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THE FRIENDLY VIRUSES

BY HELENA CURTIS

NATURE IS REGARDED, and quite properly, as indifferent to the attempts of man to probe her secrets. Yet from time to time she seems to drop a clue in the explorer's path, a special gift to aid the wayfarer. Among such treasures are the chromosomes of the salivary glands of Drosophila, the giant axon of the squid, the translucent embryo of the sea urchin, and, clearly, the T-even bacteriophages. More recently, in the laboratories of Professor Norton Zinder of Rockefeller, another special clue of this sort has been uncovered. It is the f2 bacterial virus, the smallest entity we know that can possibly be conceived of as alive. In Professor Zinder's laboratories and in a number of others throughout the world, this tiny speck of life is being examined and reexamined; taken apart and put back together again; analyzed chemically, hopefully down to its last submolecule; and, at the same moment, observed as a living organism with its own biological history, organized in space and time.

In the last decade, biology has offered brilliant new tools and concepts for understanding the processes known as "living"—and concomitantly has raised some tantalizing questions. There are some scientists, Dr. Zinder included, who believe that the tiny, harmless f2 may well prove to be the first creature that scientists, using these new tools and concepts, will be able to understand in every detail. At the very least f2 is providing new fundamental information about the nature of genetic material and the organization of living systems.

Although the bacterial viruses have undoubtedly existed for millennia, this particular one, f2, was found only a few years ago. Its discoverers were Dr. Zinder and Timothy Loeb, who was then a graduate student in Professor Zinder's laboratory. Dr. Loeb, who received the Ph.D. from the University in 1962 and is now Assistant Professor in the Universidad del Valle, Colombia, was originally interested in studying the fertility factor in the bacteria, *Escherichia coli* or *E. coli* as it is commonly called. Joshua Lederberg and Edward L. Tatum had shown many years before that certain varieties of *E. coli* are able to mate. Two cells come together—as electron micrographs later revealed—a cytoplasmic tunnel forms between them, and the genetic material of one passes through this tunnel into the other cell. Cells that are able to donate their genetic material in this way, Lederberg later found, contain a genetic factor which he called F, for fertility. During conjugation the fertility factor is passed from the male, or donor, cell to the female, or recipient, cell, which thus in turn, processing F, becomes a donor type. Further work by a number of investigators revealed that donor and recipient cells adhere to one another because of a specific chemical substance on the surface of the cell containing the F factor. This substance was called the sex antigen.

Loeb was interested in identifying this chemical substance and on the basis of some previous work by Professor Walther Goebel, he and Dr. Zinder thought of a possible ingenious shortcut. Dr. Goebel and his group had been working with the T-even bacteriophage, the large DNA-containing bacterial viruses which made possible so many of the early discoveries in molecular biology. Dr. Goebel had shown that whether or not a particular T-even bacteriophage can attach to the cell wall of a particular *E. coli* depends on the presence on the surface of the bacterial wall of a substance which serves as a receptor site for that special variety of bacteriophage. (It has subsequently been shown that the specificity of polio and many other viruses for particular human cells depends also upon the cell's having a specific receptor—its point of vulnerability—for that particular virus.) Dr. Goebel and co-workers isolated and purified the receptor substances which they were

able to identify as complex lipoproteins. These substances, even when isolated from the cell, would react with their specific bacteriophage. The specificity of this reaction made it much simpler to study the nature of the receptor material.

Suppose, the investigators reasoned, one could find a bacteriophage whose receptor site was the same substance that made the male cell stick to the female cell, that is, the sex antigen. If they could do that, they could then follow Dr. Goebel's procedures for isolating and identifying the sex antigen, and its reaction with the bacteriophage would provide a useful testing system.

First, the investigators tried all the regular laboratory strains of bacteriophage to see if any one would specifically attack male *E. coli.* None did. Second, they collected water samples from a sewage disposal plant on Ward's Island; *E. coli* is a common and usually harmless inhabitant of the human intestinal tract and where *E. coli* can be found, there, too, are presumably its common parasites, the bacterial viruses. They tested the Ward's Island samples on separate colonies of male and female cells. They grew the bacterial cells on agar and, following methods developed by the early phage workers, spread the samples thin over the agar. Each time a bare patch – or plaque, as it is known – appeared in the bacterial lawn, it meant a virus was present. And there were many holes, in both the male and female colonies. Then they cross-tested the samples. All of the viruses that infected the female cells also infected male cells. But of about one hundred and fifty viruses that formed plaques in the male colony, seven did not infect the female cells. In short, seven bacterial viruses specific for *E. coli* males had been found.

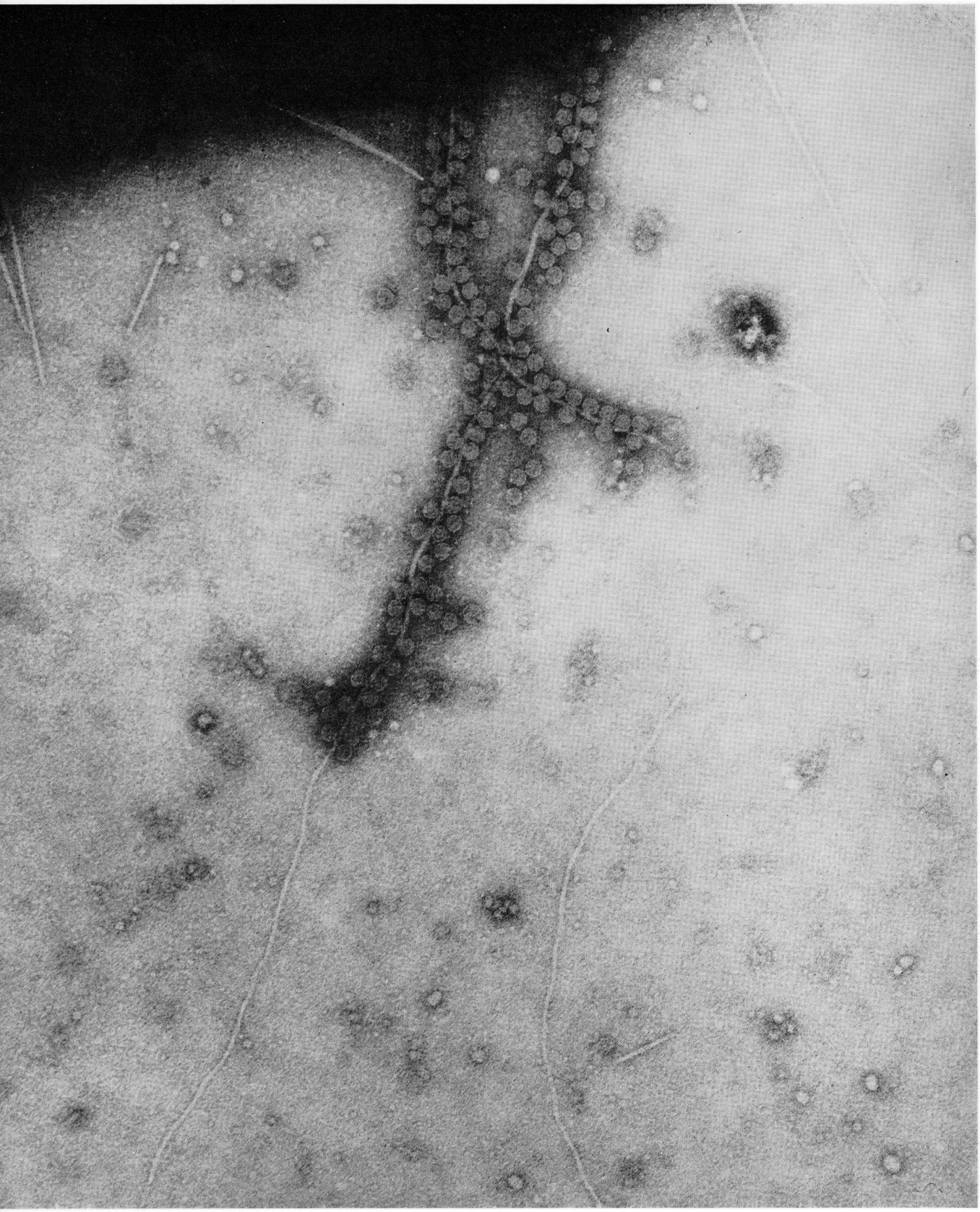
The seven viruses

At first, the viruses were considered merely as welcome tools for the intended project, but on closer inspection the tools themselves proved so fascinating that the original project was soon set aside. (It might be noted parenthetically that such a turn of events came as no surprise to Professor Zinder whose own well-known discovery of bacteriophage transduction came about while he was vainly seeking evidence of conjugation in Salmonella.) Indeed, Professor Zinder and many of the members of his laboratory have been engaged in studying the nature of these viruses almost since the moment of their discovery.

In keeping with the old bacteriophage tradition, the viruses were named by letter-number combinations: f, for fertility factor, and numbers 1 through 7. F1 proved to be unique. It is a very long slender filament, 8500 Ångstroms in length (more than twice as long as the familiar tobacco mosaic virus and, indeed, almost as long as *E. coli* itself), but only about 50 Ångstroms wide. Within this slim tube is a single molecule of DNA, not coiled in the now familiar helix, but stretched out in one long slender strand.

Although less spectacular electron-micrographically speaking, f2 through f7 proved as interesting as f1. In the first place, they contain RNA; although a number of plant and animal viruses – notably tobacco mosaic virus, influenza, and polio – have been shown to contain RNA rather than DNA, all the previously discovered bacteriophages were DNA viruses. Loeb established that f2 through f7 were all closely related immunologically, indicating their probable descent from a common ancestor. Since the report of their discovery (which appeared in *Science* in 1960) a number of other small RNA-containing, male-specific bacteriophages have been isolated in other laboratories and all of these also appear to be immunologically related to the f family. For this reason, although most of the work with the RNA phages has been carried out with f2, it is generally assumed that the findings are applicable to the entire group. In overall dimensions, f2 through f7 are a little smaller than polio – some 200 Ångstroms in diameter. Their total genetic material, however, is only about half that of polio. It is estimated that their strand of RNA contains about 3000 submolecules, or

F2 viruses attaching to the pili of the bacterial cell. The dark area in the upper left is a small portion of the bacterium, which is relatively huge at this scale. The small spherical particles are f2 bacteriophages and the long slender filaments to which they are attached are the pili. The filaments devoid of f2 particles but similar in appearance to the pili are f1 viruses. x 165,000

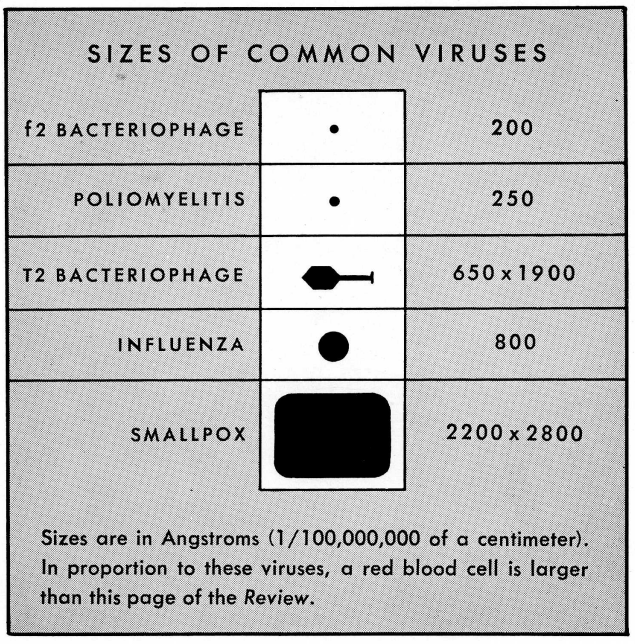


nucleotides – as compared with about 300,000 for the T-even bacteriophage and the ten billion estimated to be in a human cell. In short, the methods now becoming available may make it possible to identify each submolecule – every symbol, so to speak, of the "genetic code" – of this particular organism. Analysis of the complete hereditary message of other living things appears to lie scores of years beyond our reach.

