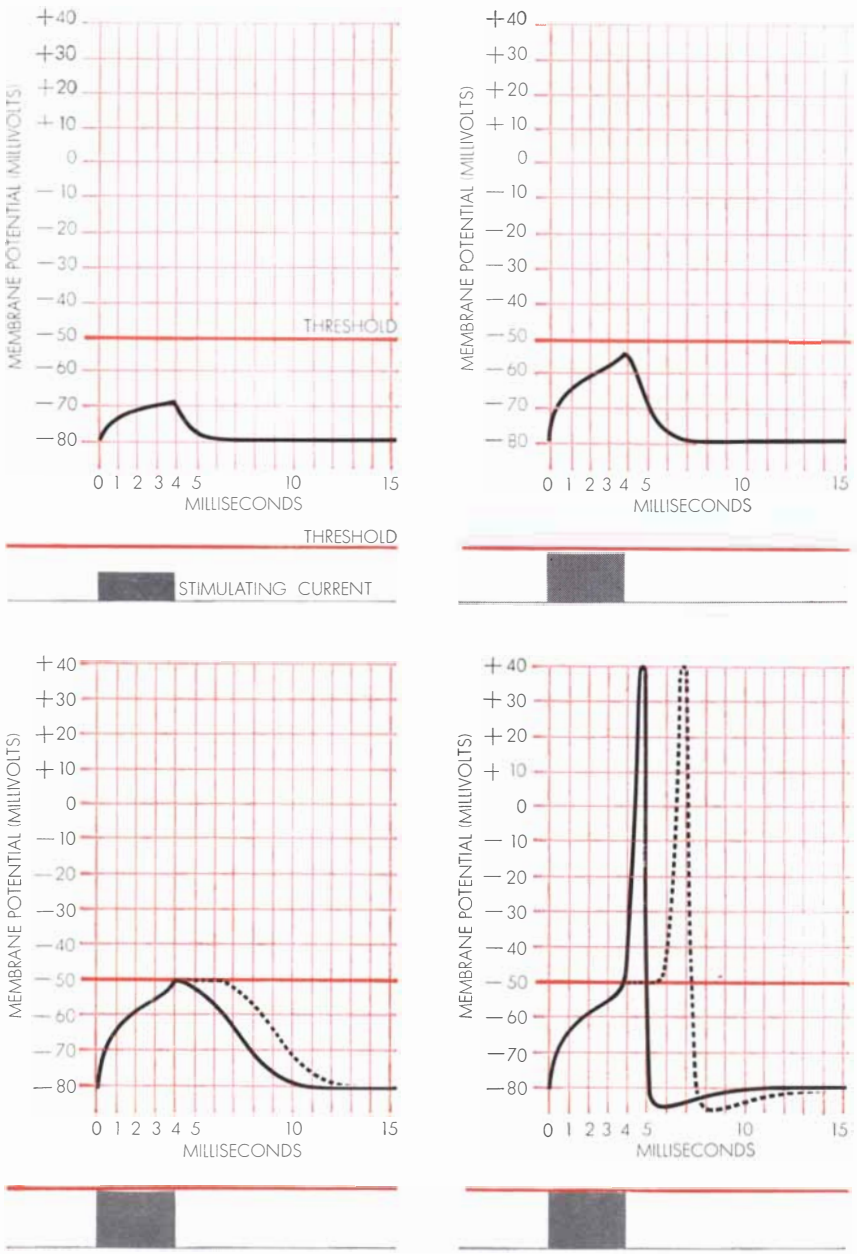
REFLEX ARC illustrates the minimum nerve circuit between stimulus and response. A sensory fiber arising in a muscle spindle enters the spinal cord, where it makes synaptic contact with a motor neuron whose axon returns to the muscle containing the spindle.



NERVE-CELL NETWORK IN THE RETINA, here magnified about 600 diameters, exemplifies the retinal complexity in man and apes. The top layer, where light strikes, is pigmented epithelium; behind it lie the rods and thicker cones, which are the photoreceptor cells. These cells have rich connections with a wide variety of nerve cells; some conduct impulses to the rear (in the direction of the optic nerve), whereas others evidently transmit impulses laterally and even, in some cases, forward (*upward in the diagram*).



INVESTIGATION OF NERVE FIBER is carried out with two microelectrodes. One provides a stimulating pulse, the other measures changes in membrane potential (*see below*).



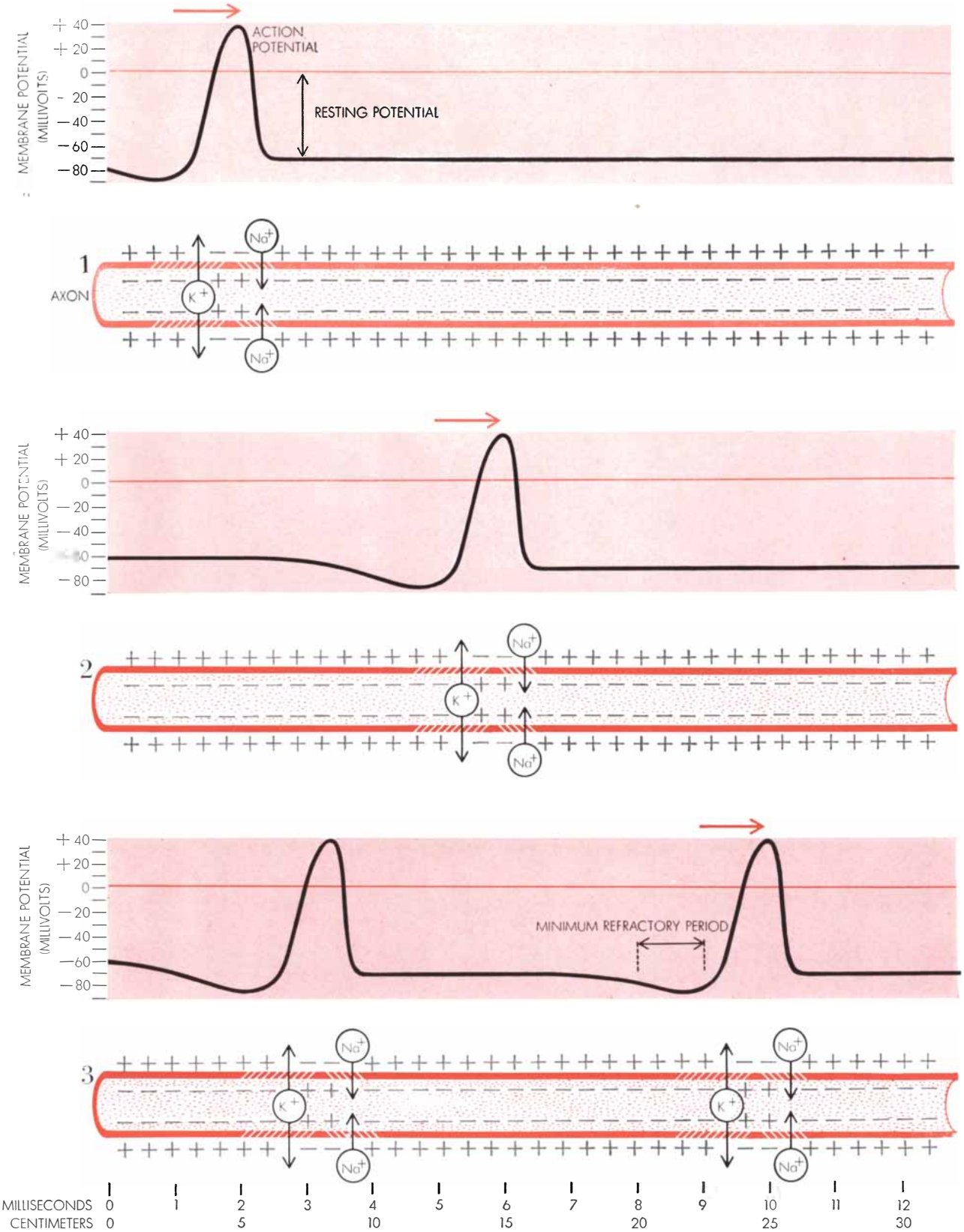
ELECTRICAL PROPERTIES OF NERVE FIBER are elucidated by measuring voltage changes across the axon membrane when stimulating pulses of varying size are applied. In the resting state the interior of the axon is about 80 millivolts negative. Subthreshold stimulating pulses (*top left and top right*) shift the potential upward momentarily. Larger pulses push the potential to its threshold, where it becomes unstable, either subsiding (*bottom left*) or flaring up into an "action potential" (*bottom right*) with a variable delay (*broken curve*).

state, but within one or two milliseconds it is ready to fire again.

The electrochemical events that underlie the nerve impulse—or action potential, as it is called—have been greatly clarified within the past 15 years. As we have seen, the voltage difference across the membrane is determined largely by the membrane's differential permeability to sodium and potassium ions. Many kinds of selective membrane, natural and artificial, show such differences. What makes the nerve membrane distinctive is that its permeability is in turn regulated by the voltage difference across the membrane, and this peculiar mutual influence is in fact the basis of the signaling process.

It was shown by A. L. Hodgkin and A. F. Huxley of the University of Cambridge that when the voltage difference across the membrane is artificially lowered, the immediate effect is to increase its sodium permeability. We do not know why the ionic insulation of the membrane is altered in this specific way, but the consequences are far-reaching. As sodium ions, with their positive charges, leak through the membrane they cancel out locally a portion of the excess negative charge inside the axon, thereby further reducing the voltage drop across the membrane. This is a regenerative process that leads to automatic self-reinforcement; the flow of some sodium ions through the membrane makes it easier for others to follow. When the voltage drop across the membrane has been reduced to the threshold level, sodium ions enter in such numbers that they change the internal potential of the membrane from negative to positive; the process "ignites" and flares up to create the nerve impulse, or action potential. The impulse, which shows up as a spike on the oscilloscope, changes the permeability of the axon membrane immediately ahead of it and sets up the conditions for sodium to flow into the axon, repeating the whole regenerative process in a progressive wave until the spike has traveled the length of the axon [*see illustration on opposite page*].

Immediately after the peak of the wave other events are taking place. The "sodium gates," which had opened during the rise of the spike, are closed again, and the "potassium gates" are opened briefly. This causes a rapid outflow of the positive potassium ions, which restores the original negative charge of the interior of the axon. For a few milliseconds after the membrane voltage has been driven toward its initial level it is difficult to displace the voltage and

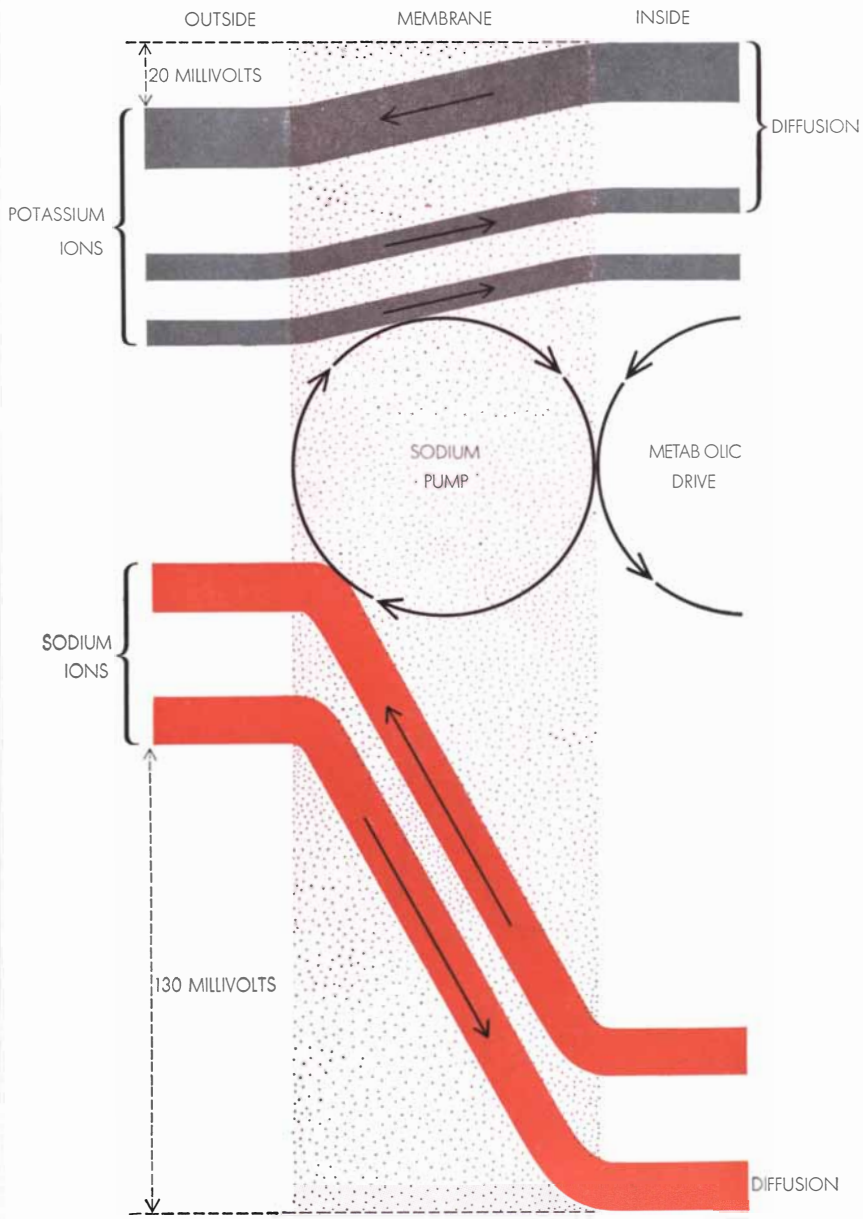


PROPAGATION OF NERVE IMPULSE coincides with changes in the permeability of the axon membrane. Normally the axon interior is rich in potassium ions and poor in sodium ions; the fluid outside has a reverse composition. When a nerve impulse arises, having been triggered in some fashion, a "gate" opens and lets sodium ions pour into the axon in advance of the impulse, making the axon interior locally positive. In the wake of the impulse the sodium gate closes and a potassium gate opens, allowing potassium ions to flow out, restoring the normal negative potential. As the nerve impulse moves along the axon (*1 and 2*) it leaves the axon in a refractory state briefly, after which a second impulse can follow (*3*). The impulse propagation speed is that of a squid axon.

set up another impulse. But the ionic permeabilities quickly return to their initial condition and the cell is ready to fire another impulse.

The inflow of sodium ions and subsequent outflow of potassium ions is so brief and involves so few particles that the over-all internal composition of the axon is scarcely affected. Even without replenishment the store of potassium ions inside the axon is sufficient to provide tens of thousands of impulses. In the living organism the cellular enzyme system that runs the sodium pump has no difficulty keeping nerves in continuous firing condition.

This intricate process—signal conduction through a leaky cable coupled with repeated automatic boosting along the transmission path—provides the long-distance communication needs of our nervous system. It imposes a certain stereotyped form of "coding" on our signaling channels: brief pulses of almost

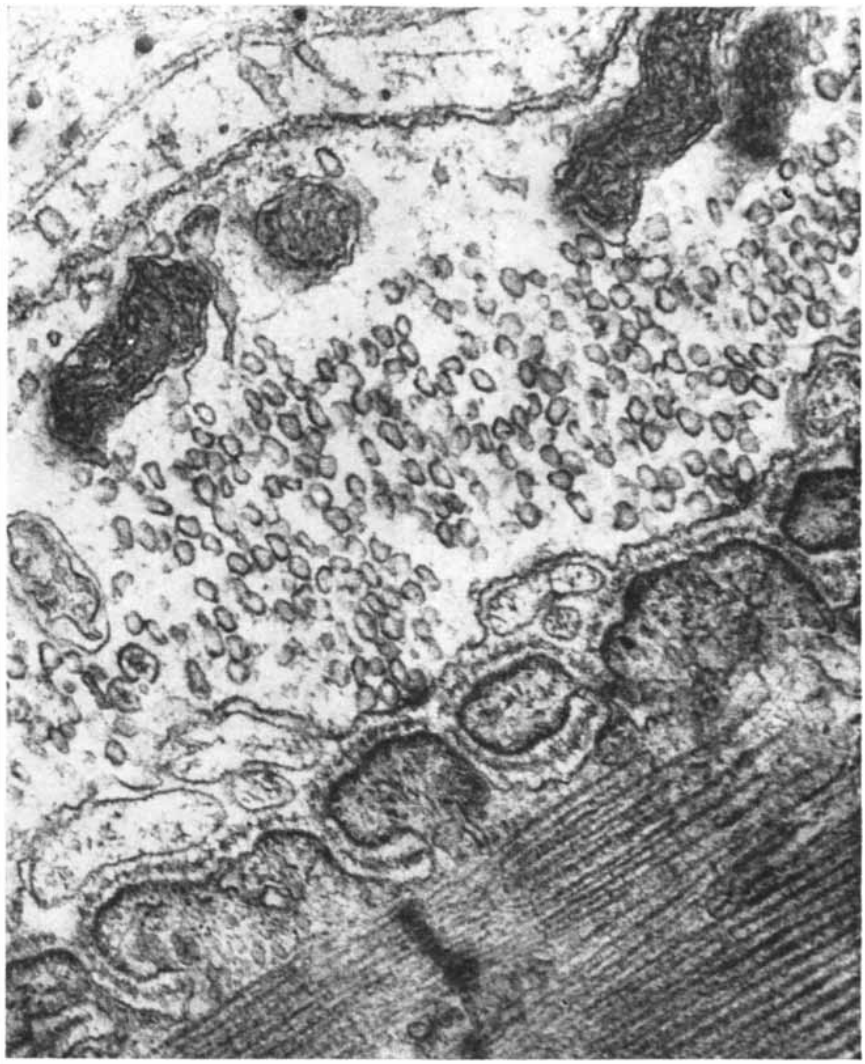


"SODIUM PUMP," details unknown, is required to expel sodium ions from the interior of the nerve axon so that the interior sodium-ion concentration is held to about 10 per cent that of the exterior fluid. At the same time the pump drives potassium ions "uphill" from a low external concentration to a 30-times-higher internal concentration. The pumping rate must keep up with the "downhill" leakage of the two kinds of ion. Since both are positively charged, sodium ions have the higher leakage rate (expressed in terms of millivolts of driving force) because they are attracted to the negatively charged interior of the axon, whereas potassium ions tend to be retained. But there is still a net outward leakage of potassium.

constant amplitude following each other at variable intervals, limited only by the refractory period of the nerve cell. To make up for the limitations of this simple coding system, large numbers of axon channels, each a separate nerve cell, are provided and arranged in parallel. For example, in the optic nerve trunk emerging from the eye there are more than a million channels running close together, all capable of transmitting separate signals to the higher centers of the brain.

Let us now turn to the question of what happens at a synapse, the point at which the impulse reaches the end of one cell and encounters another nerve cell. The self-amplifying cable process that serves within the borders of any one cell is not designed to jump automatically across the border to adjacent cells. Indeed, if there were such "cross talk" between adjacent channels, for instance among the fibers closely packed together in our nerve bundles, the system would become quite useless. It is true that at functional synaptic contacts the separation between the cell membranes is only 100 to a few hundred angstroms. But from what we know of the dimensions of the contact area, and of the insulating properties of cell membranes, it is unlikely that an effective cable connection could exist between the terminal of one nerve cell and the interior of its neighbor. This can easily be demonstrated by trying to pass a subthreshold pulse—that is, one that does not trigger a spike—across the synapse that separates a motor nerve from a muscle fiber. A recording probe located just inside the muscle detects no signal when a weak pulse is applied to the motor nerve close to the synapse. Clearly the cable linkage is broken at the synapse and some other process must take its place.

The nature of this process was discovered some 25 years ago by Sir Henry Dale and his collaborators at the National Institute for Medical Research in London. In some ways it resembles the hormonal mechanism mentioned at the beginning of this article. The motor nerve terminals act rather like glands secreting a chemical messenger. Upon arrival of an impulse, the terminals release a special substance, acetylcholine, that quickly and efficiently diffuses across the short synaptic gap. Acetylcholine molecules combine with receptor molecules in the contact area of the muscle fiber and somehow open its ionic gates, allowing sodium to flow in and trigger an impulse. The same result can be obtained by artificially applying ace-



NERVE-MUSCLE SYNAPSE is the site at which a nerve impulse activates the contraction of a muscle fiber. In this electron micrograph (made by R. Birks, H. E. Huxley and the author) the region of the synapse is enlarged 53,000 diameters. Motor nerve terminal runs diagonally from lower left to upper right, being bounded at upper left by a Schwann cell. Muscle fiber is the dark striated area at lower right, with a folded membrane. Nerve terminal is populated with "synaptic vesicles" that may contain acetylcholine, which is released into the synaptic cleft by a nerve impulse and evokes electrical activity in the muscle.

tylcholine to the contact region of the muscle fiber. It is probable that similar processes of chemical mediation take place at the majority of cell contacts in our central nervous system. But it is most unlikely that acetylcholine is the universal mediator at all these points, and an intensive search is being made by many workers for other naturally occurring transmitter substances.

Synaptic transmission presents two quite distinct sets of problems. First, exactly how does a nerve impulse manage to cause the secretion of the chemical mediator? Second, what are the physicochemical factors that decide whether a mediator will stimulate the next cell to fire in some cases or inhibit it from firing in others? So far we have said nothing about inhibition, even though it occurs throughout the nervous system and is one of the most curious modes of nervous activity. Inhibition takes place when a nerve impulse acts as a brake on the next cell, preventing it from becoming activated by excitatory messages that may be arriving along other channels at the same time. The impulse that travels along an inhibitory axon cannot be distinguished electrically from an impulse traveling in an excitatory axon. But the physicochemical effect that it induces at a synapse must be different in kind. Presumably inhibition results from a process that in some way stabilizes the membrane potential (degree of electrification) of the receiving cell and prevents it from being driven to its unstable threshold, or "ignition" point.

There are several processes by which

such a stabilization could be achieved. One of them has already been mentioned; it occurs in the refractory period immediately after a spike has been generated. In this period the membrane potential is driven to a high stable level (some 80 to 90 millivolts negative inside the membrane) because, to put it somewhat crudely, the potassium gates are wide open and the sodium gates are firmly shut. If the transmitter substance can produce one or both of these states of ionic permeability, it will undoubtedly act as an inhibitor. There are good reasons for believing that this is the way impulses from the vagus nerve slow down and inhibit the heartbeat; incidentally, the transmitter substance released from the vagus nerve is again acetylcholine, as was discovered by Otto Loewi 40 years ago. Similar effects occur at various inhibitory synapses in the spinal cord, but there the chemical nature of the transmitter has so far eluded identification.

Inhibition would also result if two "antagonistic" axons converged on the same spot of a third nerve cell and released chemically competing molecules. Although a natural example of this kind has not yet been demonstrated, the chemical and pharmacological use of competitive inhibitors is well established. (For example, the paralyzing effect of the drug curare arises from its competitive attachment to the region of the muscle fiber that is normally free to react with acetylcholine.) Alternatively, a substance released by an inhibitory nerve ending could act on the excitatory nerve terminal in such a way as to reduce its secretory power, thereby causing less of the excitatory transmitter substance to be released.

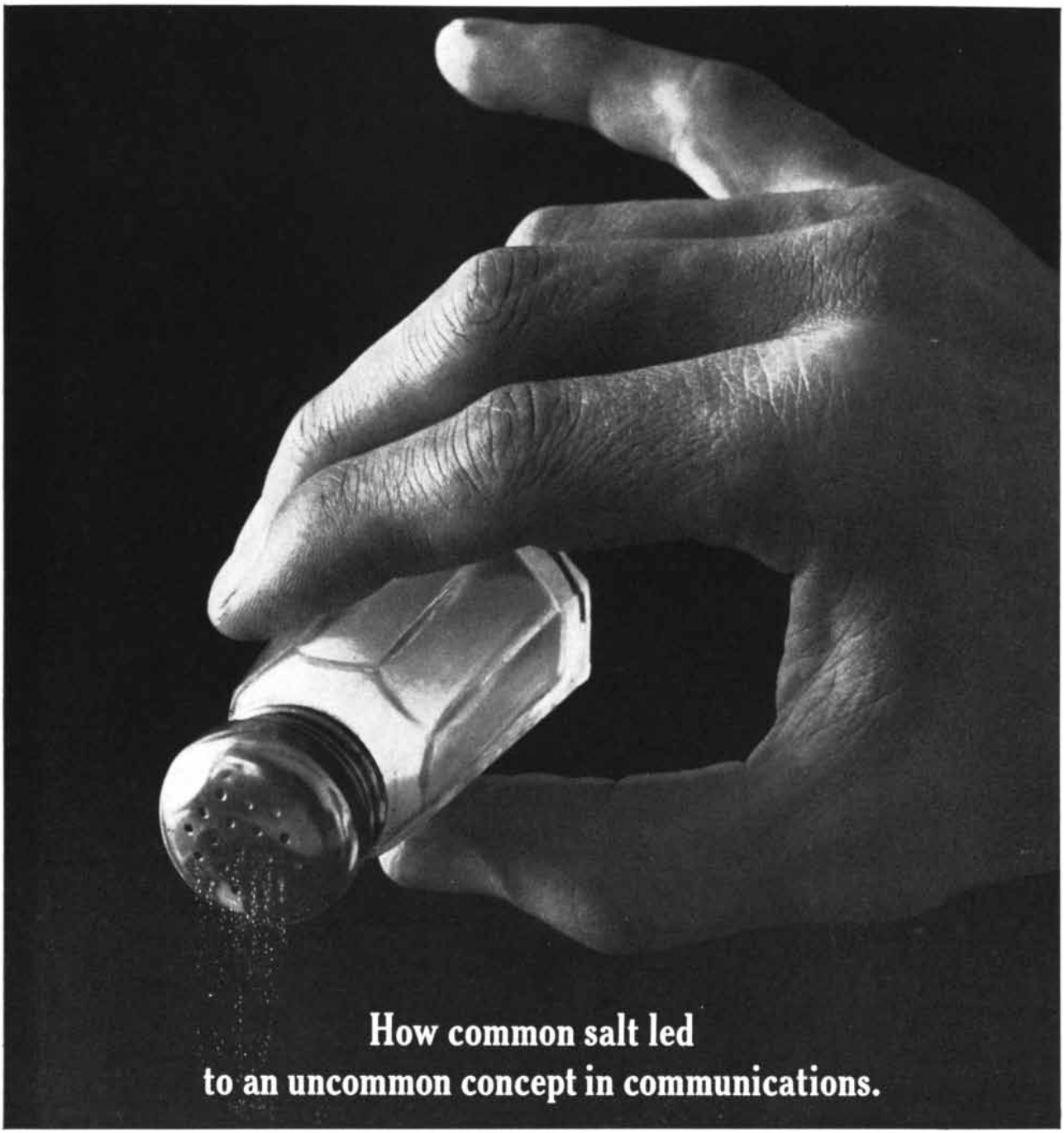
This brings us back to the question: How does a nerve impulse lead to the secretion of transmitter substances? Recent experiments on the nerve-muscle junction have shown that the effect of the nerve impulse is not to initiate a process of secretion but rather, by altering the membrane potential, to change the rate of a secretory process that goes on all the time. Even in the absence of any form of stimulation, packets of acetylcholine are released from discrete spots of the nerve terminals at random intervals, each packet containing a large number—probably thousands—of molecules.

Each time one of these quanta of transmitter molecules is liberated spontaneously, it is possible to detect a sudden minute local response in the muscle fiber on the other side of the synapse. Within a millisecond there is a drop of

.5 millivolt in the potential of the muscle membrane, which takes about 20 milliseconds to recover. By systematically altering the potential of the membrane of the nerve ending it has been possible to work out the characteristic relation between the membrane potential of the axon terminal and the rate of secretion of transmitter packets. It appears that the rate of release increases by a factor of about 100 times for each 30-millivolt lowering of membrane potential. In the resting condition there is a random discharge of about one packet per second at each nerve-muscle junction. But during the brief 120-millivolt change associated with the nerve impulse the frequency rises momentarily by a factor of nearly a million, providing a synchronous release of a few hundred packets within a fraction of a millisecond.

It is significant that the transmitter is released not in independent molecular doses but always in multimolecular parcels of standard size. The explanation of this feature is probably to be found in the microstructural make-up of the nerve terminals. They contain a characteristic accumulation of so-called vesicles, each about 500 angstroms in diameter, which may contain the transmitter substance parceled and ready for release [*see illustration on page 218*]. Conceivably when the vesicles collide with the axon membrane, as they often must, the collision may sometimes cause the vesicular content to spill into the synaptic cleft. Such ideas have yet to be proved by direct evidence, but they provide a reasonable explanation of all that is known about the quantal spontaneous release of acetylcholine and its accelerated release under various natural and experimental conditions. At any rate, the ideas provide an interesting meeting point between the functional and structural approaches to a common problem.

Because of the sparseness of existing knowledge, we have left out of this discussion many fascinating problems of the long-term interactions and adaptive modifications that must certainly take place in nerve pathways. For handling such problems investigators will probably have to develop very different methods from those followed in the past. It may be that our preoccupation with the techniques that have been so successful in illuminating the brief reactions of excitable cells has prevented us from making inroads on the problems of learning, of memory, of conditioning and of the structural and operating relations between nerve cells and their neighbors.



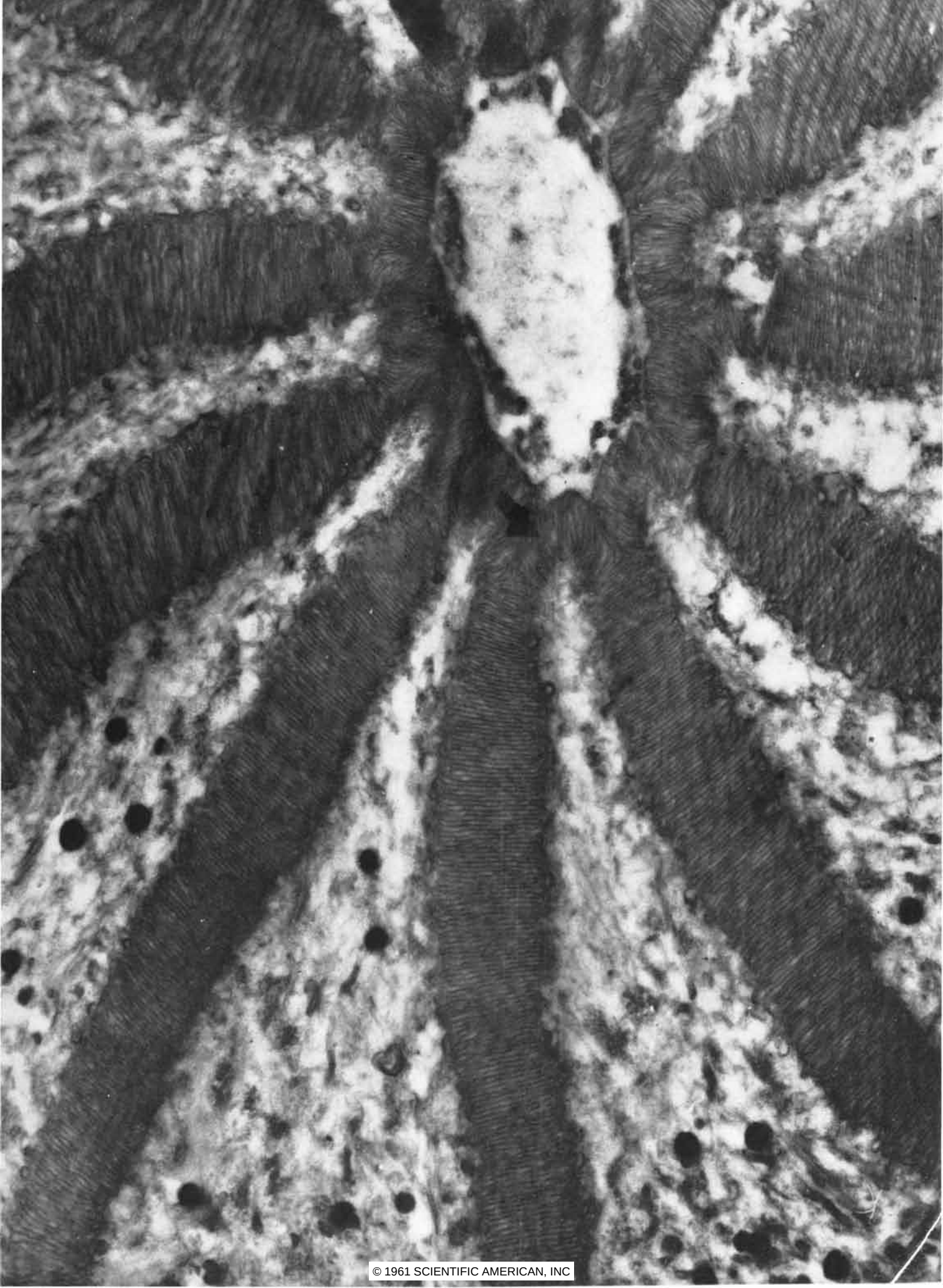
An unusual new device to increase radio reflectivity, now under development at Northrop's Radioplane Division, may well revolutionize the field of space communications. Called ADSAT (for Anomalous Dispersion Spherical Array Target), it should extend the usefulness of passive communications satellites out to 22,000 miles—the 24-hour orbit.