A third useful feature of the RNA phages is their enormous prolificacy. When the bacteria are kept closely packed, which inhibits their breaking open to release their viral contents, some 20,000 to 40,000 particles are produced per bacterial cell. Under these conditions, the equivalent of some five per cent of the original bacterial mass is turned into virus. This means, in practical terms, that 10 to 20 milligrams per liter of pure phage can be obtained, a wealth of material to the molecular biologist. It also means, as Professor Zinder has pointed out, that the RNA phage is currently the most populous organism in the world.

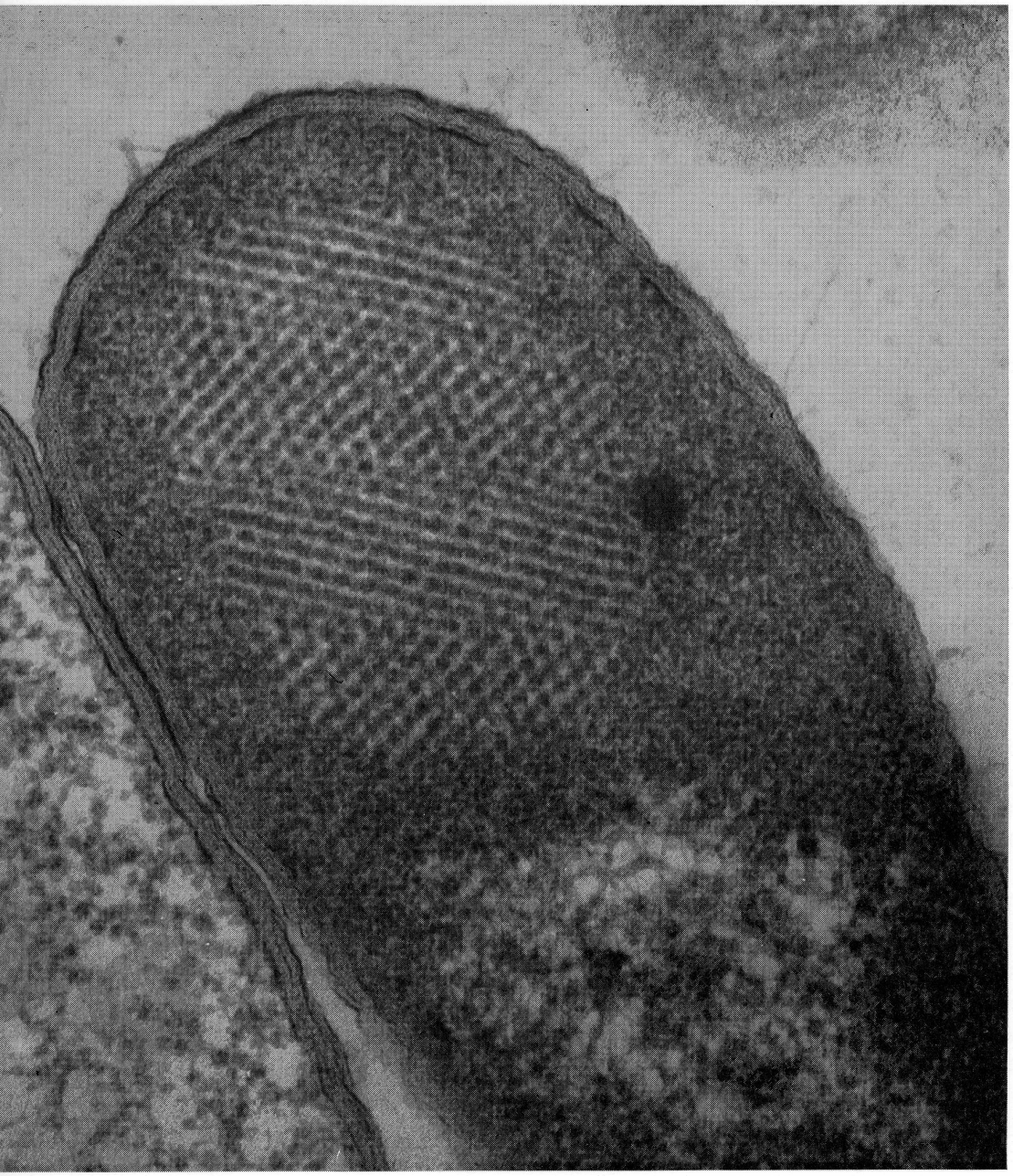
Biography of a virus

Infection starts, like all viral infections, with the attachment of the particle to the cell. Recently it has been found that the viruses stick to certain pili, long hairlike processes which are found on bacterial cells. Curiously – is it a coincidence? – these pili have the same dimensions and appearance as the strange f1 phage. All *E. coli* have such pili but some are associated only with "maleness"; when *E. coli* mate, the recipient cell, the original "female," grows four new pili when it receives the F factor so becoming "male." It is to these pili, and these alone, that the f2 viruses adhere. So, as it turns out, Timothy Loeb did find what he was originally seeking, the sex antigen.



The pili are hollow, like long slender straws. The viruses are roughly spherical, with a coat of protein on the inside and the molecule of RNA packed tightly inside. Apparently the RNA molecule slips out of its protein package or coating into the hollow pilus, and glides down into the bacterial cell. Then it disappears. Five to ten minutes later, a new enzyme system shows up in the infected bacterium, RNA polymerase. This enzyme system (which also appears in other types of cells infected by other RNA viruses, such as polio) has recently been intriguing a number of investigators. Double-stranded DNA duplicates, as suggested by Watson and Crick a decade ago, by each strand serving as the template for its complementary strand. In other words, you start out with strands A and B, and after duplication, you get the old A strand with a new B, and the old B strand with a new A. But with single-stranded RNA, you start out with strand A and get more strand A. The most reasonable current hypothesis is that strand A makes a strand B, with the help of one enzyme, and that B or double-stranded AB then serves as the template for the thousands of new strand A's which are required for the viral progeny. Professor Zinder and his co-workers have managed to glimpse a double-stranded RNA within the infected cell, supporting this notion. So it seems likely that RNA polymerase is actually two enzymes, one directing each step in this two-step process. This then is one of the activities in the life history of f2: it makes new enzymes to make more of itself.

This RNA polymerase accumulates in the cell for about 25 minutes, and then stops accumulating; something turns off the switch. Second in the sequence of detectable events, new viral RNA begins to form and is stockpiled in the cell. Third, protein molecules for the viral coat appear. Finally the coat protein and viral RNA are assembled into finished particles. These events are ordered not only chronologically but quantitatively. For instance, every



Bacterial cell packed with f2 particles in a crystalline array. X *135,000*

molecule of RNA requires 150 molecules of coat protein to encapsulate it. And, apparently, for every molecule of viral RNA produced, just about 150 molecules of coat protein are run off on the viral assembly line – at least no gross excess of either has ever been detected.

What turns the genes of the virus on and off? There are some clues. For instance, Professor Zinder has found that if the coat protein is defective, excess RNA polymerase is produced, which suggests that accumulation of coat protein somehow turns off the genes that make the polymerase. But what starts the production of coat protein in the first place? And what controls the relative amounts of RNA and protein produced? These are questions intimately involving not only the biography of f2 but also the life history of all creatures.

The amount of genetic material contained in each

viral particle is so minute that it could theoretically provide for only four or five proteins. One or two of these must be the enzymes involved in making more viral RNA. Another, it is known, is the protein that makes up the virus coat. So the investigators are tantalizingly close to understanding the total biochemical life of f2 – though filling in the missing pieces turns out to be difficult.

In Dr. Zinder's laboratory, they are attacking the problem in two ways. One is by dissection – taking apart the various products of virus infection and analyzing them separately. For instance, they have now shown that the virus coat is made up of about 150 identical protein molecules and that each of these molecules contains 133 amino acids. This piece of information led to a very exciting new observation, reported in the January issue of the *Proceedings of the National Academy of Sciences,* which suggests an answer to one of the most puzzling current questions in molecular biology: how is the genetic code punctuated? In other words, if one long continuous strand of nucleic acid dictates all the proteins, what determines where the orders for one protein end and another protein begins? Dr. Zinder and co-workers, using extracts from *E. coli* and virus RNA, attempted for a long time to get the viral RNA to make coat protein in the test tube. But the protein that was produced was not exactly like coat protein, no matter how often or how carefully the experiments were done. When the aberrant test-tube-produced protein was analyzed, amino acid by amino acid, the difference was discovered. At the beginning of the molecule of test tube protein there was an unusual amino acid not present in the final coat protein. The function of this group seems to be to spell out the order START HERE; in fact, START HERE is mandatory, because the beginning amino acid is so constructed that other amino acids can only hook onto one end. When the protein molecules are assembled into virus coats, the START HERE's are apparently all dropped out. These starter molecules, or something very like them, are believed to be universal.

The second way that the biography of the virus is being studied is by interrupting and restarting its life cycle. This is accomplished by the use of conditional lethal mutants, an extremely simple but crucial scientific method first used some twenty years ago by George Beadle and Edward L. Tatum. Professors Beadle and Tatum (who received the Nobel prize for this work, sharing it with Joshua Lederberg and Tatum for the work on bacterial conjugation) found mutant strains of the red bread mold *Neurospora crassa* that would grow only in media containing particular amino acids not needed by nonmutant strains. This enabled them to analyze exactly what was wrong with the mutant – that is, what biochemical function it was lacking – and led to the famous one gene-one protein hypothesis that forms one of the foundations of modern biology, including the work in which Professor Zinder and his colleagues are involved today.

In the case of the f2 viruses, mutants have been found which will grow under certain conditions and not others. Some mutants are temperature-sensitive, for instance: their genes do not work at higher temperatures, although "normal" genes do. These are in effect very much like the genes that produce color in the Siamese cat; the cat is darker-colored only at his "points," or extremities, because his color-producing genes operate only in these cooler, outlying areas. By raising and lowering the temperature of cultures of heat-sensitive f2 mutants, one can start and stop their life cycles. Using this method, Professor Zinder has been able to show that f2 not only has genes that make RNA-duplicating enzymes and coat protein but a gene that serves as an assembler. Even if perfect viral RNA and coat protein are produced, no complete virus particles are formed unless the "assembler" gene is turned on. Understanding of the nature of such a gene may be the necessary link between modern molecular biology and the classic question of morphogenesis which has intrigued biologists since the time of Aristotle as it will in the centuries ahead.

Professor Zinder makes no predictions about when the work will be completed or indeed, even which group of scientists will finally unravel the clue. But he does say, "In time it is certain that the whole story of these phages can be encompassed; and, with this, there will be one independent bit of genetic material about which we can say, 'We know and we understand.'"

A full account of the work described here and a complete bibliography may be found in Professor Zinder's review "RNA Phages" in the *Annual Review of Microbiology,* Vol. 19, 1965; pages 455-472.

COLD SPRING HARBOR: PAST AND FUTURE

IN THE SUMMER of 1873, on Penikese Island in Buzzards Bay, Professor Louis Agassiz organized a marine laboratory and offered a course in natural history to a few young biologists. Among those who took the course that summer – the last summer of Agassiz's life, as it turned out – was Dr. Franklin W. Hooper, who later became director of the Brooklyn Institute of Arts and Sciences. Agassiz's course made a strong impression on Hooper, an impression vividly recalled in 1890 when he paid his first visit to Cold Spring Harbor. He saw instantly in the little bay on Long Island's green north shore an ideal spot for a biological laboratory, immediately laid his plans, and conducted the first session that same summer.

Summer sessions at Cold Spring Harbor, although greatly changed in scope and character and beset by numerous administrative upheavals, have continued uninterrupted for seventy-five years. For more than thirty of these years scientists from The Rockefeller University have participated in these summer activities – as students, teachers, investigators, lecturers, and visitors. In fact, according to a recent tally of the scientists attending the summer courses more have come from the Rockefeller than from any other institution. Because of the close and long-standing ties

Cold Spring Harbor 1962, looking south. The buildings of the Cold Spring Harbor Laboratory of Quantitative Biology are scattered along the west shore, and the arrow marks the location of the auditorium shown in the photograph on page 10

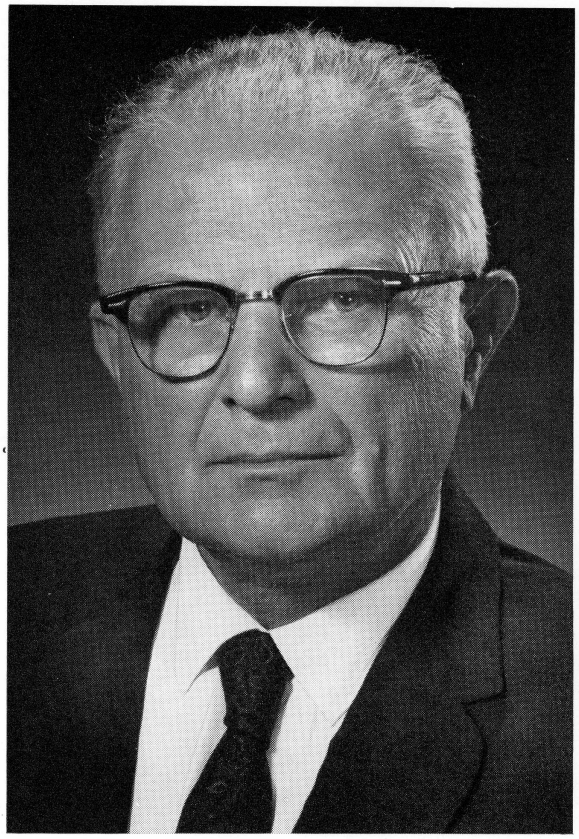
between the two institutions, it was more than appropriate that when the new Cold Spring Harbor Laboratory of Quantitative Biology was incorporated last year The Rockefeller University should volunteer its support as one of the participating institutions. The new Board of Trustees, of which Rockefeller Professor Edward L. Tatum is Chairman, has the relatively simple function of guiding the vigorous and continuing programs of the Laboratory, and the far more difficult task of finding adequate funds for its operation.

In 1890, at the time of Hooper's first visit, the community of Cold Spring Harbor was old, established, and prospering. Purchased from the Matenecock Sachem, Raseokan, in 1653, the rich land around the harbor provided fertile farms for the early settlers, the streams that fed it offered water power for grist, textile, and paper mills, and the harbor itself provided easy transportation for the products of the mills and, in the great days of whaling, a snug haven for the vessels.

The first summer sessions were held at the New York State Fish Hatchery, which is still in existence at the tip of the five-mile inlet. The hatchery had been created in 1880 by E. G. Blackford, a Fulton Market fish dealer and the New York State Commissioner of Fisheries. Cold Spring Harbor was considered an ideal site because of its fine supply of pure spring water as well as brackish and salt waters, providing for the culture of many types of marine life. The Biological Laboratory, officially a branch of the Brooklyn Institute, and the Hatchery so flourished in their activities that *Minerva, the Yearbook of the Learned World* listed the "little fishing village of Cold Spring Harbor" as a center of learning and research together with places such as Cambridge, Oxford, Paris, Göttingen, and Padua.

The first decade

For three summers the Fish Hatchery was host to the Biological Laboratory until in 1894 Mr. John D. Jones, a prominent local citizen, erected a new building nearby, on the west side of the bay, and for the Laboratory; this building is still standing and in use. He also made available to the Laboratory several houses that had been left vacant after the collapse of the whaling industry. A few years later Mrs. Blackford gave funds for the erection of a memorial to her husband; Blackford Hall, one of the few buildings at the Laboratory which is not of wood frame construction, still serves as a dining hall, assembly room, and dormitory.



MILISLAV DEMEREC
Director 1941-1960

In 1904 the Carnegie Institution of Washington established a laboratory at the Harbor, The Station for Experimental Evolution — "to harness the forces of evolution for man." One of the early practical triumphs of the Station was Dr. George Shull's development of hybrid corn. The Station, which later took on the less ambitious title of the Department of Genetics, conducted a year-round program which greatly enriched the summer biological sessions and, although the two operations were administratively separate, served to change their character. The Carnegie Institution built its own laboratory buildings at Cold Spring Harbor — laboratories made famous by the now classic work of Alfred Hershey and Barbara McClintock.

In 1924 the Biological Laboratory underwent the first of a series of drastic administrative changes. The

Brooklyn Institute's interest in the summer program declined and so an organization of local citizens, the Long Island Biological Association, was incorporated to take over the ownership of the Laboratory. For a number of years, the Carnegie Institution's Department of Genetics and the Association continued their technically separate but actually complementary activities.

In 1933 the now famous Cold Spring Harbor Symposia of Quantitative Biology were initiated. Of 29 participants in the first Symposium, seven were from The Rockefeller Institute, including Professors W. J. V. Osterhout and Theodore Shedlovsky. As Dr. Shedlovsky explains, the purpose of these early symposia — and hence the term "quantitative biology" — was to apply physicochemical ideas and principles of measurement to biology — which in those days was largely a descriptive science. During the 1930's Dr. Shedlovsky continued to visit Cold Spring Harbor, spending one entire summer there with his family. Among the workers he recalls from those early days were Calvin Bridges, who at that time had just begun his studies of the giant chromosomes of the salivary gland of *Drosophila,* as well as Kenneth Cole, Howard Curtis (whose son Brian was recently a student at Rockefeller), and Harold Abramson.

The annual meetings have always been relatively small — the auditorium at the Harbor holds less than 250 persons — and informal, but many scientists consider them among the most significant and provocative of all international gatherings in the field of biology. Their subjects have included: photo-chemical reactions, hormones, the permeability of cell surfaces, proteins, the evolution of man, the genetics of microorganisms, and biological clocks. It was at one of these, for example, that Watson and Crick first made public their theories on the structure of the DNA molecule; James Watson was no stranger to the Laboratory, having previously spent a summer at Cold Spring Harbor as a graduate student.

1941 was an important year in the history of the Laboratory. Dr. Milislav Demerec, who had been a member of the Carnegie Institution's staff since 1923, became joint director of the Department of Genetics and of the Laboratory, thus coordinating the activities of the two groups. Under Dr. Demerec's guidance, the Department of Genetics made distinguished contributions to the war effort, including the development of a strain of Penicillium which more than doubled the output of the drug at a time when the need for it was great. More recently, Dr. Demerec's own work on the analysis of the origin of bacterial resistance to antibiotics has led the way to development of methods for avoiding the emergence of drug-fast strains. Perhaps more important than these direct contributions was Dr. Demerec's imagination and enthusiasm. As Dr. Rollin Hotchkiss recalls, he was one of those rare scientists who moved easily from maize and delphinium to the fruitfly, the bacterial cell, and the bacteriophage as each new system for exploring the nature of the gene became available.

Also in 1941, Dr. Max Delbrück and Dr. Salvador Luria first joined forces at Cold Spring Harbor, beginning the long association that was to prove so important to present-day biology. Both were enemy aliens and so excluded from the war effort; they spent these years laying the foundations of modern virology and much of modern genetics, attracting by their presence a growing nucleus of workers in the field — A. H. Doermann, Mark Adams, Seymour Cohen, and T. F. Anderson. Each summer they returned to Cold Spring Harbor. The Laboratory became the international focus for bacteriophage research and, as a consequence, for molecular biology.

Another scientist who was present at the Laboratory in 1941 was Dr. Alfred Mirsky, who came there as a summer investigator and a speaker at the Symposium. One of the initial attractions for Dr. Mirsky was the Hatchery with its abundance of fish sperm, long prized as a source of nucleoproteins. In a prophetic report of his summer activities, Dr. Mirsky wrote:

> The field I work in (protein chemistry) is beginning to make contact with genetics, and there can be little doubt that these contacts are destined to have a profound influence on both genetics and biochemistry.... My work along these lines has only just begun.

In 1945, with the close of the war, the first of the now famous summer courses in bacteriophage techniques was taught by Dr. Delbrück. Among those in attendance was Dr. Rollin Hotchkiss, then dividing his time between the Rockefeller and the United States Navy. Dr. Hotchkiss persuaded Dr. Thomas Rivers to give him an extra week's vacation to attend the course. Since that time Professor Hotchkiss has

Participants in the 1965 symposium on quantitative biology leaving the auditorium

spent some portion of almost every summer at Cold Spring Harbor, at least half a dozen times as a guest investigator, often as a speaker at the Symposia or at a seminar given in connection with one of the courses, or, as this year, just as a visitor. One of the most important aspects of "vacationing" at Cold Spring Harbor, from Dr. Hotchkiss's point of view, is the total lack of what he calls "vertical organization." Distinctions of academic rank are discarded, along with neckties and suit jackets. Full professors may be found in the bacteriophage workshop side by side with graduate students, and all share the cafeteria, the beach, and the dormitories. The only question visitors ask one another is: "What are you interested in?"