The germ of the ADSAT idea actually came from early X-ray diffraction experiments with ordinary salt crystals which yielded a pattern of intense bright and dark spots. This hint of resonance with the crystal lattice led Northrop researchers to attempt to duplicate this effect at radio frequencies—and the first version of ADSAT looked much like a molecular model, with silver-coated ping-pong balls serving as "atoms." The size of the balls and the intervals between them were carefully calculated to resonate with and reinforce the incoming frequencies.

In its present, basic form, the ADSAT satellite is a collapsible, spherical network, 100 to 400 feet across, with the resonant balls at each intersection of the network. It is designed to be launched in a small package, and inflated in orbit, much like Echo. The reflected signal, however, can be 1,000 times as strong as that obtained from a simple, Echo-type target of equal size.

The development of the ADSAT concept demonstrates once again Northrop's unique ability to visualize problems in space technology, decide what should be done, and come up with solid, workable answers.

RADIOPLANE
A DIVISION OF
NORTHROP



How Cells Receive Stimuli

In complex organisms certain cells are highly specialized to detect changes in the environment. The properties of such cells have been elucidated by studies of the visual receptors of the horseshoe crab

by William H. Miller, Floyd Ratliff and H. K. Hartline

The survival of every living thing depends ultimately on its ability to respond to the world around it and to regulate its own internal environment. In most multicellular animals this response and regulation is made possible by specialized receptor cells that are sensitive to a wide variety of physical, chemical and mechanical stimuli.

In many animals, including man, these receptors provide information that far exceeds that furnished by the traditional five senses (sight, hearing, smell, taste and touch). Sense organs of which we are less aware include equally important receptors that monitor the internal environment. Receptor organs in the muscles, called muscle spindles, provide a continuous measure of muscle stretch, and other receptors sense the movement of joints. Without such receptors it would be difficult to move or talk. Receptor cells in the hypothalamus, a part of the brain, are sensitive to the temperature of the blood; pressure-sensitive cells in the carotid sinus measure the blood pressure. Still other internal receptors monitor carbon dioxide in special regions of the large arteries. Pain receptors, widely distributed throughout the body, respond to noxious stimuli of almost any nature that are likely to cause tissue damage.

Receptor cells not only have diverse functions and structures but also connect in various ways with the nerve fibers channeling into the central nervous system. Some receptor cells give rise directly to nerve fibers of their own; others make contact with nerve fibers originating elsewhere. All receptors, however, share a common function: the generation of nerve impulses. This does not imply that impulses necessarily occur in the receptor cells themselves. For example, in the eyes of vertebrates no one has yet been able to detect impulses in the photoreceptor cells: the rods and cones. Nevertheless, the rods and cones, when struck by light, set up the physicochemical conditions that trigger impulses in nerve cells lying behind them. Typical nerve impulses are readily detected in the optic nerve itself, which is composed of fibers of ganglion cells separated from the rods and cones by at least one intervening group of nerve cells.

Eventually physiologists hope to unravel the detailed train of events by which a receptor cell gives rise to a discharge of nerve impulses following mechanical deformation, absorption of light or heat, or stimulation by a particular molecule. In no case have all the events been traced out. In our discussion we will begin with the one final event common to all sensory reception—the generation of nerve impulses. We will then examine in some detail the events occurring in one particular receptor: the photoreceptor of *Limulus*, the horseshoe crab. Finally, we will describe some characteristics of the output of receptors acting singly and in concert with others.

The nerve fiber, or axon, is a thread-like extension of the nerve-cell body. The entire surface membrane of the cell, including that of the axon, is electrically polarized; the inside of the cell is some 70 millivolts negative with respect to the outside. This potential difference is called the membrane potential. In response to a suitable triggering event the membrane potential is momentarily and locally altered, giving rise to a nerve impulse, which is then propagated the whole length of the axon [see "How Cells Communicate," page 209].

In any particular nerve fiber the impulses are always of essentially the same magnitude and form and they travel with the same speed. This has been known for some 30 years, since the pioneering studies of E. D. Adrian at the University of Cambridge. He and his colleagues found that varying the intensity of the stimulus applied to a receptor cell affects not the size of the impulses but the frequency with which they are discharged; the greater the intensity, the greater the frequency of nerve impulses generated by the receptor. Thus all sensory messages—concerning light, sound, muscle position and so on—are conveyed in the same code of individual nerve impulses. The animal is able to decode the various messages because each type of receptor communicates to the higher nerve centers only through its own private set of nerve channels.

Adrian and others have investigated the problem of how the receptor cell triggers sensory nerve impulses. Adrian suggested that the receptor must somehow diminish the resting membrane potential of its nerve fiber; that is, it must locally depolarize the axon membrane. The existence of local potentials in the eye has been known since 1865, and much later similar potentials were recorded in other sense organs. But the

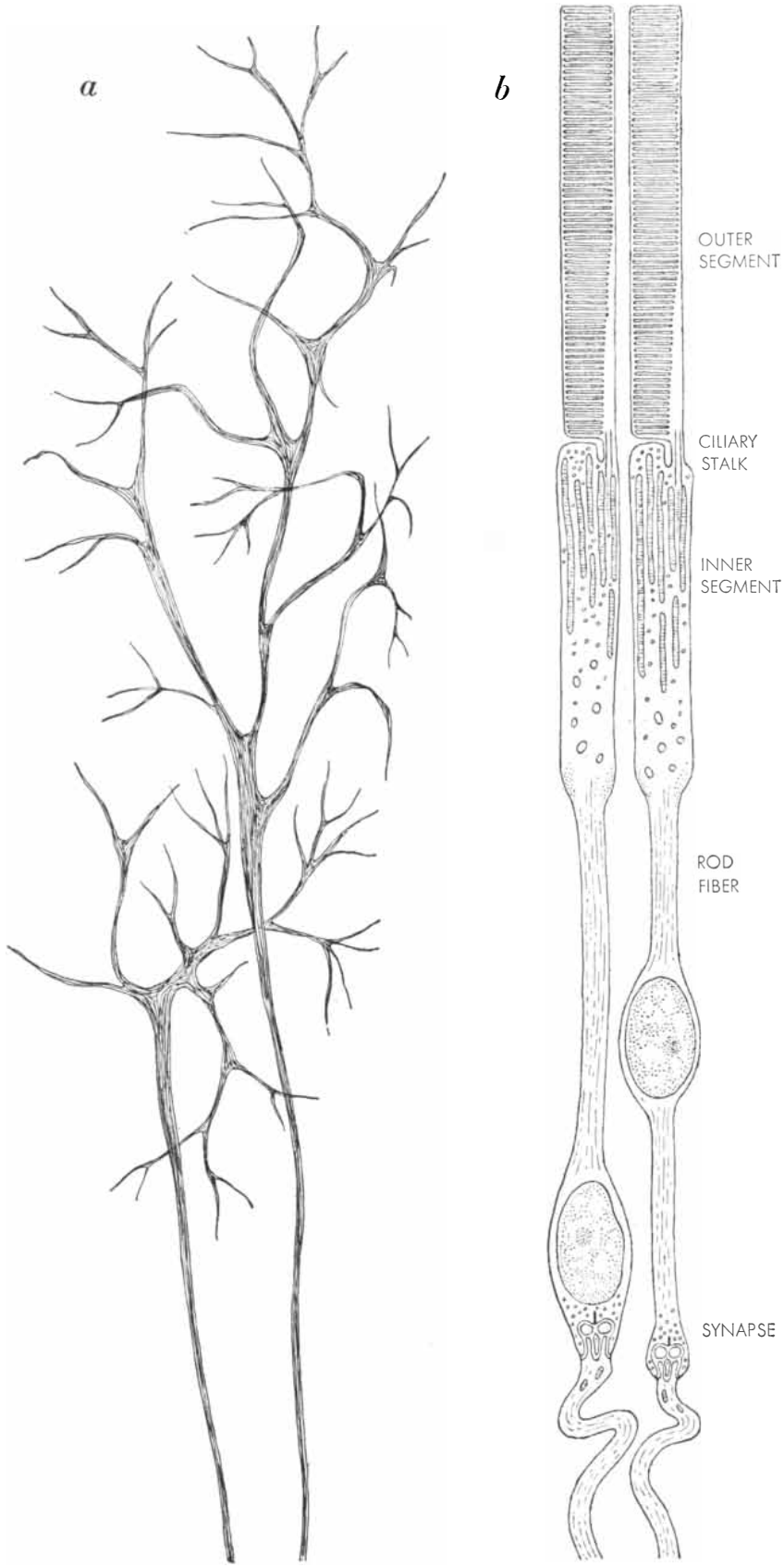
VISUAL RECEPTOR of the horseshoe crab (*Limulus*) is enlarged 19,000 diameters in the electron micrograph on the opposite page. Called an ommatidium, it is one of about 1,000 photoreceptor units in the compound eye of *Limulus*. Here the ommatidium is seen in cross section; the individual receptor cells are arranged radially like segments of a tangerine around a nerve filament (dendrite) arising from an associated nerve cell (*see illustration on page 227*). The dark ring around the dendrite and spokelike areas may contain photosensitive pigment. The electron micrograph was made by William H. Miller, one of the authors.

relationship of these gross electrical changes to the discharge of nerve impulses was not clear. For some simple eyes, however, the polarity of the local potential changes in the receptors is such that they appear to depolarize the sensory nerve fibers. This led Ragnar Granit of the Royal Caroline Institute in Stockholm to propose that they be called "generator" potentials. The present view is that stimulation of the receptor cell gives rise to a sustained local depolarization of the sensory nerve fiber, which thereupon generates a train of impulses.

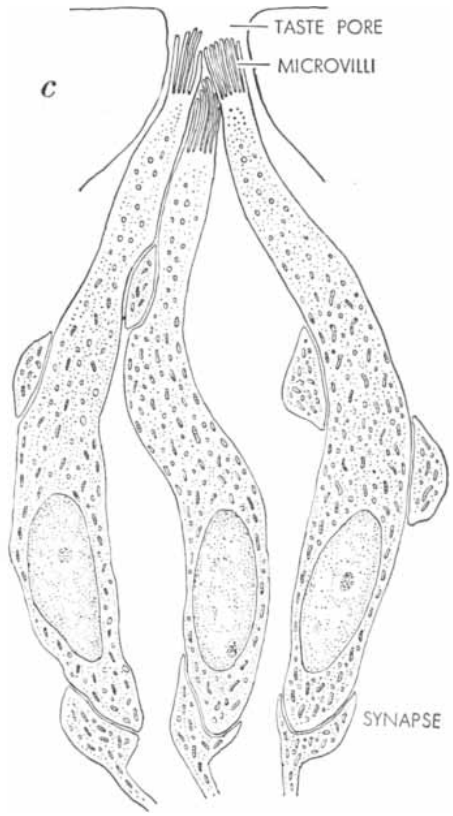
Some of the first direct evidence for generator potentials at the cellular level was produced in 1935 by one of the authors of this article (Hartline), then working at the Johnson Research Foundation of the University of Pennsylvania. He found what appeared to be a generator potential when he recorded the activity of a single optic nerve fiber and its receptor in the compound eye of *Limulus*. Superimposed on the potential was a train of nerve impulses [*see illustration on page 228*].

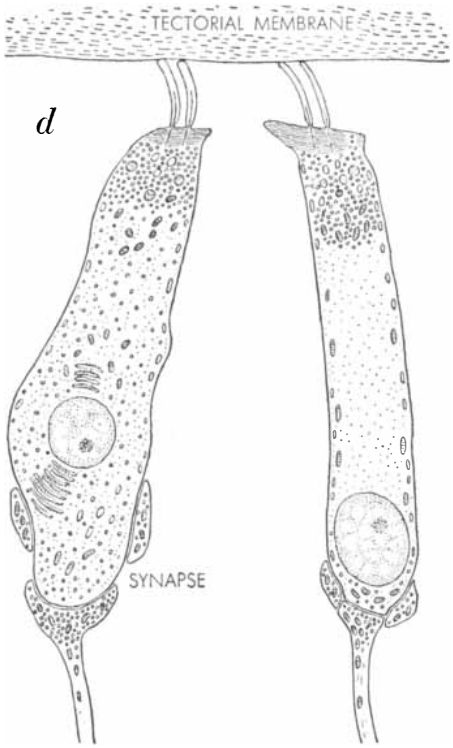
In 1950 Bernhard Katz of University College London obtained unmistakable evidence for a generator potential in a somewhat simpler receptor: the vertebrate muscle spindle. When the spindle was stretched, a small, steady depolarization could be recorded in the nerve fiber coming from the spindle. As viewed on the oscilloscope, it appeared that the base line of the recorded signal had been shifted slightly upward. Superimposed on the shifted signal, or local potential, was a series of "spikes" representing individual nerve impulses. The stronger or the more rapid the stretch, the greater the magnitude of the potential shift and the greater the frequency of the impulses [*see illustration on page 226*]. Analysis of many such records showed that in the steady state the frequency of nerve impulses depends directly on the magnitude of the altered potential. If a local anesthetic is applied to the spindle, the impulses are abolished but the potential shift remains. Katz concluded that this potential shift is an essential link between the stretching of the spindle and the discharge of nerve impulses; indeed, that it is the generator potential. Moreover, the potential can be detected only very close to the spindle, showing that it is conducted passively—which is to say poorly—along the nerve fiber.

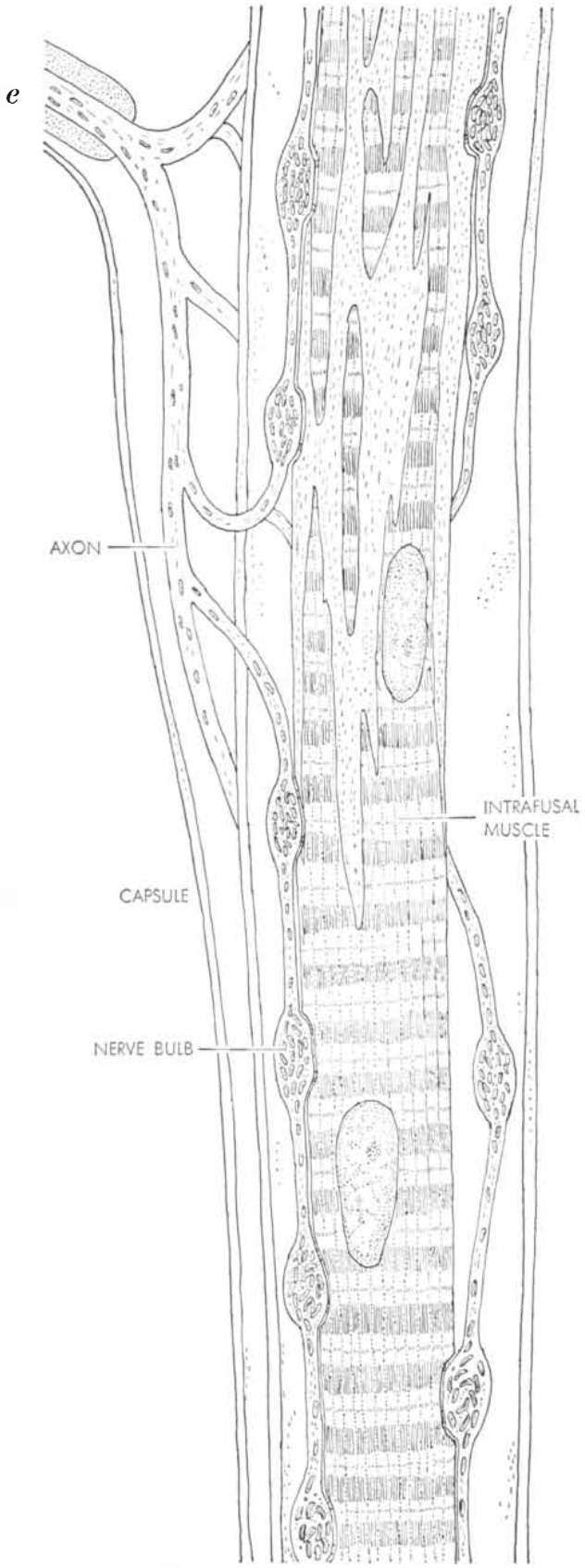
Important confirmation of the role of the generator potential was provided by the work of Stephen W. Kuffler and



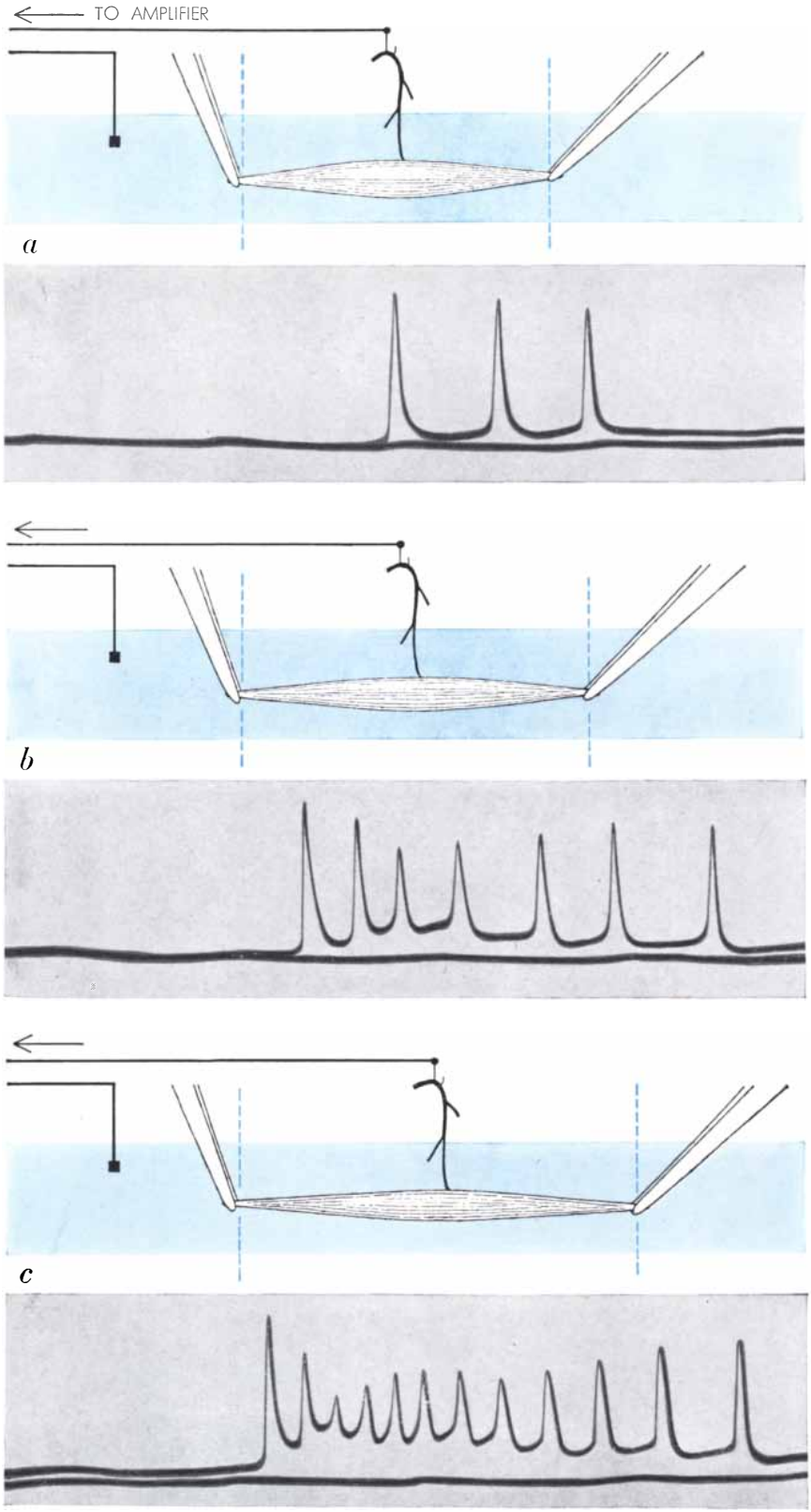
RECEPTOR CELLS, typical of those found in vertebrates, respond to a variety of stimuli: heat, light, chemicals and mechanical deformation. The "pit" on the head of the pit viper contains a network of free nerve endings (*a*) that are sensitive to heat and help the viper locate its prey. Rods (*b*) are light-sensitive cells in the retina of the eye; photosensitive pig-







ment is in the laminar structure at top of drawing. Taste buds (*c*) are chemoreceptor cells embedded in the tongue. The cochlea, a spiral tube in the inner ear, contains thousands of sensitive cells (*d*) in the so-called organs of Corti. When the hairlike bristles of these cells are mechanically deformed by sound vibrations, impulses are generated in the auditory nerve fibers leading to brain. Muscle spindle (*e*) contains a number of nerve endings that respond sensitively to stretching of muscle fibers surrounding them.



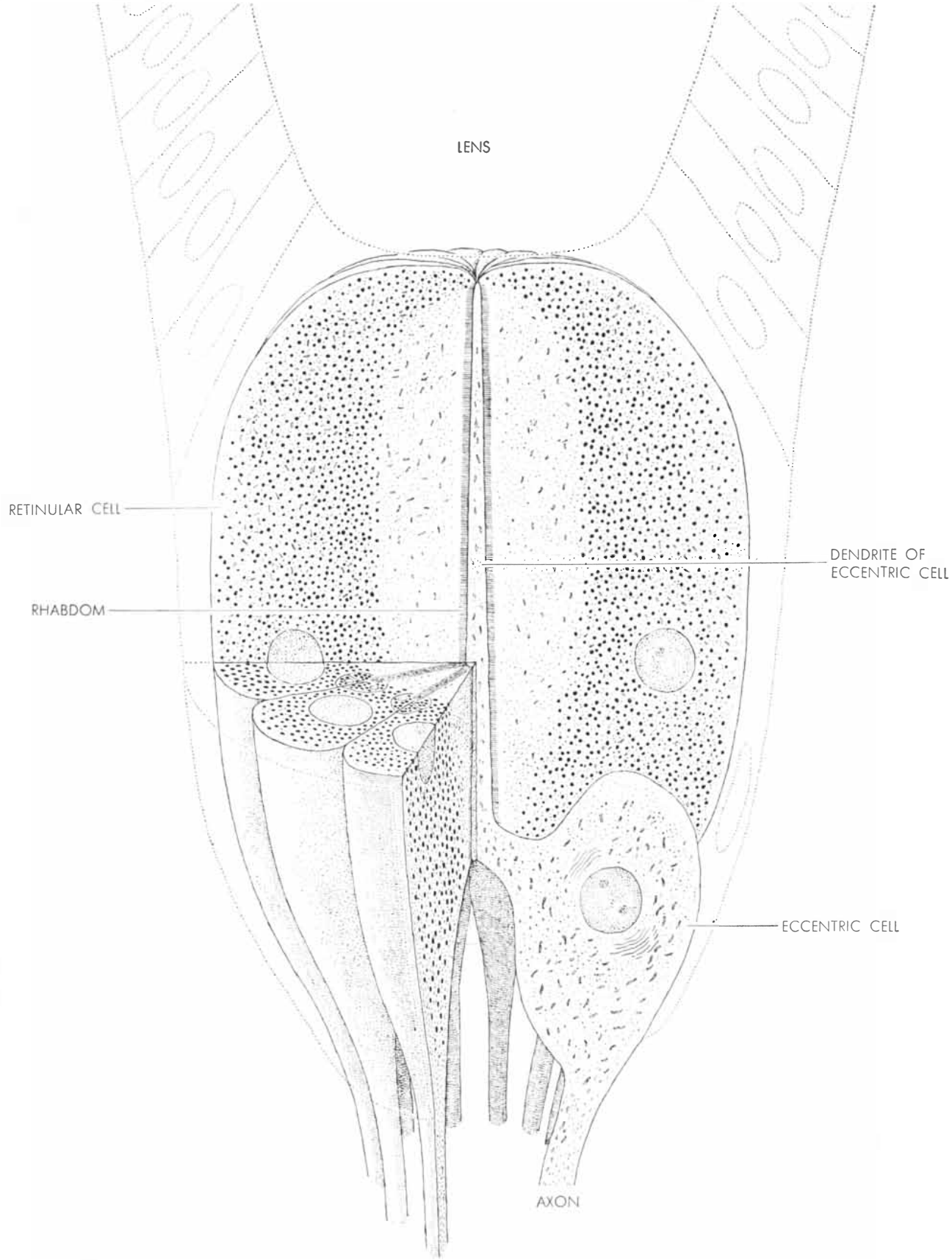
MUSCLE SPINDLE responds to stretch by firing nerve impulses at a rate proportional to the degree and speed of stretching. These recordings made by Bernhard Katz of University College London were the first to show that stretching causes depolarization of the nerve near the spindle (*base line shifted upward in the traces*) and that this depolarization is the precondition for the firing of nerve impulses. The shift is called the generator potential.

Carlos Eyzaguirre, then at Johns Hopkins University, using the so-called Alexandrowicz stretch-receptor cells in crustaceans. These are large single receptor cells with dendrites (short fibers) that are embedded in specialized receptor muscles. Kuffler was able to insert a microelectrode within the cell and record its membrane potential as well as the nerve impulses in its axon. He found that when he distorted the cell's dendrites by stretching the receptor muscle, the cell body became depolarized and the depolarization spread passively to the site of impulse generation, which is probably in the axon close to where it emerges from the cell body. When this generator potential reached a critical level, the cell fired a train of nerve impulses; the greater the depolarization of the axon above this critical level, the higher the frequency of the discharge.

There is now abundant evidence that a receptor cell triggers a train of nerve impulses by locally depolarizing the adjacent nerve fiber—either its own fiber or one provided by another cell. With few exceptions, a fiber of a nerve trunk will not respond repetitively if one passes a sustained depolarizing current through it; it responds only briefly with one to several impulses and then accommodates to the stimulus and responds no more. Evidently that part of the sensory nerve fiber close to the receptor must be specialized so that it does not speedily accommodate to the generator potential. It is nonetheless true that a certain amount of accommodation, or adaptation, almost always takes place when a receptor cell is exposed to a sustained stimulus. In any event, the initiation of nerve impulses in the axons of receptor cells by means of a generator potential appears to be a general phenomenon.

The question still remains: How does the external stimulus produce the generator potential? In most of the receptors studied there is no evidence whatever on this point. Only in the photoreceptor do we have precise knowledge of the first step in the excitation of the sense cell. Yet the study of the photoreceptor is beset by special difficulties. In most eyes the receptors are small and densely packed, and their associated neural structures are complex and highly organized. A fortunate exception is the compound eye of *Limulus*, which provided early evidence for the generator potential. In this eye the receptor cells are large and the neural organization is relatively simple.

The coarsely faceted compound eye

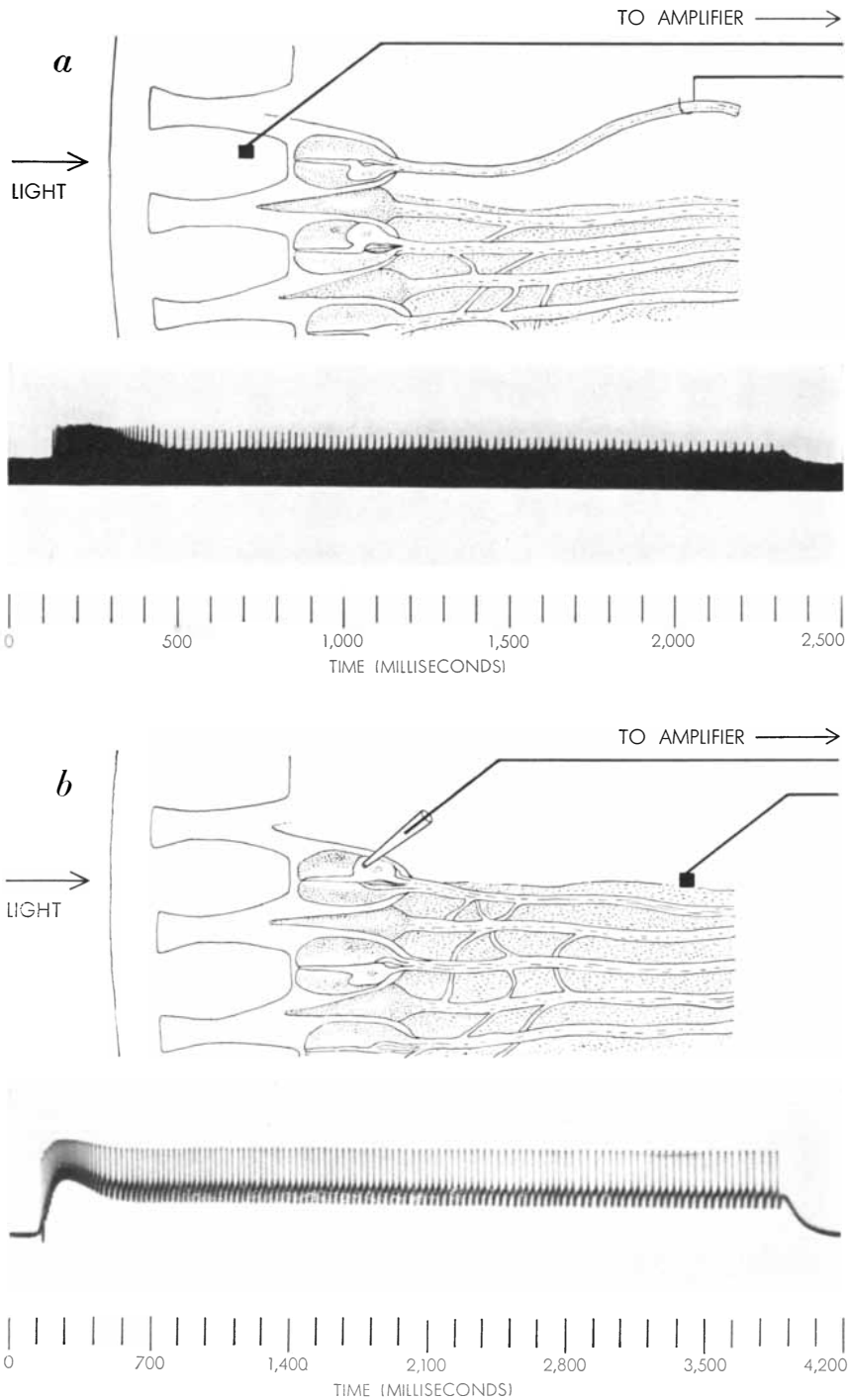


OMMATIDIUM OF LIMULUS is a remarkable structure roughly the size of a pencil lead. About 1,000 form the crab's compound eye. The ommatidium consists of about 12 wedge-shaped retinular cells clustered around a central fiber, which is the dendrite (sensitive process) of a nerve cell, the eccentric cell shown at lower right. When light strikes the ommatidium (*at the top*), the eccentric cell gives rise to nerve impulses (*see illustration on next page*). Photosensitive pigment rhodopsin is believed to be in the rhabdom.

of *Limulus* has some 1,000 ommatidia ("little eyes"), each of which contains about a dozen cells. The cells in each ommatidium have a regular arrangement. The retinular cells—the receptors—are arranged radially like the segments of a tangerine around the dendrite of an associated neuron: a single eccentric cell within each ommatidium [*see illustration on preceding page*].

Hartline, H. G. Wagner and E. F. MacNichol, Jr., working at Johns Hopkins University, found by the use of microelectrodes that the eccentric cell gives rise to the nerve impulses that can be recorded farther down in the nerve strand leaving the ommatidium. The microelectrode also records the generator potential of the ommatidium. Because of the anatomical complexity of the ommatidium, the site of origin of the generator potential has not been identified with certainty. Nor has activity yet been detected in the axons of the retinular cells. As in the vertebrate and invertebrate stretch receptors, local anesthetics extinguish the nerve impulses without destroying the generator potential. Moreover, as in the stretch receptors, there is a proportional relationship between the degree of depolarization and the frequency of nerve impulses.