It was during one of these summer visits, in 1949, that Dr. Hotchkiss encountered Norton Zinder, then a graduate student at the University of Wisconsin. This meeting eventually resulted in Dr. Zinder's joining the Rockefeller staff in 1953. Professor Zinder has also been back to Cold Spring Harbor every year since 1949, teaching the course on bacterial genetics five times, often maintaining a summer laboratory there, and nearly always participating, as he did last year and will again this year, in the seminars.

Another faithful visitor to Cold Spring Harbor during these years was Professor Sam Granick. Dr. Granick had a small laboratory at Cold Spring Harbor in which he did occasional experiments and wrote several reviews and manuscripts. Dr. Granick was not working in the field of genetics – at least he did not think that he was at that time – but he visited there regularly to keep up with the rapid progress being made in molecular genetics. He himself had long been working on the relationships between the red pigment of hemoglobin and the green pigment of chlorophyll. "Just for something to fool around with," as he says, he began to grow Euglena, a small green phytoflagellate which is a common contributor to pond scum. As he began to study the chloroplasts, the chlorophyll-containing bodies of this little plant-like animal, he discovered himself in the full current of modern genetics. These bodies, he found, had their own DNA which did not arise from the nucleus. This finding was one of the first well-established examples that a cytoplasmic organelle contained and made its own unique DNA.

Similarly, a summer or two later, Dr. Granick was standing on the beach at Cold Spring Harbor with another problem in the back of his mind: how to track down the biochemical defect associated with acute porphyria, a serious and tragic disease leading to mental illness, extreme physical pain, and, all too often, death. The scientist with whom Dr. Granick was standing was thinking about his own work, which involved growing chick embryo liver cells in tissue culture, and described the simplicities and advantages of tissue culture technique with great enthusiasm. When Dr. Granick returned to Rockefeller he tried chick embryo cells for himself and they proved an almost ideal system for his biochemical studies. This was the beginning of a long series of studies "on the trail of acute porphyria" which eventually led to the establishment of a more rational treatment for the disease.

In 1960 Dr. Demerec resigned as Director. The present Director is British-born Dr. John Cairns, formerly at the Australian National University. Dr. Cairns is a distinguished molecular geneticist particularly noted for his work in radioautography, but like most men who find administrative responsibilities thrust upon them, he is finding that they preempt much of his laboratory time. And it must be admitted that Dr. Cairns's administrative problems are particularly anguishing. Although the research activities and symposia are supported by a number of government agencies – such as the National Institutes of Health, the National Science Foundation, and the New York State Science and Technology Foundation – there has been no outside support for maintenance. Many of the Laboratory's buildings are over one hundred years old, and no substantial funds have ever been available in the history of Cold Spring Harbor for their maintenance and repair. The Davenport Laboratory, for example, where the summer courses are held, contains tens of thousands of dollars worth of scientific equipment on its second floor; its first floor, however, is three feet under one of the numerous streams of Cold Spring Harbor. Outside his office window Dr. Cairns has planted a young Australian Eucalyptus, a reminder of more peaceful days.

But the intellectual activities continue with undiminished vigor. Although the Carnegie Institution has now officially withdrawn from Cold Spring Harbor, turning over its buildings to the new Cold Spring Harbor Laboratory of Quantitative Biology, Doctors McClintock and Hershey are continuing their studies in space now rented by the Carnegie Institution. The Laboratory itself maintains a winter research program with about half a dozen principal investigators, including Dr. Cairns, whose work is largely focused on genetic research and molecular biology. Last year's Symposium, attended as usual by a large contingent from The Rockefeller University, was on the subject of sensory receptors. Professor H. Keffer Hartline was chairman of the session on photoreceptor physiology. Also, four summer courses were given, the traditional ones on bacteriophage, and bacterial genetics, a newer course on the animal viruses, and one on *Phycomyces* which was given last year for the first time by Dr. Delbrück. Students from The Rockefeller University last summer included Erwin J. Fleissner, Magda Gábor, Jean-Lucas Lenard, and Masao Takeda. As part of the usual, ongoing program, a nature course was held for local high school teachers to acquaint them with the flora and fauna of the local area, and some three hundred junior investigators, aged six to fourteen, were given courses ranging from General Nature Study through Vertebate Zoology to Advanced Ecology, following the same trails through the woods and along the narrow sandy beaches that were first traveled by scientific explorers three-quarters of a century ago.

Catalyst of ideas

Plans for this summer are well under way. The Symposium, which will be held from June 2 to June 9, is on "the genetic code." Professor Fritz Lipmann will chair the session on codons in vitro, and Norton Zinder, Clelia Ganoza, and Daniel Rifkin will be among those presenting papers. One familiar face will be missing. Dr. Demerec, long the guiding spirit of the laboratories, died in his home in Laurel Hollow, Long Island on April 12 at the age of 71. As Dr. Tatum points out: "During the past two decades, Cold Spring Harbor has been a focus for practically every major development in genetics.... It has been the special function of the Biological Laboratory to serve as a catalyst of ideas, and incalculable benefit to science has flowed from the exchange here of facts, opinions, and frank speculations and from the opportunity for visitors to learn the skills needed for new and exciting fields of biological research."

DE GUSTIBUS

THE STUDY OF TASTE comprises a host of fundamental biological problems: the way in which different molecular configurations can act selectively on receptor cells; the way in which these stimuli, once received, are relayed to the brain; and, perhaps most interesting of all, the way in which the chemical stimulus of taste can interact with a changing pattern of needs and desires to produce specific and often extraordinarily adaptive behavioral responses. In these recollections of his experiences in this field – which constitute in effect a brief history of modern scientific study of taste – Professor Carl Pfaffmann describes the ways in which these problems are being approached and some of the answers which have been found. The article is freely adapted from a lecture given by Dr. Pfaffmann in 1964 after he received the Distinguished Science Contribution Award of the American Psychological Association.

BY CARL PFAFFMANN

Morally considered, [gourmandism] denotes implicit obedience to the commands of the Creator, Who, when He bade us eat that we might live, gave us the inducement of appetite, the encouragement of taste, and the reward of pleasure.

ANTHELME BRILLAT-SAVARIN c. 1825

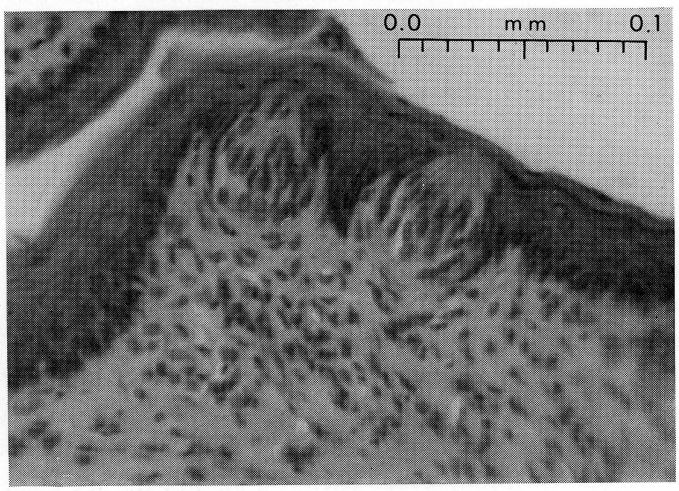
I SHOULD LIKE to begin with a few reminiscences about sensory psychology and the developments in this field over the last three or more decades, decades that have been characterized by the great developments in sensory electrophysiology. I remember well, and some of you will also recall, the impact of Adrian's *Basis of Sensation* in 1928, Adrian and Bronk's single unit analysis of motor nerve fiber activity, Herbert S. Gasser and Joseph Erlanger's discovery of the composite nature of the action potential in sensory and motor nerves, H. K. Hartline and Clarence Graham's records from the single photoreceptors of *Limulus polyphemus,* the horseshoe crab, and Glenn Wever and Charles Bray's discoveries of the cat's auditory nerve, and their subsequent debates with S. S. Stevens and Hallowell Davis. Nowadays, microelectrode techniques have reached the stage where nearly every sense cell and neuron of the peripheral and central nervous systems has been probed and tested. With the present "state of the art," almost anyone who can afford a CRO (cathode-ray oscilloscope) and an instruction manual, can "do it yourself." It was not always so!

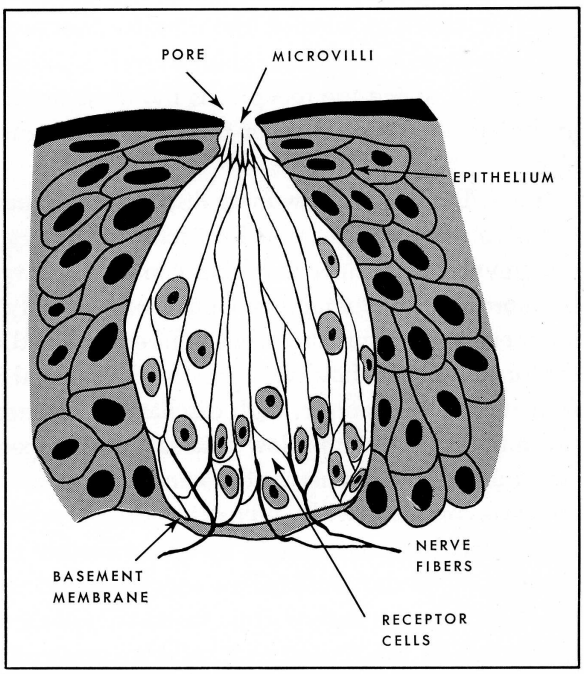
When I began research, it seemed the obvious thing to try this method on taste, to extend Zotter-

man's earlier work. I am still at it, helped mightily, I might add, by a string of excellent graduate students and colleagues over the years who have all had a part in the research for which I have been honored. I was also fortunate to be able to spend my graduate years in England, first at Oxford and then at Cambridge with the master, Lord Adrian.

But I must tell you about our early apparatus. Bryan Matthews, while still an undergraduate at Cambridge in 1928, invented a moving iron-tongue oscillograph, the Matthews Oscillograph, a kind of glorified magnetic loud-speaker movement which carried a mounted mirror. It was rugged and relatively foolproof with a good frequency response for neural activity. The slow recording film of that day required a high intensity which only an arc light could produce. The one I used was run by clockwork; it smoked and sputtered and sometimes went out at crucial moments. Part of the light from the oscillograph mirror was reflected to a rotating mirror which in turn spread an image of the spikes and waves upon a cylindrical waxed-paper screen. Amplifiers were not readily available; in fact, I recall having built my own two-stage preamp "bread-board style," but it did so well that I used it all the time I worked at Cambridge. It was mounted inside a Celotex-muffled box lined with aluminum (aluminium) screening, placed in turn on top of an inflated inner tube to protect it from vibrations and sound-induced microphonics. The whole assembly was placed conveniently on the floor beneath my operating table so that a well-placed kick would stop the microphonics and sometimes correct other malfunctions.

It was necessary, before being accepted for an advanced degree at Cambridge, to propose a thesis topic *in advance*. Adrian accepted my proposal to search for the salt, sour, bitter, and sweet primary taste receptors that experimental psychologists of the preceding era had hypothesized. To make a long story short, after two years of searching, I could not find them. I did record from single taste nerve fibers in the cat, and they, indeed, responded selectively to different chemicals to varying degrees, but rarely to only one of the basic taste stimuli. In the cat, all receptors were stimulated by acid, some were stimulated by acid plus salt, and still others by acids plus quinine. Sugar-responsive units were not found but we now know that they are scarce in this species. I can very well remember that Adrian became much more interested in this project when these unexpected results turned up — when I did not "confirm the hypothesis." I suppose he might have asked, had I found what I expected, "Why bother to do the experiment?"





The taste bud, photographed in section (LEFT) *and shown in schematic drawing* (RIGHT), *is a cluster of 20 to 25 sensory cells in the form of a goblet. Stimulating solutions reach the receptor cells through the gustatory pore at top*

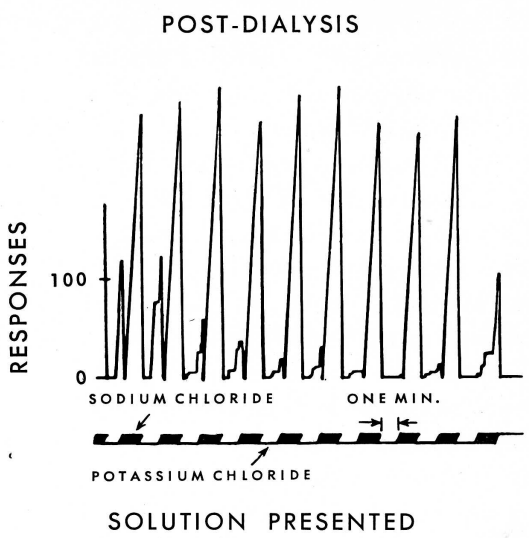
Each papilla carries a number of taste-beakers, clusters of taste-cells and supporting cells, which constitute the end-organs of taste.

E. B. TITCHENER, *Experimental Psychology*, 1901

MULTIPLE-TASTE SENSITIVITY One possible explanation for the multiple-taste sensitivity of individual receptor cells, which we observed in these early experiments, might have been that each individual cell is innervated by more than one nerve fiber. We now know, however, that multiple innervation is not the sole basis for multiple sensitivity. Kimura and Beidler have recorded electrical potentials from single taste-cell receptors with a microelectrode. They have shown that the range of taste stimuli that initiate an electrical response from any one cell is in fact very similar to the range of stimuli that activate an individual nerve fiber.

Although one might expect increasing selectivity as one ascends the phylogenetic scale, even the primates studied so far have displayed a somewhat "broadly tuned" taste system at the single unit – receptor or fiber – level. Taste cells display differential rather than absolute specificity, and a single cell may show a maximal response to more than one stimulus. When the taste stimuli are presented at suprathreshold levels – that is, at concentrations well above the lowest level that the animal can detect – the cell may show a more vigorous response to some "tastes" than to others. The data are not sufficiently systematic, however, to tell us whether the stimulus that evokes the most vigorous responses at high levels is the same stimulus to which the receptor is the most sensitive at the lowest detectable – or threshold – concentration.

It is difficult to see how mere discharge of a multisensitive receptor-fiber unit by itself could carry an unequivocal code since that fiber can be discharged by more than one stimulus. Concurrent activity in another parallel but somewhat differently tuned receptor unit could, however, provide the needed information. For example, high discharge of a sugar-salt unit coupled with a low acid-salt unit response could signal sugar, whereas the same high sugar-salt response combined with a high acid-salt unit response might signal salt. One might speculate further that, since many of the mammalian sugar-reactive units we know now are sugar-salt units, this double sensitivity may be the reason why weak concentrations



Animals make subtle taste discriminations. Height of cumulative response record indicates rat's preferential drinking of sodium chloride over potassium chloride when each is presented to the animal alternately for one-minute intervals as indicated by signal marker below

of salt taste sweet to man. Only at concentrations clearly above the threshold would the afferent pattern of activity characteristic of salt be clearly established. Thus, the electrophysiological evidence suggests that the taste input should be looked at as a distributed input through parallel afferent channels which provide the basis for taste discrimination.

Recent psychophysical experiments in man by v. Bekesy have re-affirmed the idea that human taste papillae contain receptors, each of which gives rise to only one of the four basic taste sensations, salty, sour, bitter, or sweet, when stimulated by chemical or electrical stimuli. Even here there is some question about the unitary character of the taste sensation. The quality of the sweetness produced by punctate electrical stimulation is different from that produced by solutions of sucrose, dextrose, fructose, or lactose. All sugars have "over-tastes" compared with the so-called monogustatory sweetness produced by electrical stimulation. Many other chemical stimuli do not elicit pure primary taste sensations.

Electrophysiological recording provides information on the link between stimulus and afferent nerve response, psychophysics between stimulus and sensation. The link between nerve response and arousal

of sensations of taste which so far has been amenable only to indirect study requires single unit nerve recordings in man.

> *In no case may we interpret an action as the outcome of the exercise of a higher physical faculty if it can be interpreted as the outcome of the exercise of one which stands lower in the psychological scale.*
>
> C. L. MORGAN, *Comparative Psychology*, 1894

BEHAVIORAL DATA We now have sufficiently detailed behavioral data to show that the animals from which we record the electrophysiological data can make subtle taste discriminations. This fact is important if we are to offer useful hypotheses concerning the mechanisms by which such discriminations are made. The classical work of Richter showed that rats, when salt-deficient, can detect and discriminate sodium from nonsodium salts in the two-bottle preference test. Fisher in our laboratory obtained an even more striking demonstration of discrimination by rats between sodium chloride and potassium chloride. In his experiment the rats were subjected to intraperitoneal dialysis with a five per cent glucose solution, a procedure which induces an acute loss of body sodium. The illustration compares the rates at which the rats licked the two solutions during a control period preceding intraperitoneal dialysis with the licking rates following dialysis. Although the rats drank some of the potassium salt solution after dialysis, they did not drink as much of the potassium as of the sodium and they soon ceased to drink it altogether. Discrimination between the two is clear.

The ability of rats to discriminate between at least two groups of salts, one characterized by potassium and the other by sodium, has now been confirmed and amplified by many investigators. On the other hand, discrimination between sodium chloride and related salts like lithium chloride is poor. The adrenalectomized rat has a high sodium requirement since its ability to retain salt is impaired. It will accept either sodium chloride or lithium chloride indiscriminately the first time the two solutions are presented. The physiologically afferent impulse discharge is very similar for the two salts. But the animal that drinks the lithium solution becomes ill. After recovering, it avoids the toxic lithium chloride and the beneficial sodium chloride as well. Only after protracted exposure to the toxic salt, can the animal learn to make the subtle discrimination in taste. It is of interest that man also finds the tastes of lithium chloride and sodium chloride very similar.

Although we have been stressing here the role of taste alone in behavior, in most cases the ingestion of the substance tasted leads to immediate and long-term postingestion effects. Some methods have been devised, however, by which the effects of taste can be isolated from the effects of ingestion. Recently, for example, Mook reported on the development of an "electronic esophagus." By the use of this device, the experimenter can divert the solutions that the rat has ingested, through an esophageal fistula, while simultaneously pumping other solutions into the rat's stomach through a gastric tube. In this way, the effects of fluids entering the oral cavity can be dissociated from the effects of those actually ingested. In experiments on rats drinking saline solution, he found that if no fluid entered the stomach, saline intake was enhanced, but if water was simultaneously introduced into the stomach, the saline consumption was little greater than normal water consumption. In this case, the postingestion effects of water were more powerful than the role of taste alone.

Recent studies by Fisher in our laboratory indicate, however, that animals that are not thirsty truly prefer saline to water. He developed a "contingent lick" experiment in which animals can, by taking a specified number of licks at one drinking tube, produce a second drinking tube. In this way, for example, a rat can lick at a water tube and produce saline or at a saline tube and produce water. The first, or contingent, tube remains available after the second one has appeared. If saline is presented first, the animal that has not been deprived of water will continue to drink from the salt tube, rather than shift to the water tube when it is offered also. Conversely, when the water tube is made available first, the animal licks it only often enough to produce the saline tube and then shifts to saline. In other words, the nonthirsty animal will work for salt, demonstrating that saline drinking is a true preference.

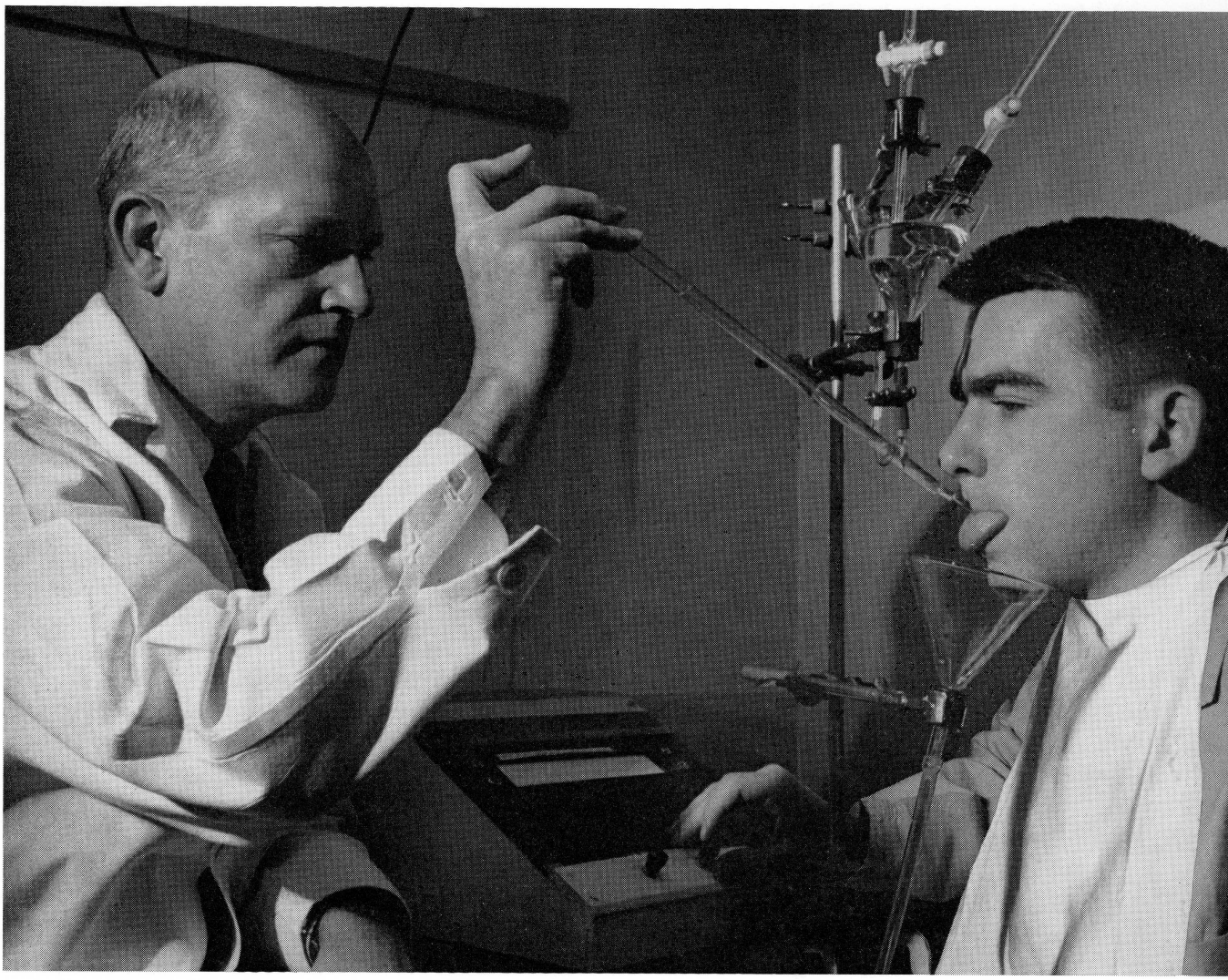
Not all behavior tests are equally sensitive. For example, it is only under certain conditions that the rat will learn to go to the arm of a T maze containing