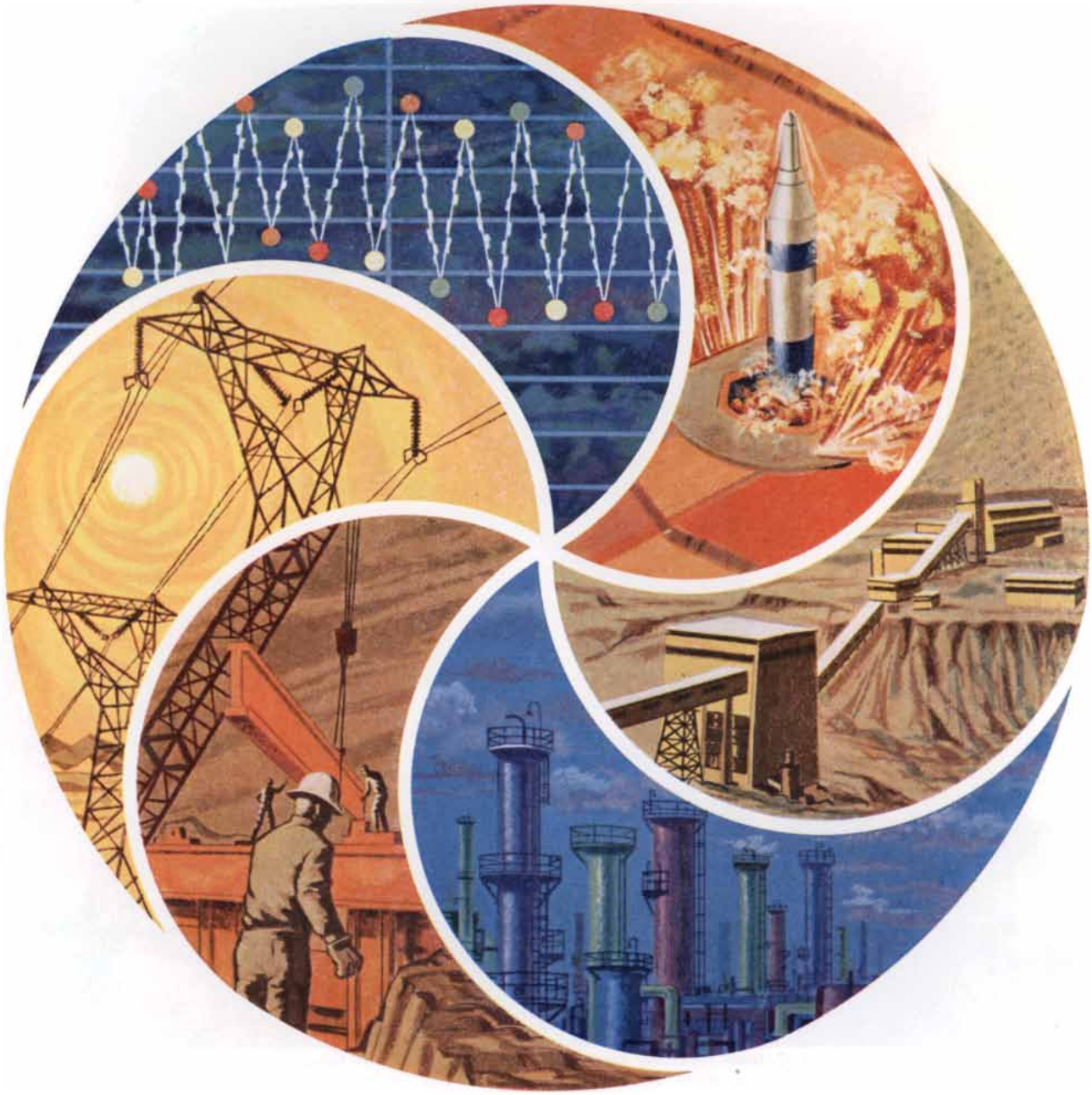
Recently M. G. F. Fuortes of the National Institute of Neurological Diseases and Blindness has shown that illumination increases the conductance of the eccentric cell. He postulates that the increase is produced by a chemical transmitter substance that is released by the action of light and acts on the eccentric cell's dendrite. Presumably the increased conductance of the dendrite results in a depolarization that spreads passively to the site of impulse generation, where it acts as the generator potential.



RECORDINGS FROM OMMATIDIA show trains of nerve impulses evoked by light. The upper recording from a nerve bundle (*a*) was made by one of the authors, H. K. Hartline, some 25 years ago. Shift of base line underlying nerve spikes is the generator potential. Lower recording, made with microelectrode (*b*), shows generator potential more clearly.

In photosensory cells—alone among all receptors—there exists direct experimental evidence of the initial molecular events in the receptor process. It has been known for about a century that visual receptor cells in both vertebrates and invertebrates have specially differentiated organelles containing a photosensitive pigment. In vertebrates this reddish pigment, called rhodopsin, can be clearly seen in the outer segments of rods. The absorption spectrum of human rhodopsin corresponds closely to the light-sensitivity curve for human vision under conditions of dim illumination, when only the rods of the retina are operative. This is strong evidence that rhodopsin brings about the first active event in rod vision: the absorption of light by the photoreceptor structure. (There is evidence for similar pigments in the outer segments of cones, but they have proved more difficult to isolate and study.)

The visual pigments are known to be complex proteins, but the light-absorbing part of the pigment, called the chromophore, has been found to be a relatively simple substance: vitamin A aldehyde. Because it contains a number of double chemical bonds in its make-up, vitamin A aldehyde can exist in various molecular configurations known as "*cis*" and "*trans*" isomers. We know from the work of Ruth Hubbard, George Wald and their colleagues at Harvard University that the absorption of light changes the chromophore from



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These "geysers" actually consist of steam rocketing up from deep in the ground. From this well area, operated by Magma and Thermal Power Companies, steam is conducted by pipeline to The Geysers Power Plant a quarter-mile away.

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With nickel in it, stainless steel is more than a match for this corrosive steam. This ability plays a key role in turning out power every day of the year, with virtually no maintenance in a plant designed for unattended operation.

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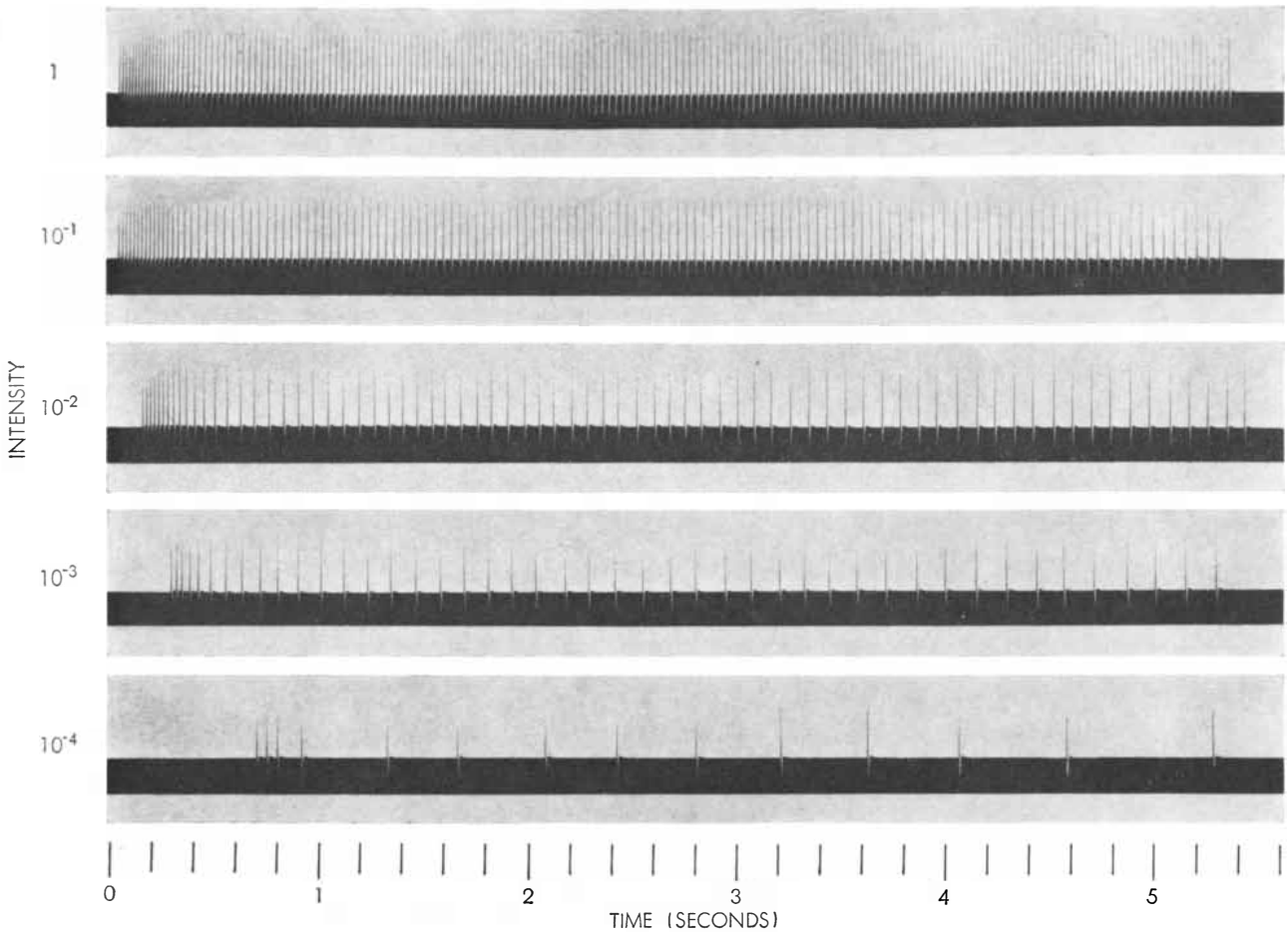
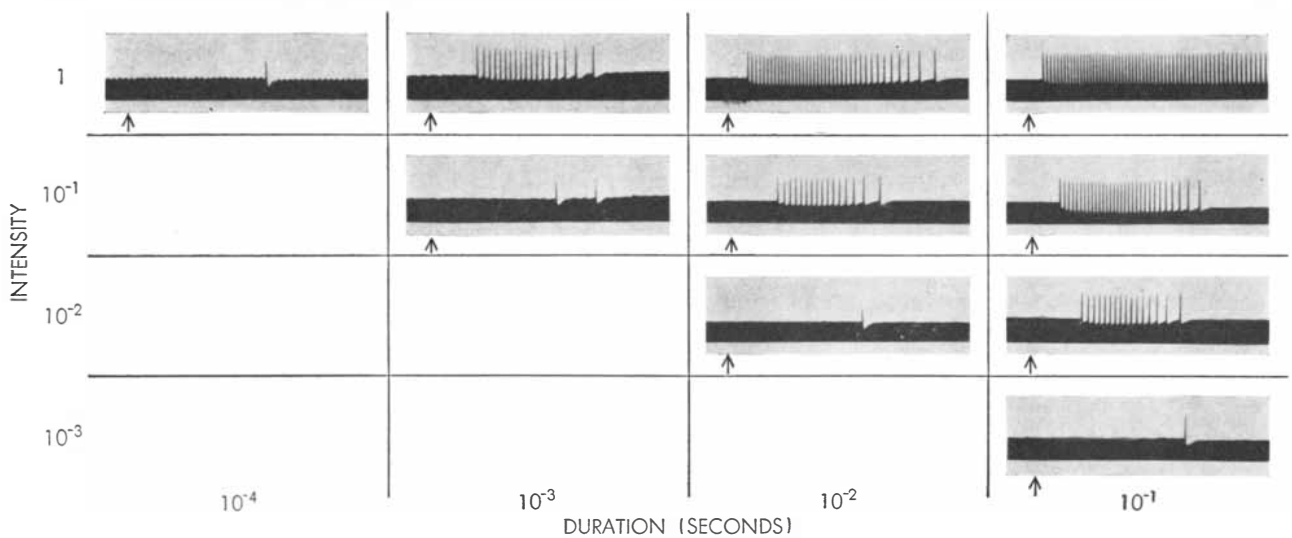
11-*cis* vitamin A aldehyde to the *trans* configuration. This photochemical reaction is the first step that leads, through a chain of chemical and physical events as yet unknown, to the initiation of the generator potential of the receptor cell and finally to the discharge of impulses in the optic nerve. This is the only case in which the specific molecular mechanism is known whereby a receptor cell detects environmental conditions.

Supporting evidence that rhodopsin governs the response to a light stimulus can be found by comparing the absorption spectrum of *Limulus* rhodopsin with the sensitivity of the *Limulus* eye at various wavelengths. In 1935 Clarence H. Graham and Hartline measured the intensity of flashes at several wavelengths required to produce a fixed number of impulses in the *Limulus*



NERVE IMPULSES TRIGGERED BY LIGHT are directly related to intensity of steady light falling on the *Limulus* eye. Recordings were made from the optic nerve fiber arising from one ommatidium. At high light intensity (*top*) the nerve fires about 30 times per second. As intensity is reduced by factors of 10, firing is reduced in uniform steps, falling to a low of two or three impulses per second.

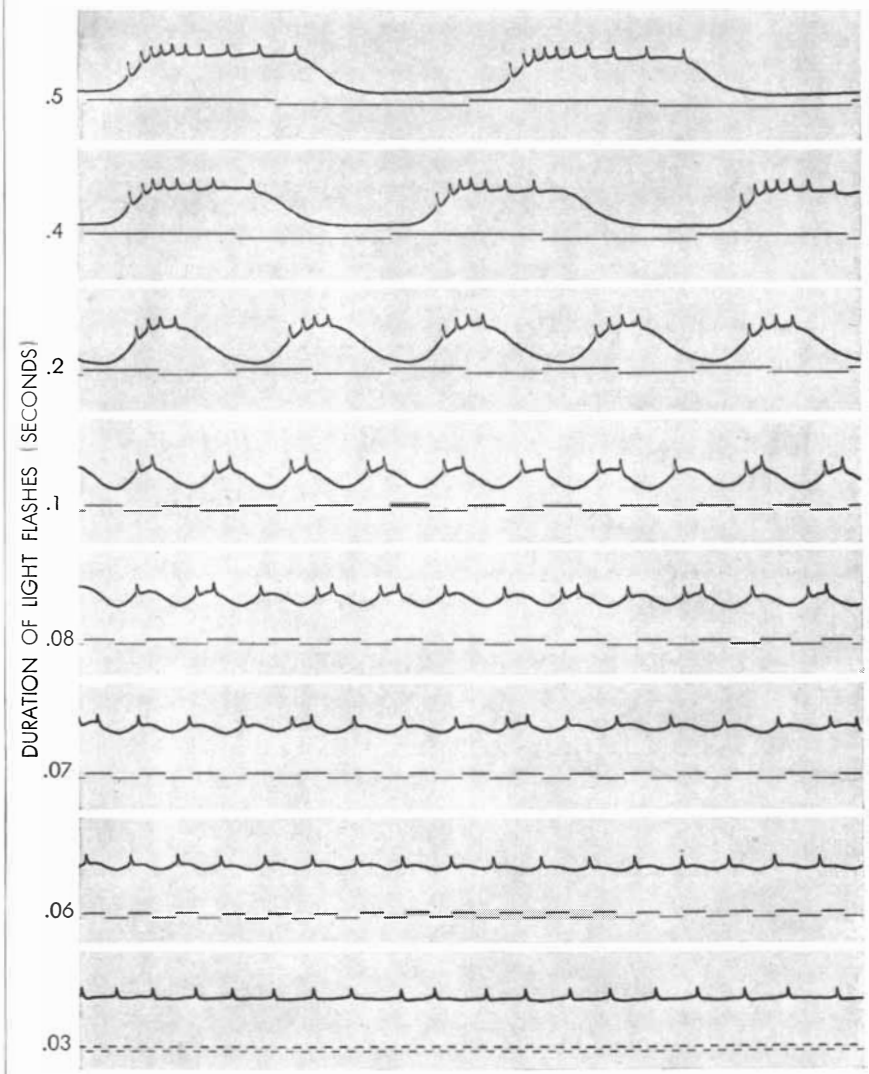


DURATION AND INTENSITY OF LIGHT have equivalent effect on the *Limulus* eye. Evidently the receptor responds to the total amount of energy received in a brief flash (*arrows*) regardless of how the energy is "packaged" in duration and intensity. Thus a brief intense flash (*top left*) evokes about the same response as a flash a 1,000th as bright lasting 1,000 times longer (*bottom right*).

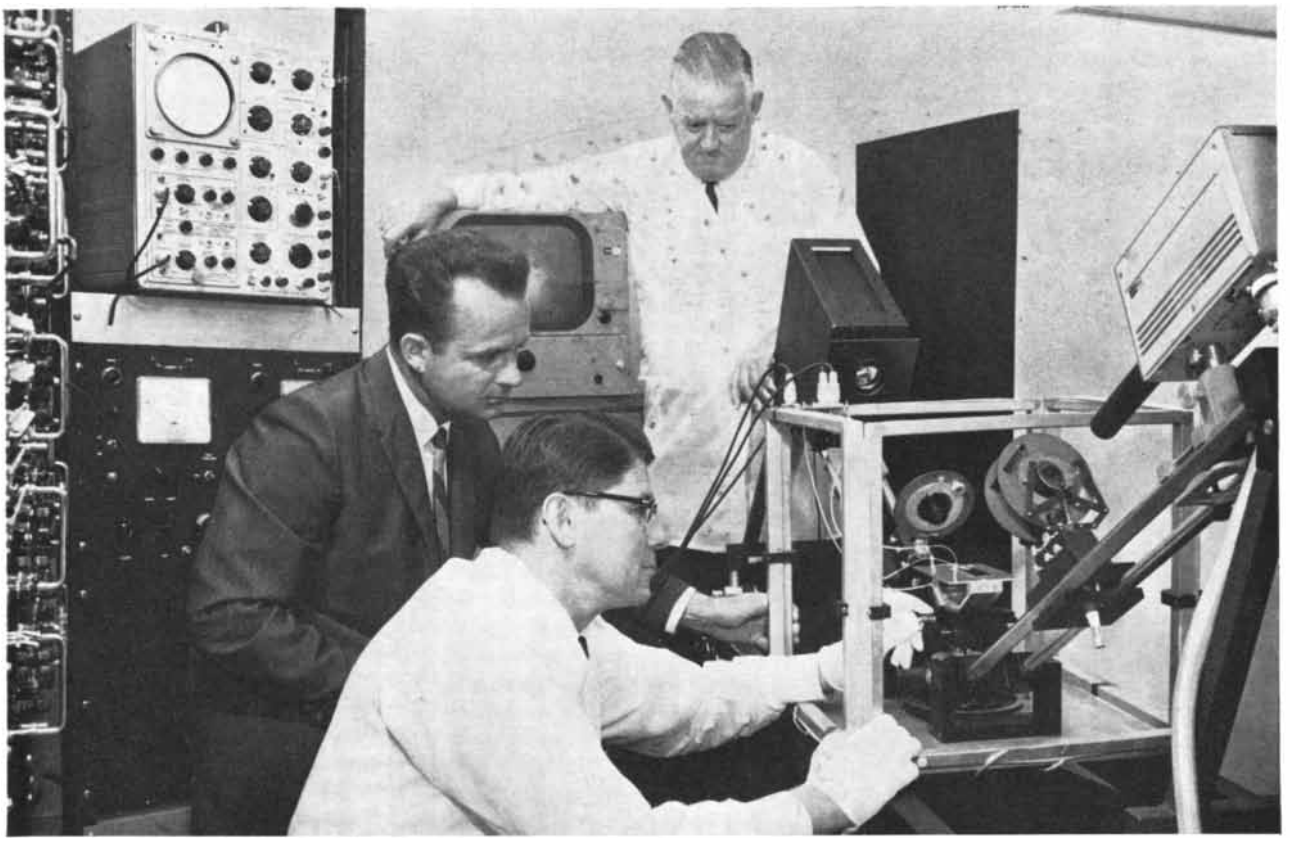
optic nerve. When a sensitivity curve obtained from this experiment is superimposed on the absorption curve found by Hubbard and Wald for *Limulus* rhodopsin, the two match almost perfectly. At a wavelength of about 520 angstrom units, where rhodopsin absorbs light most strongly, the *Limulus* eye generates the highest number of impulses for a given quantity of light energy received. It turns out that the wavelength sensitivity of the *Limulus* eye is close to that of the human eye in dim light when rod vision dominates.

Many other familiar sensory experiences are manifestations of the properties of individual sense cells. Perhaps the most elementary experience is our ability to perceive when a stimulus has been increased in intensity. Under such circumstances we can be sure that the sensory fibers conveying information to the brain are firing more rapidly as the stimulus is increased. We are also familiar with the experience of sensory adaptation; for example, a strong odor usually seems to decrease in intensity after a time, although objective measurements would show that its intensity has remained constant.

We know from photography that shutter speed and lens opening can be interchanged to produce a constant exposure, which is the same as saying that intensity and duration of illumination can be interchanged (within limits) to produce a constant photochemical effect. The same equivalence holds for the



EFFECT OF FLICKERING LIGHT on the *Limulus* ommatidium provides a basis for explaining "flicker fusion": the inability to perceive a rapid flicker. The recordings show the response of the ommatidium to a light flickering at various rates; when the horizontal line is raised, the light is on. At low flicker rates the generator potential, indicated by a rise in base potential, rises and falls. As flicker rate increases, the generator potential no longer falls between flashes, and spacing between nerve impulses becomes more uniform.



Watching a magnetic thin-film shift register in operation: Mr. K. D. Broadbent (center) and Mr. A. W. Vance (standing) of the Research Laboratories, with Mr. G. Cokas of Technical Plans and Programs.

A special report from American Systems Incorporated...

Thin-Film Digital Devices

Supporting the trend in computer technology toward higher speeds, smaller size, and increased reliability, American Systems Incorporated has been conducting an intensive research and development program in thin-film digital devices.

The first of these, a microminiature magnetic thin-film shift register, is in the prototype production stage. This register, mounted on a 1-inch by 3-inch base, can store 256 bits and operate up to 1 megacycle per second. Originated by Kent D. Broadbent, ASI Research Laboratories scientist, the new register is characterized by precise bit definition, high immunity to noise, and low power requirement.

Advanced magnetic thin-film devices now under development include three-dimensional multiple plane systems. In these, complete logical sequences may be performed within the magnetic structure, without the need to convert information at intervals into electronic signals. Research interests include dielectric, conducting, semiconducting, and superconducting films, and crystal growth and ordering phenomena in films.

Complementing the work of the Research Laboratories, technical programs are under way at American Systems in six other Divisions:

INFORMATION SCIENCES
Mathematical and statistical research; computer programming, and advanced programming systems; computation services; digital system studies; logical design, advanced systems analysis.

DATA PROCESSING
Data processing subsystems research and development; logic of command and control complexes; optical recognition systems.

ELECTROMAGNETIC SYSTEMS
Electromagnetic physics; electronic and mechanical scanning antenna systems; development and manufacturing of complete sensor systems and special microwave components.

INSTRUMENTS
Research and development in analytical instruments; detection and monitoring of toxic high-energy missile fuel vapors; gas leak and water vapor detection; on-stream and process control instrumentation.

COMPONENT DEVELOPMENT
Advanced component technology; materials and processes; computer component development; chemical deposition of magnetic surfaces on drums, disks, rods.

AUDIO-VISUAL
Audio-visual (INSTRUCTRON) devices for assembly line and instructional applications; production of work stations designed on human factors principles.

Qualified scientists and engineers who are interested and experienced in these fields of activity are encouraged to investigate career opportunities with American Systems. All qualified applicants will receive consideration regardless of race, creed, color, or national origin.

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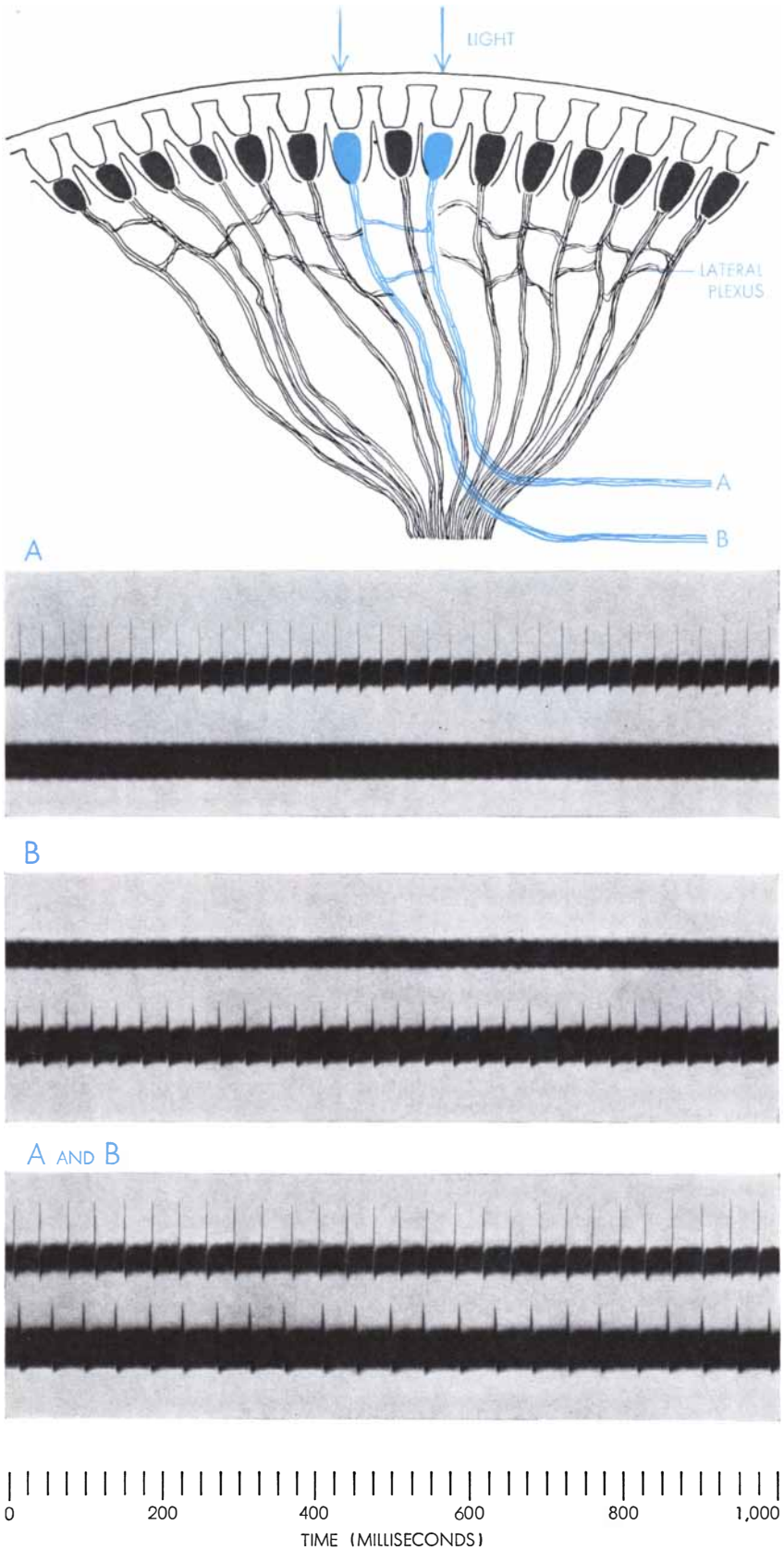


MUTUAL INHIBITION results when two neighboring ommatidia are illuminated at the same time (*top*). The inhibition is exerted by cross connections among nerve fibers. When ommatidia attached to fiber *A* and fiber *B* were illuminated separately, 34 and 30 impulses were recorded respectively in one second. Illuminated together, they fired less often.

human eye exposed to short flashes of light, and the equivalence can be demonstrated in the photoreceptor of *Limulus*. About the same number of nerve impulses are produced by exposing the ommatidium to a weak light for a 10th of a second as by exposing it to light 10 times as bright for a 100th of a second [*see bottom illustration on page 231*].

We also know from watching motion pictures or television that a light flickering at a high rate appears not to be flickering at all. A neural basis for this phenomenon can be seen in the generator potentials and nerve impulses recorded when a *Limulus* ommatidium is exposed to a light flickering at various rates [*see illustration on page 232*]. Flicker is detectable as fluctuations in the generator potential, which in turn gives rise to bursts of impulses. As the repetition rate increases, the rate of discharge becomes steadier and finally is indistinguishable from a response to continuous illumination. As can be seen from the records, this "flicker fusion" is directly attributable to the generator potential, which becomes smooth at the highest repetition rates.

The experiments described so far were carried out on single cells or single sensory units. In the eye, ear and other organs, however, receptor cells are grouped close together and usually act in concert. In fact, modern studies show that receptor cells of complex sense organs seldom act independently. In such organs the receptor cells are interconnected neurally and as a result of these connections new functional properties arise.

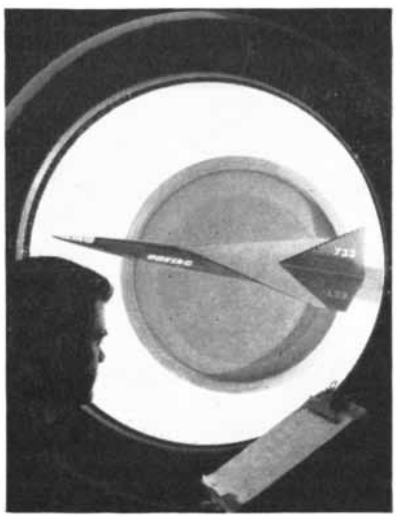
Although the compound eye of *Limulus* is much less complex than the eyes of vertebrates, it still shows clearly the effects of neural interaction. In *Limulus* the activity of each photoreceptor unit is affected to some degree by the activity of adjacent ommatidia. The frequency of discharge of impulses in an optic nerve fiber from a particular ommatidium is decreased—that is, inhibited—when light falls on its neighbors. Since each ommatidium is a neighbor of its neighbors, mutual inhibition takes place. This inhibition is brought about by a branching array of nerve axons that make synaptic contact with each other in a feltwork of fine fibers behind the ommatidia. The inhibition probably results from a decrease in the magnitude of the generator potential at the site of origin of the nerve impulses, as a consequence of which the rate of firing is slowed down.

When two adjacent ommatidia are

JET TEST BOAT. Boeing jet-powered research hydroplane, capable of speeds up to 100 knots, is newest addition to Boeing equipment devoted to advancing man's knowledge. Aqua-Jet will be used to test experimental hydrofoil designs. Test model is suspended between prows from structure which controls action of model being pushed through water. These hydrodynamic design studies are typical of expanding Boeing efforts in marine field, which include building a hydrofoil patrol craft for U.S. Navy.

Capability has many faces at Boeing

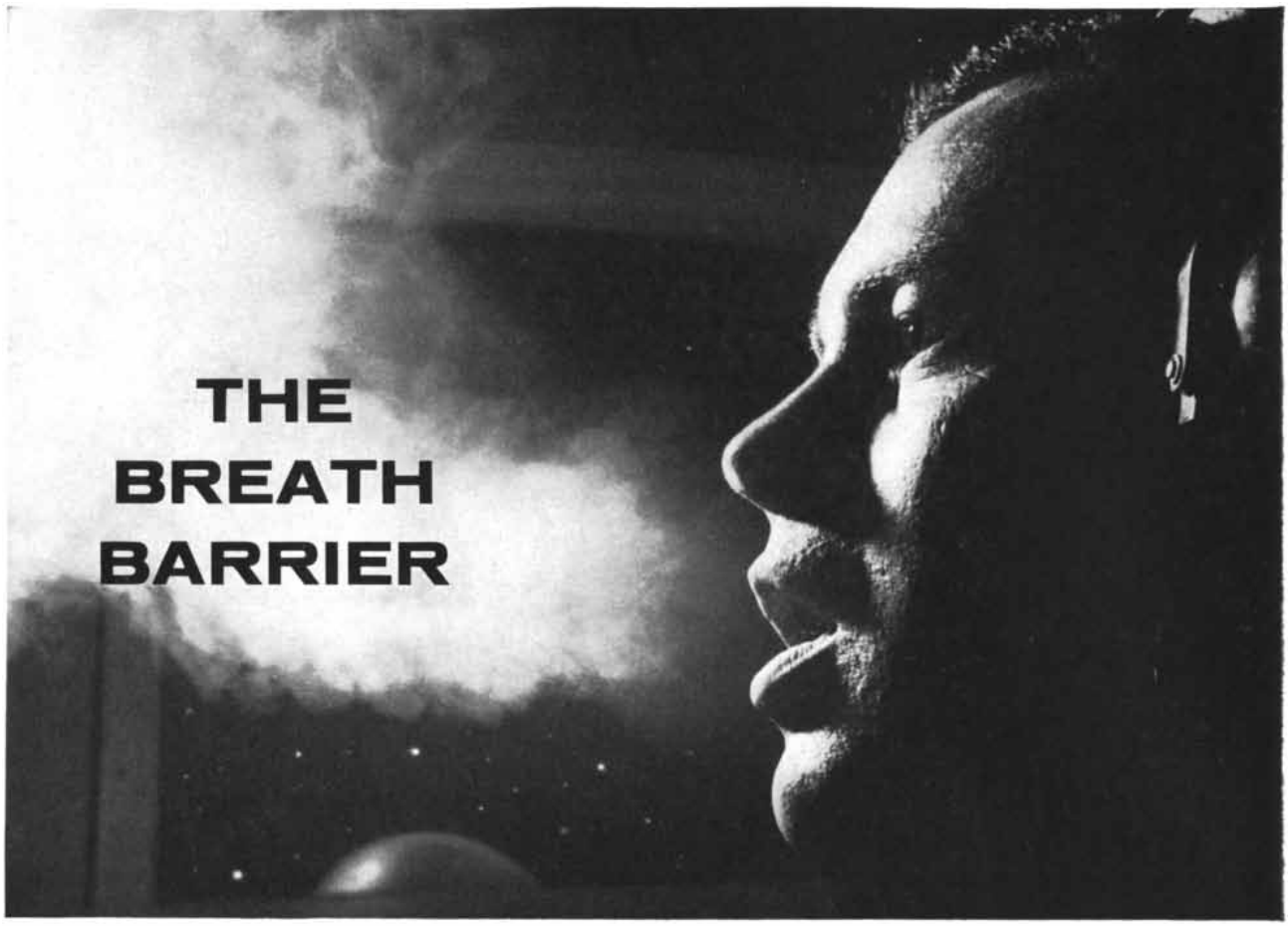
CARGO-JET. Boeing C-135 cargo-jet, first of 30 ordered by the Military Air Transport Service, has already been delivered. These 30 C-135s will provide MATS with work capability equivalent to 100 propeller-driven transports.