saline. Preference and reinforcement are not synonymous, unless we take into account the several contributing factors in the situation being examined. Sodium chloride is a much preferred substance, for instance, when postingestive factors support or enhance the moderate salt preference. But sodium chloride by itself appears incapable of reinforcing such instrumental behavior as bar pressing; without the added motivation of water or food deprivation, the animals do not work. This is not the case with sugar, as we shall see later in the section on "Sugars and Hedonism."

"A man's palate can, in time, become accustomed to anything." NAPOLEON I to Gaspard Gourgaud at St. Helena, c. 1815

TASTE ADAPTION Another facet of the response to saline solutions raises questions which we once thought we had answered. Salt-deprived animals have an obviously lower salt-behavior threshold; in other words, they respond to weak saline solutions toward which normal animals are indifferent. It had been suggested that the lowered threshold reflected increased sensitivity of the taste receptors. A number

If the tongue of a human subject is washed for a protracted period with a salt solution, the salt sensation disappears

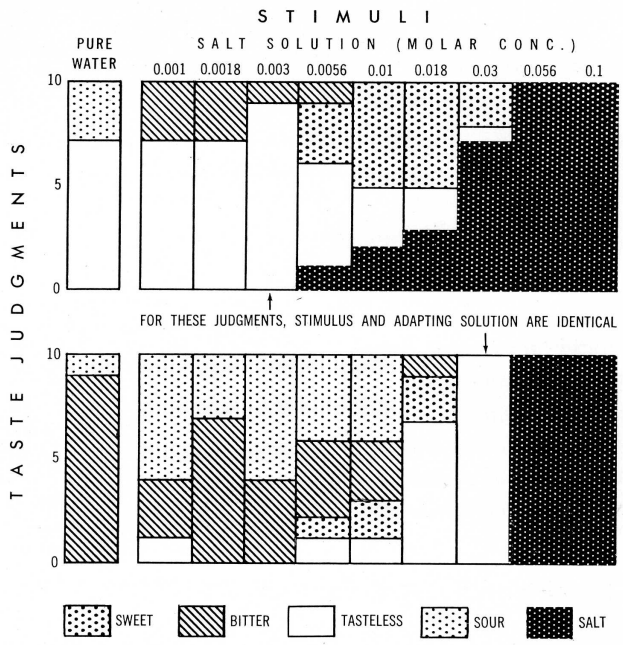


of years ago, Bare and I, and more recently Nachman and I, tested this hypothesis by the electrophysiological method. We found no difference in the electrophysiological-neural responses to salt in normal and salt-deficient animals. Further, the relative magnitudes of the responses to different salts at suprathreshold concentrations were not modified by deprivation.

Other investigators, including Carr in 1952 and Harriman and MacLeod in 1953, trained rats to avoid a salt solution by giving them an electric shock a few seconds after they started drinking. The animals soon learned to stop drinking as soon as they tasted salt. If, however, concentrations were very low, they were unable to detect the salt and so could not avoid the punishment. The level of salt concentration at which discrimination failed, it was found, was the same in both normal and severely deprived animals. In other words, it seems as if the lowered response thresholds observed in salt-deficient animals reflect some interaction in the central nervous system rather than any peripheral change in sensitivity.

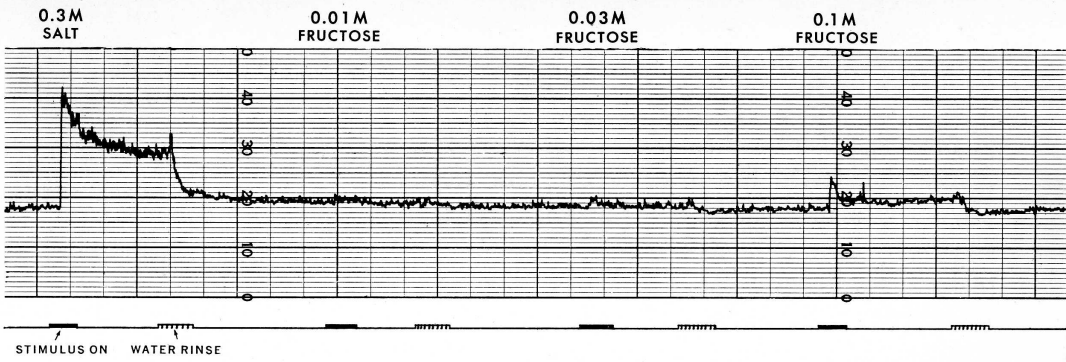
On the other hand, McBurney and I showed in 1963 that the salt-taste threshold in man is a function of prevailing concentration of sodium in the saliva. The sodium chloride threshold lay just above the concentration of salt in the subjects' saliva. But the threshold could be shifted by adapting the tongue to weaker or higher concentrations of salt. In every case, the taste threshold was just a little above the adapting stimulus concentration. Thus, taste sensitivity may reflect changes in composition of the saliva as a consequence of metabolic state.

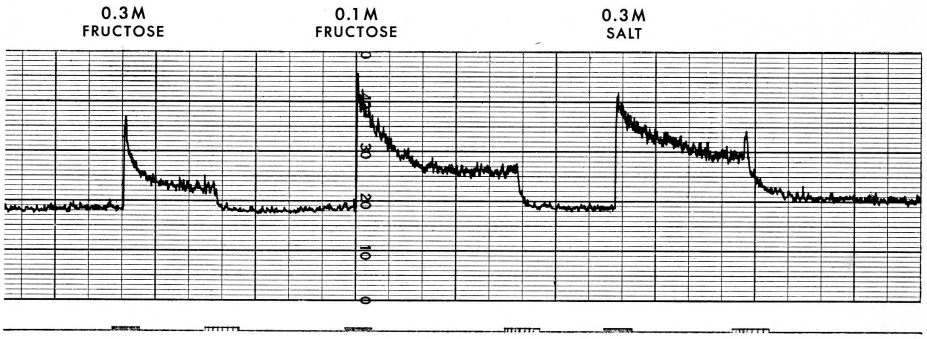
Taste adaptation may be more important than previously thought for another reason, namely the recently observed qualitative changes produced by adaptation in human subjects. Bartoshuk, McBurney, and I showed that if we flushed the tongue of human subjects for a protracted period with a saline solution, the salt sensation produced by that particular concentration of salt disappeared, as we expected. Salt solutions slightly more concentrated than the adapting solution still tasted salty, although less salty than they normally would, but those less concentrated than the adapting solution had a contrasting taste — an "antitaste," if you like — which was sweet, sour, or bitter or some combination of the three, depending on the subject. The lower the salt concentration in relation to the adaptation level, the stronger the antitaste, the maximum antitaste being produced by water alone. By subjective scaling methods, McBurney was able to show that the antitastes were exceedingly strong, not merely fleeting or evanescent uncertainty responses. After adaptation to 0.1 NaCl solution, subjects described the taste produced by water as a sour-bitter sensation of a magnitude almost as intense as the salt sensation produced by 0.1 NaCl before adaptation. After adaptation, of course, 0.1 salt solution produced almost no taste response at all.



Salt solutions may taste salty, sour, bitter, or sweet depending on the human subject's prior adaptation. To this subject, salt solutions less concentrated than the adapting solution had a contrasting taste — an "antitaste" — which was sour, sweet, bitter, or some combination of the three

That the taste of water and other substances can be affected by prior adaptation has been long known. Thus, water is said to taste sweet following adaptations to acid. These new observations, which are really old, however, indicate that these so-called contrasts or antitastes are proportional to concentration, and that such responses occur not only to water (a zero stimulus?) but to all concentrations weaker than that to which the tongue has been adapted. Further systematic study of qualitative and quanti-





A squirrel monkey responds electrophysiologically to sugar. Summator records discharge from monkey's chorda tympani nerve in response to increasing concentrations of sugar and a standard test salt, ammonium chloride

tative changes resulting from adaptation are clearly needed to answer many intriguing questions. Is there a sliding scale of taste anchored at some adaptation level? Do all increments in stimulus above this level induce the typical taste response, and all decrements the complementary antitastes? There are a number of interesting physiological questions with regard to changes in the afferent neural code induced by adaptation. The main point is that by adaptation we can give salt solutions any one of the four primary tastes: salty, sour, bitter, or sweet.

> *a perpetual feast of nectared sweets*
> *Where no crude surfeit reigns.*
>
> JOHN MILTON, *Comus,* 1637

SUGARS AND HEDONISM Of major interest is the question of how taste influences behavior. How and where in the central nervous system are the primary afferent taste impulses received, how are they integrated, how do they instigate motor behavior and influence appetite? For answers to these questions, we do well to examine the responses to the sugars, for nearly all organisms, with few exceptions, find sugars both palatable and reinforcing.

A number of investigators have shown that the reinforcing effectiveness of sucrose solutions is proportional to concentration. We have been interested, especially, in correlating the electrophysiological responses to sugar with behavioral data. It has long been known in man that changes in molecular configuration affect sweetness of sugars. We would like to know how these differences are reflected in preferences for the different sugars. In our current studies, we have turned from the rat, whose chorda tympani yields a relatively weak sugar response, to the primate. We find the little squirrel monkey most suited for electrophysiological studies, and its chorda tympani shows significant neural activity to sugars and other behaviorally interesting taste stimuli. The illustration shows a recent recording by Snell from the squirrel monkey chorda tympani nerve. Note the clear responses to a standard test salt, NH_4Cl, and to an ascending sugar series, fructose.

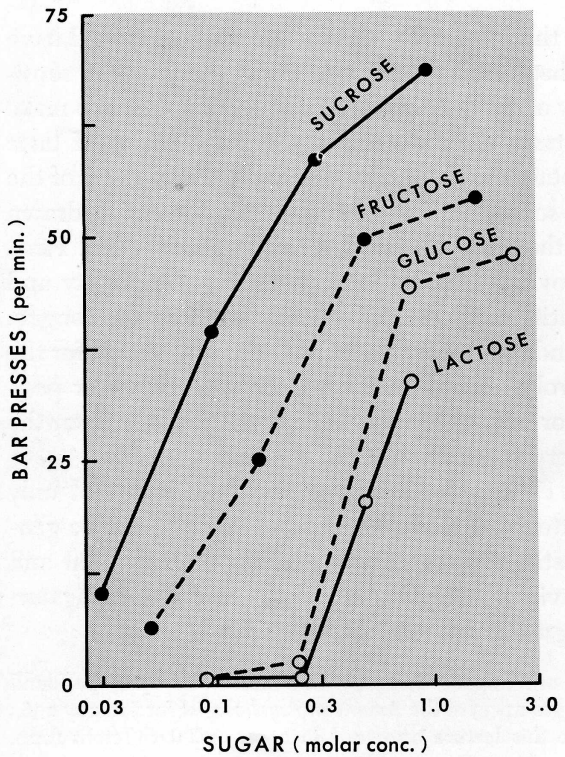
If we compare the different sugars in terms of electrophysiological effects, we find that fructose produces the most marked response, followed by sucrose, glucose, and then lactose. However, when the sugar solution is used as a reinforcing agent in experiments in which the monkey presses a bar in order to receive a drop of sweetened water, the order changes. The monkeys work hardest for sucrose, less hard for fructose, glucose, and lactose, in that order. In short, fructose is the most effective taste stimulus, sucrose the most effective reinforcer. The weaker sugars, lactose and glucose, are not as strikingly different electrophysiologically, nor are they so behav-

iorally. They both lie below sucrose and fructose, which is what one would expect if the reinforcing efficiency of these stimuli is directly related to the degree of chorda tympani response. But the discrepancy between fructose and sucrose suggests that our behavioral test has not, in fact, revealed pure oral determinants of the behavior. Perhaps we have not sufficiently minimized postingestive factors. Fructose, although a stronger oral factor than sucrose, is absorbed much less slowly, which might reduce its postingestive effect. But both sucrose and fructose are sufficiently sweeter than the other sugars so that the postingestional contributions to reinforcement might be overridden, thus revealing the oral determinant. We would expect that as the intake of sugar is restricted, reducing the postingestion effects, the influence of oral factors might be enhanced.

I have been emphasizing stimulus properties as prime determinants of the hedonic effect, but let me hastily point out that specific training and experience may make some unpleasant odors and tastes acceptable or even preferred. I am reminded here of the whiskey drinker's development so aptly described by Judson Brown.

Straight whiskey when first ingested typically effects rather violent defense reactions. Because of this, the novice drinker usually begins with sweet liqueurs, "pink ladies," and wines, and slowly works his way through a series of beverages characterized by the gradual disappearance of cola and ginger ale additives. Finally, only plain water or even nothing need be mixed with the raw product. To the hardened drinker, straight whiskey does not taste bad – not bad at all! (It is thus that a product euphemistically labeled "neutral spirits" becomes indeed psychologically neutral.)

Monkeys work hardest for sucrose. Sucrose is the most effective reinforcing agent in this experiment in which a monkey presses a bar in order to receive a drop of sweetened water



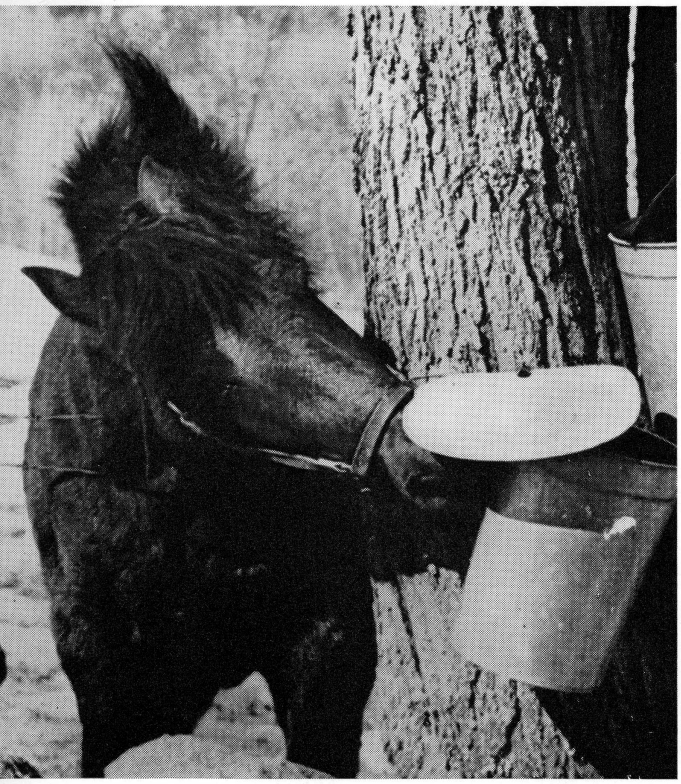
Pleasure and nobility between them supply the motivations for all actions whatsoever.

ARISTOTLE c. 340 B.C. *The Nicomachean Ethics*

MOLECULES FOR MOTIVATION Some years ago, after reviewing the behavioral data from man and animals and the relation of these data to afferent neural activity, I noted the following:

Thus it is abundantly clear that instigation of consummatory response (or of rejection), reinforcement of instrumental responses, and elicitation of hedonic effect, are all closely related and that reproducible stimulus functions can be demonstrated for each. . . . I would like to propose that sensory stimulation per se together with its ensuing central neural events be considered as a prime determinant in the chain of events culminating in acceptance behavior, reinforcement, and hedonic effect.

Although it can be shown that different learning variables can affect the pattern of response, I would maintain it is the taste stimulus itself and the degree of sensory activation aroused that determine behavior. It is indeed remarkable that a particular molecular configuration and its associated pattern of afferent inputs should have such profound effects upon behavior. For this, I like to coin the slogan, "molecules for motivation." The elimination of the sensory input at the thalamic level – as Ables and Benjamin, and Oakley and Pfaffmann have shown – makes it clear that the impoverishment of taste input by neural lesions reduces not only ingestive preference but also the power of reinforcement. Yet only the taste is lost. The caloric and other metabolic aspects of the stimulus are still present.



Molecules may motivate outside the laboratory too. Horse nudges lid off sap bucket hanging from maple tree in New Hampshire (LEFT), *and moose in Sweden licks salt placed on gravel road to make a firmer surface* (RIGHT)

To date in our electrophysiology we have learned most about the taste responses of the receptors and the direct taste systems of the brain, but it is clear that other neural components must be involved. Weiskrantz, for example, has shown that bilateral medial temporal cortical lesions in monkeys can produce changes in preference behavior but not in sensory threshold. Exaggeration of taste preference has been seen in hypothalamic hyperphagic rats, and Morrison has observed that anterior limbic lesions appear to modify the preference for saline without affecting discriminatory ability. The motivational aspects of taste seem to be neurally dissociable from the largely sensory features. But these studies are merely clues to the downstream neural mechanisms which convert sensory input into motivating output. To my mind, the question of how particular sensory messages are converted into potent determinants of behavior, not only in taste but other sensory domains, poses an important challenge for future physiological and behavioral research.

In this informal review of the study of taste, I have touched upon several questions: the multiple sensitivity of the taste buds, the ability of animals to make fine taste discriminations, the mechanisms of taste adaptation and, finally, the motivating powers of the taste sensation. The general conclusion can be drawn that the sense of taste has two major features. First, it provides information concerning the quality and quantity of diverse chemical stimuli on the tongue. Second, this information provides motivation for the control of behavior. Such motivation, whether positive or negative, appears to result directly from the sensory stimulation itself.

In closing, let me hope you now have not only a better picture *de gustibus* but *de gustibus* as a general stimulus-response model for physiological and behavioral analysis and why, for this investigator, *"De gustibus non est disputandum."*

A list of references on the work described here may be found on pages 21-33 of the *American Psychologist* for January 1965 where this lecture appeared in a somewhat different form.

National Academy of Sciences

PROFESSOR Floyd Ratliff was elected a Member of the National Academy of Sciences at the 103rd Annual Meeting on April 26. Other members of the faculty of the University who figured prominently in the proceedings were Professor Norton D. Zinder (see next page), Professor Donald R. Griffin, who gave a paper in conjunction with P. C. Williams and J. M. Williams on "Visual Orientation in Homing Bats," and Dr. Edward Reich, Associate Professor, who spoke on "Agents that Affect Nucleic Acid Metabolism."

Dr. Ratliff is noted for his work on the physiology of vision, in particular, the spatial and temporal properties of mutual inhibitory interactions of elements in the retina. His book, *Mach Bands: Quantitative Studies on Neural Networks in the Retina*, was published last year. Election to the Academy, which has a total membership of 745, is considered one of the highest honors that an American scientist can achieve.

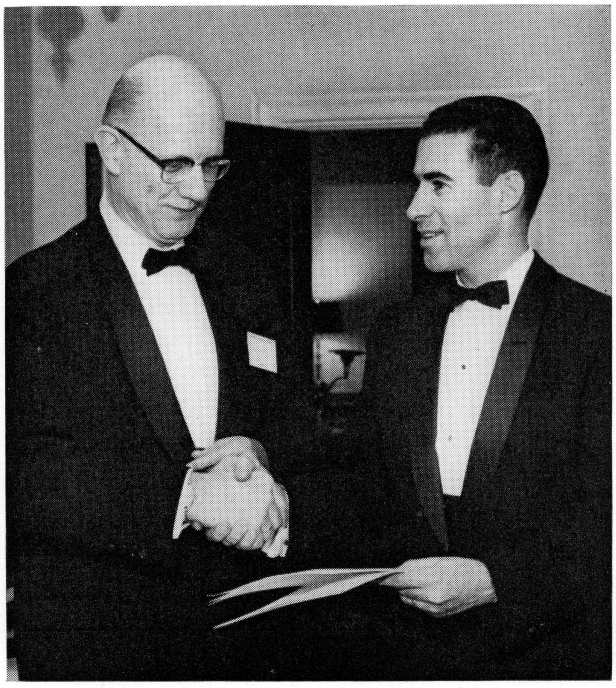
At the 62nd Annual Meeting of the Society of Experimental Psychologists on April 1, Dr. Ratliff was also awarded The Howard Crosby Warren Medal "For his distinguished research on the spatial and temporal characteristics of vision." Other members of Rockefeller who have received this award are H. Keffer Hartline, Neal E. Miller, and Carl Pfaffmann.