SUPERSONIC transport model being tested in Boeing wind tunnel. Boeing is investing substantial sums in supersonic transport research. Future skyliners would be able to fly from New York to London in less than three hours.

SPACE GLIDER. Drawing of Dyna-Soar, U.S. Air Force manned space glider designed to rocket into space, then re-enter earth's atmosphere for conventional pilot-controlled landing. Dyna-Soar is being developed by U.S. Air Force in cooperation with NASA, with Boeing as prime contractor for both the system and the glider.

BOEING



Providing a safe atmosphere for man on extended flights into space will demand the most ingenious environment control system ever devised

Sustaining human life over long periods of time in a sealed space capsule is one of today's highest priority engineering tasks. The prime need: an infallible environment control system which will supply a safe breathing atmosphere . . . regulate temperature, humidity, pressure . . . remove toxic gases and other air contaminants . . . and still be so simple in design and construction that the crew can maintain it.

This system must not only satisfy classic airborne requirements for lightness, efficiency, compactness—but solve a myriad of new and extreme problems. Minute flow rates of liquids and gases must be metered under weightless conditions. Improved components must be developed to prevent gases from leaking—even in infinitesimal amounts. Proven techniques in system integration must be applied to assure fool-proof operation.

An intensive program, begun three years ago at Hamilton Standard, has already produced much of the basic data needed to build such a system. For example, a Hamilton Standard carbon dioxide removal subsystem, soon to be tested by the National Aeronautics & Space Administration, could, in present form, sustain three men in a sealed capsule indefinitely. Development of this unit and other devices to control humidity, temperature and pressure in space vehicles are logical extensions of experience Hamilton Standard has gained in building environment control systems for such advanced aircraft as the F-104, B-58, and the new B-70 bomber.

Life support research typifies Hamilton Standard's expanding capabilities in space and new fields of science. Other activities include solar power generators . . . missiles and space systems . . . electronics . . . ground support equipment . . . aerospace and industrial engine controls, starters, air-conditioning systems . . . electron beam welding and cutting machines . . . and new propellers.

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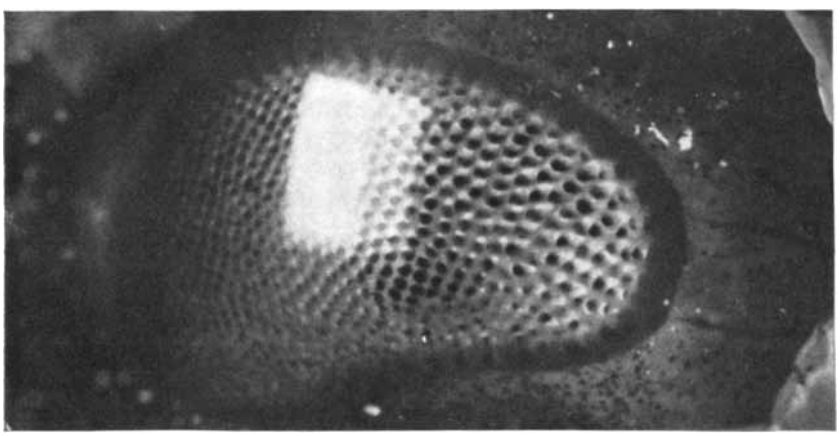
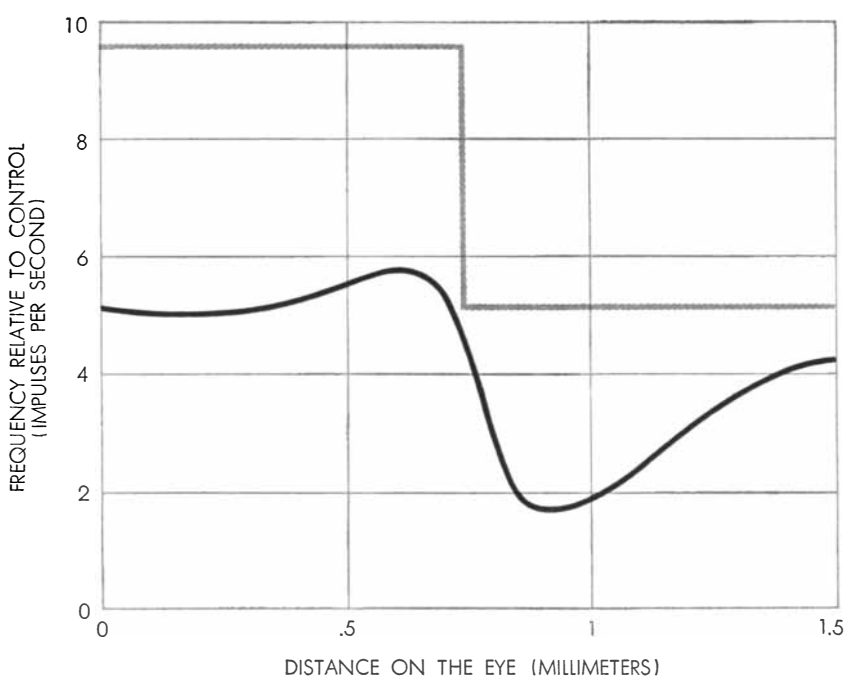
LIFE SUPPORT SYSTEMS

illuminated at the same time, each discharges fewer impulses than when it receives the same amount of light by itself [*see illustration on preceding page*]. The magnitude of the inhibition exerted on each ommatidium (in the steady state) depends only on the frequency of the response of the other. The more widely separated the ommatidia, the smaller the mutual inhibitory effect. When several ommatidia are illuminated at the same time, the inhibition of each is given by the sum of the inhibitory effects from all others.

Inhibitory interaction can produce important visual effects. The more intensely illuminated retinal regions exert a stronger inhibition on the less intensely illuminated ones than the latter do on the former. As a result differences in neural activity from differently lighted retinal regions are exaggerated. In this way contrast is heightened and certain significant features of the retinal image tend to be accentuated at the expense of fidelity of representation.

This has been shown by illuminating the *Limulus* compound eye with a "step" pattern: a bright rectangle next to a dimmer one [*see illustration below*]. The eye was masked so that only one ommatidium "observed" the pattern, which was moved to various positions on the retinal mosaic. At each position the steady-state frequency of discharge was measured. The result was





CONTRAST HEIGHTENING AT CONTOURS is demonstrated by letting "step" pattern of light, a bright area next to a darker one, fall on the *Limulus* compound eye (*top*). If eye is masked so light strikes only one ommatidium, a recording of its output forms a simple step-shaped curve (*bottom*) as the pattern is moved across the eye. If the eye is unmasked, the output of the single ommatidium is inhibited in varying degrees by the light striking its neighbors. The net effect (*lower curve*) is to heighten contrast at light-dark boundaries.

a faithful reproduction (in terms of frequency of impulses) of the form of the pattern. Then the eye was unmasked so that all the ommatidia observed the pattern, and a recording was again made from the single ommatidium. This time the frequency increased on the bright side of the step and decreased near the dim side. This is expected because near the bright side of the step the neighboring ommatidia illuminated by the dim part of the step pattern have a low frequency of firing and therefore do not exert much inhibition. Consequently the frequency of discharge of the receptors on the bright side of the step is higher than its equally illuminated but more distant neighbors. Similar reasoning explains the decrease in frequency on the dim side of the step. The net effect of this pattern of response is to enhance contours, an effect we can easily demonstrate in our own vision by looking at a step pattern consisting of a series of uniform gray bands graded from white to black. Artists are quite familiar with the existence of "border contrast" and may even heighten it in their paintings. And as we all know, significant information is conveyed by contours alone, as is demonstrated by cartoons and other line drawings. Georg von Békésy of Harvard University has suggested that a similar reciprocal inhibition in the auditory system would lead to a sharpening of the sense of pitch.

There is also evidence that in many sense organs the response can be modified by neural influences exerted back onto them by higher centers of the nervous system. Thus the sensitivity of the vertebrate stretch receptor or muscle spindle is established by variations in the length of the spindle fibers, and this length is dependent both on the output of the receptor and on its interaction with higher centers. The sensitivity of the vertebrate olfactory receptors can also be altered, in all probability, by the flow of impulses from above. Similar influences, not yet well understood, also seem to be at work in the retina of the eye.

It is evident, then, that the responses of complex sense organs are determined by the fundamental properties of the individual receptor cells, by the influences they exert on one another and by control exerted on them by other organs. In this way the activity of the receptor cells is integrated into complex patterns of nervous activity that enable organisms to survive in a world of endless variety and change.

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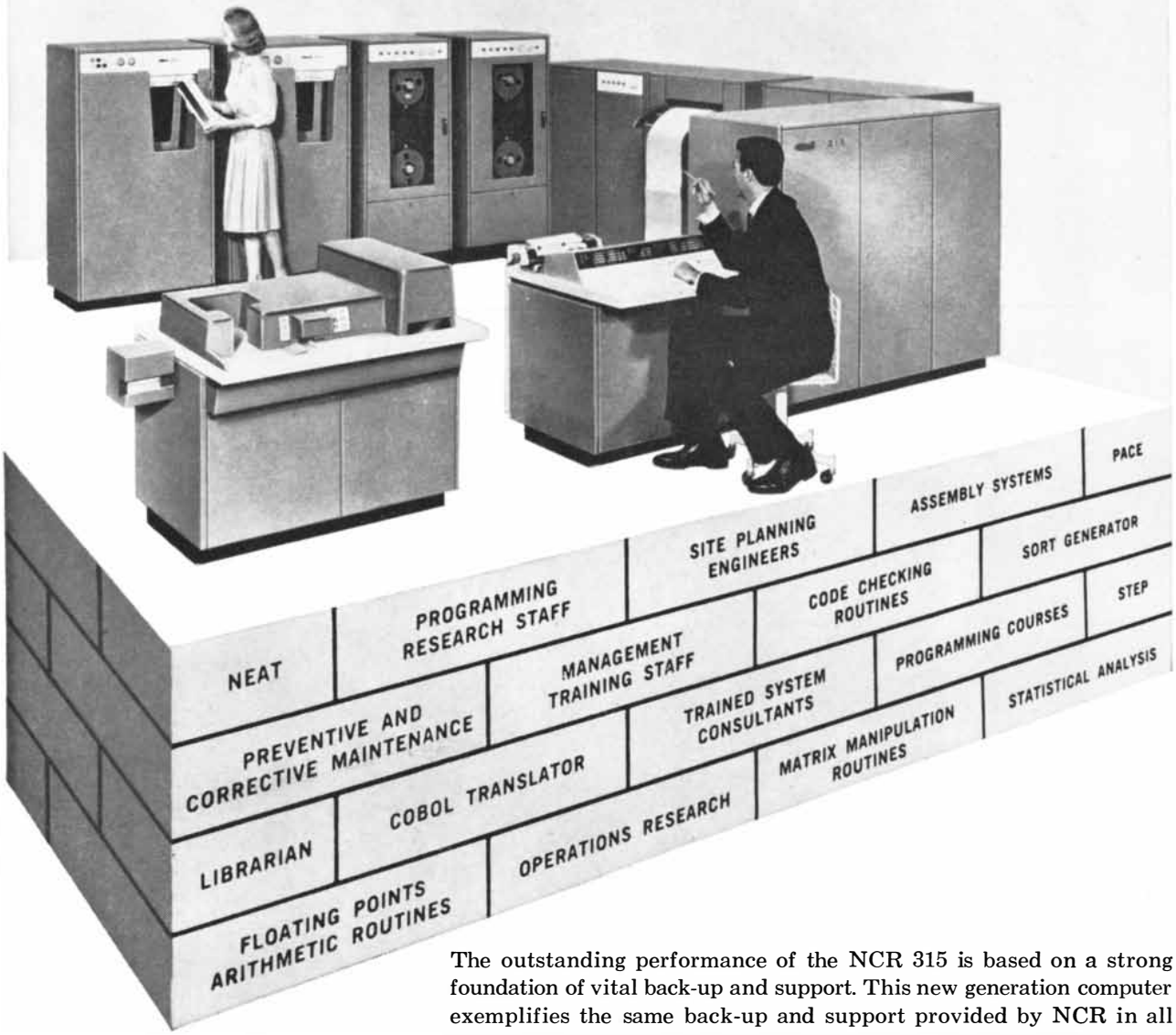

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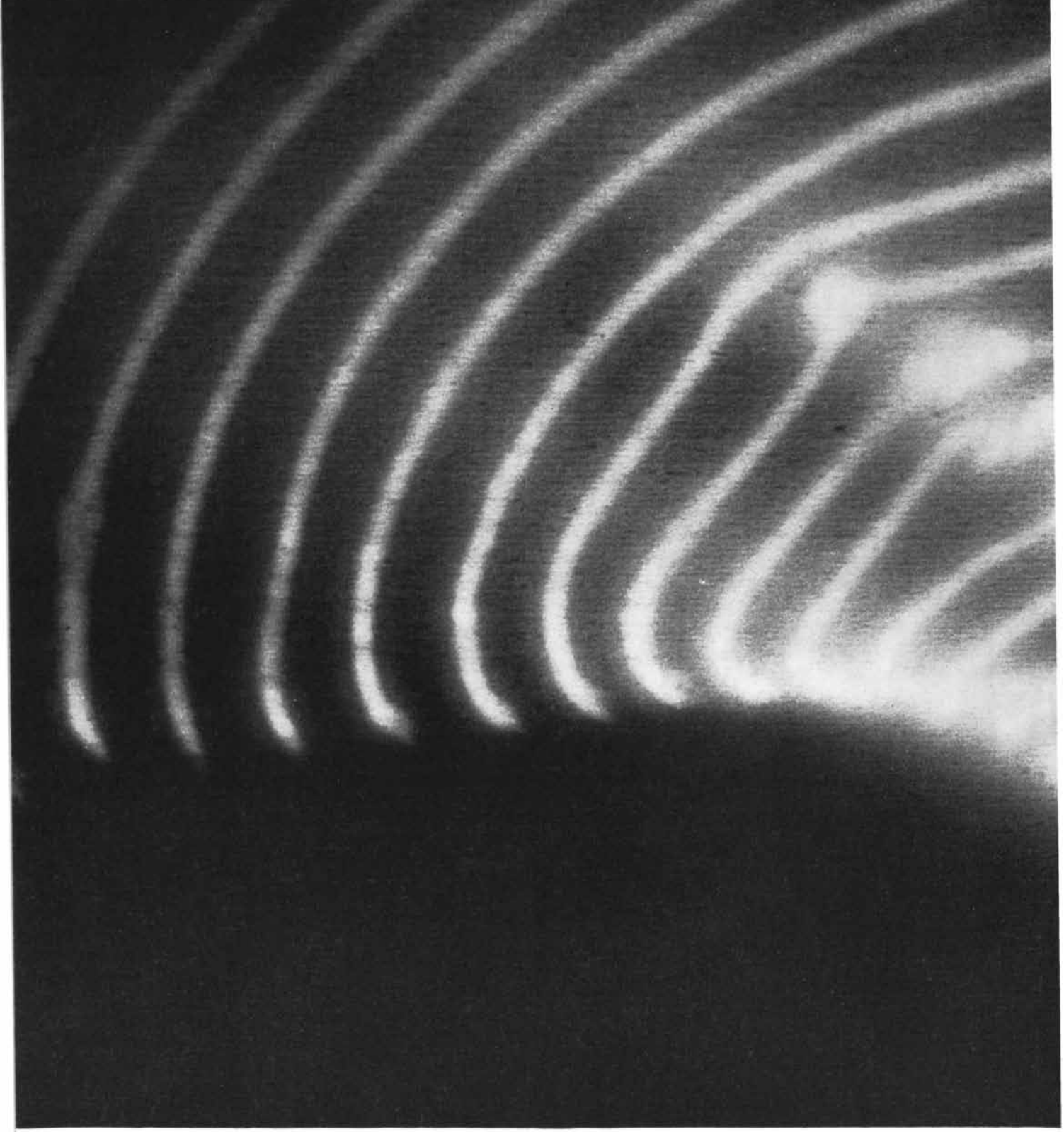

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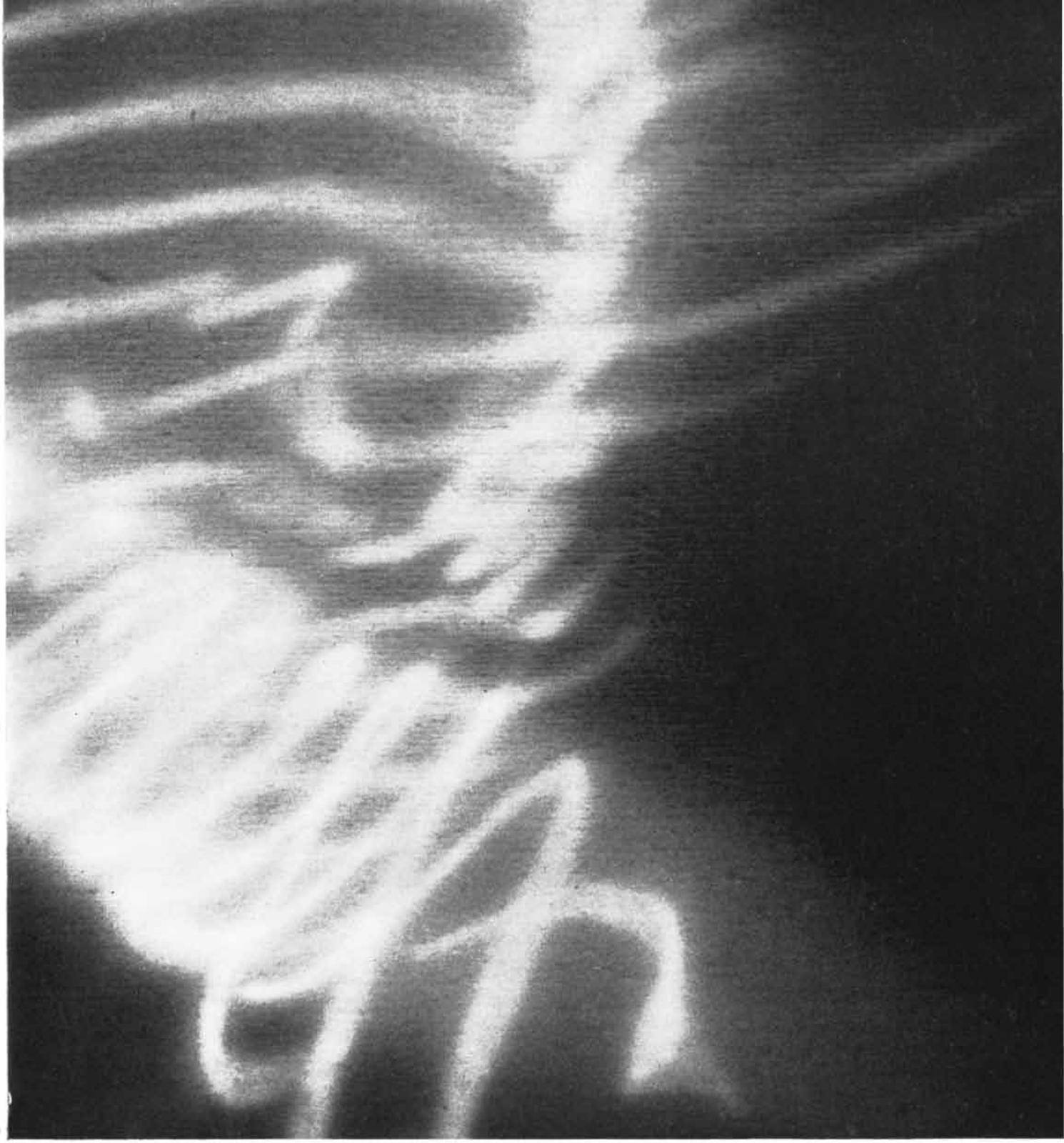

You're so sure the answer's there. From what you already know... from what's been proved so far, it has to be. But that's when your hardest work begins. To give your answer precise shape and substance. To prove it. And use it to move to the next step. At some point during your quest, there's a good chance CEC can come in and help. Because this is exactly what CEC men do for a living — find the means and build the instruments to measure, record, and analyze some of the things that can help supply you with the answer you must have. Are you in the middle of such an answer search right now? Or looking for a starting point on a problem? Call in a man from the CEC sales and service office nearest you. It's worth a try.

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MATHEMATICAL GAMES

Surfaces with edges linked in the same way as the three rings of a well-known design

by Martin Gardner

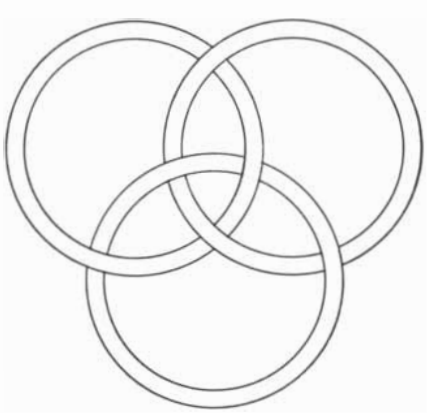
Three curiously interlocked rings, familiar to many people in this country as the trade-mark of a popular brand of beer, are shown in the illustration below. Because they appear in the coat of arms of the famous Italian Renaissance family of Borromeo they are sometimes called Borromean rings. Although the three rings cannot be separated, no two of them are linked. It is easy to see that if any one ring is taken from the set, the remaining two are not linked.

In a chapter on paper models of topological surfaces, which appears in *The First Scientific American Book of Mathematical Puzzles and Diversions*, I mentioned that I knew of no paper model of a single surface, free of self-intersection, that has three edges linked in the manner of the Borromean rings. "Perhaps," I wrote, "a clever reader can succeed in constructing one."

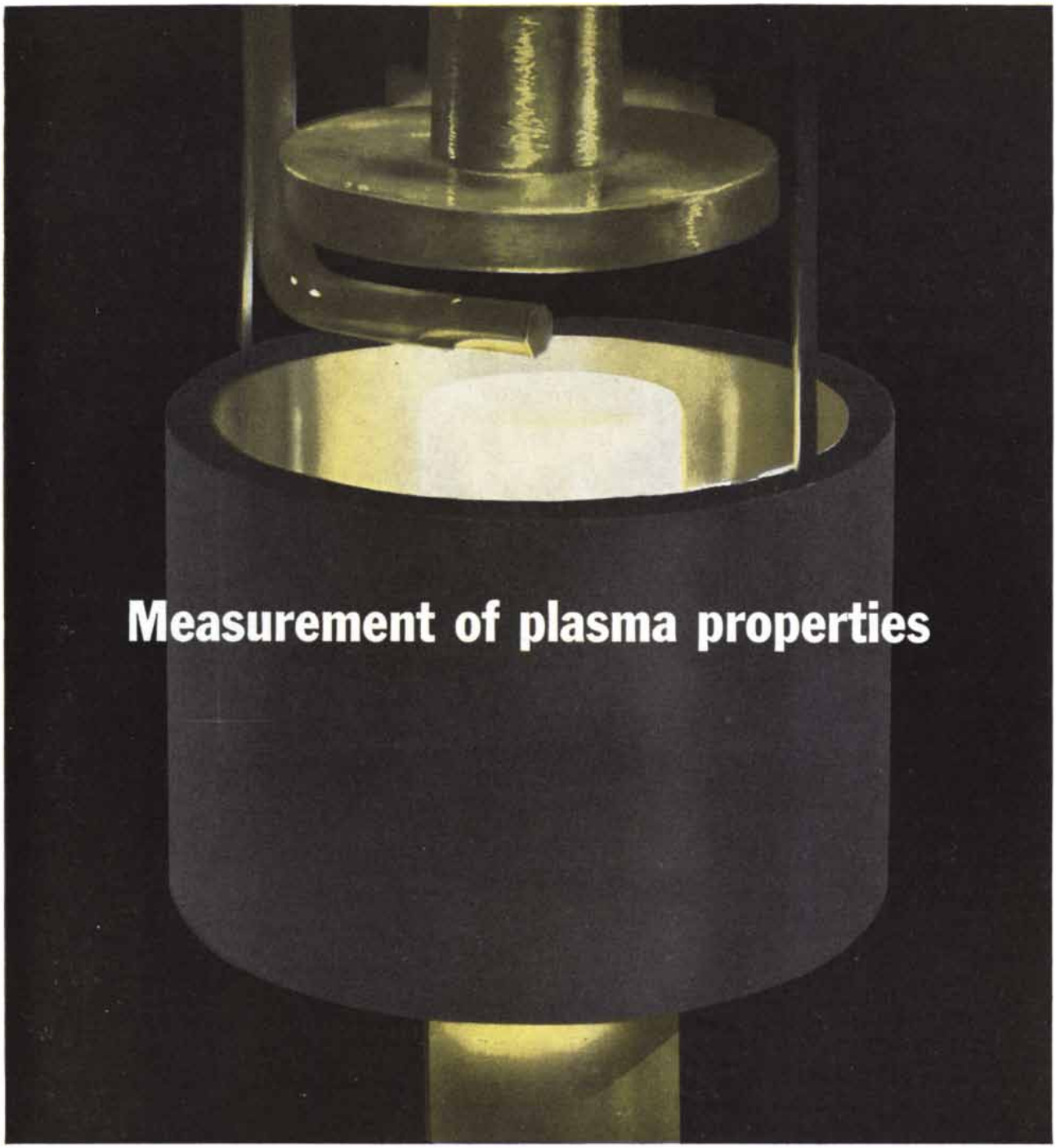
This challenge was first met in the fall of 1959 by David A. Huffman, associate professor of electrical engineering at the Massachusetts Institute of Technology. Huffman not only succeeded in making models of several different types of surface with Borromean edges; in doing so he also hit upon some beautifully simple methods by which one can construct paper models of a surface with edges that correspond to any type of knot or set of knots—interlaced, interwoven or linked in any manner whatever. Later he discovered that essentially the same methods have been known to topologists since the early 1930's, but because they had been described only in German publications they had escaped the attention of everyone except the specialists.

Before applying one of these methods to the Borromean rings, let us see how the method works with a less complex structure. The simplest closed curve in space is, of course, a curve that is not knotted. Mathematicians sometimes call it a knot with zero crossings, just as they sometimes call a straight line a curve with zero curvature. Diagram 1 in the illustration on page 244 is such a curve. The colored area in the diagram represents a two-sided surface whose edge corresponds to the curve. It is easy to cut the surface out of a sheet of paper. The actual shape of the cutout does not matter, because we are interested only in the fact that its edge is a simple closed curve. But there is another way to color the diagram. We can color the *outside* of the curve [*diagram 2 in the illustration on page 244*] and imagine that the diagram is on the surface of a sphere. Here the closed curve surrounds a *hole* in the sphere. The two models—the first cutout and the sphere with the hole—are topologically equivalent. When put together edge to edge, they form the closed, two-sided surface of a sphere.

Now let us try the same method on a slightly more complicated diagram [*diagram 3 in the illustration*] of the same space curve. Think of this curve as a piece of rope. At the crossing we indicate that one segment of rope passes under the other, like a highway underpass, by breaking the line as shown. This curve also is a knot of zero crossings, because it can be manipulated so that the crossing is eliminated. (The order of a knot is the minimum number of crossings to which the knot can be reduced by deformation.) As before, we shade the



The three Borromean rings



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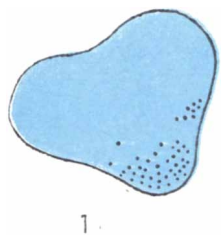
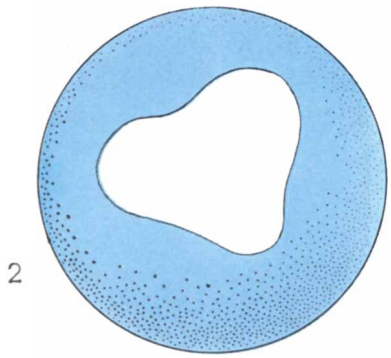
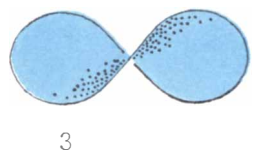
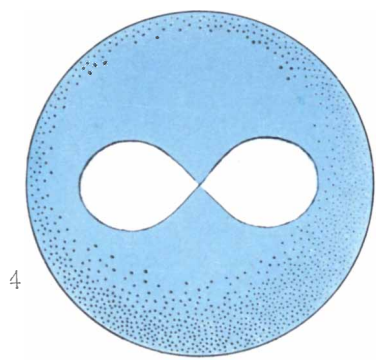








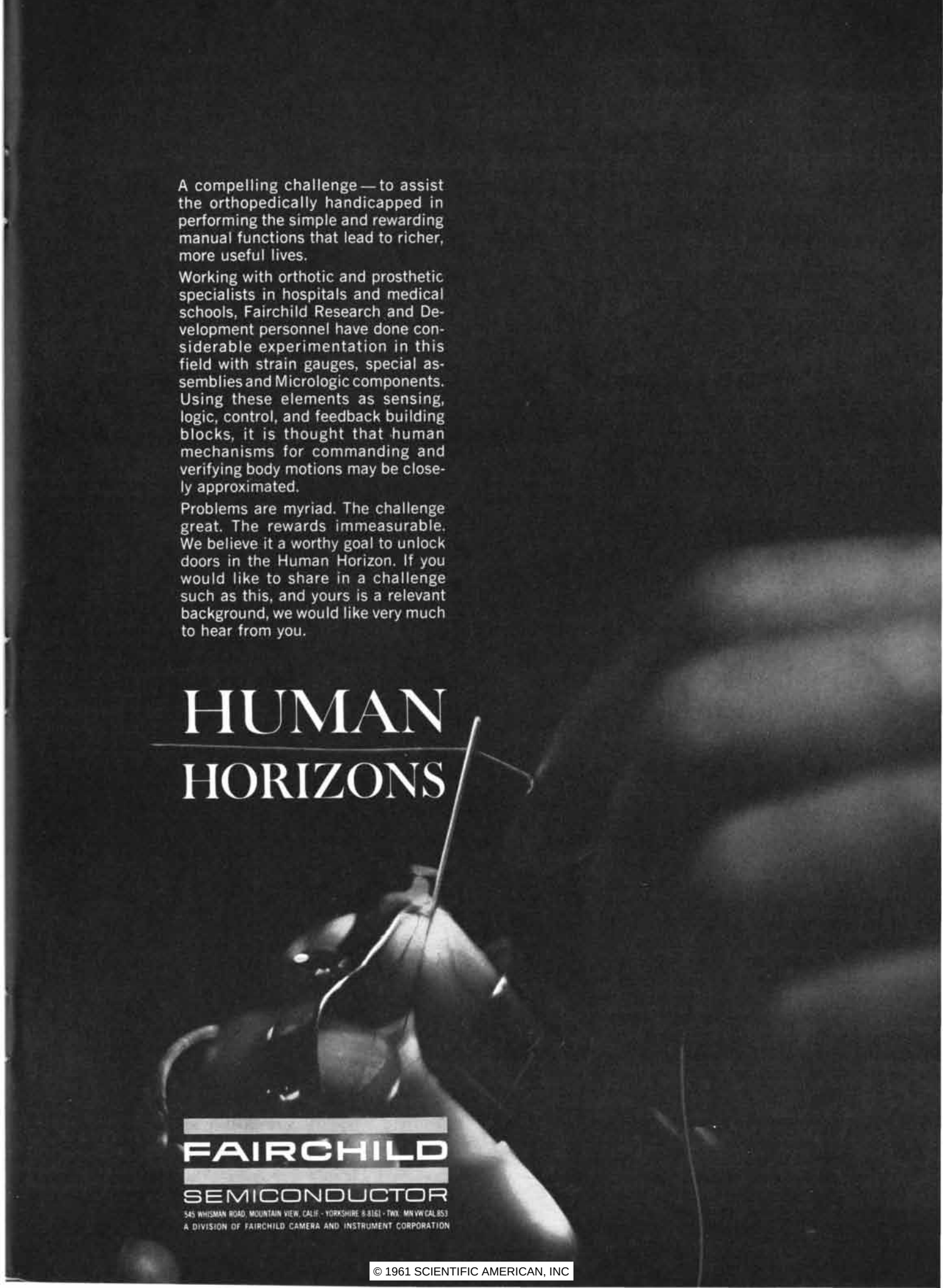
Models of surfaces with an unknotted edge

diagram with two colors, tinting it so that no two regions with a common boundary have the same color. This can always be done in two different ways, one a reverse print of the other.

If we color diagram 3 as shown in the illustration, the model is merely a sheet of paper with a half-twist. It is two-sided and topologically equivalent to each of the previous models. But when we color the diagram in the alternate way [*diagram 4*], regarding the white spaces as holes in a sphere, we obtain a surface that is a Möbius strip. It too has an edge that is a knot of zero crossings (that is, not a knot), but now the surface is one-sided and topologically distinct from the preceding model. The closed, no-edged surface that results when the two models are fitted together is a cross cap, or projective plane: a one-sided surface that cannot be constructed without self-intersection.

The same general procedure can be applied to the diagram of any knot or group of knots, linked together in any manner. Let us see how it applies to the Borromean rings. The first step is to map the rings as a system of underpasses, making sure that no more than two roads cross at each pass. Next, we color the map in the two ways possible [*diagrams 1 and 2 in the illustration on page 246*]. Each crossing represents a spot where the paper surface (the shaded areas) is given a half-twist in the direction indicated. The one-sided surface shown in diagram 1 is easily made with paper, either in the elegant symmetrical form shown or in topologically equivalent forms such as the one depicted in diagram 3. The model that results from diagram 2, with the Borromean rings outlining the holes in a sphere, seems at first glance quite different from the preceding model. Actually it is topologically the same. Sometimes the two methods of coloring lead to equivalent models, sometimes not.

It can be proved that this double procedure can be applied to any desired knot or group of knots, of any order, linked together in any manner. Most models obtained in this way, however, turn out to be one-sided, or what topologists call "nonorientable." Sometimes it is possible to rearrange the crossings of the diagram so as to yield an orientable (two-sided) surface, but usually it is extremely difficult to see how to make this sort of modification. The following



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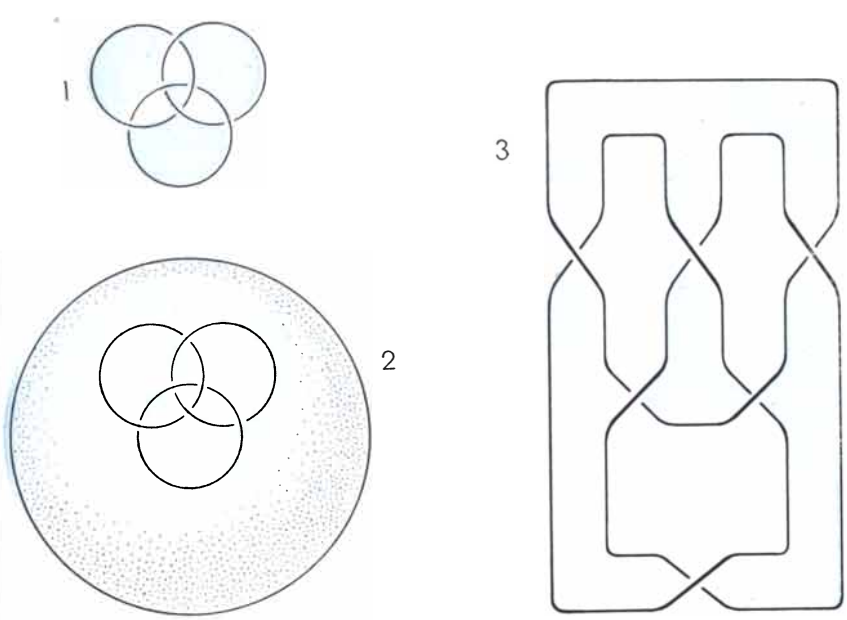
method, also rediscovered by Huffman, guarantees a two-sided model.

To illustrate the procedure, let us apply it to the Borromean rings. First draw the diagram, but with light pencil lines. Place the point of the pencil on any one of the curves and trace it around, in either direction, back to the starting point. At each crossing make a small arrow to indicate the direction in which you are traveling. Do the same with each of the other two curves. The result is diagram 1 in the illustration on page 248.

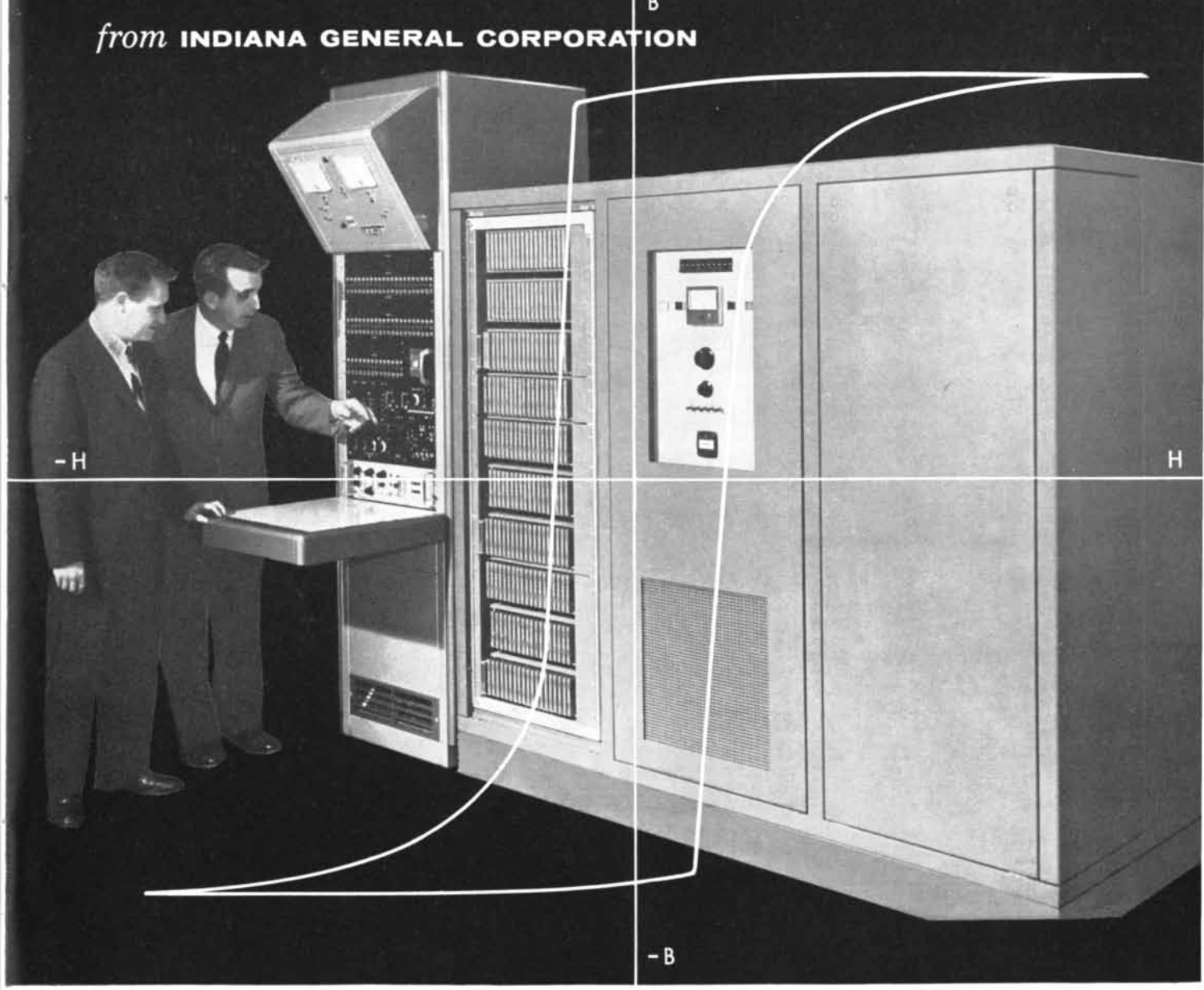
Now go over this diagram with a heavier pencil or crayon, starting at any point and moving in the direction of the arrows for that curve. Each time you come to a crossing turn either right or left as indicated by the arrows on the intersecting strand. Continue along the other strand until you reach another crossing, then turn again, and so on. It is as if you were driving on a highway and each time you reached an underpass or overpass you leaped to the other road and continued in the direction its traffic was moving. You are sure to return to your starting point after tracing out a simple closed curve. Now place the crayon at any other point on the diagram and repeat the procedure. Continue until you have gone over the entire diagram. Interestingly enough, the closed paths produced in this way will never intersect one another. In this case the result will look like diagram 2 in the illustration on page 248.

Each closed curve represents an area of paper. Where two areas are alongside each other, the touching points represent half-twists (in the direction indicated on the original diagram) that join the areas. Where one area is *inside* another, the smaller area is regarded as being above the larger, like two floor levels in a parking garage. The touching points represent half-twists, but now the twists must be thought of as twisted ramps that join the two levels. The finished model is shown at 3 in the illustration on page 248; it is two-sided and its three edges are Borromean. It can be proved that any model constructed by this procedure will be two-sided. This means that it can be painted in two contrasting colors, or constructed from paper that is differently colored on its two sides, without having one color run into the other.

The reader may enjoy building models of other knots and linkages. The figure-of-eight knot, for example, leads to very pleasing, symmetrical surfaces. The first diagram in the illustration on page 251 is one way in which this familiar knot can be mapped. Diagrams of this sort, by the way, are used in knot theory for determining the algebraic expression for a given knot. Equivalent knots, in the sense that one can be deformed into the other, have the same algebraic formula, but not all knots with the same formula are equivalent. It is always assumed, of course, that the knots are tied in closed curves in three-dimensional space. Knots in ropes open at the ends, or in closed curves



Topologically equivalent one-sided surfaces with Borromean-ring edges



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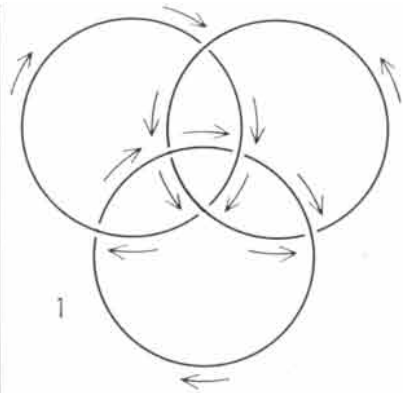
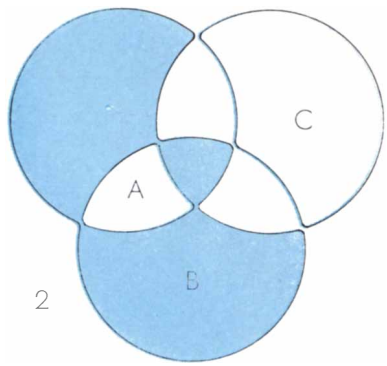
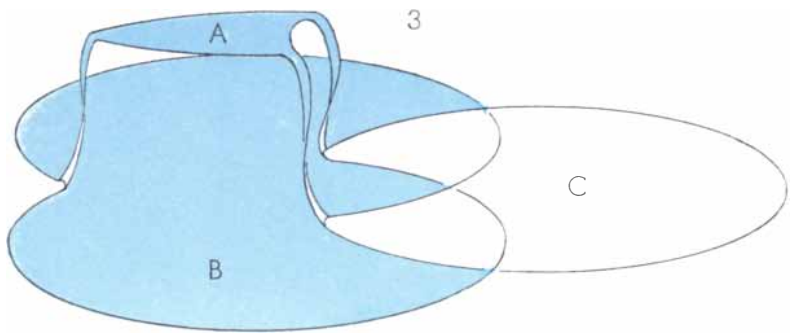






Steps in making a two-sided surface with Borromean-ring edges

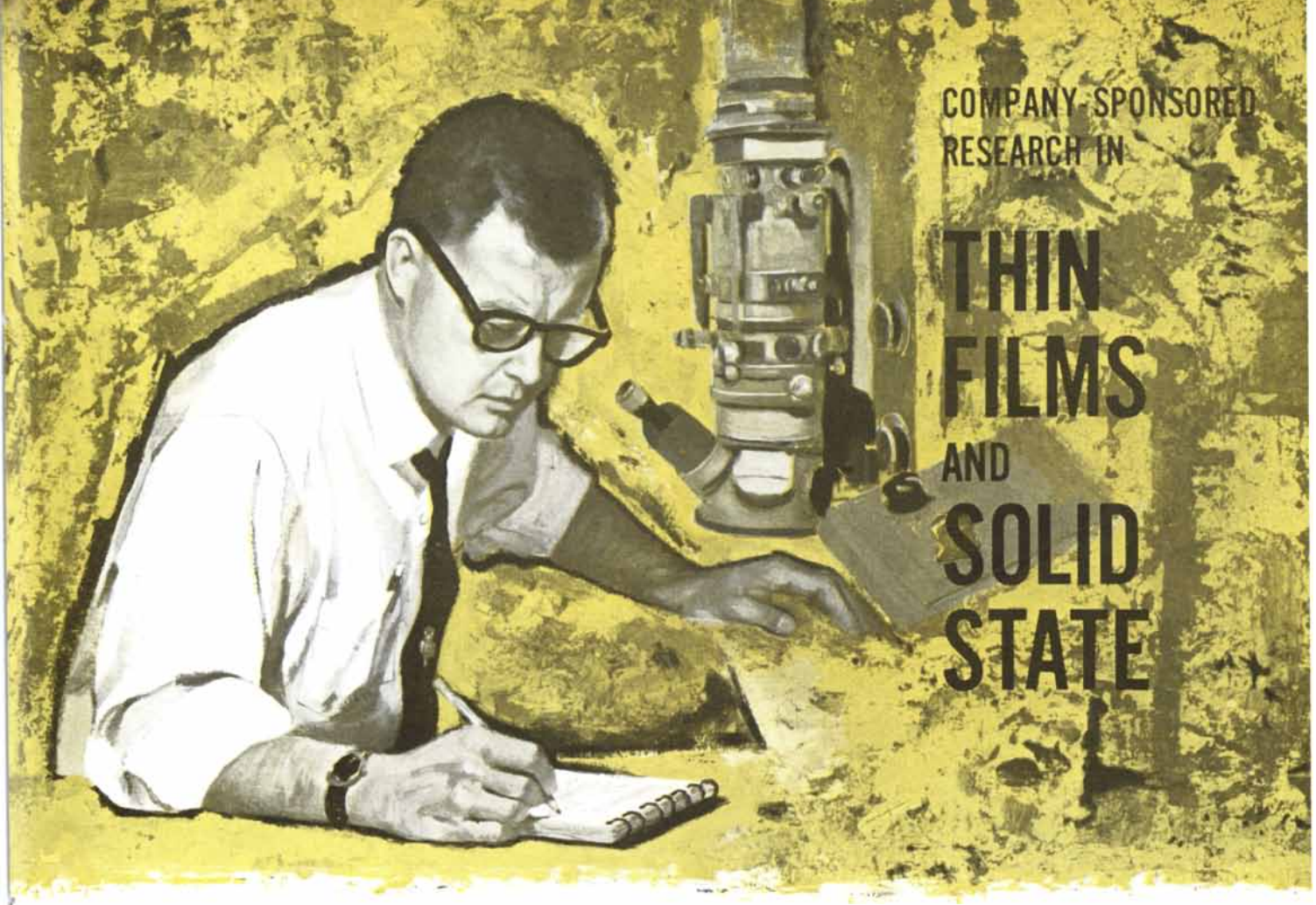
in four-dimensional space, can all be untied and are therefore equivalent to no knots at all.

The figure-of-eight knot is the only knot that reduces to a minimum of four crossings, just as the overhand or trefoil knot is the only type that has a minimum of three crossings. Unlike the trefoil, however, the figure-of-eight knot has no mirror image, or rather it can be deformed into its mirror image. Such knots are called "amphicheiral," meaning that they "fit either hand," like a rubber glove that can be turned inside out.

No knots are possible with one or two crossings. There are two five-crossers, five six-crossers, eight seven-crossers [*see illustration on page 251*]. This tabulation does not include mirror-image knots but does include knots that can be deformed into two simpler knots side by side. Thus the square knot [*knot 7 in the illustration*] is the "product" of a trefoil and its mirror image; the granny [*knot 8*] is the "product" of two trefoils of the same handedness. Knots 3 and 16 have very simple models. You have only to give a strip five half-twists and join the ends to make its edge form knot 3, seven half-twists to make it form knot 16.

A knot that cannot be deformed into simpler knots side by side is called a prime knot. All the knots in the illustration are prime except 7, 8 and 9 (knot 9 is a product of a trefoil and a figure-of-eight). Knots have been carefully tabulated up through 10 crossings, but no formula has yet emerged by which the number of different knots, given n crossings, can be determined. The number of prime knots with 10 crossings is thought to be 167, but since this number is based on empirical techniques, no knot theorist can be certain it is correct. Only wild guesses can be made as to the number of prime knots with 11 and 12 crossings.

Like topology, to which it obviously is closely related, the theory of knots is riddled with unsolved, knotty problems. There is not even a general method known for deciding whether or not any two given knots are equivalent or for telling whether a tangled space curve is knotted or not. To illustrate the latter difficulty, I have concocted the puzzle depicted in the illustration on page 252. This strange-looking surface is one-sided and one-edged, like a Möbius strip, but is the edge knotted? If so, what kind of knot is it? The reader is invited to study the picture, make a guess, then test his guess by the following empirical method. Construct the



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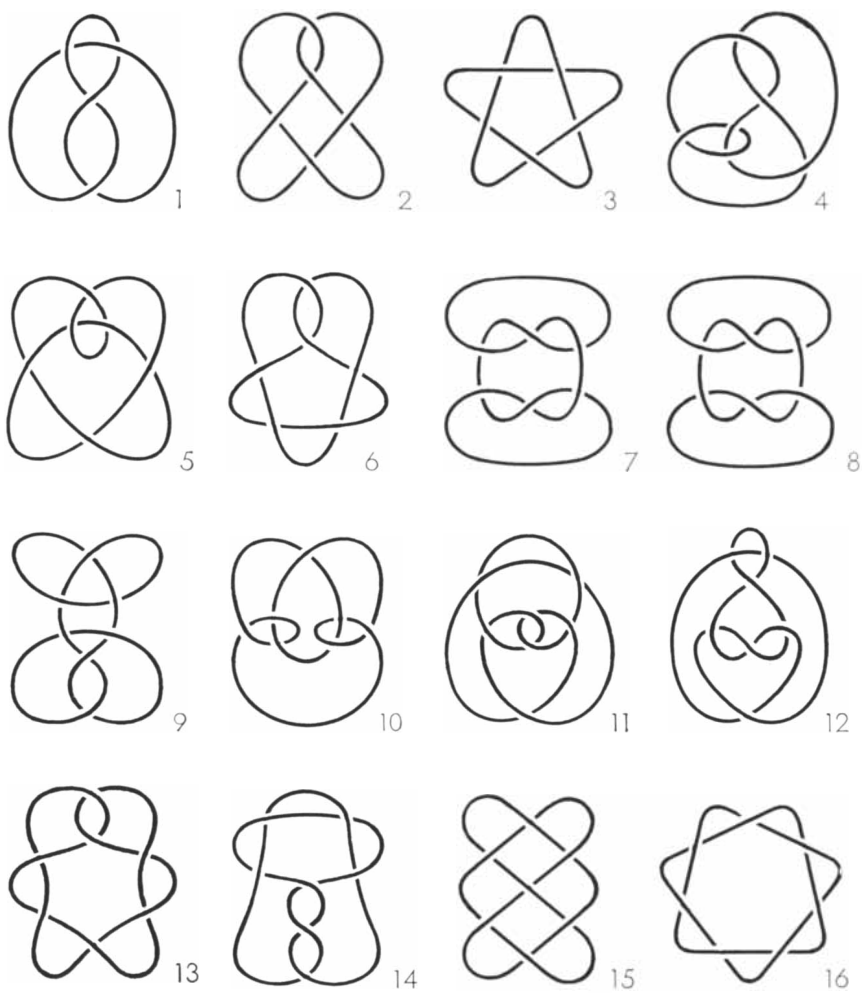
surface with paper and cut it along the colored line. This will produce one single strip that will be tied in the same type of knot as the edge of the original surface. By manipulating the strip carefully so as not to tear the paper you can reduce it to its simplest form and see if your guess is verified. The result may surprise you.

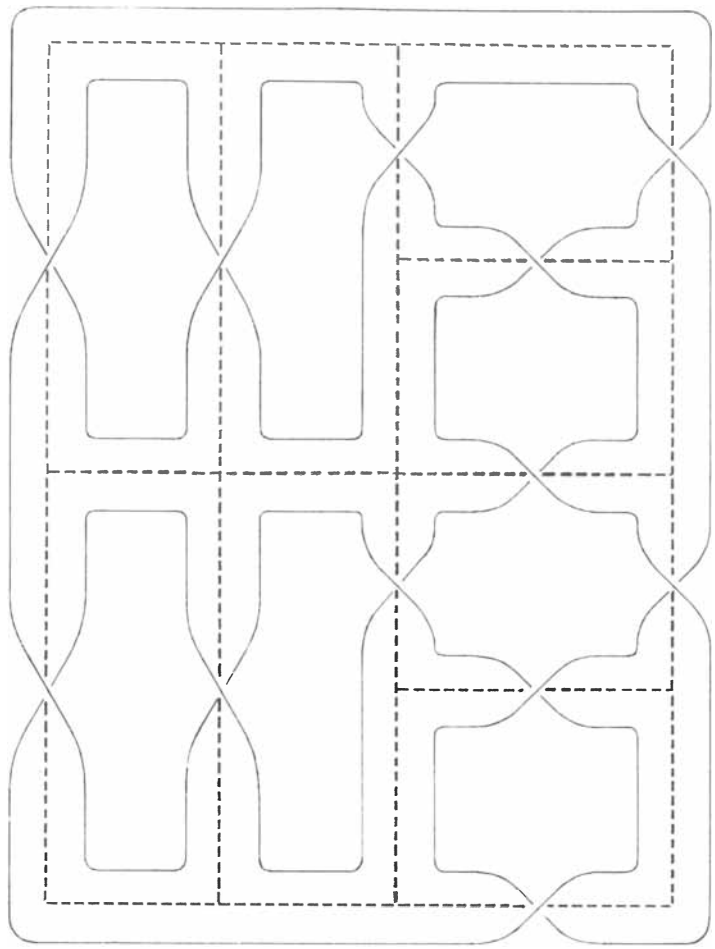
In the 1860's the British physicist William Thomson (later Lord Kelvin) developed a theory in which atoms are vortex rings in an incompressible, frictionless, all-pervading ether. J. J. Thomson, another British physicist, later suggested that molecules might be the result of various knots and linkages of Lord Kelvin's vortex rings. This led to a flurry of interest in topology on the part of physicists (notably the Scottish physicist Peter Guthrie Tait), but when the vortex theory was discarded, the interest waned. Perhaps it will revive now that chemists at the Bell Telephone Laboratories have produced radically new compounds, called catenanes, that consist of carbon molecules in the form of rings that are actually linked. It is now theoretically possible to synthesize compounds made up of closed chains that can be knotted and interlocked in bizarre ways. Who can guess what outlandish properties a carbon compound might have if all its molecules were, say, figure-of-eight knots? Or if its molecules were joined into triplets, each triplet interlocked like a set of Borromean rings?

Last month's problem was: How many different triangles can be formed with n straight lines? It takes at least three lines to make one triangle, four lines will make four triangles, five lines will make 10 triangles. Applying the calculus of finite differences, as explained last month, one draws up the table at the top of page 254.

The three rows of differences indicate a cubic function. Using Newton's formula, the function is found to be:



Knots of four crossings (1), *five crossings* (2, 3), *six crossings* (4–8) *and seven* (9–16)



A one-sided, one-edged surface. Is the edge knotted?

$\frac{1}{6}n(n-1)(n-2)$. This will generate the series 0, 0, 0, 1, 4, 10. . . and therefore has a good chance of being the formula for the maximum number of triangles that can be made with n lines. But it is still just a guess, based on a small number of pencil and paper tests. It can be verified by the following reasoning.

The lines must be drawn so that no two are parallel and no more than two intersect at the same point. Each line is then sure to intersect every other line, and every set of three lines must form one triangle. It is not possible for the same three lines to form more than one triangle, so the number of triangles formed in this way is the maximum. The problem is equivalent, therefore, to the question: In how many different ways can n lines be taken three at a time? Elementary combinatorial theory supplies the answer: the same as the formula obtained empirically.

Solomon W. Golomb, a mathematician at the Jet Propulsion Laboratory of the California Institute of Technology, was kind enough to send me his solution to the necklace problem mentioned last month. The problem was to find a formula for the number of different necklaces that can be formed with n beads, assuming that each bead can be one of two colors and not counting rotations and reflections of a necklace as being different. The formula proves to be far beyond the power of the simple method of differences explained last month.

Let the divisors of n (including 1 and n) be represented by d_1, d_2, d_3. . . For each divisor we find what is called Euler's phi function for that divisor, symbolized $\Phi(d)$. This function is the number of integers that are prime to d; that is, which have no common divisor with d. It is assumed that 1 is such an integer, but not d. Thus Φ (8) is 4, because 8 has the following four integers that are prime to it: 1, 3, 5, 7. By convention, Φ (1) is taken to be 1. Euler's phi functions for 2, 3, 4, 5, 6, 7 are 1, 2, 2, 4, 2, 6, in the same order. Let a stand for the number of different colors each bead can be. For necklaces with an odd number of beads the formula for the number of different necklaces with n beads is the one given at the top of the

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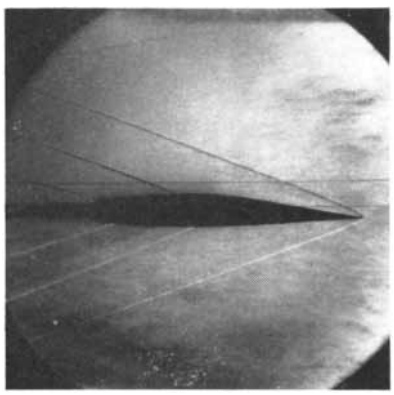

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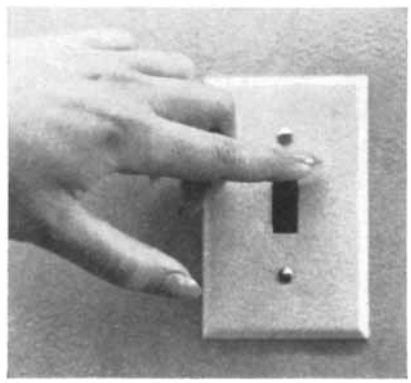

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illustration at the bottom of this page. When n is even, the formula is the one at the bottom of the illustration.

The single dots are symbols for multiplication. Golomb expressed these formulas in a more compressed, technical form, but I think the above forms will be clearer to most readers. They are more general than the formulas asked for, because they apply to beads that may have any specified number of colors.

This is my first opportunity to comment on the many letters received concerning the short problems presented in this department for June. In the problem about the old-fashioned toaster nothing was said to exclude the procedure of letting one side of a piece of bread toast partially, taking it out and putting it back later to finish the toasting. With this permitted, R. J. Davis, Jr., of General Precision, Inc., was the first to send in a solution cutting the total time for toasting and buttering three slices to the record of 111 seconds.

Davis' procedure is as follows, the numbers referring to the number of seconds after the start of the procedure:

1. Put in slice A.
3. Put in slice B.
18. Remove A (it has toasted 15 seconds on one side).
21. Put in slice C.
36. Remove B.
39. Put in A, turned.
42. Butter B.
54. Remove C.
57. Put in B.
60. Butter C.
72. Remove A.
75. Put in C.
78. Butter A.
90. Remove B.
93. Put in A, turned to complete the toasting on its partially toasted side.
108. Remove C.
111. All three slices now toasted and buttered, with A still in toaster.

Even if A must be removed from the toaster to complete the entire operation, the time is 114 seconds; this is six seconds less than 120, the solution that was given.

NUMBER OF LINES	0	1	2	3	4	5
NUMBER OF TRIANGLES	0	0	0	1	4	10
FIRST DIFFERENCES		0	0	1	3	6
SECOND DIFFERENCES			0	1	2	3
THIRD DIFFERENCES				1	1	1

The answer to last month's problem

In the problem of finding the number of distinct types of hexahedron, I neglected to say that only convex hexahedrons were to be considered. It would have been a better problem to include the concave forms, because there are only three, thus bringing the total to the round number of 10. T. Wyatt Johnston and P. Y. Southam, both at the research laboratories of the RCA Victor Company in Montreal, were the first to call my attention to the three concave forms. They can be cut from a tetrahedron as shown in the illustration at the top of page 256.

My most serious error was that of completely misinterpreting Seth Zimmerman's procedure for minimizing the number of yes-no questions in attempting to guess an object when the possible objects can be given probability values. The correct procedure can be applied only when the probability values for each object are known and is best made clear by an example.

Assume that a deck of cards consists of one ace of spades, two deuces of spades, three threes and so on up to nine nines, making 45 spade cards in all. The deck is shuffled; someone draws a card. You are to guess it by asking yes-no questions. How can you minimize the number of questions?

The first step is to list in order the probability values for the nine elements: 1/45, 2/45, 3/45. . . The two lowest values are combined to form a new element: 1/45 plus 2/45 equals 3/45. In other words, the probability that the chosen card is either an ace or deuce is 3/45. There are now eight elements: the ace-deuce set, the three, the four, and so on up to nine. Again the two lowest probabilities are combined: the ace-deuce

$$\frac{1}{2n}\left[\phi(d_1)\cdot a^{\frac{n}{d_1}}+\phi(d_2)\cdot a^{\frac{n}{d_2}}\ldots+n\cdot a^{\frac{n+1}{2}}\right]$$

$$\frac{1}{2n}\left[\phi(d_1)\cdot a^{\frac{n}{d_1}}+\phi(d_2)\cdot a^{\frac{n}{d_2}}\ldots+\frac{n}{2}\cdot 1+a\cdot a^{\frac{n}{2}}\right]$$

Equations for the solution of the necklace problem

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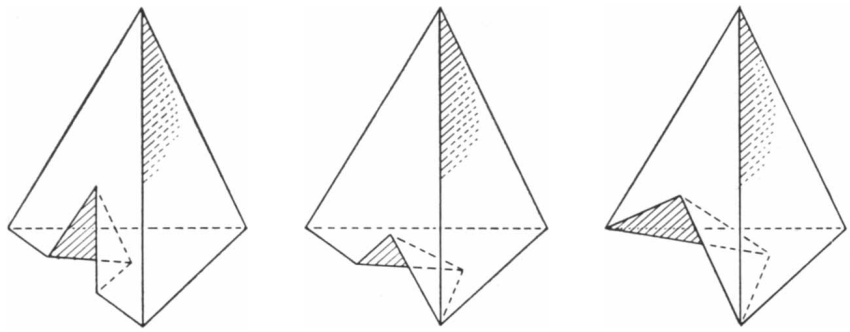
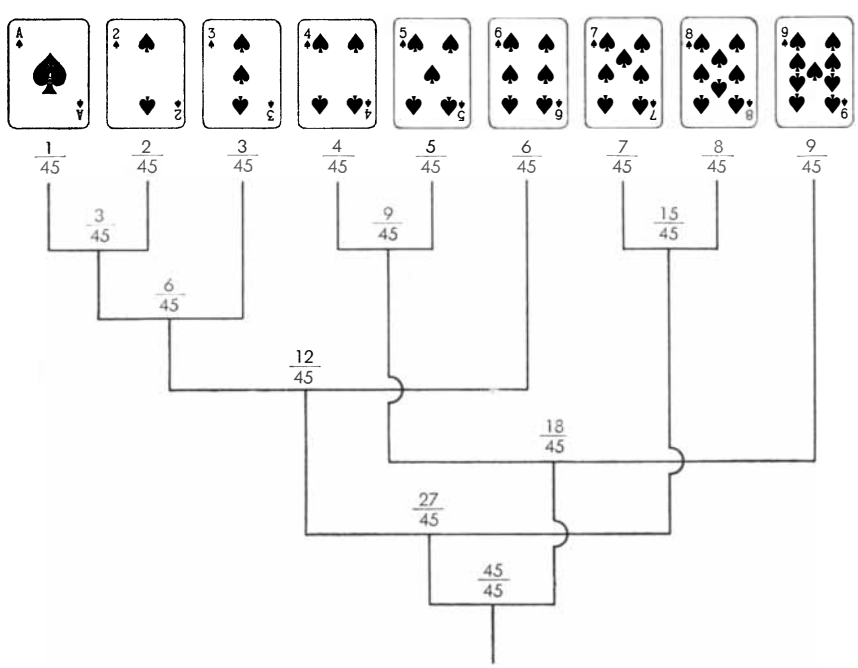


The three concave hexahedrons

value of 3/45 and the 3/45 probability that the card is a three. This new element, consisting of aces, deuces and threes, has a probability value of 6/45. This is greater than the values for either the fours or fives, so when the two lowest values are combined again, we must pair the fours and fives to obtain an element with the value of 9/45. This procedure of pairing the lowest elements is continued until only one element remains. It will have the probability value of 45/45, or 1. The chart below shows how the elements are combined. The strategy for minimizing the number of questions is to take these pairings in reverse order. Thus the first question could be: Is the card in the set of fours, fives and nines? If not, you know it is in the other set so you ask next: Is it a seven or eight? And so on until the card is guessed.

Note that if the card should be an ace or deuce it will take five questions to pin-point it. A binary strategy, of simply dividing the elements as nearly as possible into halves for each question, will ensure that no more than four questions need be asked, and you might even guess the card in three. Nevertheless, Zimmerman's procedure will give a slightly lower expected minimum number of questions in the long run; in fact, the lowest possible. In this case, the minimum number is three.

The minimum is computed as follows: Five questions are needed if the card is an ace. Five are also needed if the card is a deuce, but there are two deuces, making 10 questions in all. Similarly, the three threes call for three times four, or 12, questions. The total number of questions for all 45 cards is 135, or an average of three questions per card.