U. S. Steel Award

PROFESSOR Norton D. Zinder of The Rockefeller University received the United States Steel Foundation Award for distinguished work in molecular biology, on April 25. The award, administered by the National Academy of Sciences, was presented to Professor Zinder by Dr. Frederick Seitz, President of the Academy, at a special evening ceremony held during the 103rd Annual Meeting. Dr. Zinder, who was selected for the honor "for the discovery of RNA phages and for the analysis of the mechanisms of their replication," was given a certificate and the sum of $5,000.

Dr. Zinder won early recognition of his work with his publication, in conjunction with Professor Joshua

FLOYD RATLIFF



FREDERICK SEITZ AND NORTON ZINDER

Lederberg, of experiments demonstrating that bacterial viruses may transmit the genetic information of one bacterial cell to another. This phenomenon, known as transduction, was discovered in the course of his graduate studies at the University of Wisconsin. Dr. Zinder, who received his A.B. from Columbia in 1947, has been with The Rockefeller University since receiving his Ph.D. in 1952. For the last several years he has been concerned with work on RNA bacteriophages, a newly discovered group of bacterial viruses which because of their small size and rapid rate of multiplication have proved valuable for studies of fundamental genetic processes. Some aspects of Dr. Zinder's work with the RNA bacteriophages are described in the article, "The Friendly Viruses," which appears on pages 1-6 of this issue of the *Review*.

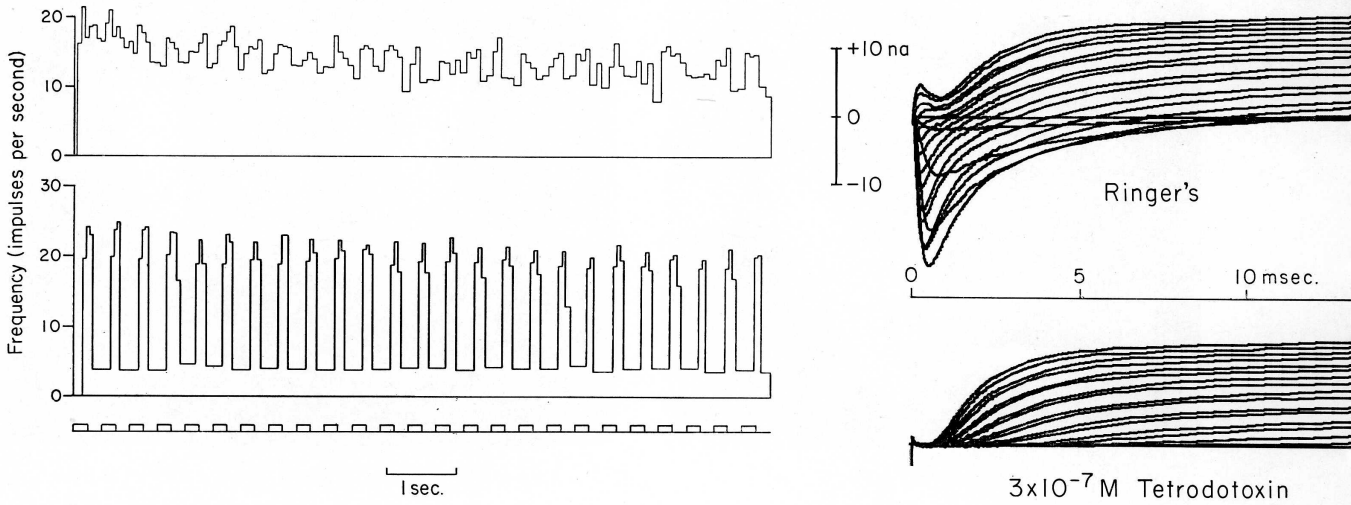
AIBS Meeting

AN UNUSUAL SILENCE pervaded some of the laboratories of the University during the week of April 11 as scores of its faculty members and students took part in the annual migration of scientists to Atlantic City for the meetings of the American Institute of Biological Sciences. The chief subjects of papers presented by Rockefeller personnel were viruses and immunology. Studies on the electron microscopy of viruses were reported by Harutaka Tanaka and Dan H. Moore on the mouse mammary tumor agent; Richard W. Compans, Kathryn V. Holmes, Samuel Dales, and Purnell W. Choppin on simian virus 5; and Nicholas H. Acheson and Igor Tamm on Semliki Forest virus. Papers on various aspects of the immune response were presented by Josephine A. Morello and Robert E. Franzl on inhibition of antibody formation; Charles C. Carter, Nicholas T. Macris and M. W. Chase on picrylation of proteins; Johanna M. Lee on allergic encephalomyelitis; Michel Rabinovitch on microbial immunology; Stephen D. Litwin and H. G. Kunkel on the structure of human gamma globulin; and John M. Stewart on antibody specificity. Alan F. Hofmann participated in the Symposium on Gastroenterology held on April 12.

New Computer

ARRIVALS ON campus this spring include a Control Data Corporation Computer which, with its accessory equipment, has been installed in Room 307 of South Laboratory. This new installation is the result of recommendations made by a committee appointed by President Bronk last fall to review the University's special needs in the computer field. The CDC-160-G,

Computer plotter recordings "off-line" LEFT *of response from two receptors in the eye of the horseshoe crab, one under steady illumination, the other under flickering light (Hartline); and "on-line"* RIGHT *from a single frog nerve in a normal solution and in the Japanese puffer fish poison, tetrodotoxin (Hille).*



as it is officially known, is "modest" as computers go, to use the language of the committee, and it is for this very modesty that this particular digital computer was chosen. One of the important requirements, the committee decided, was a facility suitable for student use. Another consideration was the adaptability of this particular computer for "on-line" use in connection with scientific experiments. More massive "off-line" computations can best be handled at large computer centers, of which there are several in the New York area. In a small computer laboratory students can be encouraged to become more familiar with the workings of the computer, to program their own studies, and to actually operate the computer themselves — which is impractical, of course, in a larger center. In addition, faculty members will be able to explore the use of the computer in varied ways. Although computers are now standard equipment for investigators in the physical sciences, most observers agree that they have potentialities for biological research that are still largely undeveloped.

Such opportunities became evident over the last several years as increasing numbers of faculty members and students have visited the laboratories of Professors Hartline and Ratliff where a smaller model, the CDC-160-A, is installed. The primary use of this smaller computer has been the analysis of data received from the experimental stimulation of nerve fibers. In general, it has been used "on-line," which means that the information is received into the computer, analyzed, recorded, and made available while the experiment is going on — all in a matter of seconds. Such analyses require not only the experimental setup plus the computer and its recording devices but also a special adapting unit — the interface — which translates the information coming from the experiment into data which can be handled by the computer. The interface unit in Dr. Hartline's laboratory was especially designed for him by personnel in the University's Electronics Laboratory. An advantage of such use of the computer is, of course, that experiments can be modified or rerun at the moment on the basis of the information received. Another advantage of such "on-line" work, in addition to the time-saving feature, is the effect on the investigator — the stimulation of being able to monitor his own experiment as it is going on. This relatively small facility was soon overloaded, however, and last fall it became apparent that another computer was required for the expanding needs of the University.

In addition to the computer itself with its auxiliary memory module, the new installation includes two magnetic tape transports, an input-output typewriter which can send information into the computer and receive outcoming data from it at a brisk ten characters per second; a card punch; a line printer which records data at the rate of 150 lines per minute; and a plotter for recording computational output in chart form. The new facility does not yet have the necessary interfaces for "on-line" work, but these will be developed.

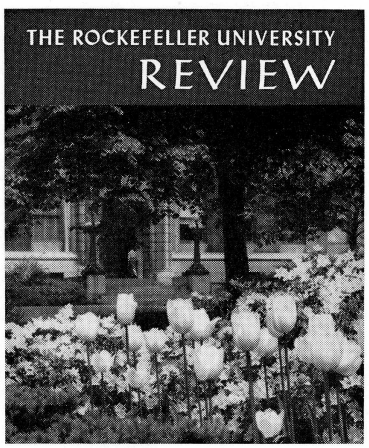
Responsible for guiding University personnel in the operation of the computer is Associate Professor Robert L. Schoenfeld of the Electronics Laboratory. With his help any student or faculty member who has qualified will have free access to the new facilities. Classes will be conducted by a teacher from the Control Data Corporation during the second week of June, and a more advanced course on computer use will be offered by Dr. Schoenfeld and his staff next fall.

¶

¶ President Bronk presented the major addresses at the dedication of the new Brumbaugh Science Center of Juniata College on April 16 and of the Justin S. Morrill Science Building of the University of Rhode Island on April 30. At the University of Rhode Island Dr. Bronk received his 50th honorary degree.

¶ Professor H. Keffer Hartline was elected Foreign Member of The Royal Society of London in April. This brings to five the number of Rockefeller faculty who are members of the oldest academy of science: Doctors Rous, Bronk, Lipmann, Dobzhansky, and Hartline—among only 65 living scientists throughout the world who have been thus honored.

¶ Dr. James G. Hirsch, Professor of the University and Senior Physician to the University Hospital, was elected member of the Association of American Physicians at the annual meeting of the Association in Atlantic City on May 4.



TULIPS, andromeda, azaleas, and branches of overhanging linden provide a frame of natural beauty for the entrance to Flexner Hall on a spring day. Photographed by Joseph Barnell.

ACKNOWLEDGMENTS: Page 3 micrograph courtesy of Dr. Lucien G. Caro, Oak Ridge National Laboratory. Page 4 chart adapted from *The Unseen World* by René Dubos, The Rockefeller University Press, 1962. Page 5 micrograph courtesy of Frances M. Schwartz, Graduate Fellow. Pages 7 and 10 photographs courtesy of Cold Spring Harbor Laboratory of Quantitative Biology. Page 8 photograph courtesy of Brookhaven National Laboratory. Page 12 "De Gustibus" was freely adapted from the *American Psychologist* for January 1965 with the kind permission of the publisher. Page 13 photograph courtesy of *The Journal of Comparative and Physiological Psychology,* 45: 393-400, 1952; drawing, The Rockefeller University Illustration Service. Page 14 graph courtesy of G. L. Fisher (personal communication 1963), *American Scientist,* 52: 201, 1964. Page 16 photograph by Dan Bernstein and reproduced with his kind permission. Page 17 chart adapted from *Science,* 143: 967-968, 28 February 1964: L. M. Bartoshuk, D. H. McBurney, and C. Pfaffmann. Page 18 summator record courtesy of *American Psychologist,* 20: 29, 1965 (T. Snell, unpublished data). Page 19 graph adapted from *American Psychologist,* 20: 31, 1965 (Jay and Fisher, unpublished data). Page 20 photographs *left* permission of Wide World Photos, Inc.; *right* by Hadar Olsson and reproduced with his kind permission. Page 21 photographs *left* The Rockefeller University Illustration Service; *right* by George Tames. Page 22 computer plotter recordings courtesy of Professor H. Keffer Hartline and Bertil Hille, Graduate Fellow.