Strategy for minimizing the number of yes-no questions in guessing a card

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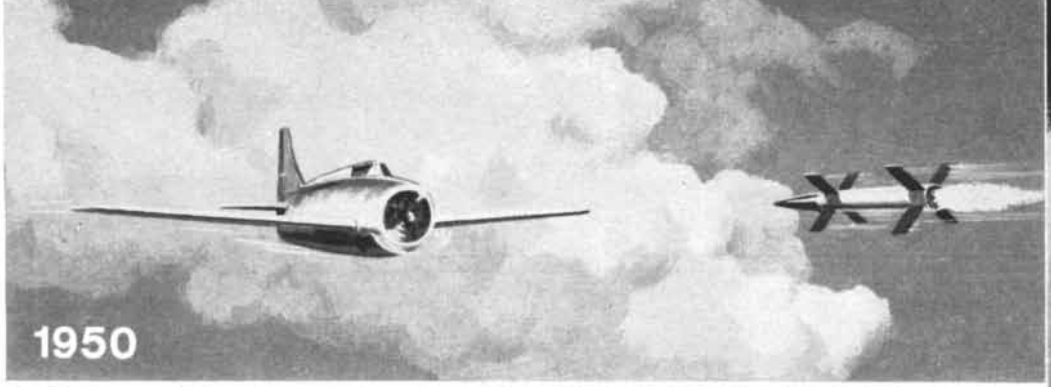
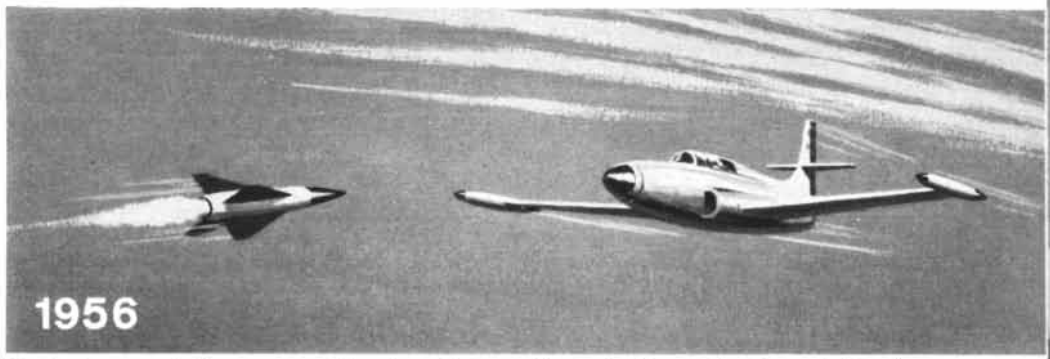
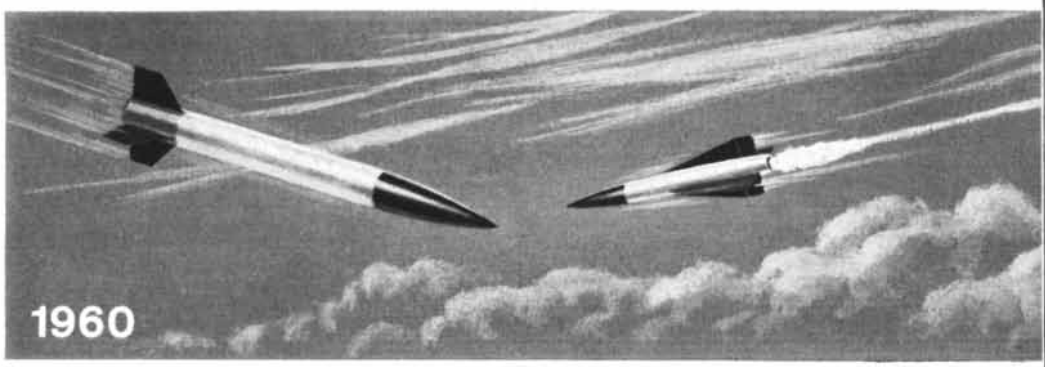


FIRST successful intercept of piston aircraft by guided missile... Raytheon's Lark.



FIRST successful intercept of jet aircraft by guided missile . . . Raytheon's Hawk.



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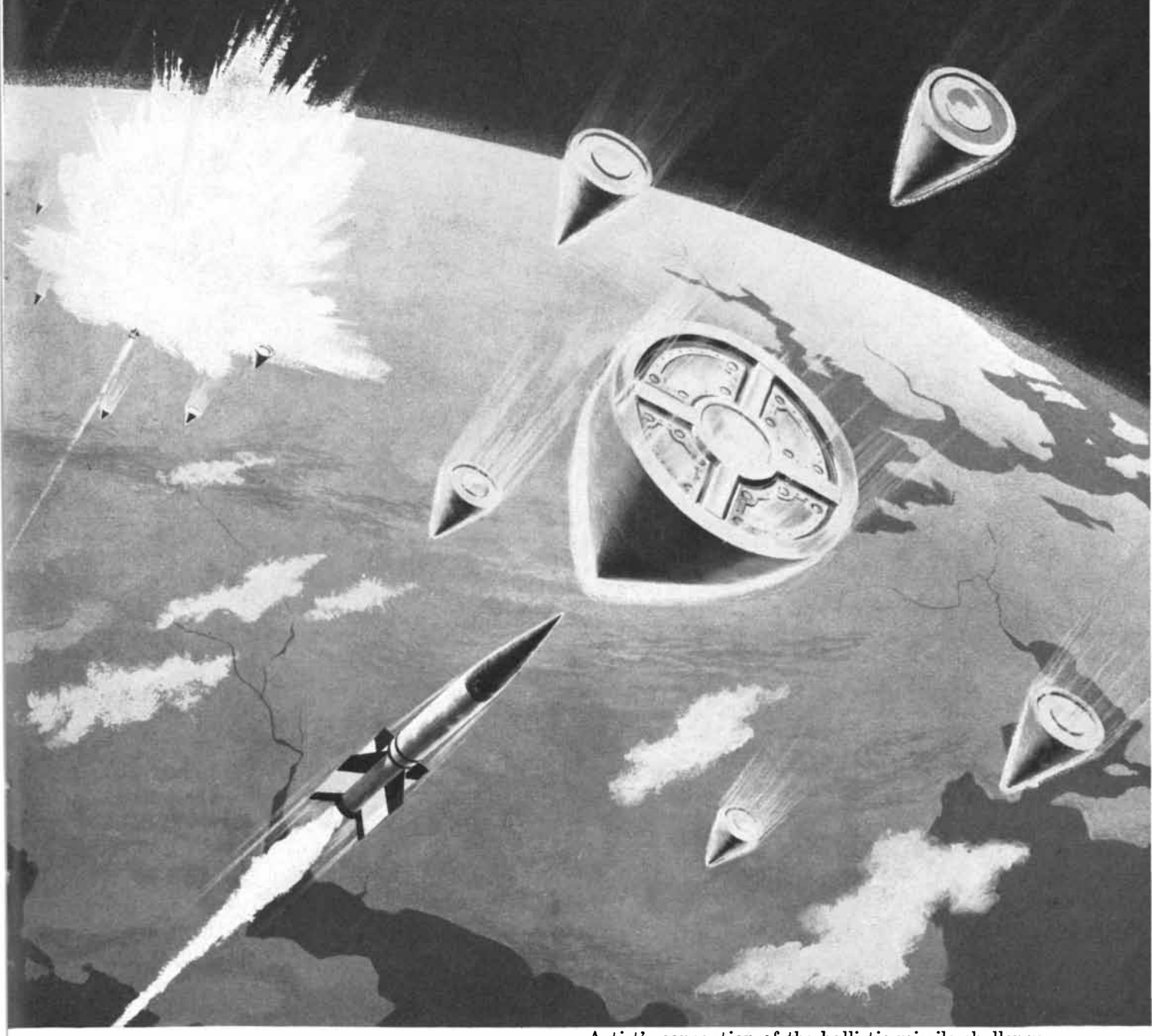

Artist's conception of the ballistic missile challenge.

challenge of ballistic missile defense

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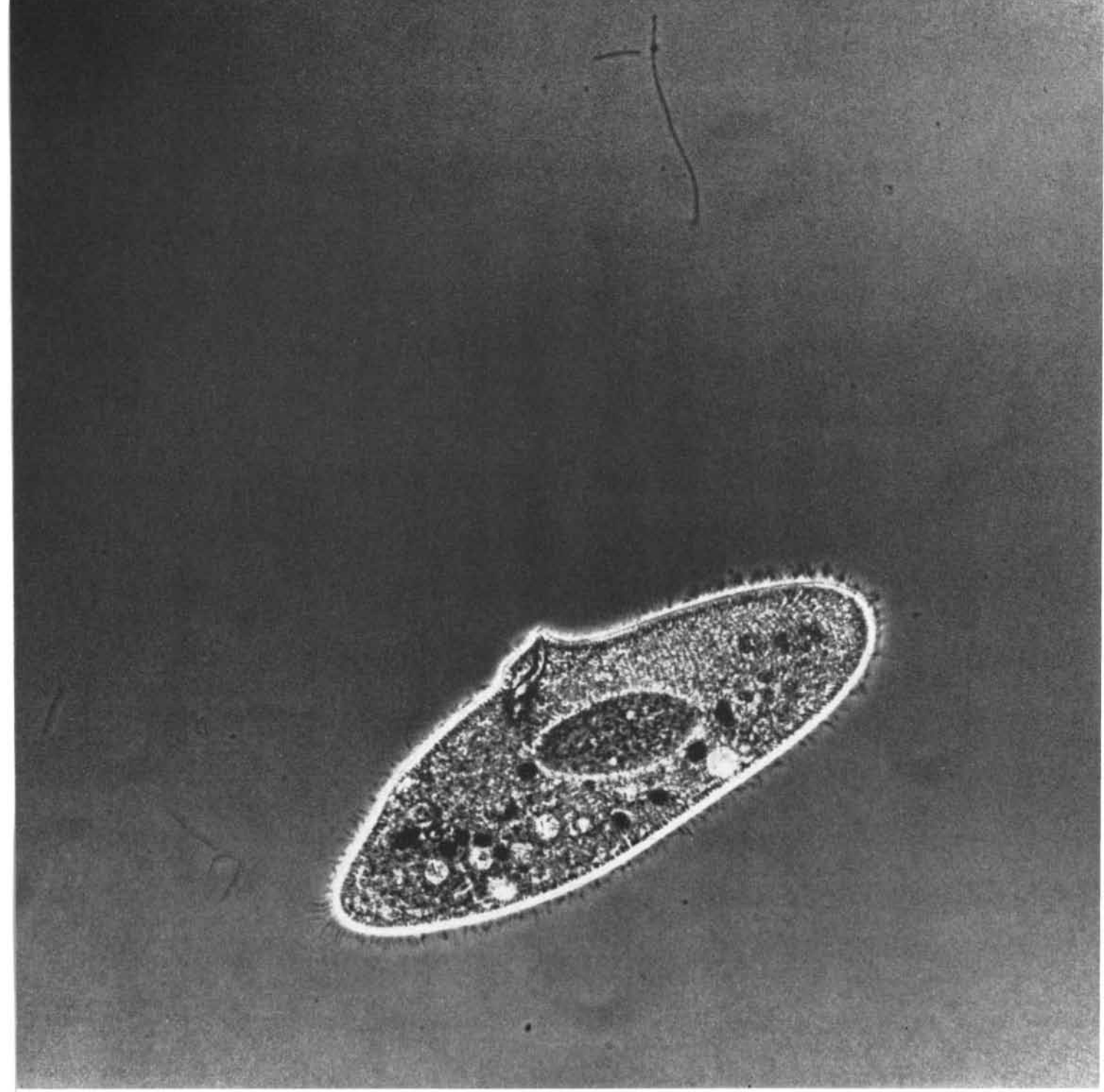

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THE AMATEUR SCIENTIST

How the amateur can experiment with films only one molecule thick

Conducted by C. L. Stong

Substances that spread out over other substances in a layer one molecule thick can give rise to fascinating effects. One such effect made a lasting impression on me when I was a boy. My uncle fashioned a wonderful toy boat from a flat stick about three inches long; the bow end was cut to a point and the stern end had a rectangular notch. After smearing everything but the stern with a film of white vaseline, he pressed a small lump of gum camphor into the notch and launched the boat in the bathtub. To my amazement the boat promptly took off under its own power and circled the tub at a lively clip. Almost as astonishing was my uncle's method of steering the boat: he could set it on a new course merely by dipping his finger into the water beside the hull. His finger seemed to repel the bow, even from a distance of several inches. What made the boat go? Why did it avoid his finger?

Eventually I learned that such boats are driven by the camphor molecules that rush from the stern and spread as a layer one molecule thick on the otherwise clean surface of the water. The layer of camphor molecules lowers the surface tension of the water behind the boat, and the higher surface tension in front of the boat pulls it forward. Other substances, such as oils, also form monomolecular layers on water. Molecules of the oil naturally present in my uncle's skin spread on the water from his finger and exerted enough pressure on the boat to change its course.

The pressure developed by such monolayers varies with the size and structure of their constituent molecules. By measuring the pressure the experimenter can determine how the atoms in the molecule are grouped and how the monolayer interacts with other substances [see "Monomolecular Films," by Herman E. Ries, Jr.; SCIENTIFIC AMERICAN, March]. Although some of these studies are beyond the reach of the amateur, he can perform many engrossing and even useful monolayer experiments with apparatus assembled from materials ordinarily found in the kitchen and bathroom. By adding a few items from the hardware store and the drugstore it is possible to measure the thickness of films down to a small fraction of the wavelength of light, to determine the pressure exerted by a film, to learn the size and general shape of the molecules in a film, to deposit monolayers on glass that produce striking patterns of iridescence and to substitute surface tension for conventional standards of weight in the calibration of laboratory balances.

The experiments are not difficult even for beginners. With information supplied by Robert B. Dean, a physical chemist of Bainbridge, N.Y., I set up the apparatus and made most of it work on the first try.

"To have any luck at all in experimenting with monolayers," Dean writes, "you must set up a clean place in which to work and give careful attention to detail. The quantity of material comprising a monolayer is so minute that our ordinary standards of cleanliness must be revised by at least two orders of magnitude. A flyspeck constitutes gross contamination.

"The disproportion between the area and the volume of a monolayer, which makes cleanliness so important in these experiments, was observed in 1765 by Benjamin Franklin. He spread oil on a pond in London to learn why oil slicks tend to 'quiet troubled waters.' 'At length being at Clapham,' he wrote, 'where there is on the common a large pond which I observed one day to be very rough with the wind, I fetched out a cruet of oil and dropped a little of it on the water. I saw it spread itself with surprising swiftness upon the surface; but the effect of smoothing the waves was not produced; for I had applied it first on the leeward side of the pond where the waves were greatest, and the wind drove my oil back upon the shore. I then went to the windward side where they began to form; and there the oil, though not more than a teaspoonful, produced an instant calm over a space several yards square which spread amazingly and extended itself gradually till it reached the lee-side, making all that quarter of the pond, perhaps half an acre, as smooth as a looking glass.'

"By dividing the known volume of his oil by the estimated area of the pond that it covered, Franklin concluded that the thickness of the film must be on the order of one ten-millionth of an inch. It is interesting to repeat Franklin's experiment. He used olive oil, but any good salad oil should work as well. A cubic inch of oil (half an ounce) should calm 10 million square inches of water (about 1.6 acres). Consider how much the volume of the oil is reduced when the area of the pond is scaled down to laboratory proportions—say to a dish eight inches wide by 12 inches long. On the assumption that the monolayer is a ten-millionth of an inch thick, the volume occupied by a film covering the water in the dish would be only one hundred-thousandth of a cubic inch, which is small even as flyspecks go.

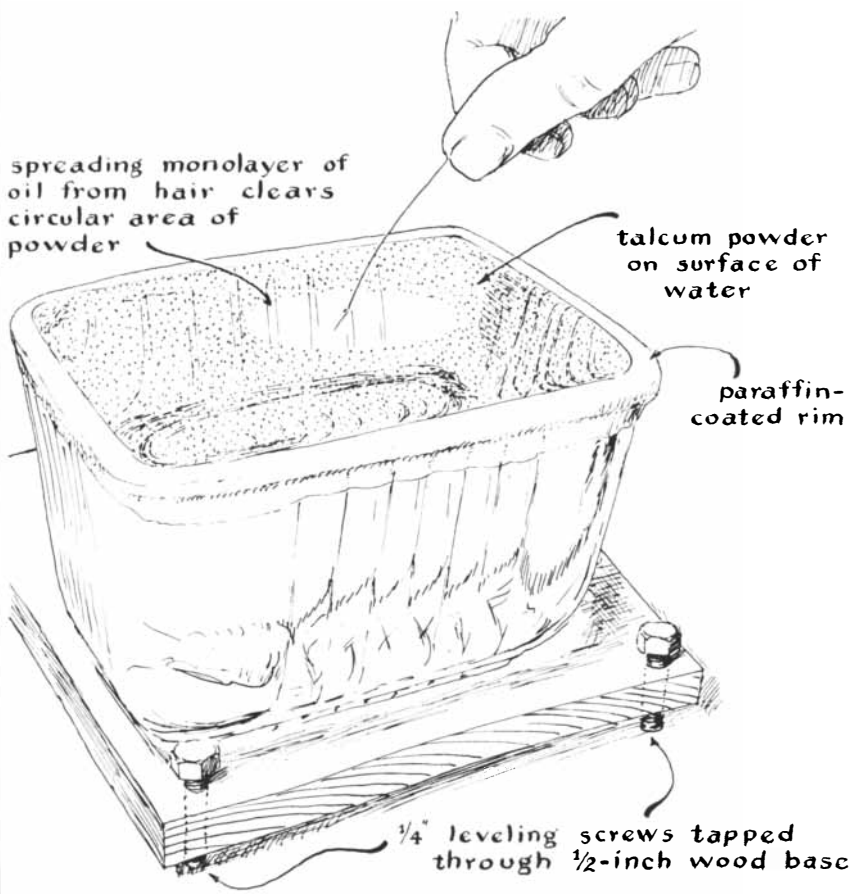
"The inch is rather an unwieldy unit for measuring films so thin. For this reason those who experiment with monolayers customarily turn to the metric system for a more convenient scale: the angstrom unit. (One angstrom unit is one ten-millionth of a millimeter, or about four hundred-millionths of an inch.)

"To determine the over-all dimensions of a molecule in a monolayer (the proportions of the volume that it occupies) the experimenter must know approximately how many molecules the layer contains. This is found by an indirect method. For example, standard reference texts show that glyceryl trioleate, the principal constituent of olive oil, has a molecular weight of 885 and a density of .915. One gram molecular weight (the weight of 6×10^{23} molecules) occupies 967 cubic centimeters, or 967×10^{24} cubic angstrom units. One molecule of glyceryl trioleate will therefore occupy

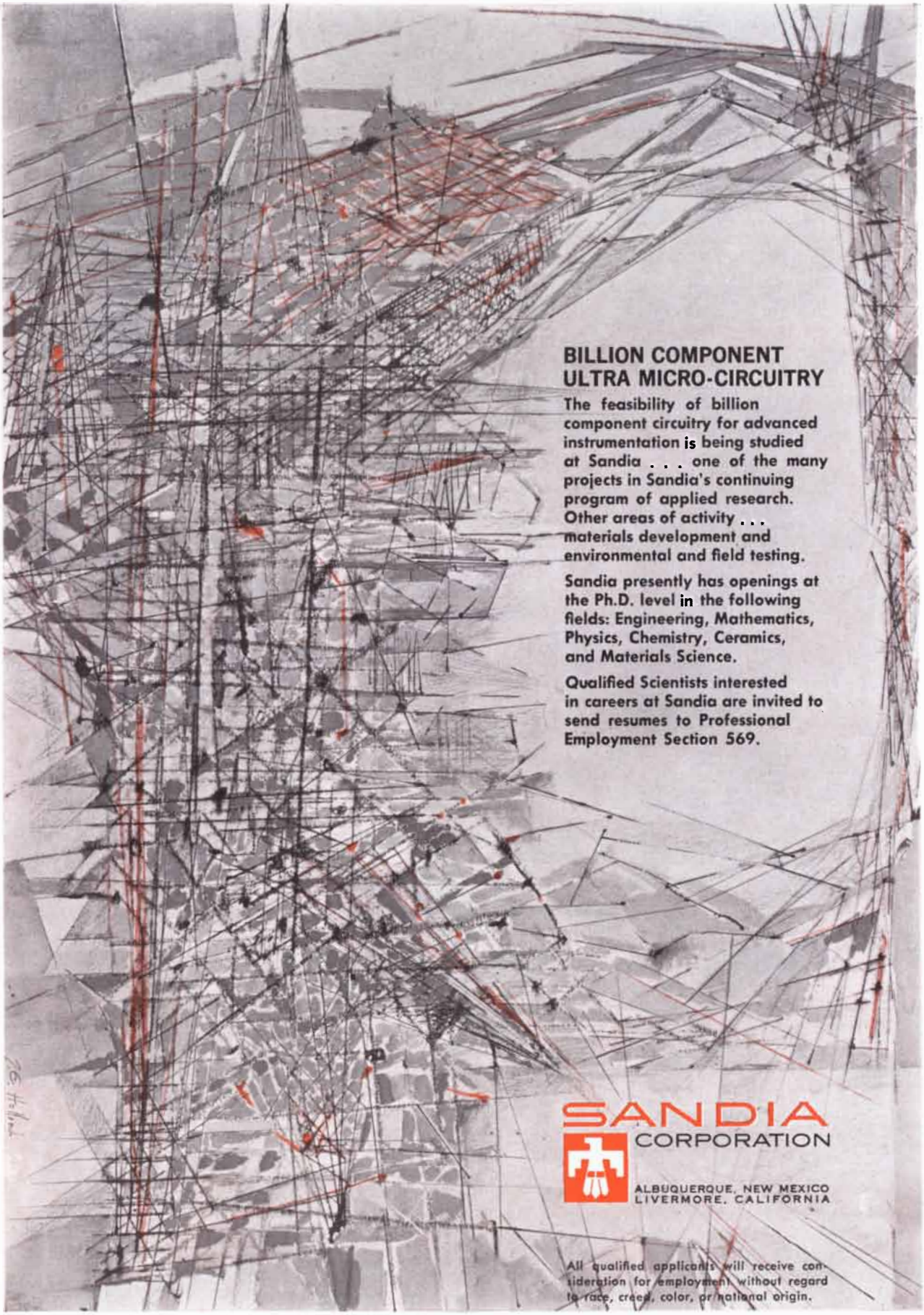
6×10^{23} of this volume, or 1,612 cubic angstrom units. Franklin's estimate of the thickness of his film—one ten-millionth of an inch—is equivalent to about 25 angstroms. If this had been the correct value, each molecule in his monolayer would have occupied an area of only 65 square angstroms. But relatively simple measurements that any careful amateur can make prove that a molecule of glyceryl trioleate has a cross-sectional area of 97 square angstroms, which corresponds to a monolayer thickness of only 16 angstroms. We must conclude that some of Franklin's oil was lost on the edges of the pond.

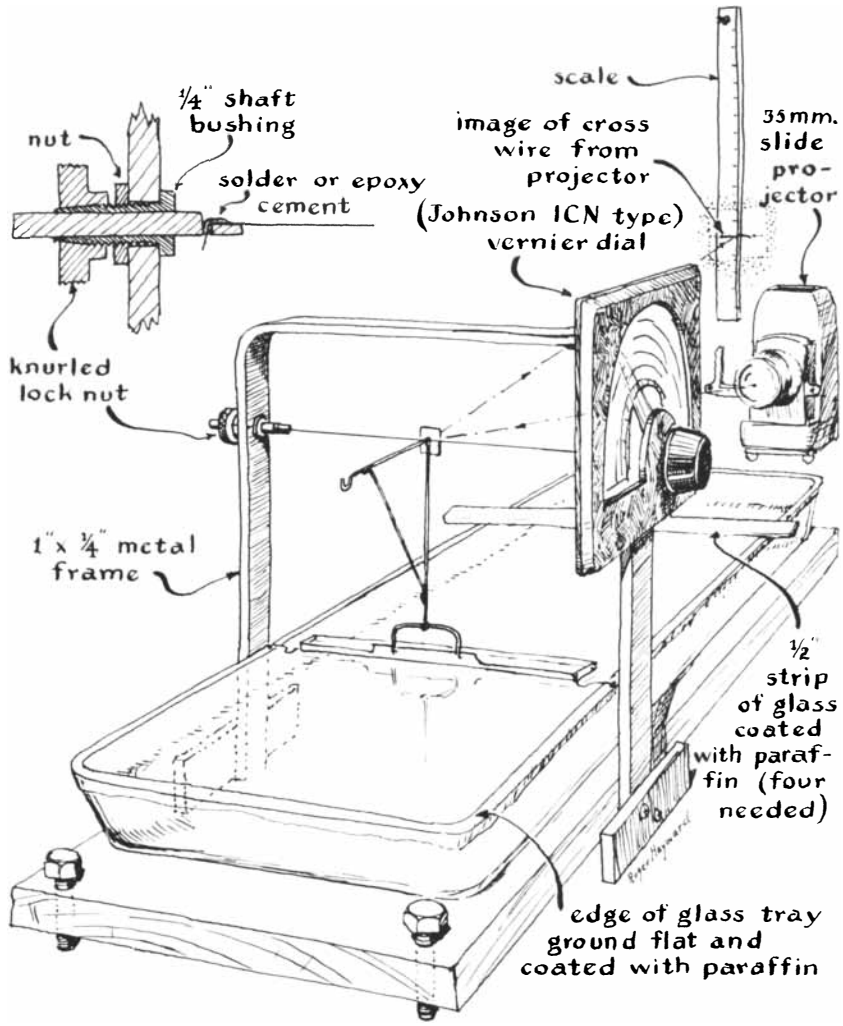
"All possible precautions are taken in the laboratory to avoid errors of this sort. The material under investigation is first mixed with an insoluble spreading agent, such as hexane, that evaporates quickly and completely. An accurately weighed amount of the mixture is then gently floated on the clean surface of a trough of water. To assure even distribution somewhat less material is applied to the water than is required for a complete monolayer. The monolayer is subjected to pressure by sliding a waterproofed strip of glass or metal, called a barrier, across the surface of the trough from one end toward the other. This squeezes the molecules into a continuous layer that presses against a floating barrier at the far end of the trough. The floating barrier is linked mechanically to a sensitive balance that registers the pressure transmitted by the monolayer. In troughs of typical dimensions (in excess of 600 square centimeters) many substances are capable of transmitting pressures on the order of half a gram. If pressure is applied beyond the amount needed to pack the molecules closely, the monolayer buckles; this establishes an upper limit to the pressure that can be applied to the floating barrier. When the pointer of the balance stops moving up the scale, the experimenter knows that a closely packed layer has been formed. The area occupied by each molecule is then computed by dividing the known area of the monolayer by the known number of molecules. The length of the molecules, which in many substances is equal to the thickness of the film, is determined by dividing the known volume of the monolayer by its area.

"As an introduction to monolayer experiments, clean a container, say a glass



Talcum powder is used to demonstrate how the oil on a hair spreads over a water surface





A hydrophilic balance to measure the spreading pressure of monomolecular layers

baking dish about six inches square, with scouring powder and rinse with tap water until the glass wets completely. Dry the dish with a paper towel. Keep your fingers off! Then with a paper towel apply a film of white vaseline around the rim of the dish. Set the dish level and fill it to the brim with water. Let the water overflow for a time to carry away as much surface contamination as possible. In spite of such measures the surface of the water will most certainly be covered by a contaminating monolayer of some sort. To detect the monolayer, dust some talcum powder on the surface and blow it around gently. (You must use unperfumed, unmedicated talcum powder of the kind supplied to hospitals. You can buy it at a drugstore.) Try to compress the monolayer. Pressure can be applied by the edge of a clean, untouched piece of wax paper. Place one edge of the paper against the water where it curves up from the edge of the dish and pass it across the surface toward the opposite side. Particles of powder some distance from the edge of the paper will move, as if acted on 'at a distance' by the paper.

"Sweep the powder (and monolayer) off the opposite side of the dish. Repeat the experiment, using clean paper each time, until the powder is not pushed 'at a distance.' The classical tool for removing contamination from water surfaces is a strip of glass or metal coated with paraffin. Usually several are used. The sweep is started with one barrier; when it has been advanced some distance, another sweep is started with a second barrier and so on. The strips are simply laid across the end of the container and advanced slowly toward the other end. The surface can also be sucked clean; in the case of Franklin's pond it had been blown clean by the wind. No method gets all the dirt in one sweep. I prefer to wipe the surface with ordinary paper and then sweep it with paraffined glass barriers. In this initial experiment, how-

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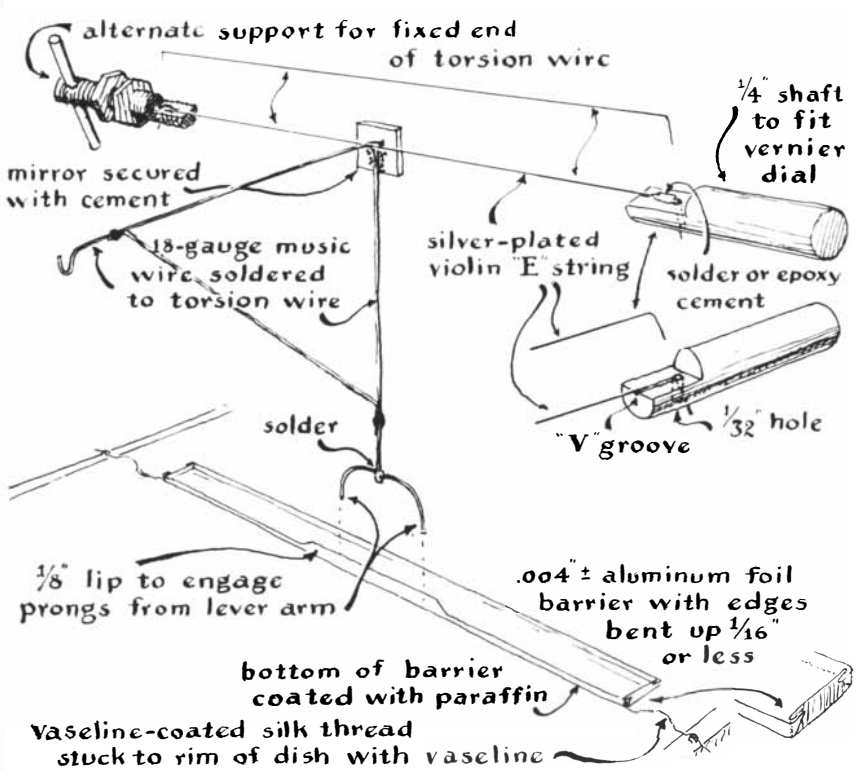
ever, wax paper is adequate. Add powder as necessary during the sweeping so that you can follow your progress. When at last the movement of the paper does not push nearby particles of powder, you have a reasonably clean surface on which to deposit your first monolayer.

"Before depositing the monolayer take a pinch of powder with the untouched edge of a paper scoop and dust the surface lightly. Then touch the surface with the tip of a single hair from your head. Unless your hair is exceptionally free of oil, a circular area ranging upward from the size of a dime will dart out from the hair. If you have dry hair, it may be necessary to dip the hair in olive or salad oil. Wipe the hair clean with a paper towel. There will still be enough oil sticking to the hair to drive the talcum completely off the surface. A more elegant tool for applying the oil is a freshly drawn glass fiber. It is clean and so enables you to choose any material you wish for the monolayer.

"Oils and other materials that form monolayers on water are characterized by comparatively large, insoluble molecules that include one group of atoms that is attracted to water and another group that is repelled by water. In many substances—for example, olive oil—the hydrophilic, or 'water-loving,' group of atoms is situated at the end of the molecule. It is the attraction between this end and the water that accounts for the formation of the monolayer. The area occupied by a monolayer depends on how the molecules are arranged. If they are oriented at random, the area may be relatively large. But when the layer is compressed, as by pushing against its edge with a piece of wax paper, the molecules crowd against one another and are believed to upend in tight formation, with the hydrophilic ends in contact with the surface. If more molecules are present than can be accommodated in the monolayer, they may clump together as drops. Or, to put it another way, the monolayer is in equilibrium with the floating drops. You can see such droplets on the surface of clear soup. When portions of the monolayer are skimmed off, the droplets supply replacing molecules to the monolayer. Conversely, such droplets can be made to grow by compressing the monolayer into a smaller area."

The editor of this department tried the above experiment with a monolayer of olive oil on a dish that measured eight by 16 inches. Half an hour of skimming failed to diminish the apparent size of the droplet, even when it was examined by a 10-power magnifying glass. When the layer was compressed between barriers and viewed at a low angle, however, random points of reflected light appeared on the surface, possibly indicating places where oil from the buckled



Details of the hydrophilic balance

Automation through communications

works wonders in moving mountains of paperwork

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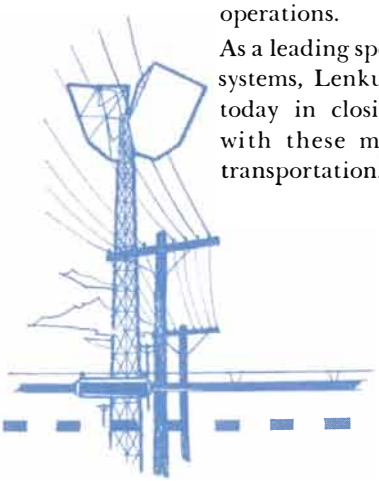

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monolayer gathered as minute droplets.

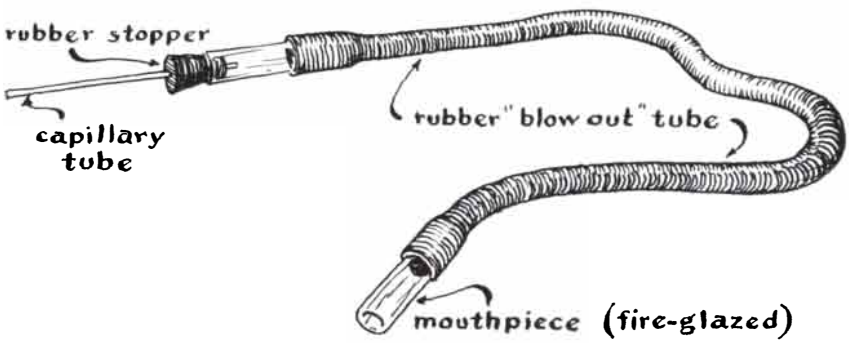
My results were more gratifying in another experiment suggested by Dean for demonstrating differences in the spreading pressure of substances that form monolayers. "Each oil," he writes, "has its own spreading pressure. An oil with higher spreading pressure will displace one of lower spreading pressure. To observe the effect, prepare a clean surface of water. Then cut a length of fine silk thread (or a thread of nylon or rayon) about half again as long as the width of the dish. Smear the thread with a film of vaseline, using a piece of paper towel for the applicator, and lower it zigzag onto the surface of the water. The ends are draped over the sides of the dish about a quarter of an inch and stuck down with dabs of vaseline. (Use a clean toothpick to handle the vaseline.) Sweep the surface on each side of the thread with a barrier until the water is clean. A monolayer of egg albumin is now applied to the cleaned surface on one side of the thread by dipping a clean toothpick into the white of a freshly opened egg and touching it to the surface. The spreading monolayer will exert pressure on the thread, causing it to bend into the clean area. If a bit of olive oil is now applied to the clean surface, the resulting monolayer will cause the thread to exert a pressure of about 20 dynes (1/1,400 ounce) per centimeter against the albumin and collapse it. In experiments of this sort, where one monolayer is used to apply pressure to another, the movable barrier (the vaseline-coated thread) is called the piston and the driving substance the piston oil. Tricresyl phosphate exerts a spreading pressure of about 10 dynes per centimeter of thread length, somewhat less than is needed to collapse a monolayer of albumin, and can therefore be used as a piston oil to keep an albumin monolayer under pressure.

"Tricresyl phosphate is a plasticizer used in gasoline and in vinyl plastics. The spreading pressure and surface behavior of most other plasticizers have not been reported in the literature. Many of them would doubtless make good piston oils and their measurement could well be undertaken by amateurs."

I had a lot of fun setting up pistons. It turned out that our medicine cabinet was stocked with a variety of monolayer-forming substances ranging from insect repellents to hand lotions. In many cases the name of the substance was printed on the label. By pairing these off and testing each against the others I found it possible to arrange them in order of ascending spreading pressure. Care must be taken not to apply too much piston oil to the water or the piston will snap into a tight bow and the piston oil will spill over into the compressed monolayer. The pressures that I recorded were merely relative, of course. With Dean's encouragement I next undertook the construction of a hydrophilic balance for making quantitative measurements of spreading pressures.

The apparatus consists of three principal subassemblies: a trough for holding the water and monolayer, a base for leveling the trough and a calibrated torsion balance [*see illustration on page 264*]. The construction can be varied dimensionally or otherwise to suit the whim of the builder and the materials at hand. One primary design consideration should be kept in mind, however: The experimenter will spend most of his time cleaning the apparatus. Keep it simple and easy to take apart.

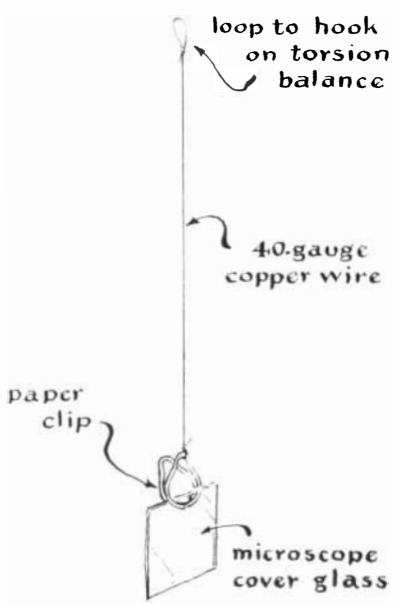
The trough is a glass baking dish eight inches wide, 16 inches long and two inches deep. The rim of the dish is ground flat so that a glass barrier that spans the dish can be slid from one end to the other without rocking. Invert the dish on a piece of plate glass and grind it down with successive grades of wet carborundum. I used No. 180 grit for 10 minutes and No. 240 for about the same interval. Apply firm pressure as the dish is pushed back and forth. Add water and additional carborundum as the grit



Micropipette for depositing monolayers

becomes gummy. Don't worry if a few pits made by the coarse grades of abrasive remain after grinding with the finer grades. After being ground the dish is first cleaned with scouring powder, then with household ammonia, and is rinsed in running water for several minutes. According to Dean this procedure, if vigorously followed, should suffice. I gave the inner surface an additional scrubbing with a swab dipped in nitric acid and rinsed the acid away with running water—the final step used by amateur telescope makers in cleaning glass for silvering. If acid is used, remember that it is corrosive, highly poisonous and should not be used in the kitchen. The rim of the dish is then coated with paraffin. Either of two methods works well. The glass can be heated in the oven to a temperature above the melting point of the wax and a block of paraffin of the grade used for sealing jelly glasses rubbed completely around the rim. No harm will be done if melted wax runs down the sides of the dish. Alternatively, the wax can be dissolved in hexane and painted on the rim with an oil-free brush. In making up this solution use about one part paraffin to 20 parts of hexane. If you are in a hurry, shave the paraffin. It dissolves slowly in hexane.

My sweeping barriers are half-inch strips of window glass 10 inches long. Half a dozen were cut with an ordinary glass cutter of the wheel type. The edges were rounded slightly by grinding on plate glass with No. 240 carborundum grit and water. They were cleaned with scouring powder, rinsed, dried and dipped in melted paraffin. Floating barriers of several types were tried; all of them worked. The simplest was a soda straw. After the straw was cut to a length of seven inches (an inch less than the width of the trough) an 11-inch length of vaseline-coated silk thread was run through the straw. The ends of the straw were then sealed with a few drops of melted paraffin. A wooden strip about 3/8 inch wide, seven inches long and 1/8 inch thick, coated with paraffin, was also successful. Vaseline-coated silk threads two inches long were attached to the underside of the strip with dabs of paraffin. The third version is the rectangular boat of aluminum foil shown in the illustration on page 264. It was also coated with paraffin and equipped with threads. It seemed to respond to surface pressures somewhat more promptly than the soda straw or stick, doubtless because it is less massive.



Fixture for measuring surface tension

The balance consists of (1) a torsion fiber supported by and in axial alignment with a pair of shafts, (2) a beam in the form of a bell crank attached to the fiber and fitted with an optical lever and (3) a supporting framework of strap iron. One shaft can be rotated with a vernier dial for adjusting the torsion fiber. The other shaft can be rotated as well as shifted along its axis to any desired position. The arms of the beam are equal in length, and force applied to either arm twists the torsion fiber the same amount. The magnitude of the force can be measured either by applying a measured twist to the fiber in the opposite direction (by means of the calibrated dial) until the beam is restored to its original position or by observing the displacement of the optical lever. When calibrated with care, the balance is accurate to better than 1 per cent from one to 500 milligrams and is sensitive to a small fraction of a milligram.

The torsion fiber was made from the *E* string of a violin and is .01 inch in diameter. The beam was made from the *G* string of a guitar and is .027 inch in diameter. I used strings instead of bulk music wire because they are long enough, available in any music store and cost only 30 cents. The torsion fiber is 12 inches long. The apex of the beam is soldered to the middle of the fiber. Acid-core solder and a hot iron were used to make the joint. Some strings are chromium-plated but can be soldered easily if the plating is sanded off with 00 grade carborundum cloth. A small hook is bent in the horizontal arm and an inverted U, bent from *G*-string stock, is soldered to the bottom of the vertical arm. The U engages the floating barrier as shown in the illustration on page 266. A brace of the same wire is soldered between the horizontal and vertical arms of the beam.

The reflector of the optical lever was cut from a thin pocket mirror of the type available at the cosmetic counter of a novelty store. It is about a quarter of an inch square and is attached to the apex of the beam by quick-drying cement. It reflects the image of a silk thread from a 35-millimeter slide projector to a screen on the wall. The thread is stretched across an empty slide holder. The screen is a strip of white cardboard with a vertical scale divided into 10-minute intervals of arc.

The assembled balance was set up on the bench and, after the torsion fiber was pulled tight, oriented so the mirror would reflect the image of the silk thread onto the screen. The image was centered on the zero graduation in the middle of the scale by turning the clamped shaft. A coil of No. 36 bare copper wire that weighed one gram was then suspended from the hook of the horizontal arm and the dial was rotated until the beam was restored to its zero position. As luck would have it, this required precisely one full turn. (A 25-foot length of No. 36 copper wire should weigh approximately one gram according to the handbook, but the weight of commercial wire may vary as much as 5 per cent. A gram of wire should be weighed out on an accurate analytical balance.) The wire was then cut precisely in the middle and half of the coil was suspended by the beam. Zero was again restored, this time by turning the dial through 180 degrees. A quarter of the coil required 90 degrees of dial rotation, and so on. Each degree of rotation therefore corresponded to 2.78 milligrams.

To prepare the balance for measuring the surface pressure of a monolayer the glass trough is cleaned, the rim of the trough is given a fresh coat of paraffin and the trough is leveled so that it can be filled to the brim with water. The surface is then swept by the barriers until free of contamination. Next, the floating barrier is placed on the water about a quarter of the length of the trough from one end. The associated threads, which act as seals to prevent the monolayer from leaking past the barrier, are draped over the rim of the trough about a quarter of an inch and are stuck fast with dabs of vaseline. The torsion balance is then placed over the trough so the ends of the inverted U just touch the floating barrier. The ends of the U are stuck to the barrier with dabs of vaseline. The projector and screen are placed so that the image of the thread falls on the

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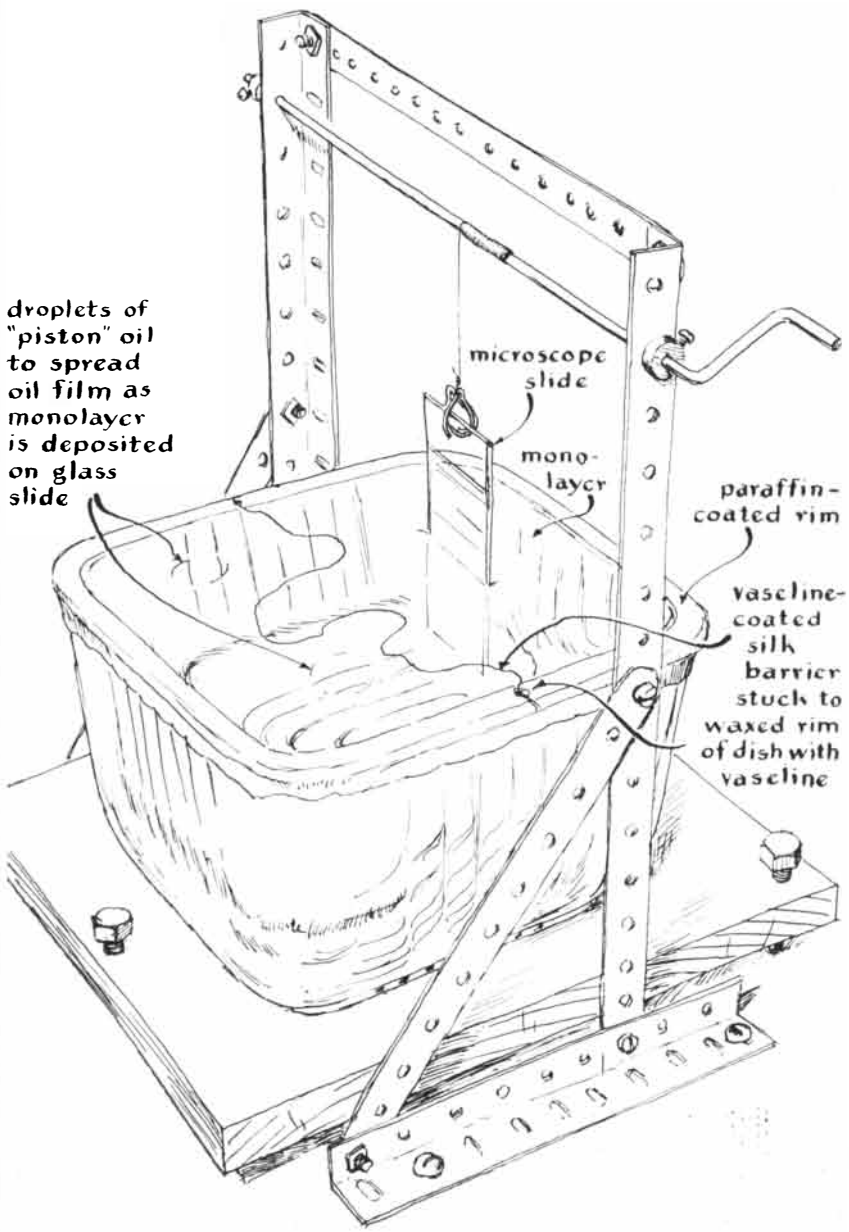
zero graduation of the screen. Both areas of the water surface are again swept with the barriers.

A monolayer is now placed on the larger of the two uncontaminated surfaces. For the initial experiment Dean recommends measuring the spreading pressure of stearic acid. Chemicals of the highest purity must be used or the measurements will not agree with the values tabulated in reference texts. (To obtain these chemicals you may want to have your druggist write Distillation Products Industries, Rochester 3, N.Y., for ordering information. He should ask for list No. 42 of organic chemicals.) One cubic centimeter of stearic acid is mixed with 49 cubic centimeters of hexane. Five cubic millimeters of this solution are then carefully floated onto the water with a micropipette. This volume contains enough molecules to cover a surface of some 400 square centimeters with a monolayer. To make a calibrated micropipette, buy or draw a glass tube with an inner diameter of about one millimeter. This capillary tube is then pushed into a rubber stopper that in turn fits into a larger section of tubing fitted with a length of rubber hose and mouthpiece [*see illustration on page 269*]. Before inserting the capillary into the stopper weigh it on the torsion balance. Then dip the outer end in a con-



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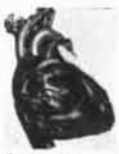

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tainer of water tinted with food coloring. Capillary attraction will draw water into the tube. Measure the length of the water column and immediately weigh the capillary. The difference in weight between the empty and filled capillary in milligrams is equal to the volume in cubic millimeters that is occupied by water. Paint a mark across the tube at the inner end of the water column. Work quickly so that water is not lost by evaporation. Use India ink for marking the graduations and apply it with a single hair. Divide the remainder of the tube (from the mark to the outer end) into as many equal intervals as the water weighed in milligrams and mark off the intervals with ink lines. This method of calibration is adequate if the tube does not taper. Finally, coat the inner and outer surfaces of the capillary with silicone oil.

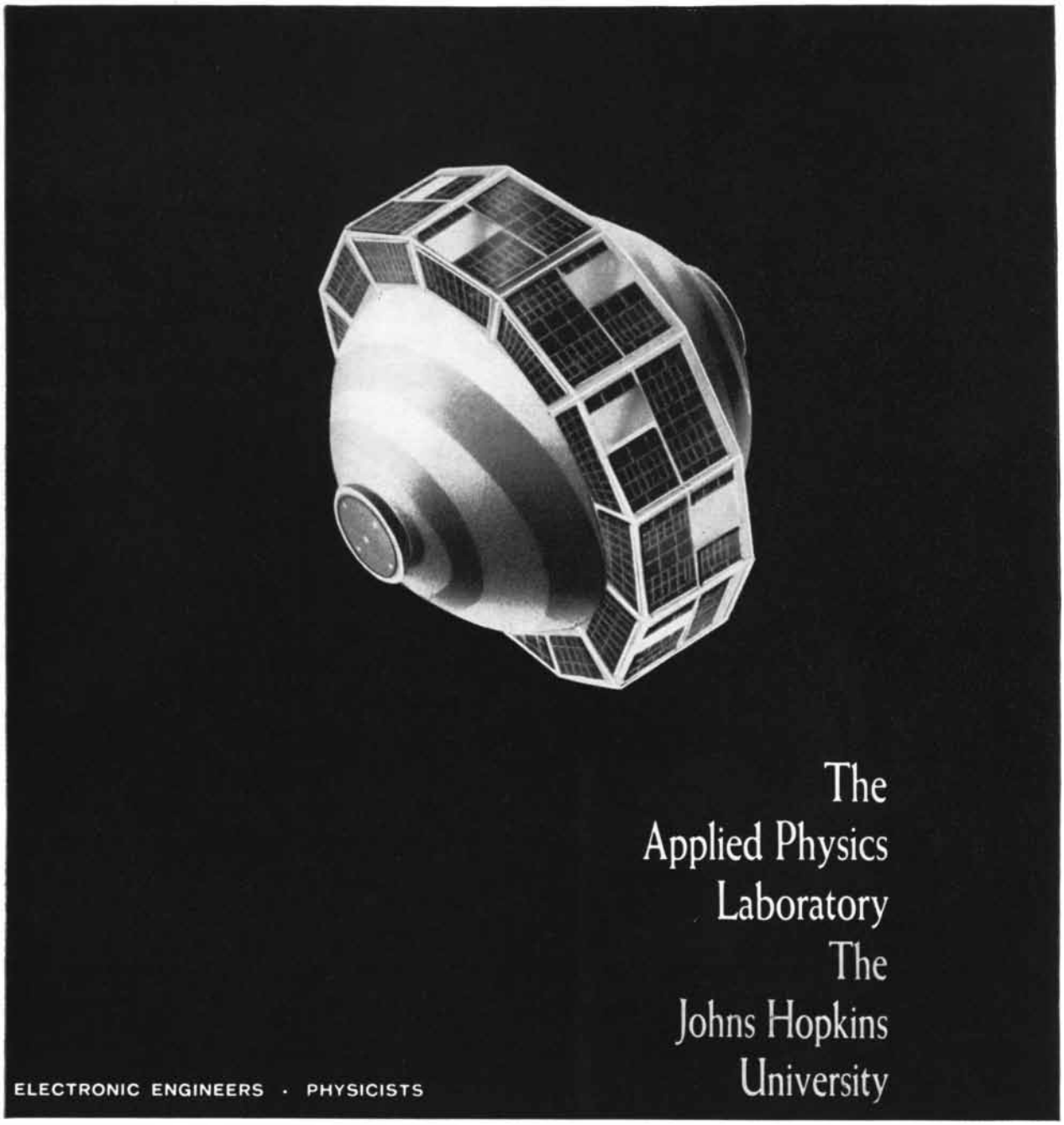
The hexane will evaporate, leaving an uncompressed monolayer on the surface that has a volume of .1 cubic millimeter. A clean barrier is now slid gently onto the water at the end of the trough farthest from the floating barrier and gradually pushed toward the barrier.

As the area is thus reduced, the balance will begin to respond to growing pressure exerted by the monolayer; eventually the reading will mount sharply to a maximum value. The maximum pressure (in grams) indicated by the balance is divided by the length (in centimeters) of the floating barrier plus half the distance between the ends of the barrier and the edges of the tank. The quotient is multiplied by 980 to get spreading pressure in dynes per centimeter. The spreading pressure of stearic acid at 25 degrees centigrade is about 30 dynes per centimeter, and its molecule occupies 20 square angstroms.

Spreading pressure can also be determined by measuring the surface tension of a monolayer and that of water. Suspend a *clean* glass slide, such as a microscope cover slip, by a small chain or wire as shown in the illustration on page 270. Hook the chain to the horizontal arm of the torsion balance and adjust the balance to zero. Then bring a container of water up under the glass until the surface of the water touches the bottom edge of the glass. Surface tension will pull it into the water. Now turn the dial of the torsion balance until the bottom of the cover slip is raised precisely even with the surface of the water. (Ignore the meniscus of liquid that clings to the glass.) To find the surface tension of the water in dynes per centimeter, multiply by 980 the weight (in grams) that is indicated by the torsion balance when the bottom of the wet slide is even with the surface and divide by twice the length (in centimeters) of glass in contact with the water. If the temperature of the water is 0 degrees C., the result should be 75.6 dynes per centimeter; at 20 degrees it should be 72.7 dynes per centimeter. By reversing the formula you can use this procedure as a primitive method of establishing a standard of mass for calibrating balances. At 20 degrees C. the downward pull on the balance (in grams) caused by surface tension is equal to the product of 145.4 times the length of the glass in contact with the water divided by 980. A weight, such as a length of wire, is then cut to produce the same deflection and used as the standard of mass. I have found the method accurate to about one part in 200.

A clean slide is then fully immersed in water that has been swept free of contamination, a monolayer is floated on the surface and the slide is carefully raised by rotating the dial of the balance. The surface tension of the monolayer is then computed as in the previous experiment. The difference between the surface tension of the water and that of the monolayer is equal to the spreading pressure of the monolayer.

One final experiment: Set up a clean dish about four inches deep and fill it to the brim with water containing a few drops of barium hydroxide (approximately a .01 normal solution). Divide the surface with a piston, float a monolayer of stearic acid on one side and a monolayer of olive oil on the other. Then, with a small windlass improvised from handy materials [*see illustration on page 272*], slowly lower a clean microscope slide into the stearic acid and pull it up again. With practice you can make a monolayer of acid cling to the glass surface on each pass. Observe the action by watching the piston. Continue dipping the slide and replenish the monolayer as required. After about 20 monolayers have been applied the glass will begin to take on color (caused by the interference of light waves). Continued dipping may produce a pattern of color like that observed on soap bubbles and oil slicks. If the layers are evenly deposited, the color will consist of a single hue and the slide will function as an interference filter. Certain thicknesses will act as nonreflecting coatings. According to Dean, by immersing the slide fully on the first dip and to successively shallower depths thereafter it is even possible to build up a step gauge for measuring thicknesses optically.



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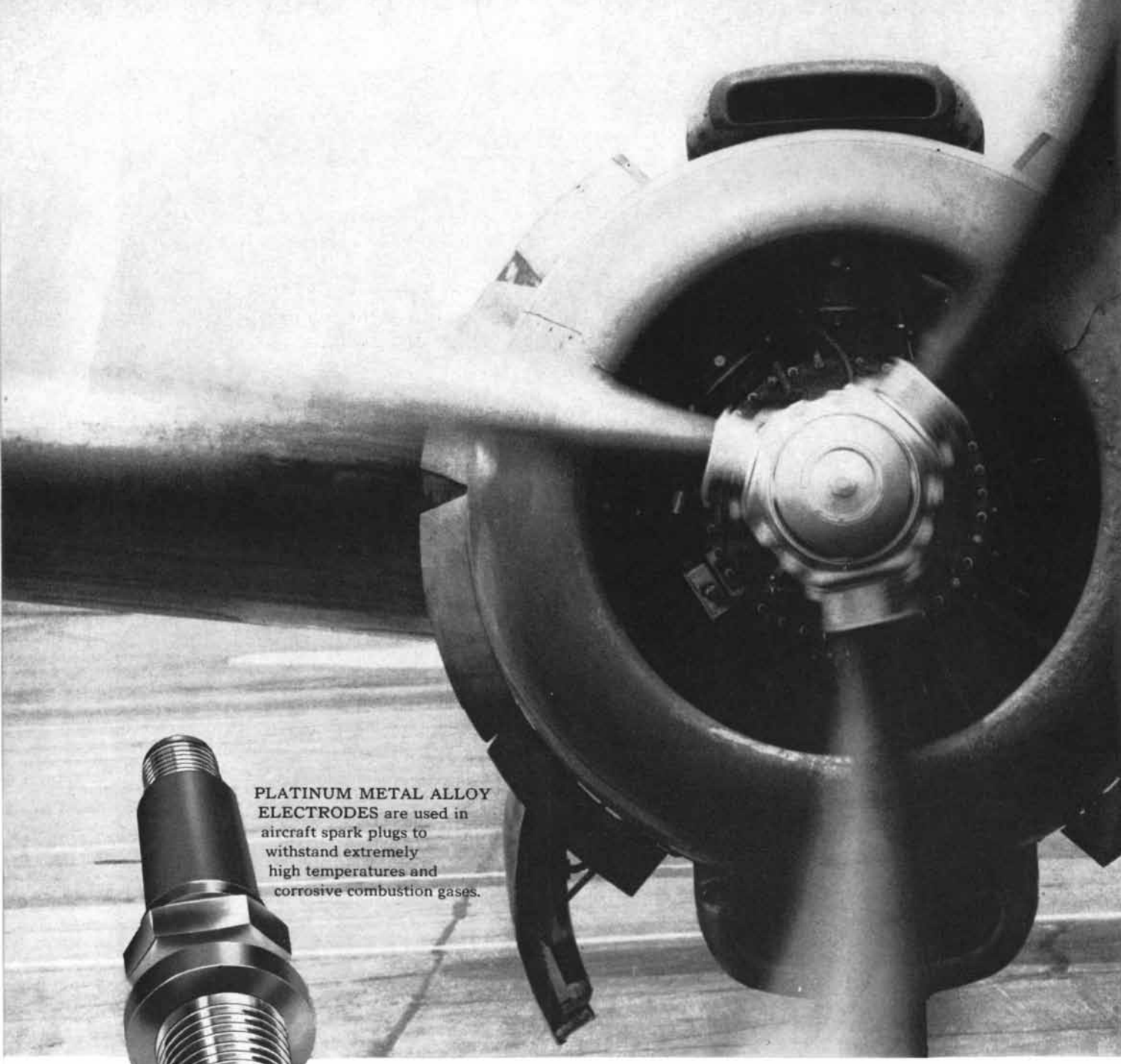

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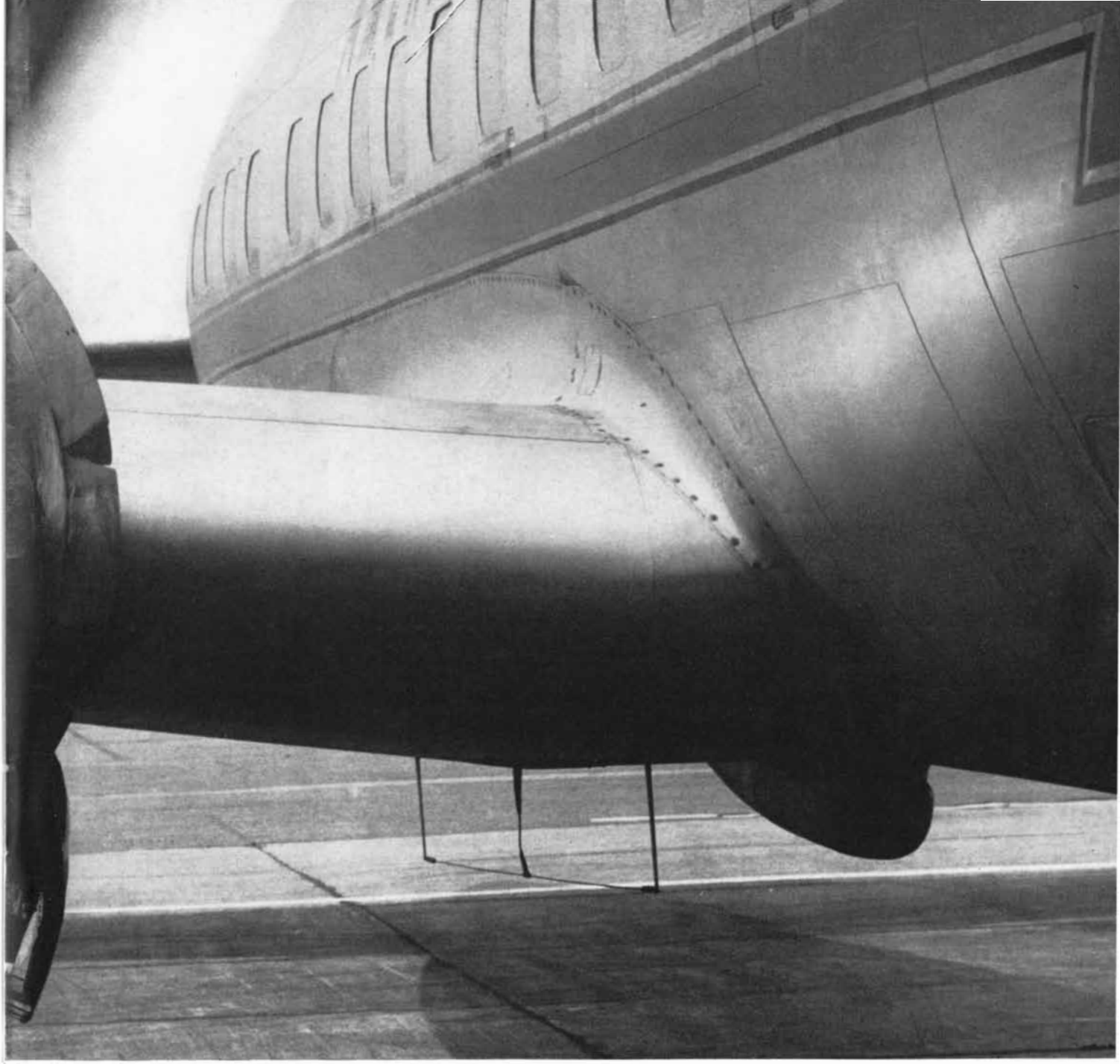

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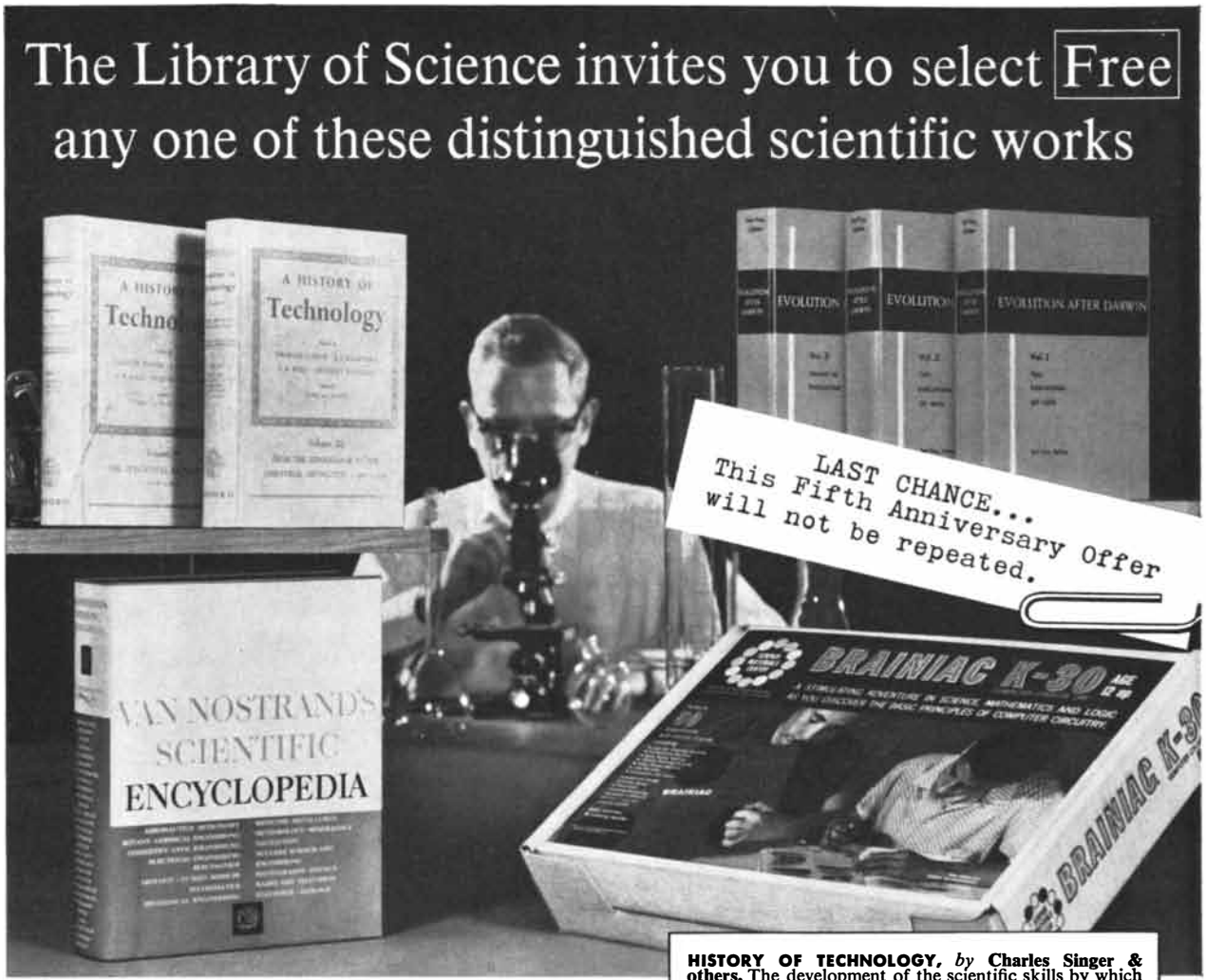

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BOOKS

A geographical study of Africa in transition

by F. Fraser Darling

TROPICAL AFRICA, by George H. T. Kimble. Twentieth Century Fund ($15).

When one picks up a work like this—two well-produced octavo volumes totaling 1,100 pages—one's first reaction is almost reverential: a man has labored devotedly for an appreciable fraction of his life. Moreover, as one soon discovers, Professor Kimble has not worked alone; he has papers from nearly 50 authorities and has had a panel of consultants. One reads the titles of the two volumes and approves: *Land and Livelihood* and *Society and Polity*. Then one thumbs through the volumes and looks at the photographs (for none of us is quite grown up); made by Omar Marcus and arranged by Anita Ventura, these handsomely illustrate the rich variety of the newer Africa and the beauty of the African. Thus conditioned to a favorable view of the work, one begins to dip into the text in an unorganized way; one encounters a passage with which one wholly agrees, then another with which one wholly disagrees, then a piece of curious information one did not know, then an account of a territory one has not visited. Enough for that evening, but one is eager for a serious reading.

Then comes the awkward period when one looks up some aspect on which one thinks one had special knowledge, and one is disappointed. One says to oneself that it is not quite fair to make a judgment in this way, until one meets another specialist, who says he is sure that it is a good book but a little scrappy in his particular field. Now one goes back to work, analyzing and attempting a new synthesis of opinion. What does the work attempt in the newer fields of geography? How does this book compare with Lord Hailey's monumental *African Survey* and John Gunther's *Inside Africa?*

It should not be compared with them at all, for it is almost certain Kimble decided at the outset that his book must be entirely different from them and an example of the "team" approach to geographical research. Hailey's work took several years, he being a retired Governor of Bengal, practically the highest position attainable in the Indian civil service, which has bred some of Britain's finest administrators; his book is essentially an administrator's work about administration. Kimble has used it well in the masterly condensation that is his Chapter 21: "The Machinery of Government." Gunther's remarkable book is a piece of excellent, vivid reporting that from time to time irritated me to the point of scratching my head, and I see little influence of this book in the present work.

Kimble has been a most able charioteer in managing a variety of steeds whose style and ways of thought must have been quite different, for the book reads well throughout. Indeed, he finishes the race with a source book and a reflective synthesis of unequaled quality for Africa. Of course, the book is already out of date; any book presently written about Africa must be out of date by the time it is published. Prime Minister Macmillan, in his elegant, wafting way, speaks of "the wind of change" in Africa, but the metaphor is altogether too gentle. As one who has made seven journeys of depth into Africa in the last six years, I am not inclined to call the blast of an explosion anything so politically and poetically soothing as a wind. Kimble's book nonetheless arranges a large mass of enduring factual detail effectively, and it will serve well as a textbook because of its scholarly yet discursive style of discussion.

One of the newer directions of geographical research, against which Kimble's work should be evaluated, is the much stronger concentration on the study of economic growth. The stimulus for this trend probably arose during and immediately following World War II, when the increased accessibility and social interchange of the regions of the world, an upwelling nationalism and the provision of large-scale foreign aid made the economic growth of "lesser" countries inevitable.

An indication of the response to this stimulus is the unparalleled flow during the past decade of speculative material concerning the development potentials of what are termed, rightly or wrongly, the underdeveloped countries of the world. This outpouring of literature has been sponsored and financed primarily by government agencies of the "greater" countries, by international bodies such as the United Nations and by large philanthropic foundations. To assimilate and digest this material and to provide additional information, there are now several new periodicals, new college courses and a number of major research centers devoted entirely to the study of economic growth.

Largely as a result of the political interest in supplying aid to underdeveloped countries, many young researchers are being called upon to assist in the formulation and implementation of technical assistance programs. Geographers and workers in neighboring disciplines are being asked to undertake not scholarly theoretical studies but investigations of problems of a practical sort. Yet the work of examining the nature of the economic growth process and of understanding the changes that growth brings to underdeveloped countries has barely begun.

The evolution of scholarly knowledge is gradual and does not always advance on an even front. But this view of scientific inquiry cannot prevail in a deluge of foreign aid and technically trained assistants. And it is not a view of research that would be upheld by governments and peoples intent on raising standards of living by the medium of accepting cold-war foreign aid that may not be available tomorrow.

Kimble's book is definitely concerned with Africa as an underdeveloped continent rather than as a region of intrinsic geographic interest. The book may well be a timely achievement in that it has got its scholarly foot in the door before the door has been shut by the urgent

pragmatists charged with spending a lot of money in a short time. What a pity it is that foreign aid cannot be contained in a reservoir letting out a steady stream instead of the unmanageable flood required by political expediency. Kenneth E. Boulding has written a pungent piece of poetry that expresses this idea very well:

Poor countries are inclined to dicker
With those who'll make them richer quicker:
This gives the conflict added zest
Between the Russians and the West.
And they might well be Doubting Thomases
Who trust in other people's promises,
When all development must roll
On Thought, Work, Thrift, and Self-Control.

The reflective study of the influences of geographic processes on the economic growth of underdeveloped countries involves a large number of variables. Obviously an understanding becomes possible only with some attempt to isolate and group the variables into components, then to analyze the role of each component in turn. The notion of the "ecological matrix" applied in Norton S. Ginsburg's new *Atlas of Economic Development* groups the variables into four simple components: population, resource endowment, areal organization and technology. The description of societies is assumed to be satisfactory when the contribution of each component is given and the relationships among them are understood.

It is an interesting exercise to read Kimble's two volumes with this ecological view of society as a point of departure. The first volume, *Land and Livelihood*, opens with an overview of the economic life of Africa at the turn of the century; this, the author asserts, is to show the kind of place Africa was before the changes occurred. In succeeding chapters primary emphasis is given to the population and resource-endowment components of the ecological matrix. The second volume, *Society and Polity*, is devoted almost entirely to organization and related governmental policy, with additional chapters on African populations, their ignorances and diseases. The last two chapters are Kimble's attempt to give us hints as to what will produce desirable patterns of economic growth in Africa. Here he also raises fundamental questions regarding the influences of geographical processes on economic growth.

In general the book lends itself to the ecological breakdown; the components of the matrix can be considered individually and related to one another. The two volumes combined should prove useful to economists in the application of the matrix concept to a construction of "socioeconomic landscapes"—profiles of African societies. This may well assist our progress toward understanding the economic growth of underdeveloped countries and the organizational and technical skills that are associated with that process.

Like so many geographers, however, Kimble has failed to stress adequately the implications of technological change on the resources situation of Africa. This is my major criticism of his work. The reader must realize that Kimble is not omniscient and that he has had to depend on the papers of his contributors for much of his information. It was inevitable that some of these helpers should be too close to what they were describing. For example, the resettlement of large numbers of the Kamba of Kenya in the Makueni scheme "is already being spoken of by some of its promoters as an assured success." I doubt that anyone except some of its promoters would think so. The land resettled will not withstand permanent agriculture, and in the present drought conditions the situation is critical. The distinct possibility that the scheme has merely created another semiarid desert is not mentioned in the Kimble book, nor is the fact that 1,000 rhinoceroses were slaughtered to make the scheme possible. I am sure that this information never reached him. He was probably dependent on some agricultural adviser, and if you know anything about British colonial administration it is that the administrator, who is himself generally devoid of any technical knowledge (but who has a sublime integrity), listens to his agricultural officers. These are men who may know something about agriculture but who know too little about the basic problem of how plants and animals (including man) survive in a region of finite biological productivity.

Indeed, it is one of the amazing shortcomings of a country that has produced an Oxford and a Cambridge that until very recently there was not one British university that gave basic training in science and scientific thinking to its agricultural students. The agricultural curriculums produce capable technicians but not scientists, with the result that the colonial service became cluttered with individuals who thought in terms of increasing agricultural production instead of asking what the terrain of Africa

would take in the way of major interference. The best land scientists of British Africa have come from other disciplines, some of them even from administrators trained in the humanities. The most wonderful scientific development in British tropical Africa came almost too late: the establishment of the East African Agricultural and Forestry Research Organization (EAAFRO) and the East African Veterinary Research Organization (EAVRO). These two institutions have made a substantial contribution to the basic scientific work that should have been done long ago.

Kimble describes in restrained terms some of the failures of British agricultural schemes, including the colossal groundnut debacle of Tanganyika (although when he states the cost as being 26 million pounds he has made a slip—it was 36 million). This was an instance of technically rather than scientifically trained people being let loose with modern earth-moving machinery—the paraphernalia of megalomania. Absolutely no ecological reconnaissance was done beforehand, and as one of those who did his best to get some such work going I can vouch for the difficulties put in the way of its being done.

It is perhaps unfortunate that an ecologist convinced of the organic value of the wildlife of Africa to the economy of the continent should have been asked to review this book, for the subject has not been merely inadequately treated but left out altogether. Such indifference or unawareness is common among economists, and the in-a-hurry do-gooders simply cannot be bothered—they must get busy growing more starch in order that more Africans can be ill-fed or more bored. But I am surprised that the importance of wildlife in the conservation of these ancient habitats of Africa should have been ignored by a geographer with a biological sensitivity. It may be mentioned here that an international conference of representatives of African governments and biologists, called by the Scientific Council for Africa South of the Sahara and the International Union for Conservation of Nature and Natural Resources, will meet in Tanganyika this month to discuss the place of wildlife in the African economy. The fatuous remark, "Well, if I have to choose between animals and people, I choose people," will not be heard in Africa much longer, if only because it is coming to be understood that the choice is not between animals and people. There is reciprocity. The cattle-raising peoples of Africa, such as the Dinka, Nuer and Shilluk of the Sudan, knew this quite well and still do, but the cash crop turns man against nature.

Africa is tragedy on the grandest scale: the good and the laying aside of false pride will come, but at a terrible cost. Why must a political scale of 10 years be set against a cultural scale of possibly 1,000 years? I notice that time after time Kimble comes back in discussion to West Africa, which must have been more civilized 500 years ago than some parts of Africa are today. Africa needs time, and few will give it to her, least of all her more clamant politicians.

Some of my own ancestors must have been among those violent savages called Anglo-Saxons, yet the advent of the Greek humanist Theodore as Archbishop of Canterbury set in train a process that in 200 years made England the most civilized country in Europe. Theodore was the link from classical Greece and Christian Rome, which held painfully until the new intellectual upheaval of the Renaissance, when men drank again at the springs of Hellas and spread a revived spirit throughout Europe. Paganism was not dead in Britain even in my own youth, in spite of the cruel suppressions in the name of Christianity in the 17th century. But the dark animism of pagans did not matter any more. In Africa animism still matters. The vast majority of Africans still regard nature and everything in it as possessing feelings and emotions; physical objects of certain shapes and textures are thought to have physiological and even anatomical influences. This view pervades all of African life and gravely hampers the rational solution of Africa's problems. Animism will take a long time to remove, and in so far as we may try to crush it or ignore it we shall do wrong, because we shall destroy some tones of a cultural heritage that the new Africa will need.

Are the next few decades to be the African Renaissance? Almost everyone earnestly hopes so and prays for the absence of political despotisms. Christianity has brought a pearl of great worth to Africa; the deeply convinced Christian African who does not look back over his shoulder is probably the most civilized African. But the handmaiden of Christianity, implementing its compassionate virtues, has been science. And science as we see it being applied compassionately in Africa, without science's own sterner disciplines, is going to substitute new miseries for those it is alleviating.

The greatest moral force in Africa has been Islam. This religion has done far more to stem the miasmic ooze of animism than any other. Kimble remarks

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how black Mohammedans think themselves better people than the pagans. Indeed they are, for the moral power of Islam affects every hour of their waking life. It is immeasurably more civilized than African paganism can be and is less of a veneer than much African Christianity. My own impression is that the European administrative powers (except France) have blocked off Islam from the black races because of the shadow of past slave dealing, though the Western slave trade was Christian. But the forward march Islam is making in Africa will help rather than hold back the civilizing process. Christianity and the overwhelming scientific advantage it can command would do well to meet Islam in Africa and go forward to the urgent task. Meanwhile the science-pouring process from the Western world should be examined in the spirit of science and not squandered in a spate of politically expedient technology of questionable value.

Short Reviews

PALAEOLITHIC ART, by Paolo Graziosi. McGraw-Hill Book Company, Inc. ($35). A beautifully illustrated, authoritative, all-embracing survey of the great works of art produced by the cave dwellers of the end of the Old Stone Age: the period known as the upper Paleolithic, from about 30,000 to 12,000 years ago. During this period, as indeed during the entire Pleistocene epoch, men lived on game and wild plants, fashioned weapons and tools out of stone, bone and antler (and probably wood, although no such implements have survived). At the beginning of the upper Paleolithic, Homo sapiens appeared. Like his forebears, sapiens was a hunter, not a herder or grower. But he differed from the men who came before him not only in his physical characteristics but also in his impulse to create nonutilitarian artifacts and to decorate his implements. These artifacts were of two kinds: mobiliary art, that is, portable objects of bone, ivory and stone which were carved, engraved, painted and sculptured; and cave art, consisting of figures painted, engraved or carved on the walls of caves and rock shelters. Paleolithic art has been known for almost a century. In the 1860's carved objects were found in the south of France, such things as a "*bâton de commandement*" engraved with an ibex and a leafy twig, the antler of a deer engraved with a bear, and the famous Magdalenian sculpture in ivory of two reindeer following each other. Cave art was uncovered a little later with the

discovery one day in the summer of 1879 by the 12-year-old daughter of a Spanish nobleman, Marcelino de Sautuola, of the magnificent paintings in the cave of Altamira. Movable art objects have since been found in many sites in France, Spain, Germany, Italy, the U.S.S.R., Belgium, Czechoslovakia and elsewhere in Europe; cave art is almost entirely limited to France (65 sites) and Spain (29). Climate and ecology were of course major factors in determining human migrations and therefore in determining the geographical distribution of Paleolithic art. Much less well understood are its significance and purpose. Magic undoubtedly played the greatest role in cave painting: the artist drew a bison or a reindeer or a mammoth transfixed with a javelin to assure success in the hunt. Reproduction and copulation were celebrated in mobiliary as well as in cave art; enormously fat women with gigantic breasts and monstrous buttocks were a tribute to fertility. But this is by no means the whole story. Women do not have to be fat to be fertile; there are many other specimens of prehistoric art which are much more understandable when they are regarded as expressions of joy, love, fear, sorrow and the like, and as pure aesthetic exercises, rather than as propitiatory or other magical offerings. There have been many books on the subject—the Abbé Henri Breuil's superb *Four Hundred Centuries of Cave Art* is a classic that comes readily to mind—but Graziosi's survey is a landmark in itself, remarkable in its representation of the entire range of artistic expression in Paleolithic times. The text is balanced, clear and not overwritten. The illustrations include 55 fine color plates, 795 black-and-white plates and 363 drawings. This book is not cheap, but it is a bargain.

SCIENCE IN SPACE, edited by Lloyd V. Berkner and Hugh Odishaw. McGraw-Hill Book Company, Inc. ($7). "The history of the human race is a continuous struggle from darkness toward light. It is therefore of no purpose to discuss the use of knowledge—man wants to know and when he ceases to do so he is no longer man." These words of the Norwegian explorer Fridtjof Nansen are singularly appropriate to the study of space: its boundless regions, its planets, stars and galaxies, its life—if it exists elsewhere than on earth. The subject has provoked, as was to be expected, a large literature. With few exceptions it has been a shoddy literature: uninformed, hasty, preoccupied with missileering and with jingo notions about us

getting there—wherever it is—first. This book is one of the exceptions. It is written by men who know what they are talking about; they are among those who will make the science of space. Their outlook, both humane and rational, is worthy of the high adventure that beckons. The first chapter, by the editors, is the best statement which has appeared of the dimensions and problems of space research. They discuss what has already been learned through rocket probes and from satellites placed in orbit, and what information is to be sought in future activities; the different types of space vehicle; the cost of space explorations by man and by automata; what is involved in landing on the moon; the possibility, so far as can now be envisioned, of getting to Mars or Venus. A most important point, which Berkner and Odishaw stress, is the need for international co-operation in space research. The big projects are fearfully expensive; competition is absurd. Sensible, fruitful patterns of joint effort were established during the International Geophysical Year and should be followed. If ever there was an opportunity for all men to work together in a constructive effort, this is it. Other chapters of the book consider the nature of gravitation, questions about the earth that space research may help answer, the moon and the planets, fields and particles in space, the chance to learn more about the stars, the bearing of space research on the life sciences. An illuminating symposium.

A HISTORY OF METALLOGRAPHY, by Cyril Stanley Smith. University of Chicago Press ($8.50). Long before metallography became a science, armorers, swordmakers and other artisans studied the surfaces and the fractures of metals in order to improve and beautify their work. So over the centuries a large, though disorganized, body of knowledge came into being. By the middle of the 19th century physics and chemistry were well enough advanced to supply the knowledge needed for a more systematic examination of metal structure and for a reform of age-old metallurgical practices; yet it was pressure for increased production of iron and steel which led to changes in technology, rather than the kind of scientific curiosity which in many other fields has prompted study and experiment. It was not until 1890 that metallography began to crystallize into a definite discipline. Henry Sorby, a brilliant amateur living in the steelmaking center of Sheffield, developed thin-section polarized light techniques for studying rocks and was

led through an interest in the crystalline structure of meteorites to study the structure of steels and irons; some years later X-ray diffraction was introduced and became a spectacularly successful method of revealing the anatomy of metals. Even so, metallography is one of the exemplars of an applied science which owes more to practical cookery, to economic incentives, to the need for understanding the still not fully understood complex process of hardening steel than it does to the concepts of a separately developed basic science. This book presents a history of the subject from the days of the Merovingian and Islamic blade makers to 1890. It is full of interesting material, ably written and admirably illustrated; it is an excellent contribution to the history of technology and an aid to perspective in one's understanding of the intriguingly illogical growth of a branch of scientific thought.

CHEMISTRY OF THE AMINO ACIDS, by Jesse P. Greenstein and Milton Winitz. John Wiley & Sons, Inc. ($100). This authoritative, comprehensive treatise deals with the organic and physical chemistry of an immensely versatile group of substances of first importance in their biological duties. As the preface points out, the amino acids have the ability to form acid salts and base salts, the capacity to increase the dielectric constant of the medium in which they are dissolved, and reactive groups which undergo a wide range of chemical alterations. As a result of these and other properties the amino acids are indispensable components of the diet of all animals, participate in "crucial metabolic reactions on which life depends" and are the basic constituents of protein molecules. In preparation for this work the late Jesse Greenstein and his coauthor reviewed thousands of pertinent papers up to the close of 1958, covering the theoretical and experimental sides of the subject, and interpolated in the text reports of a large number of illustrative experimental procedures tested or developed in their own laboratory at the National Cancer Institute. This is a major contribution to the literature of biochemistry.

GALILEO GALILEI: DISCOURSE ON BODIES IN WATER, translated by Thomas Salusbury. University of Illinois Press ($5). A facsimile reprint of the very rare original edition of Thomas Salusbury's 1665 translation of an important but not familiar scientific work by Galileo: his first published contribution to experimental physics. The *Dis-*

course arose from a notorious dispute between Galileo and certain professors of philosophy at the University of Pisa about the causes of the floating and sinking of bodies in liquid. The professors, and others aligned with them, were adherents of Aristotle, whose views on hydrostatics were not particularly enlightening; Galileo was not only well acquainted with Archimedes' great treatise on the subject but also had the annoying habit of thinking things out for himself, devising experiments and using his eyes. First there was a private argument on the principles involved, then a public debate in which Galileo cut through the quibbles and routed his opponent. The story is well told, as always, by Stillman Drake—the distinguished student of Galileo who in learning is equal to and in literacy leagues ahead of most of the professional historians of science—in an introduction to this volume. Drake also supplies useful notes. An attractive item.

THE DISEASE CONCEPT OF ALCOHOLISM, by E. M. Jellinek. Hillhouse Press ($6). Is alcoholism a disease? How physicians, scientists, social workers, educators, legislators and others concerned with the many problems of alcoholism answer this question is obviously a matter of importance, since this will determine their actions. For example, if drug addiction is treated as a crime instead of as a disease, very little progress can be made in curing the addict. The same was for centuries true of insanity; the same continues to be true of alcoholism. The present study of attitudes toward the disease concept of alcoholism was undertaken with this circumstance in mind. The author is the founder of the Yale Plan Clinic and has had vast experience in dealing with the subject. He has done his job carefully and has attempted to classify different types of alcoholism according to scientific principles, upon which a reasonable disease concept can be founded.

VITRUVIUS: THE TEN BOOKS OF ARCHITECTURE, translated by Morris Hicky Morgan. Dover Publications, Inc. ($2) A reissue in inexpensive format of a standard English translation (first published in 1914) of Vitruvius' famous work (written in the time of Augustus Caesar). It not only deals with all practical aspects of architecture, from the education of the architect to the method of constructing city walls and laying out streets, planning and building theaters, harbors, farmhouses, aqueducts and temples, but also treats of symmetry and

proportion, how rooms in a house "should be suited to the station of the owner," the various tests for good water, astrology, the winds, sundials and water clocks, hoisting machines, engines for raising water, the pump of Ctesibius, the water organ, the odometer, catapults, ballistae, the stringing of catapults, the tortoise (a device for filling ditches), weather prediction, Archimedes in his bath. The digressions are as entertaining and instructive as the central matter of this influential classic. Illustrations.

CONTEMPORARY EUROPEAN PHILOSOPHY, by I. M. Bocheński. University of California Press ($1.75). A paperbacked edition of Bocheński's survey (translated from the German) of European philosophies of matter (Bertrand Russell, neopositivism, dialectical materialism), the idea (Benedetto Croce, Léon Brunschvicg, Neo-Kantianism), life (Henri Bergson, pragmatism, historicism), essence (Edmund Husserl, Max Scheler), existence (existentialism, Martin Heidegger, Jean Paul Sartre, Gabriel Marcel, Karl Jaspers), being (Nicolai Hartmann, Alfred North Whitehead, Thomism). An appendix deals with mathematical logic and international philosophical organizations. Excellent bibliography.

THERMODYNAMICS, by Gilbert Newton Lewis and Merle Randall; revised by Kenneth S. Pitzer and Leo Brewer. McGraw-Hill Book Company, Inc. ($12.50). This book, first published in 1923, is a textbook but more than a textbook, for it bears throughout the stamp of the distinguished chemists who wrote it: authority, clarity, an admirable style, the "friendly usages of colloquial speech." For these reasons it is regarded as a classic of chemical literature, an excellent presentation of the three basic laws of thermodynamics and their application to chemical problems. It has now been thoroughly revised, the object being to preserve the merits of the original while incorporating material that has accrued during the past 38 years.

AMERICAN BUILDING ART: THE TWENTIETH CENTURY, by Carl W. Condit. Oxford University Press ($15). The author continues the story of building techniques and structural art begun in his volume on the 19th century, noted last year in these columns. The method of presentation is the same; that is, the chapters correspond to the division of the building art into its basic structural types and the primary structural materials in which they are embodied. The

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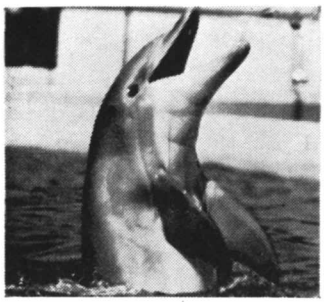
THE CONCISE ENCYCLOPEDIA OF ARCHAEOLOGY, edited by Leonard Cottrell. Hawthorn Books, Inc. ($15). Another sound handbook in this series. Most of the major aspects of archaeology are considered, ranging from the antiquity of the Far East, Europe and the Middle East to the pre-Columbian cultures of South America, the American Indians and the Eskimos. There are useful short defining entries, many illuminating long articles by leading specialists, 160 photographs in black and white and 16 pages of color. As good a concise survey of the digger's science and what it has produced as one can find.

LOUIS AGASSIZ: A LIFE IN SCIENCE, by Edward Lurie. University of Chicago Press ($7.50). A full-scale life of the Swiss scientist who came to the U.S. in 1846 already known for his "ice age" theory and who continued to enlarge his reputation as a naturalist and a great teacher at Harvard. Agassiz was opposed to the Darwinian theory of evolution, and in other views was occasionally quite wrongheaded; but his eloquence, his capacity for instilling enthusiasm in his students and his influence on the study of nature in the U.S. were almost beyond compare in his time. They continued long after his death to promote the interests of education and science.

SOURCE BOOK IN ASTRONOMY, 1900–1950, edited by Harlow Shapley. Harvard University Press ($10). A supplement to the same publisher's standard source book in astronomy, this book contains some 70 contributions illustrating the extraordinary advances of astronomical science in the first half of the present century. There are sections on instrumentation, the sun, the planetary



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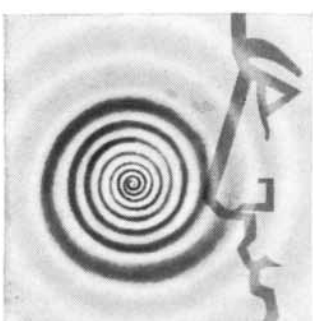

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OUR AMERICAN WEATHER, by George H. T. Kimble. Indiana University Press ($1.95). A geographer gives a month-by-month, coast-to-coast breakdown of the changing and recurring weather patterns, explaining the phenomena involved. Paper-backed reprint of a book first published in 1955.

ARIZONA FLORA, by Thomas H. Kearney, Robert H. Peebles and others. University of California Press ($12.50). The second edition of this book of flora, first published in 1951, contains an added section of more than 50 pages.

THE MATHEMATICS OF RADIATIVE TRANSFER, by I. W. Busbridge. Cambridge University Press ($5). A mathematical tract on problems which arise in the theory of the transfer of radiation through the atmosphere of a star.

THE STRUCTURE OF THE EYE, edited by George K. Smelser. Academic Press Inc. ($15). Proceedings of a 1960 symposium dealing with different problems in the field of the fine structure of different parts of the eye. Illustrations.

ARGONAUTS OF THE WESTERN PACIFIC, by Bronislaw Malinowski. E. P. Dutton & Company, Inc. ($2.45). A paper-backed reprint of Malinowski's admirable book, a major achievement in anthropological research and interpretation. Sixty-five illustrations and five maps.

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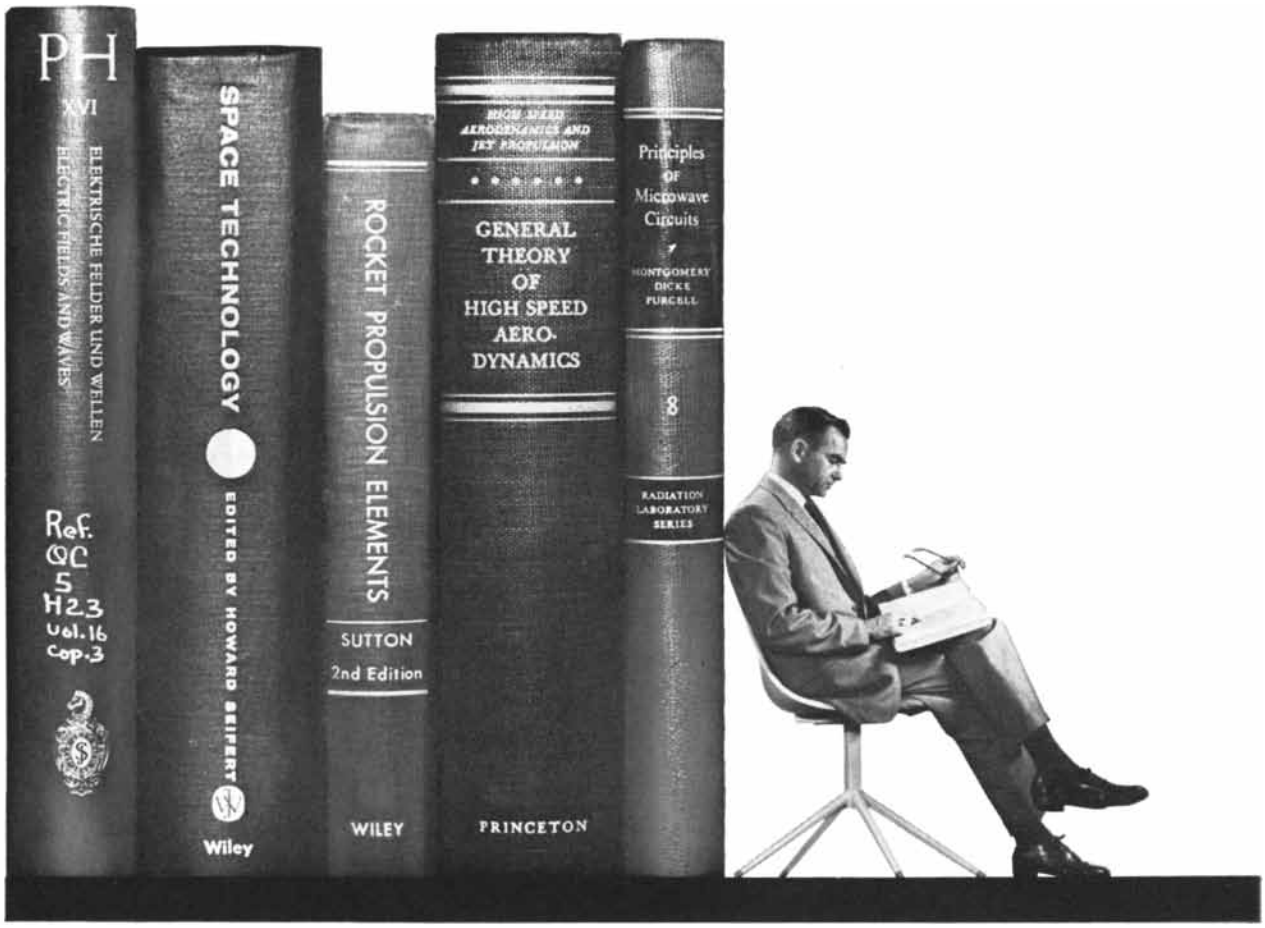

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VARIATIONAL PRINCIPLES IN DYNAMICS AND QUANTUM THEORY, by Wolfgang Yourgrau and Stanley Mandelstam. Pitman Publishing Corporation ($5.75). The second edition of this interesting book, which was reviewed on first publication in these columns some years ago, contains a new chapter on the Feynman and Schwinger principles in quantum mechanics, and certain other materials.

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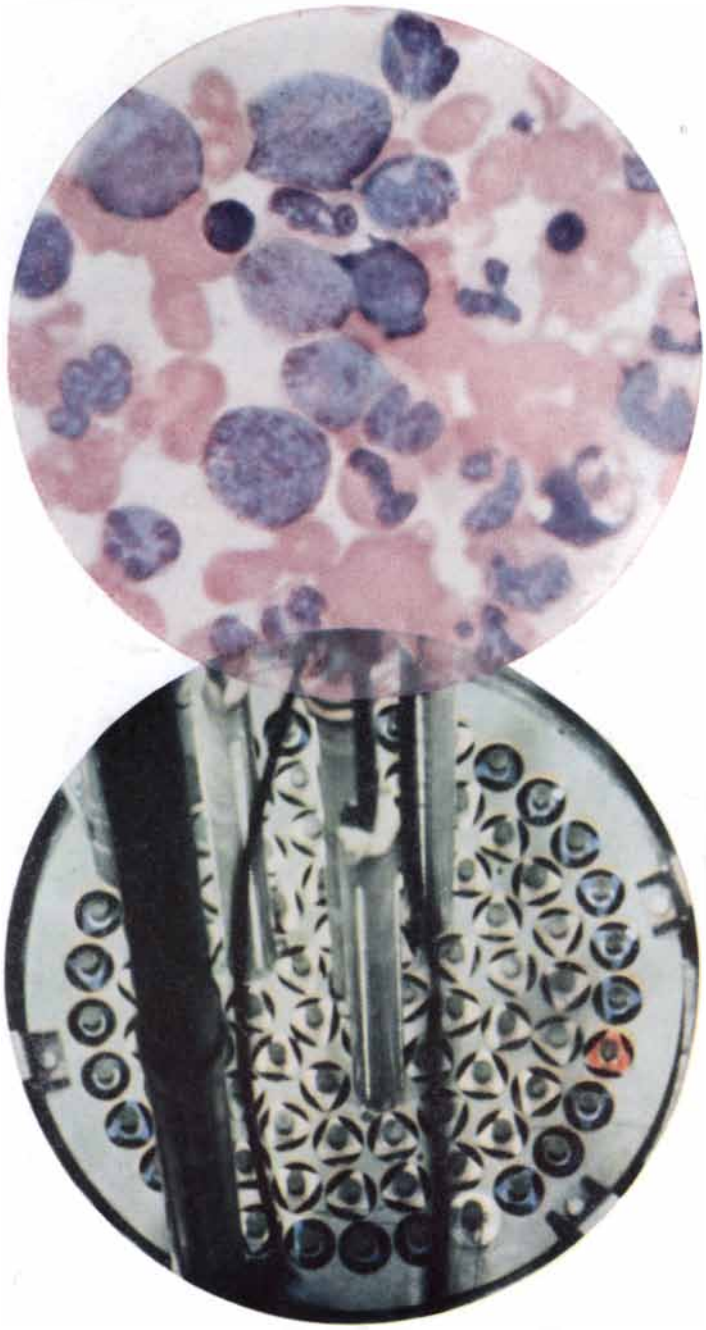

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